Maternal depression in childhood and aggression in young adulthood: evidence for mediation by offspring amygdala–hippocampal volume ratio

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Background: There is abundant evidence that offspring of depressed mothers are at increased risk for persistent behavior problems related to emotion regulation, but the mechanisms by which offspring incur this risk are not entirely clear. Early adverse caregiving experiences have been associated with structural alterations in the amygdala and hippocampus, which parallel findings of cortical regions altered in adults with behavior problems related to emotion regulation. This study examined whether exposure to maternal depression during childhood might predict increased aggression and/or depression in early adulthood, and whether offspring amygdala:hippocampal volume ratio might mediate this relationship. **Methods:** Participants were 258 mothers and sons at socioeconomic risk for behavior problems. Sons' trajectories of exposure to maternal depression were generated from eight reports collected prospectively from offspring ages 18 months to 10 years. Offspring brain structure, aggression, and depression were assessed at age 20 ($n = 170$). **Results:** Persistent, moderately high trajectories of maternal depression during childhood predicted increased aggression in adult offspring. In contrast, stable and very elevated trajectories of maternal depression during childhood predicted depression in adult offspring. Increased amygdala: hippocampal volume ratios at age 20 were significantly associated with concurrently increased aggression, but not depression, in adult offspring. Offspring amygdala: hippocampal volume ratio mediated the relationship found between trajectories of moderately elevated maternal depression during childhood and aggression in adult offspring. **Conclusions:** Alterations in the relative size of brain structures implicated in emotion regulation may be one mechanism by which offspring of depressed mothers incur increased risk for the development of aggression. **Keywords:** Maternal depression, aggression, brain imaging, longitudinal studies.

Introduction

Maternal depression has become a focus of public concern, developmental psychopathology research, and clinical intervention efforts, not only because of its considerable prevalence – nearly 50% of low-income mothers with young children show elevated rates of depressive symptoms (Hall, Williams, & Greenberg, 1985) – but also because of its consistent association with emotional and behavioral problems in offspring (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Shaw, Hyde, & Brennan, 2012). For example, offspring of depressed parents show more persistent and more dysregulated aggression from early to middle childhood relative to offspring of nondepressed parents (Hay, Pawlby, Angold, Harold, & Sharp, 2003; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005; Zahn-Waxler, Iannotti, Cummings, & Denham, 1990). This pattern is particularly problematic because early starting (vs. adolescent-onset) patterns of aggression have been most strongly linked with serious types of violence in adulthood (Odgers et al., 2008). In fact, a recent longitudinal study by Shaw and colleagues found that among multiple risk factors in early childhood, maternal depression was the most consistent predictor of trajectories of antisocial behavior during adolescence (Shaw et al., 2012).

The mechanisms by which offspring of depressed mothers incur this increased risk for persistent aggression are not entirely understood. Depressed mothers show increased rates of unresponsive and rejecting parenting (Field, 1998; Shaw et al., 2012), both of which have been linked with offspring conduct problems in early childhood (Shaw et al., 1998). Furthermore, one longitudinal study found that toddlers of depressed mothers who showed more responsive, proactive parenting showed fewer conduct problems in later childhood (Zahn-Waxler et al., 1990). In addition to parenting practices, chronicity and severity of maternal depressive symptoms have been related to the strength of the association between maternal depression and offspring behavior problems (Brennan et al., 2000). While evidence suggests that greater chronicity of maternal depressive symptoms predicts more severe conduct problems in offspring, results regarding severity are somewhat mixed (Brennan et al., 2000; Shaw, Gross, & Moilanen, 2009). Surprisingly, there is some evidence to suspect that moderately (vs.

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severely) high levels of maternal depressive symptoms may be most strongly linked with later problem behavior (Gross, Shaw, Burwell, & Nagin, 2009; Hammen & Brennan, 2003). As theorized by Rutter (1990), it may be that children of severely depressed mothers are better able to understand their mothers as 'ill,' and thus rely more on others (e.g. fathers, grandparents, themselves) for emotion regulation, whereas children of more moderately depressed mothers may still look to their mothers for support and modeling of emotion regulation skills.

It has also been theorized that maladaptive caregiver-infant emotion regulation processes during the first years of life (i.e. attachment) may result in lasting disruptions in subsequent self-regulatory processes (Sroufe, 2000). Given cooccurring sensitive periods for early socialization processes such as attachment (Goodman & Gotlib, 1999; Hammen & Brennan, 2003) and brain development (Goodman, 2007) during early childhood, there are compelling reasons to suspect that neurodevelopmental processes play a role in the transmission of risk for difficulties with emotion regulation to offspring of depressed mothers. Excessive reactivity of hypothalamic–pituitary–adrenal axis (which includes the amygdala and hippocampus) has been linked with emotionally 'reactive' (but not proactive) types of aggressive behavior (Lopez-Duran, Olson, Hajal, Felt, & Vazquez, 2009). The amygdala facilitates recognition and response to affectively salient (e.g. threatening) stimuli, operating in combination with the hippocampus to modulate the selective encoding of memories and regulation of HPA sensitivity across contexts (Aggleton, 1993; Jacobson & Sapolsky, 1991). Following exposure to an environmental stressor, increased occupation of glucocorticoid receptors in the amygdala facilitates HPA axis activity, whereas occupation of glucocorticoid receptors in the hippocampus inhibits HPA axis activity (i.e. the stress response is 'called off;' Tottenham & Sheridan, 2009). In very early childhood, the limbic system is developing rapidly (Schore, 1994). For this reason, the amygdala–hippocampal complex may be particularly susceptible to the effects of early and chronic stress.

Findings of disrupted hypothalamic-pituitary-adrenal (HPA) axis functioning in offspring of depressed mothers suggest that impairments in parenting may serve as salient stressors in early childhood (Essex, Klein, Cho, & Kalin, 2002; Lupien, King, Meaney, & McEwen, 2000). Rodent studies have found that early life stressors (e.g. maternal separation, unresponsive caregiving) predict subsequent reductions in adult hippocampal volumes and accelerated development and early myelination of the amygdala (Ono et al., 2008; Tottenham & Sheridan, 2009). However, results linking particular kinds of early life stress/trauma to discrete amygdala/hippocampal morphology in humans have been somewhat inconsistent (Woon & Hedges,

2008). Rearing in both Asian and Eastern European orphanages in the first 2 years of life has been associated with relatively enlarged amygdala volumes in late childhood (Tottenham et al., 2010). Similar enlargements of the amygdala have been found in ten-year old children of chronically depressed (vs. nondepressed) mothers, while hippocampal volumes were comparable (Lupien et al., 2011). In contrast, there is some evidence to suggest that morphological differences in the hippocampus associated with early life stress may not emerge until later in development (i.e. adolescence, early adulthood; Andersen & Teicher, 2004). This is perhaps not surprising given its protracted developmental trajectory (i.e. persisting into adulthood) relative to the amygdala (Tottenham & Sheridan, 2009).

Changes in amygdala and hippocampal development in response to early caregiving experiences likely have functional significance, as morphological alterations in these same structures have been linked with problem behavior related to emotional dysregulation in adulthood (Heim, Owens, Plotsky, & Nemeroff, 1997; Kaufman, Plotsky, Nemeroff, & Charney, 2000). The extant literature indicates that aggressive and depressed adults show reductions in hippocampal volume, whereas findings with regard to amygdala volume are somewhat mixed (van Eijndhoven et al., 2009; Hanson et al., in press; Lange & Irle, 2004; Weber, Habel, Amunts, & Schneider, 2008).

More recently, studies of the amygdala and hippocampus have begun to examine these subcortical structures in the context of one another as two parts of a functionally and structurally connected network (Thompson & Swanson, 2010). For example, larger amygdala and smaller hippocampal volumes within the same individual (i.e. larger amygdala:hippocampal volume ratios) have been linked with increased problems related to emotion regulation as compared with alterations in either structure assessed separately (Gerritsen et al., 2012; MacMillan et al., 2003). This is consistent with a growing body of literature indicating that the morphology of neural structures in relation to other structures that are part of functionally or structurally connected systems may have functional significance above and beyond that of alterations in individual structures measured in isolation (Gerritsen et al., 2012; Gur et al., 2004). No study to our knowledge has examined the role of relative amygdala:hippocampal volume ratio in the association between exposure to maternal depression in childhood and aggression during early adulthood.

This study therefore examined direct associations between developmental trajectories of exposure to maternal depression from 1.5 to 10 years (consistent with Lupien et al., 2011) and relative amygdala and hippocampal volume as well as aggression and depression in emerging adulthood in a cohort of high-risk males. Concurrent associations between

amygdala:hippocampal volume ratio and these behavior problems in young adulthood were also assessed. We hypothesized that developmental trajectories characterized by moderately elevated maternal depressive symptoms in early childhood would be most strongly related to aggression and, possibly, depression, in adulthood. We further hypothesized that individual differences in amygdala:hippocampal volume ratio would mediate any relationships found between exposure to maternal depression in development and problem behavior in emerging adulthood. Specifically, on the basis of the perspective proposed by Rutter (1990) and empirical validation of this hypothesis (Gross et al., 2009; Hammen & Brennan, 2003), we anticipated that persistent and moderately elevated levels of maternal depressive symptoms in early and middle childhood (vs. persistently high levels) would directly predict problem behavior in emerging adulthood and that this direct association would be mediated by greater amygdala:hippocampal volume ratio. Adult depression was included as an outcome in addition to aggression because it is also based in difficulties with emotion regulation and can be used to test the specificity of our hypothesized links between exposure to maternal depression in childhood and brain structure and aggression in their adult sons.

Methods
Participants

Participants were 258 mother-son dyads from a longitudinal study of vulnerability to behavior problems in high-risk youth (Shaw, Gilliom, Ingoldsby, & Nagin, 2003). Beginning in 1991, 310 families were recruited from Women, Infants, and Children (WIC) Nutrition Supplement Centers in Pittsburgh on the basis of their high risk for the development of behavior problems (i.e. low income, ≥1 sibling living at home, male sex). 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 (e.g. 36% African American; 5% Biracial; 6% other). All participants provided informed consent, and the study was reviewed and approved by the local IRB.

Mothers' self-report of depressive symptoms were collected at child ages 1.5, 3.5, 5, 5.5, 6, 8, and 10 years. Measures of self-reported depression, delinquency, and aggression as well as neuroanatomical magnetic resonance images were obtained from offspring at age 20.

At age 20, the sample retention rate was 83%, with 258 participants completing behavioral measures and 186 participants completing the MRI scan. Sixteen participants were excluded from MRI analyses for this study. Reasons for exclusion included poor quality scan (n = 1), poor registration to the standard template (n = 12), poor quality of segmentation upon visual inspection (n = 2), and structural anomalies (n = 1). Of the remaining 170 participants, one did not complete the delinquency/aggression measure and five did not complete the depression measure. Therefore, analyses relating brain structure to delinquency/aggression and depression were based on 169 and 165 participants, respectively. There were no significant differences in early childhood socioeconomic status, maternal depression trajectory class or depressive symptoms for participants who completed or did not

complete MRI scans. However, participants without scans reported higher rates of delinquency (F(1, 251)= 4.19, p = .04). This discrepancy was not unexpected, based upon exclusion criteria for scanning (e.g. bullet fragments, history of concussion) and constraints on ability to visit the lab (e.g. legal issues due to criminal activity).

Measures

Maternal depressive symptoms. Mothers completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) at eleven assessments from child ages 1.5 to 10. The BDI consists of 21 items concerning severity of depressive symptoms over the previous 6 months. Items are then summed to generate one factor for depressive symptoms per mother per time point (across eight assessments, α = .87).

Aggression. First, the Self-Report of Delinquency (SRD, Elliott, Huizinga, & Ageton, 1985) was used to assess young adults' overall frequency of antisocial behavior at age 20. The SRD is a self-report questionnaire that assesses frequency of engaging in specific antisocial behaviors over the past year, with items summed to generate an overall delinquency score. Young adults' overall delinquency score includes items concerning reactive types of aggressive behavior (i.e. acts of aggression typically carried out without planning or forethought such as '[hitting] someone with the idea of hurting them') and proactive types of aggressive behavior (i.e. acts of aggression typically carried out with forethought and/or in service of a goal, such as, '[using] a weapon, force, or strong arm methods to get money'), as well as other problem behaviors (α = .90). Next, eight of these items that focused specifically on *reactive* aggression (i.e. not proactive aggressive or other kinds of problem behavior) were selected and summed to generate an 'aggression' factor (α = .75).

Offspring depressive symptoms. The BDI was also used to assess young adult depressive symptoms at age 20 (α = .82).

Amygdala and hippocampal volume. Amygdala and hippocampal volumes were acquired from high-resolution (1.2 × 1 × 1 mm) T1-weighted brain images using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol. Participants were all scanned on the same 3.0 Tesla Siemens TIM Trio magnet at the Magnetic Resonance Research Center at the University of Pittsburgh. FMRIB Software Library's empirically supported, fully automated (FMRIB) Integrated Registration and Segmentation Tool (FIRST; Smith et al., 2004) was used to register and segment subcortical regions, and images were visually inspected to ensure quality of registration and segmentation. Amygdala, hippocampus, thalamus (as a control region), and intracranial volume (ICV; aggregate of gray and white matter and cerebrospinal fluid volumes) were extracted from each participant's image.

Data analytic strategy

To more fully evaluate links between timing, chronicity, and severity of maternal depressive symptoms and offspring aggression and depression at age 20, a semiparametric, group based method (Nagin, 2005) was utilized to identify groups of individuals with similar symptom trajectories. Trajectory groups were dummy-coded and multiple linear regression was used to assess associations between trajectory group membership and amygdala:hippocampal volume ratio as well as aggression and depression. Associations between amygdala: hippocampal volume ratio and self-reports of aggressive

behaviors and depression were assessed using Pearson correlations. Then, mediation analyses were conducted to determine whether amygdala:hippocampal volume ratio statistically accounted for associations between trajectory group membership and aggression/depression. The distribution of product of the coefficients method (PRODCLIN; Tofighi & MacKinnon, 2011) was then used to determine whether mediation was significant. Intracranial volume (ICV) was included as a covariate in exploratory analyses of discrete regional brain volumes, as regional differences in cerebral volume may be confounded by variation in head size (Whitwell, Crum, Watt, & Fox, 2001). To correct for nonnormality of the distribution of the aggression factor from the SRD, scores were transformed by the logarithm function.

Results

A three-group model was chosen on the basis of several theoretical considerations and model fit indices, including its small Bayesian Information Criteria (BIC) value, high posterior probability, and adequate size of its smallest group (Jung & Wickrama, 2008; See Table 1 for model fit indices). Trajectory groups did not differ significantly with regard to socioeconomic status, derived from Hollingshead Index at ages 1.5, 2, and 3.5 (Hollingshead, 1975). Trajectory group 1 ($n = 184$; 59.8% of the sample) was characterized by consistently low depressive symptoms throughout the assessment period ($M = 4.15$), and will be referred to as the 'low' group. Group 2 ($n = 104$; 32.5%), referred to as the 'moderate' group, showed

moderately elevated BDI symptom counts ($M = 10.68$) with a slight decreasing pattern of symptoms from early childhood through adolescence. Group 3 ($n = 23$; 7.7%) reported extremely high symptoms ($M = 20.45$), which decreased across the course of development, and is called the 'high' group (See Figure 1). Table 2 provides descriptive statistics and correlations between the study's primary independent and dependent variables. As expected, no relationships were found between thalamic or intracranial volume and any of the study's primary variables. Participants' aggression scores were highly correlated with their reports of delinquency ($r = .74$, $p < .01$), and young adult depressive symptoms were correlated with both aggression and overall SRD score ($r = .38$ and $.40$, respectively, both $p < .01$). Table 3 provides descriptive statistics by trajectory group.

Maternal depression, aggression, and brain structure in early adulthood

When mean scores for aggression in adult offspring were compared by trajectory group using ANOVA, a nonsignificant trend was found overall ($F(2, 250) = 2.69$, $p = .070$); however, follow-up t-tests between individual groups revealed that young men in the moderate maternal depression group showed significantly higher rates of aggression at age 20 as compared with young men in the low maternal depression group ($\beta = .14$, $t(253) = 2.18$, $p = .03$). Comparisons among other groups were not significant. Likewise, while the ANOVA predicting offspring depressive symptoms at age 20 by trajectory group yielded only a nonsignificant trend overall $F(2, 250) = 2.95$, $p = .054$, follow-up t-tests indicated that young men in the high maternal depression trajectory class showed higher rates of depressive symptoms at age 20 compared to young men in the low maternal depression group ($\beta = .15$, $t(250) = 2.34$, $p = .02$). Again, comparisons among the other groups were not significant.

Table 1 Model fit indices and diagnostic statistics

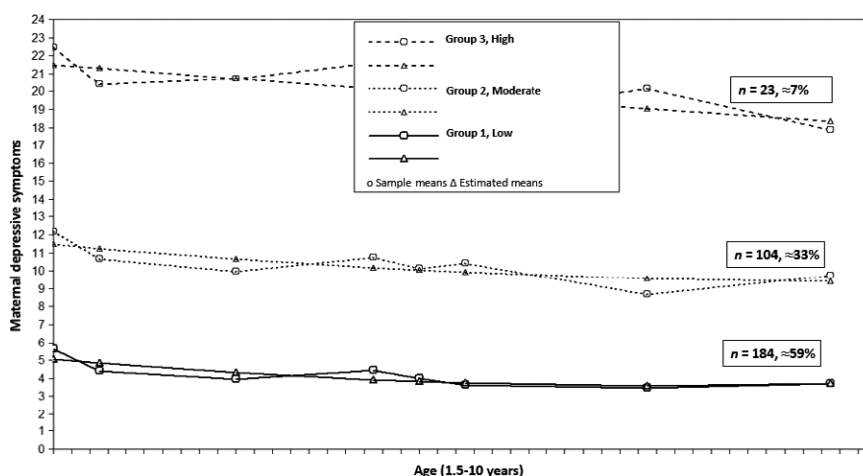| # of classes	BIC*	Average posterior probability	Smallest number assigned to a group
1	14124.523		
2	13432.541	0.93	71
3	13132.689	0.89	23
4	13131.119	0.90	15
5	13088.696	0.89	2

*BIC, Bayesian Information Criteria value.

Figure 1 Maternal depression trajectory classes from child ages 1.5–10

Table 2 Descriptives and pearson correlations between dependent variables

	N	M (SD)	1	2	3	4
1. Ratio of Amygdala: Hippocampal Volume	170	.35 (.06)				
2. Aggression Factor (log-transformed)	253	.99 (.06)	.19[a]			
3. Overall SRD at Age 20	253	63.42 (8.89)	.08	.74[b]		
4. Youth BDI at Age 20	253	5.44 (6.28)	.12	.38[b]	.40[b]	

SRD, Self-Report of Delinquency; BDI, Beck Depression Inventory.
[a]Correlation is significant at the .05 level (2-tailed).
[b]Correlation is significant at the .01 level (2-tailed).

Table 3 Descriptive statistics by maternal depression trajectory class

Group	Amyg:Hipp Ratio; M (SD)	Amygdala volume in mm^3; M (SD)	Hippocampal volume in mm^3; M (SD)	Aggression (Log); M (SD)	Total SRD M (SD)	BDI M (SD)
1	.35 (.05)	2767.87 (438.22)	8012.69 (846.48)	.98 (.06)	62.78 (8.08)	4.78 (5.47)
2	.37 (.07)	2865.96 (561.04)	7857.42 (893.30)	1.00 (.07)	64.53 (9.73)	5.82 (6.94)
3	.37 (.06)	2829.00 (569.12)	7715.40 (906.32)	1.00 (.07)	63.00 (10.28)	8.42 (7.73)

SRD, Self-Report of Delinquency; BDI, Beck Depression Inventory.

Maternal depression trajectory groups did not discriminate discrete amygdala or hippocampal volume in adult offspring, but showed a nonsignificant trend for discriminating amygdala:hippocampal ratios ($F(2, 167) = 2.63$, $p = .075$). Furthermore, follow-up t-tests revealed that young men in the moderate maternal depression group showed significantly higher amygdala:hippocampal volume ratios at age 20 compared to young men in the low maternal depression group ($\beta = .17$, $t(167) = 2.17$, $p = .03$). Comparisons among other groups were not significant.

Amygdala:hippocampal volume ratio was positively associated with aggression in the predicted direction ($r = .19$, $p = .016$). Amygdala:hippocampal volume ratio was not linked to general delinquency or depression. Neither discrete amygdala nor hippocampal volumes, measured separately, were related to young adult delinquency, aggression, or depression.

Mediation by amygdala:hippocampal volume ratio

Next, we assessed whether the relationship between moderate (vs. low) maternal depression trajectory class and aggression might be mediated by amygdala:hippocampal volume. As hypothesized, the standardized regression coefficient between trajectory class and aggression ($\beta = .14$, $p = .03$) decreased substantially when controlling for amygdala:hippocampal volume ($\beta = .03$, ns), becoming nonsignificant. In addition, R^2 change statistics revealed that the inclusion of trajectory groupings in the regression model to amygdala:hippocampal volume ratio did not contribute significant variance to young adult aggression (R^2 change value = .004). The mediation of amygdala:hippocampal volume ratio on the effect of maternal depression trajectory

class on aggression was found to be significant using the distribution of product of the coefficients method (CI [.000244, .008876]; PRODCLIN; Tofighi & MacKinnon, 2011). See Figure 2.

Discussion

The purpose of this study was to examine whether developmental trajectories of exposure to maternal depression in childhood would be associated with individual differences in brain structure (i.e. amygdala:hippocampal volume ratio) and problem behavior in a sample of young men. An additional aim of this study was to assess whether individual differences in brain structure would mediate the relationship between exposure to maternal depression and young adult problem behavior. Developmental trajectories of exposure to maternal depression characterized by moderate elevations of maternal depressive symptoms throughout childhood predicted larger amygdala:hippocampal volume ratios and increased self-report of aggression in emerging adulthood. In contrast, persistently high rates of maternal depressive symptoms across childhood predicted offspring depressive symptoms in emerging adulthood. Amygdala:hippocampal volume ratios were positively related to young adult aggression but not depression. Results support a mediating role for offspring amygdala:hippocampal volume ratio in the association between exposure to maternal depression in childhood and aggression in emerging adulthood.

Although omnibus tests of the association between trajectories of maternal depression and offspring aggression at age 20 were not significant, young men in the moderate maternal depression group reported significantly more aggressive
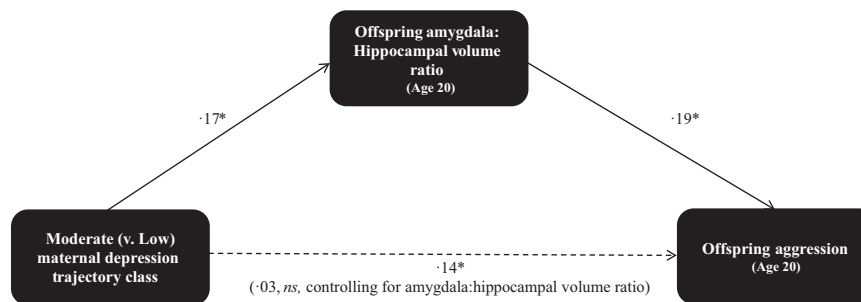
Figure 2 Mediation model for moderate (vs. low) maternal depression trajectory, offspring amygdala: hippocampal volume ratio at Age 20, and self-reported aggression at age 20. *Correlation is significant at the .05 level (2-tailed)

behavior as compared with those in the low maternal depression group. No other discrete trajectory group comparisons yielded significant differences in aggression. While this finding is somewhat counter-intuitive and should be interpreted with consideration of the modest (i.e. trend level) association between trajectories of maternal depression, as a whole, and adult offspring aggression, this finding is also consistent with some extant evidence (Gross et al., 2009; Hammen & Brennan, 2003). For example, a previous study of this sample found that moderately high (vs. low or severe) trajectories of maternal depression during childhood were most strongly related to earlier kinds of antisocial behavior in their adolescent sons (Gross et al., 2009). Consistent with the theoretical perspective of Rutter (1990), moderate maternal depressive symptoms may be strong enough to affect parenting practices, but not to result in someone else taking the role of primary caregiver. Thus, offspring of caregivers with moderate (vs. extremely high) levels of depression might be more likely to be exposed to unresponsive or rejecting parenting.

This finding may be specific to reactive types of offspring aggression (vs. depression or general delinquency), despite its considerable correlation with the overall delinquency factor ($\beta = .38*$ and $.74**$, respectively). High (not moderate) trajectories of maternal depressive symptoms during childhood were most strongly linked with depression at age 20. Although admittedly speculative, this is consistent with evidence that the heritability of depression may vary with severity of symptoms, such that severe (vs. mild/moderate) depression is more heritable and more strongly linked with genetic and nonshared (e.g. not family) environmental factors (Lyons et al., 1998). Thus, despite inevitable confounding of genetic and socialization processes, our trajectory analyses may give reason to suspect that shared environmental factors across childhood (e.g. parenting) might be relatively less important for intergenerational transmission of depression as compared with genetic predisposition for the disorder. In contrast, our trajectory analyses may suggest that shared environmental factors (e.g. impaired parenting related to moderate

depressive symptomatology) could be relatively more important in offspring's incurring risk for aggression. With regard to general delinquency, one might speculate that reactive aggressive (vs. 'proactive', i.e. calculated or goal-driven) behaviors are more susceptible to the effects of early disruptions in dyadic emotion regulation processes. Thus, the specificity of the present results could be speculated to provide support for links between depression-related disruptions in the parenting of mothers (who may still be 'well' enough to act as the primary caregiver) and persistent, reactive types of aggression in offspring. Albeit modest in size, these findings suggest that moderate/subclinical levels of maternal depressive symptoms may constitute a particular risk for long-term patterns of dysregulated affect regulation and related aggression in offspring, and therefore merit consideration alongside more severe depressive symptomatology as a target of prevention and intervention efforts for children with dysregulated or reactive types of aggression. Future research should further explore whether family/social support (e.g. fathers, grandparents, siblings) might mediate the relationship found between moderate levels of maternal depressive symptomatology and offspring reactive aggression, perhaps by giving children an alternative referent for learning emotion regulation skills.

Results also add to an increasing literature finding that relative volume of neural structures in relation to other functionally/structurally connected systems may have greater functional significance as compared with alterations in individual structures (Gerritsen et al., 2012; Gur et al., 2004). The present finding of a significant positive correlation between amygdala:hippocampal volume ratio and self-reported reactive aggression adds to extant evidence that relative amygdala and hippocampal volume may be more strongly linked with emotional dysregulation as compared with volumetric alterations of either structure assessed separately (MacMillan et al., 2003). Given the interrelated but opposing roles of the amygdala and hippocampus in HPA axis stress response (activation and deactivation, respectively), it may be that altered

amygdala:hippocampal volume ratios reflect or even cause some imbalance in the functioning of this circuit and associated emotion regulation processes.

This 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 at high risk for problem behavior, as well as the inclusion of both neuroanatomical and behavioral data on offspring at age 20. The sample is particularly large and ethnically diverse relative to those of many neuroimaging studies. In addition, 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, findings should be interpreted with caution given the lack of any formal correction for multiple comparisons in regression analyses. However, of the twelve total tests conducted (five main effect; six follow-up *t*-tests; 1 test for mediation), one would expect about one test to be significant by chance. Here, five hypothesized relationships were significant. Second, while we chose to focus on an all-male sample because boys are at higher risk for the development of antisocial behavior (Patterson, De-Baryshe, & Ramsey, 1989), findings have limited generalizability to mixed-sex samples in light of sex differences in associations between maternal depressive symptoms and later behavioral outcomes (Gross, Shaw, & Moilanen, 2008) and trajectories of brain development (Giedd, Castellanos, Rajapakse, Vaituzis, & Rapoport, 1997). For example, there is evidence to suggest that sensitivity to the effects of disrupted parenting behaviors may be more strongly linked with hippocampal volumes in females as compared with males (Whittle et al., 2011). Third, it is unclear what cellular properties contribute to the relative alterations in amygdala and hippocampus volume observed (e.g. cell number, dendritic branching). Fourth, additional studies should assess whether structural alterations in other brain regions implicated in organizing behavior in response to emotionally salient information (e.g. the orbitofrontal cortex; Smith, Stephan, Rugg, & Dolan, 2006) might modulate the relationships found in the present study. Finally, the present study's examination of brain structure and socio-emotional outcomes only cross-sectionally, without longitudinal measurement of brain structure throughout development, introduces inferential limitations. Future prospective studies including mixed-sex samples are needed to clarify whether the relations found among maternal depression, brain structure, and youth aggression are age- or sex-dependent and/or modifiable with early intervention.

Conclusions

This study helps clarify interrelationships among chronic exposure to moderate maternal depressive symptoms, relative size of brain structures implicated in emotion regulation, and aggression in adult male offspring. Although additional, prospective research is needed to delineate ways in which neurobiological and social developmental processes interact in the intergenerational transmission of problems with emotion regulation, the present findings suggest regions of interest for longitudinal neuroimaging efforts to explore whether these relative cortical morphological alterations constitute risk factors (e.g. neural profiles that confer increased vulnerability to the effects of stressful experiences) or consequences (e.g. more stressful life circumstances) of aggressive behavior. A better understanding of the mechanisms linking exposure to maternal depression to offspring aggression could help highlight symptom profiles and developmental periods as targets for prevention and intervention efforts, and also reveal mechanisms by which empirically supported prevention and interventions efforts work. The present findings suggest that interventions to reduce maternal depressive symptoms during childhood could be particularly important for preventing, not only the disruption of important socialization processes but also long-term alterations in offspring cortical morphology and behavior.

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Key points

- Offspring of depressed mothers show higher rates of aggression.
- Early adverse caregiving experiences have been linked with structural alterations in the amygdala and hippocampus, which parallel findings of regional alterations in emotionally dysregulated adults.
- The present study finds direct links between moderately elevated maternal depressive symptoms in childhood and increased offspring amygdala:hippocampal volume ratio as well as aggressive behavior in early adulthood.
- Amygdala:hippocampal volume ratio is positively correlated with reactive aggression in emerging adulthood, and, furthermore, mediates the association found between moderate maternal depression during childhood and aggressive behavior in adult offspring.
- These findings suggest mechanisms by which exposure to maternal depression during childhood may be related to long-term patterns of offspring neural development and behavior.
- Future, longitudinal neuroimaging studies are needed to clarify how and when regional brain volumes develop in relation to one another and maternal depressive symptoms over the course of childhood and adolescence.

References

Aggleton, J.P. (1993). The contribution of the amygdala to normal and abnormal emotional states. *Trends in Neurosciences, 16*, 328–333.

Andersen, S.L., & Teicher, M.H. (2004). Delayed effects of early stress on hippocampal development. *Neuropsychopharmacology, 29*, 1988–1993.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571.

Brennan, P.A., Hammen, C., Andersen, M.J., Bor, W., Najman, J.M., & Williams, G.M. (2000). Chronicity, severity, and timing of maternal depressive symptoms: Relationships with child outcomes at age 5. *Developmental Psychology, 36*, 759.

van Eijndhoven, P., van Wingen, G., van Oijen, K., Rijpkema, M., Goraj, B., Verkes, R.J., … & Tendolkar, I. (2009). Amygdala volume marks the acute state in the early course of depression. *Biological Psychiatry, 65*, 812–818.

Elliott, D.S., Huizinga, D., & Ageton, S.S. (1985). *Explaining delinquency and drug use.* Thousand Oaks, CA: Sage.

Essex, M.J., Klein, M.H., Cho, E., & Kalin, N.H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. *Biological Psychiatry, 52*, 776–784.

Field, T. (1998). Maternal depression effects on infants and early interventions. *Preventive Medicine, 27*, 200–203.

Gerritsen, L., Rijpkema, M., van Oostrom, I., Buitelaar, J., Franke, B., Fernández, G., & Tendolkar, I. (2012). Amygdala to hippocampal volume ratio is associated with negative memory bias in healthy subjects. *Psychological Medicine, 42*, 335–343.

Giedd, J.N., Castellanos, F.X., Rajapakse, J.C., Vaituzis, A.C., & Rapoport, J.L. (1997). Sexual dimorphism of the developing human brain. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 21*, 1185–1201.

Goodman, S.H. (2007). Depression in mothers. *Annu. Rev. Clin. Psychol, 3*, 107–135.

Goodman, S.H., & Gotlib, I.H. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review, 106*, 458–490.

Gross, H.E., Shaw, D.S., Burwell, R.A., & Nagin, D.S. (2009). Transactional processes in child disruptive behavior and maternal depression: A longitudinal study from early childhood to adolescence. *Development and Psychopathology, 21*, 139–156.

Gross, H.E., Shaw, D.S., & Moilanen, K.L. (2008). Reciprocal associations between boys' externalizing problems and mothers' depressive symptoms. *Journal of Abnormal Child Psychology, 36*, 693–709.

Gur, R.E., Kohler, C., Turetsky, B.I., Siegel, S.J., Kanes, S.J., Bilker, W.B., … & Gur, R.C. (2004). A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. *Biological Psychiatry, 55*, 512–517.

Hall, L.A., Williams, C.A., & Greenberg, R.S. (1985). Supports, stressors, and depressive symptoms in low-income mothers of young children. *American Journal of Public Health, 75*, 518–522.

Hammen, C.L., & Brennan, P.A. (2003). Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Archives of General Psychiatry, 60*, 253–258.

Hanson, J.L., Nacewicz, B.M., Sutterer, M.J., Cayo, A.A., Schaefer, S.M., Rudolph, K.D., … & Davidson, R.J. (In Press). Behavior problems after early life stress: Contributions of the hippocampus and amygdala. *Biological Psychiatry.*

Hay, D.F., Pawlby, S., Angold, A., Harold, G.T., & Sharp, D. (2003). Pathways to violence in the children of mothers who were depressed postpartum. *Developmental Psychology, 39*, 1083–1094.

Heim, C., Owens, M.J., Plotsky, P.M., & Nemeroff, C.B. (1997). The role of early adverse life events in the etiology of depression and posttraumatic stress disorder: Focus on corticotropin-releasing factor. *Annals of the New York Academy of Sciences, 821*, 194–207.

Hollingshead, A.B. (1975). Four factor index of social status. Self-published.

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews, 12*, 118–134.

Jung, T., & Wickrama, K.A.S. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass, 2*, 302–317.

Kaufman, J., Plotsky, P.M., Nemeroff, C.B., & Charney, D.S. (2000). Effects of early adverse experiences on brain structure and function: Clinical implications. *Biological Psychiatry, 48*, 778–790.

Kim-Cohen, J., Moffitt, T.E., Taylor, A., Pawlby, S.J., & Caspi, A. (2005). Maternal depression and children's antisocial behavior: Nature and nurture effects. *Archives of General Psychiatry, 62*, 173–181.

Klein, D., Lewinsohn, P., Rohde, P., Seeley, J., & Olino, T. (2005). Psychopathology in the adolescent and young adult offspring of a community sample of mothers and fathers with major depression. *Psychological Medicine, 35*, 353–365.

Lange, C., & Irle, E. (2004). Enlarged amygdala volume and reduced hippocampal volume in young women with major depression. *Psychological Medicine, 34*, 1059–1064.

Lopez-Duran, N.L., Olson, S.L., Hajal, N.J., Felt, B.T., & Vazquez, D.M. (2009). Hypothalamic pituitary adrenal axis functioning in reactive and proactive aggression in children. *Journal of Abnormal Child Psychology, 37*, 169–182.

Lupien, S.J., King, S., Meaney, M.J., & McEwen, B.S. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biological Psychiatry, 48*, 976–980.

Lupien, S.J., Parent, S., Evans, A.C., Tremblay, R.E., Zelazo, P.D., Corbo, V., . . . & Seguin, J.R. (2011). Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences, 108*, 14324–14329.

Lyons, M.J., Eisen, S.A., Goldberg, J., True, W., Lin, N., Meyer, J.M., . . . & Tsuang, M.T. (1998). A registry-based twin study of depression in men. *Archives of General Psychiatry, 55*, 468–472.

MacMillan, S., Szeszko, P.R., Moore, G.J., Madden, R., Lorch, E., Ivey, J., & Rosenberg, D.R. (2003). Increased amygdala: Hippocampal volume ratios associated with severity of anxiety in pediatric major depression. *Journal of Child and Adolescent Psychopharmacology, 13*, 65–73.

Nagin, D.S. (2005). *Group-based modeling of development.* Cambridge, MA: Harvard University Press.

Odgers, C.L., Moffitt, T.E., Broadbent, J.M., Dickson, N., Hancox, R.J., Harrington, H., . . . & Caspi, A. (2008). Female and male antisocial trajectories: From childhood origins to adult outcomes. *Development and Psychopathology, 20*, 673–716.

Ono, M., Kikusui, T., Sasaki, N., Ichikawa, M., Mori, Y., & Murakami-Murofushi, K. (2008). Early weaning induces anxiety and precocious myelination in the anterior part of the basolateral amygdala of male Balb/c mice. *Neuroscience, 156*, 1103–1110.

Patterson, G.R., DeBaryshe, B.D., & Ramsey, E. (1989). A developmental perspective on antisocial behavior. *American Psychologist, 44*, 329.

Rutter, M. (1990). Commentary: Some focus and process considerations regarding effects of parental depression on children. *Developmental Psychology, 26*, 60.

Schore, A.N. (1994). *Affect regulation and the origin of the self: The neurobiology of emotional development.* Hillsdale, NJ: Erlbaum.

Shaw, D.S., Gilliom, M., Ingoldsby, E.M., & Nagin, D.S. (2003). Trajectories leading to school-age conduct problems. *Developmental Psychology, 39*, 189–200.

Shaw, D.S., Gross, H., & Moilanen, K. (2009). Developmental transactions between boys' conduct problems and mothers' depressive symptoms. In A. Sameroff (Ed.), *Transactional processes in development* (pp. 77–96). Washington, DC: American Psychological Association.

Shaw, D.S., Hyde, L.W., & Brennan, L.M. (2012). Early predictors of boys' antisocial trajectories. *Development and Psychopathology, 24*, 871–888.

Shaw, D.S., Winslow, E.B., Owens, E.B., Vondra, J.I., Cohn, J.F., & Bell, R.Q. (1998). The development of early externalizing problems among children from low-income families: A transformational perspective. *Journal of Abnormal Child Psychology, 26*, 95–107.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., . . . & Matthews, P.M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage, 23*, 208–219.

Smith, A.P., Stephan, K.E., Rugg, M.D., & Dolan, R.J. (2006). Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron, 49*, 631–638.

Sroufe, L.A. (2000). Early relationships and the development of children. *Infant Mental Health Journal, 21*, 67–74.

Thompson, R.H., & Swanson, L.W. (2010). Hypothesis-driven structural connectivity analysis supports network over hierarchical model of brain architecture. *Proceedings of the National Academy of Sciences, 107*, 15235–15239.

Tofighi, D., & MacKinnon, D.P. (2011). RMediation: An R package for mediation analysis confidence intervals. *Behavior Research Methods, 43*, 692–700.

Tottenham, N., & Sheridan, M.A. (2009). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Frontiers in Human Neuroscience, 3*, 68.

Tottenham, N., Hare, T.A., Quinn, B.T., McCarry, T.W., Nurse, M., Gilhooly, T., . . . & Casey, B.J. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental Science, 13*, 46–61.

Weber, S., Habel, U., Amunts, K., & Schneider, F. (2008). Structural brain abnormalities in psychopaths—A review. *Behavioral Sciences & the Law, 26*, 7–28.

Whittle, S., Yap, M.B., Sheeber, L., Dudgeon, P., Yücel, M., Pantelis, C., . . . & Allen, N.B. (2011). Hippocampal volume and sensitivity to maternal aggressive behavior: A prospective study of adolescent depressive symptoms. *Development and Psychopathology, 23*, 115–129.

Whitwell, J.L., Crum, W.R., Watt, H.C., & Fox, N.C. (2001). Normalization of cerebral volumes by use of intracranial volume: Implications for longitudinal quantitative MR imaging. *American Journal of Neuroradiology, 22*, 1483–1489.

Woon, F.L., & Hedges, D.W. (2008). Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. *Hippocampus, 18*, 729–736.

Zahn-Waxler, C., Iannotti, R.J., Cummings, E.M., & Denham, S. (1990). Antecedents of problem behaviors in children of depressed mothers. *Development and Psychopathology, 2*, 271–291.