

Summer 8-2017

Emotion Dysregulation and Functional Connectivity in Children With and Without a History of Major Depressive Disorder

Katherine Lopez

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WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological and Brain Sciences

Emotion Dysregulation and Functional Connectivity in Children

With and Without a History of Major Depressive Disorder

by

Katherine C. Lopez

A thesis presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Master of Arts

August 2017
St. Louis, Missouri

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Acknowledgements

I would like to thank Dr. Deanna Barch, my faculty advisor and chair of my committee, for her advice and guidance on this project and, more generally, for her support and mentorship during my time as a student at Washington University in St. Louis. I would also like to thank Drs. Joan Luby and Andrew Belden, whose input on and revisions of the manuscript has been instrumental. Finally, I would like to thank Drs. Ryan Bogdan and Desiree White for serving on my thesis committee.

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August, 2017

ABSTRACT OF THE THESIS

Emotion dysregulation and functional connectivity in children with and without a history of Major Depressive Disorder

by

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Masters of Arts in Psychology

Washington University in St. Louis, 2017

Professor Deanna Barch, Chair

Recent interest has emerged in understanding the neural mechanisms by which deficits in emotion regulation (ER) may relate to the development of depression. Cortico-limbic alterations reported in emotion dysregulation and depression may be one possible link. We examined the relationships between emotion dysregulation in school age, corticolimbic resting state functional connectivity (rs-FC) in preadolescence, and depressive symptoms in adolescence. Participants were 143 children from a longitudinal preschool onset depression study who completed the Children Sadness Management Scale (CSMS), Child Depression Inventory (CDI), and two resting state MRI scans. We examined rs-FC between four primary regions of interest (ROIs; bilateral dorsolateral prefrontal cortex (dlPFC) and amygdalae) and six target ROIs thought to contribute to ER. Findings showed that greater school-age emotion dysregulation (higher CSMS) predicted: 1) increased bilateral dlPFC connectivity with bilateral insula and vmPFC in children with and without a history of depression; 2) greater right dlPFC- dACC rs-FC in children with a history of depression; and 3) greater positive rs-FC change from childhood to preadolescence between the bilateral dlPFC and right insula in all children. rs-FC during preadolescence, but not school age emotion dysregulation, predicted later CDI scores. These results suggest that

childhood emotion dysregulation predicts rs-FC in preadolescence, which in turn, predicts depressive symptoms in adolescence. These findings elucidate one possible neurobehavioral trajectory for the developmental psychopathology of depression.

Keywords: resting state; functional connectivity; emotion dysregulation; major depressive disorder; dorsolateral prefrontal cortex

Introduction

Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide (World Health Organization, 2016). A large body of neuroimaging research has implicated alterations in cortico-limbic circuitry in MDD, particularly, prefrontal cortices and the amygdala (Rive et al., 2013; Seminowicz et al., 2004). This cortico-limbic circuitry is thought to support emotion processing and emotion regulation (ER; Buhle et al., 2014; Frank et al., 2014; Ochsner, Silvers, & Buhle, 2012). This literature converges with another line of investigation in MDD, which posits that emotion dysregulation is central to understanding alterations in cognition, emotion, and behavior in depression (Joormann & Gotlib, 2010; Joormann & Quinn, 2014). As such, there has been increasing interest in understanding the neural correlates of ER deficits and their relationship to the development of depression (Belden, Pagliaccio, Murphy, Luby, & Barch, 2015; Rive et al., 2013). An extension of this work into earlier developmental periods is critical to understand the developmental psychopathology of this disorder and identify early risk factors for depression in adolescence, a period marked by increased rates of depression in both girls and boys (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Merikangas et al., 2010; Wiens et al., 2017). Thus, the goal of the current study was to examine the relationships between emotion regulation at school age, resting state functional connectivity (rs-FC) in cortico-limbic regions in preadolescence, and their relationships to depressive symptoms in adolescence.

Research on ER using primarily functional MRI has identified a host of brain regions involved in cognitive control functions and emotion processing in populations of healthy adults. In particular, interconnections between prefrontal cortices and limbic areas are theorized to support processes that adaptively regulate emotions according to one's goals (Buhle et al., 2014; Frank et al., 2014; Ochsner et al., 2012). Brain structures associated with effective

downregulation of negative emotion include cognitive control regions such as the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), and dorsal ACC (dACC) and emotion processing regions such as the amygdala (Frank et al., 2014). A common finding during explicit emotion regulation tasks is that cognitive control regions exhibit increased activation while emotion processing regions show reduced activation (Buhle et al., 2014; Frank et al., 2014; Ochsner et al., 2012). A number of studies have hypothesized that successful down regulation of emotions is reliant on greater frontal suppression over emotionally reactive subcortical regions (Frank et al., 2014). In addition, regions such as the ventromedial prefrontal cortex (vmPFC; Schiller & Delgado, 2010; Winecoff et al., 2013) and anterior insula (Menon & Uddin, 2010) are thought to facilitate communication between frontal and subcortical regions, leading to their description as “intermediate” cortices (Ochsner et al., 2012). Together, these sets of brain structures form a distributed network through which control regions may influence, and be influenced by, emotion processing structures and thus contribute to effective ER.

The research described above primarily focused on patterns of activation during emotion regulation tasks. Functional connectivity between structures of the cortico-limbic network described above has also been investigated in relation to emotion regulation. Functional connectivity examines the brain’s functional organization by measuring temporal correlations of blood oxygenation level dependent (BOLD) fluctuations between brain regions. Functional connectivity can be examined during resting conditions (e.g., resting state functional connectivity or rs-FC) or while performing a task. In the absence of an explicit task (e.g. at rest), cognitive control regions (e.g. dlPFC) tend to exhibit negative rs-FC with amygdala in healthy subjects (Roy et al., 2009). In task-based fMRI studies, functional connectivity between the amygdala and a host of prefrontal areas has been identified during explicit cognitive reappraisal tasks (e.g.

down regulation of negative emotions), such that greater negative amygdala-PFC connectivity tends to be associated with successful emotion regulation (e.g. Banks, Eddy, Angstadt, Nathan, & Phan, 2007). rs-FC has also been correlated with measurements of emotion regulation (ER), as evidenced by an association between downregulation success and increasingly negative connectivity between amygdala and medial PFC on a cognitive reappraisal task (Uchida et al., 2014).

Disturbances in the function and/or connectivity of this cortico-limbic network may alter one's ability to modulate emotions effectively. Indeed, task-based fMRI studies examining ER in depression in adults have consistently linked deficits in ER performance to hypoactivity in lateral prefrontal (e.g. vIPFC and dlPFC) and intermediate cortices (e.g. dACC; Rive et al., 2013), and increased activity in the amygdala (Zilverstand, Parvaz, & Goldstein, 2016). Importantly, research using rs-FC has shown that adults with MDD exhibit connectivity alterations in several components of this ER cortico-limbic network. A meta-analysis by Kaiser and colleagues (2015) found that individuals with MDD exhibit decreased positive rs-FC within the frontoparietal/central executive network, increased positive connectivity within the default mode network, and hypoconnectivity between DMN and the salience network. It is important to note that while these connectivity profiles have been widely implicated in emotion regulation, only one study directly examined rs-FC in relation to emotion dysregulation measures, showing positive correlations between rumination and increased rs-FC within the DMN (Zhu et al., 2012).

There is also evidence to suggest that abnormalities in ER corticolimbic networks in depression emerge at earlier stages of development. rs-FC studies in adolescents with depression have shown reduced connectivity between the amygdala and ACC (Connolly et al., 2013), between the dACC and frontal areas including the dlPFC and vIPFC (Pannekoek et al., 2014),

and increased connectivity within the DMN (Ho et al., 2015). Further, greater emotion dysregulation and depressive symptoms have been associated with lower functional connectivity between the amygdala and insula in youth, including depressed adolescents (Bebko et al., 2015). Corticolimbic rs-FC abnormalities studies have also been identified in early childhood samples with MDD. Gaffrey et al. 2010 found atypical connectivity profiles with the subgenual ACC (sgACC) in depressed children, such that greater rs-FC between the sgACC and dorsomedial PFC was significantly associated with greater emotion dysregulation. Chai et al., 2016 also identified greater positive connectivity between the sgACC and nodes of the DMN in children at-risk for depression, in addition to decreased positive connectivity within the cognitive control network and increased negative connectivity between the dlPFC and sgACC. Early onset depression has also been associated with atypical connectivity with the amygdala (Luking et al., 2011), ventral attention network (including the vlPFC; Sylvester et al., 2013), and DMN (Gaffrey, Luby, Botteron, Repovš, & Barch, 2012). Finally, functional connectivity abnormalities in this cortico-limbic network have been identified during explicit cognitive reappraisal tasks. Specifically, Murphy and colleagues (2016) found that depressed children with greater ruminative behaviors exhibited increased functional connectivity between amygdala and cognitive control brain areas during cognitive reappraisal (Murphy, Barch, Pagliaccio, Luby, & Belden, 2016). Together, these findings suggest that 1) rs-FC dysfunction in several brain structures comprising the emotion regulation circuit emerge as early as school age, and 2) many of these abnormalities are associated with concurrent emotion dysregulation and/or depression.

While the literature above suggests a relationship between alterations in ER cortico-limbic networks and depression, significant gaps remain in our understanding of these relationships over the course of development. One such gap is whether early emotion regulation

and or altered rs-FC in cortico-limbic networks predict the emergence or worsening of depression in adolescence, a period marked by increased risk for MDD. Given the evidence that emotion dysregulation may be a risk factor for depression (Berking, Wirtz, Svaldi, & Hofmann, 2014; Joormann & Gotlib, 2010b; Silk, Steinberg, & Morris, 2003), it is possible that rs-FC in the ER cortico-limbic network may act as a mediator between emotion dysregulation in school age and depressive symptoms in adolescence.

The primary objective of the present study was to examine the relationships between emotion dysregulation in school age, rs-FC of the ER cortico-limbic network in pre-adolescence, and depressive symptoms in adolescence in a longitudinal study of children with and without a history of depression. Based on the extant literatures of depression and emotion regulation, four primary regions of interest (ROIs; e.g. bilateral dlPFC and amygdala) and six target seeds (e.g. bilateral vlPFC, bilateral insula, vmPFC and dACC) were investigated. We examined whether: (1) emotion dysregulation in school aged children predicted individual differences in rs-FC in the cortico-limbic network in preadolescence in children with or without a history of MDD; (2) emotion dysregulation in school age predicted rs-FC change from childhood to pre-adolescence; (3) rs-FC in preadolescence predicted depressive symptoms in adolescence; (4) emotion dysregulation in school age predicted depressive symptoms in adolescence; and 5) rs-FC mediated any relationship between emotion dysregulation in school age and depression in adolescence.

Method

Participants

Participants for this study were from The Preschool Depression Study (PDS), a prospective 12-year longitudinal study examining the developmental trajectories of preschool

onset depression. Data acquisition, including neuroimaging and assessment data, is ongoing at the Early Emotional Developmental Program at Washington University School of Medicine in St. Louis, MO. Information regarding recruitment, study parameters (e.g. inclusion and exclusion criteria), and assessment measures have been previously described in Luby, Si, Belden, Tandon, & Spitznagel, 2009. Of relevance, all subjects participating in the Neuroimaging arm of the PDS underwent MRI scanning and completed a battery of behavioral assessments. Participants were evaluated in roughly eighteen-month intervals for a total of three waves. In Scan Waves 1 (S1), 2 (S2), 3 (S3), participants ranged from 7-12, 9-14, and 10-16 years of age, respectively. We recognize that there was spread in the ages assessed at each scan, with some overlap in ages across scans. However, for heuristic purposes, we treated each scan wave as a rough approximation of three developmental periods; school age (S1), preadolescence (S2), and adolescence (S3). All study procedures were reviewed and approved by the Institutional Review Board at Washington University School of Medicine. All parents provided written informed consent while children gave either oral or written assent or consent (depending upon age) following a description of the nature and objectives of the study.

To examine our primary objective of whether early emotion regulation predicts subsequent connectivity, we focused on emotion regulation assessed at S1, rs-FC connectivity at S2, and depressive symptoms measured at S3 to allow a temporal dissociation in order to test our mediation hypotheses. Thus, the present study included all children that had 1) CSMS data at S1; and 2) usable resting state scans at S2. A total of 143 participants met inclusion criteria for the current analysis. Participants were divided into groups based on their diagnostic status (for more information see *Diagnostic Measures*): history of MDD (N=58) and no history of MDD

(N=85). Table 1 provides a summary of relevant demographic and clinical characteristics of this sample.

Diagnostic Measures

All participants underwent a diagnostic assessment using the Preschool Age Psychiatric Assessment (Egger et al., 2006) or the Child and Adolescent Psychiatric Assessment (Angold et al., 2009) administered by trained research assistants to assess for psychopathology in preschool aged children <8 and children \geq 8 years old, respectively. Both the PAPA and CAPA are semi-structured interviews designed to assess a wide range of mental disorders based on DSM-IV diagnostic criteria. Both instruments have established reliability and validity (Angold et al., 2009; Egger et al., 2006). Children who met developmentally appropriate diagnostic criteria for Major Depressive Disorder at any time prior to or including S1 were categorized into the MDD group (Luby et al., 2003). Participants were clustered into the No-MDD group if they 1) met diagnostic criteria for clinical disorders other than MDD (including anxiety disorders, ADHD, and conduct disorders) at any point prior to or including S1 or 2) did not meet diagnostic criteria for any clinical disorder (e.g. healthy controls).

Self-report Measures

All participants and their parent/legal guardian completed a battery of questionnaires at each scan wave. Two measures of interest were examined for the present study: the Children Sadness Management Scale (CSMS; Zeman, Shipman, & Penza-clyve, 2001) and the Child Depression Inventory- Child Report (CDI; Helsel & Matson, 1984). The CSMS assesses children's ability to manage or regulate their experience with sadness via three dimension scores: Inhibition (overcontrol of sadness), Dysregulated Expression (undercontrol of sadness) and Coping (ability to regulate the intensity and duration of sadness). To evaluate sadness

dysregulation, the present study focused on the Dysregulated Expression Scale. Greater scores on the Dysregulation Expression Scale indicated poorer abilities to modulate sadness. The CDI was used to evaluate the severity of developmentally appropriate depressive symptoms. Psychometric properties for both instruments have been previously established (Knight, Hensley, & Waters, 1988; Smucker, Craighead, Craighead, & Green, 1986; Zeman et al., 2001)

Neuroimaging

All participants completed a battery of neuroimaging scans on a 3-T TIM TRIO scanner at Washington University. This battery included high-resolution structural scans, diffusion weighted images, and task-based and resting state functional scans. The present study examined resting state scans acquired from this battery. Specifically, two resting state scans; each including 164 frames (~ 6.8 minutes) were acquired. Participants were instructed to remain awake during scanning with their eyes closed. Images were acquired using a spin-echo, echo-planar sequence sensitive to blood-oxygen-level-dependent (BOLD) contrast (T_2^*) (TR=2500 ms, TE=27 ms, field of view=256 mm, flip=90°, voxel size=4X4X4 mm, slices=36). Additionally, T_1 -weighted structural images were acquired in the sagittal plane using a magnetization-prepared rapid gradient-echo (MP-RAGE) three-dimensional sequence (TR=2400 ms, TE=3.16 ms, flip angle=8°, 176 slices, field of view=256 mm, voxel size=1X1X1 mm). For registration purposes, T_2 -weighted images were acquired using a 3D-SPACE acquisition (TR=3200 ms, TE=497 ms, 160 slices, field of view=256 mm, voxel size=1X1X1 mm).

Preprocessing

All resting state scans for each participant underwent eight pre-processing steps: (1) image correction for slice-dependent time shifts; (2) removal of the first four images of each resting state scan to allow BOLD signal to reach steady state; (3) removal of odd/even slice

intensity differences due to interpolated acquisition; (4) image realignment within and across scans to reduce rigid body motion; (5) scan intensity normalization to a whole-brain mode value of 1,000; (6) registration of the T1 scan to an atlas template (WU 711-2B) in the Talairach coordinate system using a 12-parameter affine transform and re-sampled to 1-mm cubic representation; (7) co-registration of the three-dimensional fMRI volume to the T2 and the T2 to the participant's T1 structural image; (8) and transformation of the fMRI data to 3X3X3 mm voxel atlas space using a single affine 12-parameter transform.

Functional Connectivity Processing

The following additional four processing steps were conducted on all rs-FC scans using in-house software (Luking et al., 2011; Sylvester et al., 2013). First, the following nuisance variables were regressed from the BOLD data: average signal from ventricles, white matter, and whole brain parcellations indexed Freesurfer, as well as, 6 head realignment parameters and their derivatives (24 parameters from Volterra series expansion). Additionally, a temporal band-pass filter ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$) and spatial smoothing (6 mm full width at half maximum) were applied. Finally, to reduced motion and signal artifact, average global signal and its derivate were regressed out. Scans with excess head motion artifact were censored based on frame-wise displacement values greater than 0.2, as previously described by (Power et al., 2014).

Additionally, scan runs with less than 40 frames remaining after censoring and participants with less than 110 total frames remaining across all available runs were excluded from further analyses. After excess motion scans were identified and censored, all of the above steps were repeated with the raw data (output of the initial preprocessing) interpolating over the censored frames.

Resting-State Functional Connectivity Analyses

Based on the neuroimaging literature on emotion regulation and depression, the present study selected four primary seed ROI's (bilateral dlPFC and bilateral amygdala) and six additional target seeds (bilateral vlPFC, bilateral insula, vmPFC, and dACC) thought to be important for emotion dysregulation. Bilateral amygdalae were anatomically defined using Freesurfer's subcortical parcellations (Pagliaccio et al., 2014). The vmPFC region was created using a spherical ROI 12 mm in diameter and based on Gee et al., 2013 coordinates (-3, 35, 1). The remaining ROIs were also created using spherical ROIs 12 mm in diameter and were based on coordinates from the Buhle et al., 2014 emotion regulation meta-analysis. The seed coordinates were as follows: bilateral dlPFC (-/+ 32, 31, 30), dACC (-8, 22, 30), right insula (43, 9, 4), left insula (-36, 16, -1), right vlPFC (47, 24, -4), and left vlPFC (-47, 25, -6). For each participant, we computed the correlation of BOLD time-series between each of the four primary seed ROIs (averaging across voxels within the ROIs) to each of the other primary ROIs, as well as, the six additional target ROIs. We converted these correlations into Fisher's r to Z transforms, which were the dependent variables in all subsequent analyses.

Statistical Analyses

We used a series of linear regressions that included age and gender as covariates; an MDD history (MDD-hx) dummy variable coding for the presence of either a history of MDD or no lifetime history of depression (other diagnosis or healthy); and an interaction term between MDD-Hx and the other predictors of interest to determine if relationships to functional connectivity differed as a function of diagnostic status. To protect against false positives, we applied False Discovery Rate (FDR) to correct for the number of analyses conducted for each seed region as shown in Table 2. To address the question of whether S1 emotion dysregulation predicted S2 functional connectivity, we first conducted linear regressions on each pairwise

correlation at S2— the four seed ROIs to each other and the six target ROIs— using CSMS scores to predict functional connectivity. For any significant regressions in this first step, we conducted a follow-up regression to determine whether CSMS scores at S1 predicted connectivity at S2 above and beyond concurrent measures of emotion regulation at S2. To assess for connectivity change from S1 to S2 we took significant regressions in step 1 and examined whether S1 CSMS continued to predict S2 functional connectivity when controlling for S1 functional connectivity. We also examined whether functional connectivity at S2 predicted CDI scores at S3. Next, we assessed whether CSMS scores at S1 predicted depressive symptoms at S3. We also examined whether significant functional connectivity profiles at S2 mediated the relationship between CSMS at S1 and CDI scores at S3 using PROCESS (model 4; bootstrap confidence interval). Finally, to confirm that psychopathology in the No-MDD group was not attenuating group differences between the MDD and No-MDD groups, post-hoc regressions were conducted between children with MDD, other diagnoses (e.g. children with other clinical disorders but not MDD), and healthy children in predicting rs-FC. These post-hoc analyses included an Other-dx dummy variable coding for the presence of other clinical disorders other than depression (e.g. anxiety disorder and ADHD) and an interaction term between CSMS and Other-dx. Post-hoc regressions were conducted for all significant regressions that survived FDR correction in step 1 (see Supplementary table 1).

Results

Clinical Characteristics

Table 1 provides a summary of clinical and demographic characteristics. Children with a history of MDD did not differ from children without a history of depression in sex, age, and ethnicity. CSMS at S1 and S3 differed between groups, with children positive for a history of

MDD showing higher CSMS scores than children without a history of MDD. A similar trend was found for CSMS at S2. Finally, children with a history of MDD demonstrated significantly higher depressive symptoms at S3 than children without a history of depression.

[INSERT TABLE 1]

Does emotion regulation in school age predict functional connectivity in pre-adolescence adolescence in children with or without a history of MDD?

Table 2 provides the average connectivity values for each pairwise connection (e.g., positive or negative), as well as the results of the regressions. The linear regressions examining whether CSMS scores in school age (S1) predicted rs-FC in preadolescent stages indicated that greater CSMS scores at S1 predicted less negative rs-FC between bilateral DLPFC and vmPFC at S2. Greater CSMS scores at S1 also greater positive rs-FC between bilateral dlPFC and bilateral insula (see Table 2 for data; see Figure 2a for an example graph of main effect). Additionally, higher CSMS scores significantly predicted stronger negative rs-FC between the right amygdala with the dACC (See Table 2 for data and Figure 1A for a schematic of results). These CSMS to rs-FC relationships, with the exception of right amygdala to dACC, survived multiple comparison correction. See Supplementary Figure 1 for a graphical illustration of all main effect relationships that survived FDR correction.

[INSERT FIGURE 1 HERE]

In addition to these main effects of CSMS, there were several significant interactions between CSMS scores and MDD-Hx in predicting connectivity (see Table 2). The relationship between CSMS at S1 and rs-FC between right DLPFC to dACC, right to left DLPFC, right amygdala to left insula, and left amygdala to right vlPFC significantly differed by MDD history (See Figure 1A). Of these interactions, the right DLPFC to dACC (illustrated in Figure 2B)

survived multiple comparison correction. To further explore the source of this interaction, additional regressions were conducted separately in children with and without a history of MDD. These regressions demonstrated that CSMS scores in children with a history of MDD ($p=.002$, $t=3.11$, $B=.369$), but not in children without depression ($p=.648$, $t=1.409$, $B=-.053$), predicted greater positive rs-FC between dlPFC and dACC (see Figure 2b).

[INSERT TABLE 2 HERE]

[INSERT FIGURE 2 HERE]

Does emotion regulation in school age continue to predict functional connectivity in preadolescence above and beyond preadolescent emotion dysregulation

To examine whether the relationships between CSMS at S1 and rs-FC at S2 held above and beyond concurrent emotion dysregulation, CSMS at S2 was added as covariate for all regressions that survived multiple comparison. As shown in Table 3, S1 CSMS continued to significantly predict S2 rs-FC between bilateral dlPFC and bilateral insula, as well as, bilateral dlPFC and vmPFC. Additionally, the CSMS by MDD-hx interaction effect remained significant.

[INSERT TABLE 3 HERE]

Does emotion regulation in school age predict connectivity change from childhood to pre-adolescence/adolescence?

To determine whether CSMS at S1 predicted rs-FC at S2 even when controlling for rs-FC at S1 (e.g., change from S1 to S2), rs-FC at S1 was used as a covariate for regressions that survived FDR correction. As shown in Table 4, CSMS at S1 continued to predict greater positive left dlPFC-right insula and right dlPFC-right insula rs-FC across diagnostic status. Of note, the CSMSxMDD interaction effect for right dlPFC-dACC at S2 is no longer significant when controlling for right dlPFC-dACC rs-FC at S1.

[INSERT TABLE 4 HERE]

Does emotion dysregulation in school age and preadolescence predict depressive symptoms in adolescence?

CSMS scores at S1 did not significantly predict CDI scores at S3 ($p= 0.188$, $t= 1.321$, $B= 0.101$). However, CSMS scores at S2 significantly predicted S3 CDI scores ($p=.019$, $t= 2.370$, $B= 0.189$); with greater S2 CSMS scores (more dysregulation) predicting higher depressive symptoms. There were no significant interactions between either S1 or S2 CSMS and MDD history in predicting S3 CDI (child report) scores.

3.6 Does function connectivity in preadolescence predict depressive symptoms in adolescence?

A significant main effect for a relationship between right dlPFC to dACC connectivity and CDI scores ($p=.05$, $t=1.965$, $B= .180$) was found. Greater right dlPFC-dACC connectivity predicted higher CDI scores.

Mediation Analyses

The rs-FC measures in Table 1 that survived FDR did not mediate the relationship between CSMS at S1 and CDI at S3. See Supplementary Table 3 for mediation results of all rs-FC regions. For an overview of findings for all research questions see Figure 3.

[INSERT FIGURE 3 HERE]

Post Hoc Analyses

As shown in Supplementary Table 1, there were no significant effects in Other-dx (main effect) and CSMSxOther-dx (interaction effect) in predicting rs-FC.

Discussion

The present study investigated a number of research questions in an effort to characterize the relationship between school age emotion dysregulation, preadolescent rs-FC in ER networks, and depressive symptoms in early adolescence. Specifically, we examined whether emotion dysregulation in school age predicted 1) individual differences in rs-FC in the ER cortio-limbic network in preadolescence; and 2) rs-FC change from school age to preadolescence. Additionally, we examined relations between preadolescent rs-FC and school age emotion dysregulation, as well as, adolescent depressive symptoms. Finally, we assessed whether rs-FC served as a mediator between emotion dysregulation in school age and depressive symptoms in adolescence.

Examination of the relationship between emotion dysregulation in school age and rs-FC in preadolescence indicated two main effect findings and one interaction finding. For our main effect analyses, we observed that higher school age emotion dysregulation predicted 1) less negative rs-FC between the right dlPFC and vmPFC; and 2) a shift from negative to positive connectivity between the left dlPFC and vmPFC during preadolescence in children with and without a history of depression. The dlPFC is a primary anchor of the Central Executive Network (CEN; Power et al., 2011) and is involved in cognitive control functions including attention and working memory (Okon-Singer, Hendler, Pessoa, & Shackman, 2015). Work on the functional organization of the healthy brain has demonstrated that the CEN (including the dlPFC) typically exhibits negative connectivity with the vmPFC (part of the DMN; Greicius, Krasnow, Reiss, & Menon, 2003). Our findings, which show a relationship between a weakening in the typical negative connectivity between the dlPFC and the DMN and greater emotion dysregulation, might suggest possible alterations in executive networks' regulation of the DMN and its functions.

Abnormalities in DMN connectivity (e.g. hyperconnectivity) have been linked to deficits in shifting focus from oneself to external stimuli/environment, consistent with rumination (Berman et al., 2011; Sheline et al., 2009; Zhu et al., 2012) and have been noted in a wide range of psychopathologies (Broyd et al., 2009) including depression (Gaffrey et al., 2012; Ho et al., 2015; Sheline et al., 2009). This is one potential mechanism by which children with emotion dysregulation might allocate greater attentional resources to self-processing, consistent with reports that children with various psychopathologies engage in maladaptive negative self-focused emotion regulation strategies such as ruminative thoughts (Aldao, Nolen-Hoeksema, & Schweizer, 2010).

We also found that greater emotion dysregulation was associated with stronger positive connectivity between the dlPFC and insula. As one of the main nodes for the salience network, the insula is involved in detecting salient information and attaching valuations to incoming stimulus (Menon & Uddin, 2010). The insula typically exhibits modest positive connectivity with the dlPFC in healthy functioning (Seeley et al., 2007), though they participate in different networks (Power et al., 2011). Interestingly, connectivity within the SN, particularly between right frontal cortices and anterior insula, is thought to play a causal role in activating the CEN and deactivating the DMN (Sridharan, Levitin, & Menon, 2008). The anterior insula might therefore serve as transfer node in the interaction between CEN and DMN. One speculation for the strengthening in dlPFC-insula connectivity seen in the present study is that children who experience greater emotion dysregulation might activate the SN more frequently, potentially disrupting network shifting between the control and default mode networks. Additional longitudinal work examining the role of the SN in network switching throughout development will be needed to confirm this hypothesis. It is important to note that the connectivity

relationships described above remained significant after controlling for the effects of concurrent emotion dysregulation. This is consistent with the hypothesis that alterations in rs-FC were related to school age emotion dysregulation and did not merely reflect current ER function in preadolescence.

We also investigated whether school age dysregulation predicted the rs-FC profiles when controlling for school age rs-FC. Our findings demonstrated that, across diagnostic status, greater dysregulation was associated with increasing positive rs-FC between bilateral dlPFC and right insula from childhood to preadolescence. An intriguing observation was an apparent rightwards lateralization of insula connectivity (See Table 4). However, upon closer inspection, we observed trend level relationships between bilateral dlPFC and left insula, in addition to the dlPFC-right insula relationship, which survived FDR correction, consistent with the notion that the insula may be an important transfer node that facilitates shifting between the CEN and DMN. One speculative hypothesis for this finding is that positive insula- dlPFC connectivity, which intensifies from childhood to preadolescence with greater dysregulation, might set the stage for later impairments in network interaction between CEN and DMN.

Notably, the relationships described above did not interact with history of depression. However, we did observe that higher school-age dysregulation in children with a positive history of depression, but not those without, was associated with stronger positive connectivity between right dlPFC and dACC. Early work with PET (Koski & Paus, 2000) and recent work using rs-fMRI (Margulies et al., 2007) indicate that dlPFC and dorsal portions of the ACC are typically only weakly positively correlated. The dACC is a key node of the cingulo-opercular network (CON) and its connections with CEN (e.g. dlPFC) has been found to form a larger system important for top-down control processes (Dosenbach et al., 2007) Further, there is a large body

of work suggesting that the CON is activated when individuals experience conflict or make errors (Carter et al., 2017; Holmes & Pizzagalli, 2008; Stevens, Kiehl, Pearlson, & Vince, 2009). Our findings suggest that disruptions in the relationships among networks involved in cognitive control processes are present in children with a history of depression. Indeed, individuals with depression have been reported to show impairments in detecting errors during high conflict trials of stroop tasks (Ottowitz, Dougherty, & Savage, 2002), as well as slower reaction times during these interference trials (Mitterschiffthaler et al., 2008; Ottowitz et al., 2002). Notably, these impairments have been directly tied to abnormalities in dlPFC-dACC co-activation (Holmes and Pizzagalli, 2008). Resting state studies have also noted disruptions in dlPFC-dACC connectivity (Aizenstein et al., 2010; Ye et al., 2012). One such study displayed similar rs-FC patterns to our findings, showing that individuals with first-episode MDD exhibited increased positive connectivity between the left dlPFC and dACC (Ye et al., 2012). These studies offer converging evidence to suggest that alterations in dlPFC-dACC connectivity might be a mechanism by which emotion regulation impairments arise in depression. Future work assessing whether conflict monitoring impairments, in particular, are present in children with a history of depression is warranted.

Another key component of this study was to examine whether rs-FC in preadolescence mediated the relationship between school age emotion dysregulation and depressive symptoms in adolescence. While ER in preadolescence predicted later depressive symptoms, we did not find a relationship between school age ER and adolescent depressive symptoms. However, greater positive connectivity between the right dlPFC and dACC was associated with higher depressive symptoms in adolescence in children across diagnostic history groups (see Figure 4 for an overview of all findings). This finding is interesting given our interaction effect finding showing

stronger dlPFC-dACC connectivity in association with greater emotion dysregulation in depressed children, a link consistent with the hypothesis that dlPFC-dACC connectivity might be an important neural substrate to understanding the dynamics of depression throughout development. Surprisingly, however, we did not find that rs-FC between dlPFC-dACC or any other connectivity profile mediated the relationship between school age emotion dysregulation and depressive symptoms in adolescence. These mixed findings highlight the need for further investigation on the possible neural mechanisms involved in the relationship between school age emotion dysregulation and later depression.

Interestingly, we found that relationships between emotion dysregulation and rs-FC of the amygdala were much weaker than the findings for the DLPFC. A few modest relationships with the amygdala were observed, but none of these survived FDR (See Table 2). This is surprising given that altered amygdala rs-FC has been frequently linked to depression (Anand et al., 2005; Luking et al., 2011; Veer et al., 2010) and emotion dysregulation (Bebko et al., 2015; Morawetz et al., 2016; Veer et al., 2010) in adults and adolescents. One possible explanation is that alterations in amygdala rs-FC with prefrontal areas might become more strongly apparent during explicit demands of emotion regulation. This would be consistent with Murphy et al., 2016 findings, which showed that children with depression and greater ruminative symptoms displayed increased amygdala connectivity with cortical control regions during explicit cognitive reappraisal. Another possibility is that amygdala connectivity might vary more strongly with brain regions other than those examined in this investigation. Indeed, Cullen et al., 2014 demonstrated that adolescents with MDD exhibited decreased positive functional connectivity between amygdala and a host of perirhinal structures including the hippocampus.

Our findings should be considered in light of several limitations. First, the absence of

measures of cognitive control tasks during scan precludes us from determining whether the connectivity profiles revealed by this study are directly related to impairments in top-down control functions. The inclusion of cognitive measures in future studies will enable a more direct assessment of functions such as attentional and conflict monitoring and their relationship to altered rs-FC in preadolescence. In addition, the present study used a self-report measure of emotion dysregulation, raising a potential limitation in our ability to objectively capture deficits in emotion regulation abilities. Thus, future work would benefit from using objective measures of emotion dysregulation. Additionally, we would have ideally had measures of rs-FC even prior to childhood as studies have suggested that resting state networks are present as early as infancy (e.g. Fransson et al., 2007) might demonstrate continuities into adolescence. Thus, rs-FC measures in children younger than 7 years old would have allowed for a better assessment of the temporal evolution of connectivity profiles and its developmental relationships with emotion dysregulation and depressive symptoms. A fourth limitation is that the present study oversampled for early onset depression, possibly limiting the generalizability of our findings.

Conclusion

In summary, our findings demonstrate that emotion regulation in school age predicted alterations in DLPFC connectivity with a host of intermediate cortices in children with and without a history of MDD during preadolescence, as well as, between dLPFC-dACC in children with a history of depression. These profiles are consistent with the hypothesis that emotion dysregulation is associated with abnormalities in top down control functions that could compromise adequate self-referential processing and salience detection. The extent to which these relationships might confer greater risk for later depression remains unclear. Thus, future work examining the role of control networks in emotion regulation throughout development will

be important to understanding the mechanisms by which emotion dysregulation contributes to depression.

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Tables and Figures

Table 1. Demographic and clinical characteristics of children with and without a history of MDD.

	MDD-hx	NoMDD-Hx	Statistic	p
N	58	85	--	--
Male/Female	30/28	49/66	0.471 ¹	0.492
Ethnicity (% white)	53.44	47.05	0.586 ¹	0.746
Age	9.74 (1.23)	9.76 (1.34)	0.105 ²	0.916
CSMS at S1 (N=143)	5.41 (1.49)	4.76 (1.29)	-2.757 ²	0.006**
CSMS at S2 (N= 139)	5.05 (1.47)	4.60 (1.32)	-1.891 ²	0.060
CSMS at S3 (N=109)	4.86 (1.39)	4.36 (1.18)	-1.995 ²	0.048*
CDI at S3 (N=124)	43.94(8.96)	39.20 (4.90)	-3.787 ²	0.000**

Data are presented as Mean (SD)

** p<.001

* p<.05

¹ chi-square statistic

²t statistic

Table 2. CSMS scores at S1 significantly predicted functional connectivity at S2

Connectivity S2 Seed-ROI	Intercept	CSMS S1			MDD-hx			CSMS S1*MDD-hx		
		t	B	p	t	B	p	t	B	p
Right dIPFC										
vmPFC	-0.1078	1.995	0.019	0.024**	-1.140	-0.115	0.127	1.426	0.027	0.078
dACC	0.2044	1.887	0.016	0.030**	-2.304	-0.212	0.011*	2.503	0.043	0.006**
R Insula	0.2188	2.558	0.030	0.005**	-1.383	-0.173	0.084	1.252	0.029	0.106
L Insula	0.1564	1.870	0.018	0.031**	-1.372	-0.140	0.086	1.134	0.021	0.129
R vIPFC	0.0052	-1.296	-0.013	0.098	-1.500	-0.166	0.067	1.339	0.028	0.091
L vIPFC	-0.0659	-0.063	-0.000	0.474	-0.260	-0.030	0.397	0.308	0.006	0.379
Left dIPFC										
R dIPFC	0.4624	0.147	0.001	0.441	-1.646	-0.202	0.051	1.851	0.042	0.033*
vmPFC	-0.0631	2.100	0.021	0.018**	-0.243	-0.026	0.404	0.219	0.004	0.413
dACC	0.2831	1.455	0.013	0.073	-0.997	-0.095	0.160	0.825	0.014	0.205
R Insula	0.1844	2.240	0.024	0.013**	-0.324	-0.037	0.373	0.118	0.002	0.452
L insula	0.1722	2.999	0.032	0.001**	-0.457	-0.052	0.324	0.300	0.006	0.382
R vIPFC	-0.0240	0.523	0.005	0.300	0.149	0.016	0.440	-0.445	-0.009	0.328
L vIPFC	-0.0690	-1.195	-0.012	0.116	-0.792	-0.087	0.214	0.567	0.011	0.285
Right Amygdala										
R dIPFC	-0.1420	-0.109	-0.000	0.456	0.132	0.009	0.447	0.026	0.000	0.489
L dIPFC	-0.1610	-0.489	-0.002	0.312	0.713	0.044	0.238	-0.782	-0.009	0.215
vmPFC	0.0330	-0.300	-0.003	0.382	0.985	0.108	0.163	-0.363	-0.007	0.358
dACC	-0.0765	-1.773	-0.014	0.039*	-0.305	-0.025	0.380	0.744	0.011	0.228
R Insula	-0.0075	-0.412	-0.004	0.340	-1.152	-0.122	0.125	1.298	0.026	0.098
L Insula	-0.0561	-0.659	-0.006	0.255	-2.024	-0.208	0.022*	2.322	0.045	0.010*
R vIPFC	-0.0384	0.618	0.005	0.268	-1.130	-0.113	0.130	1.304	0.024	0.097
L vIPFC	-0.0396	-0.517	-0.004	0.302	0.665	0.062	0.253	-0.299	-0.005	0.382
Left Amygdala										
R dIPFC	-0.1696	0.095	0.000	0.461	-1.116	-0.073	0.133	1.214	0.015	0.113
L dIPFC	-0.1434	1.163	0.006	0.123	0.379	0.023	0.352	-0.782	-0.008	0.217
R Amygdala	0.3809	0.334	0.003	0.369	0.914	0.090	0.181	-0.975	-0.018	0.165
vmPFC	0.0519	-0.005	-0.000	0.497	0.268	0.029	0.394	-0.125	-0.002	0.450
dACC	-0.0743	-0.735	-0.006	0.231	-0.320	-0.029	0.374	0.482	0.008	0.315
R Insula	-0.0400	-0.329	-0.003	0.371	-0.220	-0.022	0.412	0.446	0.008	0.327
L Insula	-0.0565	-0.315	-0.002	0.376	-1.197	-0.119	0.116	1.365	0.025	0.087
R vIPFC	-0.0482	1.221	0.010	0.111	-1.557	-0.136	0.060	1.796	0.029	0.037*
L vIPFC	-0.0297	0.336	0.002	0.368	-0.401	-0.031	0.344	0.566	0.008	0.286

Data were controlled for sex and age.

*p<.05, nominal significance only (Light gray shade)

** Passed FDR Correction for that Seed (Dark gray shade)

Table 3. CSMS at S1 significantly predicted functional connectivity at S2, above and beyond CSMS score at S2

Connectivity S2 Seed-ROI	Intercept	CSMS S1			CSMS S2			MDD-hx			CSMS S1*MDD-hx			CSMS S2*MDD-hx		
		t	B	p	t	B	p	t	B	p	t	B	p	t	B	p
Right dIPFC																
vmPFC	-0.091	1.920	0.019	0.028*	-1.261	-0.013	0.104	-1.223	-0.157	0.111	1.179	0.024	0.120	0.758	0.015	0.224
dACC	-0.015	1.610	0.014	0.054*	0.702	0.006	0.241	-2.057	-0.236	0.020*	2.377	0.043	0.009**	0.250	0.004	0.401
L Insula	0.012	1.849	0.018	0.033*	-0.129	-0.001	0.448	-1.458	-0.185	0.073	1.043	0.021	0.149	0.552	0.011	0.290
R Insula	-0.125	2.079	0.025	0.019*	1.321	0.016	0.094	-2.216	-0.340	0.014*	0.857	0.021	0.196	1.734	0.043	0.042*
Left dIPFC																
vmPFC	-0.076	2.110	0.022	0.018*	0.045	0.000	0.481	-0.877	-0.117	0.191	-0.093	-0.001	0.463	1.220	0.026	0.112
L insula	0.058	3.018	0.034	0.001**	-0.507	-0.006	0.306	-0.465	-0.066	0.321	0.269	0.006	0.393	-0.172	0.003	0.431
R Insula	0.093	2.005	0.023	0.023*	0.057	0.000	0.477	-1.158	-0.166	0.124	-0.169	-0.003	0.432	1.446	0.033	0.075

Data represents all significant relationships that survived FDR correction

Data were controlled for sex and age.

*p<.05

** p<.01

Table 4. CSMS at S1 scores significantly predicted connectivity change from S1 to S2.

Connectivity S2 Seed-ROI	Intercept	CSMS S1			Connectivity S1			MDD-hx			Connectivity S1*MDD-hx			CSMS S1*MDD-hx		
		t	B	p	t	B	p	t	B	p	t	B	p	t	B	p
Right dIPFC																
vmPFC	-0.040	1.362	0.146	0.176	-1.987	-0.207	0.0503	-0.879	-0.324	0.382	-0.310	-0.040	0.757	1.003	0.376	0.318
dACC	0.000	1.169	0.000	0.244	7.953	1.000	0.000**	1.355	0.000	0.177	-2.584	0.000	0.010*	-0.360	0.000	0.719
L Insula	0.000	-1.881	0.000	0.062	3.935	1.000	0.000**	-1.174	0.000	0.242	-0.320	0.000	0.7495	1.202	0.000	0.231
R Insula	0.076	2.838	0.291	0.005**	-0.137	-0.013	0.891	-2.112	-0.743	0.037	-1.093	-0.108	0.277	2.233	0.800	0.028*
Left dIPFC																
vmPFC	0.000	1.362	0.000	0.175	1.543	1.000	0.000**	-0.768	0.000	0.444	-0.778	0.000	0.438	-0.807	0.000	0.421
L insula	0.000	1.682	0.000	0.094	1.404	1.000	0.000**	1.011	0.000	0.313	1.012	0.000	0.313	-1.154	0.000	0.250
R Insula	0.125	2.055	0.216	0.043*	0.246	0.024	0.806	-0.764	-0.282	0.447	0.820	0.117	0.414	0.898	0.330	0.372

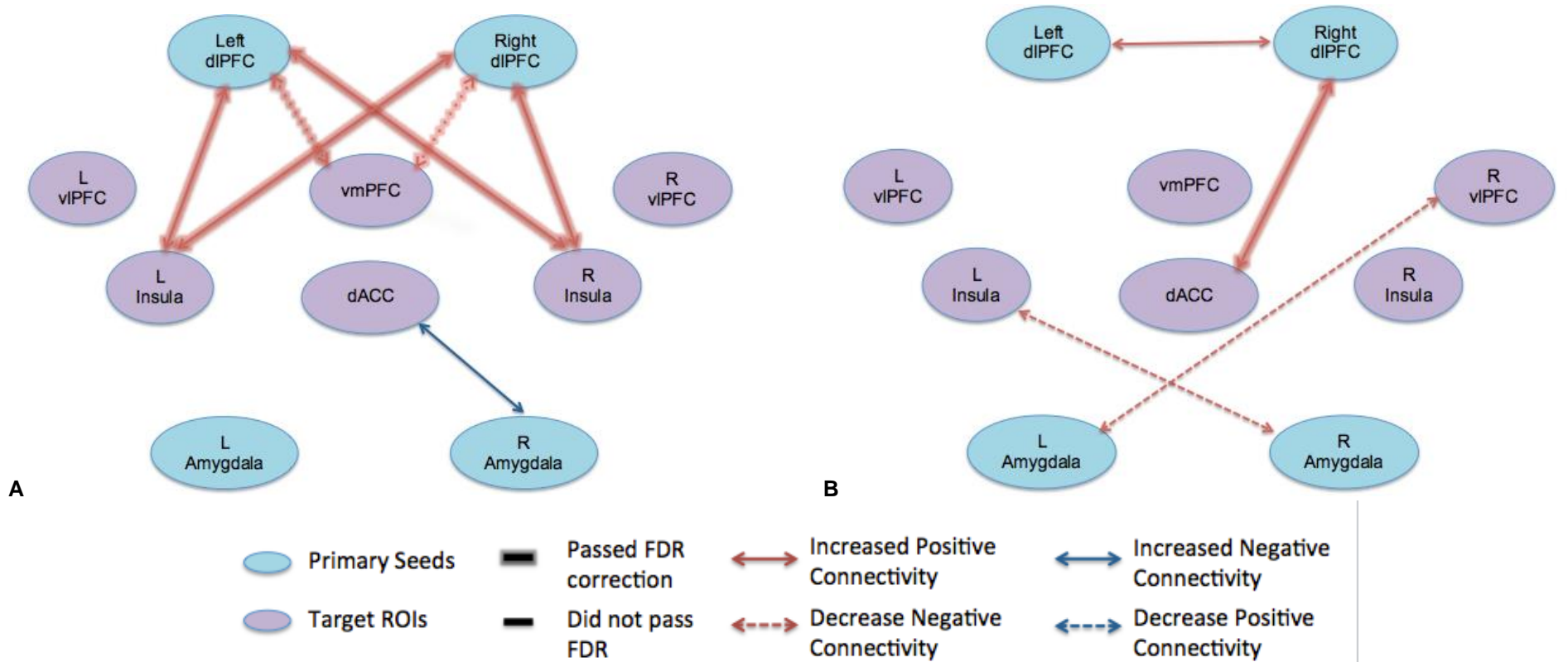
Data represents all significant relationships that survived FDR correction

Data were controlled for sex and age.

*p<.05

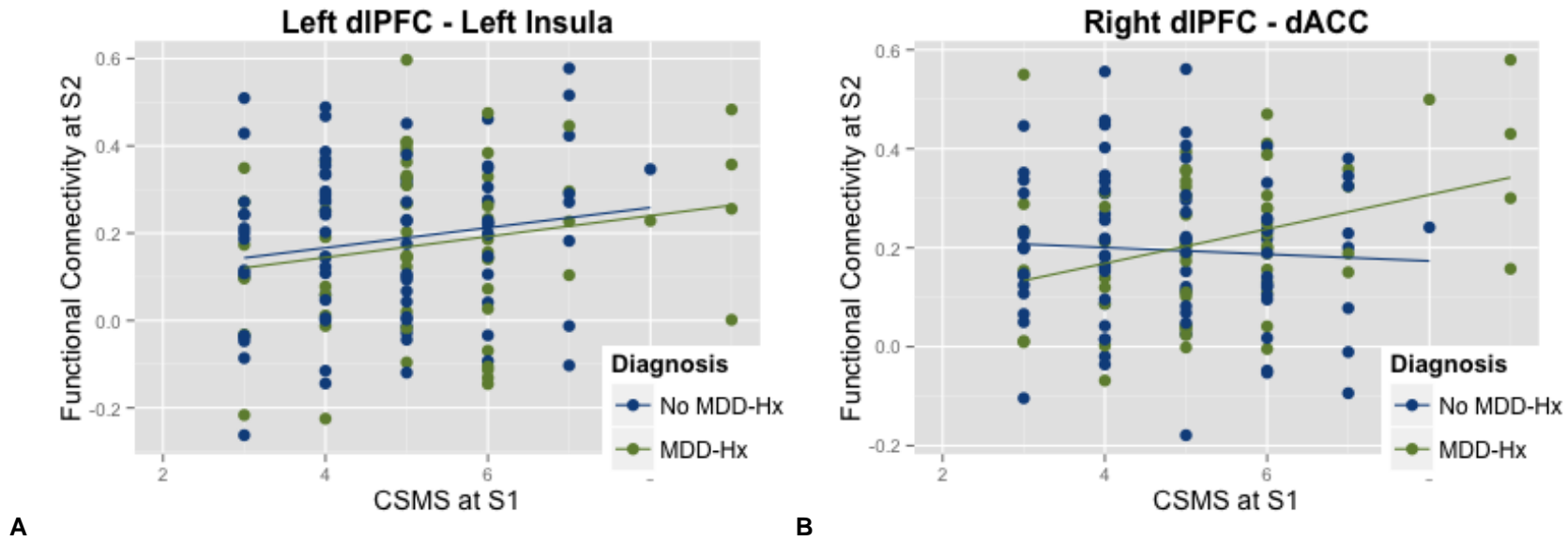
** p<.01

Figure 1. Schematic of ROI-ROI connectivity.



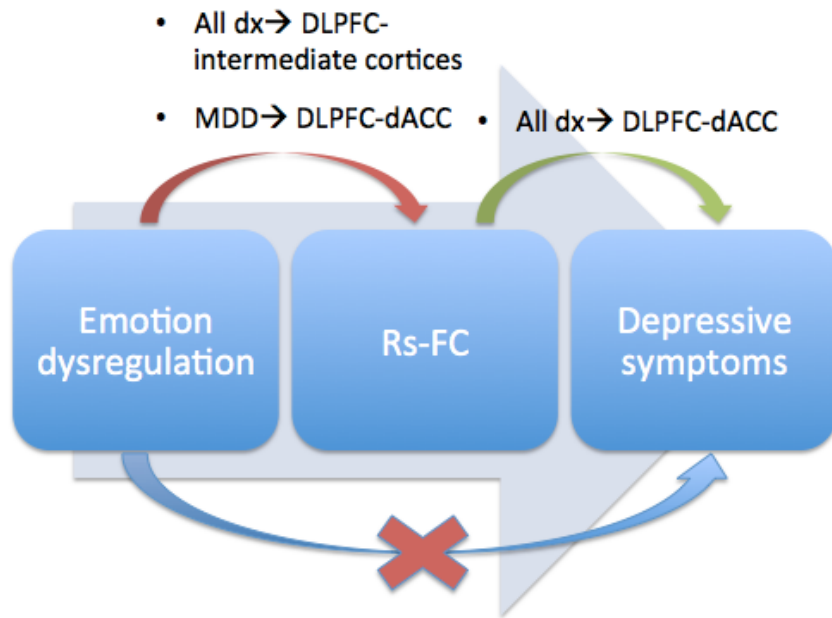
Note: A) ROI-ROI connectivity that was significantly predicted by S1 CSMS scores B) Schematic of ROI-ROI connectivity that was significantly predicted by CSMS * MDD-hx interaction.

Figure 2. Childhood emotion regulation predicts functional connectivity in pre-adolescence.



Graphs illustrate significant, FDR-corrected relationships. A) Main effect of CSMS and left dIPFC to insula connectivity in all children. See Supplementary Figure 1 for all main effect, FDR corrected relationships B) Interaction effect of CSMS and right dIPFC to dACC connectivity in children with positive MDD history relative to those without depression,

Figure 3. Overview of findings for all research questions



Note: Red upper arrow represents significant findings from research question 1 and 2. Green upper arrow represents significant findings from research question 3. Blue lower arrow represents findings from research questions 4 and 5, which were not significant. Middle gray arrow represents movement throughout time (and not causal inference)

Supplementary Tables and Figure

Table 1. Post-hoc regressions of CSMS scores at S1 predicting functional connectivity at S2 between MDD, Other Dx, and healthy controls.

Connectivity S2 Seed-ROI	Intercept	CSMS S1			MDD-hx			Other-Dx (no MDD)			CSMS S1*MDD-hx			CSMS S1*Other-Dx		
		t	B	p	t	B	p	t	B	p	t	B	p	t	B	p
Right dlPFC																
vmPFC	-0.010	0.828	0.114	0.409	-0.488	-0.170	0.626	1.116	0.387	0.266	0.887	0.310	0.377	-0.776	-0.298	0.439
dACC	-0.007	1.869	0.249	0.063	-2.279	-0.771	0.024*	-0.618	-0.207	0.537	2.552	0.866	0.011*	0.788	0.293	0.432
L Insula	0.003	1.297	0.177	0.196	-1.402	-0.487	0.163	-0.275	-0.094	0.783	1.121	0.390	0.264	0.115	0.043	0.908
R Insula	0.001	1.928	0.260	0.056	-1.284	-0.440	0.201	-0.174	-0.059	0.862	1.221	0.419	0.224	0.284	0.107	0.776
Left dlPFC																
R dlPFC	0.000	0.281	0.038	0.779	-1.907	-0.666	0.058	-0.718	-0.249	0.474	1.937	0.679	0.054	0.342	0.131	0.732
vmPFC	-0.003	2.182	0.298	0.030*	-0.487	-0.168	0.627	-0.802	-0.276	0.424	0.525	0.182	0.600	0.956	0.182	0.340
L insula	0.009	1.755	0.241	0.081	-0.289	-0.100	0.773	0.316	0.109	0.752	0.141	0.049	0.888	-0.318	-0.122	0.750
R Insula	0.009	0.759	0.105	0.449	0.018	0.006	0.986	0.868	0.303	0.387	-0.265	-0.093	0.791	-0.969	-0.375	0.334

Data were controlled for sex and age.

*p<.05

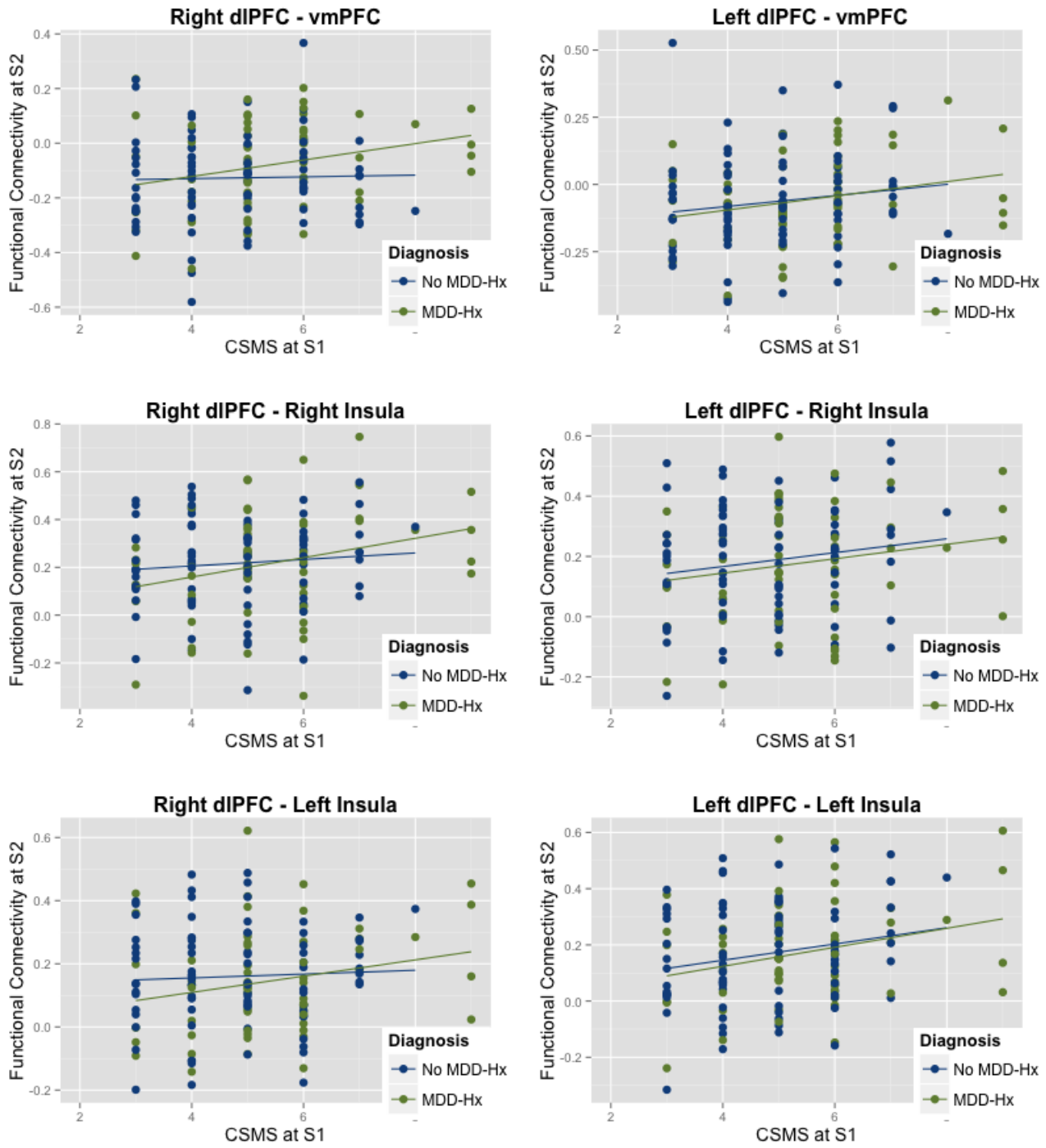
** p<.01

Table 2. Mediation Analysis: indirect effect of childhood emotion dysregulation and depressive symptoms in adolescence

Connectivity S2 Seed-ROI	Effect	Standard Error	Lower limit CI	Upper limit CI
Right dlPFC				
vmPFC	.0738	.1030	-.0453	.4158
dACC	.1290	.1154	-.209	.4722
L Insula	-.0336	.0853	-.2523	.1038
R Insula	-.0143	.1098	-.3009	.1623
Left dlPFC				
vmPFC	.0940	.1132	-.0334	.4632
L insula	-.0175	.1429	-.3079	.2676
R Insula	.0008	.0723	-.1450	.1610

CI: Confidence Interval

Figure 1 All significant main effect relationships between childhood emotion regulation and functional connectivity in pre-adolescence.



Graphs illustrate significant, FDR-corrected relationships