EXPOSURE TO MATERNAL DEPRESSION DURING CHILDHOOD AND ADOLESCENCE AND PROBLEM BEHAVIOR IN EARLY ADULTHOOD: A POSSIBLE MEDIATING ROLE FOR BRAIN STRUCTURE

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The purpose of the present study was to advance our understanding of neurobiological processes related to the intergenerational transmission of behavior problems related to emotional dysregulation by examining whether earlier and/or more chronic exposure to maternal depression would be associated with increased depressive symptoms and reactive aggressive behaviors in young adult offspring, and whether individual differences in amygdala volume, hippocampal volume, and/or amygdala:hippocampus volume ratio would mediate this association. Results were mixed, indicating that maternal depression evident in early childhood or chronic maternal depression was positively associated with offspring depression and reactive aggression in early adulthood in some but not all cases. Maternal depression was not significantly associated with the volume of any individual brain regions in offspring, but was, in some analyses, significantly associated with larger amygdala:hippocampal volume ratios. Likewise, the volume of individual brain regions was not linked with concurrent young adult depression or reactive aggression, but amygdala:hippocampal volume ratio was linked to young adult reactive aggression. Results did not support a mediating role for any individual brain region in the associations found between maternal depression and offspring depression or reactive aggression, but did suggest a mediating

role for offspring amygdala:hippocampal volume ratio in the association between maternal depression trajectory grouping and offspring reactive aggression in young adulthood. Findings support a role for relative amygdala and hippocampus size in the intergenerational transmission of problems related to emotion regulation.

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PREFACE

Thank you to all the participants and their families, as well as the staff of the Pitt Mother & Child Project, for making the research possible. The research reported in this article was supported by National Institute of Mental Health Grants MH 50907 and MH 01666 awarded to Daniel S. Shaw.

1.0 INTRODUCTION

There is an abundance of evidence that offspring of mothers with elevated rates of depressive symptoms are at increased risk for internalizing and externalizing behavior problems that in some cases persist into adulthood (Goodman, 2007; Klein et al., 2005). Less clear, however, are the social and biological mechanisms by which this elevated vulnerability to the development of problem behaviors is transmitted to offspring. Recent findings from the behavioral and neural sciences provide important clues as to how neurobiological mechanisms such as subcortical brain development (Andersen et al., 2004) might operate in combination with early caregiving experiences in the intergenerational transmission of problem behavior.

Recently, it was found that ten-year-old children exposed to elevated maternal depressive symptoms since birth show larger amygdala volumes relative to children never exposed to maternal depressive symptoms, whereas hippocampal volumes were comparable between the two groups (Lupien et al., 2011). However, there is evidence to suggest that effects of early life stress on hippocampal structure may be protracted relative to those on amygdala structure, not observable until adolescence or even adulthood (Andersen & Teicher, 2004; Andersen & Teicher, 2008; Rao et al., 2010). Thus, an examination of the same subcortical brain structures in adult offspring exposed to maternal depressive symptoms during various developmental periods may more fully characterize how timing and chronicity of exposure to maternal depression may

be related to subsequent hippocampal (and amygdala) development. Furthermore, analyses of links between amygdala/hippocampal volume in emerging adulthood and concurrent dimensions of problem behavior related to difficulties in emotion regulation may improve our understanding of the behavioral correlates of these anomalies of brain structure. Finally, such an investigation might yield evidence as to whether individual differences in brain structure may potentially mediate associations between exposure to maternal depression and problems in emotion regulation during emerging adulthood.

The present study therefore examined: 1) direct associations between exposure to maternal depressive symptoms during four different developmental periods (i.e., early childhood, school-age, early adolescence, adolescence) and amygdala and hippocampal volume/amygdala:hippocampal volume ratio as well as depressive and antisocial behaviors at age 20; 2) concurrent associations between amygdala and hippocampal volume/amygdala:hippocampal volume ratio and both depressive and antisocial behaviors in young adulthood; and 3) whether variation in amygdala and hippocampal volume or amygdala:hippocampal volume ratios mediated the relationship between the timing and duration of exposure to maternal depressive symptoms and problem behavior at age 20. Participants were drawn from an ongoing longitudinal study of a cohort of 186 low-SES males at high risk for behavior problems followed from infancy to age 20. Using 11 reports of maternal depression from child age 1.5 through 17, associations between timing and chronicity of exposure to maternal depressive symptoms and both brain structure and problem behavior at age 20 were assessed.

2.0 LITERATURE REVIEW

This review will focus on developmental and neurobiological mechanisms by which exposure to maternal depressive symptoms might confer increased risk for problem behavior to adult offspring of depressed mothers. First, ways in which exposure to maternal depression during childhood and adolescence has been linked with problem behaviors related to emotional dysregulation in adulthood will be delineated. Next, neuroanatomical correlates of emotion regulation problems in adulthood will be described. Finally, findings from prior developmental psychopathology and neuroimaging studies will be presented to provide an evidence base for the present study's examination of possible neurobiological pathways through which exposure to maternal depressive symptoms may be related to the development of problem behaviors related to emotion regulation in adulthood.

Maternal Depression.

Major depression is characterized by persistently depressed mood and/or loss of interest or pleasure in most activities, among other symptoms (DSM-IV-R). Approximately 17% of mothers of young children show elevated depressive symptoms (Horwitz et al., 2007), with rates approaching 50% among low-income mothers of young children (Hall, et al., 1985). Beyond its considerable prevalence, however, maternal depression has become a matter of public concern

because of its consistent association with increased psychopathology in offspring, even as compared with paternal depression (Keller et al., 1986; Klein et al., 2005).

Throughout this thesis, the term "maternal depression" will be applied both to mothers meeting DSM-IV criteria for Major Depressive Disorder (MDD) and dysthymia, and mothers with elevated depressive symptom counts, based on evidence that both clinical depression and elevated depressive symptom counts are significantly and comparably associated with child behavior outcomes, including internalizing and externalizing problem behaviors (Cummings et al., 2005).

Problem Behavior in Offspring of Depressed Mothers.

Children of mothers with depression show elevated rates of internalizing and externalizing behavior problems, including depression and aggression (Goodman & Tully, 2006; Hammen & Brennan, 2003; Keller et al., 1986; Silk et al., 2006; Warner et al., 1992; Zahn-Waxler et al., 1990). In some cases, this heightened vulnerability to psychopathology and problem behavior persists into adulthood (Klein et al., 2005; Weissman et al., 1997). For example, elevated rates of internalizing problems, particularly depression, have been found in school-age, adolescent and adult offspring of depressed mothers (Beardslee et al., 1998; Cummings et al., 2005; Goodman & Gotlib, 1999; Hammen & Brennan, 2003; Hammen et al., 1990, 1991; Leve et al., 2005; Weissman et al., 1997). Offspring of depressed parents also show increased rates of conduct problems in childhood (Hay et al., 2003; Kim-Cohen et al., 2005; Radke-Yarrow, 1992) and more serious forms of antisocial behavior during adolescence (Shaw et al., 2012).

It is perhaps not surprising that exposure to maternal depressive symptoms has been associated with both internalizing and externalizing forms of problem behaviors, as substantial

epidemiological evidence indicates that internalizing and externalizing problems commonly co-occur (Gould, Bird, & Jaramillo, 1993; Rose, Rose, & Feldman, 1989; Weiss & Catron, 1994). However, the mechanisms by which offspring of depressed mothers incur elevated risk in both depressive and antisocial types of behavior problems are not entirely clear. It is possible that depressive behaviors and specific types of antisocial behaviors are associated with related behavioral, cognitive, and/or neurobiological processes. For instance, both depressive symptoms and aggression involve dysregulation of negative affect that may be learned or exacerbated by contextual risk. For example, depressed mothers and their three-month-old infants have been found to match negative behavior states more often and positive behavior states less often than non-depressed dyads (Field et al., 1990). Shared cognitive biases (e.g., hostile attribution biases) may also underlie both depressive and reactive problem behavior (Quiggle et al., 1992). Finally, both internalizing and externalizing behavior problems have been linked with deficits in emotion regulation abilities (i.e., skills related to managing feeling-states and related physiological processes in service of a goal; Eisenberg et al., 2000, 2001; Gross et al., 1995, 2009). Children of depressed mothers have demonstrated deficits in emotion regulation in laboratory mood induction paradigms (Silk et al., 2006).

Based on evidence that the effects of mothers' expression of emotion on child problem behavior and social competence are mediated by child regulatory skills (Eisenberg, Gershoff et al., 2001), it is possible that antisocial behaviors related to emotion regulation might be differentially susceptible to exposure to maternal depression as compared with more "calculated," proactive antisocial behaviors. Excessive reactivity of hypothalamic-pituitary-adrenal (HPA) axis stress responses has been associated with reactive aggression (i.e., aggressive responses to perceived provocations), but not proactive aggression (i.e., aggressive behavior in

service of reward; Lopez-Duran et al., 2009). As antisocial behaviors and, to some extent, depressive behaviors show continuity through childhood, adolescence and adulthood (Digdon & Gotlib, 1985; Fergusson, et al., 1996; Harrington et al., 1996; Hofstra et al., 2002), it may be that exposure to maternal depression during childhood and adolescence confers increased risk for contemporaneous difficulties in emotion regulation and for subsequent problem behaviors related to difficulties in regulating emotions in emerging adulthood, specifically depression and reactive aggression. However, the social and biological mechanisms by which this persistent pattern of vulnerability to the development of problem behaviors is incurred remain uncertain.

Mechanisms for the Intergenerational Transmission of Problem Behaviors.

Several interrelated processes have been hypothesized to explain the transmission of risk from depressed mothers to offspring including genetics (Sullivan et al., 2000), exposure to environmental stressors (e.g., impaired parenting/socialization processes, stressful contexts), and neurobiological mechanisms (e.g., anomalies of brain function/structure; Goodman et al., 1999). There is substantial evidence, for instance, to suggest that maternal depression is associated with impaired parenting (e.g., hostile/rejecting, intrusive, withdrawn/disengaged, insensitive or neglectful parenting; Field et al., 1998; Murray et al., 2003; Lovejoy et al., 2000; Shaw et al., 2012) and modeling of maladaptive emotion regulation strategies (Garber et al., 1991; Silk et al., 2006; Shaw et al., 2006). Impairments in parenting behavior may serve as stressors, acting in combination with genetic and/or neurobiological processes to confer increased risk for problem behaviors (Beardslee et al., 1983; Cohn, et al., 1990; Cummings & Davies, 1994; DeMulder & Radke-Yarrow, 1991; Goodman et al., 1999).

However, there is some evidence to suggest that the quality/severity of offspring behavior problems associated with exposure to maternal depression may vary with the timing of maternal

depression because of sensitive periods for the development of specific age-related processes (e.g., attachment, effortful control in early childhood; Brennan et al., 2000; Goodman & Gotlib, 1999; Hammen & Brennan, 2003). Indeed, contingently responsive and sensitive parenting behaviors assessed during infancy have been linked with multiple indices of prosocial and problem behavior during the toddler, preschool, and school-age periods (Aguilar et al., 2000; Martin, 1981; Shaw et al., 1994, 1998). However, less consistent associations have been found between maternal responsiveness and child outcomes when the former has been assessed in middle childhood (Landry et al., 2003). Likewise, exposure to maternal depression during very early childhood has been linked with more severe/enduring problem behaviors as compared with exposure to maternal depression during later developmental periods (Alpern & Lyons-Ruth, 1993; Essex & Klein 2001; Murray et al, 1999; Sinclair & Murray, 1998). This age-dependent pattern of increased vulnerability coincides with a "sensitive period" for neural development, in which the brain develops at a relatively rapid pace over the first two postnatal years (Chugani & Phelps, 1986; Goodman et al., 2007). Exposure to stressors (e.g., maternal depression) in early childhood may be particularly influential for subsequent socioemotional development because early childhood constitutes a neural sensitive period (i.e., a time in which a particular neural system exhibits increases plasticity and thus increased susceptibility to environmental influences; Casey et al., 2000; Knudsen, 2004; Lupien et al., 2009; Tottenham & Sheridan, 2010).

Evidence of increased hypothalamic-pituitary-adrenal (HPA) axis activity (i.e., increased circulation of glucocorticoids) in child and adolescent offspring of depressed versus non-depressed mothers (Ashman et al., 2002; Essex et al., 2002; Halligan et al., 2007; Lupien et al., 2000) indicates that maternal depression indeed serves as a significant stressor in early life (Hops et al., 1990). Dysregulated HPA axis functioning associated with early life stress is linked with

anomalous structural development in neural systems implicated in stress processing, specifically in the amygdala and hippocampus (Gruss, 2008; Andersen, 2004; Kikusui, 2009; Ono, 2008). These anatomically and functionally connected limbic structures responsible for stress processing (Charil et al., 2010; Pitkanen et al., 2000) are both particularly vulnerable to the effects of HPA axis dysregulation due to their high concentration of receptors for glucocorticoid and corticotrophin-releasing hormones (CRH) (Tottenham & Sheridan, 2010). Chronic exposure to stressors such as maternal depression may alter offspring HPA axis functioning. Increased occupation of glucocorticoid receptors in the amygdala following an environmental stressor results in increased HPA axis activity (i.e., increased production of CRH), whereas occupation of glucocorticoid receptors in the hippocampus results in inhibited HPA axis activity (i.e., the stress response is "called off;" Tottenham & Sheridan, 2010). Chronically high levels of stress have been linked with increased mRNA for CRH receptors in the amygdala and hypothalamus and, in turn, lower "thresholds" for stress activation, as well as the "down-regulation" of hippocampal glucocorticoid receptors (Tottenham & Sheridan, 2010).

Poor maternal caregiving in very young rodents has been associated with accelerated development and early myelination of the amygdala (Ono et al., 2008). This vulnerability to stress related to adverse caregiving experiences coincides with the most rapid rate of amygdala development, which takes place during a relatively narrow window of time during the early postnatal period and levels off soon after according to findings from non-human primate studies (Payne et al. 2010). Likewise, chronic occupation of glucocorticoid receptors in the hippocampus in very early life (i.e., the period at which these glucocorticoid receptors are at their peak concentration) has been associated with subsequent disruptions in hippocampal structural development (Tottenham & Sheridan, 2010). Anomalies of amygdala and hippocampal

development in response to early-life stress related to disrupted caregiving experiences may have functional significance, as these same structures show anomalous variation in adults with behavior problems related to emotion regulation (Arborelius et al., 1999; Heim et al., 1997; Kaufman et al., 2000).

Specifically, adults with depression show reduced hippocampal volume (Bremner et al., 2000; Lloyd et al., 2004; MacQueen et al., 2003; Sheline et al., 1996) and enlarged amygdala volume (Frodl et al., 2002; Eijndhoven, 2009; Lange et al., 2004). While findings regarding the neural profile associated with antisocial behavior are more complex and have not differentiated between reactive and proactive antisocial behavior, significant reductions in both amygdala volume (Tiihonen et al., 2000) and hippocampal volume (Laakso et al., 2001) have been found in violent offending adults. It is possible that neurobiological changes associated with early stressful experiences such as exposure to maternal depression confers increased risk for the development of behavior problems related to emotion regulation later in development (Kaufman & Charney, 2001).

Timing and chronicity of disrupted caregiving have also been assessed in relation to offspring neural outcomes in both animal and human studies. Non-human primate studies have linked relatively earlier maternal deprivation (i.e., separation from mother at one week of age vs. one month of age vs. maternally-raised) with increased severity of alterations in amygdala development (Kikusui & Mori, 2009; Ono et al., 2008). In humans, rearing in Asian and Eastern European orphanages in the first two years of life (prior to adoption) has been associated with relatively enlarged amygdala volumes in late childhood (Tottenham et al., 2010). Furthermore, chronicity of exposure to Romanian orphanage rearing (i.e., adopted > 15 months versus < 15 months of age) shows a dose-like positive relationship to amygdala volume in late childhood

(Mehta et al., 2009). A recent longitudinal study of exposure to maternal depressive symptoms in a large cohort of 10-year old children followed longitudinally since infancy found larger amygdala volumes but comparable hippocampal volumes in 10-year-old children of mothers presenting depressive symptoms since birth as compared with offspring of non-depressed mothers (Lupien et al., 2011).

However, findings relating stressful experiences to brain structure are likely contingent on the concurrent developmental status of the brain structure in question and timing of the environmental 'assault' (Brunson et al., 2001; Tottenham & Sheridan, 2009). For example, rodents and primates exposed to poor/absent maternal care in the neonatal period show relative reductions in hippocampal volume that are first observable in adolescence/adulthood (Gruss et al., 2008; Liu et al., 1997; Sanchez et al., 2001). The protracted nature of these hippocampal volume reductions in response to early life stress is likely a function of the hippocampus's relatively extended developmental trajectory. Neuroimaging studies of typical brain development in humans confirm that early childhood constitutes a sensitive period of rapid amygdala development (Casey et al., 2000; Knudsen, 2004; Lupien et al., 2009), whereas hippocampal development is relatively protracted, persisting into adulthood (Benes, 1994; Giedd et al., 1996; Gogtay et al., 2006). An examination of hippocampal structure in adult offspring of depressed mothers would more fully encompass its maturation and thus assess any delayed effects of earlier exposure than examination of the same structure in child populations.

There is increasing evidence to suggest that amygdala and hippocampal structure develop and relate to socioemotional outcomes as two parts of a functionally and structurally connected network (Thompson et al., 2010). Chronic stress has been linked with degeneration in the animal hippocampus (McEwen, 2001; Czeh & Lucassen, 2007). Reductions in hippocampal volume

have, in turn, been associated with hyperactivation of the amygdala (Suzuki et al., 2013). Interrelated patterns of functional and structural alterations of the amygdala and hippocampus have likewise been implicated in problems with emotion regulation. Specifically, the amygdala has been theorized and found to modulate the encoding and storage of hippocampal-dependent memories, whereas the hippocampus has been found to form representations of the emotional significance of events that, in turn, influence amygdala pathology and evoked response to emotional stimuli (Phelps et al., 2004; Richardson et al., 2004; Richter-Levin & Akirav, 2000). Regarding structure, larger amygdala and smaller hippocampal volumes within the same individual (i.e., larger amygdala:hippocampal volume ratios) have been linked to increased problems related to emotion regulation as compared with alterations in either structure assessed separately (Gerritsen et al., 2012; MacMillan et al., 2003). Thus, it is possible that both the degree of past environmental "assault" and potential for future difficulties linked with alterations of these individual structures may be best understood in the context of alterations in the other, reciprocally-functioning structure.

3.0 STATEMENT OF PURPOSE

While it is well established that the adult offspring of depressed mothers are at elevated risk for behavior problems (Goodman, 2007; Klein et al., 2005), the mechanisms underlying this intergenerational transmission of problem behavior are not entirely clear. Recent neuroimaging findings suggest that children exposed to maternal depression show altered structural development in brain regions implicated in stress processing (Lupien et al., 2011). The current study sought to extend our understanding of how the same subcortical brain structures in adult offspring of depressed mothers are influenced by the timing and chronicity of exposure to maternal depression, how subcortical brain structure is related, in turn, to problem behavior related to emotion regulation, and whether individual differences in brain structure might potentially mediate associations between exposure to maternal depression and problem behavior related to emotion regulation during emerging adulthood.

Specifically, the following hypotheses were tested:

Hypothesis 1A. It was hypothesized that exposure to maternal depressive symptoms measured from early childhood through adolescence would be positively associated with depressive symptoms and reactive aggression in adult offspring measured at age 20, such that:

Hypothesis 1B. Chronicity of maternal depression would be positively associated with young adult depression and reactive aggression; and

Hypothesis 1C. Earlier timing of maternal depression would be positively associated with young adult depression and reactive aggression.

Hypothesis 2: It was hypothesized that chronicity and timing of exposure to maternal depressive symptoms assessed throughout childhood and adolescence would be related to brain structure measured at age 20, such that greater chronicity of exposure to maternal depression (i.e., more total years of exposure to elevated depressive symptoms) and relatively earlier exposure (i.e., exposure in early versus late childhood, early adolescence or adolescence) each would be associated with increased amygdala volume and decreased hippocampal volume, and increased amygdala:hippocampal volume ratio.

Hypothesis 3: It was hypothesized that relatively larger amygdala volume, relatively smaller hippocampal volumes and relatively higher amygdala:hippocampal volume ratios would be associated with higher levels of depressive symptoms in early adulthood. Relatively smaller amygdala and hippocampal volumes were expected to be related to higher levels of reactive aggression in early adulthood. However, larger amygdala:hippocampal volume ratios were expected to be associated with higher levels of reactive aggression in early adulthood. It was further hypothesized that there would be a significant interaction effect such that alterations in amygdala and hippocampal volumes within the same individual would be associated with higher levels of young adult depressive symptoms and reactive aggressive behaviors, respectively, as compared with alterations in just one of the two structures.

Hypothesis 4: It was hypothesized that associations between exposure to maternal depressive symptoms and young adult depressive symptomatology would be mediated by individual differences in brain structure (i.e., larger amygdala and smaller hippocampal volumes; larger amygdala:hippocampal volume ratio), with paths stronger between maternal depression

and brain structure for more persistent and earlier-occurring periods of maternal depression. It was further hypothesized that associations between exposure to maternal depressive symptoms and young adult reactive aggressive behaviors would be mediated by individual differences in brain structure (i.e., smaller amygdala and smaller hippocampal volumes; larger amygdala:hippocampal volume ratio). Again, it was predicted that links would be stronger between maternal depression and brain structure for more persistent and earlier-occurring periods of maternal depression (see Figure 1).

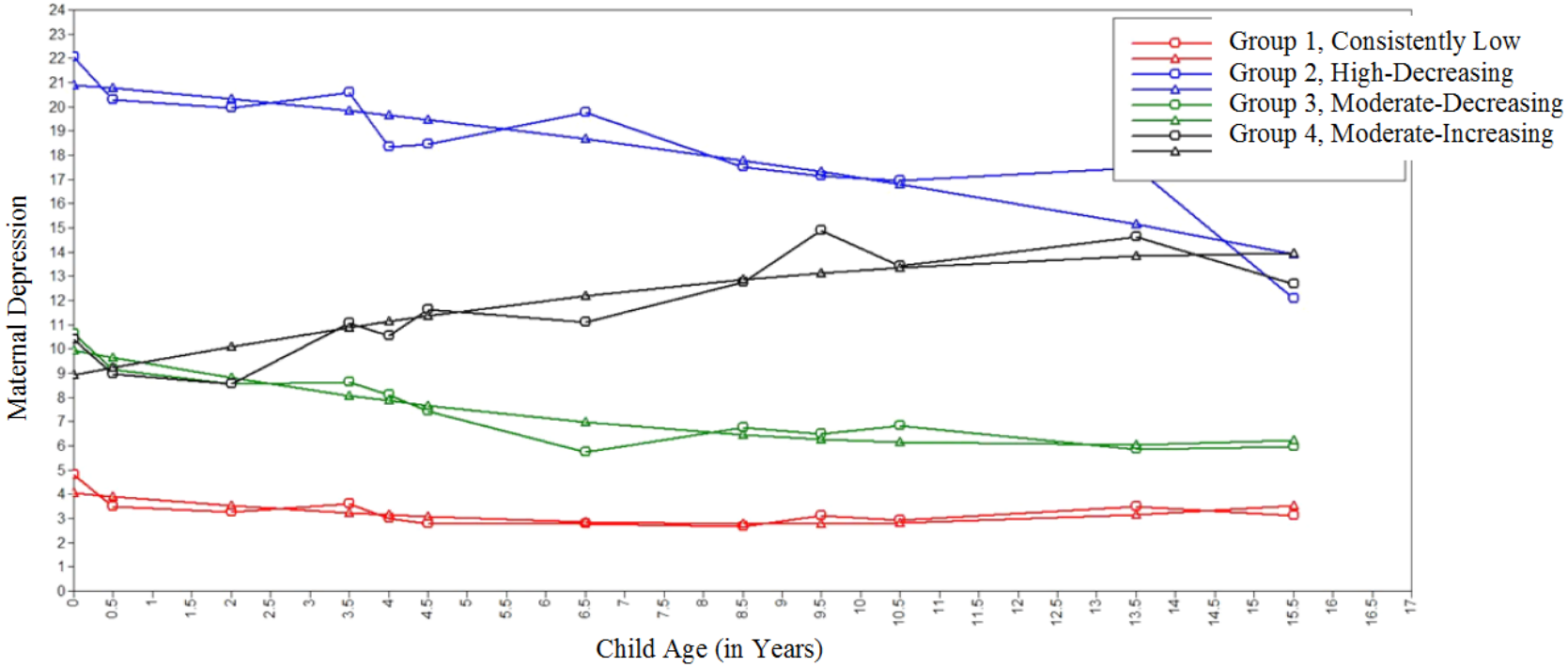

Figure 1. Trajectory Groups for Exposure to Maternal Depression from Child Ages 1.5-15.

4.0 METHODS

Participants

Participants were drawn from the Pitt Mother and Child Project (PMCP), an ongoing, prospective study of vulnerability and resiliency to behavior problems and/or substance use amongst low-income, high-risk youth (Shaw et al., 2003). Beginning in 1991, 310 families with male infants were recruited from Women, Infants, and Children (WIC) Nutrition Supplement Centers in the Pittsburgh metropolitan area. Criteria for identifying high-risk youth were (1) the family's eligibility for participating in WIC based on income regulations and (2) at least one other child living at home, thereby increasing family risk. Two-thirds of mothers had 12 or fewer years of education, and mean per capita income was $2,892 per year. The PMCP sample was also ethnically diverse (53% of children are White; 36% African American; 5% Biracial; 6% other).

Assessments were first conducted when the boys were 18 months old with follow-up assessments at child ages 2, 3.5, 5, 5.5, 6, 8, 10, 11, 12, 15, 17, and 20 years, with additional data collected through phone or internet interviews or through mailed questionnaires at child ages 3, 16, 18, and 21. Measures of self-reported depression and reactive aggression and high resolution, T-1 weighted neuroanatomical magnetic resonance images were obtained from the target youth at age 20 during a four-hour laboratory visit. Self-report measures of depressive and reactive

aggressive behaviors were obtained via self-administered laptop questionnaires as part of a structured interview. Participants were then introduced to MRI procedures through use of a MRI simulator. During the subsequent ten-minute structural MRI scan, participants were instructed to lie still, with their eyes closed. Magnetic resonance scanning took approximately one hour. Participants were all scanned on the same 3.0 Tesla Siemens magnet at the Magnetic Resonance Research Center at the University of Pittsburgh.

Retention rates have been consistently high throughout the 20 years of data collection (i.e., 83% at age 20 for interview data). The present study includes 186 men whose mothers were assessed for maternal depression at multiple points throughout their childhood and adolescence and who completed self-reported measures of depression and delinquency as well as structural magnetic resonance imaging scans at age 20.

Measures

Maternal Depressive Symptoms. Mothers completed the Beck Depression Inventory (BDI; Beck et al., 1961; Rehm et al., 1988) at all of the in-person assessments described above from child ages 1.5 to 17. The BDI is a well-established and widely used measure of depressive symptoms containing 21 items concerning depressive symptoms over the previous six months. Individuals rate their level of symptoms concerning the previous six months, each rated on a 0 to 3 scale of severity. Items are then summed to generate one factor for depressive symptoms per mother per time point. A higher score reflects relatively more depressive symptoms.

A composite maternal depression score for each of the following time periods was generated for analyses examining how the timing and chronicity of maternal depression are related to later brain structure and problem behavior: early childhood (ages 1.5, 2, 3.5); middle childhood (ages 5, 6 & 8); early adolescence (ages 10, 11 & 12); and adolescence (ages 15 &

17). Average internal consistency across mother reports for the one factor generated from the BDI from ages 1.5 to 17 for the BDI was α = .87, ranging from .83 at child age 2 to .90 at age 17.

Offspring Depressive Symptoms. The BDI was also used to assess young adult depressive symptoms at age 20 (see description above), for which internal consistency was α = .82.

Reactive Aggression. Nine items from the Self-Report of Delinquency (SRD, Elliott et al., 1985) were used to assess young adults' reactive aggression (See Table 1). The SRD is a self-report questionnaire that assesses the frequency with which an individual has engaged in specific antisocial behaviors. Participants rated each item based on how often it has occurred during the past year on a 3-point scale (0 = never, 1 = once/twice, 2 = more often), with items summed to generate a total score. For purposes of the current study, items were selected from the SRD that reflect reactive (vs. proactive) aggression based on the following criteria: 1) behaviors which are more often than not carried out without planning or forethought; 2) behaviors which are aggressive in nature (i.e., hitting someone with the idea of hurting them; on purpose breaking, damaging, or destroying things that did not belong to you). Internal consistency for the reactive aggression factor is α = .75.

Amygdala and Hippocampal Volume. Amygdala and hippocampal volumes were acquired from high-resolution (1.2 x 1 x 1 mm) T1-weighted brain images using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol. All images were collected on a 3T Siemens Allegra scanner. FMRIB Software Library's empirically-supported, model-based (FMRIB) Integrated Registration and Segmentation Tool (FIRST; Patenaude et al., 2011; Smith et al., 2004) was used for segmentation and volumetric analyses. This registration and segmentation tool is fully-automated, which should minimize any effects of experimenter error, and is designed specifically to quantify the volume of subcortical structures like the amygdala

and the hippocampus. To determine intracranial volume (ICV), the sum of gray, white, and cerebrospinal fluid volumes were aggregated.

Table 1. SRD-based reactive aggressive items used for composite. Adapted from "'Hinshaw' Self-Reported Delinquency" Self-Report of Delinquency Questionnaire (SRD); Elliot et al., 1985.

Item Number	Content
1	Have you on purpose broken or damaged or destroyed things that did not belong to you?
20	Have you thrown rocks or bottles at people?
21	Have you bullied, threatened, or intimidated someone else?
23	Have you threatened anyone with a weapon (like a bat, brick, broken bottle, knife or gun)?
24	Have you attached someone with a weapon or with the idea of seriously hurting or killing them?
25	Have you hit someone with the idea of hurting them?
50	Have you forced someone into sexual activity with you?
52	Have you forced someone to have unsafe sex with you (i.e., sex without a condom)?

5.0 DATA ANALYSIS

To evaluate the study's hypotheses, correlations (hypotheses 1-3), hierarchical multiple regressions (hypotheses 2-4), ANOVAs, and semi-parametric growth curve modeling (hypotheses 1 and 4) were utilized. In some multivariate analyses, average socioeconomic status over the first three assessments (measured at ages 1.5, 2, 3.5) was included as a covariate because of relationships among maternal depression, socioeconomic status, and child behavioral outcomes (Harnish, Dodge et al., 1995; Pettersen & Albers, 2001; Shaw et al., 1996). Correction for intracranial volume (ICV) was included as a covariate in analyses involving discrete regional brain volumes, as regional differences in cerebral volume may be confounded by differences in head size between individuals (Blatter et al., 1995; Whitwell et al., 2001).

Maternal BDI symptom counts from each of the twelve time points from offspring age 1.5 years to 17 years were combined in a variety of ways (i.e., overall average score, percentage of years assessed in which mother's score was in clinical range, average score over discrete developmental periods) to more fully characterize exposure to maternal depression. Composite maternal depression scores were created from the available data points (i.e., if data were missing at age 3.5, only age 1.5 and 2 scores were used to compute average maternal BDI in early childhood). Discrete regional brain volumes (i.e., amygdala, hippocampus, thalamus), in voxels, were obtained from neuroanatomical MR images using fully-automated methods (FSL; Smith et

al., 2004). While anomalies of thalamic volume are frequently implicated in the pathophysiology of schizophrenia (Adriano et al., 2010), no relationships were expected between thalamic volume and depressive symptoms or reactive aggressive symptoms in this sample. Rather, the region was included in analyses to clarify the regional specificity of any findings. As hypothesized, no such relationships were found; therefore, these data are not presented here. In addition to discrete volumes of individual brain regions, amygdala:hippocampal volume ratios were assessed.

As previously described, offspring depressive symptoms at age 20 were assessed using the BDI, and the reactive aggression factor was derived from youth-report on the SRD. To correct for non-normality of the distribution of scores on the SRD, scores were transformed by the logarithm function. For analyses of the effects of maternal depression on offspring depression and reactive aggression at age 20, all individuals with maternal depression symptom counts, early childhood SES data, and Age 20 BDI and SRD data were included (n = 251). For analyses involving brain structure, all individuals with neuroanatomical data at age 20 and the relevant maternal depression and youth BDI and SRD data were included (n = 169 and n = 165, respectively) with the exception of one outlier, whose hippocampal volume was approximately 11.5 standard deviations above the mean. Variance inflation factor (VIF) and tolerance statistics were also assessed to rule out the possibility that multicollinearity issues might be affecting regression results. Descriptive statistics of the sample and statistical procedures and findings for the four hypotheses are described below.

6.0 RESULTS

Descriptive Statistics

Table 2 contains descriptive statistics and correlations among the study's primary independent and dependent variables. Mothers reported the most depressive symptoms when their children were in early childhood (M = 8.1 between 1.5 and 3.5 years of age). However, by the time their children reached middle childhood (ages 6 to 10), maternal depressive symptoms were significantly reduced (M = 7.1; $t(287) = 2.95$; $p < .01$). Maternal depressive symptoms continued to decrease, albeit non-significantly, as children reached early and middle adolescence. As SES obtained during early childhood (i.e., child's age 18 to 42 months) was significantly related to early childhood maternal BDI scores (r = -.14, $p < .05$), early childhood SES was included as a covariate in all regression analyses involving these two predictors. As early childhood SES was related to young adult amygdala volume (r = .15, $p < .05$) after covarying for intracranial volume (ICV), and marginally related to hippocampal volume after covarying for ICV (r = .14, p = .07), early childhood SES was also used as a covariate in analyses of amygdala and hippocampal volume. Amygdala and hippocampal volume were correlated (r = .49, $p < .05$), as were young adult depressive symptoms and reactive aggression (r = .40, $p < .05$).

Table 2. Descriptives and Pearson Correlations between Primary Variables. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed); † Correlation trends toward significance at the 0.10 level (2-tailed).

	N	M (SD)	1	2	3	4	5	6	7	8	9	10	11
1. Mean Overall Maternal BDI	308	7.4 (5.1)											
2. Percentage of Years Mother > 16 on BDI	312	10 (20)	.85**										
3. Mean Maternal BDI during Early Childhood	303	8.1 (6.0)	.83**	.69**									
4. Mean Maternal BDI during Middle Childhood	296	7.1 (5.9)	.86**	.70**	.63**								
5. Mean Maternal BDI during Early Adolescence	267	7.1 (6.2)	.84*	.71**	.51**	.66**							
6. Mean Maternal BDI during Adolescence	246	6.4 (6.6)	.71**	.64**	.38**	.45**	.61**						
7. Amygdala Volume	170	2802 (485)	.05	-.01	.08	.05	.01	.01					
8. Hippocampal Volume	170	7949 (863)	-.06	-.11	-.09	-.04	-.07	-.00	.49**				
9. Ratio of Amygdala: Hippocampal Volume	170	.35 (.06)	.09	.06	.16*	.08	.03	.00	.77**	-.17*			
10. Youth BDI at Age 20	264	5.4 (6.3)	.15*	.14*	.07	.21**	.18**	-.00	.07	-.07	.12		
11. Reactive Aggression Factor (log-transformed)	254	.99 (.06)	.09	.04	.07	.12†	.13*	-.07	.11	-.09	.19*	.40**	

1a. Direct Associations Between Mean Overall Exposure to Maternal Depression and Offspring Depression and Reactive Aggression in Adulthood

To test the hypothesis that exposure to maternal depression would be positively associated with youth depressive symptoms and reactive aggressive behaviors at age 20, two Pearson correlation coefficients were computed using composites (i.e., early childhood, middle childhood) of maternal BDI scores generated from the 12 assessments between ages 1.5 years and 17 years and youth self-reports of depressive and reactive aggressive behaviors at age 20. As shown in Table 2, hypothesis 1a was partially supported, as the overall mean maternal BDI score from child ages 1.5 to 17 was significantly positively correlated with young adult reports on the BDI at age 20 (r =.15, p < .05), with SES in early childhood failing to attenuate this association. In contrast to expectations, mean overall maternal BDI score was not significantly related to offspring reactive aggression at age 20 (r =.09, *ns*).

1b. Direct Associations Between Chronicity of Maternal Depression and Offspring Depression and Reactive Aggression in Adulthood.

To assess whether chronicity of exposure to maternal depression would be positively associated with youth depressive symptoms and reactive aggressive behaviors at age 20, two additional Pearson correlation coefficients were computed using the percentage of assessments from child ages 1.5 years to 17 years in which mothers showed a BDI score in the clinical range (i.e., 16 or higher) and young adult self-reports of depression and reactive aggression at age 20. Again, findings partially supported the hypotheses, as chronicity of maternal depression was significantly positively correlated with offspring BDI symptoms counts at age 20 (r =.14, p < .05). Contrary to expectations, chronicity of exposure to maternal depression was not significantly related to offspring reactive aggression at age 20.

Hypothesis 1c. Direct Associations Between Timing of Maternal Depression and Offspring Depression and Reactive Aggression in Adulthood

To determine whether associations were present between developmental timing of exposure to maternal depression and offspring depression and reactive aggression in young adulthood, four Pearson correlations were conducted using average maternal BDI score over four discrete developmental periods (i.e., early childhood, middle childhood, early adolescence, middle adolescence) and young adult depression and reactive aggression at age 20. The hypothesis that relatively earlier exposure to maternal depression would be most highly correlated with youth depressive and reactive aggressive symptoms/behaviors in adulthood was not supported (r =. 07, *ns* in both cases). However, average maternal depression in middle childhood (r =. 21, $p < .05$) and early adolescence (r = .18, $p < .05$) were both positively associated with young adult depressive symptoms at age 20. In relation to age-20 reactive aggression, only maternal depression during early adolescence was significantly related (r =.13, $p < .05$), with a trend in the expected direction for middle childhood maternal depression (r = .12, p = .06).

To more fully evaluate links between developmental timing, chronicity, and severity of maternal depressive symptoms and offspring depression and reactive aggression at age 20, a semi-parametric, group based method (Nagin, 2005) was utilized to initially identify trajectory groups of maternal depressive symptoms. Using this method, individuals in the sample with similar symptom trajectories were classified into groups. This model addresses missing data by adjusting equations in the base model to accommodate missing data, while adjusting sample size to exclude missing data points (Nagin, 2005). After examining several models ranging from one to five classes (see Table 3), a four-group model was chosen on the basis of theoretical

Table 3. Model Fit Indices and Diagnostic Statistics for Judging Model Selection.

# of Classes	BIC	Average Posterior Probability	Smallest number assigned to a group
1	20341.954		
2	19398.599	0.93	75
3	19121.316	0.89	29
4	19042.247	0.83	27
5	18954.826	0.89	12

considerations and the following model fit indices: 1) Bayesian Information Criteria (BIC) value (lower values indicate a better fit)*;* 2) estimates of individuals' probability of belonging to each trajectory group (posterior probabilities); and finally 3) sample size of the smallest group being greater than 5% of the sample or an *n* of greater than 10 (D'Unger, Land, McCall, & Nagin, 1998; Kass & Raffery, 1995). As shown in Table 3, the 4-group model showed an improved BIC value relative to the three-class model; however, BIC scores generally improve with the addition of classes, and are therefore limited in their usefulness for discriminating the best-fitting model from several choices (Nagin, 2005). Posterior probabilities for all models were above the recommended threshold for assignment of .7 (Nagin, 2005). The 4-group model was selected over the 5-group model because the addition of the 5th group created two relatively small groups (i.e., 10 and 12 participants or 3.7 and 3.8 % of the sample, respectively), whereas the smallest group in the 4-group model contained 27 participants or 8.4% of the sample.

Descriptive statistics for maternal depression trajectory groups are presented in tables 4-5. The largest group, Group 1 (n = 137; 43% of the sample) was characterized by consistently low depressive symptomatology throughout the assessment period (M = 3.35 across the twelve assessments), and will therefore be referred to as the "persistently low" group. Group 2, which will be referred to as the "persistently high" group, showed consistently and extremely elevated BDI symptom counts (M = 18.83 across all assessments) with a slight decreasing pattern of symptoms from early childhood through adolescence (M = 21.19 in early childhood versus M = 15.78 in adolescence). The persistently high group was composed of a modest 8.4% of the sample (n = 27). The second largest group, Group 3 (n = 114; 35.2% of the sample), showed moderately high symptomatology (M = 8.02 across all time points), which decreased across the course of development (M = 9.77 in early childhood versus M = 5.77 in adolescence). This group is referred to as the "moderate decreasing" group. Finally, Group 4 (n = 35; 13.3% of sample) showed moderate symptomatology (M = 11.99 over all twelve assessments), which increased across the course of development (M = 9.29 in early childhood versus M = 14.78 in adolescence). This group will therefore be referred to as the "moderate increasing" group (See Figure 1).

A series of ANOVAs were computed to assess associations between trajectory group membership and young adult depression and reactive aggression at age 20 (see Table 4). For the overall ANOVA, there was a nonsignificant trend in predicting youth BDI at age 20, $F(3, 252) = 2.58$, $p = .054$. Tukey post-hoc comparisons of the trajectory groups indicate that young men in the persistently high maternal depression group (Group 2; M = 8.41, 95% CI [5.84, 10.98]) showed significantly higher rates of depressive symptomatology at age 20 as compared with

Table 4. Descriptive Statistics and ANOVA for Offspring Self-reported Depressive Symptoms (BDI) and Reactive Aggressive Behaviors (SRD; log-transformed) by Trajectory Group. Note: Superscripts reflect significant differences between other trajectory groups in that column, based on t-test comparisons.

Group	***N***	**BDI M (SD)**	**SRD-RA M (SD)**
1	137	4.58 (5.3)[2]	0.98 (.05)[3]
2	27	8.41 (7.53)[1]	1.00 (.06)
3	114	5.73 (6.98)	1.01 (.07)[1]
4	35	5.00 (5.32)	0.98 (.05)
F		2.58	3.78
Df		252	252
Sig.		.05	.01

Table 5. Descriptive statistics for Amygdala, Hippocampus Volume (in voxels) and Amygdala:Hippocampal Volume Ratio by Trajectory Group. Note: Superscripts reflect significant differences between other trajectory groups in that column, based on t-test comparisons.

Group	***N***	**Amygdala Volume M (SD)**	**Hippocampus Volume M (SD)**	**Amygdala:Hippocampal Volume Ratio**
1	137	2738.22 (402.48)	7994.02 (837.94)	0.34 (.05)
2	27	2788.94 (519.92)	7656.09 (830.30)	0.36 (.06)
3	114	2866.67 (580.04)	7894.22 (926.00)	0.36 (.07)
4	35	2902.55 (481.43)	8121.41 (799.40)	0.36 (.06)
F		1.09	.90	1.73
Df		169	169	169
Sig.		.36	.44	.16

young men in the persistently low maternal depression group (Group 1; *M* = 4.58, 95% CI [3.47, 5.70]), *p* = .04. Comparisons among the other groups were not significant.

Age-20 reactive aggression differed significantly across the trajectory groups, *F*(3, 252)= 3.36=7, *p* < .05. Tukey post-hoc comparisons of the trajectory groups indicate that young men in the moderate-decreasing maternal depression group (Group 3; *M* = 1.01, 95% CI [.99, 1.02]) showed significantly higher rates of reactive aggression (log transformed) at age 20 as compared with young men in the persistently low maternal depression group (Group 1; *M* = .98, 95% CI [.97, .99]), *p* < .01. Socioeconomic status in early childhood failed to attenuate this association. Comparisons among other individual groups were not significant.

To further clarify any relationships between developmental timing of exposure to maternal depression and youth reactive aggression at age 20, groups 2 and 3 (the two groups with the highest average maternal depressive symptom counts during early childhood; M = 21.19 and M = 9.77 in early childhood, respectively) were combined and contrasted with groups 1 and 4 (the two groups with lower maternal depressive symptomatology during early childhood; M = 3.76 and M = 9.29 in early childhood). Consistent with the original hypothesis that relatively earlier exposure to maternal depression might be more strongly associated with reactive aggressive behaviors in adulthood, Groups 2 & 3 (the "high-decreasing" and "moderate-decreasing") report more reactive aggressive behaviors compared with groups 1 & 4 (the "consistently low" and the "moderate-increasing;" *F*(1, 251)= 10.96, p < .001). Again, socioeconomic status in early childhood did not affect this relationship.

2. Direct Associations Between Exposure to Maternal Depression and Amygdala Volume, Hippocampal Volume, and Amygdala: hippocampus Volume Ratio

To test the hypothesis that exposure to maternal depression would be positively associated with amygdala volume, negatively associated with hippocampal volume, and positively associated with amygdala:hippocampal volume ratio at age 20, a series of Pearson correlation coefficients was computed. This hypothesis was assessed using each of the methods described above for capturing BDI symptomatology from the twelve assessments (i.e., mean overall BDI, percentage of years mother was in clinical range, mean BDI scores during discrete developmental periods) in combination with amygdala and hippocampal volume (covarying for ICV), and amygdala: hippocampal volume ratio. As shown in Table 2, hypothesis 1a was partially supported. Neither overall maternal BDI score nor chronicity of maternal depression was significantly correlated with Age 20 regional brain volumes or ratios. Mean BDI in early childhood (controlling for early childhood SES) did predict amygdala:hippocampal volume ratio at Age 20 ($r = .16$, $p < .05$), but maternal depression during any other developmental period was not significantly correlated with offspring brain volumes or ratios in adulthood. Finally, using the same trajectories of maternal depression used in Hypothesis 1c (above), two ANOVAs were conducted in which trajectory group served as the independent variable and amygdala and hippocampal volume served as the respective dependent variables.

Individual maternal depression trajectory groups did not discriminate discrete brain volumes of any region or amygdala:hippocampal volume ratio. To further clarify the relationship between developmental timing of exposure to maternal depression and young adult brain structure at age 20, groups 2 and 3 (the two groups with the highest average maternal depressive symptom counts during early childhood; $M = 21.19$ and $M = 9.77$ in early childhood, respectively) were combined and contrasted with groups 1 and 4 (the two groups with lower maternal depressive symptomatology during early childhood; $M = 3.76$ and $M = 9.29$ in early

childhood). Consistent with the original hypothesis that relatively earlier exposure to maternal depression might be more strongly associated with disruptions in brain structure as compared with relatively later exposure, Groups 2 & 3 (the "high-decreasing" and "moderate-decreasing") demonstrated higher amygdala:hippocampal volume ratio compared with groups 1 & 4 (the "consistently low" and the "moderate-increasing;" $F(1, 169)= 4.14$, $p < .01$).

Hypothesis 3. Associations between amygdala and hippocampal volume, amygdala: hippocampal volume ratio and young adult depression and reactive aggression

To examine whether amygdala volume, hippocampal volume, and amygdala: hippocampal volume ratio were related to young adult depressive symptoms and reactive aggression at age 20, a series of Pearson correlation coefficients was computed. Although neither amygdala nor hippocampal volumes were related to young adult depressive symptoms($r = .07$, *ns*, and $r = -.08$, *ns*, respectively), or reactive aggressive behaviors ($r = .11$, *ns*; and $r = -.09$, *ns*, respectively), amygdala:hippocampal volume ratio was positively associated with reactive aggression in the predicted direction ($r = .19$; $p < .05$). Amygdala/hippocampal volume ratio trended toward predicting young adult depression ($r = .12$, *ns*).

To assess any possible interaction effects for amygdala and hippocampal volume on youth reactive aggression, hierarchical multiple regression analyses were computed in which young adult depression and reactive aggression was regressed onto early childhood SES, ICV, then either 1) amygdala volume, and then amygdala and hippocampal volume together, or 2) hippocampal volume, and then hippocampus and amygdala volume together, and finally, the interaction term between amygdala and hippocampal volume. Independent variables were centered before interaction terms were created.

Findings showed no significant interactions between amygdala and hippocampal volume for young adult depression or reactive aggression. However, regardless of whether amygdala or hippocampal volume was entered first in the hierarchical multiple regression, when examined together in a multivariate framework, both amygdala (β = .22, p < .05) and hippocampal volume (β = -.18, p < .05) were related to reactive aggressive behaviors in the predicted direction. Similarly, when examined together in a multivariate framework, both amygdala (β = .15, p = .08) and hippocampal volume (β = -.16, p = .09) were marginally related to young adult depressive symptoms in the predicted direction. Detailed results are presented in Tables 8-11.

Hypothesis 4. Mediating role of brain structure in relation to exposure to maternal depression and young adult depression and reactive aggression

To examine the hypothesis that amygdala:hippocampal volume ratio would mediate the association between exposure to maternal depression trajectory-grouping and later young adult report of reactive aggression, a series of hierarchical multiple regression analyses was computed. Independent variables were centered before interaction terms were created. Amygdala:hippocampal volume ratio was entered prior to entering the maternal depression variable (i.e., using trajectory group combinations from Hypothesis 1C) to see if the direct effect of maternal depression on young adult reactive aggression was partially or fully mediated by amygdala:hippocampal volume. Then these steps were repeated entering SES and/or ICV as a first step in the regression equations. Detailed results are presented in Tables 6 and 7.

With regard to analyses contrasting the two groups with the highest exposure to maternal depression in early childhood with the two groups with lower exposure to maternal depression in early childhood (Groups 3 and 2 versus 1 and 4), once amygdala:hippocampal volumes were accounted for, including nonsignificant associations for socioeconomic status in early childhood

(β = -.11, *ns*) and ICV (β = -.02, *ns*), respectively, the relationship between maternal depression trajectory grouping and young adult reactive aggression became nonsignificant (β = .26, *ns*). In addition, R^2 change statistics revealed that, after accounting for covariates, the inclusion of trajectory groupings in the regression models did not contribute significant variance to young adult reactive aggression (R^2change value=.008). As shown in Figure 2, the standardized regression coefficient between trajectory grouping and reactive aggression (β = .20, $p < .05$)

Table 6. Regression Results for Predicting Self-Report of Reactive Aggressive Behaviors at Age 20 and Amygdala:Hippocampal Volume Ratio using Maternal Depression Trajectory Grouping (Two Highest Groups during Early Childhood vs. Two Lowest Groups during the same period). *p < .05, **p < .01

	Reactive Aggression		**Amygdala:Hippocampal Volume Ratio**	
Trajectory Grouping	**B (SE)**	**β**	**B (SE)**	**β**
Highest EC vs. Else	.03 (.01)	.21**	.02 (.01)	.16*

Table 7. Hierarchical Multiple Regression Results for Predicting Self-Report of Reactive Aggressive Behaviors at Age 20 using Amygdala:Hippocampal Volume Ratio and Maternal Depression Trajectory Grouping (Two Highest Groups during Early Childhood vs. Two Lowest Groups during the same period).*p < .05, **p < .01

	Model One		**Model Two**	
Predictor Variable	**B (SE)**	**β**	**B (SE)**	**β**
Amygdala:Hippocampal Volume Ratio	.18 (.08)	.19*	.17 (.08)	.17*
Highest EC vs. Else			.01 (.01)	.09

Table 8. Summary of Hierarchical Multiple Regression Results of SES, ICV, Amygdala Volume, Hippocampal Volume, and Amygdala*Hippocampal Volume Predicting Reactive Aggression (Log transform of SRD-RA factor) ** Significant at the 0.01 level (2-tailed); * Significant at the 0.05 level (2-tailed); † Trends toward significance at the 0.10 level (2-tailed). Note: SES, ICV, Amygdala Volume, Hippocampus Volume, and Amygdala*Hippocampus were all mean-centered.

	Model One		**Model Two**		**Model Three**		**Model Four**		**Model Five**	
Variable	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**
SES	-.00 (.00)	-.09	-.00 (.00)	-.09	-.00 (.00)	-.11	-.00 (.00)	-.10	-.00 (.00)	-.11
ICV			.00 (.00)	.00	.00 (.00)	.00	-.00 (.00)	-.02	-.00 (.00)	-.02
Amygdala					.00 (.00)	.13	.00 (.00)	.22*	-.00 (.00)	-.03
Hippocampus							-.00 (.00)	-.18*	-.00 (.00)	-.34
Amygdala x Hippocampus									.00 (.00)	.34
R^2	.01		.01		.03		.05		.05	
F	1.40		.70		1.37		2.12†		1.71	

Table 9. Summary of Hierarchical Multiple Regression Results of SES, ICV, Hippocampus Volume, Amygdala Volume, and Amygdala*Hippocampal Volume Predicting Reactive Aggression (Log transform of SRD-RA factor). ** Significant at the 0.01 level (2-tailed); * Significant at the 0.05 level (2-tailed); † Trends toward significance at the 0.10 level (2-tailed). Note: SES, ICV, Amygdala Volume, Hippocampus Volume, and Amygdala*Hippocampus were all mean-centered.

	Model One		**Model Two**		**Model Three**		**Model Four**		**Model Five**	
Variable	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**
SES	-.00 (.00)	-.09	-.00 (.00)	-.09	-.00 (.00)	-.08	-.00 (.00)	-.10	-.00 (.00)	-.11
ICV			.00 (.00)	.00	-.00 (.00)	-.00	-.00 (.00)	-.02	-.00 (.00)	-.02
Hippocampus					-.00 (.00)	-.08	.00 (.00)	-.18*	-.00 (.00)	-.34
Amygdala							-.00 (.00)	.22*	-.00 (.00)	-.03
Amygdala x Hippocampus									.00 (.00)	.34
R^2	.01		.01		.02		.05		.05	
F	1.40		.70		.81		2.12†		1.71	

Table 10. Summary of Hierarchical Multiple Regression Results of SES, ICV, Amygdala Volume, Hippocampus Volume, and Amygdala*Hippocampus Volume Predicting Depression (BDI score). ** Significant at the 0.01 level (2-tailed); * Significant at the 0.05 level (2-tailed); † Trends toward significance at the 0.10 level (2-tailed). Note: SES, ICV, Amygdala Volume, Hippocampus Volume, and Amygdala*Hippocampus were all mean-centered.

	Model One		**Model Two**		**Model Three**		**Model Four**		**Model Five**	
Variable	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**
SES	.00 (.06)	.00	-.00 (.06)	-.01	-.01 (.06)	.02	-.01 (.06)	-.01	-.01 (.06)	-.01
ICV			-.00 (.00)	-.11	-.00 (.00)	-.11	-.00 (.00)	-.13	-.00 (.00)	-.13
Amygdala					.00 (.00)	.08	-.00 (.00)	.15†	.00 (.00)	.15
Hippocampus							-.00 (.00)	-.16†	-.00 (.00)	-.16
Amygdala x Hippocampus									.00 (.00)	.00
R^2	.00		.01		.03		.04		.04	
F	.00		.94		.95		1.48		1.18	

Table 11. Summary of Hierarchical Multiple Regression Results of SES, ICV, Hippocampus Volume, Amygdala Volume, and Amygdala*Hippocampal Volume Predicting Depression (BDI score). ** Significant at the 0.01 level (2-tailed); * Significant at the 0.05 level (2-tailed); † Trends toward significance at the 0.10 level (2-tailed). Note: SES, ICV, Amygdala Volume, Hippocampus Volume, and Amygdala*Hippocampus were all mean-centered.

	Model One		**Model Two**		**Model Three**		**Model Four**		**Model Five**	
Variable	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**
SES	.00 (.06)	.00	-.00 (.06)	-.01	.00 (.06)	.00	-.01 (.06)	-.01	-.01 (.06)	-.01
ICV			-.00 (.00)	-.11	-.00 (.00)	-.12	-.00 (.00)	-.13	-.00 (.00)	-.13
Hippocampus					-.00 (.00)	-.08	-.00 (.00)	-.16†	-.00 (.00)	-.16
Amygdala							.00 (.00)	.15†	.00 (.00)	.15
Amygdala x Hippocampus									.00 (.00)	.00
R^2	.00		.01		.02		.04		.04	
F	.00		.94		1.00		1.48		1.18	

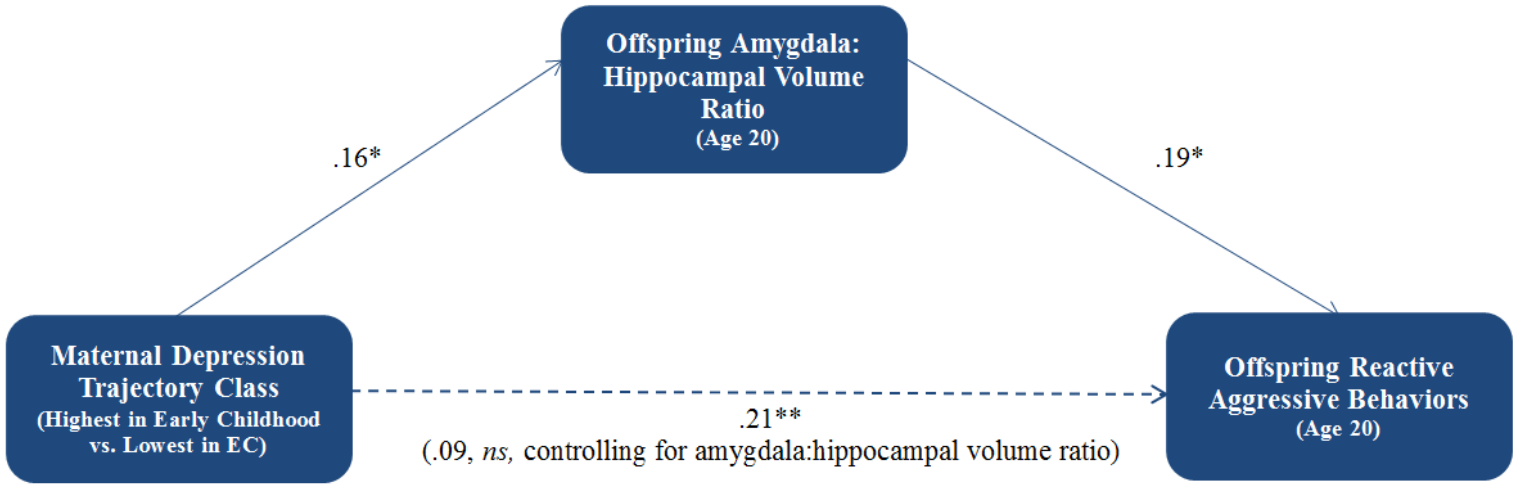

Figure 2. Mediation Model for Maternal Depression Trajectory Grouping, Offspring Amygdala: Hippocampal Volume Ratio at Age 20, and Self-Reported Reactive Aggression at Age 20.

decreased substantially when controlling for amygdala:hippocampal volume (β = .09, *ns*). Next, RMediation was used to compute asymmetric confidence intervals (CI) for the mediated effects using the distribution of product of the coefficients method (PRODCLIN; Tofighi & MacKinnon, 2011) to test the significance of the mediation effect. For a significant mediation effect to be evident, their asymmetric CIs should not include zero. The mediation of amygdala:hippocampal volume ratio on the effect of maternal depression trajectory grouping on reactive aggression reports was significant CI [.000006, .007947]. In summary, in accordance with hypothesis 4, the relationship between maternal depression trajectory grouping (i.e., groups 2 and 3 versus 1 and 4) and offspring self-report of reactive aggression at age 20 was mediated by amygdala:hippocampal volume ratio.

7.0 DISCUSSION

The purpose of the present study was to examine whether exposure to maternal depression during different developmental stages of childhood and adolescence would be associated with individual differences in brain structure (i.e., amygdala and hippocampal volume, amygdala:hippocampal volume ratio) and depressive symptoms and reactive aggression in a sample of young adult male offspring.. An additional aim of the present study was to assess whether individual differences in brain structure would mediate the relationship between exposure to maternal depression and young adult outcomes. Results indicated that maternal depression was linked with offspring depression and reactive aggression in early adulthood in some cases but not in others. Maternal depression did not predict volumes of any discrete brain regions in offspring, but did, in some cases, predict amygdala:hippocampal volume ratios. Neither amygdala nor hippocampal volume was associated with concurrent depression or reactive aggression in adulthood, but amygdala:hippocampal volume ratios were significantly related to young adult reactive aggression. Likewise, results did not support a mediating role for amygdala or hippocampal volume in associations between maternal depression and young adult depression or reactive aggression. However, one analysis did support a mediating role for offspring amygdala:hippocampal volume ratio in the association between maternal depression and young adult reactive aggression. Consistent with previously published findings (Bremner et

al., 2003; Lupien et al., 2011), the current study demonstrated links between early adverse caregiving experiences, later anomalies of brain structure, and behavior problems related to emotion regulation. Results suggest that the structure of neural regions in relation to one another, but not in isolation, may mediate these associations.

Maternal Depression and Offspring Depressive Symptoms and Reactive Aggression

The hypothesized link between maternal depression and young adult depressive symptoms was supported in some instances and not others (i.e., in 57 % or 4 of 7 analyses). The hypothesized link between maternal depression and young adult reactive aggressive behaviors also was supported, albeit even less frequently (i.e., in 29 % or 2 of 7 analyses). More specifically, both average overall exposure and chronicity of exposure to maternal depression were associated with higher depressive symptoms in young adult offspring. Contrary to expectations, however, neither average overall exposure to maternal depression nor chronicity of exposure was significantly related to offspring reactive aggression at age 20. The hypothesis that earlier exposure to maternal depression would be most highly correlated with young adult depression and reactive aggression was likewise not supported in analyses of discrete developmental periods. Rather, mothers' depressive symptoms during middle childhood predicted offspring depressive symptoms in early adulthood, whereas mothers' depressive symptoms during early adolescence predicted both depressive symptoms *and* reactive aggressive behaviors. Maternal depression in early childhood and adolescence were not associated with these socioemotional outcomes in adult offspring. It is important to note, however, that while some correlations between maternal depression and offspring socioemotional outcomes were significantly different from zero and others were not, the magnitude of correlations between

maternal depression in any discrete developmental period and young adult outcomes did not differ significantly from one another when Fisher-Z tests were computed.

Although admittedly speculative, it seems possible that exposure to maternal depression during middle childhood and early adolescence might be predictive of depressive symptoms in young adult offspring because older children/pre-teens may be more developmentally apt to attend to, internalize and emulate the modeling of dysregulated affect (as compared with toddlers), and also likely to spend more time in the home environment relative to older adolescents.

While results of analyses involving discrete developmental periods suggested that middle childhood and early adolescence were more important developmental periods for exposure to maternal depression for young adult offspring reactive aggression than early childhood, trajectory analyses suggested that being exposed to maternal depression in early childhood was more critical for offspring reactive aggression among mothers whose levels of maternal depressive symptoms improved after early childhood. Therefore, exploratory post-hoc analyses were conducted to examine whether the relation between exposure to maternal depression in early adolescence and reactive aggression in adulthood was moderated by to levels of maternal depression during early childhood. Specifically, participants were divided into three groups based on their mothers' mean BDI scores during their early childhood. Interestingly, for offspring of mothers with low levels of depressive symptoms during early childhood (i.e., mean scores of ≤ 9, $n = 138$) and for offspring of mothers with high levels of depressive symptoms during early childhood (mean scores of ≥ 16, $n = 18$), correlations between maternal depression in early adolescence and reactive aggression in adulthood were comparable ($r = .23$, $p < .01$ for those with low levels of early childhood depression; $r = .21$, *ns* for those with elevated levels

during early childhood). In contrast, for those participants whose mothers experienced moderate levels of maternal depression during early childhood, maternal depressive symptoms during early adolescence and young adult aggression were negatively correlated (n = 81, r = -.10, *ns*). Based on these analyses, one might speculate that two distinct pathways for increased reactive aggression might be possible. First, 'late-starting' mothers who previously experienced few or no depressive symptoms and whose young adolescent children are at high risk for reactive aggressive types of behaviors might show more depressive symptoms (i.e., child effects). Second, offspring of chronically depressed mothers (although relatively few) might also show elevated rates of reactive aggression. These findings provide additional support for prior research indicating that offspring of depressed parents are not only at increased risk for depression but also antisocial behavior during adolescence (Shaw et al., 2012). These findings are also in line with previous research demonstrating that while children of depressed mothers show elevated rates of both internalizing and externalizing symptoms, there is a tendency for maternal depression to be more strongly linked to internalizing symptoms in girls and externalizing symptoms in boys (Essex et al., 2003).

A four-group trajectory model emerged as the best fit for capturing the chronicity, severity and course of depressive symptoms in this sample of mothers. The largest group, not unexpectedly, was comprised of mothers showing consistently low depressive symptomatology. However, consistent with prior research finding chronically high levels of depressive symptoms in a subset of adult women (Belsher & Costello, 1988; Keller, 2003), one group emerged that showed consistently elevated levels of depressive symptoms (although decreasing during late childhood and adolescence). Finally, two groups showing moderate levels of depressive

symptoms emerged, one of which showed a slight increasing pattern and another of which showed a slight decreasing pattern.

As expected, young men whose mothers showed persistently high depressive symptoms reported more depressive symptoms at age 20 as compared with young men in the persistently low maternal depression group. Regarding reactive aggression, young men in the "moderate-decreasing" group reported significantly more reactive aggressive behavior as compared with those in the "consistently-low" maternal depression group. No other discrete trajectory group comparisons yielded significant differences in reactive aggression. Although counterintuitive, this finding is somewhat consistent with a prior study using this sample in which Gross, Shaw and colleagues (2009) found that sons of mothers in a moderately high maternal depression trajectory group, rather than a persistently high group, showed the most consistently elevated rates of antisocial outcomes during adolescence. Prior theory and evidence have suggested that offspring of chronically depressed mothers may be more likely to understand their parents' behavior as indicative of their illness and/or benefit from other sources of social support (e.g., grandparents) as compared with offspring of moderately depressed mothers (Hammen & Brennan, 2003; Rutter, 1990).

To test the original hypothesis that relatively earlier exposure to maternal depression might be more strongly associated with reactive aggressive behaviors in adulthood, offspring from the two trajectory groups with the highest average maternal depressive symptom counts during early childhood were combined and contrasted with the two groups with the lowest maternal depression counts in early childhood. Offspring from the groups with initially higher (albeit marginally higher with respect to groups 2 and 3) maternal depressive symptoms reported more reactive aggressive behaviors at age 20 as compared with the two groups that showed

initially lower depressive symptomatology. Thus, the trajectory analyses—unlike the analyses of mean overall exposure to maternal depression, chronicity of maternal depression, or exposure during discrete developmental periods—partially supported the hypothesis that relatively earlier exposure to maternal depression would be most highly correlated with reactive aggression. However, in light of the relatively small difference in early childhood maternal depressive symptoms between the "moderate-increasing" and "moderate-decreasing" groups, this finding should be interpreted with caution.

Maternal Depression and Brain Structure in Young Adult Offspring

In contrast to hypotheses, exposure to maternal depressive symptomatology was not associated with young adult amygdala volume or hippocampal volume. Consistent with hypotheses, however, maternal depressive symptoms in early childhood were related to offspring amygdala:hippocampal volume ratio at age 20 in the predicted direction. Likewise, developmental trajectories of maternal depression were not associated with either amygdala or hippocampal volume in early adulthood, but the two trajectory groups with the highest maternal depressive symptoms in early childhood showed higher amygdala:hippocampal volume ratios as compared with the other two groups. This finding is consistent with prior research indicating that infancy and early childhood may constitute a sensitive period for environmental influences on cortical structures (Lupien et al., 2009; Bremner et al., 2003).

It is not entirely clear why relative, but not absolute, subcortical volumetric anomalies were found in adults exposed to early-onset maternal depression. Chronic stress has been associated with hippocampal degeneration (McEwen, 2001; Czeh & Lucassen, 2007) while relative reductions in hippocampal volume have been associated with hyperactivation of the

amygdala (Suzuki et al., 2013). Thus, enlarged amygdala volumes may reflect altered patterns of activation that have been linked with reductions in hippocampal volume, and vice versa.

Brain Structure and Depressive Symptoms and Reactive Aggressive Behaviors in Young Adulthood

The hypothesized link between amygdala and hippocampal volume and depression and reactive aggression in adulthood was partially supported such that, while neither independent amygdala nor hippocampal volumes were related to young adult depressive symptoms or reactive aggressive behaviors, amygdala:hippocampal volume ratio was positively associated with reactive aggression. Previous research has suggested that larger amygdala and smaller hippocampal volumes within the same individual may be more strongly related to problems with emotion regulation as compared with alterations in either structure alone (Gerritsen et al., 2012; MacMillan et al., 2003). It is possible that typical hippocampal structure and functioning might help individuals encode and retrieve contextual information concerning their hostile attributions and matched, aggressive responses, and thereby attenuate any behavioral correlates of enlarged amygdala volume. Amygdala:hippocampal volume ratio did not predict depressive symptoms. The lack of findings of relations between discrete amygdala/hippocampal volumes and depressive and/or reactive aggressive behaviors, while unexpected, is consistent with mixed findings in the extant literature (Anand & Shekhar, 2003; MacMillan et al., 2003; Rosso et al., 2005).

While initial analyses found no direct effects for amygdala and hippocampal volume in relation to reactive aggression, examined within the context of other relevant covariates (e.g., socioeconomic status, intracranial volume), both amygdala and hippocampal volume were related to reactive aggressive behaviors in the predicted direction. Taken together with the ratio

findings, these results suggest that the amygdala and hippocampus are related to reactive aggression, in part, through their relation to one another. Incidentally, when examined within the context of the same covariates (e.g., socioeconomic status, intracranial volume), both amygdala and hippocampal volume were marginally related to young adult depressive symptoms in the predicted direction.

Maternal Depression and Offspring Reactive Aggression Mediated by Brain Structure.

In contrast to expectations, neither amygdala nor hippocampal volume, measured separately, mediated the association between exposure to maternal depression in childhood and adolescence and depressive symptoms or reactive aggressive behavior in young adulthood. However, the relationship between maternal depression trajectory grouping and offspring reactive aggression at age 20 was mediated by amygdala:hippocampal volume ratio. This finding is consistent with previous research indicating that increased amygdala:hippocampal volume ratio is associated with cognitive vulnerabilities for problems related to emotion regulation (i.e., negative memory bias) in non-clinical samples (Gerritsen et al., 2012). However, it is important to note that neuroanatomical data were collected concurrently with self-reports of behavior. Thus, issues related to temporal precedence necessitate further, prospective research to clarify whether amygdala:hippocampal volume ratio represents a marker of vulnerability to reactive aggression, or a marker of learned patterns of hostile/fearful attributions and reactive responses to stimuli, or both.

Limitations and Future Directions.

The current study had several strengths, including the use of a long-term prospective, longitudinal design for assessing relations between maternal depression and the socioemotional outcomes of male offspring who had previously been documented to be at risk for multiple types

of problem behavior, including difficulties with the regulation of emotions, as well as the inclusion of neuroanatomical and behavioral data on offspring at age 20. The sample is particularly large and more ethnically diverse relative to those most frequently seen in neuroimaging studies. It has been argued that brain structure is particularly well-suited as a target for capturing the sensitivity and/or vulnerability of the stress response system, as it is more temporally stable than other indices of biological reactivity (e.g., adrenocortical indices) and may contain valuable evidence about the cumulative results of disruptions of neurobiological processes over time (Whittle et al., 2011). However, the present study also has several limitations. First, the present study examines brain structure and socioemotional outcomes only cross-sectionally (i.e., at one time point in early adulthood), introducing confusion as to whether amygdala:hippocampal volume ratio represents a vulnerability factor (Whittle et al., 2011) or a marker of previous or concurrent symptoms (McKinnon et al., 2009), or both. The present study of high-risk males also may have limited generalizability, particularly in light of research finding sex differences in associations between maternal depressive symptoms and later behavioral outcomes (Gross et al., 2008; Leve et al., 2005), as well as sex differences in the trajectories of brain development (Benes et al, 1994; Giedd et al., 1997; Suzuki et al., 2005). Future prospective studies including male and female samples are needed to clarify whether the relations found amongst maternal depression, brain structure, and youth reactive aggression are age- or sex-dependent.

In summary, the current study was conducted to advance our knowledge of the association between exposure to maternal depression and depressive symptoms and reactive aggressive behaviors in adult offspring, and to determine whether brain structure might mediate that relationship. Exposure to maternal depression, particularly when levels were high beginning

in early childhood, was linked to amygdala:hippocampal volume ratio and depressive symptoms and reactive aggressive behaviors in young adult offspring. In this sample of high-risk, young adult males, amygdala and hippocampal volume were concurrently related to increased rates of reactive aggression, not in isolation, but as a function of their balance in sizes in relation to one another. Amygdala:hippocampal volume ratio also mediated the relation found between exposure to maternal depression and reactive aggression in young adulthood. These findings contribute to our understanding of the structural and functional interrelatedness of the amygdala and hippocampus, particularly as they interact to modulate aggressive types of emotional reactivity. Additionally, these findings indicate that amygdala:hippocampal volume ratios may contribute important information beyond discrete volumes of either structure in isolation. Additional research clarifying ways in which neurobiological and social developmental processes interact in the intergenerational transmission of problems with emotion regulation has the potential to highlight important developmental periods, relationships and behaviors as targets for intervention.

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