ABSTRACT

Title of Thesis:	HIPPOCAMPAL SUBREGION VOLUME IN HIGH-RISK OFFSPRING PREDICTS INCREASES IN DEPRESSIVE SYMPTOMS ACROSS THE TRANSITION TO ADOLESCENCE
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The hippocampus has been implicated in the pathophysiology of depression. This study examined whether youth hippocampal subregion volumes were differentially associated with maternal depression history and youth's depressive symptoms across the transition to adolescence. 74 preadolescent offspring (M_{age}=10.74+/-.84 years) of mothers with (n=33) and without a lifetime depression history (n=41) completed a structural brain scan. Youth depressive symptoms were assessed prior to the neuroimaging assessment at age 9 (M_{age}=9.08+/-.29 years), at the neuroimaging assessment, and in early adolescence (M_{age}=12.56+/-.40 years). Maternal depression was associated with preadolescent offspring's reduced bilateral hippocampal head volumes and increased left hippocampal body volume. Reduced bilateral head volumes were associated with offspring's increased concurrent depressive symptoms. Furthermore, reduced right hippocampal head volume mediated associations between maternal depression and increases in offspring depressive

symptoms from age 9 to age 12. Findings implicate reductions in hippocampal head volume in the intergenerational transmission of risk from parents to offspring.

HIPPOCAMPAL SUBREGION VOLUME IN HIGH-RISK OFFSPRING PREDICTS INCREASES IN DEPRESSIVE SYMPTOMS ACROSS THE TRANSITION TO ADOLESCENCE

by

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Chapter 1: Introduction

The offspring of depressed parents are at increased risk for negative outcomes throughout the lifespan, including depressive and other psychiatric disorders, and greater morbidity and mortality (Gotlib & Hammen, 2009; Weissman et al., 2006, 2016). A major focus of research is to understand the complex array of biological, genetic, and environmental mechanisms by which risk is transmitted from parents to offspring (Garber, 2006; Sullivan et al., 2000). The hippocampus, a stress-sensitive brain structure, has been implicated in the pathophysiology of depression and the intergenerational transmission of risk (Campbell & Macqueen, 2004; MacQueen & Frodl, 2011). Volumetric hippocampal differences between depressed and non-depressed adults and youth have been observed (Campbell et al., 2004; McKinnon et al., 2009; Santos et al., 2018), and are associated with poorer course (Buddeke et al., 2017; MacQueen et al., 2003; Taylor et al., 2014; Treadway et al., 2015) and treatment response (Colle et al., 2018; MacQueen et al., 2008; Maller et al., 2018; Nogovitsyn et al., 2020). Surprisingly, little work has examined hippocampal volume as a neurological correlate of risk in the transmission of depression from parent to offspring (Rao et al., 2010). The current study sought to address this gap by evaluating hippocampal volume as a mediator in the association between maternal depression and future depressive symptoms in offspring across the transition to adolescence using a prospective, longitudinal study.

Prior work using structural magnetic resonance imaging (MRI) has observed reduced hippocampal volume in adolescent offspring (ages 12-20) of parents with a history of depression (Rao et al., 2010) and in offspring (ages 9-15) exposed to maternal depression (Chen et al., 2010), although one study (Lupien et al., 2011) reported no

differences in exposed preadolescent offspring (age 10). These few studies measured total left and right hippocampal volumes, rather than hippocampal subregion (head, body, and tail) volumes, despite evidence in adults that specific hippocampal subregions may be differentially impacted in depression (Maller et al., 2007, 2018; Malykhin et al., 2010; Nifosì et al., 2010; Nogovitsyn et al., 2020) and uniquely predict depression course and treatment response (MacQueen et al., 2008; Maller et al., 2018; Nogovitsyn et al., 2020; Travis et al., 2015). Specifically, adults with major depressive disorder (MDD) demonstrate reductions in hippocampal head, body and tail volumes (Maller et al., 2007; Malykhin et al., 2010; Nifosì et al., 2010; Nogovitsyn et al., 2020), although Maller et al., (2018) reported increased hippocampal tail volume in adults with MDD. Furthermore, adults at high familial risk for depression showed reduced hippocampal head and body volumes (Carballedo et al., 2012) and differences in hippocampal head shape (Durmusoglu et al., 2018). Given evidence in adults implicating specific hippocampal subregions in the pathophysiology of depression, it is important to examine hippocampal subregion volumes in youth prior to depression onset to clarify whether specific subregions may differentially confer risk for depression.

Research suggests that hippocampal subregions serve distinct roles in hippocampal functioning due to their differential connectivity to other brain regions (DeMaster et al., 2014; Ghetti & Bunge, 2012; Poppenk & Moscovitch, 2011). Hippocampal subregions demonstrate unique, differential growth trajectories in early childhood (Riggins et al., 2018) and throughout later childhood and adolescence (Daugherty et al., 2017; DeMaster et al., 2014). Furthermore, studies have shown that associations between hippocampal subregion volumes and different cognitive processes

(e.g., episodic memory) that rely on the hippocampus, and are also impaired in depressed individuals, may change throughout development (DeMaster et al., 2014; Riggins et al., 2015; 2018). Without consideration of hippocampal subregions and their developmental context, the effects of parental depression on hippocampal volume may be obscured by age-related changes in hippocampal subregions. It is especially critical that such effects be examined with greater specificity during developmental periods in which risk for depression is increased, such as the transition to adolescence. The transition to adolescence is marked by increases in depressive symptoms (Hankin & Abela, 2005) alongside developmental changes in hippocampal subregions (Daugherty et al., 2017; DeMaster et al., 2014; Gogtay et al., 2006). Assessment of hippocampal subregion volume in the high-risk offspring of depressed parents may allow us to better understand why risk for depression begins to increase across the transition to adolescence.

The current study sought to address the gaps in the present literature by using a prospective, longitudinal design to evaluate associations between hippocampal subregion volume and changes in depressive symptomatology in a sample of 74 youth (58.11% male) across the transition to adolescence. Only one prior study (Rao et al., 2010), to our knowledge, examined hippocampal volume as a predictor of future depression in high-risk offspring ages 12-20 years-old. In the current study, maternal depression history was initially assessed when offspring were three years old (baseline) and reassessed when offspring were nine years old using a structured diagnostic interview with mothers. Youth depressive symptoms were assessed at three time points from preadolescence (age 9 assessment) to early adolescence (age 12 assessment) using clinical interviews with both the parent and child, and parent- and youth-reported measures of depressive symptoms.

Youth hippocampal volume was assessed following the age 9 assessment but prior to the age 12 assessment (mean age=10.74 years, *SD*=.84, range=9.23-12.54).

The study aims (a) to evaluate the association between maternal depression history and offspring's hippocampal subregion volume in preadolescence, (b) to assess whether neuroanatomical differences in hippocampal volume in preadolescence predict changes in depressive symptomatology from preadolescence (age 9) to early adolescence (age 12), and (c) to test whether hippocampal subregion volume mediates the association between maternal depression and changes in offspring's depressive symptoms across the transition to adolescence. We hypothesized that reductions in hippocampal subregions during preadolescence would be associated with maternal lifetime depression history and youth's higher levels of depressive symptoms. Furthermore, we hypothesized that the association between maternal depression history and increases in depressive symptoms across the transition to adolescence would be mediated by reduced hippocampal subregion volumes. Given that this is the first study to examine hippocampal subregion volume in youth offspring of parents with depression, we did not formulate a priori hypotheses regarding specific hippocampal subregions.

Chapter 2: Method

Participants

Participants in this study were selected from the Stony Brook Temperament Study, a longitudinal study of early childhood temperament and other risk factors and the development of internalizing disorders (Klein & Finsaas, 2017). The study sample and recruitment methods have been described extensively elsewhere (Klein & Finsaas, 2017; Kopala-Sibley et al., 2018). The study includes an unselected, community-based sample of 609 youth and their biological parents, assessed at ages 3, 6, 9, and 12 years. Between the age 9 and age 12 assessments, a subset of 79 participants were selected to participate in a MRI assessment (Huang et al., 2016). Two participants withdrew and three participants were excluded due to poor data quality, yielding a final sample of 74 youth with usable MRI data (mean age=10.74 years, *SD*=.84, 58.11% male). The MRI assessment oversampled youth with temperament high in negative emotionality, low in positive emotionality, and high in behavioral inhibition at age 3 based on the Laboratory Temperament Assessment Battery (. The majority of the MRI subsample was White and non-Hispanic (77.03%) and middle-class based on the Hollingshead Four Factor Index of Social Status (*M*=45.45, *SD*=10.10; Hollingshead, 1975). The majority of parents in the MRI subsample were married (94.6%) and well-educated (67.6% of families had at least one parent who graduated college). There were no significant differences between the MRI subsample and the general study sample with respect to child race/ethnicity, family income, or parental education (*p*s>0.05). All procedures were approved by the Stony Brook University Institutional Review Board. Parents provided informed written consent, and youths provided informed written assent.

Procedures

At baseline (age 3), biological mothers completed a structured diagnostic interview to assess their psychiatric history, which was reassessed at the age 9 assessment. At the age 9 and age 12 assessments, youth psychopathology was assessed using diagnostic interviews with both the parent and youth, and parent- and youth-reported measures of depressive symptoms. At the MRI assessment, the subsample completed a brain scan and parent- and youth-reported measures of youth depressive symptoms.

Measures

Maternal depression history. At baseline, biological mothers were interviewed using the Structured Clinical Interview for DSM-IV, Non-Patient version (SCID-NP; First, Spitzer, Gibbon, & Williams, 2002). These interviews were conducted by phone by a Masters-level clinician; phone interviews yield similar results to in-person interviews (Rohde et al., 1997). At the age 9 assessment, biological mothers were reassessed in order to update psychiatric history. Inter-rater reliability, which was evaluated using audiotaped interviews coded by a second trained interviewer, were excellent for lifetime mood disorders (kappa=.93, *n*=30 at baseline; kappa=.91, *n*=74 at the age 9 assessment). Maternal lifetime depressive disorder (Major Depressive Disorder or Dysthymic Disorder) was coded as absent or present. In the MRI subsample, 33 (44.59%) biological mothers had a lifetime history of depressive disorder.

Youth depressive symptoms. Youth and one of their biological parents (92% mothers at age 9, 88% mothers at age 12) were interviewed using the Kiddie-Schedule of Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL; Kaufman et

al., 1997) at the age 9 and age 12 assessments. The interviews were administered in-person separately to the parent and youth, and if necessary, additional information was obtained to resolve discrepancies. Interviews were conducted by masters-level clinicians or doctoral students in clinical psychology who were supervised in a group format by a licensed clinical psychologist and experienced youth psychiatrist. A dimensional score for current depressive symptoms was created by summing the ratings (on a 3 point scale) for symptom items (age 9 α=0.86; age 12 α=0.85). Interrater reliability was evaluated using independently derived scores by a second rater from videotapes of 74 participants at each assessment. The intraclass correlation coefficient (ICC) demonstrated good interrater reliability for the K-SADS depressive symptoms scales at age 9 (ICC = 0.83) and age 12 (ICC = .97).

To further assess youth depressive symptoms, parents completed the 17-item and youth completed the 27-item Child Depression Inventory (CDI; Kovacs, 1983) at the age 9 assessment (youth-report α=0.74, parent-report α=0.79), the MRI assessment (youth-report α=.89, parent-report α=.83), and age 12 assessment (youth-report α=0.82, parent-report α=.77). Parent and youth scores were significantly correlated with one another (r=0.30-0.47) and with K-SADS depressive symptoms (r=0.28-0.48) at each time point. A composite score for youth depressive symptoms at age 9 and age 12 was created by averaging the K-SADS depressive symptoms and parent- and youth-reported CDI scores. Composite measures for youth depressive symptoms at the MRI assessment was created by averaging parent- and youth-reported CDI scores.

Pubertal development. Youth pubertal development has been linked to hippocampal volume and depressive symptoms (Ellis et al., 2019; Satterthwaite et al.,

2014). Parents and youth completed the six-item Pubertal Development Scale (PDS; Carskadon & Acebo, 1993) at the MRI (youth self-report α=0.68 for males, 0.69 for females; parent-report α=0.66 for males, 0.88 for females), and the age 12 (youth self-report α=0.72 for males, 0.72 for females; parent-report α=0.80 for males, 0.81 for females) assessments. Youth and parent ratings were significantly correlated at the MRI assessment (r=0.55) and the age 12 assessment (r=0.73), and thus were averaged to create a composite score for pubertal development at each time point.

MRI Acquisition and Analysis. At the MRI assessment, all participants first completed a mock scan in an MRI simulator (Model number: PST-100355 from Psychological Software Tools; Sharpsburg, PA) to become acclimated to the scanning environment while receiving real-time head motion feedback with the Flock of Birds motion tracking system (Ascension Technology Corporation; Shelburne, VT) and MoTrack motion tracking software (Psychology Software Tools). Structural MRI images were obtained using a Siemens trio 3T scanner (Siemens Healthcare, Malvern, PA). T1-weighted high resolution structural images were collected with the magnetization prepared rapid gradient echo (MPRAGE) sequence: slices=176, slice thickness=1 mm, repetition time (TR)=2,400ms, echo time (TE)=3.16ms, flip angle=8 degrees, matrix size=256 x 256, field of view (FOV)=256 x 256 mm, resolution=1 x 1 x 1 cubic millimeters. Inplane T2-weighted structural images were acquired in the axial oblique plane, parallel to the anterior commissure-posterior commissure (AC-PC) plane with the following parameters: slices=37, slice thickness=3.5 mm, TR=6,450 ms, TE=88 ms, flip angle=120 degrees, matrix size=256 x 256 mm, FOV=256 x 256, resolution=1 x 1 x 3.5 cubic millimeters.

Freesurfer Version 6.0, a standard automatic volumetric segmentation software, was used to process the structural MRI images (Fischl, 2012). Research has demonstrated validity of this software in children 4 years and older (Ghosh et al., 2010). A series of processing steps were applied to T1-weighted images, including registration, skull stripping, gray and white matter segmentation, and volumetric labeling of brain structures. T2-weighted images were included in the processing stream to further refine skull stripping. Data was then oriented into anterior commissure-posterior commissure space in order to attain the most accurate evaluation of hippocampal volume (Poppenk & Moscovitch, 2011).

Structural images of left and right hippocampi were manually inspected for accuracy and segmented into hippocampal subregions (left and right head, left and right body, and left and right tail) using standard anatomical landmarks (Weiss et al., 2005). The hippocampal head included the slices from the most anterior slice of the hippocampus to the most posterior slice in which the uncal apex was present from a coronal viewpoint. The hippocampal tail included all slices posterior to the separation of the fornix from the hippocampus. The hippocampal body included all remaining slices found between the head and tail. Interrater reliability for segmentation of head and tail was was excellent (ICCs ranged from .96 to .99, n=61). Raters were unaware of the maternal and youth psychopathology data. Hippocampal volumes were further refined using the software Automatic Segmentation Adapter Tool (ASAT; www.nitrc.org/projects/segadapter; Wang et al., 2011), which accounts for systematic errors that result from the automatic segmentation. Finally, an experienced reviewer (MB) inspected left and right hippocampi for accuracy and conducted manual edits when

necessary. Only small errors (i.e., small deviations in border) were observed, and edits were made only if errors persisted for 7 slices or more (n=3 scans).

Additionally, measurements of total intracranial volume (ICV) was extracted using Freesurfer. ICV was used to adjust hippocampal volumes using an analysis of covariance approach in order to control for differences in total brain size in data analysis using the method reported in Raz et al. (2005). The adjustment was carried out for all subjects, and all reported analyses use the adjusted volumes.

Data Analysis Plan

Statistical analyses were conducted in SPSS Version 24.0. First, analyses of covariance (ANCOVA) were conducted to compare the hippocampal subregion volumes of offspring of mothers with and without a depression history, controlling for youth sex, pubertal development, and age at the time of the MRI assessment. Next, multiple linear regression analyses evaluated associations between youth's hippocampal volumes and both concurrent and later early adolescent (age 12) depressive symptoms, controlling for youth sex, pubertal development, and age at the MRI assessment. In order to assess whether hippocampal volume predicts change in symptoms across the transition to adolescence, we controlled for depressive symptoms prior to the MRI assessment (age 9) when the dependent variable was age 12 depressive symptoms. By controlling for prior symptoms, the dependent variable represents residuals, and the effects of hippocampal subregion volume on depressive symptoms at age 12 reflect change in depressive symptoms from age 9 to age 12.

Finally, we evaluated the presence of indirect effects of maternal depression on youth depressive symptoms at age 12, controlling for depressive symptoms at age 9,

through hippocampal subregion volumes. We used the SPSS PROCESS Macro Version 3.3 to conduct mediation analyses with 5,000 bootstrapped samples. This nonparametric bootstrapping method calculates an indirect effect and corresponding confidence interval using the product of the association between the independent variable (maternal depression) and the mediator variable (hippocampal subregion volume) and the association between the mediator variable and the dependent variable (youth depressive symptoms). Statistical significance of the indirect effect is demonstrated with a confidence interval that does not contain zero.

Chapter 3: Results

All bivariate correlations between study variables are presented in Table 2. Youth sex (male=0, female=1) was associated with left (r=-0.30, p<0.01) and right (r=-0.28, p=0.02) hippocampal head volumes, with females demonstrating smaller bilateral hippocampal head volumes than males. Youth age at the MRI assessment was positively associated with right hippocampal tail volume (r=0.24, p=0.04). Youth pubertal development at the MRI assessment was not associated with any hippocampal volume measures. Female pubertal development was significantly more advanced (M=12.06, SD=2.60) than male pubertal development (M=10.05, SD=2.73), $t(70)$=-3.17, $p < .01$, at the age 12 assessment, but not at the MRI assessment (p=0.32).

Maternal psychopathology and offspring hippocampal subregion volumes

Results of one-way ANCOVAs revealed significant differences between the offspring of mothers with and without a history of depression in the left, F(1,69)=4.55, p=0.04, and right, F(1,69)=10.29, p< 0.01, hippocampal head volumes and left hippocampal body volume, F(1,69)=4.02, p=0.049, controlling for youth sex, pubertal development, and age at the MRI assessment. Both the left (M=1662.34, SD=201.65, N=33) and right (M=1492.35, SD=242.49, N=33) hippocampal head volumes of offspring of mothers with lifetime depression were smaller than the left (M=1754.98, SD=153.99, N=41, partial η^2=0.06) and right (M=1655.69, SD=192.75, N=41, partial η^2=0.13) hippocampal head volumes of offspring of mothers with no lifetime depression. In contrast, left hippocampal body volume (M=1323.83, SD=171.95, N=33) of offspring of mothers with lifetime depression was significantly larger than the left hippocampal body volume (M=1235.05, SD=178.62, N=44, partial η^2=0.06) of offspring of mothers with no

lifetime depression. There were no significant differences between the offspring of mothers with and without a history of depression in total left or right hippocampal volumes (ps>.21).

Hippocampal subregion volumes and offspring depressive symptoms

As seen in Figures 1a and 1b, reduced left (b<-0.01, SE<0.01, pr=-0.30, p=0.01) and right (b<-0.01, SE<0.01, pr=-0.25, p=0.04) hippocampal head volumes were concurrently associated with greater youth depressive symptoms at the MRI assessment, controlling for youth sex, pubertal development, and age at the MRI assessment. Reduced right hippocampal head volume was also associated with greater youth depressive symptoms at the age 12 assessment (b<-0.01 , SE<0.01, pr=-0.25, p=0.04), controlling for youth sex, pubertal development, and age at the MRI assessment (Figure 1c). Furthermore, reduced right hippocampal head volume (b<-0.01, SE < 0.01, pr=-0.34, p<0.01) predicted increases in depressive symptoms from age 9 to age 12. No significant associations were observed between hippocampal subregion volume and age 9 depressive symptoms or between total hippocampal volume measures and youth's depressive symptoms at any time point.

Mediation analyses

Finally, mediation analyses were conducted to evaluate the presence of an indirect effect of maternal depression on youth depressive symptoms across the transition to adolescence through hippocampal subregion volumes. We observed a significant indirect effect of maternal depression on depressive symptoms at age 12 through reduced right hippocampal head volume (ab [5,000 bootstrapped samples]=0.18, SE=0.13, bias-corrected 95% CI [0.01, 0.49]), controlling for depressive symptoms at age 9 (Figure 2).

Similarly, we observed significant indirect effects of maternal depression on concurrent depressive symptoms assessed at the time of the MRI assessment through reduced left (*ab* [5,000 bootstrapped samples]=0.11, *SE*=0.07, bias-corrected 95% CI [0.002, 0.265]) and right (*ab* [5,000 bootstrapped samples]=0.12, *SE*=0.07, bias-corrected 95% CI [0.0007, 0.2614]) hippocampal head volumes, controlling for depressive symptoms at age 9.

Additional analyses

To test whether differences in hippocampal subregion volumes were due to prior depression, analyses were run excluding participants with a lifetime diagnosis of a depressive disorder based on the K-SADS assessment at age 9. One participant had a prior diagnosis of a depressive disorder, and no participant had a current diagnosis of a depressive disorder. All results persisted when excluding the one participant with a prior depressive disorder diagnosis.

We also ran additional analyses controlling for participant race/ethnicity (0=non-White or Hispanic, 1=White and non-Hispanic) and parental education (0=neither parent with a four-year college degree, 1=either parent with a four-year college degree,). All significant findings held with one exception: the association between maternal depression history and preadolescents' left hippocampal body volume was no longer significant when controlling for parent education level (p=0.12).

Chapter 4: Discussion

The present study observed reduced bilateral hippocampal head volumes and increased left hippocampal body volumes in the offspring of mothers with a history of depression. Reduced bilateral hippocampal head volumes were also associated with higher levels of concurrent depressive symptoms in preadolescence, and, furthermore, reduced right hippocampal head volume mediated the longitudinal association between maternal depression history and increases in depressive symptoms from preadolescence (age 9) to early adolescence (age 12). Our findings add to the few prospective studies in youth examining hippocampal volume and depression risk (Little et al., 2014, 2015; Rao et al., 2010; Whittle et al., 2011). The current findings uniquely implicate hippocampal subregion volume in the pathophysiology of depression and reveal that reduced hippocampal head volume, present in youth prior to illness onset, may represent an important biomarker for depression risk that predicts the rise in depressive symptomatology in adolescence.

Hippocampal subregion volume and depression risk

Our findings linked reduced bilateral hippocampal head volumes and larger left hippocampal body volume to risk for depression in youth, although the latter finding was no longer significant after accounting for parental education. Differences in hippocampal head and body volumes have been observed in adults with a familial history of depression (Carballedo et al., 2012; Durmusoglu et al., 2018). Studies with depressed adults also largely support reductions in hippocampal head, body and tail volumes (Maller et al., 2007; Malykhin et al., 2010; Nifosì et al., 2010; Nogovitsyn et al., 2020). What warrants attention is that reduced hippocampal head volume has consistently been observed in

association with depression risk not only in our study in youth but also in prior work with adults (Carballedo et al., 2012; Durmusoglu et al., 2018; Malykhin et al., 2010). Thus, it is possible that further differences in the hippocampal body and tail may emerge later in development or relate to disease progression and severity. Our findings are particularly noteworthy given that differences in offspring hippocampal subregion volumes were present prior to onset of a depressive disorder, and therefore may represent vulnerability markers for later depression risk.

Prior research in children and adolescents of depressed parents has relied solely on total hippocampal volume measures (Chen et al., 2010; Lupien et al., 2011; Rao et al., 2010). Two studies reported reduced left hippocampal volumes in youth ages 9-15 (Chen et al., 2010) and reduced total hippocampal volumes in youth ages 12-20 (Rao et al., 2010). In contrast, studies that assessed youth across a narrow age range during preadolescence, including the current study and Lupien et al. (2011)'s study of 10 year-old youth, did not observe differences in total hippocampal volume. Thus, our findings highlight the importance of examining hippocampal subregions volumes, along with total hippocampal volume measures, and call for specific attention to developmental timing of the assessments. Future research is needed to assess hippocampal subregion volumes repeatedly across development to elucidate the temporal unfolding of changes in hippocampal subregion volumes among offspring of depressed mothers and how these changes relate to the development and course of depression.

Our findings further support the mediating role of right hippocampal head volume in the association between maternal depression and increased depressive symptoms across the transition to adolescence. This finding contributes to a growing body of

literature implicating the hippocampus in youth at risk for depression and provides evidence for a pathway in the intergenerational transmission of depression through the hippocampal head. Research has supported theories of the functional segregation of the hippocampus proposing that anterior subregions primarily contribute to social-emotional and motivational cognitive processes, whereas posterior subregions contribute to other cognitive processes, such as navigation and spatial processing (Grady, 2020; Poppenk et al., 2013). Given that emotion and motivation are core processes impaired in depression, it may be that reductions in hippocampal head volume observed in high-risk youth reflect disturbances in these processes related to depression.

Little is known about the mechanisms underlying this pathway involving the hippocampus. Given that the hippocampus is a stress-sensitive brain structure with a high density of glucocorticoid receptors, one such mechanism may be overexposure to stress hormones (Ortiz & Conrad, 2018). Research has suggested that offspring of depressed mothers experience greater life stress than offspring of non-depressed mothers, and there are documented links between stress system dysfunction, particularly hypercortisolism, in the offspring of depressed parents and in depressed individuals (Feurer et al., 2016, 2017; Nandam et al., 2019). Thus, environmental and familial, possibly genetic, factors associated with maternal depression may lead to overexposure to stress hormones (e.g. cortisol) in offspring of depressed parents, resulting in reductions in dendritic branching, synaptic plasticity, spine density, and, ultimately, alterations in hippocampal structure and function (Feurer et al., 2017; Frodl & O'Keane, 2013). Prior work has further supported that a combination of genetic, biological, and environmental factors influences hippocampal volume and depression onset (Little et al., 2014, 2015; Rao et al., 2010;

Whittle et al., 2011). Thus, future research is needed to identify the complex mechanisms contributing to changes in hippocampal subregion volumes in high-risk youth to inform our understanding of the pathophysiology of depression and to identify treatment targets.

Strengths and Limitations

This study had several notable strengths. First, segmentation of the hippocampus permitted the assessment of nuanced associations between hippocampal subregion structure and depressive symptoms across the transition to adolescence. Second, hippocampal subregion volumes were assessed in a narrow age range, mitigating confounds related to age-related differences in hippocampal volume on our findings. Finally, youth depressive symptoms were assessed using multiple informants and measures (interview, parent- and youth-reports) at three time points across the transition to adolescence, a developmental period characterized by a rise in depression symptoms and thus greater risk for depression in later adolescence (Hankin & Abela, 2005).

The study also had limitations. First, the sample size was modest, and thus replication is essential in larger, more diverse samples. Second, given that structural MRI was obtained at only one time point, conclusions cannot be drawn regarding the developmental change of hippocampal subregions over time. Third, inferences cannot be made regarding the functional significance of hippocampal subregions in relation to depressive symptoms. Future research would benefit from the use of multiple time points of neuroimaging data in order to assess how changes in hippocampal subregion structure and function map onto the development of depression. Finally, given that the finding of larger left hippocampal body volume in high-risk offspring did not persist after

accounting for parent education, future work should seek to investigate this association further.

Conclusions

In sum, our findings inform current models of the pathophysiology of depression and support hippocampal head volume as a potential early-emerging biomarker for depression in high-risk youth. Furthermore, our findings identify a pathway from maternal depression to youth's later increases in depressive symptoms via reduced right hippocampal head volume. Future work should examine hippocampal subregion structure and function alongside the course of depression to clarify the unique roles of hippocampal subregions in illness progression across development. Moreover, these findings provide potential biological targets for treatment in high-risk youth, particularly as prior work suggests that antidepressant treatment for depression may function by recovering neural atrophy or encouraging neurogenesis in the hippocampus (Boku et al., 2018).

Tables

Table 1. Characteristics of the study sample (*N*=74).

	Age 9 Assessment		MRI Assessment		Age 12 Assessment	
Demographics						
Youth sex, male; *n* (%)	43	(58.1)				
Youth age in years; *M* (*SD*), range	9.08 (0.29)	8.75-10.5	10.74 (0.84)	9.23-12.54	12.56 (0.40)	11.83-13.42
Maternal Psychopathology; *n* (%)						
Maternal lifetime depression	33 (44.59)					
Youth Depressive Symptoms; *M* (*SD*), range						
K-SADS depression scale	0.49 (1.87)	0-13	/	/	0.89 (2.94)	0-18
Child Depression Inventory, youth-report	5.57 (4.37)	0-20	3.78 (3.68)	0-15.95	5.28 (5.31)	0-23
Child Depression Inventory, maternal-report	7.15 (5.18)	0-28	7.62 (5.01)	0-21	7.75 (5.56)	0-22
Youth Pubertal Development; *M* (*SD*), range						
Pubertal Development Scale, youth-report	6.80 (1.66)	5-13	8.50 (2.54)	5-17	11.5 (3.09)	5-19
Pubertal Development Scale, parent-report	8.15 (1.73)	5-12	8.07 (2.60)	5-14	10.35 (3.04)	5-16
Hippocampal volumes (mm^3); *M* (*SD*), range						
Total hippocampus			6898.69 (434.53)	6162.72-8318.87		
Left hippocampus			3467.34 (224.42)	3093.62-4279.31		
Left hippocampal head			1713.67 (181.57)	1157.52-2087.47		
Left hippocampal body			1274.64 (180.04)	862.30-1772.77		
Left hippocampal tail			479.03 (112.16)	145.77-750.59		
Right hippocampus			3431.35 (241.01)	2965.92-4089.12		
Right hippocampal head			1582.85 (229.81)	1135.71-2138.07		
Right hippocampal body			1313.23 (182.25)	822.93-1668.82		
Right hippocampal tail			535.27 (124.25)	195.20-859.29		

Table 2. Bivariate correlations between study variables.

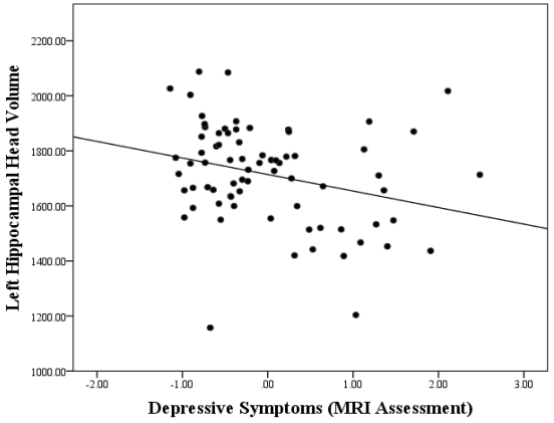
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Youth Sex	-																		
Youth Age																			
2. Age 9	-.04	-																	
3. MRI	-.24*	.55**	-																
4. Age 12	-.24*	.58**	.91**	-															
Pubertal Status																			
5. MRI	.12	.30**	.19	.19	-														
6. Age 12	.35**	.12	-.02	.00	.50**	-													
Dep. Symptoms																			
7. Age 9	-.08	.04	.09	.07	.10	.22	-												
8. MRI	-.04	.15	.22	.19	.05	.20	.53**	-											
9. Age 12	.11	.04	.07	.04	.04	.16	.58**	.60**	-										
Maternal Dx.																			
10. Depression	-.03	.11	.00	-.06	.07	.05	.15	.25*	.29*	-									
Hipp. Volumes																			
11. Total	-.17	-.06	.14	.11	.05	-.12	.14	-.11	-.05	-.17	-								
12. Left Total	-.15	-.08	.12	.09	.00	-.19	.09	-.14	-.09	-.15	.93**	-							
13. Left Head	-.30**	-.21	.00	-.06	-.22	-.33**	.00	-.29*	-.07	-.31**	.53**	.50**	-						
14. Left Body	.18	.17	.07	.03	.19	.12	.15	.16	-.09	.23*	.33**	.42**	-.43**	-					
15. Left Tail	-.10	-.10	.14	.20	.05	-.06	-.06	-.07	.07	-.17	.48**	.52**	.08	-.06	-				
16. Right Total	-.16	-.03	.14	.12	.08	-.04	.17	-.06	-.01	-.17	.94**	.74**	.49**	.19	.38**	-			
17. Right Head	-.28*	-.12	.01	-.01	-.13	-.20	.00	-.23*	-.28*	-.36**	.51**	.38**	.71**	-.31**	.11	.57**	-		
18. Right Body	.19	.10	.01	-.00	.16	.18	.20	.14	.24*	.23*	.24*	.16	-.29*	.55**	-.09	.29*	-.48**	-	
19. Right Tail	-.08	.03	.24*	.25*	.16	.02	.03	.11	.12	-.01	.52**	.50**	.07	.15	.66**	.47**	-.04	-.02	-

Note: *p<.05, **p<.01; Maternal depression was coded as absent = 0 and present = 1. Youth sex was coded as male = 0 and female = 1. Depressive symptoms at the age 9 and age 12 assessments were an average of the K-SADS and youth and parent Child Depression Inventory (CDI) depression scores. Depressive symptoms at the MRI assessment were an average of youth and parent CDI depression scores. Pubertal development was an average of the youth and parent Pubertal Development Scale scores.

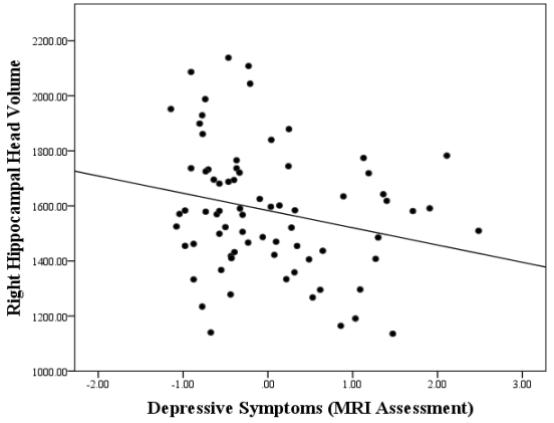
Figures

Figure 1. Associations between (a) left hippocampal head volume and concurrent youth depressive symptoms at the MRI assessment, (b) right hippocampal head volume and concurrent youth depressive symptoms at the MRI assessment, and (c) right hippocampal head volume and subsequent youth depressive symptoms at the age 12 assessment. Hippocampal subregion volumes were adjusted for total intracranial volume. Covariates for all analyses included youth sex, age, and pubertal development at the MRI assessment.

a)



b)



c)

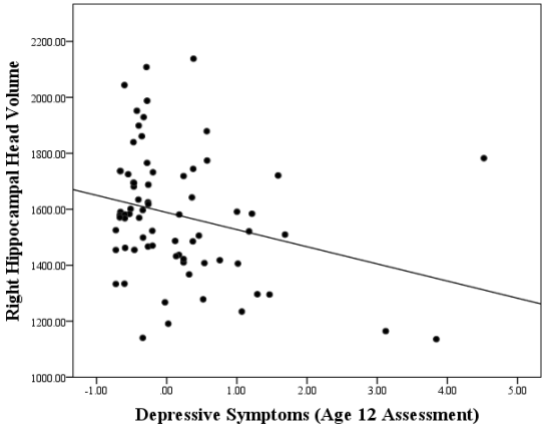
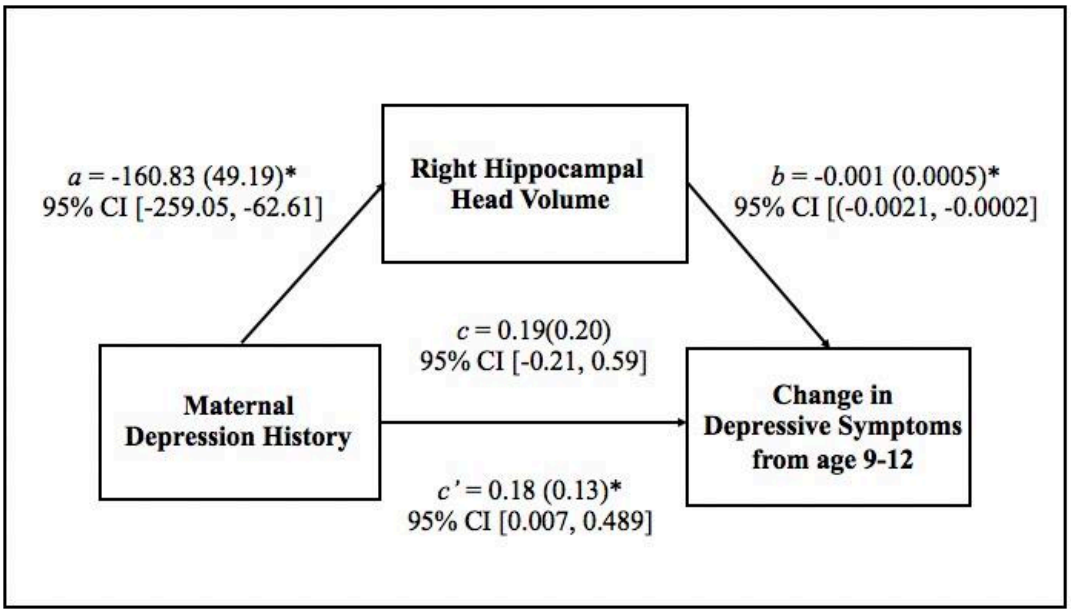


Figure 2. Standardized regression coefficients for the association between maternal depression and change in depressive symptoms from age 9 to age 12, as mediated by right hippocampal head volume.



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