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

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Abstract

Objective—Children of parents with depression are 2–3 times more likely to develop major depressive disorder (MDD) than those without a parental history; however, subcortical brain volume abnormalities characterizing MDD 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 MRI data were acquired from 9–10-year-old children ($n=11,876$; release 1.1=4,521; release 2.0.1=7,355). Approximately one-third of the children had a parental depressive history; providing sufficient power to test differences between low- and high-risk youth in subcortical brain volume. 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 youth with a lifetime depressive disorder history.

Results—Parental depressive history was related to smaller right putamen volume in the discovery (release 1.1; Cohen's $d=-0.10$) 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 relation with putamen volume ($d=-0.09$). Further, high-risk children exhibited a near 2-fold greater occurrence of depressive

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disorders relative to low-risk youth (maternal history OR=1.99; paternal history OR=1.45), but youth 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 MDD.

Keywords

adolescent depression; subcortical brain volume; dorsal striatum; ventral striatum; ABCD

Introduction

Depression is common, debilitating, and typically onsets 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 2–3 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 20–40% 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 sample with or at risk for depression, potentially due to sample sizes ($n < 200$ participants) that limit power to detect effects that are presumed to be small.^{9–11} Additionally, heterogeneity in disease course (e.g., age of onset, number of episodes, comorbidity) and treatment history (e.g., antidepressant medication may protect against volume loss¹²) 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 9–10-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 youth 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 youth¹³ and adults with depression,^{14,15} several studies report no volumetric differences compared to 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 while non-use 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, youth^{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 loss¹²). 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 to healthy individuals.^{22–24,40,41} Yet, other work finds no significant differences,^{9,42–44} differences by sex,⁴⁵ and associations with key clinical variables (e.g. 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 youth 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 youth with depression while youth 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 Youth

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.⁵¹ 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.⁵³ Hippocampal findings also are mixed when comparing high- to low-risk youth, suggesting decreased volume^{57–58} or no volumetric differences.^{51,59} Data regarding other subcortical regions in high-risk youth 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 utilizing larger samples to elucidate which biomarkers precede MDD onset.

Major Depressive Disorder and High-Risk Youth

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 (e.g., ^{4,7,61}). We leveraged ABCD data to clarify whether the prevalence of mental disorders, particularly MDD, differed among low- and high-risk children prior to the typical escalation of disorder onset during the transition from middle to late adolescence.² Moreover, we tested whether subcortical differences identified in youth at high risk for MDD were present in individuals with a personal lifetime depressive history. Showing the same subcortical brain volume differences in youth at high risk for MDD with a lifetime depressive history would not definitively clarify whether the abnormalities are a *cause* versus *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 was used to compare children at low- versus high-risk based on a parental depressive history. In light of prior research (e.g., ^{4,7,9}), the primary aim was to test whether a parental depressive history was associated with children's subcortical brain volume (i.e., 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 youth. Then, we sought to replicate these effects examining children from the ABCD release 2.0.1. Secondary analyses tested whether, relative to low-risk youth, 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 multi-site study with the goal of: (a) assessing variability in adolescent brain and cognitive development and (b) understanding factors that influence development.⁶² Using a school-based recruitment strategy, the study collects clinical, behavioral, and neuroimaging data from 9–10-year-old children.⁶³ 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/10.15154/150404>). 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 youth (<http://dx.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 Magnetic Resonance Imaging

Children across the sites participated in a baseline MRI session on a GE, Siemens, or Phillips scanner.⁶⁴ This included high-resolution T1weighted structural MRI images (1mm isotropic voxels). All structural MRI data were processed by the ABCD Study team using FreeSurfer version v5.3.0 (<http://surfer.nmr.mgh.harvard.edu/>; ^{65,66}) according to standardized processing pipelines.⁶⁴ This includes removal of non-brain tissue, segmentation

of subcortical white matter and gray matter structures,⁶⁷ and cortical parcellation.⁶⁸ 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 ⁶⁹), 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 ⁷⁰). Study measures examined in the current analyses are briefly summarized below (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 two weeks that they hardly ate or slept or couldn't 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 Kiddie-Schedule for Affective Disorders (KSADS) ⁷¹ 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 defiant disorder. Parents/guardians completed the Child Behavior Checklist (CBCL⁷²) 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 Toolbox⁷³ and age-corrected total cognition scores were examined, as a standardized normed index ($M=100$, $SD=15$) of fluid and crystallized intelligence comparable to commonly used IQ measures.⁷⁴ Pubertal development was assessed based on the average of parent- and child-report (range=1–4) on the Pubertal Development Scale.⁷⁵ Children's height was included as a covariate in structural analyses to account for overall body size/development.

Analysis

All analyses were performed in R v3.5.3⁷⁶ 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 those with no parental depressive history to those 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 Cohen's d or odds ratios (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* package⁷⁷) 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 multi-level 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 ten 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 ABCD⁷⁸ to calibrate the sample to the demographic and socio-economic distribution of all 9–10-year-old children in the United States as estimated by the nationally representative American Community Survey (ACS). This accounts for potential demographic and socio-economic selection bias and sampling limitations of ABCD. Participants missing any covariates were excluded using list-wise 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 atlas⁷⁹. 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), 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 $>3SD$ from the mean was Winsorized to the next non-outlier value for all volume and thickness variables. Effect size estimates for maternal and paternal depressive history, adjusting for covariates, were calculated using Cohen's d .⁸⁰ 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 assure that familial clustering did not influence the result, we excluded participants to retain only one individual per family in the cases where siblings participated in the study (and accordingly removing the random effect for family). To further confirm results, models with significant effects of maternal or paternal depressive history were run: (a) controlling for maternal and paternal substance use history (see Supplement 1, available online), (b) excluding children with current MDD, dysthymia, or unspecified depressive disorder, (c) excluding children taking psychotropic medications, and (d) 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 KSADS PTSD section (max=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 a 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%], $\chi^2=.001$, $p=.97$, 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 to those without a parental depressive history, children with a parental depressive history were more likely to be white, more likely to be Hispanic, had lower family income, were less likely to have parents who were married or together, and experienced more potentially traumatic live events (Table 1). In release 1.1 only, children with a parental depressive history were slightly younger, 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 $n=373$ [10.0%]; release 2.0.1 $n=645$ [11.1%], $\chi^2=2.64$, $p=.10$; 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 for dysthymia (0.2%), 553 (5.7%) for an unspecified depressive disorder. Of the full sample, 1,018 (10.5%) children met criteria for any lifetime depressive disorder. As expected, depressive disorders were more common among those 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, CI₉₅=1.67–2.37, $z=7.71$, $p=1.29 \times 10^{-14}$) and paternal depressive history ($b=0.39$, OR=1.45, CI₉₅=1.21–1.81, $z=3.78$, $p=.0002$) 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 fourteen LME models (Tables 2 and 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; 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; 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, i.e. 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- $p<.06$, $p<.02$, $k=-2.30$, $d=-0.09$; 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 re-ran 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.⁷⁹ 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: (a) 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), (b) excluding children with current depressive disorder diagnoses ($n=54$; right putamen: $t=-2.89$ $p=.004$, $d=-0.14$; right accumbens: $t=-3.50$ $p=.0005$, $d=-0.15$), (c) excluding those on 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 (d) 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).

Brain Structure (Replication: ABCD 2.0.1)

Replication analyses tested whether high-risk youth exhibited smaller volumes in the right putamen and accumbens compared to low-risk children. To avoid issues of non-independence 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 ($n=1,540$) youth. 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; Figure 1). This parental depressive history result also was observed in the full sample combining data across releases (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: (a) 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), (b) excluding children with a current depressive disorder ($n=38$; $t=-1.92$, $p=.06$, $d=-0.09$), (c) excluding those on psychotropic medications ($n=129$; $t=-2.16$, $p=.03$, $d=-0.10$), and (d) 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 9–10-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 replicated among children added in release 2.0.1 but was driven by paternal depressive history. Findings within the accumbens, however, did not replicate. Second, as expected, children with a parental history of depression had a near 2-fold greater likelihood of depression themselves. Third, subcortical abnormalities identified in high-risk youth were not identified in those with a personal lifetime depressive history. Nevertheless, findings

from high-risk youth 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 encoding⁸¹ as well as motor planning,⁸² and reduced putamen volume in youth prospectively predicts anhedonia severity—a core symptom of MDD.⁸³ Thus, reduced volume of putamen may contribute to initial anhedonia onset—a transdiagnostic factor implicated in a range of mental disorders^{84–93} and suicidal behaviors⁹⁴—through impaired reward learning and motor alterations (e.g., reduced energy, diminished motivation) that then acts as a *gateway* to MDD (and other mental disorders) across the lifespan.

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 youth (e.g.,^{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 those with recurrent MDD.⁹ Collectively, these findings suggest that smaller amygdala and hippocampal volume may be a *consequence* versus 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 utilization of a large, representative dataset intended to clarify structural differences among youth 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, and/or comorbid medical conditions. Relatedly, a biological diathesis may not be sufficient to result in MDD. For example, decades of stress generation research has shown that women with history of MDD generate a greater preponderance of interpersonal stress, which then increases risk for future MDD episodes.⁹⁵ Consequently, high-risk youth may be susceptible because of their diathesis (i.e., 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 youth, 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 a Parental Depressive History

Our results indicated that a parental depressive history was related to subcortical volume differences in 9–10-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, i.e., 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 ~50% heritable highlighting the critical nature of these familial mechanisms.^{96,97} A nascent body of work also has begun testing concordance of brain structures between mothers and their high-risk youth;⁹⁸ yet, concordance of subcortical volumes has not been tested. Furthermore, early exposure to stress during developmentally sensitive periods likely helps to shape neural development.⁹⁹ More generally, the broader question at large poses many challenges: (i) *How does the timing of the prenatal and/or postnatal stress exposure influence subcortical brain development?*; (ii) *What is the influence of prenatal exposure to psychiatric medication?*; (iii) *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. Last, our main hypotheses centered on alterations in subcortical volumes, but we also provide results examining cortical thickness from the Destrieux atlas⁷⁹ 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.⁸³

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Auerbach RP, Mortier P, Bruffaerts R, Alonso J, Benjet C, Cuijpers P, Demyttenaere K, Ebert DD, Green JG, Hasking P, Murray E, Nock MK, Pinder-Amaker S, Sampson NA, Stein DJ, Vilagut G, Zaslavsky AM, Kessler RC, Collaborators WW-I WHO World Mental Health Surveys International College Student Project: Prevalence and distribution of mental disorders. *J Abnorm Psychol*. 2018;127(7):623–638. [PubMed: 30211576]
2. Avenevoli S, Swendsen J, He JP, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. *J Am Acad Child Adolesc Psychiatry*. 2015;54(1):37–44 e32. [PubMed: 25524788]
3. Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001–2004 NHANES. *Pediatrics*. 2010;125(1):75–81. [PubMed: 20008426]
4. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdelli H, Pilowsky DJ, Grillon C, Bruder G. Families at high and low risk for depression: a 3-generation study. *Arch Gen Psychiatry*. 2005;62(1):29–36. [PubMed: 15630070]
5. Joormann J, Eugene F, Gotlib I. Parental depression: Impact on offspring and mechanisms underlying transmission of risk. *Handbook of depression in adolescents*. 2009:441–472.
6. Goodman SH, Gotlib IH. Transmission of risk to children of depressed parents: Integration and conclusions. *Psychol Rev*. 1999;106(3):458–490. [PubMed: 10467895]
7. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdelli H. Offspring of depressed parents: 20 years later. *Am J Psychiatry*. 2006;163(6):1001–1008. [PubMed: 16741200]
8. Hammen C, Adrian C, Gordon D, Burge D, Jaenicke C, Hiroto D. Children of depressed mothers: maternal strain and symptom predictors of dysfunction. *J Abnorm Psychol*. 1987;96(3):190–198. [PubMed: 3680756]
9. Schmaal L, Veltman DJ, van Erp TG, Sämann P, Frodl T, Jahanshad N, Loehrer E, Tiemeier H, Hofman A, Niessen W. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry*. 2016;21(6):806. [PubMed: 26122586]

10. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafò MR. Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*. 2013;14(5):365. [PubMed: 23571845]
11. Kempton MJ, Salvador Z, Munafo MR, Geddes JR, Simmons A, Frangou S, Williams SC. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry*. 2011;68.
12. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry*. 2003;160(8):1516–1518. [PubMed: 12900317]
13. Rosso IM, Cintron CM, Steingard RJ, Renshaw PF, Young AD, Yurgelun-Todd DA. Amygdala and hippocampus volumes in pediatric major depression. *Biol Psychiatry*. 2005;57(1):21–26. [PubMed: 15607296]
14. Saleh K, Carballedo A, Lisiecka D, Fagan AJ, Connolly G, Boyle G, Frodl T. Impact of family history and depression on amygdala volume. *Psychiatry Research: Neuroimaging*. 2012;203(1):24–30.
15. Kronenberg G, van Elst LT, Regen F, Deuschle M, Heuser I, Colla M. Reduced amygdala volume in newly admitted psychiatric in-patients with unipolar major depression. *J Psychiatr Res*. 2009;43(13):1112–1117. [PubMed: 19394960]
16. MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. *BMC medicine*. 2004;2(1):2. [PubMed: 14969587]
17. Caetano SC, Fonseca M, Hatch JP, Olvera RL, Nicoletti M, Hunter K, Lafer B, Pliszka SR, Soares JC. Medial temporal lobe abnormalities in pediatric unipolar depression. *Neurosci Lett*. 2007;427(3):142–147. [PubMed: 17949901]
18. Grieve SM, Korgaonkar MS, Koslow SH, Gordon E, Williams LM. Widespread reductions in gray matter volume in depression. *NeuroImage: Clinical*. 2013;3:332–339. [PubMed: 24273717]
19. Caetano SC, Kaur S, Brambilla P, Nicoletti M, Hatch JP, Sassi RB, Mallinger AG, Keshavan MS, Kupfer DJ, Frank E. Smaller cingulate volumes in unipolar depressed patients. *Biol Psychiatry*. 2006;59(8):702–706. [PubMed: 16414029]
20. Frodl T, Meisenzahl EM, Zetzsche T, Höhne T, Banac S, Schorr C, Jäger M, Leinsinger G, Bottlender R, Reiser M. Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. *J Clin Psychiatry*. 2004.
21. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. *American Journal of Psychiatry*. 2000;157(1):115–118. [PubMed: 10618023]
22. Arnone D, McIntosh A, Ebmeier K, Munafò M, Anderson I. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *European Neuropsychopharmacology*. 2012;22(1):1–16. [PubMed: 21723712]
23. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord*. 2012;138(1–2):9–18. [PubMed: 21511342]
24. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp*. 2009;30(11):3719–3735. [PubMed: 19441021]
25. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience*. 1999;19(12):5034–5043. [PubMed: 10366636]
26. Hastings RS, Parsey RV, Oquendo MA, Arango V, Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology*. 2004;29(5):952. [PubMed: 14997169]
27. Frodl TS, Koutsouleris N, Bottlender R, Born C, Jäger M, Scupin I, Reiser M, Möller H-J, Meisenzahl EM. Depression-related variation in brain morphology over 3 years: effects of stress? *Arch Gen Psychiatry*. 2008;65(10):1156–1165. [PubMed: 18838632]
28. Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Mol Psychiatry*. 2008;13(11):993. [PubMed: 18504424]

29. Dillon DG. The neuroscience of positive memory deficits in depression. *Frontiers in psychology*. 2015;6:1295. [PubMed: 26441703]
30. Jaworska N, Yücel K, Courtright A, MacMaster FP, Sembo M, MacQueen G. Subgenual anterior cingulate cortex and hippocampal volumes in depressed youth: the role of comorbidity and age. *J Affect Disord*. 2016;190:726–732. [PubMed: 26600415]
31. MacMaster FP, Mirza Y, Szeszko PR, Kmiecik LE, Easter PC, Taormina SP, Lynch M, Rose M, Moore GJ, Rosenberg DR. Amygdala and hippocampal volumes in familial early onset major depressive disorder. *Biol Psychiatry*. 2008;63(4):385–390. [PubMed: 17640621]
32. Shad MU, Muddasani S, Rao U. Gray matter differences between healthy and depressed adolescents: a voxel-based morphometry study. *J Child Adolesc Psychopharmacol*. 2012;22(3):190–197. [PubMed: 22537357]
33. Vasic N, Walter H, Höse A, Wolf RC. Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *J Affect Disord*. 2008;109(1–2):107–116. [PubMed: 18191459]
34. Janssen J, Pol HEH, Lampe IK, Schnack HG, de Leeuw F-E, Kahn RS, Heeren TJ. Hippocampal changes and white matter lesions in early-onset depression. *Biol Psychiatry*. 2004;56(11):825–831. [PubMed: 15576058]
35. Tang Y, Wang F, Xie G, Liu J, Li L, Su L, Liu Y, Hu X, He Z, Blumberg HP. Reduced ventral anterior cingulate and amygdala volumes in medication-naïve females with major depressive disorder: a voxel-based morphometric magnetic resonance imaging study. *Psychiatry Research: Neuroimaging*. 2007;156(1):83–86.
36. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *American Journal of Psychiatry*. 2004;161(4):598–607. [PubMed: 15056502]
37. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry*. 2004;161(11):1957–1966. [PubMed: 15514393]
38. McKinnon MC, Yucel K, Nazarov A, MacQueen GM. A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of psychiatry & neuroscience: JPN*. 2009;34(1):41. [PubMed: 19125212]
39. Matsuo K, Rosenberg DR, Easter PC, MacMaster FP, Chen H-H, Nicoletti M, Caetano SC, Hatch JP, Soares JC. Striatal volume abnormalities in treatment-naïve patients diagnosed with pediatric major depressive disorder. *J Child Adolesc Psychopharmacol*. 2008;18(2):121–131. [PubMed: 18439110]
40. Parashos IA, Tupler LA, Blitchington T, Krishnan KRR. Magnetic-resonance morphometry in patients with major depression. *Psychiatry Research: Neuroimaging*. 1998;84(1):7–15.
41. Husain MM, McDonald WM, Doraiswamy PM, Figiel GS, Na C, Escalona PR, Boyko OB, Nemeroff CB, Krishnan KRR. A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Research: Neuroimaging*. 1991;40(2):95–99.
42. Lenze EJ, Sheline YI. Absence of striatal volume differences between depressed subjects with no comorbid medical illness and matched comparison subjects. *American Journal of Psychiatry*. 1999;156(12):1989–1991. [PubMed: 10588417]
43. Pillay SS, Renshaw PF, Bonello CM, Lafer B, Fava M, Yurgelun-Todd D. A quantitative magnetic resonance imaging study of caudate and lenticular nucleus gray matter volume in primary unipolar major depression: relationship to treatment response and clinical severity. *Psychiatry Research: Neuroimaging*. 1998;84(2–3):61–74.
44. Lacerda AL, Brambilla P, Sassi RB, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Anatomical MRI study of corpus callosum in unipolar depression. *J Psychiatr Res*. 2005;39(4):347–354. [PubMed: 15804385]
45. Whittle S, Lichter R, Dennison M, Vijayakumar N, Schwartz O, Byrne ML, Simmons JG, Yücel M, Pantelis C, McGorry P. Structural brain development and depression onset during adolescence: a prospective longitudinal study. *American Journal of Psychiatry*. 2014;171(5):564–571. [PubMed: 24577365]

46. Lacerda AL, Nicoletti MA, Brambilla P, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC. Anatomical MRI study of basal ganglia in major depressive disorder. *Psychiatry Research: Neuroimaging*. 2003;124(3):129–140.
47. Baumann B, Danos P, Krell D, Diekmann S, Leschinger A, Stauch R, Wurthmann C, Bernstein H-G, Bogerts B. Reduced volume of limbic system-affiliated basal ganglia in mood disorders: preliminary data from a postmortem study. *J Neuropsychiatry Clin Neurosci*. 1999;11(1):71–78. [PubMed: 9990559]
48. Hagan CC, Graham JM, Tait R, Widmer B, van Nieuwenhuizen AO, Ooi C, Whitaker KJ, Simas T, Bullmore ET, Lennox BR. Adolescents with current major depressive disorder show dissimilar patterns of age-related differences in ACC and thalamus. *NeuroImage: Clinical*. 2015;7:391–399. [PubMed: 25685707]
49. Kim MJ, Hamilton JP, Gotlib IH. Reduced caudate gray matter volume in women with major depressive disorder. *Psychiatry Research: Neuroimaging*. 2008;164(2):114–122.
50. Romanczuk-Seiferth N, Pöhland L, Mohnke S, Garbusow M, Erk S, Haddad L, Grimm O, Tost H, Meyer-Lindenberg A, Walter H. Larger amygdala volume in first-degree relatives of patients with major depression. *NeuroImage: Clinical*. 2014;5:62–68. [PubMed: 25003028]
51. Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, Pruessner JC, Séguin JR. 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*. 2011;108(34):14324–14329.
52. Ozalay O, Aksoy B, Tunay S, Simsek F, Chandhoki S, Kitis O, Eker C, Gonul AS. Cortical thickness and VBM in young women at risk for familial depression and their depressed mothers with positive family history. *Psychiatry Research: Neuroimaging*. 2016;252:1–9. [PubMed: 27136662]
53. Nickson T, Chan SWY, Papmeyer M, Romaniuk L, Macdonald A, Stewart T, Kielty S, Lawrie SM, Hall J, Sussmann JE, McIntosh AM, Whalley HC. Prospective longitudinal voxel-based morphometry study of major depressive disorder in young individuals at high familial risk. *Psychol Med*. 2016;46(11):2351–2361. [PubMed: 27282778]
54. Opel N, Zwanzger P, Redlich R, Grotegerd D, Dohm K, Arolt V, Heindel W, Kugel H, Dannlowski U. Differing brain structural correlates of familial and environmental risk for major depressive disorder revealed by a combined VBM/pattern recognition approach. *Psychol Med*. 2016;46(2):277–290. [PubMed: 26355299]
55. Amico F, Meisenzahl E, Koutsouleris N, Reiser M, Möller H-J, Frodl T. Structural MRI correlates for vulnerability and resilience to major depressive disorder. *Journal of psychiatry & neuroscience: JPN*. 2011;36(1):15. [PubMed: 20964952]
56. Baaré WF, Vinberg M, Knudsen GM, Paulson OB, Langkilde AR, Jernigan TL, Kessing LV. Hippocampal volume changes in healthy subjects at risk of unipolar depression. *J Psychiatr Res*. 2010;44(10):655–662. [PubMed: 20096419]
57. Chen MC, Hamilton JP, Gotlib IH. Decreased hippocampal volume in healthy girls at risk of depression. *Arch Gen Psychiatry*. 2010;67(3):270–276. [PubMed: 20194827]
58. Rao U, Chen L-A, Bidesi AS, Shad MU, Thomas MA, Hammen CL. Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biol Psychiatry*. 2010;67(4):357–364. [PubMed: 20015483]
59. Mannie Z, Filippini N, Williams C, Near J, Mackay C, Cowen P. Structural and functional imaging of the hippocampus in young people at familial risk of depression. *Psychol Med*. 2014;44(14):2939–2948. [PubMed: 25066547]
60. Durmusoglu E, Ugurlu O, Akan S, Simsek F, Kizilates G, Kitis O, Ozkul BA, Eker C, Coburn KL, Gonul AS. Hippocampal shape alterations in healthy young women with familial risk for unipolar depression. *Comprehensive psychiatry*. 2018;82:7–13. [PubMed: 29367060]
61. Joormann J, Cooney RE, Henry ML, Gotlib IH. Neural correlates of automatic mood regulation in girls at high risk for depression. *J Abnorm Psychol*. 2012;121(1):61–72. [PubMed: 21895344]
62. Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, Perez-Stable EJ, Riley WT, Bloch MH, Conway K, Deeds BG, Dowling GJ, Grant S, Howlett KD, Matochik JA, Morgan GD, Murray MM, Noronha A, Spong CY, Wargo EM, Warren KR, Weiss SRB. The conception of

the ABCD study: From substance use to a broad NIH collaboration. *Dev Cogn Neurosci*. 2018;32:4–7. [PubMed: 29051027]

63. Garavan H, Bartsch H, Conway K, Decastro A, Goldstein RZ, Heeringa S, Jernigan T, Potter A, Thompson W, Zahs D. Recruiting the ABCD sample: Design considerations and procedures. *Dev Cogn Neurosci*. 2018;32:16–22. [PubMed: 29703560]
64. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, Soules ME, Teslovich T, Dellarco DV, Garavan H, Orr CA, Wager TD, Banich MT, Speer NK, Sutherland MT, Riedel MC, Dick AS, Bjork JM, Thomas KM, Chaarani B, Mejia MH, Hagler DJ Jr., Daniela Cornejo M, Sicat CS, Harms MP, Dosenbach NUF, Rosenberg M, Earl E, Bartsch H, Watts R, Polimeni JR, Kuperman JM, Fair DA, Dale AM, Workgroup AIA. The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Dev Cogn Neurosci*. 2018;32:43–54. [PubMed: 29567376]
65. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*. 1999;9(2):179–194. [PubMed: 9931268]
66. Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp*. 1999;8(4):272–284. [PubMed: 10619420]
67. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341–355. [PubMed: 11832223]
68. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004;14(1):11–22. [PubMed: 14654453]
69. Hagler DJ, Hatton SN, Makowski C, Cornejo MD, Fair DA, Dick AS, Sutherland MT, Casey B, Barch DM, Harms MP. Image processing and analysis methods for the Adolescent Brain Cognitive Development Study. *bioRxiv*. 2018:457739.
70. Barch DM, Albaugh MD, Avenevoli S, Chang L, Clark DB, Glantz MD, Hudziak JJ, Jernigan TL, Tapert SF, Yurgelun-Todd D, Alia-Klein N, Potter AS, Paulus MP, Prouty D, Zucker RA, Sher KJ. Demographic, physical and mental health assessments in the adolescent brain and cognitive development study: Rationale and description. *Dev Cogn Neurosci*. 2018;32:55–66. [PubMed: 29113758]
71. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988. [PubMed: 9204677]
72. Achenbach Rescorla. Manual for the Achenbach system of empirically based assessment school-age forms profiles. Burlington, VT: Aseba 2001.
73. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Bauer PJ, Carlozzi NE, Slotkin J, Blitz D, Wallner-Allen K, Fox NA, Beaumont JL, Mungas D, Nowinski CJ, Richler J, Deocampo JA, Anderson JE, Manly JJ, Borosh B, Havlik R, Conway K, Edwards E, Freund L, King JW, Moy C, Witt E, Gershon RC. Cognition assessment using the NIH Toolbox. *Neurology*. 2013;80(11 Suppl 3):S54–64. [PubMed: 23479546]
74. Akshoomoff N, Beaumont JL, Bauer PJ, Dikmen SS, Gershon RC, Mungas D, Slotkin J, Tulsky D, Weintraub S, Zelazo PD, Heaton RK. VIII. NIH Toolbox Cognition Battery (CB): composite scores of crystallized, fluid, and overall cognition. *Monogr Soc Res Child Dev*. 2013;78(4):119–132. [PubMed: 23952206]
75. Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of youth and adolescence*. 1988;17(2):117–133. [PubMed: 24277579]
76. R: A language and environment for statistical computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2015.
77. Bates D, Mächler M, Bolker B, Japa Walker S. Fitting linear mixed-effects models using lme4. 2014.

78. Heeringa SG, Berglund PA. A Guide for Population-based Analysis of the Adolescent Brain Cognitive Development (ABCD) Study Baseline Data. in prep.
79. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage*. 2010;53(1):1–15. [PubMed: 20547229]
80. Cohen J Statistical power analysis for the behavioural sciences. Hillsdale, NJ: erlbaum; 1988.
81. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*. 2006;442(7106):1042–1045. [PubMed: 16929307]
82. Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat*. 2003;26(4):317–330. [PubMed: 14729134]
83. Auerbach RP, Pisoni A, Bondy E, Kumar P, Stewart JG, Yendiki A, Pizzagalli DA. Neuroanatomical Prediction of Anhedonia in Adolescents. *Neuropsychopharmacology*. 2017;42(10):2087–2095. [PubMed: 28165037]
84. Forbes EE, Hariri AR, Martin SL, Silk JS, Moyses DL, Fisher PM, Brown SM, Ryan ND, Birmaher B, Axelson DA, Dahl RE. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry*. 2009;166.
85. Lewinsohn PM, Petit JW, Joiner TE Jr, Seeley JR. The symptomatic expression of major depressive disorder in adolescents and young adults. *J Abnorm Psychol*. 2003;112(2):244. [PubMed: 12784834]
86. Gabbay V, Ely BA, Li Q, Bangaru SD, Panzer AM, Alonso CM, Castellanos FX, Milham MP. Striatum-based circuitry of adolescent depression and anhedonia. *J Am Acad Child Adolesc Psychiatry*. 2013;52(6):628–641 e613. [PubMed: 23702452]
87. Boger KD, Auerbach RP, Pechtel P, Busch AB, Greenfield SF, Pizzagalli DA. Co-Occurring Depressive and Substance Use Disorders in Adolescents: An Examination of Reward Responsiveness During Treatment. *J Psychother Integr*. 2014;24(2):109–121. [PubMed: 25663795]
88. Chuang C-WI, Chan C, Leventhal AM. Adolescent Emotional Pathology and Lifetime History of Alcohol or Drug Use with and without Comorbid Tobacco Use. *Journal of dual diagnosis*. 2016;12(1):27–35. [PubMed: 26829183]
89. Garfield JBB, Allen NB, Cheetham A, Simmons JG, Lubman DI. Attention to pleasant stimuli in early adolescence predicts alcohol-related problems in mid-adolescence. *Biological Psychology*. 2015;108:43–50. [PubMed: 25818044]
90. Alloy LB, Nusslock R, Boland EM. The development and course of bipolar spectrum disorders: an integrated reward and circadian rhythm dysregulation model. *Annu Rev Clin Psychol*. 2015;11:213–250. [PubMed: 25581235]
91. Wozniak J, Spencer T, Biederman J, Kwon A, Monuteaux M, Rettew J, Lail K. The clinical characteristics of unipolar vs. bipolar major depression in ADHD youth. *J Affect Disord*. 2004;82, Supplement:S59–S69. [PubMed: 15571791]
92. Ronald A, Sieradzka D, Cardno AG, Haworth CMA, McGuire P, Freeman D. Characterization of Psychotic Experiences in Adolescence Using the Specific Psychotic Experiences Questionnaire: Findings From a Study of 5000 16-Year-Old Twins. *Schizophr Bull*. 2014;40(4):868–877. [PubMed: 24062593]
93. Tarbox SI, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Heinssen R, McGlashan TH, Woods SW. Premorbid functional development and conversion to psychosis in clinical high-risk youths. *Dev Psychopathol*. 2013;25(4pt1):1171–1186. [PubMed: 24229556]
94. Auerbach RP, Millner AJ, Stewart JG, Esposito EC. Identifying differences between depressed adolescent suicide ideators and attempters. *J Affect Disord*. 2015;186:127–133. [PubMed: 26233323]
95. C. H Stress and depression. *Annu Rev Clin Psychol*. 2005;1:293–319. [PubMed: 17716090]
96. Pagliaccio D, Barch DM, Bogdan R, Wood PK, Lynskey MT, Heath AC, Agrawal A. Shared predisposition in the association between cannabis use and subcortical brain structure. *JAMA psychiatry*. 2015;72(10):994–1001. [PubMed: 26308883]
97. Swagerman S, Brouwer R, de Geus E, Hulshoff Pol H, Boomsma D. Development and heritability of subcortical brain volumes at ages 9 and 12. *Genes, Brain and Behavior*. 2014;13(8):733–742.

98. Foland-Ross LC, Behzadian N, LeMoult J, Gotlib IH. Concordant patterns of brain structure in mothers with recurrent depression and their never-table s daughters. *Developmental neuroscience*. 2016;38(2):115–123. [PubMed: 27198667]
99. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *J Neuropsychiatry Clin Neurosci*. 2008;20(3):292–301. [PubMed: 18806232]

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Figure 1: Association Between Parental Depressive History and Subcortical Volumes

Note. Cohen's *d* effect sizes values 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 (ICV), age, sex, race, ethnicity, parental marital status, parental education, income, pubertal, status, cognition, height, Child Behavior Checklist (CBCL) scores, and T1 signal to noise. Models also included random effects for family (for release 1.1; siblings excluded for release 2.0.1) nested within scanner serial number. Results from the release 1.1 discovery sample are in panel A and those from the release 2.0.1 sample are in panel B. The two effects passing false discovery rate correction for multiple comparisons in the discovery sample (right putamen, right accumbens) are outlined in black.

Table 1:

Demographic and Clinical Characteristics

Parental Depressive History	Release 1.1			Release 2.0.1		
	No	Yes	d/OR	No	Yes	d/OR
N (%)	2644 (69.8%)	1144 (30.2%)	-	4136 (69.75%)	1794 (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 (%)	1233 (46.6%)	546 (47.7%)	1.04	1984 (48.0%)	861 (48.0%)	1.00
Race – White N (%)	2124 (80.3%)	984 (86.0%)	1.51 ***	2917 (70.5%)	1349 (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 (%)	2117 (80.4%)	798 (70.0%)	0.57 ***	3122 (76.3%)	1169 (65.9%)	0.60 ***
Parental Education – college N (%)	2243 (84.9%)	1021 (89.4%)	1.50 ***	3353 (81.1%)	1479 (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 the 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 while count (%) 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: Cohen's d for continuous variables and odds ratio (OR) for categorical variables. Income was an ordinal variable where a score of 7 indicated income between \$50,000–75,000 (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 1–4. Number of lifetime diagnoses

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was a count of depressive, anxiety, oppositional, conduct, or disruptive mood dysregulation disorder diagnoses (max=11). A count of endorsed events from the Kiddie-Schedule for Affective Disorders (K-SADS) posttraumatic stress disorder (PTSD) module was included (max=17). Signal-to-noise of the T1 structural image is denoted based on the mean/SD signal intensity. All significant group differences passed FDR correction for the tests examined here.

* $p < .05$
** $p < .01$
*** $p < .001$

Table 2:

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

	Release 1.1				Release 2.0.1			
	ICV	Subcortical	R Accumbens	R Putamen	ICV	Subcortical	R Accumbens	R 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: 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 intracranial volume (ICV), age, sex, race, ethnicity, parental marital status, parental education, income, pubertal, status, cognition, height, Child Behavior Checklist (CBCL) scores, and T1 signal to noise (individuals with missing covariates were excluded with list-wise deletion (1.1: n=626 of 3788; 2.0.1: n=721 of 5008)). 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 Cohen's *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 (in bold) that passed false discovery rate (FDR) 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.

* $p < .05$

** $p < .01$

*** $p < .001$