Title

Associations Between Family History of Alcohol and/or Substance Use Problems and Frontal Cortical Development From 9 to 13 Years of Age: A Longitudinal Analysis of the ABCD Study

Journal

Biological Psychiatry Global Open Science, 4(2)

ISSN

2667-1743

Authors

Gonçalves, Priscila Dib

Martins, Silvia S

Gebru, Nioud Mulugeta

et al.

Publication Date

2024-03-01

DOI

10.1016/j.bpsgos.2023.100284

Peer reviewed

Archival Report

Biological Psychiatry: GOS

Associations Between Family History of Alcohol and/or Substance Use Problems and Frontal Cortical Development From 9 to 13 Years of Age: A Longitudinal Analysis of the ABCD Study

Priscila Dib Gonçalves, Silvia S. Martins, Nioud Mulugeta Gebru, Stacy R. Ryan-Pettes, Nicholas Allgaier, Alexandra Potter, Wesley K. Thompson, Micah E. Johnson, Hugh Garavan, Ardesheer Talati, and Matthew D. Albaugh

ABSTRACT

BACKGROUND: Previous investigations that have examined associations between family history (FH) of alcohol/substance use and adolescent brain development have been primarily cross-sectional. Here, leveraging a large population-based sample of youths, we characterized frontal cortical trajectories among 9- to 13-year-olds with (FH+) versus without (FH−) an FH and examined sex as a potential moderator.

METHODS: We used data from 9710 participants in the Adolescent Brain Cognitive Development (ABCD) Study (release 4.0). FH+ was defined as having ≥1 biological parents and/or ≥2 biological grandparents with a history of alcohol/substance use problems (n = 2433). Our primary outcome was frontal cortical structural measures obtained at baseline (ages 9–11) and year 2 follow-up (ages 11–13). We used linear mixed-effects models to examine the extent to which FH status qualified frontal cortical development over the age span studied. Finally, we ran additional interactions with sex to test whether observed associations between FH and cortical development differed significantly between sexes.

RESULTS: For FH+ (vs. FH−) youths, we observed increased cortical thinning from 9 to 13 years across the frontal cortex as a whole. When we probed for sex differences, we observed significant declines in frontal cortical thickness among boys but not girls from ages 9 to 13 years. No associations were observed between FH and frontal cortical surface area or volume.

CONCLUSIONS: Having a FH+ is associated with more rapid thinning of the frontal cortex across ages 9 to 13, with this effect driven primarily by male participants. Future studies will need to test whether the observed pattern of accelerated thinning predicts future substance use outcomes.

https://doi.org/10.1016/j.bpsgos.2023.100284

Having a family history of alcohol and/or substance use (FH+) is a recognized risk factor for substance initiation, misuse, and the development of alcohol and substance use disorders in youths (1–6). Family history may increase risk for substance use and misuse via a number of overlapping mechanisms, including genetic propensity, increased substance availability, substance-related life disruptions, and negative parenting roles or behaviors (4,5,7–11).

Having a positive FH has been associated with altered brain development, particularly of the prefrontal cortex (7,8,12–17). For example, previous cross-sectional studies have shown that FH+ children (ages 9–10 years) had lower whole-brain mean cortical thickness, including thinner cortices in the left precentral and paracentral lobules, and greater cortical area in the right precentral lobule than children without an FH (FH−) (7). FH+ adolescents exhibited thinner frontal cortices, including the pars triangularis aspect of the inferior frontal gyrus as well as the lateral and medial orbital frontal cortices (8). However, differences in orbital frontal cortical volume were not observed in adolescents aged 12 to 14 years when FH+ and FH− individuals were compared (16). Other studies have shown that FH+ individuals exhibit worse executive functioning and higher impulsivity levels than FH− individuals, which could reflect underlying differences in frontal brain structures (8,13,17–21) and contribute to future substance use and misuse (20–27).

The above inconsistencies may be a function of the studies largely being cross-sectional (7–9,12,28,29), with wide age ranges of the children studied [e.g., 13–18 years (8) or 9–23 years (29)], varying degrees of alcohol use among the offspring (12) (which can itself disrupt cortical development and thus serve as a confounder) (30), and small and/or nonrepresentative samples (12,31). Furthermore, because many of the above studies did not specifically control for maternal

ISSN: 2667-1743

prenatal use and pubertal development, the overall effects of FH may be partially confounded by the direct in utero effects of prenatal exposure or differences in pubertal stages (32–35).

Perhaps most importantly, cross-sectional studies are unable to examine potential ties between FH+ and within-participant change in brain structure over time. This point is particularly relevant during periadolescence, when there is rapid maturing of the key frontal circuits that govern executive functioning and reward behaviors (36–44). Multiple processes play a role in the maturation of the frontal cortex during adolescence. Mechanisms such as dendritic development, synaptic pruning, change in glial cell density, and myelination likely contribute to magnetic resonance imaging (MRI)–assessed thinning of the frontal cortex (36–44). Additionally, different study designs (cross-sectional vs. longitudinal) can interfere and underestimate age-related brain changes, as reported in a recent study in which different statistical methods were compared using large neuroimage datasets (45). In addition, recent studies have highlighted the benefits of large samples when examining structural brain trajectories (31,46). To date, although robust associations between cognitive functioning, income, and mental health with MRI-assessed cortical structure have been reported, the exact neurobiological mechanism that underpins MRI-assessed trajectories of cortical structures remains understudied (47–49).

Interestingly, sex assigned at birth (hereafter, "sex") has not been fully explored because most structural neuroimaging studies have not included sex as a covariate in their models (7,8,12) or have conducted analyses on all-male samples. (9). Evidence suggests that there may be differences in brain development and sex (with males presenting larger brain volume) (40,50,51), differences in rates of alcohol and substance use and sex (with males presenting higher rates of alcohol and other substance use than females) (52), and interactions of frontal cortex, alcohol use, and sex (with declines consistently demonstrated in prefrontal cortex volume among adolescents aged 14–21) (53). Furthermore, previous research has already shown sex-specific transmission of genetic risk factors for alcohol use disorder (e.g., males seem to be mainly affected by genetic factors, and females are more influenced by environmental factors) (54). However, little is known about sex differences in the ways that FH may be associated with different trajectories of frontal development. Therefore, there is a gap in our knowledge about how sex could potentially differentially impact frontal brain trajectories during preadolescent development.

Longitudinal studies that have examined associations between FH and frontal neurodevelopment are limited. While some studies have shown higher impulsivity behavioral trajectories as a function of FH in preadolescents (13,15), to our knowledge, no study has examined frontal cortical trajectories among FH+ preadolescents prior to substance use exposure. In this study, we leveraged the large, diverse, and longitudinal nature of the Adolescent Brain Cognitive Development (ABCD) Study cohort to examine the developmental trajectories of the frontal cortex as a function of FH status before the initiation of offspring substance use. Specifically, we tested whether having a positive FH alters the trajectories of development of frontal cortical thickness, surface areas, and gray matter volume from age 9 to 13; whether these trajectories vary by sex; and how individual frontal regions contribute to these trajectories.

METHODS AND MATERIALS

We used the ABCD Study data release 4.0 (https://nda.nih.gov/abcd) and selected youths with structural MRI measures who passed quality control (55) and with complete data on sociodemographic, prenatal exposure, and FH variables at 2 time points (baseline [n = 9710], mean age in years = 9.92, range = 8.92–11.00; 2-year follow-up [n = 4896], mean age = 11.92, range = 10.58–13.50). We used questions answered by the parents at baseline, using a modified version of the Family History Assessment Module Screener (56), to identify individuals with an FH of substance use–related problems (e.g., alcohol/substance use–related separation/divorce, being laid off/fired related to alcohol/substance use problems, arrests/driving under the influence, being suspended or expelled from school 2 or more times, alcohol/substance harming health, being in an alcohol/substance treatment program, and causing arguments or being drunk/intoxicated a lot).

FH+ (n = 2433, 25.1%) was defined as having ≥1 biological parents and/or ≥2 biological grandparents with a history of substance use–related problems. Individuals who had neither parents nor grandparents with a history of substance use–related problems were classified as FH− (n = 5910, 60.9%), consistent with previous studies including those that have used ABCD Study data (7,57). Preadolescents who had only one grandparent with a history of substance problems (n = 1367, 14.1%) (7,57) were not included because these participants would have a minimal genetic load of previous generations with FH; however, they could not be classified as having a FH−. This definition has been used in previous neuroimaging research (7,57), and it considers a broader representation of FH (first- and second-degree relatives).

Our outcome variables were surface area, average cortical thickness, and gray matter volume within 11 frontal regions of interest (ROIs) (caudal middle frontal, frontal pole, lateral orbital and medial orbital frontal, paracentral, pars orbitalis, pars opercularis, pars triangularis, precentral, superior frontal, and rostral middle frontal), based on the Desikan-Killiany cortical parcellation atlas (58). All structural neuroimaging processing was completed according to standardized processing pipelines for the ABCD Study (55). Cortical reconstruction and volumetric segmentation were performed by the ABCD Data Analysis, Informatics and Resource Center using the FreeSurfer image analysis suite (details are described elsewhere) (59–62).

Statistical Analyses

We ran descriptive analyses of the following baseline variables: sex (male, female), race (Asian, Black, other/mixed, White), Hispanic (yes/no), parental marital status (married: yes/no), household income (≤$50,000, >$50,000 and <$100,000, ≥$100,000), any prenatal tobacco exposure (yes/no), any prenatal alcohol exposure (yes/no), any prenatal cannabis exposure (yes/no), any prenatal substance (i.e., cocaine, crack, opioids, other substances) exposure (yes/no), and Child

Behavior Checklist internalizing and externalizing symptoms using T scores, comparing differences among the 3 distinct family history groups (FH+, FH−, and only 1 grandparent).

Linear mixed-effects models were chosen as our primary approach because these models allow using both fixed and random effects, thereby capturing individual-specific variations (random effects) in the data while concurrently modeling the broader trends and relationships (fixed effects). Our primary analyses consisted of 3 separate models: one for surface area, another for cortical thickness, and a third model for volume. The focus of each one of our 3 models was the overall frontal region, which we represented as a new variable (region). This approach involved accounting for the simultaneous variation of individual frontal ROIs, as well as the effects of FH and age, collectively influencing frontal cortical trajectories.

For example, to evaluate the overall frontal surface area (dependent variable), first, we standardized (normalized) each frontal ROI separately (i.e., 11 ROIs, a total of 22 including right and left hemispheres), and then the dataset was stacked so that each row represents 1 ROI of 1 participant at 1 time point (22 rows). A linear mixed model was fit with the triple interaction between the frontal ROIs, age, and FH plus independent main effects for baseline sociodemographic variables (i.e., sex, race/ethnicity, parental marital status, household income) as fixed effects. Given that prenatal exposure has the potential to interfere with brain development (34,35), we controlled for it using 4 variables for any prenatal exposure (self-reported substance use at baseline before and/or after knowledge of pregnancy) for each substance separately—tobacco, alcohol, cannabis, and other substances—and we included a time-varying total intracranial volume as a fixed effect. Random intercepts for family relatedness, MRI scanner device, and participant ID were included, implying a compound symmetry covariance structure for the repeated measures. Categorical variables were parameterized as sum-to-zero contrasts, and the model effects were assessed with type III sum of squares in an analysis of deviance table. Estimated marginal means (i.e., model-based predicted values) were computed for each factor combination in the triple interaction and selected age values to better assess FH and ROI differences at each age; multiplicity correction for these means comparisons was done using Tukey's method. Model diagnostics were carried out with quantile-quantile plots to evaluate residual and random effects normality and fitted values against the square root of absolute standardized residuals plot to assess homoscedasticity. Finally, we ran separate models without an interaction term and 2-way interactions (Tables S6, S7) and models using nesting structure with individuals within families (i.e., 1 | family relatedness/participant ID).

To probe for potential sex differences, we conducted analyses exploring sex differences and frontal trajectories that included all participants because FH was not the primary exposure in these models (see Table S1 and Figure S1). Next, we used a 4-way interaction (FH status, age, sex, frontal cortical regions) in the same 3 main models, adjusting for the same variables in our main models while including the puberty development scale (63,64). As we did for the aforementioned primary models, for sex differences analyses, we ran a model without interaction terms, with 2-way and 3-way interactions (see Tables S1–S7).

Next, we generated estimated marginal means based on the full model, running pairwise comparisons for each ROI to examine differences in specific frontal cortical regions between FH+ and FH− individuals at ages 9.9 (mean age at baseline) and 11.9 years (mean age at the 2-year follow-up) (see Tables S1–S7). We performed a Bonferroni correction to adjust for each modality (i.e., surface area, cortical thickness, and volume), and an alpha of .017 or lower was considered significant.

We ran exploratory analyses to investigate whether structural brain development was related to FH in other brain regions. We ran similar models, with outcome variables being the average cortical thicknesses of parietal, temporal, and occipital lobes (see Tables S1–S7). In a series of post hoc exploratory analyses, we first added pubertal stage measures [e.g., the puberty development scale (63,64)] as a time-varying covariate. Then, as noted above, because prenatal substance exposure has been associated with atypical cortical development (65–67), we removed these variables to probe for potential differences that could be attributed to them. Next, we ran analyses excluding participants who self-reported alcohol and/or cannabis use initiation (defined as having 1+ standard drink of alcohol and/or puffing cannabis at the 1-year and/or 2-year follow-up) and any alcohol and cannabis use including sipping alcohol to isolate observed effects of FH on neurodevelopment from youth substance use (20,68,69). These sensitivity analyses were run because previous research had found that 4.1% of the total ABCD sample reported alcohol/substance use initiation (i.e., ≥1 standard drink, > puff/taste cannabis or nicotine, or any other substance use) at the 2-year follow-up, and 12.7% reported alcohol sipping at the 1-year follow-up and 12.6% at the 2-year follow-up (70). In addition, we repeated our primary analyses (linear mixed-effects models 3-way interaction) and sex (4-way interaction) including only participants with complete MRI data (see Tables S1–S7). Finally, we examined nonlinear effects of age and frontal cortical development by modeling age as a quadradic function in our analyses (i.e., age^2). All analyses were conducted using the *lme4* (71) and *emmeans* (72) packages, and we used *ggseg* (73) for visualization and interpretation of our findings in R version 4.1.3.

RESULTS

Sociodemographic Characteristics

Baseline characteristics are shown in Table 1. Overall, groups differed by race, ethnicity, parental marital status, and household income. Lower proportions of individuals who identified as Asian and parents reporting being married as well as higher proportions of those reporting a household income <$50,000 were seen in the FH+ group. FH+ adolescents had greater prenatal exposure to tobacco, alcohol, cannabis, and other substances than those in the FH− group and greater levels of internalizing and externalizing symptomatology at baseline.

FH, Age, and Frontal Cortex

We first ran models to test whether the effects of age on average surface area, thickness, or volume might vary as a

Table 1. Sociodemographic Characteristics at Baseline According to FH of Alcohol and/or Substance Use–Related Problems at Baseline, *n* = 9710

	Overall, *n* = 9710	FH+, *n* = 2433	FH−, *n* = 5910	Only 1 Grandparent, *n* = 1367	*p* Value
Sex Assigned at Birth, Female	47.9%	49.0%	48.1%	45.0%	.052
Race					
Asian	2.0%	0.6%	2.8%	0.7%	<.001
Black	13.7%	14.9%	13.9%	10.7%	
Other/mixed	16.8%	20.3%	15.4%	16.2%	
White	67.6%	64.2%	67.8%	72.4%	
Hispanic, Yes	19.0%	21.4%	18.4%	17.3%	.002
Parental Marital Status, Married, Yes	70.4%	51.8%	76.8%	76.3%	<.001
Household Income, $					
<50,000	28.3%	40.4%	25.2%	20.2%	<.001
≥50,000 and <100,000	43.0%	28.9%	47.8%	47.5%	
≥100,000	28.7%	30.7%	27.0%	32.3%	
Prenatal Exposure to Substances					
Tobacco	13.2%	27.9%	7.5%	11.7%	<.001
Alcohol	26.1%	33.0%	21.9%	32.0%	<.001
Cannabis	5.7%	13.3%	2.8%	4.5%	<.001
Drugs (cocaine, crack, opioids, other drugs)	1.8%	5.6%	0.6%	0.3%	<.001
CBCL Internalizing Symptoms	48.49 (10.58)	51.08 (11.13)	47.33 (10.19)	48.84 (10.41)	<.001
CBCL Externalizing Symptoms	45.60 (10.25)	48.78 (11.06)	44.29 (9.69)	45.60 (9.82)	<.001

Values are presented as % or mean (SD). After adjusting for multiple comparisons, an alpha < .017 is considered significant. FH+ refers to ≥1 biological parents and/or ≥2 biological grandparents with history of alcohol/substance use related problems. FH− refers to no parent or grandparent with history of alcohol/substance use related problems.

CBCL, Child Behavior Checklist; FH, family history.

function of FH. The results are shown in Table 2, with significant age × FH interaction terms indicating that frontal trajectories differed by FH. We found significant interactions for average frontal cortical thickness (p = .002) but not for surface area (p = .31) or volume (p = .30). To visualize this interaction, we plotted the trajectories of frontal cortical thickness across ages 9 to 13 for the FH+ and FH− groups separately. As shown in Figure 1, differences in cortical thickness by FH increased with age. For example, at age 9, the overall mean of frontal cortical thickness (standardized mean) in the FH+ group was 0.144 (95% CI, 0.074 to 0.214) and FH− was 0.146 (95% CI, 0.076 to 0.217). At age 13, the FH+ group had a standardized mean of −0.401 (95% CI, −0.473 to −0.330), while the FH− group's mean was −0.351 (95% CI, −0.422 to −0.280), indicating a more rapid thinning in FH+ individuals.

We were interested in testing whether the relationship between FH and thinning differed based on sex. As a first step, we plotted the impact of sex on these trajectories independently of FH. We then added an additional sex interaction term to test whether the above trajectories varied by sex (Table S1). Our results showed a significant interaction between sex and age, with females showing more rapid thinning than males (Figure S1). For example, at age 9, the overall mean of frontal cortical thickness (standardized mean) in the female group was 0.187 (95% CI, 0.116 to 0.257) and in the male group was 0.103 (95% CI, 0.034 to 0.173). At age 13, the female group had a standardized mean of −0.334 (95% CI, −0.405 to −0.264) while the male group's mean was −0.418 (95% CI, −0.488 to −0.348).

Next, we conducted our 4-way interaction models, and the results indicated that the association between FH status, age, and frontal cortical thickness was qualified by sex (Table 3). To examine the nature of this interaction, we plotted the trajectories of frontal cortical thickness across

Table 2. Association Among FH (FH+ vs. FH−), Age, and Cortical Frontal Brain Development

Models With a 3-Way Interaction Term[a]	Frontal Lobe		
	Area *p* Value	Thickness *p* Value	Volume *p* Value
FH+ vs. FH−	.40	.013	.54
Age	<.001	<.001	<.001
Region (11 Frontal Parcellations)	<.001	<.001	<.001
FH × Age	.31	.002	.30
FH × Region	.98	.48	.69
Age × Region	<.001	<.001	<.001
FH × Age × Region	.98	.21	.62

All the models were adjusted by intracranial volume, and for the following baseline variables as fixed effects: sex assigned at birth, race/ethnicity, parental marital status, household income, and prenatal exposure to tobacco, alcohol, cannabis, and substance use. The models were also adjusted to random effects of magnetic resonance imaging device, family relationship, and participant ID. After adjusting for multiple comparisons, an alpha < .017 is considered significant.

FH, family history.

[a]We ran 3 models with 3-way interaction term: FH × age × region (one for each of the cortical measures: area, thickness, and volume).

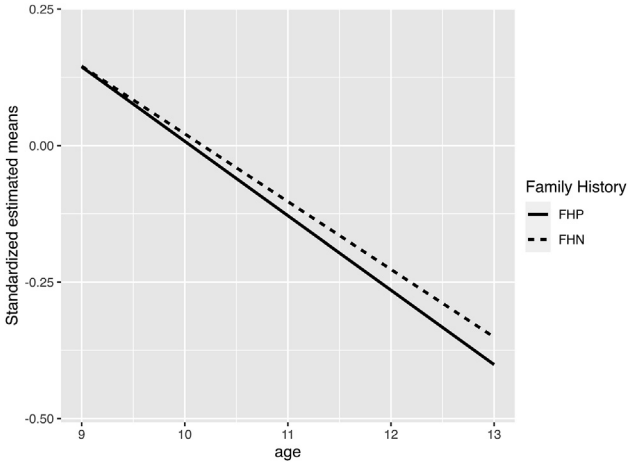

Figure 1. Development of frontal cortical thickness and family history of substance misuse. For example, at age 9, the overall mean of frontal cortical thickness (standardized mean) in the family history positive (FHP) group was 0.144 and family history negative (FHN) was 0.146, and at age 13, the FHP group had a standardized mean of −0.401 while the FHN group's mean was −0.351, indicating a more rapid thinning of the overall frontal thickness in the FHP group. The model was adjusted by intracranial volume, and for the following baseline variables as fixed effects: sex assigned at birth, race/ethnicity, parental marital status, household income, and prenatal exposure to tobacco, alcohol, cannabis, and other substance use. The model was also adjusted to random effects of magnetic resonance imaging device, family relationship, and participant ID.

ages 9 to 13 for the male and female groups separately. As shown in Figure 2, effects of FH on thickness were observed in males but not in females. For example, for females, the FH+ group mean was 0.194 (95% CI, 0.118 to 0.270) and the FH− group mean was 0.219 (95% CI, 0.144 to 0.293). At age 13, the FH+ group had a standardized mean of −0.325 (95% CI, −0.405 to −0.246) while the FH− group's mean was −0.297 (95% CI, −0.374 to −0.220). For males at age 9, the overall mean of frontal cortical thickness (standardized mean) in the FH+ group was 0.097 (95% CI, 0.022 to 0.017) and in the FH− group was 0.075 (95% CI, 0.002 to 0.149). At age 13, the FH+ group had a standardized mean of −0.408 (95% CI, −0.486 to −0.330) while the FH− group's mean was −0.341 (95% CI, −0.415 to −0.266), indicating a more rapid thinning of the overall frontal thickness among FH+ males (compared with FH+ females, p = .0002 at age 9 and p = .006 at age 13; results were obtained from pairwise comparisons using emmeans between sex at ages 9 and 13 years for participants classified as FH+).

Testing Specificity to Frontal Cortical Thickness

To test whether the associations described above were specific to the frontal cortex, we ran analogous models for average cortical thickness for the parietal, temporal, and occipital lobes, but found no associations for the temporal and occipital lobes (Table S3). No significant interactions were noted in any of the 9 models (3 models for each lobe: surface area, cortical thickness, and volume) (Table S3).

Table 3. Association Among FH, Frontal Brain Development, and Sex Assigned at Birth

Models With 4-Way Interaction[a]	Area p Value	Thickness p Value	Volume p Value
FH, FH+ vs. FH−	.65	.78	.78
Age	<.001	<.001	<.001
Region, 11 Frontal Parcellations	.02	<.001	.86
Sex Assigned at Birth	.05	<.001	<.001
FH × Age	.47	.89	.87
FH × Region	.95	.68	.58
Age × Region	.49	<.001	<.001
FH × Sex Assigned at Birth	.89	.007	.42
Age × Sex Assigned at Birth	.10	<.001	.14
Region × Sex Assigned at Birth	.49	.18	.59
FH × Age × Region	.97	.39	.46
FH × Age × Sex Assigned at Birth	.68	.007	.61
FH × Region × Sex Assigned at Birth	.90	.96	.83
Age × Region × Sex Assigned at Birth	.86	.81	.94
FH × Age × Region × Sex Assigned at Birth	.91	.93	.81

All the models were adjusted by intracranial volume and puberty scale, and for the following baseline variables as fixed effects: sex assigned at birth, race/ethnicity, parental marital status, household income, and prenatal exposure to tobacco, alcohol, cannabis and substance use. The models were also adjusted to random effects of magnetic resonance imaging device, family relationship and participant ID. After adjusting for multiple comparisons, an alpha < .017 is considered significant.

FH, family history.

[a]We ran 3 models with 4-way interaction term: FH × age × region × sex assigned at birth (one for each of the cortical measures: area, thickness, and volume).

Exploratory Post Hoc Examination Analyses

To examine the potential influence of confounding factors, we ran models similar to our primary analyses, with the following modifications: 1) accounting for puberty using a time-varying pubertal scale; 2) removing participants with prenatal tobacco, alcohol, cannabis, and substance exposure variables; 3) excluding children with alcohol and cannabis initiation to rule out the possibility that cortical trajectories were being influenced by substance use; 4) removing participants who reported alcohol/cannabis experimentation; and 5) including internalizing and externalizing symptoms as time-varying variables in the model. Our main findings were similar in all these models (a total of 15 models, 3 for each criterion of inclusion of variables or exclusion of participants). Afterward, our findings from the repeated primary analyses (linear mixed-effects models with 3-way interaction) and sex (4-way interaction) that only included participants with complete MRI data remained the same (Tables S4, S5). Also, when rerunning our primary analyses with nested random effects, our findings were not meaningfully changed (3-way interaction model, p value = .002 [interaction term: FH × age]; 4-way interaction model, p value = .0008 [FH × age × sex assigned at birth]). Finally, our results were not meaningfully altered when frontal

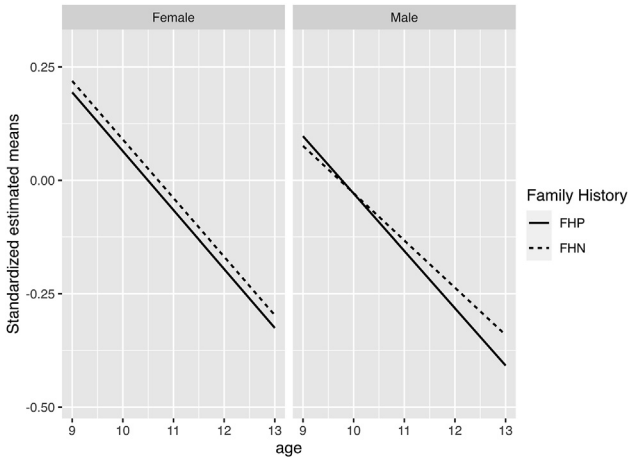

Figure 2. Development of frontal cortical thickness, family history of substance misuse, and sex assigned at birth. For example, for males at age 9, the overall mean of frontal cortical thickness (standardized mean) in the family history positive (FHP) group was 0.097 and family history negative (FHN), 0.075, and at age 13, the FHP group had a standardized mean of −0.408 while the FHN group's mean was −0.341, indicating a more rapid thinning of the overall frontal thickness among males with a FHP. While for females, the FHP group was 0.194 and FHN, 0.219, and at age 13, the FHP group had a standardized mean of −0.325 while the FHN group's mean was −0.297. The model was adjusted by intracranial volume and pubertal scale, and for the following baseline variables as fixed effects: race/ethnicity, parental marital status, household income, and prenatal exposure to tobacco, alcohol, cannabis, and substance use. The model was also adjusted to random effects of magnetic resonance imaging device, family relationship, and participant ID.

cortical trajectories (surface area, cortical thickness, and volume) were modeled as a quadratic function.

DISCUSSION

This is the first large longitudinal study to examine the associations between FH of alcohol and/or substance use and frontal cortical thickness trajectories across a critical peri-adolescent window (ages 9–13 years). Our findings suggest that from pre- through early adolescence (approximately 9 through 13 years), there is more rapid age-related thinning in the frontal cortex among FH+ than among FH− individuals. Results are consistent with previous research (7,8) indicating that the neurological development of youths may be affected by FH of alcohol/substance use problems. Additionally, thinner cortices in early adolescence were associated with increased risk for initiating alcohol use in a longitudinal study of 137 adolescents, assessed at ages 12 to 14 and again by age 18 (26). In addition, prefrontal cortex thinning has been reported among adults with substance use disorders (74). Therefore, the thinner cortical structures observed among FH+ youths in the current investigation add to the literature and may help explain differences in future alcohol/substance use outcomes.

When testing FH × sex interactions, we observed that FH+ males exhibited a greater rate of age-related prefrontal thinning than FH+ females (Table 3; Figure 2). While examining sex differences, our analyses revealed that females presented a more rapid frontal cortical thinning (than males) when evaluated independently of their FH status (Table S1; Figure S1). These results indicate that our primary findings seem to be primarily driven by males. Interestingly, previous functional MRI and FH investigations have observed similar sex differences in frontal regions (75,76). For example, FH+ individuals had greater activation in the left anterior insula and inferior frontal gyrus during successful inhibitions on the stop-signal task, an effect also driven mainly by males (75). In addition, FH+ males exposed to childhood maltreatment had greater blood oxygen level–dependent response on functional MRI during the stop-signal task in the bilateral middle frontal gyrus, left inferior frontal gyrus, dorsomedial prefrontal cortex, and posterior cingulate cortex; the same effect was not observed in females (76). Although previous research has already shown sex-specific transmission of genetic risk factors for alcohol use disorder (e.g., males seem to be mainly affected by genetic factors, and females are more influenced by environmental factors) (54), more research investigating how FH impacts frontal cortical trajectories, future alcohol use, and development of alcohol use disorder is needed.

Previous studies have reported associations between behavioral traits (e.g., aggression, hyperactivity, and impulsivity) and alterations in frontal cortical trajectories among children and adolescents (77–80), with mixed findings on sex differences (79,81–83). Additionally, the impact of FH on behavior and brain development trajectories should be further explored in large longitudinal studies. For example, there is a critical need to understand how neurodevelopmental trajectories may mediate the relationship between an FH of alcohol/substance use and behavioral traits and how sex assigned at birth may moderate these putative associations. A better understanding of these relationships could help inform future intervention strategies.

Results showing differences in cortical structure between FH+ and FH− youths at baseline, as well as evidence of accentuated differences across development, suggest persistent effects of FH+ on the neurodevelopment of youths' brains. Past research indicates that FH+ youths may be impacted by developmental alterations in their neurological maturation (84). Because the ABCD Study sample is still young, future analyses will examine whether the frontal cortical trajectories continue, stabilize, or normalize and whether they predict future alcohol and/or substance use and misuse as the youths get older.

Taken together with previous research, our results suggest that more longitudinal approaches to studying the effects of FH of substance use on neuroanatomical development of youths are warranted. Incorporating trajectories of frontal cortical changes can offer more comprehensive information about future risk for initiation and escalation of substance use.

This study has significant strengths including a large longitudinal sample of participants, and 2 neuroimaging timepoints scanning a critical period of development using state-of-the-art neuroimaging protocols (31). Some limitations should also be noted. First, data on FH of alcohol and substance use problems were provided by one parent (most often the mother) for all parents and grandparents, leading to potential reporting misclassification. FH variables were created based on problems related to use, and not necessarily a DSM diagnosis. Nonetheless, examining associations between FH and trajectories of frontal cortical development will lay the

foundation for subsequent studies to delineate causal pathways by first demonstrating associations between FH and frontal cortical development. Follow-up work can then examine the extent to which genetic, environmental, and interactions between genetic and environmental mechanisms may account for observed associations. Finally, future research could use different thresholds (e.g., severity of substance use, dependence, or other clinical diagnoses) to examine effects on youth neurobiological development and subsequent substance use.

FH effects likely comprise a combination of environmental and genetic influences, and future investigations should be conducted with the aim of disentangling whether the observed associations between cortical thickness and family risk are predominately related to genetic risk factors or psychosocial risk factors (e.g., adverse childhood experiences) or to the interplay between genetics and psychosocial risk factors

Conclusions

This is the largest longitudinal study to date to observe that having a positive FH for alcohol and/or substance-related problems is associated with more thinning of the frontal cortex across ages 9 to 13, a critical period for neurodevelopment, reinforcing the value of examining FH effects over a time continuum in youths.

ACKNOWLEDGMENTS AND DISCLOSURES

This work is supported by National Institutes of Health, National Institute on Drug Abuse (Grant No. T32DA031099 [to Deborah Hasin and SSM]; Grant No. U01DA051039-02S1 [to HG and AP]; Grant Nos. K01DA052679 [to MEJ]; and R25DA050735-01 [to Kimberly Ann Johnson and MEJ]); National Institute of Mental Health (Grant No. K08 MH121654 [to MDA]); National Institute on Alcohol Abuse and Alcoholism (Grant No. T32 AA07459 [to NMG]), and a NARSAD/Brain Behavior Research Foundation grant (to MDA). This manuscript reflects the views of the authors and may not reflect the opinions or views of the National Institutes of Health or ABCD consortium investigators.

PDG, MDA, and AT conceptualized and designed the study. PDG, NMG, and SRR-P managed the literature searches and summaries of previous related work. PDG undertook the statistical analysis, and PDG, MDA, AT, and WKT participated in the interpretation of the data. All authors contributed to the critical revision of the manuscript for important intellectual content and have approved the final manuscript.

Presented as a poster at the Annual meeting of the American College of Neuropsychopharmacology, December 2022, Phoenix, Arizona.

Data used in the preparation of this manuscript were obtained from the ABCD Study (https://abcdstudy.org), held in the National Institute of Mental Health Data Archive. This is a multisite, longitudinal study designed to recruit more than 10,000 children ages 9 to 10 years and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners (Award Nos. U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, and U24DA041147). A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Epidemiology, Columbia University Mailman School of Public Health, New York, New York (PDG, SSM); New York State Psychiatric Institute and Department of Psychiatry, Columbia University, New York, New York (PDG, AT); Center for Alcohol and Addiction Studies, Department of Behavioral and Social Sciences, Brown University School of Public Health, Providence, Rhode Island (NMG); Department of Psychology and Neuroscience Baylor University, Waco, Texas (SRR-P); Department of Psychiatry, University of Vermont, Burlington, Vermont (NA, AP, HG, MDA); Center for Population Neuroscience and Genetics, Laureate Institute for Brain Research, Tulsa, Oklahoma (WKT); and the Department of Mental Health Law and Policy, College of Behavioral and Community Sciences, University of South Florida, Tampa, Florida (MEJ).

AT and MDA contributed equally to this work as joint senior authors.

Address correspondence to Priscila Dib Gonçalves, Ph.D., at priscila.dibgoncalves@nyspi.columbia.edu.

Received Jul 13, 2023; revised Nov 24, 2023; accepted Dec 2, 2023.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsgos.2023.100284.

REFERENCES

1. Volkow ND, Boyle M (2018): Neuroscience of addiction: Relevance to prevention and treatment. Am J Psychiatry 175:729–740.
2. Squeglia LM, Cservenka A (2017): Adolescence and drug use vulnerability: Findings from neuroimaging. Curr Opin Behav Sci 13:164–170.
3. Dawson DA, Harford TC, Grant BF (1992): Family history as a predictor of alcohol dependence. Alcohol Clin Exp Res 16:572–575.
4. Meyers JL, Chorlian DB, Johnson EC, Pandey AK, Kamarajan C, Salvatore JE, *et al.* (2019): Association of polygenic liability for alcohol dependence and EEG connectivity in adolescence and young adulthood. Brain Sci 9:280.
5. McGovern R, Bogowicz P, Meader N, Kaner E, Alderson H, Craig D, *et al.* (2023): The association between maternal and paternal substance use and child substance use, internalizing and externalizing problems: A systematic review and meta-analysis. Addiction 118:804–818.
6. Schuckit MA (2009): An overview of genetic influences in alcoholism. J Subst Abuse Treat 36:S5–S14.
7. Lees B, Stapinski LA, Teesson M, Squeglia LM, Jacobus J, Mewton L (2021): Problems experienced by children from families with histories of substance misuse: An ABCD study®. Drug Alcohol Depend 218:108403.
8. Henderson KE, Vaidya JG, Kramer JR, Kuperman S, Langbehn DR, O'Leary DS (2018): Cortical thickness in adolescents with a family history of alcohol use disorder. Alcohol Clin Exp Res 42:89–99.
9. Holla B, Bharath RD, Venkatasubramanian G, Benegal V (2019): Altered brain cortical maturation is found in adolescents with a family history of alcoholism. Addict Biol 24:835–845.
10. Enoch MA (2006): Genetic and Environmental Influences on the Development of Alcoholism: Resilience vs. risk. Ann N Y Acad Sci 1094:193–201.
11. Stanger C, Ryan SR, Fu H, Budney AJ (2011): Parent training plus contingency management for substance abusing families: A Complier Average Causal Effects (CACE) analysis. Drug Alcohol Depend 118:119–126.
12. McPhee MD, Claus ED, Boileau I, Lee ACH, Graff-Guerrero A, Hendershot CS (2018): Does family history of alcohol use disorder relate to differences in regional brain volumes? A descriptive review with new data. Alcohol Clin Exp Res 42:2369–2384.
13. Dougherty DM, Lake SL, Mathias CW, Ryan SR, Bray BC, Charles NE, Acheson A (2015): Behavioral impulsivity and risk-taking trajectories across early adolescence in youths with and without family histories of alcohol and other drug use disorders. Alcohol Clin Exp Res 39:1501–1509.

14. Charles NE, Ryan SR, Bray BC, Mathias CW, Acheson A, Dougherty DM (2016): Altered developmental trajectories for impulsivity and sensation seeking among adolescent substance users. Addict Behav 60:235–241.
15. Acheson A, Lake SL, Bray BC, Liang Y, Mathias CW, Ryan SR, *et al.* (2016): Early adolescent trajectories of impulsiveness and sensation seeking in children of fathers with histories of alcohol and other substance use disorders. Alcohol Clin Exp Res 40:2622–2630.
16. Squeglia LM, Sorg SF, Jacobus J, Brumback T, Taylor CT, Tapert SF (2015): Structural connectivity of neural reward networks in youth at risk for substance use disorders. Psychopharmacol (Berl) 232:2217–2226.
17. Khemiri L, Kaag AM, Joos L, Dom G, Franck J, Goudriaan AE, Jayaram-Lindström N (2020): Family history of alcohol abuse associated with higher impulsivity in patients with alcohol use disorder: A multisite study. Eur Addict Res 26:85–95.
18. Adkison SE, Grohman K, Colder CR, Leonard K, Orrange-Torchia T, Peterson E, Eiden RD (2013): Impact of fathers' alcohol problems on the development of effortful control in early adolescence. J Stud Alcohol Drugs 74:674–683.
19. Kamarajan C, Pandey AK, Chorlian DB, Manz N, Stimus AT, Anokhin AP, *et al.* (2015): Deficient event-related theta oscillations in individuals at risk for alcoholism: A study of reward processing and impulsivity features. PLoS One 10:e0142659.
20. Luciana M (2020): Risks versus consequences of adolescent and young adult substance use: A focus on executive control. Curr Addict Rep 7:453–463.
21. Stanger C, Elton A, Ryan SR, James GA, Budney AJ, Kilts CD (2013): Neuroeconomics and adolescent substance abuse: Individual differences in neural networks and delay discounting. J Am Acad Child Adolesc Psychiatry 52:747–755.e6.
22. Lees B, Garcia AM, Debenham J, Kirkland AE, Bryant BE, Mewton L, Squeglia LM (2021): Promising vulnerability markers of substance use and misuse: A review of human neurobehavioral studies. Neuropharmacology 187:108500.
23. Jones CB, Meier MH, Corbin WE, Chassin L (2021): Adolescent executive cognitive functioning and trait impulsivity as predictors of young-adult risky drinking and alcohol-related problems. Psychol Addict Behav 35:187–198.
24. Khurana A, Romer D, Betancourt LM, Hurt H (2017): Working memory ability and early drug use progression as predictors of adolescent substance use disorders. Addiction 112:1220–1228.
25. Squeglia LM, Jacobus J, Nguyen-Louie TT, Tapert SF (2014): Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. Neuropsychology 28:782–790.
26. Squeglia LM, Ball TM, Jacobus J, Brumback T, McKenna BS, Nguyen-Louie TT, *et al.* (2017): Neural predictors of initiating alcohol use during adolescence. Am J Psychiatry 174:172–185.
27. Elton A, Stanger C, James GA, Ryan-Pettes S, Budney A, Kilts CD (2019): Intertemporal decision-making-related brain states predict adolescent drug abuse intervention responses. Neuroimage Clin 24:101968.
28. Filippi I, Hoertel N, Artiges E, Airagnes G, Guérin-Langlois C, Seigneurie AS, *et al.* (2019): Family history of alcohol use disorder is associated with brain structural and functional changes in healthy first-degree relatives. Eur Psychiatry 62:107–115.
29. Benegal V, Antony G, Venkatasubramanian G, Jayakumar PN (2007): Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. Addict Biol 12:122–132.
30. Sun D, Adduru VR, Phillips RD, Bouchard HC, Sotiras A, Michael AM, *et al.* (2023): Adolescent alcohol use is linked to disruptions in age-appropriate cortical thinning: An unsupervised machine learning approach. Neuropsychopharmacology 48:317–326.
31. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, *et al.* (2022): Reproducible brain-wide association studies require thousands of individuals. Nature 603:654–660.
32. Vijayakumar N, Youssef GJ, Allen NB, Anderson V, Efron D, Hazell P, *et al.* (2021): A longitudinal analysis of puberty-related cortical development. Neuroimage 228:117684.
33. Pfefferbaum A, Rohlfing T, Pohl KM, Lane B, Chu W, Kwon D, *et al.* (2016): Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. Cereb Cortex 26:4101–4121.
34. Lees B, Mewton L, Jacobus J, Valadez EA, Stapinski LA, Teesson M, *et al.* (2020): Association of prenatal alcohol exposure with psychological, behavioral, and neurodevelopmental outcomes in children from the adolescent brain cognitive development study. Am J Psychiatry 177:1060–1072.
35. Dwyer JB, McQuown SC, Leslie FM (2009): The dynamic effects of nicotine on the developing brain. Pharmacol Ther 122:125–139.
36. Petanjek Z, Judas M, Kostović I, Uylings HBM (2008): Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. Cereb Cortex 18:915–929.
37. Miller DJ, Duka T, Stimpson CD, Schapiro SJ, Baze WB, McArthur MJ, *et al.* (2012): Prolonged myelination in human neocortical evolution. Proc Natl Acad Sci USA 109:16480–16485.
38. Alemán-Gómez Y, Janssen J, Schnack H, Balaban E, Pina-Camacho L, Alfaro-Almagro F, *et al.* (2013): The human cerebral cortex flattens during adolescence. J Neurosci 33:15004–15010.
39. Ducharme S, Albaugh MD, Nguyen TV, Hudziak JJ, Mateos-Pérez JM, Labbe A, *et al.* (2016): Trajectories of cortical thickness maturation in normal brain development — The importance of quality control procedures. Neuroimage 125:267–279.
40. Vijayakumar N, Allen NB, Youssef G, Dennison M, Yücel M, Simmons JG, Whittle S (2016): Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume. Hum Brain Mapp 37:2027–2038.
41. Kolk SM, Rakic P (2022): Development of prefrontal cortex. Neuropsychopharmacology 47:41–57.
42. Casey BJ, Getz S, Galvan A (2008): The adolescent brain. Dev Rev 28:62–77.
43. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, *et al.* (1999): Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 2:861–863.
44. Friedman NP, Robbins TW (2022): The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology 47:72–89.
45. Di Biase MA, Tian YE, Bethlehem RAI, Seidlitz J, Alexander-Bloch AaronF, Yeo BTT, Zalesky A (2023): Mapping human brain charts cross-sectionally and longitudinally. Proc Natl Acad Sci USA 120: e2216798120.
46. Liu S, Abdellaoui A, Verweij KJH, Van Wingen GA (2023): Replicable brain–phenotype associations require large-scale neuroimaging data. Nat Hum Behav 7:1344–1356.
47. Tomasi D, Volkow ND (2021): Associations of family income with cognition and brain structure in USA children: Prevention implications. Mol Psychiatry 26:6619–6629.
48. Noble KG, Houston SM, Brito NH, Bartsch H, Kan E, Kuperman JM, *et al.* (2015): Family income, parental education and brain structure in children and adolescents. Nat Neurosci 18:773–778.
49. Gur RE, Moore TM, Rosen AFG, Barzilay R, Roalf DR, Calkins ME, *et al.* (2019): Burden of environmental adversity associated with psychopathology, maturation, and brain behavior parameters in youths. JAMA Psychiatry 76:966–975.
50. Mills KL, Lalonde F, Clasen LS, Giedd JN, Blakemore SJ (2014): Developmental changes in the structure of the social brain in late childhood and adolescence. Soc Cogn Affect Neurosci 9:123–131.
51. Mills KL, Goddings AL, Clasen LS, Giedd JN, Blakemore SJ (2014): The developmental mismatch in structural brain maturation during adolescence. Dev Neurosci 36:147–160.
52. Johnston L, Miech R, O'Malley P, Bachman J, Schulenberg J, Patrick M (2020): Monitoring the Future national survey results on drug use 1975–2019: Overview, key findings on adolescent drug use. Available at: https://cdn.ymaws.com/www.fadaa.org/resource/resmgr/files/resource_center/mtf-overview2019.pdf. Accessed June 13, 2021.
53. Welch KA, Carson A, Lawrie SM (2013): Brain structure in adolescents and young adults with alcohol problems: Systematic review of imaging studies. Alcohol 48:433–444.
54. Prescott CA (2002): Sex differences in the genetic risk for alcoholism. Alcohol Res Health 26:264–273.

55. Casey BJ, Cannonier T, Conley MI, Cohen AO, Barch DM, Heitzeg MM, *et al.* (2018): The adolescent brain cognitive development (ABCD) study: Imaging acquisition across 21 sites. Dev Cogn Neurosci 32:43–54.
56. Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, *et al.* (1995): Comparison of direct interview and family history diagnoses of alcohol dependence. Alcohol Clin Exp Res 19:1018–1023.
57. Cservenka A (2016): Neurobiological phenotypes associated with a family history of alcoholism. Drug Alcohol Depend 158:8–21.
58. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.
59. FreeSurfer. Available at: http://surfer.nmr.mgh.harvard.edu/. Accessed January 12, 2023.
60. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.
61. Fischl B, Sereno MI, Dale AM (1999): Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9:195–207.
62. Paulus MP, Squeglia LM, Bagot K, Jacobus J, Kuplicki R, Breslin FJ, *et al.* (2019): Screen media activity and brain structure in youth: Evidence for diverse structural correlation networks from the ABCD study. Neuroimage 185:140–153.
63. Herting MM, Sowell ER (2017): Puberty and structural brain development in humans. Front Neuroendocrinol 44:122–137.
64. Goddings AL, Beltz A, Peper JS, Crone EA, Braams BR (2019): Understanding the role of puberty in structural and functional development of the adolescent brain. J Res Adolesc 29:32–53.
65. Treit S, Zhou D, Lebel C, Rasmussen C, Andrew G, Beaulieu C (2014): Longitudinal MRI reveals impaired cortical thinning in children and adolescents prenatally exposed to alcohol. Hum Brain Mapp 35:4892–4903.
66. Treit S, Chen Z, Zhou D, Baugh L, Rasmussen C, Andrew G, *et al.* (2017): Sexual dimorphism of volume reduction but not cognitive deficit in fetal alcohol spectrum disorders: A combined diffusion tensor imaging, cortical thickness and brain volume study. Neuroimage Clin 15:284–297.
67. Hendrickson TJ, Mueller BA, Sowell ER, Mattson SN, Coles CD, Kable JA, *et al.* (2018): Two-year cortical trajectories are abnormal in children and adolescents with prenatal alcohol exposure. Dev Cogn Neurosci 30:123–133.
68. Ewing SW, Sakhardande A, Blakemore SJ (2014): The effect of alcohol consumption on the adolescent brain: A systematic review of MRI and fMRI studies of alcohol-using youth. Neuroimage Clin 5:420–437.
69. Luciana M, Collins PF, Muetzel RL, Lim KO (2013): Effects of alcohol use initiation on brain structure in typically developing adolescents. Am J Drug Alcohol Abuse 39:345–355.
70. Sullivan RM, Wade NE, Wallace AL, Tapert SF, Pelham WE, Brown SA, *et al.* (2022): Substance use patterns in 9 to 13-year-olds: Longitudinal findings from the adolescent brain cognitive development (ABCD) study. Drug Alcohol Depend Rep 5:100120.
71. Bates D, Mächler M, Bolker B, Walker S (2015): Fitting linear mixed-effects models using lme4. J Stat Softw 67:1–48.
72. R package emmeans: Estimated marginal means. Available at: https://www.rdocumentation.org/packages/emmeans/versions/1.8.8. Accessed August 26, 2023.
73. Mowinckel AM, Vidal-Piñeiro D (2019): Visualisation of Brain Statistics with R-packages ggseg and ggseg3d, version 1. https://doi.org/10.48550/ARXIV.1912.08200. Accessed August 23, 2023.
74. Navarri X, Afzali MH, Lavoie J, Sinha R, Stein DJ, Momenan R, *et al.* (2022): How do substance use disorders compare to other psychiatric conditions on structural brain abnormalities? A cross-disorder meta-analytic comparison using the ENIGMA consortium findings. Hum Brain Mapp 43:399–413.
75. DeVito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH, Pearlson GD (2013): Neural correlates of impulsivity in healthy males and females with family histories of alcoholism. Neuropsychopharmacology 38:1854–1863.
76. Elton A, Allen JH, Yorke M, Khan F, Xu P, Boettiger CA (2023): Sex moderates family history of alcohol use disorder and childhood maltreatment effects on an fMRI stop-signal task. Hum Brain Mapp 44:2436–2450.
77. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, *et al.* (2007): Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 104:19649–19654.
78. Yu G, Liu Z, Wu X, Becker B, Zhang K, Fan H, *et al.* (2023): Common and disorder-specific cortical thickness alterations in internalizing, externalizing and thought disorders during early adolescence: An Adolescent Brain and Cognitive Development study. J Psychiatry Neurosci 48:E345–E356.
79. Whittle S, Vijayakumar N, Simmons JG, Allen NB (2020): Internalizing and externalizing symptoms are associated with different trajectories of cortical development during late childhood. J Am Acad Child Adolesc Psychiatry 59:177–185.
80. Albaugh MD, Hudziak JJ, Spechler PA, Chaarani B, Lepage C, Jeon S, *et al.* (2023): Conduct problems are associated with accelerated thinning of emotion-related cortical regions in a community-based sample of adolescents. Psychiatry Res Neuroimaging 330:111614.
81. Almeida Montes LG, Prado Alcántara H, Martínez García RB, De La Torre LB, Avila Acosta D, Duarte MG (2013): Brain cortical thickness in ADHD: Age, sex, and clinical correlations. J Atten Disord 17:641–654.
82. Ducharme S, Albaugh MD, Hudziak JJ, Botteron KN, Nguyen TV, Truong C, *et al.* (2014): Anxious/depressed symptoms are linked to right ventromedial prefrontal cortical thickness maturation in healthy children and young adults. Cereb Cortex 24:2941–2950.
83. Newman E, Thompson WK, Bartsch H, Hagler DJ, Chen CH, Brown TT, *et al.* (2016): Anxiety is related to indices of cortical maturation in typically developing children and adolescents. Brain Struct Funct 221:3013–3025.
84. Spadoni AD, Simmons AN, Yang TT, Tapert SF (2013): Family history of alcohol use disorders and neuromaturation: A functional connectivity study with adolescents. Am J Drug Alcohol Abuse 39:356–364.