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Brain Volume Abnormalities in Youth at High Risk for Depression: Adolescent Brain and Cognitive Development Study

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Objective: Children of parents with depression are two to three times more likely to develop major depressive disorder than children without parental history; however, subcortical brain volume abnormalities characterizing major depressive disorder risk remain unclear. The Adolescent Brain and Cognitive Development (ABCD) Study provides an opportunity to identify subcortical differences associated with parental depressive history.

Method: Structural magnetic resonance data were acquired from 9- and 10-year-old children (N = 11,876; release 1.1, n = 4,521; release 2.0.1, n = 7,355). Approximately one-third of the children had a parental depressive history, providing sufficient power to test differences in subcortical brain volume between low- and high-risk youths. Children from release 1.1 were examined as a discovery sample, and we sought to replicate effects in release 2.0.1. Secondary analyses tested group differences in the prevalence of depressive disorders and clarified whether subcortical brain differences were present in youths with a lifetime depressive disorder history.

Results: Parental depressive history was related to smaller right putamen volume in the discovery (release 1.1; $d = -0.10$) and replication (release 2.0.1; $d = -0.10$) samples. However, in release 1.1, this effect was driven by maternal depressive history ($d = -0.14$), whereas in release 2.0.1, paternal depressive history showed a stronger relationship with putamen volume ($d = -0.09$). Furthermore, high-risk children exhibited a near twofold greater occurrence of depressive disorders relative to low-risk youths (maternal history odds ratio =1.99; paternal history odds ratio = 1.45), but youths with a lifetime depressive history did not exhibit significant subcortical abnormalities.

Conclusion: A parental depressive history was associated with smaller putamen volume, which may affect reward learning processes that confer increased risk for major depressive disorder.

Key words: ABCD, adolescent depression, dorsal striatum, subcortical brain volume, ventral striatum

J Am Acad Child Adolesc Psychiatry 2020;59(10):1178–1188.

Depression is a common, debilitating disorder with onset typically during adolescence.[1-3] Although the etiology of major depressive disorder (MDD) is complex, a parental history of MDD is one of the strongest known risk factors. Children of parents with depression are two to three times more likely to develop MDD than children of parents with no history of depression.[4,5] A maternal history of depression is particularly depressogenic such that 20% to 40% of offspring of mothers with depression develop MDD or other mental disorders in their lifetime.[6-8] Despite this consistent finding, the neural mechanisms that underlie increased risk remain unclear.

A substantial body of research among adolescents and adults has investigated neuroanatomical abnormalities in MDD, particularly in subcortical regions.[9] However, fewer studies have examined these structural differences in unaffected individuals at high risk for depression. Results have been largely mixed in samples with or at risk for depression, potentially due to sample sizes (<200 participants) that limit power to detect effects that are presumed to be small.[9-11] Additionally, heterogeneity in disease course (eg, age of onset, number of episodes, comorbidity) and treatment history (eg, antidepressant medication may protect against volume loss[12]) undoubtedly affect the reliable identification of structural abnormalities. The Adolescent Brain and Cognitive Development (ABCD) Study is a large normative cohort project that includes structural magnetic resonance imaging (MRI) data and assessments of lifetime mental disorders in 9- and 10-year-old children (N = 11,876). It provides a unique opportunity and sufficient power to identify associations between brain structure and depression risk even with small effect sizes and to address heterogeneity in a representative population. We used ABCD Study data to probe subcortical brain volume in youths at high

risk for depression by virtue of having a parental history of depression and additionally tested whether subcortical abnormalities were related to children's lifetime depression history.

Subcortical Brain Volume and Depression

Research probing subcortical structural differences in depression has yielded mixed results. Although smaller amygdala volume is often highlighted in youths[13] and adults with depression,[14,15] several studies report no volumetric differences compared with healthy adolescents[16,17] or adults[18-21] (corroborated in several meta-analyses[9,22-24]). However, evidence suggests that the occurrence of multiple depressive episodes is associated with decreased amygdala volume,[14,15,25] particularly in female participants,[26] and potentially greater decline in gray matter density over time.[27] To further complicate these mixed findings, antidepressant medication use is associated with larger amygdala volumes, whereas nonuse is associated with smaller volumes relative to healthy adults.[28]

More consistent evidence highlights hippocampal differences, which may affect episodic memory and stress regulation in MDD.[29] Relative to healthy individuals, youths[16,17,30,31] (c.f. [13,32]) and adults with depression exhibit smaller hippocampal volumes[12,20,33,34] (c.f. [18,26,35]); these findings have been supported by several meta-analyses[22,36,37] (c.f. [23]). Again, a range of factors may obscure group differences, including age,[18] recurrence,[9] duration of illness,[38] remission status,[19] and antidepressant effects (which may protect against hippocampal volume loss[12]). Collectively, these findings generally support smaller hippocampal volume in MDD, but research in unaffected individuals at high risk may serve to disambiguate whether hippocampal differences are a cause or consequence of MDD.

Structural abnormalities within the dorsal (caudate, putamen) and ventral (nucleus accumbens) striatum have been equivocal. Data suggest smaller caudate volume in adolescents with depression[32,39] and smaller caudate and putamen volume in adults with depression compared with healthy individuals.[22-24,40,41] Yet, other work finds no significant differences,[9,42-44] differences by sex,[45] or associations with key clinical variables (eg, illness course, medication use).[46] To our knowledge, no study of adults with depression has shown differences in the nucleus accumbens.[9] Although most research suggests no significant differences in pallidum volumes in adults with depression,[9,46] postmortem data suggest reduced pallidum volume in individuals with depression.[47] Greater pallidum volumes in youths with depression were identified in one study but were not significant when covarying for socioeconomic status.[32] Other data suggest that thalamic volume decreases with age in youths with depression, whereas youths without a depressive history show the opposite effect.[48] Yet, thalamic gray matter volume is seemingly unaltered in adults with depression[9,23,24,40] with the exception of a small portion of the anterior thalamic nucleus.[33,49]

Subcortical Brain Volume in High-Risk Youths

Neuroanatomical research examining high-risk children and adolescents (owing to a family history of MDD) is comparably equivocal. In healthy, high-risk adolescents, there are reports of greater amygdala volumes relative to low-risk adolescents.[50] Other findings suggest decreases in amygdala volume in high-risk adolescents who developed MDD relative to participants who remained healthy during the follow-up period.[51] Hippocampal findings also are mixed when comparing high- with low-risk youths, suggesting decreased volume[52,53] or no volumetric differences.[50,54] Data regarding other subcortical regions in high-risk youths are lacking. As a whole, although subcortical brain volume is likely altered among individuals with depression as well as individuals at risk for depression, widespread inconsistencies underscore the need for research using larger samples to elucidate which biomarkers precede MDD onset.

MDD and High-Risk Youths

Prior research has shown greater MDD prevalence in high-risk individuals, but these studies have often relied on older populations of adolescents and adults with relatively small sample sizes (eg, [4,7,55]). We leveraged ABCD data to clarify whether the prevalence of mental disorders, particularly MDD, differed among low- and high-risk children before the typical escalation of disorder onset during the transition from middle to late adolescence.[2] Moreover, we tested whether subcortical differences identified in youths at high risk for MDD were present in individuals with a personal lifetime depressive history. Showing the same subcortical brain volume differences in youths at high risk for MDD with a lifetime depressive history would not definitively clarify whether the abnormalities are a cause vs consequence of MDD, but it would provide key information about how early these differences can be detected.

Goals of the Current Study

ABCD Study data were used to compare children at low vs high risk based on a parental depressive history. In light of prior research (eg, [4,7,9]), the primary aim was to test whether a parental depressive history was associated with children's subcortical brain volume (ie, amygdala, hippocampus, striatum [caudate, nucleus accumbens, putamen], pallidum, and thalamus volumes). We examined children from the initial ABCD release 1.1 as a discovery sample to test subcortical differences in low- and high-risk youths. Then

we sought to replicate these effects examining children from ABCD release 2.0.1. Secondary analyses tested whether, relative to low-risk youths, high-risk children exhibited a higher prevalence of depressive disorders and whether brain volume abnormalities were associated with children's own lifetime depressive disorder history.

METHOD

The ABCD Study is a multisite study with the goals of assessing variability in adolescent brain and cognitive development and understanding factors that influence development.[56] Using a school-based recruitment strategy, the study collects clinical, behavioral, and neuroimaging data from 9- and 10-year-old children.[57] The present study examines data from the second public release of baseline ABCD Study data (version 2.0.1, released July 2019; http://dx.doi.org/10.15154/1504041). We focus on the children who were part of the first public release (version 1.1, released November 2018 [n = 4,521]) as a discovery sample to probe differences among low- and high-risk youths (https://doi.org/10.15154/1460410). Then we aimed to replicate these results examining children added as part of the 2.0.1 release (n = 7,355).

Structural MRI

Children across the sites participated in a baseline MRI session using scanner from GE Healthcare (Waukesha, Wisconsin), Siemens Healthcare (Erlangen, Germany), or Philips Healthcare (Andover, Massachusetts).[58] This included high-resolution T1-weighted structural MRI (1-mm isotropic voxels). All structural MRI data were processed by the ABCD Study team using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/)[59,60] according to standardized processing pipelines.[58] This includes removal of nonbrain tissue, segmentation of subcortical white matter and gray matter structures,[61] and cortical parcellation.[62] Quality control procedures were performed by the ABCD team (including visual inspection of T1 images and FreeSurfer outputs for quality as well as a neuroradiological read for incidental structural findings; for details see Hagler *et al.*[63]), and data that did not pass inspections were excluded (see Supplement 1, available online).

Clinical Assessment

Children and their parent/guardian completed an extensive battery of clinical interviews, self- and parent-report instruments, and neurocognitive tests (see Barch *et al.*[64]). Study measures examined in the current analyses are briefly summarized here (and see Supplement 1, available online). Parent-reported demographic information was collected, including child age at assessment, sex, race, ethnicity, total family income, highest parental education level, and parental marital status. The parent/guardian completing the questionnaire battery also was asked about the family's mental health history. For example, to assess family history of depression, parents/guardians were asked, "Has any blood relative of your child ever suffered from depression, that is, have they felt so low for a period of at least 2 weeks that they hardly ate or slept or could not work or do whatever they usually do?" A positive endorsement for the child's biological mother or father was used to operationalize maternal and paternal depressive history, respectively.

Children and their parent/guardian completed the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)[65] to assess children's lifetime mental disorders. For the current analyses, a composite variable for lifetime history of depressive disorders was created to characterize children meeting criteria for present, past, or remitted MDD, dysthymia, or an unspecified depressive disorder based on child or parent report. Similarly, lifetime history of anxiety disorders was determined based on report of separation anxiety disorder, social anxiety disorder, or generalized anxiety disorder; a variable for externalizing disorders was created combining those meeting criteria for conduct or oppositional deficient disorder. Parents/guardians completed the Child Behavior Checklist (CBCL)[66] to assess their child's psychiatric symptom severity; the internalizing and externalizing subscales were used as covariates in structural analyses to control for associations with child psychopathology.

Neurocognitive performance was assessed using the NIH Toolbox,[67] and age-corrected total cognition scores were examined as a standardized normed index (mean [SD] 100 [15]) of fluid and crystallized intelligence comparable to commonly used IQ measures.[68] Pubertal development was assessed based on the average of parent and child report (range, 1–4) on the Pubertal Development Scale.[69] Children's height was included as a covariate in structural analyses to account for overall body size and development.

Analysis

All analyses were performed in R 3.5.3[70] examining only children with structural T1 data passing quality control and with maternal and/or paternal depressive history information completed by a biological parent. Variables of interest were summarized comparing youths with no parental depressive history vs youths with a parental (maternal or paternal) depressive history. Group differences as a function of parental depressive history were tested using a two-sample t test for continuous variables and χ^2 tests for categorical variables. Effect size was indicated with d or odds ratio (OR) for continuous or categorical variables, respectively. False

discovery rate (FDR) was used to correct for multiple comparisons in the primary discovery sample analyses.

Linear mixed-effects (LME) models (*lme4* package[71]) were used to examine associations of maternal and paternal depressive history with children's psychopathology (lifetime history of depressive disorders; CBCL T scores) and brain structure. All models included random effects for family nested within acquisition site to account for multilevel clustering of siblings within families and participants within site locations. All models included fixed effects for relevant covariates: age, sex, race (separate binary variables for White and Black), ethnicity (binary variable for Hispanic or not), total family income (ordinal variable across 10 bins), highest parental education (binarized as completing at least some college or not), parental marital status (binarized as married/living together or not), pubertal status, and cognition. Logistic generalized LME models (*glmer*) were used when predicting binary outcomes (depressive diagnoses). All LME models weighted participants based on propensity weighting methodologies employed by the ABCD Study (S. G. Heeringa, PhD, P. A. Berglund, MBA, unpublished data, 2019) to calibrate the sample to the demographic and socioeconomic distribution of all 9- and 10-year-old children in the United States as estimated by the nationally representative American Community Survey. This accounts for potential demographic and socioeconomic selection bias and sampling limitations of ABCD. Participants missing any covariates were excluded using listwise deletion.

The main analyses examined structural measures across the whole brain, primarily investigating differences in subcortical brain volumes with additional analyses examining thickness across the whole cortex based on the Destrieux *et al.* 2010 atlas.[72] All LME analyses examining brain structure included the same covariates noted and also included a random effect for MRI device serial number (instead of site) and fixed effects for CBCL internalizing and externalizing T scores, height, and T1 image signal-to-noise (whole-brain intensity mean [SD]). Intracranial volume (ICV) was included as a covariate in all subcortical volume analyses. Any outlier >3 SD from the mean was Winsorized to the next nonoutlier value for all volume and thickness variables. Effect size estimates for maternal and paternal depressive history, adjusting for covariates, were calculated using *d*.[73] FDR was used to correct for multiple comparisons across volume analyses and cortical thickness analyses.

Several follow-up tests were run to confirm any significant effects of parental depressive history. First, to ensure that familial clustering did not influence the result, in the cases where siblings participated in the study (accordingly removing the random effect for family), we excluded participants to retain only one individual per family. To further confirm results, models with significant effects of maternal or paternal depressive history were run controlling for maternal and paternal substance use history (see Supplement 1, available online); excluding children with current MDD, dysthymia, or unspecified depressive disorder; excluding children taking psychotropic medications; and excluding for maternal psychotropic medication use during pregnancy (see Supplement 1, available online). Additionally, a count of potentially traumatic events was created from the parent report on the K-SADS posttraumatic stress disorder section (maximum 17 events), which was used to test whether parental depressive history effects may be accounted for by stress exposure. Finally, significant effects passing FDR correction in release 1.1 were aimed to be replicated using data from children added in release 2.0.1.

RESULTS

Participants

The final sample included children from ABCD data release 1.1 (n = 3,788 [83.79%]) and 2.0.1 (n=5,930 [80.63%]) who had structural data that passed ABCD quality control and parental depressive history information completed by a biological parent (see Supplement 1, available online). Parental depressive history rates were comparable across releases (release 1.1 = 1,281 [30.6%], release 2.0.1 = 2,045 [30.3%], χ^2 = .001, p = .97) (Table S1, available online). This was mostly accounted for by maternal history (release 1.1 = 949 [22.8%], release 2.0.1 = 1,545 [22.9%], $\chi^2 = 0.45$, $p = .50$) (Table S1, available online) vs paternal history (release 1.1 = 575 [14.1%], release 2.0.1 = 963 [14.6%], $\chi^2 = 0.23$, $p = .63$) (Table S1, available online). Sex, pubertal status, and cognition did not differ significantly by parental depressive history (Table 1). Compared with children without a parental depressive history, children with such a history were more likely to be White, were more likely to be Hispanic, had lower family income, were less likely to have parents who were married or together, and had experienced more potentially traumatic life events (Table 1). In release 1.1 only, children with a parental depressive history were slightly younger, were more likely to have a parent complete college, and were slightly shorter; these effects were similar but not significant in release 2.0.1 (see Table S1, available online, for demographic comparison across releases).

Depression Risk

Rates of depressive disorders among the children were comparable across the two releases (release 1.1 = 373 [10.0%], release 2.0.1 =645 [11.1%], χ^2 = 2.64, p = .10) (Table S1, available online). Although most participants across the full sample reported no mental disorder

history, 498 (5.1%) children met criteria for lifetime MDD, 21 met criteria for dysthymia (0.2%), and 553 (5.7%) met criteria for an unspecified depressive disorder. Among the full sample, 1,018 (10.5%) children met criteria for any lifetime depressive disorder. As expected, depressive disorders were more common in children with (16.6%) vs without (8.1%) a parental history of depression ($\chi^2_1 = 155.12$, $p = 2.2 \times 10^{-16}$). In a logistic regression predicting the occurrence of children's lifetime depressive disorders, maternal ($b = 0.69$, OR = 1.99, 95% confidence interval = 1.67–2.37, z = 7.71, $p = 1.29 \times 10^{-14}$) and paternal ($b = 0.39$, OR = 1.45, 95% confidence interval = 1.21–1.81, z = 3.78, $p = .0002$) depressive history were significant predictors above and beyond other covariates (see Table S2, available online, for full LME model and maternal and paternal depressive history effects on children's CBCL scores).

Subcortical Volume Differences

Brain Structure (Discovery: ABCD 1.1). First, maternal and paternal depressive history were examined in association with global brain volumes (ICV and total subcortical volume). A paternal, but not maternal, depressive history was associated with larger ICV ($b = 17531.30$, B = 0.12, $t_{2861.95} = 2.91$, $p = .004$, $d = 0.15$) (Table 2). Conversely, a maternal, but not paternal, depressive history was associated with smaller subcortical volume, controlling for ICV and other covariates ($b = -366.64$, B = −0.07, $t_{2851.82} = -2.92$, $p = .004$, $d = -0.13$) (Table 2).

Second, maternal and paternal depressive history were examined in association with individual subcortical regional volumes: left and right amygdala, hippocampus, caudate, putamen, nucleus accumbens, pallidum, and thalamus volumes. FDR was used to correct for multiple comparisons across the 14 LME models (Table 2 and Table S3, available online). No significant effects of paternal depressive history were noted, whereas maternal depression was related to smaller volumes of the right putamen ($b = -67.29$, B = −0.11, $t_{2834.72} = -2.88$, $p = .004$, FDR-corrected $p = .03$, $d = -0.14$) (Table 2 and Figure 1) and right accumbens ($b = -14.33$, B = −0.15, $t_{2783.91} = -3.80$, $p = .0001$, FDR-corrected $p = .002$, $d = -0.16$) (Table 2 and Figure 1); for exploratory analyses of sex differences, see Table S4, available online. Smaller right putamen and accumbens volumes were similarly noted when examining parental depressive history, ie, combining either maternal or paternal (Table S3, available online). Maternal depressive history was associated with smaller left accumbens, pallidum, and amygdala volumes, but this did not pass FDR correction (FDR-adjusted $p < .06$, $p < .02$, $t < -2.30$, $d < -0.09$) (Table S2, available online). Examining the estimated marginal means from the main models above (Table S5, available online), a maternal depressive history was associated with 1.16% smaller right putamen and 2.29% smaller right accumbens volumes. To provide a more conservative test of parental depressive history effects removing any potential influence of familial clustering, we reran analyses retaining only one individual per family (n = 3,335). Maternal depressive history remained a significant predictor of right putamen ($b = -59.88$, B = −0.10, $t_{2724.27} = -2.57$, $p = .01$, $d = -0.12$) and right accumbens ($b = -13.40$, B = −0.14, $t_{2718.31} = -3.57$, $p = .0004$, $d = -0.16$) volumes. Although subcortical volumes were the key outcome of interest, for completeness, we tested differences in cortical thickness from the Destrieux *et al.* 2010 atlas.[72] Unexpectedly, two regions exhibited greater cortical thickness (FDR-corrected) in children with a paternal depressive history: the left medial occipitotemporal sulcus and the right calcarine sulcus (Table S6, available online).

Third, to test the robustness of our findings, follow-up analyses were completed for the two FDR-corrected subcortical volume effects. The maternal depressive history effects remained significant when controlling for maternal (n = 180) and paternal (n = 580) substance use history (right putamen: $t = -2.72$, $p = .007$, $d = -0.13$; right accumbens: $t = -3.57$, $p = .0004$, $d = -0.16$; substance use history did not predict volumes beyond maternal depressive history and other covariates); excluding children with current depressive disorder diagnoses (n = 54; right putamen: $t = -2.89$, $p = .004$, $d = -0.14$; right accumbens: $t = -3.50$, $p = .0005$, $d = -0.15$); excluding children receiving psychotropic medications (n = 95; right putamen: $t = -2.25$, $p = .02$, $d = -0.11$; right accumbens: $t = -3.58$, $p = .0003$, $d = -0.16$); and excluding for maternal psychotropic medication use during pregnancy (n = 189; right putamen: $t = -3.22$, $p = .001$, $d = -0.16$; right accumbens: $t = -3.91$, $p = .00009$, $d = -0.18$). Maternal depressive history also remained a significant predictor of right putamen and accumbens volumes when controlling for the stressor count. Stress exposure significantly predicted smaller right putamen, but not accumbens, volumes (Table S7, available online).

Last, analyses tested whether brain volume abnormalities were associated with a personal lifetime depressive disorder history. Analyses revealed no significant associations (after FDR correction) between subcortical volumes and children's lifetime depressive disorder history or when stratifying by parental depressive history (Table S8, available online).

TABLE 1 Demographic and Clinical Characteristics

	Release 1.1			Release 2.0.1		
Parental depressive history	**No**	**Yes**	***d*/OR**	**No**	**Yes**	***d*/OR**
n (%)	2,644 (69.8%)	1,144 (30.2%)	—	4,136 (69.75%)	1,794 (30.25%)	—
Age	120.19 (7.29)	119.62 (7.30)	−0.08*	118.40 (7.49)	118.20 (7.52)	−0.03
Sex, female, n (%)	1,233 (46.6%)	546 (47.7%)	1.04	1,984 (48.0%)	861 (48.0%)	1.00
Race, White, n (%)	2,124 (80.3%)	984 (86.0%)	1.51***	2,917 (70.5%)	1,349 (75.2%)	1.27***
Race, Black, n (%)	379 (14.3%)	151 (13.2%)	0.91	947 (22.9%)	439 (24.5%)	1.09
Ethnicity, Hispanic, n (%)	574 (21.9%)	178 (15.8%)	−1.50***	945 (23.1%)	330 (18.7%)	−1.31***
Income	7.62 (2.22)	7.30 (2.20)	−0.14***	7.23 (2.50)	6.76 (2.50)	−0.19***
Marital status, parents together, n (%)	2,117 (80.4%)	798 (70.0%)	0.57***	3,122 (76.3%)	1,169 (65.9%)	0.60***
Parental education, college, n (%)	2,243 (84.9%)	1,021 (89.4%)	1.50***	3,353 (81.1%)	1,479 (82.7%)	1.11
Height, inches	55.55 (3.11)	55.16 (3.23)	−0.12***	55.22 (3.19)	55.07 (3.29)	−0.04
Pubertal status	1.66 (0.71)	1.68 (0.72)	0.02	1.68 (0.71)	1.72 (0.72)	0.05
Cognition total score	102.64 (17.89)	102.93 (16.52)	0.02	99.99 (18.18)	99.31 (17.27)	−0.04
CBCL internalizing T score	46.91 (9.87)	52.01 (10.87)	0.50***	46.69 (10.05)	51.93 (11.14)	0.50***
CBCL externalizing T score	44.12 (9.40)	47.81 (10.42)	0.38***	44.02 (9.59)	48.84 (10.98)	0.48***
CBCL total problems T score	43.85 (10.41)	49.39 (10.83)	0.53***	43.65 (10.80)	49.90 (11.49)	0.57***
K-SADS lifetime depressive disorder, n (%)	193 (7.4%)	180 (15.9%)	2.37***	344 (8.5%)	301 (17.1%)	2.23***
K-SADS lifetime anxiety disorder, n (%)	274 (10.5%)	285 (25.2%)	2.87***	410 (10.1%)	404 (22.9%)	2.64***
K-SADS lifetime conduct or oppositional defiant disorder, n (%)	298 (11.4%)	242 (21.4%)	2.10***	438 (10.7%)	418 (23.7%)	2.58***
Number of lifetime diagnoses	0.49 (0.90)	1.04 (1.35)	0.52***	0.49 (0.91)	1.10 (1.41)	0.56***
PTSD traumatic events count	0.39 (1.11)	0.67 (1.41)	0.23***	0.40 (0.81)	0.72 (1.17)	0.34***
T1 mean (SD) signal	2.68 (0.19)	2.69 (0.19)	0.05	2.69 (0.19)	2.69 (0.19)	0.002

Note: *Demographic and clinical characteristics of release 1.1 and release 2.0.1 samples are presented split by the presence of a parental (maternal or paternal) depressive history. Mean (SD) values are presented for each group for each continuous variable, whereas count (percentage) of participants in each group are presented for categorical variables. Group differences within each release were tested for all variables. The d/OR column indicates the effect size of differences between groups:* d *for continuous variables and odds ratio (OR) for categorical variables. Income was an ordinal variable where a score of 7 indicated income between $50,000 and $75,000 (see Supplement 1, available online). Marital status was a binary variable indicating whether or not a child's parents were married or living together. Parental education was a binary variable indicating whether or not a child's parent completed at least some college. Pubertal status was a composite score ranging from 1 to 4. Number of lifetime diagnoses was a count of depressive, anxiety, oppositional, conduct, or disruptive mood dysregulation disorder diagnoses (maximum = 11). A count of endorsed events from the K-SADS PTSD module was included (maximum = 17). Signal-to-noise of the T1 structural image is denoted based on the mean (SD) signal intensity. All significant group differences passed false discovery rate correction for the tests examined here. CBCL = Child Behavior Checklist; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; PTSD = posttraumatic stress disorder.*
*p < .05; ***p < .001.

Brain Structure (Replication: ABCD 2.0.1). Replication analyses tested whether high-risk youths exhibited smaller volumes in the right putamen and accumbens compared with low-risk children. To avoid issues of nonindependence from familial clustering introduced by siblings split across releases, we retained one individual from each family and excluded individuals in release 2.0.1 who had siblings examined in release 1.1 (n = 244), resulting in a final sample of low-risk (n = 3,468) and high-risk (n = 1,540) youths. No significant associations were found between maternal/paternal depressive history and ICV; however, a paternal depressive history was related to smaller total subcortical volume (Table 2).

Similar to release 1.1, smaller right putamen volume was related to parental depressive history (Table S3, available online), but in contrast to release 1.1., this effect was related to paternal, not maternal, depressive history ($b = -45.75$, $B = -0.07$, $t_{4252.96} = -2.04$, $p = .04$, $d = -0.09$) (Table 2 and Figure 1). This parental depressive history result also was observed in the full sample combining data across releases

TABLE 2 Linear Mixed-Effects Model Analyses of Total and Subcortical Brain Volumes

	Release 1.1				Release 2.0.1			
	ICV	Subcortical	Right accumbens	Right putamen	ICV	Subcortical	Right accumbens	Right putamen
ICV	—	64.6***	27.05***	28.84***	—	76.36***	30.95***	33.03***
Age	−2.45*	−0.82	−4.74***	−4.14***	−5.66***	−1.68	−2.60**	−2.86**
Sex, female	−29.14***	−5.26***	−0.99	−6.96***	−37.43***	−3.28**	−0.42	−7.12***
Race, White	3.88***	0.52	0.38	−0.70	8.09***	−0.96	−0.89	−2.62**
Race, Black	−2.49*	−0.86	0.89	−2.41*	−4.67***	−1.54	−0.23	−4.4***
Ethnicity, Hispanic	−2.20*	1.29	1.32	1.30	−2.5*	2.01*	−1.37	2.01*
Marital status	0.64	−0.25	−0.04	0.09	−1.32	2.46*	0.83	1.70
Parental education	0.71	1.63	−0.70	0.18	0.8	2.45*	−0.17	1.19
Income	4.03***	0.94	1.48	1.06	3.79***	−0.39	−0.06	−0.34
Pubertal status	−0.16	−0.91	−1.29	0.44	0.34	0.52	−1.59	0.14
Cognition	5.22***	4.15***	1.66	1.96	8.3***	3.85***	−0.48	2.30*
Height	12.58***	1.32	0.72	0.18	16.92***	−0.78	−1.97*	0.29
CBCL internalizing T score	0.01	1.45	−0.40	0.91	0.59	−0.09	−1.78	−1.63
CBCL externalizing T score	−1.33	−1.89	−0.27	−0.75	−2.86**	0.09	−0.90	2.06*
T1 mean (SD) signal	7.37***	5.65***	2.87**	2.48*	10.75***	5.61***	3.93***	3.13**
Maternal depressive history	−0.22	−2.92**	**−3.8*** **	**−2.88** **	1.30	0.02	0.5	−1.02
Paternal depressive history	2.91**	0.28	0.62	0.17	−1.02	−2.38*	−1.33	−2.04*
Maternal *d*	−0.01	−0.13	**−0.16**	**−0.14**	0.05	0.00	0.02	−0.04
Paternal *d*	0.15	0.01	0.03	0.01	−0.04	−0.10	−0.06	−0.09

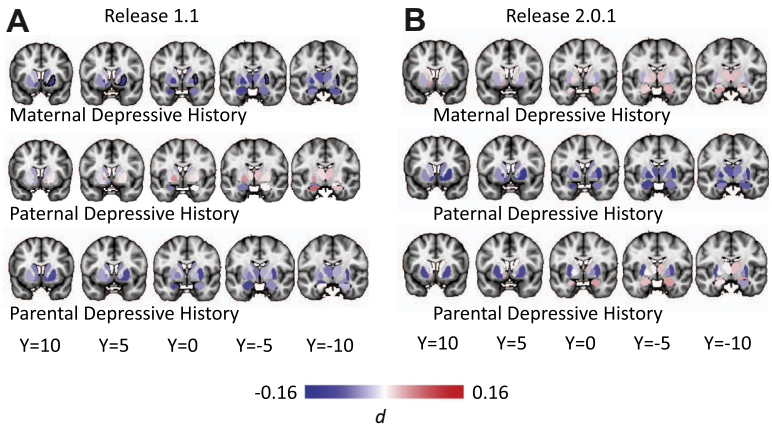
Note: Boldface types indicates significant effects of maternal depressive history in the right accumbens and putamen. Linear mixed-effects models were used to examine associations between maternal and paternal depressive history and brain volumes separately for each release (1.1: n = 3,162; 2.0.1: n = 4,287), controlling for ICV, age, sex, race, ethnicity, parental marital status, parental education, income, pubertal status, cognition, height, CBCL scores, and T1 signal-to-noise (individuals with missing covariates were excluded with listwise deletion (1.1: n = 626 of 3,788; 2.0.1: n = 721 of 5,008). These models also included random effects for family nested within scanner serial number and included the American Community Survey weights. From each model, t statistics are presented for each predictor along with d effect sizes for the effects of a maternal and paternal depressive history. Results summarize effects for global volumes values (ICV and total subcortical volume) and the right accumbens and putamen maternal depressive history effects that passed false discovery rate correction for multiple comparisons among the 14 subcortical regions tested in the discovery sample. See Table S3, available online, for summary of results from all subcortical regions. CBCL = Child Behavior Checklist; ICV = intracranial volume.
**p < .05; **p < .01; ***p < .001.*

(Table S9, Figure S1, available online) as well as in a meta-analysis examining effects across sites (Figure S2, available online). Results did not replicate within the nucleus accumbens volume or cortical regions in release 2.0.1 (left medial occipitotemporal sulcus, right calcarine sulcus) (Table S6, available online). The paternal depressive history association with putamen volume remained significant or trend level significant (with similar effect size) when controlling for maternal (n = 273) and paternal (n = 918) substance use history ($t = -1.81$, $p = .07$, $d = -0.09$; no significant effects of parental substance use history); excluding children with a current depressive disorder (n = 38; $t = -1.92$, $p = .06$, $d = -0.09$); excluding children receiving psychotropic medications (n = 129; $t = -2.16$, $p = .03$, $d = -0.10$); and excluding for maternal psychotropic medication use during pregnancy (n = 195; $t = -1.74$, $p = .08$, $d = -0.08$). No effect of stress exposure was noted for the right putamen, and paternal depressive history remained a significant predictor after accounting for stress exposure (Table S7, available online).

DISCUSSION

We leveraged data from the ABCD Study to interrogate associations with parental history of depression in 9- and 10-year-old children, and several important findings emerged. First, examining children from ABCD release 1.1, a parental history, specifically maternal depressive history, was related to smaller volumes within the right putamen and right nucleus accumbens. The effect of smaller putamen volume with a parental depressive history was replicated among children

FIGURE 1 Association Between Parental Depressive History and Subcortical Volumes



Note. d effect sizes are presented for the association between maternal and paternal depressive history and subcortical volumes from the main linear mixed-effects model analyses (Table 2) as well as parental depressive history from separate models (Table S3, available online). All models controlled for intracranial volume, age, sex, race, ethnicity, parental marital status, parental education, income, pubertal, status, cognition, height, Child Behavior Checklist (CBCL) scores, and T1 signal-to-noise ratio. Models also included random effects for family (for release 1.1; siblings excluded for release 2.0.1) nested within scanner serial number. (A) Results from release 1.1 discovery sample. (B) Results from release 2.0.1 sample. The two effects passing false discovery rate correction for multiple comparisons in the discovery sample (right putamen, right accumbens) are outlined in black. Please note color figures are available online.

added in release 2.0.1 but was driven by paternal depressive history. Findings within the accumbens, however, were not replicated. Second, as expected, children with a parental history of depression had a near twofold greater likelihood of depression themselves. Third, subcortical abnormalities identified in high-risk youths were not identified in youths with a personal lifetime depressive history. Nevertheless, findings from high-risk youths provide important insights about subcortical risk markers that may reconcile inconsistencies in past research and represent results from the largest sample of children in a nationally representative cohort study.

A parental depressive history, across ABCD release 1.1 and 2.0.1, was related to smaller putamen volume—a region implicated in reward and motivational processes. However, in release 1.1, this effect was driven largely by maternal history, whereas in release 2.0.1, this was related to paternal depressive history. Importantly, effect sizes for each sample were comparable (release 1.1. $d = -0.14$; release 2.0.1 $d = -0.09$), and, critically, both maternal (OR = 1.99) and paternal (OR = 1.45) history increased the likelihood of children's lifetime depressive disorders. Nevertheless, it remains unclear why maternal and paternal effects diverged across data releases. Prior research has shown that the putamen is involved in positive prediction error encoding[74] as well as motor planning,[75] and reduced putamen volume in youths prospectively predicts anhedonia severity—a core symptom of MDD.[76] Thus, reduced volume of putamen may contribute to initial anhedonia onset—a transdiagnostic factor implicated in a range of mental disorders[77-86] and suicidal behaviors[87]—through impaired reward learning and motor alterations (eg, reduced energy, diminished motivation) that then acts as a gateway to MDD (and other mental disorders) across the life span.

In the discovery (release 1.1) and replication (release 2.0.1) samples, we did not detect alterations in amygdala and hippocampal volumes that survived correction for multiple comparisons. Although this finding was potentially unexpected, prior research suggests that smaller amygdala volume is related to depression recurrence in adults,[14,15] and results are mixed among youths (eg, [13,16,17]). Similarly, meta-analytic findings suggest that hippocampal volume is similar between healthy controls and adults at their first depressive episode, but smaller in adults with recurrent MDD.[9] Collectively, these findings suggest that smaller amygdala and hippocampal volume may be a consequence vs a cause of MDD onset, and perhaps exposure to MDD and associated stressors may contribute to reduced volume.

A key strength of the study was the use of a large, representative dataset intended to clarify structural differences among youths at high familial risk for MDD. However, the effect sizes were small. At first, these results may be difficult to reconcile with expectations and larger effect sizes in prior work, but this literature has largely reported conflicting findings in smaller sample sizes. Part of the challenge is that depression is a heterogeneous disorder, and thus identifying discrete biological markers that confer risk across all cases may be overly optimistic. Rather, it seems more plausible that subgroups of individuals with depression may have different etiological pathways—arising from stress exposure, biological predispositions, genes, or comorbid medical conditions. Relatedly, a biological

diathesis may not be sufficient to result in MDD. For example, decades of stress generation research have shown that women with a history of MDD generate a greater preponderance of interpersonal stress, which then increases risk for future MDD episodes.[88] Consequently, high-risk youths may be susceptible because of their diathesis (ie, small putamen volume) and also may reside in more stressful environments, which could then lead to MDD. Finally, although the ABCD dataset provides a unique opportunity to probe and replicate neuroanatomical differences in a large sample of well-characterized youths, the small effect sizes obtained within the putamen may reflect the type of family history assessment used. This brief assessment likely contributed to measurement noise and may not be optimal to categorize parental risk status. A more rigorous, interview-based assessment may have resulted in stronger effect sizes. Taken together, although subcortical volume may reflect a familial risk factor for MDD, our findings underscore the importance of probing additional mechanisms and pathways that may lead to MDD onset.

Depressogenic Impact of Parental Depressive History

Our results indicated that a parental depressive history was related to subcortical volume differences in 9- and 10-year-old children with and without a personal lifetime depressive history. At the same time, subcortical abnormalities were not associated with children's own lifetime depressive history. These results will need to be followed up in future work, as effects may change as the rates of depression increase across typical development, ie, after the peak onset in middle and late adolescence.[2] Given associations between parental depression history and subcortical brain development, a key consideration is how parental depression affects the development of specific brain regions, which likely includes a number of genetic and epigenetic factors as well as prenatal and postnatal environmental factors. The volume of subcortical regions is approximately 50% heritable, highlighting the critical nature of these familial mechanisms.[89,90] A nascent body of work also has begun testing concordance of brain structures between mothers and their high-risk youths[91]; yet, concordance of subcortical volumes has not been tested. Furthermore, early exposure to stress during developmentally sensitive periods likely helps to shape neural development.[92] More generally, studying the broader question of how parental history confers risk for depression in children poses many challenges, poses many challenges: How does the timing of prenatal and/or postnatal stress exposure influence subcortical brain development? What is the influence of prenatal exposure to psychiatric medication? Given typical comorbidity, how does prenatal exposure to a range of disorders differentially affect brain development? These unresolved questions have consequences for determining the mechanisms through which a family history increases susceptibility to develop MDD.

Summary

Several limitations are noteworthy. First, although the clinical battery assesses parental mental disorders, the assessment is not a gold standard diagnostic interview and does not provide information on the timing, subtype, or severity of the depression history. This may have contributed to the small effect sizes obtained. Second, the analysis used a simple count of endorsed stressful events, but this is not a substitute for a more comprehensive stress interview. Finally, our main hypotheses centered on alterations in subcortical volumes, but we also provide results examining cortical thickness from the Destrieux *et al.* 2010 atlas[72] parcellations. This provides a preliminary test; however, the atlas parcellations are relatively coarse and average across heterogeneous aspects of cortical structure. Fine-grained analyses of cortical thickness can be performed in the future using other atlases or vertex-wise analyses.

In summary, the ABCD Study provides data for the largest comparison to date of brain structure in low- and high-risk children (owing to a parental history of depression). Results definitively underscore smaller putamen volume, which has been linked to anhedonia as well as reward learning deficits and thus may increase susceptibility to MDD.[76]

Accepted October 10, 2019.

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This study was partially supported by funds from the National Institute of Mental Health (NIMH; R21MH112330 and U01MH108168) and the Tommy Fuss Fund to Randy P. Auerbach.

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children 9 and 10 years old and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health (NIH) and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, and U24DA041147. A full list of supporters is available at https://abcdstudy.org/nih-collaborators. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/principal-investigators.html. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This article reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from [NIMH Data Archive Digital Object Identifier (http://dx.doi.org/10.15154/1504041)].

Disclosure: Drs. Pagliaccio, Marsh, Auerbach, and Ms. Alqueza have reported no biomedical financial interests or potential conflicts of interest.

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https://doi.org/10.1016/j.jaac.2019.09.032

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