ORIGINAL ARTICLE

Interaction of Parenting Experiences and Brain Structure in the Prediction of Depressive Symptoms in Adolescents

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Context: Although some evidence suggests that neuroanatomic abnormalities may confer risk for major depressive disorder, findings are inconsistent. One potential explanation for this is the moderating role of environmental context, with individuals differing in their biological sensitivity to context.

Objective: To examine the influence of adverse parenting as an environmental moderator of the association between brain structure and depressive symptoms.

Design: Cross-sectional measurement of brain structure, adverse parenting, and depressive symptoms in early adolescents.

Setting: General community.

Participants: A total of 106 students aged 11 to 13 years (55 males [51%]), recruited from primary schools in Melbourne, Australia, and their mothers. Selection was based on affective temperament, aimed at producing a sample representing a broad range of risk for major depressive disorder. No participant evidenced current or past case-level depressive, substance use, or eating disorder.

Main Outcome Measures: (1) Volumetric measures of adolescents' amygdala, hippocampus, and anterior cingulate cortex (ACC); (2) frequency of observed maternal aggressive behavior during a mother-adolescent conflict-resolution interaction; and (3) adolescent depressive symptoms.

Results: Boys with smaller right amygdalas reported more depressive symptoms. However, neither hippocampal volume nor asymmetry measures of limbic or paralimbic ACC were directly related to level of depressive symptoms. Importantly, frequency of maternal aggressive behaviors moderated the associations between both the amygdala and ACC, and adolescent symptoms. Particularly, in conditions of low levels of maternal aggressiveness, boys with larger right amygdalas, girls with smaller bilateral amygdalas, and both boys and girls with smaller left paralimbic ACC reported fewer symptoms.

Conclusions: These findings help elucidate the complex relationships between brain structure, environmental factors, and depressive symptoms. Further longitudinal research is required to examine how these factors contribute to the onset of case-level disorder, but given that family context risk factors are modifiable, our findings do suggest the potential utility of targeted early parenting interventions.

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NEUROIMAGING TECHniques have elucidated neuroanatomic correlates of major depressive disorder (MDD),[1,2] with structural abnormalities in the amygdala, hippocampus, and anterior cingulate cortex (ACC) hypothesized to underlie deficits in affective processing and regulation. Findings have been inconsistent, however, with regard to the direction of abnormalities (ie, greater vs lesser volume) with regard to the amygdala,[3,4] hippocampus,[5-7] and ACC.[8-12] Although there are likely to be a number of factors contributing to these inconsistencies, 2 key issues stand out. First, it is unclear whether the observed neuroanatomic abnormalities represent a vulnerability to MDD, underlie symptoms, or are secondary to other pathogenic processes. There is some evidence that volumes of these structures reflect levels of symptoms,[13,14] and both twin studies and studies investigating young first-episode patients provide support for volumetric changes in these structures being associated with trait or vulnerability factors for disorder.[8,15,16] Studies of brain structure in young healthy individuals with varying levels of depressive symptoms might be particularly useful to help elucidate these issues.

Second, environmental moderators may have an influence on brain-disorder asso-

ciations. That is, certain neuroanatomic features might be associated with disorder only in the context of particular environmental circumstances. This was demonstrated, for example, in a study of depressed women in whom reduced hippocampal volume, relative to healthy controls, was observed only in the subset of depressed women with a history of child abuse.[17] To date, there have been few other studies investigating the impact of environmental moderators on brain-disorder associations.

Diathesis-stress models suggest that individual differences in susceptibility to environmental experiences may be due to phenotypic differences.[18,19] To the extent that neuroanatomic abnormalities are predisposing factors for psychopathologic changes, such abnormalities may be conceptualized as biological diatheses that confer heightened risk in the context of environmental stressors. To this end, it has been proposed that genetic influences on hippocampal volume may play a causal role in psychopathologic changes by sensitizing the individual to stressful environmental circumstances.[20] Notably, some researchers propose that the effects of biological reactivity to the environment on psychiatric and biomedical outcomes are bivalent, giving rise to negative outcomes under adverse conditions and positive outcomes under low-stress conditions.[21]

There is evidence that brain volumes are highly heritable,[22] and deviant brain structure or function may constitute useful intermediate phenotypes for identifying the neurobiological pathways that represent genetic susceptibility to mood disorders.[23] Specifically, brain morphologic characteristics may serve as useful endophenotypes with which to test the moderating effects of the environment on the link between biological features and disorder.

Although a wide range of environmental factors are related to risk for mood disorders,[24] a substantial body of research indicates that the family affective climate, including the nature of parent-child interactions, is a particularly important predictor of internalizing problems and depression in young people.[25-27] Specifically, parenting characterized by high conflict or negativity has been found to predict depression in children and adolescents in prospective studies.[28-30]

This article explores parenting behavior as a developmentally salient environmental moderator of the brain-depression association in a community sample of young people who vary widely in their depressive symptoms. We examine the frequency of harsh parenting as a potential moderator of brain volume–depression associations, specifically the amygdala, hippocampus, and ACC. We use an observational measure of harsh maternal behaviors directed at the target adolescent, derived during a conflictual mother-adolescent interaction task. We hypothesize that, while there may be direct associations among the volume of selected brain structures, parenting, and adolescent depressive symptoms, the interaction between brain volume and parenting will explain additional variance in symptoms. Given research indicating sex differences in adolescent brain development,[31] brain correlates of affective processes,[32] sensitivity to disturbances in parent-child interactions,[33] and depressive symptoms,[34] sex differences in the associations between these brain structures, parenting, and adolescent depressive symptoms were also examined.

METHODS

PARTICIPANTS

The sample consisted of 106 adolescents (55 males [51%]; 102 self-identified as Australian [96%]; mean [SD] age, 12.5 [0.5] years; range, 11.4-13.6 years) recruited from schools across metropolitan Melbourne, Australia. Adolescents were recruited as part of a broader adolescent development study (see Yap et al[35] for further details) such that those with particularly high, and particularly low, temperamental risk for mental health problems were oversampled, while those with intermediate levels of risk were undersampled, resulting in a distribution of temperamental risk that retained the variance associated with the larger screening sample (n=2453) but was still normally distributed. Using the Edinburgh Handedness Inventory,[36] we identified 99 students as right-handed and 7 as left-handed. Participants were screened for Axis I disorders by trained research assistants using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic Version.[37] Ten participants met criteria for a psychiatric diagnosis (past separation anxiety disorder, n=1; social phobia, n=1; attention-deficit/hyperactivity disorder, n=1; obsessive-compulsive disorder, n=2; oppositional defiant disorder, n=1; and past oppositional defiant disorder, n=4). A small number of participants reported minimal past cigarette smoking (n=2) or alcohol consumption (n=6). Informed consent was obtained from all participants (adolescent and parent), in accordance with the guidelines of the Human Research Ethics Committee of the University of Melbourne.

FAMILY INTERACTIONS

Procedure

Adolescents and their mothers participated in a 20-minute problem-solving interaction, which was videotaped for coding purposes. Topics for the interaction were identified on the basis of parent and adolescent responses to the Issues Checklist,[38] which comprises 44 topics about which adolescents and parents may disagree, such as "[adolescent] lying" and "[adolescent] talking back to parents." Up to 5 Issues Checklist issues rated as conflictual (and recent) by parent and adolescent were chosen for dyads to discuss and resolve during the problem-solving interaction.

Observational Coding of Family Interactions

The affective and verbal content of the interactions were coded with the use of the Living in Familial Environments[39] coding system. This is an event-based coding system in which new codes are entered each time the affect or verbal content of the participant changes. The system consists of 10 affect and 27 verbal content codes. The index of aversive parenting was rate per minute of a composite construct of maternal aggressive behavior, which includes all events with contemptuous, angry, and belligerent affect, as well as disapproving, threatening, or argumentative verbal content with neutral affect. Higher frequency of negative parental behaviors distinguishes abusive and neglectful families from controls[40] and is associated with poorer cognitive and psychosocial outcomes in children.[41,42]

Video recordings were coded by 2 specially trained research assistants blind to participant characteristics (eg, symptom levels) and study hypotheses. Approximately 20% of the interactions were coded by a second observer to provide an estimate of observer agreement. The κ coefficient for the aggressive composite code was 0.77, which reflects good to excellent agreement.[43]

NEUROIMAGING

Image Acquisition

Magnetic resonance imaging was performed on a 3-T scanner (General Electric, Milwaukee, Wisconsin), using a gradient echo volumetric acquisition sequence (repetition time, 36 milliseconds; echo time, 9 milliseconds; flip angle, 35°; field of view, 20 cm^2; pixel matrix, 410×410) to obtain 124 T1-weighted contiguous 1.5-mm-thick sections (voxel dimensions, 0.4883×0.4883×1.5 mm).

Image Preprocessing

Image preprocessing was carried out with tools from the FMRIB software library (http://www.fmrib.ox.ac.uk/fsl/). Each 3-dimensional image was stripped of all nonbrain tissue,[44] aligned to the Montreal Neurological Institute 152 average template (6-parameter rigid body transform with trilinear interpolation) by means of the Flexible Image Registration Toolbox,[45] and resampled to 1 mm^3. This registration served to align each image axially along the anterior commissure–posterior commissure plane and sagittally along the interhemispheric fissure without any deformation.

Morphometric Analysis

Regions of interest (ROIs) were defined and quantified on the basis of previously published techniques (see the following paragraphs). All ROIs were traced by one of us (S.W.) on each individual's images by using the software package ANALYZE (Mayo Clinic, Rochester, Minnesota; http://mayoresearch.mayo.edu/mayo/research/robb_lab/). Brain tissue was segmented into gray matter, white matter, and cerebrospinal fluid by means of an automated algorithm, as implemented in FAST (FMRIB's [Oxford Centre for Functional MRI of the Brain] Automated Segmentation Tool.[46] An estimate of whole brain volume was obtained by summing gray and white matter pixel counts (ie, whole brain volume included cerebral gray and white matter, the cerebellum, and brainstem, but not the ventricles, cisterns, or cerebrospinal fluid). The ACC estimates were based on gray matter pixel counts contained within the defined ROIs. Amygdala and hippocampal estimates were based on total voxels within the defined ROI.

Amygdala, Hippocampus, and ACC

The guidelines for tracing the amygdala and hippocampus were adapted from those described by Velakoulis and colleagues.[47,48] These structures were traced on contiguous coronal sections. The boundaries of the amygdala were defined as follows: posterior, first appearance of gray matter above the temporal horn; lateral, temporal stem; and medial, the semilunar gyrus superiorly and subamygdaloid white matter inferiorly. Guidelines for marking the anterior boundary of the amygdala and the boundary between the amygdala and hippocampus differed slightly from those of Velakoulis and colleagues to maximize reliability. The anterior boundary of the amygdala was identified as the section posterior to the most posterior of either the point where the optic chiasm joins, or the point where the lateral sulcus closes to form the endorhinal sulcus. The protocol of Watson et al[49] was used to separate the amygdala from the hippocampus. This protocol involves using the uncal recess of the temporal horn, the alveus, or the semilunar gyrus as the inferior boundary of the amygdala, depending on the visibility of these features.

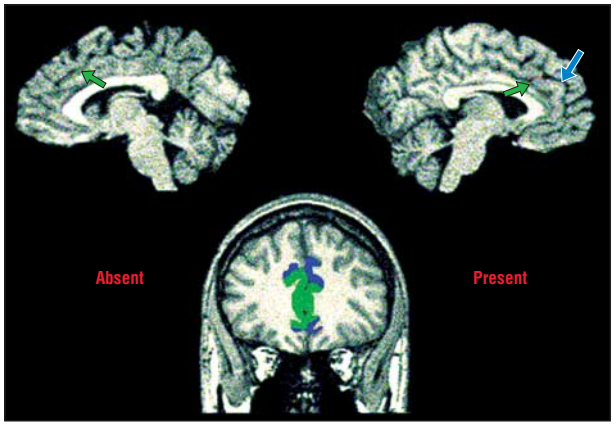

Figure 1. Example of changes in the location and extent of the limbic (ACC_L; highlighted in green) and paralimbic (ACC_P; highlighted in blue) anterior cingulate cortices as a function of variations in the cingulate sulcus (CS; green arrow, top row) and paracingulate sulcus (PCS; blue arrow, top row). A PCS is absent at left and present at right. The top 2 images present parasagittal sections through an individual's T1-weighted image. The coronal section illustrates the distinction between cases with absent (left) and present (right) PCS. Notice that the ACC_P is buried in the depths of the CS when the PCS is absent and extends over the paracingulate gyrus when the PCS is present. The same principle applies throughout consecutive coronal sections.

Hippocampal tracings included the hippocampus proper, the dendate gyrus, the subiculum, and part of the fimbria and alveus. Boundaries were defined as follows: posterior, section with the greatest length of continuous fornix; lateral, temporal horn; medial, open end of the hippocampal fissure posteriorly and the uncal fissure anteriorly; and superior, fimbria and alveus posteriorly and amygdala anteriorly.

The boundaries of the ACC have been described in detail by Fornito et al.[50] This protocol demarcates limbic (ACC_L) and paralimbic (ACC_P) portions of the ACC by taking into account individual differences in morphologic characteristics of the cingulate (CS), paracingulate (PCS), and superior rostral (SRS) sulci. Tracing was initially performed on contiguous sagittal sections, and the medial borders were edited on coronal sections. The anterior ACC_L contained all gray matter in the gyrus bound by the callosal sulcus and the CS. The borders of the ACC_P depended on the course of the PCS and SRS. The PCS was considered present or prominent if it ran parallel to the CS for at least 20 mm or at least 40 mm, respectively. Segmented sections were considered part of the PCS if they were 10 mm or greater and separated from other segments by 10 mm or less. For cases where the PCS was present or prominent, the ACC_P contained all gray matter in the gyrus bound by the CS and PCS. For cases where the PCS was either absent or not parallel along the full length of the CS, in those sections in which the PCS was absent the ACC_P included only the gray matter on the upper bank of the CS. The SRS was classified either as continuous with the CS or separate from it. In the former case, the inferior part of the ACC_P region included only gray matter on the upper bank of the CS; in the latter case, the inferior part of the ACC_P comprised gray matter between the CS and SRS. See **Figure 1** for illustration.

ADOLESCENT DEPRESSIVE SYMPTOMS

The Center for Epidemiological Studies–Depression Scale, Revised[51] has been found to be valid and reliable for adolescents.[52] In the current sample, the Cronbach α was 0.89 and scores ranged from 0 to 55 (mean, 11.58; SD, 9.54).

Table 1. Brain Measures and Tests for Sex Differences

Brain Measure[a]	Full Sample		Boys		Girls		Sex Difference	
	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	*t*	*P* Value
Left amygdala volume, mm^3	**106**	1882.44 (265.51)	55	1935.96 (263.60)	51	1824.73 (257.79)	4.81	.03
Right amygdala volume, mm^3	**106**	1844.80 (277.91)	55	1844.80 (277.91)	51	1784.37 (260.36)	1.33	.25
Left hippocampus volume, mm^3	**106**	2776.03 (323.50)	55	2820.75 (317.63)	51	2727.80 (325.92)	2.21	.14
Right hippocampus volume, mm^3	**106**	2937.24 (354.54)	55	2961.40 (356.48)	51	2911.18 (354.10)	0.53	.47
ACC_L asymmetry index	**104**	−315.16 (2386.42)	53	−672.67 (2260.72)	51	56.36 (2477.94)	2.46	.12
ACC_P asymmetry index	**101**	370.87 (2259.92)	50	441.78 (2159.52)	51	301.35 (2373.66)	0.10	.76
Maternal aggressive frequency	**106**	1.30 (0.61)	55	1.31 (0.61)	51	1.29 (0.60)	0.04	.84
Adolescent depressive symptoms, No.	**106**	11.46 (9.50)	55	12.14 (9.21)	51	10.72 (9.84)	0.58	.45

Abbreviations: ACC_L, limbic anterior cingulate cortex; ACC_P, paralimbic anterior cingulate cortex.
[a] Anterior cingulate cortex data were missing for some participants because of visualization or delineation difficulties.

STATISTICAL ANALYSIS

Interrater and intrarater reliabilities were assessed by means of the intraclass correlation coefficient (absolute agreement) using 15 brain images from a separate magnetic resonance imaging database established for this purpose. Intraclass correlation coefficient values (14 of 16 <0.90 and none <0.85) were acceptable for all ROIs. Removing the 8 left-handed participants' data from analyses did not change the pattern of results, so we have reported results from the full set of data.

Given literature suggesting that asymmetry of ACC volume may be important for aspects of executive functioning[50] and affect regulation,[53] which may in turn have implications for mood disorders, ACC volume asymmetries were also investigated. An asymmetry index was calculated for the ACC_L and ACC_P by using the formula left minus right. All brain structural measures were corrected for whole-brain size by means of a covariance adjustment method.[54] Hypotheses were tested with 6 hierarchical linear regressions, with parenting and adolescent brain structure variables used as predictors of adolescent depressive symptoms. For each regression, adolescent sex, maternal aggressive behavior, and one of the brain structure measures (ie, left or right amygdala volume, left or right hippocampal volume, and ACC_L or ACC_P asymmetry index) were entered in step 1. The three 2-way interaction terms (parenting × adolescent sex, brain × sex, and parenting × brain) were entered in step 2, and the parenting × brain × sex interaction term was entered in step 3. Interaction terms were computed after centering all continuous variables. Significant sex interactions were followed up with regression analyses for males and females separately (with parenting and the appropriate brain variable entered in step 1 and the interaction entered in step 2). Significant parenting × brain and 3-way interactions were probed following recommendations by Aiken and West,[55] with the use of O'Connor's SPSS macros[56] to compute simple slope analyses. Following Cohen and Cohen's[57] guidelines, f^2 is taken as the index of the effect size of interactions, whereby an f^2 value of 0.02 is small, 0.15 is medium, and 0.35 is large. Because changes in structural brain asymmetry may result from changes in the size of either or both hemispheres,[58] significant main effects or interactions involving asymmetry variables were followed up with 2 hierarchical regressions using left and right hemisphere ROI volumes as predictors of adolescent depressive symptoms (along with sex, parenting, and the 2- and 3-way interactions).

RESULTS

Table 1 shows means, standard deviations, and sex differences in all variables. The only significant sex difference was in the volume of the left amygdala, with boys having a larger amygdala than girls.

AMYGDALA

As summarized in **Table 2**, in analyses for the left and right amygdala, greater frequency of maternal aggressive behaviors and the 3-way interaction term (amygdala × parenting × sex) were associated with more adolescent depressive symptoms. Right amygdala volume was also negatively associated with depressive symptoms, although follow-up analyses showed that this was significant for boys but not girls. Follow-up analyses on the significant 3-way interaction showed that, in boys, only the right amygdala × parenting interaction was significant ($\beta = 0.35$, $t_{52} = 2.81$, $P = .007$, $f^2 = 0.16$). In girls, both the left and right amygdala × parenting interactions predicted depressive symptoms ($\beta = -0.44$, $t_{47} = -3.82$, $P < .001$, $f^2 = 0.30$; and $\beta = -0.46$, $t_{47} = -3.91$, $P < .001$, $f^2 = 0.34$, respectively).

Significant interactions were interpreted by plotting the simple regression lines for the high (+1 SD), average (mean), and low (−1 SD) values of maternal aggressive frequency.[55] Equations were then used to plot values of adolescent depressive symptoms at high, average, and low values of maternal aggressive frequency and at high (+2 SDs) and low (−2 SDs) values of (left or right) amygdala volume. Two-tailed *t* tests showed that, for boys, the slopes of the regression lines at low ($\beta = -0.70$, $t_{51} = -3.95$, $P < .001$) and average ($\beta = -0.37$, $t_{51} = -2.99$, $P = .004$) values of maternal aggressive frequency were significantly different from zero (**Figure 2**). Hence, while boys with a smaller right amygdala reported more depressive symptoms, in the context of low to average levels of maternal aggressiveness, larger right amygdala was also associated with fewer symptoms.

For girls, both the low ($\beta = 0.46$, $t_{47} = 2.69$, $P = .01$) and high ($\beta = -0.36$, $t_{47} = -2.56$, $P = .01$) maternal aggressiveness slopes were significant for the right amygdala (**Figure 3**). Similarly, both the low ($\beta = 0.56$, $t_{47} = 3.16$, $P = .003$) and high ($\beta = -0.30$, $t_{47} = -2.12$, $P = .04$) maternal aggressiveness slopes were significant for the left amygdala (graph similar to Figure 3, thus not shown). Hence, in girls exposed to high levels of maternal aggressiveness, there was a significant negative association be-

Table 2. Summary of 6 Regressions Predicting Adolescent Depressive Symptoms With Brain Measures and MAF[a]

Regressions	β	*t*	*P* Value	Δ*F*	ΔR^2
Regression 1 (n=106)					
Step 1				4.04	0.11
Left amygdala	−0.11	−1.11	.27		
MAF	0.29	3.19	.003		
Step 3: Left amygdala × MAF × sex	0.43	3.34	.001	11.18	0.08
Regression 2 (n=106)					
Step 1				5.83	0.15
Right amygdala	−0.23	−2.47	.02		
MAF	0.29	3.13	.002		
Step 3: Right amygdala × MAF × sex	0.59	4.75	<.001	22.54	0.15
Regression 3 (n=106)					
Step 1				3.60	0.10
Left hippocampus	−0.02	−.19	.85		
MAF	0.30	3.16	.002		
Regression 4 (n=106)					
Step 1				3.59	0.10
Right hippocampus	0.02	.17	.87		
MAF	0.30	3.18	.002		
Step 2: MAF × sex	−0.29	−2.11	.04	1.79	0.05
Regression 5 (n=104)					
Step 1				3.52	0.10
ACC_L asymmetry	−0.08	−.84	.40		
MAF	0.30	3.11	.002		
Step 2: ACC_L asymmetry × MAF	0.19	1.97	.05	3.80	0.10
Regression 6 (n=101)					
Step 1				4.06	0.11
ACC_P asymmetry	0.10	1.09	.28		
MAF	0.31	3.23	.002		
Step 3: ACC_P asymmetry × MAF × sex	−0.29	−2.13	.04	4.54	0.04

Abbreviations: ACC_L, limbic anterior cingulate cortex; ACC_P, paralimbic anterior cingulate cortex; Δ, change; MAF, maternal aggressive frequency.

[a]The first step in each model included adolescent sex coded as 1 for male and 0 for female, but it had no significant effects and hence is not shown here. Only significant interactions are shown. Change in *F* and R^2 values for 2-way interactions refer to effects of all 2-way interaction variables in that block, whereas the values for 3-way interactions are specific to the corresponding 3-way interaction variable. The ACC data were missing for some participants because of visualization or delineation difficulties.

tween amygdala volume and depressive symptoms. Conversely, in the context of low maternal aggressiveness, there was a positive association between amygdala volume and depressive symptoms.

HIPPOCAMPUS

As before, greater frequency of maternal aggressive behaviors was associated with more adolescent depressive symptoms. In addition, the parenting × sex interaction was significant in the model with the right hippocampus. Follow-up regressions showed that higher maternal aggressive frequency was associated with more depressive symptoms for girls ($\beta = 0.49$, $t_{49} = 3.92$, $P < .001$). Hippocampal volumes were not associated with depressive symptoms either as main effects or in interaction with the other variables.

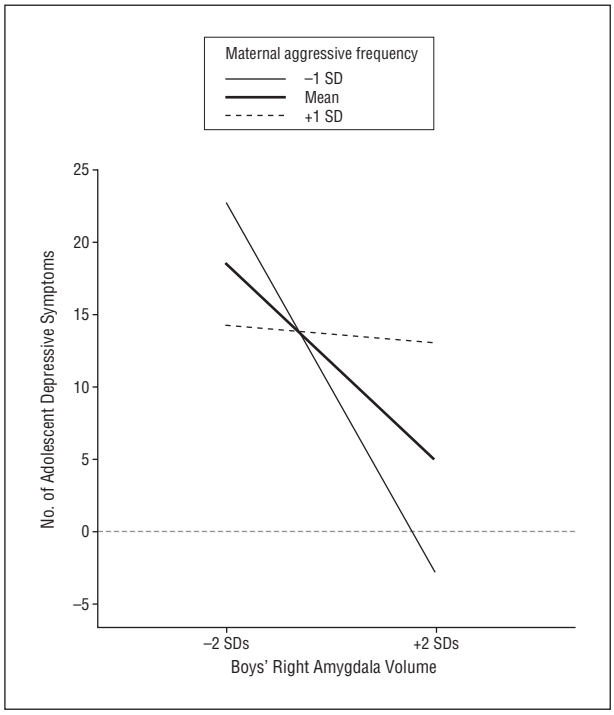

Figure 2. Plots of simple slopes showing the interaction between maternal aggressive frequency and the volume of boys' right amygdala predicting adolescent depressive symptoms (score on the Center for Epidemiological Studies–Depression Scale).

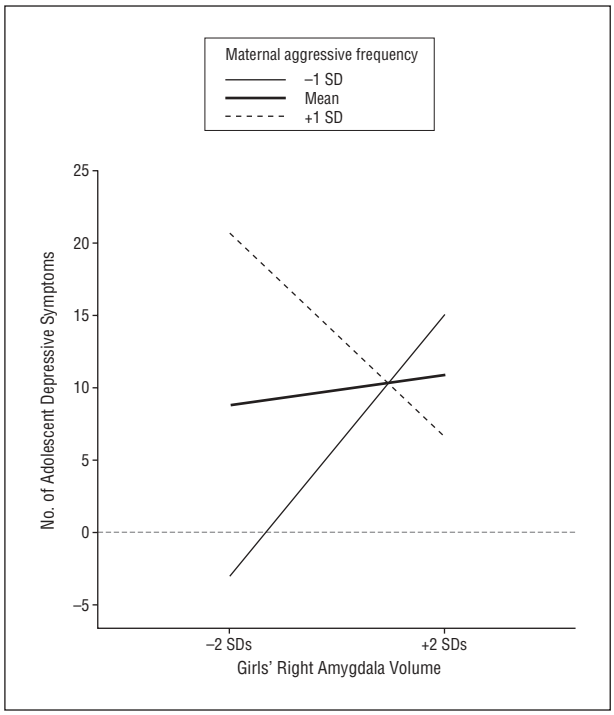

Figure 3. Plots of simple slopes showing the interaction between maternal aggressive frequency and the volume of girls' right amygdala predicting adolescent depressive symptoms (score on the Center for Epidemiological Studies–Depression Scale).

ANTERIOR CINGULATE CORTEX

Again, greater frequency of maternal aggressive behaviors was associated with more adolescent symptoms. Neither

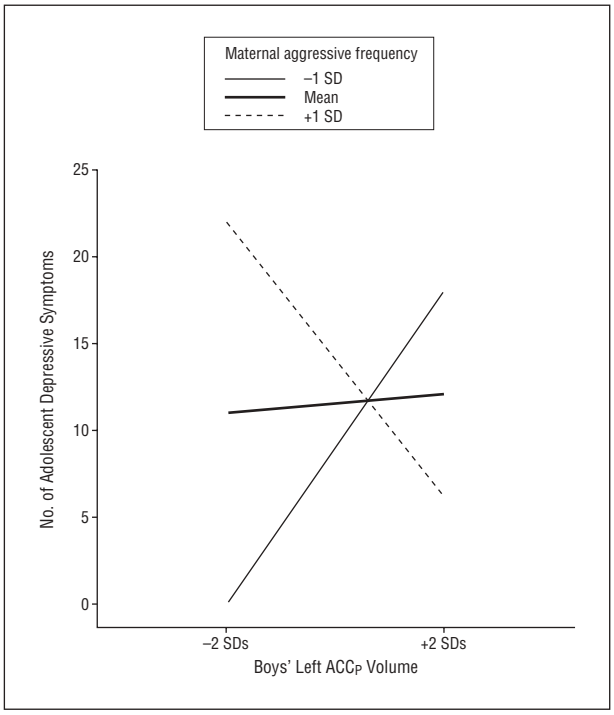

Figure 4. Plots of simple slopes showing the interaction between maternal aggressive frequency and the volume of boys' left paralimbic anterior cingulate cortex (ACC_P) region predicting adolescent depressive symptoms (score on the Center for Epidemiological Studies–Depression Scale).

asymmetry measure was significantly associated with depressive symptoms, but the ACC_P asymmetry × parenting × sex interaction term was. Follow-up analyses showed that the asymmetry × parenting interaction was significant for boys ($\beta = -0.37$, $t_{46} = -2.26$, $P = .03$, $f^2 = 0.11$) but not girls ($\beta = 0.06$, $t_{47} = 0.48$, $P = .63$). Further analyses were conducted to see whether the 3-way interaction effect was driven by the left or right ACC_P. Only the left ACC_P × parenting interaction was significantly associated with depressive symptoms ($\beta = -0.40$, $t_{50} = -2.86$, $P = .006$, $f^2 = 0.16$). The plot for the left ACC_P × parenting interaction for boys is shown in **Figure 4**. Only the slope for low maternal aggressiveness was significantly different from zero ($\beta = 0.50$, $t_{50} = 2.57$, $P = .01$). Hence, among adolescent boys exposed to low levels of maternal aggressiveness, there was a significant positive association between the left ACC_P volume and depressive symptoms.

COMMENT

In a nonclinical sample of early adolescents, there was no direct relationship between adolescent depressive symptoms and the volumes of the amygdala, hippocampus, or ACC. However, boys with smaller right amygdalas, and adolescents whose mothers displayed more frequent aggressive behaviors during a conflict resolution interaction, reported more depressive symptoms. In addition, significant interaction effects showed that amygdala volume and ACC asymmetry were associated with depressive symptoms in the context of certain levels of maternal aggressiveness, suggesting that these structures may represent markers of biological sensitivity to the parenting context.[21]

AMYGDALA

The direct association between a smaller right amygdala and elevated depressive symptoms in boys is consistent with previous findings.[59] The moderation of associations between amygdala volume and symptoms by family context and sex suggests that these factors may help account for null or contradictory findings in previous studies. Our findings indicate that, in boys overall, while a larger right amygdala is associated with reduced depressive symptoms, among boys with a larger than average right amygdala, low levels of aggressive maternal behavior further reduce the risk for symptoms. In girls, although a smaller amygdala is not directly associated with elevated symptoms, it may engender sensitivity to the effects of family affective environment. That is, girls with smaller amygdalas report more symptoms only if their mothers are frequently aggressive toward them. This is consistent with evidence from the developmental literature that girls may be more susceptible to the effect of negative family interactions[60,61] and points toward a potential neurobiological mechanism for this sex difference. Moreover, there are indications in these findings that, among girls, smaller amygdala volume is also associated with especially low levels of depressive symptoms when paired with low levels of maternal aversiveness. This suggests that smaller amygdalas might be a neuroanatomic marker of general sensitivity to environmental influences, consistent with the "differential susceptibility" hypothesis,[21,62] which proposes that some individuals (for biological reasons) are more susceptible than others to positive as well as negative aspects of the environment. It has been speculated that "sensitivity" might result from increased attention or hyperreactivity to stress.[21,62] Whether or how these factors are related to volumetric measures of the amygdala is not clear, but it is interesting that the amygdala has been noted to have distinct functions with regard to attention to environmentally salient stimuli.[63]

Notably, boys and girls benefit differentially from low levels of aversive parenting—boys with larger right amygdalas vs girls with smaller right and left amygdalas benefit more. Alternatively, boys with larger right amygdalas vs girls with smaller bilateral amygdalas may have a greater biological sensitivity to the parenting context (ie, both harmful and helpful aspects of parenting).[21] These findings add to the literature suggesting sex differences in amygdala functioning,[64] although the exact nature of these differences remains unclear. It is possible that sex differences in the rate of amygdala development during adolescence may contribute to this pattern of findings.[65,66] Longitudinal research is required to investigate the developmental trajectories of these associations.

HIPPOCAMPUS

Contrary to expectations, the hippocampus was not associated with depressive symptoms, either directly or in interaction with the parenting environment. Previous studies of hippocampal volume involving pediatric and early-onset MDD samples have been mixed, with some showing no alterations[7,59] and others finding smaller hippocampal volumes.[67-69] Because the participants in the current study were not experiencing case-level disorders, our

findings suggest that hippocampal volume is not associated with levels of depressive symptoms that are below threshold for clinical diagnosis. This is in line with the neurotoxicity hypothesis of trauma or pathogenic environments on the hippocampus,[70] suggesting that hippocampal neurodegeneration may result from severe stress associated with prolonged or recurrent psychopathologic features, or exposure to trauma. It is possible that adverse parenting as measured in this study is not a severe enough stressor to produce neurotoxic effects on the hippocampus. Alternatively, if hippocampal volume loss is an indication of an early phase of MDD or an MDD subtype, our findings may indicate that these participants are not at risk for developing such psychopathologic characteristics.

ANTERIOR CINGULATE CORTEX

The finding for paralimbic ACC volume asymmetry suggested that boys with a smaller left than right ACC_P were more sensitive to the effects of maternal aggressiveness, and this appeared to be driven by a reduction in left ACC_P volume specifically. In these individuals, low maternal aggressiveness was associated with fewer depressive symptoms. The lateralization of our finding is consistent with research showing predominantly left lateralized ACC volumetric abnormalities in MDD. Furthermore, previous research has indicated that a reduced leftward asymmetry of the PCS (which is associated with reduced size of the left ACC_P) characterizes those (particularly males) experiencing or at risk for a range of psychopathologic changes.[71-73] Moreover, there is evidence that individuals with smaller left ACC_P perform poorly on tasks of executive functioning[74] and are temperamentally prone to the experience of high negative affect.[75] The present result suggests that this structural brain feature is not necessarily associated with adverse outcomes, but rather may be associated with sensitivity to environmental factors, such that it may be related to positive outcomes given favorable environmental circumstances.[21,62]

The significance of the male specificity of our finding for the ACC_P requires further investigation; however, we speculate that this result may reflect a sensitivity engendered by the testosterone-mediated developmental lag of the male left hemisphere, which has been suggested to increase the sensitivity of this hemisphere to environmental input.[76]

Because subthreshold depressive symptoms are an early sign of a number of disorders other than MDD (eg, schizophrenia[77] and bipolar disorder[78]), the results of this study may also have implications for understanding the etiology of these disorders. In particular, our findings may provide insight into the role of the family environment in the etiologic path by which ACC structure is associated with schizophrenia. Bipolar disorders, on the other hand, may have a distinct neuroanatomic profile, particularly with regard to the course of changes in structure of the amygdala and hippocampus over the course of the disorder.[4] Longitudinal work is crucial to investigate these complex associations.

In any case, the present results suggest that early interventions that target aversive parenting in families of young people at risk for a number of psychopathologic changes may prove to be beneficial.

LIMITATIONS

The cross-sectional design of the study precludes us from drawing strong conclusions regarding the causality of relationships. That is, whether changes in regional brain volume and maternal aggressive behaviors result from, or represent early predictors of, adolescent depressive problems remains unclear. Furthermore, the marked brain reorganization and sex differences in brain development occurring during adolescence[79,80] may complicate the interpretation of findings. Finally, given the genetic contribution to brain structure, risk for psychopathologic changes, and the family environment, family history of psychopathologic characteristics may covary with some of the relationships examined herein.[81] Longitudinal assessment of parenting, brain structure, and depressive symptoms or disorder, as well as assessment of family history of psychopathologic features, is needed to resolve these issues.

A further limitation of the study concerns the generalizability of results because selection was biased to oversample adolescents with "extreme" temperaments. Further research will be required to assess the association between brain structure, parenting, and depressive symptoms in representative adolescent population samples. Another issue relevant to generalizability is that only 1 type of environmental stressor, the maternal-child relationship, was examined. Although this relationship is of particular relevance to depressive symptoms in adolescence, the patterns of results may not be generalizable to other important environmental factors such as, for example, experiences of abuse. It is also important to acknowledge that laboratory-based interactions likely differ from those that occur in day-to-day interactions. Nevertheless, laboratory-based family interactions have good predictive and convergent validity with other measures of these processes as well as with depressive syndromes, suggesting that they capture valid and important information regarding family interactions.[82,83]

Finally, a large number of analyses were conducted, raising the possibility of type 1 error. Our goal was to discover plausible patterns of interaction between environmental and biological factors, and thereby inform future more detailed research. The presentation of analyses in the current article ensures that the reader is aware of the full range of analyses that were performed; however, because of the risk of type 1 error, we emphasize the need for replication.

CONCLUSIONS

Our findings suggest that structural features of the amygdala and ACC are phenotypic markers of sensitivity to the parenting environment in a nonclinical sample of adolescents with no history of MDD. Marked sex differences in the nature of the reported associations and interactions were found. The findings suggest that taking environmental factors into consideration when examining brain/disorder associations may facilitate a clearer un-

derstanding of the nature of these associations. Low levels of aversive parenting may have protective effects for adolescents with a heightened biological sensitivity to the parenting context. Because these family context risk factors are modifiable,[84] these findings suggest the potential of targeted parenting interventions with families of at-risk adolescents.

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