NEW RESEARCH

# Preadolescent Family Conflict, Parental Depression, and Neural Circuitry Interact to Predict Adolescent Symptoms

Bailey Holt-Gosselin[a], PhD, Erin Z. Basol[a], MRes, Taylor J. Keding[a], PhD, Kathryn Rodrigues[a], BS, Jutta Joormann[a], PhD, Dylan G. Gee[a,*], PhD

**Objective:** Youth whose parents have depression histories are at elevated risk for psychopathology. Familial depression–related patterns of neurodevelopment and environmental stress (eg, family conflict) likely contribute to heightened risk. However, knowledge remains limited due to few studies, small sample sizes, and cross-sectional designs. We sought to identify how neural circuitry, familial risk for depression, and family conflict interact during preadolescence to predict adolescent psychopathology.

**Method:** Participants included healthy (no lifetime psychiatric diagnoses) youth at high (HR, n = 794; at least one parent with a depression history) and low (LR, n = 1,708; no parental history of psychopathology) familial risk for depression, aged 9 to 10, from the Adolescent Brain Cognitive Development (ABCD) Study. We tested whether functional connectivity (FC) among 12 resting-state networks interacted with risk status and family conflict at ages 9 to 10 to predict psychiatric symptoms at ages 12 to 13.

**Results:** Risk status significantly interacted with family conflict and cingulo-parietal network (CPN) FC at ages 9 to 10 to predict total problems and internalizing symptoms at ages 12 to 13 ($R^2 = 0.349$, $\Delta R^2 = 0.017$, $\eta_p^2 = 0.005$; $R^2 = 0.254$, $\Delta R^2 = 0.023$, $\eta_p^2 = 0.004$, respectively). Specifically, among youth in low (but not high) family conflict environments, there was a significant negative association between CPN FC at ages 9 to 10 and psychiatric symptoms at ages 12 to 13 for HR youth, whereas this association was significantly positive for LR youth.

**Conclusion:** Findings suggest that CPN connectivity and family conflict in preadolescence may be prognostic risk markers for future symptoms related to parental depression. These markers may shed light on brain-based processes by which environmental adversity relates to heightened familial risk for psychopathology, although small effect sizes necessitate future investigation to better understand the potential clinical relevance.

**Key words:** adolescent psychopathology; familial risk for depression; ABCD Study; resting-state fMRI; family conflict

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Youth whose parents have depression histories are at elevated risk for developing depression,[1] as well as other psychiatric disorders.[2] Heightened risk may be due to alterations in brain circuit neurodevelopment that predate the onset of psychopathology,[3-13] and to exposure to environmental stressors, such as family conflict.[14-16] Early functional neural markers of familial risk for depression have been shown to predict the onset of future psychopathology among high-risk youth.[7,12,17-20] However, to our knowledge, no study has elucidated how familial risk for depression interacts with neural circuitry and family environment to predict future mental health symptoms among youth. The identification of neural and environmental factors that contribute to the development of psychopathology among vulnerable youth is imperative for the improvement of early risk identification and intervention strategies.

A growing body of work indicates that youth at high familial risk for depression who do not have depression histories themselves exhibit differences in neural circuitry compared to youth at low familial risk.[3-12,21] In particular, differences in resting-state functional connectivity (FC) have been observed within reward- and emotion-related circuits,[4,6,7,9,10] namely, altered amygdala FC[6,9,19] and weaker striatal FC.[7,10] There is also evidence for differences in large-scale brain networks, such as the default mode network (DMN), frontoparietal network (FPN), salience network (SN), visual network, and sensorimotor network among youth at high familial risk for depression.[5,9,11-13,22] Taken together, these findings suggest that youth without a diagnostic history of depression who have family histories of depression exhibit alterations across multiple neural circuits, including those that typically develop earlier (eg, visual, sensorimotor) and later (eg, frontoparietal) in

childhood. Given the evidence for a wide range of neural circuits implicated in familial risk for depression, large, well-powered studies that use exploratory approaches aimed at quantifying circuit differences between youth at high vs low familial risk may reveal novel insights into the neurodevelopmental mechanisms of depression. Although prior studies revealing neural markers of familial risk for depression among youth have provided an important foundation, various methodological challenges have hindered the discovery of robust and replicable findings. Many prior studies have been limited to small sample sizes (eg, <200 youth) and have included high-risk youth who met diagnostic criteria for psychiatric disorders (eg, anxiety) at the time of the scan. Such study designs limit the ability to reveal vulnerability markers that are present prior to the onset of psychopathology and are thus not correlates or consequences of symptoms associated with other disorders. Research with large sample sizes examining youth without histories of psychiatric disorders is needed to fully elucidate the neural mechanisms underlying familial risk for depression among youth.

Although there have been numerous cross-sectional studies revealing neural markers of familial risk for depression among youth, relatively few studies have investigated neural circuit patterns that differentially predict the later onset of psychopathology based on familial risk status.[23] Existing research has observed functional alterations in amygdala, striatal, and prefrontal cortex (PFC; eg, anterior cingulate, dorsolateral PFC) regions that predicted subsequent onset of internalizing disorders among youth at high familial risk for depression.[7,12,17-20] However, most studies have included youth samples with large age ranges (eg, 8-14 years) and measured subsequent psychopathology at inconsistent follow-up intervals (eg, some were evaluated 2 years later, others 5 years later, within the same sample). Relatedly, prior studies have measured psychopathology less than 2 years later, which may not be long enough to detect significant changes in symptoms. These limitations hinder the ability to identify neural risk markers that may depend on the developmental period(s) at which they are assessed. Given these limitations and the minimal research in this area, longitudinal studies that identify neurobiological markers that may differentially predict future mental health outcomes based on familial risk status are warranted.

In addition to neurobiological factors, heightened risk for psychopathology among youth with family histories of depression may be partially explained by adverse experiences in their home environments.[14-16] Relative to youth at low familial risk, youth at high familial risk for depression tend to experience greater family conflict,[15,24] lower family cohesion,[14] and more punitive family environments,[16] all of which are associated with the later development of psychopathology.[25-28] Although multiple aspects of family functioning have been identified as predictors of mental health problems among youth,[29] family conflict has been one of the most robust predictors of youth psychopathology.[29] Identifying the precise environmental and/or biological conditions whereby family conflict gives rise to heightened risk for psychopathology for high familial risk youth may provide novel knowledge regarding the mechanisms underlying familial risk for depression.

Despite well-established links among family conflict, familial risk for depression, and the later development of psychopathology, no known studies have simultaneously examined these factors in the context of neurodevelopment. Some prior work has investigated the interaction between the family environment and neurobiological factors in predicting future mental health outcomes among youth (regardless of familial depression risk status).[30-32] These studies have identified structural and functional neural factors (eg, cortical thinning, reward responsivity) that interact with familial behaviors (eg, maternal aggressiveness, family conflict) to predict subsequent internalizing symptoms.[30-32] This research points to neural markers of susceptibility to adverse family contexts among youth, which may interact with familial risk to further increase psychopathology risk. However, these studies did not take into account familial depression histories. Thus, there is a critical need to understand how the unique combination of neural circuit function, family history of depression, and family-level stressors may increase risk for the subsequent development of psychopathology among youth.

The present longitudinal study leveraged a large sample of youth from the ongoing Adolescent Brain Cognitive Development (ABCD) Study[33] to explore the associations among preadolescent neural markers of familial risk for depression, family conflict, and adolescent psychiatric symptoms. Participants included 9- to 10-year-old youth with no lifetime history of any psychiatric diagnosis at the initial visit. Youth at high familial risk for depression (HR, n = 794) had at least one parent with a lifetime history of depression, whereas youth at low familial risk for depression (LR, n = 1,708) had both parents with no lifetime history of any psychopathology. We chose to examine healthy preadolescents because we sought to identify preexisting prognostic markers of psychopathology that are present before youth enter a developmental period that marks heightened risk for psychopathology (ie, adolescence).[34] Our aim was to investigate whether the interaction among familial risk status, family conflict, and

resting-state FC from 12 large-scale networks during pre-adolescence (ie, ages 9-10) predicts psychopathology 3 years later during adolescence (ie, ages 12-13).

A 3-way interaction among baseline brain function, risk status, and environmental factors predicting the future onset of psychopathology is well suited for identifying a unique set of pre-existing predictors of psychopathology that are observable when youth do not yet exhibit psychopathology. The identification of prospective predictors of psychopathology, prior to the onset of symptoms, is particularly useful for risk detection and prevention, and thus it is important to examine the interaction between baseline brain function and the environmental context that the brain was in at that time (eg, baseline family conflict). In addition, the 3-way interaction analytic approach was selected because modeling these 3 factors simultaneously (with a 3-way interaction and including lower-order 2-way interactions, as opposed to multiple models examining 2-way interactions) is the most statistically rigorous approach (for parsimony and to minimize statistical tests) and was feasible given our large sample size and statistical power.

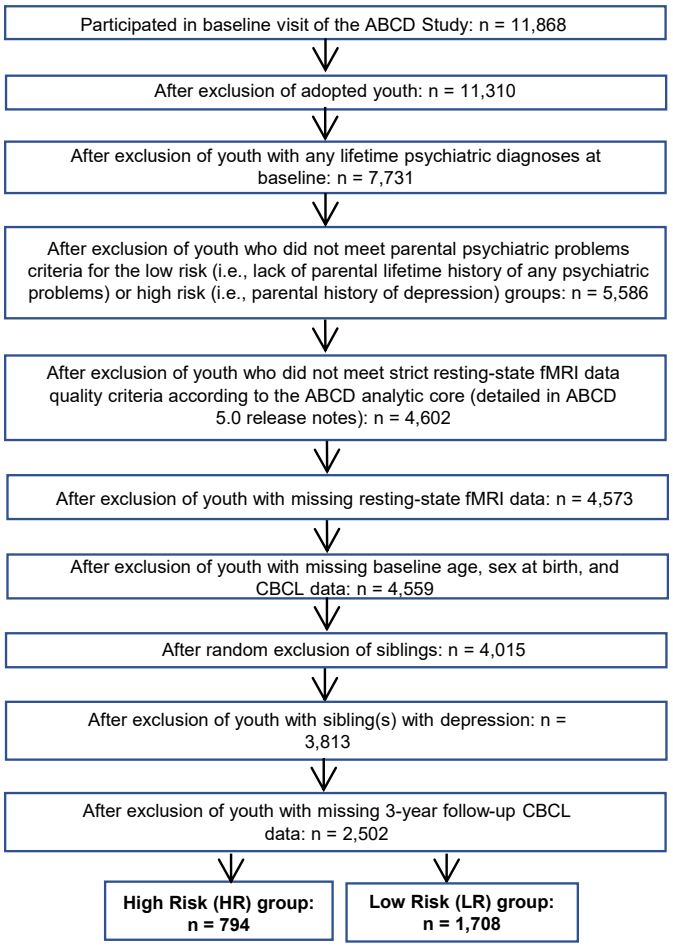
## METHOD

### Study Design and Participants

Participants were from the ABCD Study®,[33] which recruited 11,878 youth across 21 sites who are being followed over 10 years. Youth were between 9 and 10 years of age at the initial visit (between 2016 and 2018). Youth and their parents were recruited from public and private elementary schools within the catchment areas of the 21 sites. The study did not exclude twins or multiple siblings from the same family. Inclusion criteria were as follows: (1) aged 9 to 10 years at initial visit, and (2) attending a public or private elementary school in the catchment area. Exclusion criteria were as follows: (1) not fluent in English, (2) having a parent not fluent in English or Spanish, (3) major medical or neurological conditions, (4) gestational age <28 weeks or birthweight <1,200 g, (5) contraindications to magnetic resonance imaging (MRI) scanning, (6) history of traumatic brain injury, and (7) current diagnosis of schizophrenia, moderate to severe autism spectrum disorder, intellectual disability, or alcohol/substance use disorder. Participants provided informed consent or assent.

Data were derived from the ABCD Study 5.1 release (DOI: https://doi.org/10.15154/z563-zd24), which included baseline to 3-year follow-up data. For the present study, we used the ABCD Study's tabulated data, which were pre-processed and analyzed by the Consortium's data analytic core.[35] A Consolidated Standards of Reporting Trials (CONSORT) chart is provided in Figure 1. The following exclusion criteria were applied for our study: (1) youth who were adopted (given that assessment of psychiatric family history focuses on blood relatives); (2) youth with any lifetime psychiatric diagnoses at initial visit, reported by the parent about the youth (based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Youth for *DSM-5*[36]); and (3) youth with resting-state functional MRI (fMRI) data that were recommended for exclusion by the ABCD Study analytic core

**FIGURE 1** CONSORT Chart of Youth in the Final High-Risk and Low-Risk Groups




*Note: Exclusion criteria were as follows: youth who were adopted, youth with any lifetime psychiatric diagnoses at initial visit, and youth with resting-state functional magnetic resonance imaging data recommended for exclusion by the Adolescent Brain Cognitive Development (ABCD) Study analytic core. In addition, for the high-risk group only, youth were excluded if there was a lack of parental history of depression. For the low-risk group only, youth were excluded if there was a presence of parental lifetime history of any psychiatric problems. For youth with siblings, one sibling was randomly selected and the other sibling(s) was excluded. Youth who had sibling(s) with depression, and who had missing data, were excluded. Thus, the final sample included 794 high-risk youth and 1,708 low-risk youth.*

(detailed in the 5.1 release notes). Youth were included in the high risk for depression (HR) group if there was a maternal and/or paternal history of depression (based on the Family History Assessment Module Screener [FHAM-S], as detailed below). Youth were included in the low risk for psychiatric problems (LR) group if there was no parental lifetime history of any psychiatric problem. Youth with missing data (resting-state fMRI, demographic data, and/or symptom data) were excluded. For youth with siblings, one sibling was randomly selected and the other sibling(s) were excluded. In addition, youth who had sibling(s) with depression were excluded from the HR and LR groups to further isolate risk status to the parental contribution. Thus, the final sample included 794 HR youth and 1,708 LR youth.

### Demographic Information

At baseline, parents reported the youth's age, sex assigned at birth, race/ethnicity, and pubertal status, as well as parental education, marital status, and combined household income.

### Family History of Psychiatric Problems

At baseline, parents completed the FHAM-S,[37] which is a brief interview that assesses family history of psychiatric problems in all first- and second-degree biological relatives of the youth. The FHAM-S specifically assesses the presence or absence of symptoms associated with alcohol and substance use disorder, depression, anxiety, mania, psychosis, and antisocial personality disorder in all blood relatives. Our study examined parental history to facilitate comparisons across prior studies (most of which focused on parental history[7,10,12,17-19]) and because prior work has identified stronger associations between parental history and youth psychopathology compared to sibling and second-degree relative histories.[3,19] All youth in the HR group had at least one biological parent with a history of depression, and all youth in the LR group had both parents with no lifetime history of any psychiatric problems.

### Youth Psychiatric Symptoms

Youth psychiatric symptoms were assessed using the parent-report Child Behavior Checklist (CBCL)[38] at baseline (ages 9-10 years) and 3-year follow-up (ages 12-13 years). The CBCL includes questions regarding symptoms of depression, anxiety, somatic, attention-deficit/hyperactivity, oppositional defiant, and conduct disorders. Our study used the total problems and internalizing symptoms subscales.

### Family Conflict

The family conflict subscale from the parent-report of the Family Environment Scale[39] was used to assess family conflict at baseline. The family conflict subscale represents the sum of 9 items (reverse coded as appropriate), whereby higher scores indicate increased experiences of family conflict.

### Resting-State Preprocessing and Functional Connectivity Analysis

All ABCD Study imaging procedures have been described in detail in Casey *et al.*[33] At baseline, youth completed four 5-minute resting-state fMRI scans, in which the youth were instructed to fixate on a cross-hair. 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 previously described in Casey *et al.*[33] For the present study, we used the ABCD Study's tabulated data, which were pre-processed and analyzed by the Consortium's data analytic core.[35] Preprocessing steps (described in detail in Hagler *et al.*[35]) included correcting T1-weighed images for gradient nonlinearity distortions, correcting for head motion by registering each frame to the first frame using AFNI's 3dvolreg, and correcting for $B_0$ distortions using a reversing polarity method. All scans were resampled with cubic interpolation into alignment with one another using a reference scan (which was in the middle of the fMRI session). Automated registration between the spin-echo $B_0$ calibration scans (ie, field maps) and T1-weighted structural images was conducted using mutual information with coarse pre-alignment based on within-modality registration to atlas brains. The initial frames were removed, and then the voxel time series was normalized by dividing by the mean across time of each voxel. Linear regression was used to remove quadratic trends, signals correlated with estimated motion time courses, and mean time courses of white matter, ventricles, and whole brain, and their first derivatives.[40] White matter, ventricle, and whole-brain regions-of-interest (ROIs) used to calculate average time courses were derived from FreeSurfer's automated brain segmentation (ie, aseg), resampled into voxel-wise alignment with the fMRI data, and eroded by a single fMRI-resolution voxel. Motion regression included 6 parameters and their derivatives and squares. Estimated motion time courses were temporally filtered to reduce signals linked to respiration. Frames with displacement greater than 0.30 mm were excluded from the regression.[40] After regression, time courses were band-pass filtered between 0.009 and 0.08 Hz.[41]

For the present study, we examined within-network resting-state functional connectivity (FC) of 12 networks defined by the Gordon parcellation,[42] which includes the auditory network, cingulo-opercular network, default mode network, cingulo-parietal network, fronto-parietal network, retrosplenial–temporal network, ventral attention network, dorsal attention network, salience network, sensorimotor hand network, sensorimotor mouth network, and visual network. Data were analyzed by the ABCD Consortium's data analytic core[35] using a seed-based correlational approach.[43] Correlation coefficients were Fisher $Z$ transformed.[43] Within-network FC was calculated as the average correlation between all pairwise time series combinations for regions within a given network.

### Preadolescent Functional Connectivity Interaction With Familial Risk Status and Family Conflict to Predict Adolescent General Psychopathology

Mixed-effects regression analyses were conducted to test whether the 3-way interaction between familial risk status, family conflict, and within-network resting-state FC during preadolescence (ages 9-10 years) predicted psychiatric symptoms during adolescence (ages 12-13 years). The dependent variable was the CBCL total problems score at 3-year follow-up, and the independent variables included the interaction among familial risk status, family conflict, and network FC, as well as their main effects. Twelve separate models (for each of the 12 networks) were conducted. False discovery rate (FDR) correction was applied across all 12 networks to limit inflation of the false-positive rate due to multiple comparisons. Fixed-effect covariates included baseline age, average motion in the scanner (mean framewise displacement), scanner type, sex assigned at birth, and baseline CBCL total problems. A random intercept controlling for differences based on study site was also included.

### Follow-Up Analyses: Examination of Adolescent Internalizing Symptoms

Given that youth with family members with depression may be at increased risk for internalizing symptoms specifically,[44] we re-ran analyses using CBCL internalizing symptoms at 3-year follow-up (ages 12-13 years) instead of CBCL total problems at 3-year follow-up (and replaced the baseline total problems covariate with baseline internalizing symptoms).

## RESULTS

### Demographic and Clinical Characteristics

Demographic and clinical characteristics are reported in Table 1. The HR and LR groups did not differ on age, sex at birth, pubertal status, or parental education, but did differ on race and ethnicity, psychiatric symptoms (at baseline and 3-year follow-up), family conflict (at baseline and 3-year follow-up), parental marital status, and household income (all $p < .001$). Supplement 1, Results, available online, provides further details. Table S4, available online, lists parental lifetime history of psychiatric problems, and Table S5, available online, lists comorbidity of parental lifetime history of psychiatric problems. Baseline demographic and clinical differences between youth who completed the 3-year follow-up (n = 2,502) vs those who did not (n = 1,311) are reported in Table S6, available online.

### Preadolescent Functional Connectivity Interaction With Familial Risk Status and Family Conflict to Predict Adolescent Psychopathology

The 3-way interaction between familial risk status (ie, HR vs LR), family conflict, and cingulo-parietal network (CPN) FC during preadolescence predicted CBCL total problems during adolescence (ie, at 3-year follow-up) ($\beta = 0.120$, $t = 3.477$, $p_{FDR} = .006$; $\Delta R^2 = 0.017$; $\eta^2 = 0.003$; $\eta_p{}^2 = 0.005$) (Figure 2b, Figure 2c; Table S1, available online). When split by familial risk status, the 2-way interaction between family conflict and CPN FC during preadolescence predicted CBCL total problems during adolescence within HR youth ($\beta = 0.337$, $t = 2.369$, p = .018) and within LR youth ($\beta = -0.192$, $t = -2.162$, $p = .031$). Simple slope analyses revealed that for HR youth with low family conflict, there was a negative association between preadolescent CPN FC and adolescent total problems (B = −7.955, SE = 3.362, $t = -2.366$, $p = .018$) (Figure S1a, available online; Table S3, available online), whereas this association was positive for LR youth with low family conflict (B = 3.555, SE = 1.535, $t = 2.316$, $p = .021$) (Figure S1b, available online; Table S3, available online). For HR and LR youth with high family conflict, there was no association between preadolescent CPN FC and adolescent total problems ($p$ values > .05) (Table S1, available online). There were no 3-way interactions (surviving FDR correction) for any of the remaining 11 networks.

### Follow-Up Analyses: Examination of Adolescent Internalizing Symptoms

The 3-way interaction among familial risk status, family conflict, and CPN FC during preadolescence predicted CBCL internalizing symptoms during adolescence (ie, at 3-year follow-up) ($\beta = 0.122$, $t = 3.301$, $p_{FDR} = 0.012$; $\Delta R^2 = 0.023$; $\eta^2 = 0.003$; $\eta_p{}^2 = 0.004$) (Figure 2d, Figure 2e; Table S2, available online). When split by

**TABLE 1** Demographic and Clinical Characteristics in High Risk vs Low Risk Groups

| Characteristic | High risk for depression (HR group) n = 794 | Low risk for psychiatric problems (LR group) n = 1,708 | Statistical value | *p* |
|---|---|---|---|---|
| Youth age, mean (SD) | 9.50 (0.51) | 9.50 (0.51) | $t(1548.1) = 0.07$ | .942 |
| Youth sex at birth, n (%) | | | | |
| Male | 367 (46.22) | 869 (50.88)[a] | $\chi^2(1) = 4.52$ | .034[b] |
| Female | 427 (53.78)[a] | 839 (49.12) | | |
| Youth race and ethnicity, n (%) | | | | |
| Asian | 6 (0.76) | 53 (3.10)[a] | $\chi^2(4) = 45.98$ | <.001[b] |
| Black | 59 (7.43) | 177 (10.36) | | |
| Hispanic | 129 (16.25) | 408 (23.89)[a] | | |
| Native Hawaiian, Pacific Islander, Alaska Native, American Indian, or Multiracial | 80 (10.07) | 138 (8.08) | | |
| White | 520 (65.49)[a] | 932 (54.57) | | |
| Youth psychiatric symptoms[c], mean (SD) | | | | |
| Total problems | 14.70 (12.71)[a] | 9.80 (9.43) | $t(1213.9) = -9.69$ | <.001[b] |
| Total problems (3-y) | 15.74 (15.09)[a] | 9.77 (10.48) | $t(1161.1) = -10.07$ | <.001[b] |
| Depression symptoms | 1.00 (1.54)[a] | 0.54 (1.05) | $t(1149.5) = -7.54$ | <.001[b] |
| Depression symptoms (3-y) | 1.80 (2.47)[a] | 0.94 (1.64) | $t(1129.9) = -8.94$ | <.001[b] |
| Internalizing symptoms | 4.36 (4.31)[a] | 2.76 (3.13) | $t(1196.8) = -9.33$ | <.001[b] |
| Internalizing symptoms (3-y) | 5.49 (5.63)[a] | 3.17 (3.82) | $t(1143.9) = -10.51$ | <.001[b] |
| Externalizing symptoms | 3.12 (3.80)[a] | 2.09 (2.96) | $t(1256.2) = -6.77$ | <.001[b] |
| Externalizing symptoms (3-y) | 3.34 (4.40)[a] | 2.18 (3.32) | $t(1229.3) = -6.60$ | <.001[b] |
| Family conflict[d] (parent-report) | 2.47 (1.93)[a] | 1.93 (1.60) | $t(1314.6) = -6.88$ | <.001[b] |
| Family conflict (parent-report) (3-y) | 2.35 (1.95)[a] | 1.94 (1.74) | $t(1390.6) = -5.10$ | <.001[b] |
| Change in family conflict (parent-report) (3-y minus baseline) | -0.12 (1.88)[a] | -0.009 (1.73) | $t(1424.7) = -1.61$ | .011[b] |
| Family conflict[d] (child-report) | 1.88 (1.95) | 1.76 (1.80) | $t(1443.1) = -1.53$ | .126 |
| Family conflict (child-report) (3-y) | 2.03 (1.94)[a] | 1.76 (1.80) | $t(1450.1) = -3.36$ | <.001[b] |
| Change in family conflict (child-report) (3-y minus baseline) | 0.14 (2.32) | -0.002 (2.10) | $t(1416.9) = -1.55$ | .122 |
| Youth pubertal status[e], n (%) | | | | |
| Pre puberty | 416 (53.75) | 900 (53.96) | $\chi^2(4) = 3.13$ | .535 |
| Early puberty | 177 (22.87) | 400 (23.98) | | |
| Mid puberty | 169 (21.83) | 350 (20.98) | | |
| Late puberty | 11 (1.42) | 18 (1.08) | | |
| Post puberty | 1 (0.13) | 0 (0) | | |
| Parental education[f], n (%) | | | | |
| High school or less | 216 (27.27) | 475 (27.81) | $\chi^2(2) = 3.69$ | .158 |
| Bachelor's degree | 362 (45.71) | 717 (41.98) | | |
| Graduate degree | 214 (27.02) | 516 (30.21) | | |
| Parental marital status, n (%) | | | | |
| Married | 560 (70.53) | 1404 (82.20)[a] | $\chi^2(6) = 56.98$ | <.001[b] |
| Widowed | 9 (1.13) | 7 (0.41) | | |
| Divorced | 85 (10.71)[a] | 85 (4.97) | | |
| Separated | 33 (4.16)[a] | 33 (1.93) | | |
| Never married | 62 (7.82) | 105 (6.15) | | |
| Living with a partner | 42 (5.29) | 62 (3.63) | | |
| Refused to answer | 3 (0.38) | 12 (0.70) | | |

*(continued)*

**TABLE 1** Continued

| Characteristic | High risk for depression (HR group) n = 794 | Low risk for psychiatric problems (LR group) n = 1,708 | Statistical value | p |
|---|---|---|---|---|
| Household income[g], n (%) | | | | |
| <$50,000/y | 169 (21.18) | 328 (19.20) | $\chi^2(3) = 15.18$ | .002[b] |
| $50,000-$100,000/y | 250 (31.49)[a] | 448 (26.23) | | |
| >$100,000/y | 334 (42.07) | 795 (46.55) | | |
| Don't know/refused to answer | 41 (5.16) | 137 (8.02)[a] | | |

*Note: Means and SDs (continuous variables) and frequencies and percentages (categorical variables) of demographic and clinical characteristics are displayed for high-risk and low-risk groups. One-way analyses of variance (continuous variables) and $\chi^2$ tests (categorical variables) were conducted (as appropriate) for all variables of interest. All characteristics were assessed at the baseline visit (ie, 9-10 years of age) unless otherwise noted.*
[a]*Indicates that the group n or mean was significantly higher than for the other group.*
[b]Indicates significant difference between groups ($p < .05$).
[c]*Youth psychiatric symptoms were measured using the Child Behavior Checklist (CBCL).*
[d]*Family conflict was measured using the Family Environment Scale (FES).*
[e]*Youth pubertal status was measured using the parent-report of the Pubertal Development Scale (PDS).*
[f]*Based on which parent was reporting; 2,184 (87.29%) biological mothers, 318 (12.71%) biological fathers.*
[g]*Household income was measured as total household income before taxes and deductions during the last 12 months.*

familial risk status, the 2-way interaction between family conflict and CPN FC during preadolescence predicted CBCL internalizing symptoms during adolescence within HR youth ($\beta = 0.328$, $t = 2.113$, $p = .035$) and within LR youth ($\beta = -0.220$, $t = -2.350$, $p = .019$) but not within HR youth. Simple slope analyses revealed that for HR youth with low family conflict, there was a negative association between preadolescent CPN FC and adolescent internalizing symptoms (B = −2.785, SE = 1.365, $t = -2.040$, $p = .042$) (Figure S1c, available online; Table S3, available online), whereas this association was positive for LR youth with low family conflict (B = 1.430, SE = 0.590, $t = 2.423$, $p = .015$) (Figure S1d, available online; Table S3, available online). For HR and LR youth with high family conflict, there was no association between preadolescent CPN FC and adolescent internalizing symptoms ($p$ values > .05) (Table S2, available online). There were no 3-way interactions (surviving FDR correction) for any of the remaining 11 networks.

### Sensitivity Analyses: Examination of Adolescent Externalizing Symptoms

To determine whether effects were specific to internalizing symptoms, we re-ran analyses using 3-year externalizing symptoms as the dependent variable (controlling for baseline externalizing symptoms). There was no 3-way interaction among familial risk status, family conflict, and CPN FC during preadolescence predicting CBCL externalizing symptoms during adolescence (ie, at 3-year follow-up) ($\beta = 0.084$, $t = 2.299$, $p_{FDR} = .129$).

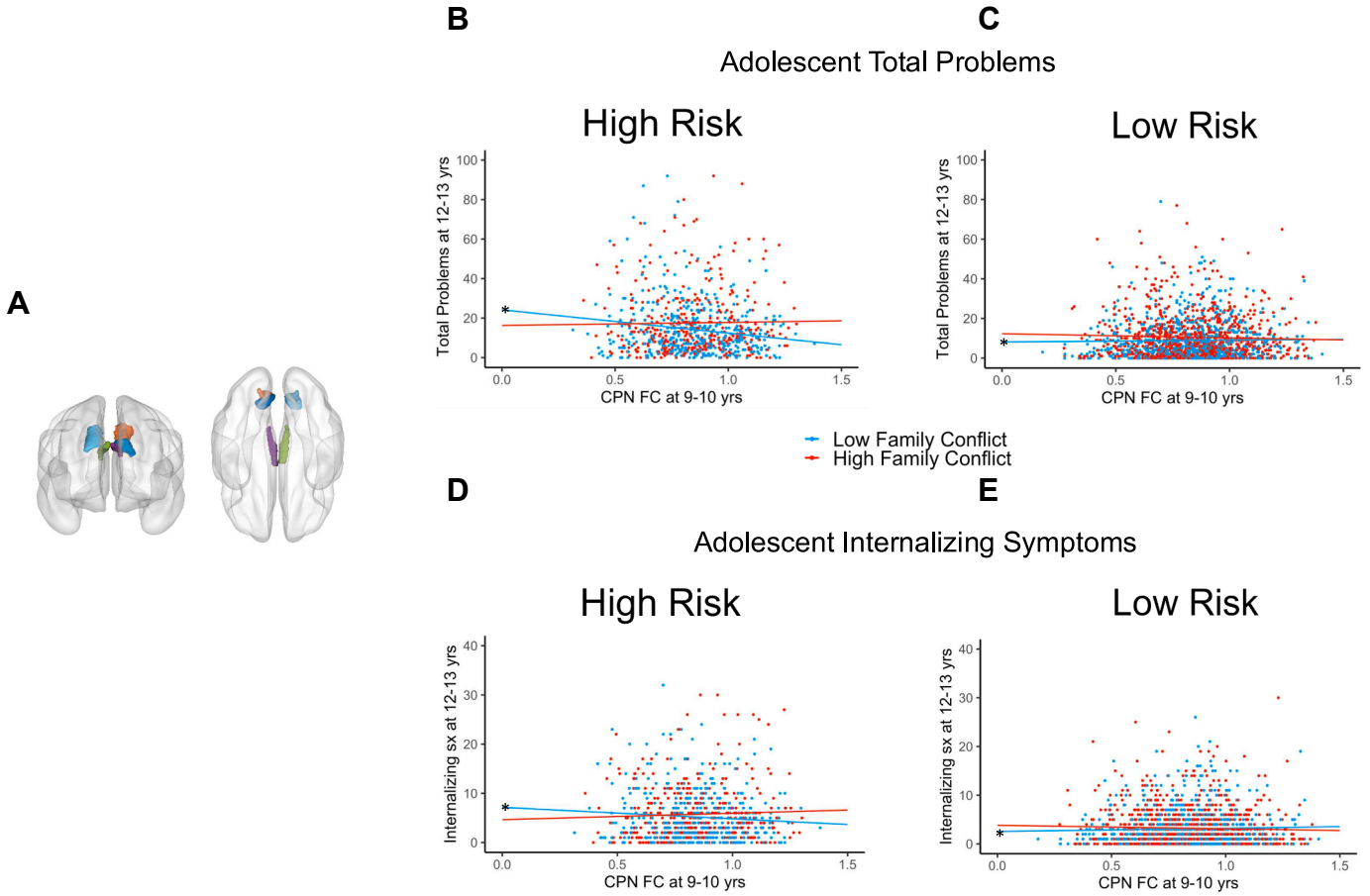
### Sensitivity Analyses: Inclusion of Demographic Variables That Differed Between Risk Groups as Covariates

Because the HR and LR groups differed in youth race and ethnicity, parental marital status, and household income, and were not initially included as original covariates in our model, we conducted sensitivity analyses to examine whether results could be better explained by these differences. All findings remained significant after covarying for these variables, with all effects of interest in the same direction.

### Sensitivity Analyses: Inclusion of Change in Family Conflict From Baseline to 3-Year Follow-up

Although the purpose of our study was to examine preadolescent (as opposed to adolescent) variables that predict later adolescent psychopathology, it is possible that changes in family conflict from baseline to 3-year follow-up may influence the association between the 3-way interaction of CPN FC, familial risk status, and family conflict during preadolescence in predicting adolescent psychopathology. Thus, we added change in family conflict (ie, 3-year follow-up minus baseline) as a covariate to our original models (wherein a more positive change score corresponds to increasing family conflict over time, and a more negative change score corresponds to decreasing family conflict over time). The 3-way interaction remained significant and in the same direction for predicting adolescent total problems ($\beta = 0.116$, $t = 3.410$, $p_{FDR} = .008$) and adolescent internalizing symptoms ($\beta = 0.120$, $t = 3.248$, $p_{FDR} = .014$).

**FIGURE 2** Preadolescent Cingulo-Parietal Network Functional Connectivity (CPN FC), Familial Risk Status, Family Conflict, and Adolescent Psychopathology




*Note:* *(a) Cingulo-parietal network. (b) High-risk (HR) youth with low family conflict demonstrated a negative association between preadolescent CPN FC and adolescent total problems, whereas this association was not significant for HR youth with high family conflict. (c) Low-risk (LR) youth with low family conflict demonstrated a positive association between preadolescent CPN FC and adolescent total problems, whereas this association was not significant for LR youth with high family conflict. (d) HR youth with low family conflict demonstrated a negative association between preadolescent CPN FC and adolescent internalizing symptoms, whereas this association was not significant for HR youth with high family conflict. (e) LR youth with low family conflict demonstrated a positive association between preadolescent CPN FC and adolescent total problems, whereas this association was not significant for LR youth with high family conflict.*

### Sensitivity Analyses: Inclusion of Pubertal Status as a Covariate

Given that prior work has demonstrated differential links between brain alterations and psychopathology[23] depending on pubertal status, we re-ran analyses after covarying for baseline pubertal status. Findings remained significant after including pubertal status as an additional covariate to our original models (Table S7, Table S8, available online).

### Sensitivity Analyses: Inclusion of Parental Psychiatric Comorbidities as a Covariate

Given that the majority of the HR youth (72.8%) had at least one parent with at least one comorbid psychiatric problem, we re-ran our analyses to include the presence or absence of comorbid problem(s) in either parent as a covariate. Results remained significant; the 3-way interaction among familial risk status, family conflict, and CPN FC during preadolescence predicted adolescent CBCL total ($\beta = 0.134$, $t = 3.705$, $p_{FDR} = .003$; $\Delta R^2 = 0.007$; $\eta^2 = 0.004$; $\eta_p^2 = 0.005$) and CBCL internalizing symptoms ($\beta = 0.121$, $t = 3.119$, $p_{FDR} = .022$; $\Delta R^2 = 0.004$).

## DISCUSSION

Our study found that the interaction between familial risk status, family conflict, and resting-state FC during preadolescence prognostically predicted psychiatric symptoms during adolescence. Specifically, for HR youth, lower preadolescent cingulo-parietal network (CPN) FC predicted greater future symptoms in environments with low

(but not high) family conflict, whereas for LR youth, higher preadolescent CPN FC predicted greater future symptoms in environments with low (but not high) family conflict. Findings were specific to total problems and internalizing (but not externalizing) symptoms during adolescence. This pattern suggests that environments with low family conflict may serve as a potential buffer preventing children from developing psychiatric symptoms into adolescence; however, the extent of this buffering may crucially depend on whether the child has a parent with depression and their current brain function/connectivity. Notably, findings remained significant when covarying for demographic variables (ie, youth race and ethnicity, parental marital status, household income) that differed between HR and LR youth. Findings also remained significant after the inclusion of pubertal status, change in family conflict from baseline to 3-year follow-up, and presence of parental psychiatric comorbidity as additional covariates. Taken together, our study suggests that CPN FC and family conflict during late childhood may represent key predictive factors underlying heightened risk for psychopathology during adolescence among youth who have parents with depression histories.

We found that the interaction among risk status, family conflict, and CPN FC during preadolescence (ages 9-10) predicted both total psychiatric symptoms and internalizing symptoms during adolescence (ages 12-13). Specifically, among HR youth in low (but not high) family conflict contexts, there was a negative association between preadolescent CPN FC and adolescent symptoms, whereas this association was positive for LR youth. Results suggest that for LR youth, high CPN FC during preadolescence may be a risk factor for future psychiatric symptoms, but for HR youth, high CPN FC may serve a protective role (ie, linked to fewer adolescent symptoms), but only for those developing in low family conflict environments. Thus, greater CPN FC may be associated with both risk and resilience, depending on the individual's familial history and current context. When either familial risk group is exposed to high family conflict, it is possible that the compounding environmental stresses overwhelm a potentially protective aspect of elevated CPN FC. We suspect that exposure to high family conflict may trigger the repeated stimulation of stress regulatory systems, which can lead to the accumulation of physiological risk factors that have an impact on brain–symptom associations.[45] Another possibility is that HR youth may exhibit heightened sensitivity to their environments as compared to LR youth. For example, elevated FC of the CPN, a network that includes regions implicated in attention,[46] may reflect enhanced attention to environmental cues. Albeit speculative, this pattern could benefit youth in low-conflict family environments, whereas heightened environmental sensitivity may be less adaptive in environments in which conflict is more common. Overall, findings align with prior studies revealing that the family environment (eg, maternal aggressiveness, family conflict) interacts with neural circuitry to predict the later development of psychopathology among youth.[30-32]

The CPN includes the anterior and posterior cingulate cortices, precuneus, and superior parietal lobule.[42,47] Our findings suggest that preadolescents who have parents with depression, who are free of a psychopathology history themselves, may show early alterations in brain circuitry involved in higher-order cognition, which may in turn further heighten their risk for the later development of psychopathology during adolescence. Although the CPN has been shown to be involved in visuospatial information processing[48] and memory retrieval,[46] we did not examine behavioral correlates of CPN FC that could help to guide interpretations about the nature of CPN functioning and extent to which it may be adaptive or maladaptive for HR youth. Additional research linking behavior with the observed neurobiological findings is warranted to further contextualize our results.

Within the 3-way interaction models, there were main effects (in the positive direction) of CPN FC, familial risk status, and family conflict during preadolescence predicting adolescent psychiatric symptoms (both total and internalizing). Consistent with the broader literature,[2,15,24] these results indicate that family conflict and having parent(s) with depression during preadolescence are individual risk factors for developing psychopathology later during adolescence. Interactions with CPN FC suggest a more nuanced association between CPN FC and symptomatology. There was a 2-way interaction between preadolescent CPN FC and risk status predicting adolescent psychopathology. Although the directionality of this finding could suggest that higher CPN FC is associated with lower future symptoms in HR (but not LR) youth, we note that the association in HR youth was only trend level. Consistent with an even more nuanced association between CPN FC and adolescent psychopathology, the significant 3-way interaction findings indicate that the links between parental depression risk and preadolescent brain function with symptoms in adolescence depend on whether youth are living in environments characterized by family conflict.

Sensitivity analyses revealed that findings remained significant after inclusion of parental comorbidity. In particular, the interaction between familial risk status, family conflict, and CPN FC during preadolescence predicted CBCL total problems and internalizing symptoms during adolescence over and above other parental

psychopathology, indicating that the presence of parental depression specifically has a unique role in the complex interactions with family context and brain function predicting future psychopathology among youth. Future work that interrogates the role of parental comorbidity in youth mental health, brain function, and family environment would help to disentangle the influence of parental depression vs other types of psychopathology.

Our study builds upon prior work that has identified preadolescent resting-state connectivity markers of familial risk (using a region of interest [ROI]–ROI approach to probe emotion- and reward-related circuitry)[10] that differentially predicted depression symptoms 2 years later in the ABCD Study.[20] The current study extends this research by incorporating the interacting role of the environment, specifically family dynamics. Although prior work has highlighted the critical role of the family environment in risk for depression,[14-16,24] understanding how the family environment interacts with familial risk for depression and brain function remains a critical gap in the literature. In addition, the current study probes large-scale neural circuitry across all brain networks (instead of ROI–ROI), and predicts general psychopathology over a longer time interval (ie, 3 years later). To our knowledge, this study is the first and largest to date to elucidate how the interactions among preadolescent brain function, family environment, and familial depression risk status predict the later onset of psychopathology during adolescence. Given the limited longitudinal research simultaneously examining the roles of familial risk status, family environment, and brain circuitry predicting future symptomatology, more research is needed to fully understand the meaning and implications of these results.

It is critical to acknowledge that the effect sizes observed in this study are relatively small. Given the ABCD Study's large sample size, we were adequately powered to detect a 3-way interaction despite a "true" small effect size.[49] It is not surprising that ABCD analyses using neuroimaging data yield small effect sizes, primarily because of its demographically diverse sample, wherein effect sizes may be "diluted" because of the differences in contextual and environmental background variables.[50] For example, the way in which we operationalized familial risk for depression is likely to demonstrate substantial between-subject variability, reflecting a combination of both familial risk for depression and other, nonspecific risk factors. Thus, the variability in the "risk" phenotype may contribute to the small effect sizes observed. Furthermore, small effect sizes observed in ABCD analyses linking brain, behavior, environment, and mental health may reflect the fact that many real-world associations are truly small.[49] Although we recognize that small effect sizes may limit potential clinical translation, there are no clear standards for differentiating clinically meaningful and non–clinically meaningful effect sizes. Additional work using deeper risk phenotyping, as well as causal methods to probe the impact of "small effect" neural alterations (eg, transcranial magnetic stimulation) will be important to further interrogate the clinical significance of these results. Although our research findings, similar to existing brain–behavior association studies with small effect sizes, may not have immediate and evident clinical impacts currently, this research can help contribute to the knowledge base required for clinical translation. Specifically, identifying pre-existing neural and environmental factors that exacerbate or buffer against the later development of psychopathology among at-risk youth is an important step toward improving early detection and intervention strategies.

In the long term, knowledge gained from neuroimaging studies of familial risk for depression has the potential to contribute to enhanced screening tools that facilitate early risk identification and intervention before the onset of psychopathology among at-risk youth. Similarly, in the future, neural vulnerability markers may also serve as targets for prevention and intervention strategies, as at-risk youth may benefit from treatments that target the specific neural circuitry associated with familial risk for depression. However, it is critical to acknowledge that there is a significant gap between the current state of neuroscience and clinical practice.[51] This gap is in part due to the need to identify markers of neural risk that are predictive at the level of individuals, not just at the group level,[52] and due to challenges with the reliability of neuroimaging.[53] In order for neuroimaging research on familial risk to contribute to long-term improvements in risk identification and prevention, studies that robustly and reliably characterize neural markers of familial risk for depression and for future psychopathology that generalize to external samples are needed. Such studies would necessitate the use of large sample sizes, consistent study designs, and inclusion of additional crucial variables that may moderate or mediate these brain–symptom associations. Although our use of the large ABCD Study sample builds upon past studies to increase statistical power, future work is needed to predict individual trajectories and to test predictors in external samples of youth. Thus, although neuroimaging research on familial risk holds substantial promise, much work remains before findings can directly translate into clinically actionable changes at the level of prevention and intervention.

Our study has various limitations. The parental depression history measure was a single interview question that did not distinguish between past or current depression, or include information about symptom severity. Studies using detailed parental psychiatric histories would

strengthen future work. Another limitation is that our study used a binary (instead of continuous) approach to classify youth based on familial risk, and focused solely on parents' history of depression. This case-control design focused on parents was selected to align with the majority of prior work to facilitate comparisons and to ensure that findings were specific to parent-based risk for depression; however, future studies could also examine familial risk broadly and dimensionally (eg, family density score,[54] familial loading score[55]). Finally, we examined the later development of psychopathology at 12 to 13 years of age to capture a period of heightened risk for psychopathology (ie, transition to adolescence).[34] However, because depression onset often peaks during late adolescence or early adulthood,[34] future studies examining longer follow-ups will be essential and feasible, given that the ABCD Study is an ongoing 10-year study.

Despite these limitations, our study has numerous strengths, including that this study is the first and largest to date to elucidate neural markers of familial risk that predict future psychopathology as a function of family environment in a youth sample. In addition, this work addresses some limitations of prior work, including examining neural circuitry within a sample with a narrow age range at baseline (ie, 9-10 years) and follow-up (ie, 12-13 years). This study design facilitated enhanced precision with regard to the timing of when neural risk markers linked to future psychopathology may emerge during development. A key strength that builds upon extant research is that we excluded youth who had any lifetime psychiatric diagnosis (ie, not only depression) at 9 to 10 years of age, making this study well suited to detect vulnerability neural markers that are present prior to the onset of psychopathology. Because intervening early in the course of illness is associated with a less severe symptom trajectory, examining youth at high risk who do not yet have psychopathology is essential for early identification and prevention.

In conclusion, findings suggest that the combination of CPN functioning during childhood and exposure to family conflict may represent key factors underlying heightened risk for psychopathology among youth who have parents with depression histories. This research can advance the field's understanding of the complex interactions between the developing brain and environment that lead to the later onset of psychopathology among at-risk youth. In addition, research informed by these findings may eventually contribute to efforts to enhance screening tools to facilitate early intervention, before the onset of psychopathology, and to optimize treatments for youth.

## CRediT authorship contribution statement

**Bailey Holt-Gosselin:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Erin Z. Basol:** Writing – review & editing. **Taylor J. Keding:** Writing – review & editing, Methodology, Formal analysis. **Kathryn Rodrigues:** Writing – review & editing, Formal analysis. **Jutta Joormann:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Dylan G. Gee:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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[a]Yale University, New Haven, Connecticut

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*Correspondence to Dylan G. Gee, PhD, Department of Psychology, Yale University, 100 College Street, New Haven, CT 06510; e-mail: dylan.gee@yale.edu



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