Neural Circuit Markers of Familial Risk for Depression Among Healthy Youths in the Adolescent Brain Cognitive Development (ABCD) Study


ABSTRACT
BACKGROUND: Family history of depression is a robust predictor of early-onset depression, which may confer risk through alterations in neural circuits that have been implicated in reward and emotional processing. These alterations may be evident in youths who are at familial risk for depression but who do not currently have depression. However, the identification of robust and replicable findings has been hindered by few studies and small sample sizes. In the current study, we sought to identify functional connectivity (FC) patterns associated with familial risk for depression.

METHODS: Participants included healthy (i.e., no lifetime psychiatric diagnoses) youths at high familial risk for depression (HR) \((n = 754)\) at least one parent with a history of depression) and healthy youths at low familial risk for psychiatric problems (LR) \((n = 1745)\) no parental history of psychopathology) who were 9 to 10 years of age and from the Adolescent Brain Cognitive Development (ABCD) Study sample. We conducted whole-brain seed-to-voxel analyses to examine group differences in resting-state FC with the amygdala, caudate, nucleus accumbens, and putamen. We hypothesized that HR youths would exhibit global amygdala hyperconnectivity and striatal hypoconnectivity patterns primarily driven by maternal risk.

RESULTS: HR youths exhibited weaker caudate-angular gyrus FC than LR youths \((\alpha = 0.04, \text{Cohen's } d = 0.17)\). HR youths with a history of maternal depression specifically exhibited weaker caudate-angular gyrus FC \((\alpha = 0.03, \text{Cohen's } d = 0.19)\) as well as weaker caudate-dorsolateral prefrontal cortex FC \((\alpha = 0.04, \text{Cohen's } d = 0.21)\) than LR youths.

CONCLUSIONS: Weaker striatal connectivity may be related to heightened familial risk for depression, primarily driven by maternal history. Identifying brain-based markers of depression risk in youth can inform approaches to improving early detection, diagnosis, and treatment.

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Depression is experienced by 264 million people worldwide (1) and is a leading cause of disability and suicide among adolescents (2–4). Family history of depression is a robust predictor of early-onset depression (5,6) as well as other psychiatric disorders (7,8) in youth. Research conducted to date suggests that a family history of depression may confer risk for depression in youth through alterations in neural circuit function associated with reward and emotional processing. Importantly, these brain changes may be evident in youths at high familial risk for depression despite their not presently experiencing depression (9–17). However, knowledge on this topic is limited due to small sample sizes in previous studies, which has hindered the identification of robust markers that distinguish neurobiological profiles among youth with and without a family history of depression. The identification of brain-based signatures of depression risk in youth is essential for advancing understanding of the precise neural mechanisms that contribute to heightened vulnerability, which may ultimately inform approaches for earlier and more accurate identification of mental health problems during adolescence. In the current study, we leveraged a large neuroimaging dataset from the ongoing Adolescent Brain Cognitive Development (ABCD) Study (18) to identify dissociable patterns of resting-state functional connectivity (FC) in emotion- and reward-related networks. Healthy (i.e., no lifetime psychiatric diagnoses) youths who had at least one parent with a lifetime history of depression (HR, \(n = 754\)) were compared with healthy youths whose parents had no lifetime history of any psychiatric problems (LR, \(n = 1745\)). This represents the largest known study to examine differential resting-state FC profiles that distinguish healthy youths at high versus low familial risk for depression.
During childhood and adolescence, neural circuitry that supports emotion and reward processing undergoes significant maturation wherein heightened plasticity corresponds to greater sensitivity to the environment (19,20), making these developmental periods essential to investigate. Relatedly, depression commonly emerges during a child’s transition to adolescence (21), which marks a period of increased risk for psychopathology (22). To improve mental health outcomes among youths who are at an elevated risk for depression and increase our understanding of the pathophysiology of depression, it is imperative to identify neural markers of vulnerability that are present before the onset of clinically significant symptoms. Previous studies that have examined never-depressed youths at high familial risk for depression have found differences in neural activation and FC within reward- and emotion-related circuits compared with youths at low familial risk (9–17,23). More specifically, alterations in activation and FC of the amygdala, caudate, putamen, and nucleus accumbens have been observed in youths at high familial risk for depression, including lower activation of and weaker connectivity with striatal regions (9,13–17), as well as heightened activation of and altered connectivity with the amygdala (11–13,17) compared with low-risk youths.

Despite significant progress elucidating the neural mechanisms that underly familial risk of depression among youths, previous studies have relied on small sample sizes (i.e., less than 150 participants), with the exception of Cai et al. (24), Freeman et al. (25), and Pagliaccio et al. (25) all of which utilized ABCD Study data. However, Cai et al. (24) focused solely on default mode network FC; Freeman et al. (23) investigated reward-related reactivity; and Pagliaccio et al. (25) examined subcortical brain volume. Notably, the studies conducted by Cai et al. (24) and Freeman et al. (23) yielded null results. Furthermore, all three of these studies included youth samples with psychiatric diagnoses, thus limiting the ability to reveal neural vulnerability markers that might have been present before the onset of psychopathology (and thus not a consequence or correlate of psychiatric symptoms). Thus, the number of large, statistically well-powered studies that have identified differences in neural function and connectivity between high- and low-risk youths, specifically among healthy youths with no lifetime psychiatric diagnoses, remains limited.

As a result of the lack of well-powered studies of healthy youths, vulnerability markers of depression, which is critical knowledge for understanding the pathophysiological mechanisms of depression, are largely unknown. Here, we aimed to uncover unique neural signatures of high familial risk for depression among healthy youths with no psychiatric diagnoses. We used data from the ABCD Study (18), and participants included healthy youths with at least one parent with a history of depression (HR, n = 754) versus healthy youths whose parents had no lifetime history of any psychiatric problems (LR, n = 1745). We utilized a whole-brain seed-to-voxel approach to examine resting-state FC patterns with the amygdala, nucleus accumbens, caudate, and putamen. Based on findings from existing studies (9–17), we hypothesized that HR youths would exhibit global patterns of amygdala hyper-connectivity and striatal hypoconnectivity compared with LR youths. In addition, exploratory analyses were conducted to assess maternal and paternal risk separately, and we hypothesized that the results would be driven by maternal risk based on evidence that maternal (vs. paternal) depression is associated with higher risk of offspring psychopathology (26,27).

METHODS AND MATERIALS

Study Design and Participants

Participants are from the ABCD Study funded by the National Institutes of Health (18), which recruited 11,878 youths across 21 study sites who are being followed over 10 years. Youths who were 9 or 10 years of age at the time of the baseline visit (between 2016 and 2018) and their parents were recruited from public and private elementary schools within the catchment areas of the 21 research sites. School selection was based on sex assigned at birth, race, ethnicity, socioeconomic status, and urbanicity (28). The study includes twins recruited from 4 sites in addition to multiplex siblings from the same family.

For the ABCD Study, inclusion criteria consisted of the following: 1) age 9 to 10 years at the time of the baseline visit and 2) attending a public or private elementary school in the catchment area. Exclusion criteria included the following: 1) not fluent in English; 2) having a parent who was not fluent in English or Spanish; 3) major medical or neurological conditions; 4) gestational age < 28 weeks or birth weight < 1200 g; 5) contraindications to magnetic resonance imaging (MRI) scanning; 6) a history of traumatic brain injury; and 7) a current diagnosis of schizophrenia, moderate to severe autism spectrum disorder, intellectual disability, or alcohol/substance use disorder. All participants provided informed consent or assent [see (29) for ethics and oversight in the ABCD Study].

We used data from the 4.0 release (DOI: https://doi.org/10.15154/1523041), which includes baseline data. A consort chart is shown in Figure 1. Exclusion criteria for the current study included the following: 1) adopted youths, given that assessment of family history of psychiatric problems focuses on blood relatives and 2) youths with any lifetime psychiatric diagnoses at the time of the baseline visit (see Supplemental Methods for details regarding specific diagnoses) as reported by the parent (based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children for DSM-5 (see below); and 3) resting-state functional MRI (fMRI) data were recommended for exclusion by the ABCD-Brain Imaging Data Structure Community Collection team (30). Youths were included in the HR group when there was a maternal and/or paternal history of depression (based on the Family History Assessment Module Screener [FHAM-S]; see below). Youths were included in the LR group when there was no parental lifetime history of any psychiatric problems. Thus, this study included healthy (i.e., no history of psychiatric diagnosis) HR youths (n = 754) or LR youths (n = 1745). We also examined maternal (n = 528) and paternal (n = 357) risk separately.

Demographic and Clinical Information

Parents reported the child’s sex assigned at birth, age, and race/ethnicity, as well as parental education, marital status, and combined household income.
The FHAM-S (31) is a brief interview (conducted by trained research assistants) that was used to assess familial history of psychiatric problems in all first- and second-degree biological relatives of the child (i.e., full and half-siblings, parents, grandparents, aunts, uncles) as reported by a parent of the youth at the baseline visit. The presence/absence of symptoms associated with alcohol and substance use disorder, depression, anxiety, mania, psychosis, and antisocial personality disorder in all blood relatives was measured. Given that most previous work has focused on parental history (e.g., (11–13,16)), the current study focused on parents to limit heterogeneity and enhance ease of comparison across studies and due to parents’ larger influence on youth psychopathology as compared to sibling and second-degree relative histories (9,32–34). The HR group included youths who had at least one biological parent with a history of depression, whereas the LR group included youth whose parents had no lifetime history of any psychiatric problems.

Current and lifetime psychiatric diagnoses for youths were obtained using the parent-reported responses to the computerized Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children for DSM-5 (35). The youths were instructed to fixate on a crosshair. Resting-state images were acquired in the axial plane using an echo-planar imaging sequence. Other resting-state imaging parameters varied by 3T scanner and have been described previously in Casey et al. (18). Data were preprocessed by the ABCD Consortium’s data analytic core (36). Human Connectome Project minimal preprocessing steps were implemented (37). We used the resting-state fmRI data that were preprocessed by the ABCD-Brain Imaging Data Structure Community Collection team (30).

The Developmental Cognition and Neuroimaging lab blood oxygen level–dependent fmRI data processing consisted of 3 steps. First, fmRI data were demeaned and detrended with respect to time such that the central tendency was estimated based on low head-movement data excluding frames with a framewise displacement (FD) threshold of 0.3 mm. Next, a general linear model was used to denoise the processed fmRI data. Regressors included mean time series for white matter, cerebrospinal fluid, and the global signal, and translational (x, y, z) and rotational (roll, pitch, and yaw) motion parameters, where the beta weights were estimated on low head-movement data (FD $< 0.3$ mm) but applied to the entire dataset. After denoising, the time series were bandpass filtered between 0.008 and 0.09 Hz using a second-order Butterworth filter applied in the forward and backward direction to avoid the introduction of lags in-phase. To avoid the introduction of head-motion artifacts when applying the bandpass filter, data coming from frames with an FD $> 0.3$ mm were replaced.

Figure 1. Consort chart of youths in the final high-risk and low-risk groups. Exclusion criteria included the following: adopted youth, youth with any lifetime psychiatric diagnoses at the time of the baseline visit, and resting-state functional magnetic resonance imaging was recommended for exclusion by the Adolescent Brain Cognitive Development (ABCD) Study–Brain Imaging Data Structure Community Collection (ABCC) team. Additionally, for the high risk for depression group only, youths were excluded if there was no parental history of depression. For the low risk for psychiatric problems group only, youths were excluded if there was a parental lifetime history of any psychiatric problems. Youths were excluded if they lacked resting-state functional magnetic resonance imaging or diagnostic data, and siblings were excluded at random. Thus, this study includes healthy youths at high risk for depression ($n = 754$) or low risk for psychiatric problems ($n = 1745$). Furthermore, maternal ($n = 528$) vs. paternal ($n = 357$) risk were examined separately and compared with the low-risk group.

The Imaging Acquisition and Preprocessing

ABCStudy imaging procedures have been described in detail in Casey et al. (18). Youths completed four 5-minute resting-state fmRI scans at the baseline visit during which
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RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics for the HR (n = 754; defined by the presence of maternal and/or paternal depression history) and LR (n = 1745) groups are reported in Table 1. Groups did not differ in age, sex assigned at birth, or parental education, but they differed in race and ethnicity (p < .001), internalizing symptoms (p < .001), externalizing symptoms (p < .001), total problems (p < .001), parental marital status (p < .001), and household income (p = .001). The same demographic and clinical differences were found when examining HR youths with maternal (n = 528) and/or paternal (n = 357) histories of depression versus LR youths (n = 1745) (see Tables S1 and S2, respectively).

Descriptive statistics for parental lifetime psychiatric problems are reported in Table S3. Table S4 shows comorbidity of parental lifetime psychiatric problems.

Risk-Related Neural Circuit Differences Between HR and LR Groups

All group-level results that survived thresholding at the voxel and cluster levels were for FC with the left caudate. No other seeds (i.e., the right caudate and bilateral amygdala, putamen, nucleus accumbens, caudate, and putamen) and all other voxels were included. FC outlier voxels were defined as those that were 3 standard deviations above or below the mean across all voxels. All analyses outlined above were conducted in the same manner for both maternal- and paternal-specific risk definitions.

Neural Circuit Differences Between HR and LR Groups Defined by Maternal or Paternal Risk

We investigated group-level results at a p = .001 voxel-level threshold to determine whether significant differences remained at the more stringent voxelwise threshold (Table S6). For maternal depression risk, the difference in left caudate-left dIPFC FC between youths at high risk for maternal depression versus those at low risk remained significant and in the same direction. However, there were no significant differences between high- and low-risk youths at a p = .001 threshold for the risk from either parent finding in left caudate-right angular gyrus FC or the maternal risk finding in left caudate-left angular gyrus FC.
Sensitivity Analyses: Risk-Related Neural Circuit Differences Between HR and LR Groups After Controlling for Additional Demographic and Clinical Variables

Because the HR and LR groups differed in youth race and ethnicity, youth psychiatric symptoms (internalizing symptoms, externalizing symptoms, and total problems), parental marital status, and household income, we conducted sensitivity analyses to examine whether group-level results could be better explained by these differences. All reported clusters remained significant after inclusion of potential confounds, with all effects of interest in the same direction (Table S9).

Follow-up Analyses: Associations Between Risk-Related Caudate FC Differences and Psychiatric Symptoms Among HR Youths

We conducted mixed-effects regression models using age (fixed effect), sex assigned at birth (fixed effect), and scanner site (random effect) as covariates to test whether caudate FC was associated with depression symptoms, internalizing symptoms, externalizing symptoms, and/or total problems within the HR group. We found that left caudate-left angular gyrus FC (which differed significantly between maternal risk groups) was associated with current depression ($\beta = 0.092, p = .044$) and internalizing symptoms ($\beta = 0.113, p = .013$) but not externalizing symptoms ($p > .05$) or total problems ($p > .05$) within the HR group.

### Table 1. Demographic and Clinical Characteristics in HR Versus LR Groups Defined by Risk Associated With Either Parent

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR, n = 754</th>
<th>LR, n = 1745</th>
<th>Statistical Value</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Years</td>
<td>9.94 (0.63)</td>
<td>9.98 (0.61)</td>
<td>$t_{1,397.4} = 1.56$</td>
<td>.119</td>
</tr>
<tr>
<td>Sex Assigned at Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>413 (54.77%)</td>
<td>925 (53.01%)</td>
<td>$\chi^2_{1} = 0.59$</td>
<td>.442</td>
</tr>
<tr>
<td>Male</td>
<td>341 (45.23%)</td>
<td>820 (46.99%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race and Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (0.66%)</td>
<td>53 (3.04%)</td>
<td>$\chi^2_{4} = 53.67$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Black</td>
<td>60 (7.96%)</td>
<td>217 (12.44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>106 (14.06%)</td>
<td>375 (21.49%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Native Hawaiian, Pacific Islander, Alaskan Native, American Indian, or Multiracial)</td>
<td>85 (11.27%)</td>
<td>150 (8.60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>498 (66.05%)</td>
<td>950 (54.44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing symptoms</td>
<td>4.04 (4.24)</td>
<td>2.77 (3.22)</td>
<td>$t_{1,147.6} = -7.37$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Externalizing symptoms</td>
<td>2.75 (3.47)</td>
<td>1.91 (2.65)</td>
<td>$t_{1,147.6} = -5.99$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Total problems</td>
<td>12.52 (11.08)</td>
<td>9.06 (8.87)</td>
<td>$t_{1,188.2} = -7.59$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Parental Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>317 (42.04%)</td>
<td>720 (41.26%)</td>
<td>$\chi^2_{2} = 1.89$</td>
<td>.388</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>236 (31.30%)</td>
<td>514 (29.46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>201 (26.66%)</td>
<td>510 (29.23%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parental Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>522 (69.23%)</td>
<td>1395 (79.94%)</td>
<td>$\chi^2_{6} = 58.46$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Widowed</td>
<td>6 (0.80%)</td>
<td>9 (0.52%)</td>
<td></td>
<td></td>
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<tr>
<td>Divorced</td>
<td>87 (11.54%)</td>
<td>88 (5.04%)</td>
<td></td>
<td></td>
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<tr>
<td>Separated</td>
<td>29 (3.85%)</td>
<td>31 (1.78%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>61 (8.09%)</td>
<td>145 (8.31%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with a partner</td>
<td>46 (6.10%)</td>
<td>63 (3.61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused to answer</td>
<td>3 (0.40%)</td>
<td>14 (0.80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household Income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $50,000/year</td>
<td>169 (22.41%)</td>
<td>351 (20.11%)</td>
<td>$\chi^2_{3} = 15.84$</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>$50,000–$100,000/year</td>
<td>235 (31.17%)</td>
<td>443 (25.39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater than $100,000/year</td>
<td>301 (39.92%)</td>
<td>791 (45.33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA/refused to answer</td>
<td>49 (6.50%)</td>
<td>160 (9.17%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) for continuous variables and as n(%) for categorical variables. Demographic and clinical characteristics are displayed for high-risk (either parent) and low-risk groups. One-way analyses of variance (for continuous variables) and $\chi^2$ tests (for categorical variables) were conducted as appropriate for all variables of interest.

CBCL, Child Behavior Checklist; HR, high risk for depression; LR, low risk for psychiatric problems; NA, does not know.

*a*Indicates that the group n or mean was significantly higher than that of the other group.

*b*Indicates a significant difference between groups ($p < .05$).

*c*Based on which parent was reporting; 2175 (86.99%) biological mothers, 325 (13.01%) biological fathers.

*d*Household income was measured as total household income before taxes and deductions during the last 12 months.
Follow-up Analyses: Neural Circuit Differences Between Youths of Parents With and Without Comorbidities

Given that most of the HR youths (74.8%) had at least one parent with at least one comorbid condition, we examined whether FC with the left caudate was associated with the presence/absence of comorbidities. We found that left caudate-right angular gyrus FC was weaker in youths whose parents with depression had at least one comorbid condition (mean = –0.056) compared with youths whose parents with depression did not have any comorbid condition (mean = –0.039; \( t_{908.41} = 2.85, p = .005 \)). In addition, left caudate-left angular gyrus FC was weaker in youths whose mothers with depression had at least one comorbid condition (mean = –0.01) than in youths whose mothers with depression did not have any comorbid condition (mean = 0.02; \( t_{548.95} = 4.43, p < .001 \)). Finally, left caudate-left dlPFC FC was weaker in youths whose mothers with depression had at least one comorbid condition (mean = 0.04) than in youths whose mothers with depression did not have any comorbid condition (mean = 0.07; \( t_{551.3} = 3.85, p < .001 \)).

DISCUSSION

In the current study, we examined differences in resting-state FC among emotion- and reward-related circuits between healthy HR youths and healthy LR youths. We found that HR youths exhibited weaker left caudate-right angular gyrus FC than LR youths. Exploratory analyses revealed that youths whose mothers had a history of depression exhibited weaker left caudate-left angular gyrus FC, as well as weaker left caudate-left dlPFC FC, than LR youths. Findings remained significant after accounting for demographic and clinical variables that differed between the HR and LR groups (i.e., youth race/ethnicity, youth psychiatric symptoms, parental marital status, household income). Consistent with our hypotheses, there were no differences in FC between youths whose fathers...
had a history of depression and LR youths. Surprisingly, there were no group differences in FC with the amygdala, putamen, or nucleus accumbens. Altogether, these findings suggest that weaker functional connections with the caudate may be related to heightened risk for depression among youths with parental depression histories and that this effect is primarily driven by maternal history. The identification of robust brain-based signatures of depression risk in youths can advance knowledge of the neural underpinnings of depression, which has the potential to inform early detection, diagnosis, and treatment approaches.

The finding that HR youths exhibited weaker FC between the caudate and angular gyrus than LR youths, a difference that was driven primarily by maternal depression history, represents a novel finding in the existing familial risk literature. While some previous studies have examined group differences in activation and FC with other striatal regions (e.g., nucleus accumbens, putamen) (9,13–17), our study demonstrated robust alterations in caudate FC among HR youths. The caudate has been implicated in numerous functions, including learning, memory, reward, motivation, and emotion processing (41). The angular gyrus is involved in cognitive emotion regulation (42), episodic memory (43,44), and executive functioning (45,46). More specifically, this region is thought to regulate emotions by producing imagined or remembered situations (42). Therefore, weaker functional connections between the caudate and angular gyrus may reveal early alterations in circuits underlying HR youths’ ability to contextually gate (based on imagined or lived experiences) reward-related emotions. Our findings are consistent with previous work indicating lower responses in the caudate during reward and emotion processing tasks among HR youths (16,47) and that individuals with depression demonstrated stronger caudate-angular gyrus connectivity following effective treatment with electroconvulsive therapy (48). Our findings are also consistent with a recent paper by Ho et al. (6) that showed that lower resting-state caudate FC was associated with higher concurrent and 1-year depression symptoms among 9- to 10-year olds in the ABCD Study. Given that our study is the first to reveal weaker caudate FC specifically among HR youths, future studies should further examine the potential role of caudate FC in conferring familial risk for depression.

Exploratory analyses revealed that youths whose mothers had a history of depression exhibited weaker FC between the caudate and dIPFC than LR youths. The dIPFC is important for various executive functions including task switching, planning, inhibition, and working memory (49–51). The dIPFC has afferent projections to the caudate that have been shown to be involved in decision making, reasoning, and inhibition (52). In addition, stronger caudate-dIPFC FC has been associated with depression (53,54), suggesting that this early marker of weaker caudate-dIPFC FC may reflect an adaptive compensatory process. The observation that specifically HR youths with a maternal history of depression had weaker caudate-dIPFC FC suggests that cognitive processes may be partially influenced by maternal depression.

It is important to note that group-level results held at the more stringent voxelwise threshold of \(p = .001\) for the maternal risk finding in caudate-dIPFC FC but not for the either (combined) parental risk finding (i.e., caudate-angular gyrus FC) or for the other maternal risk finding (i.e., caudate-angular gyrus FC). While effect sizes for our FC findings were relatively small (i.e., \(d = 0.17–0.21\)), they are comparable to effects found in other fMRI studies using ABCD Study data [e.g., (55)] and are consistent with the expectation that ABCD Study analyses would generate small effects due to the demographically diverse nature of the sample (i.e., effect sizes are more diluted due to the complex contextual and background variables) (56). This suggests that the true effects may indeed be small, which would be unsurprising given that there are many factors that can lead to depression (6), and there are numerous relationships with small effects that are considered meaningful (57). Relatedly, because it is well established that small studies often overestimate effect sizes (58–60), it is possible that previous work using small samples observed artificially inflated effects. Because even small brain differences can be clinically and behaviorally relevant, we recommend that future work further interrogate the behavioral and clinical ramifications of small effect sizes detected in the brain.

### Table 2. Functional Connectivity Differences Between Youths at High Versus Low Risk for Depression

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size, mm³</th>
<th>Peak Coordinates</th>
<th>Functional Connectivity Values, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Functional Connectivity Differences in Parental HR vs. LR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Caudate Seed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right angular gyrus</td>
<td>46</td>
<td>−36.7</td>
<td>65.5</td>
</tr>
<tr>
<td>Left Caudate Seed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left angular gyrus</td>
<td>48</td>
<td>42.5</td>
<td>70.3</td>
</tr>
<tr>
<td>Left dIPFC</td>
<td>47</td>
<td>35.3</td>
<td>−18.5</td>
</tr>
</tbody>
</table>

Cluster sizes, peak coordinates, and mean functional connectivity values displayed for high- and low-risk groups.

dIPFC, dorsolateral prefrontal cortex; HR, high risk for depression; LR, low risk for psychiatric problems.

HR group consists of youths whose mother had a history of depression.

HR group consists of youths with at least one parent with a history of depression.

Cluster sizes, peak coordinates, and mean functional connectivity values displayed for high- and low-risk groups.

HR group consists of youths whose mother had a history of depression.
Contrary to our hypotheses and to previous evidence of stronger amygdala (11–13,17) and weaker striatal (9,13–17) activation and FC among HR youth, there were no group differences in FC for the amygdala, putamen, or nucleus accumbens. Given that these regions continue to mature throughout adolescence and early adulthood (19,20), it is possible that these differences may emerge and appear more prominently later in development (e.g., during mid to late adolescence). Given the longitudinal design of the ABCD Study, this question can be addressed using future waves of data.

Follow-up analyses indicated that left caudate-left angular gyrus FC (which differed significantly between maternal risk groups) was associated with current depression and internalizing symptoms among HR youths. Despite not being able to thoroughly disentangle depression risk from psychopathology risk more broadly in the current study, these findings suggest that caudate-angular gyrus FC may reflect overall psychopathology risk but be primarily driven by dimensions of depression/internalizing symptoms more specifically. In addition, findings suggest that caudate FC associated with maternal risk may be specific to depression and internalizing symptoms in a way that caudate FC associated with paternal risk is not.

Follow-up analyses among HR youths revealed that FC with the caudate was weaker in youths whose parents had at least one comorbid condition versus youths whose parents only had depression. These findings suggest that the identified neural markers of risk may reflect a combination of parental depression and comorbid disorders and not depression specifically. Although we do not have evidence to rule out comorbid disorders as a possible explanation, the observed association between neural markers and depression/internalizing symptoms in HR youths and the lack of association with other symptom dimensions suggest greater specificity to depression. Future studies that compare youths whose parents have any type of psychopathology history to those whose parents do not have any type of psychopathology history would help disentangle depression risk from general psychopathology risk.

In our study, we found no differences in caudate FC between youths whose fathers had a history of depression compared with LR youths. This finding is consistent with existing literature indicating that maternal (vs. paternal) depression is associated with higher risk of offspring psychopathology (26,27). One possible contributor to the lack of FC alterations in paternal HR youths is that youths tend to spend more time with their mothers (61), who may have a stronger influence on youth mental health and brain development. Additionally, most of the reporters in this study were mothers (~87%), and there was more missing data regarding fathers’ mental health. This resulted in a smaller sample size for the paternal analysis, which may have affected our ability to detect significant FC differences. It is important to note that previous studies have defined risk groups by including youth with at least one parent exhibiting a history of depression (10–13,16,17,82) or merely focused on maternal history (9,14,15). However, only one study conducted to date (which investigated reward reactivity) has specifically examined associations between paternal risk for depression and offspring neural functioning (23), and no studies to date have examined resting-state FC differences between youths at high versus low paternal risk for depression. Thus, additional research is needed to further clarify the relationship between paternal depression and offspring neurobiological function.

Our study has several limitations. The measure used to define a history of parental psychiatric problems (FHAM-S) was a brief interview that did not distinguish between past and current psychiatric problems. Similarly, each psychiatric problem, including depression, was assessed using a single question. Nonetheless, the relative ease and time-efficient manner of collecting these data facilitated the collection of such data from a large sample, which represents a clear strength of this work. Relatedly, the depression question in the FHAM-S does not capture the presence of anhedonia without low mood (i.e., it only captures the presence of anhedonia with low mood). This may have resulted in underreporting of parental depression in our sample (e.g., some parents of LR youths may have had anhedonia without low mood) and also means that our findings may be more specific to depressed mood than to anhedonic symptoms. This may also have resulted in the HR group being artificially smaller. The use of a more detailed diagnostic interview that more fully captures depression symptoms would strengthen future work. An additional limitation is that this study utilized a case-control design (i.e., high- vs. low-risk groups) rather than a dimensional approach in which familial risk for depression is measured on a continuous rather than a categorical scale. The case-control design was chosen to align most closely with earlier work to facilitate comparisons; however, it would be advantageous for future studies to also examine familial risk dimensionally. Additionally, far fewer diagnoses were assessed via child report (vs. parent report) in the ABCD Study [to minimize burden on the youth, see (63)]; thus, we were unable to determine whether the results would have differed if we had relied on child report of psychopathology. Finally, to facilitate comparisons with the majority of prior research, our study focused on resting-state FC. However, given that there is evidence of differences in neural responses related to reward processing between youths who are at high versus low risk for depression (17), future research would benefit from also investigating task-based FC.

Despite these limitations, our study has numerous strengths. This study is the largest to date to reveal differential resting-state FC profiles that distinguish healthy youths at high familial risk for depression from those at low familial risk for psychopathology and represents the first resting-state FC study to examine paternal risk specifically, which was made possible by the large sample size. Second, we utilized strict imaging criteria and rigorous statistical thresholds to reveal robust FC differences. Notably, our findings remained significant after accounting for demographic and clinical variables (i.e., youth race/ethnicity, youth psychiatric symptoms, parental marital status, household income) that differed between the risk groups. Third, our study examined a narrow age range (i.e., 9- and 10-year olds), while the majority of prior studies examined larger age ranges (e.g., 8–14, 8–17 years), making it difficult to precisely elucidate the age(s) at which vulnerability markers emerge. Identifying risk markers during preadolescence is particularly important given that depression rates increase substantially during adolescence (64). Finally, our study excluded youths with any lifetime diagnoses (i.e., not only depression), thus representing the largest study to examine
neurobiological risk markers in healthy youths. Importantly, this exclusion criterion makes this study highly suitable for detecting vulnerability markers of psychopathology.

Our study provides important insights into the neurobiological mechanisms underlying risk among youths with parental histories of depression. Our findings indicate that weaker functional connections with regions involved in reward processing, specifically the caudate, may represent heightened familial risk for depression and that this effect is primarily driven by maternal history. The knowledge gained from this study and future studies of familial risk have the potential to contribute to the optimization of early detection and intervention for at-risk youths, which will ultimately help to alleviate the immense burden of depression.

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