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Parental Family History of Alcohol Use Disorder and Neural Correlates of Response Inhibition in Children From the Adolescent Brain Cognitive Development (ABCD) Study

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Background: Youth whose parents have alcohol use disorder (AUD) are at higher risk for earlier initiation and greater magnitude of alcohol use, and have a higher likelihood of developing an AUD than their peers without parental history of AUD. This increased risk may be partly attributable to altered development of inhibitory control and related neural circuitry. This study examined neural activation during a motor response inhibition Stop Signal Task (SST) in substance-naïve youth aged 9 to 10 years with and without parental family history of AUD.

Methods: Baseline cross-sectional survey and functional magnetic resonance imaging (fMRI) data were drawn from 6,898 youth in the US-based Adolescent Brain Cognitive Development Study. Generalized additive mixed models were conducted to examine the association between maternal, paternal, and parental (both mother and father) family history of AUD with neural activation during successful and failed response inhibition. Family history interactions with sex and stratification by ethnicity were explored.

Results: Of 6,898 participants, 951 (14%) were family history positive for any parental AUD. Paternal history of AUD was associated with greater activation for successful inhibition in the right medial orbital frontal gyrus, compared to youth with no family history. Maternal history of AUD was associated with greater activation for failed response inhibition among females in the cerebellum, compared to females with no such history. Parental history (both mother and father) of AUD was associated with greater activation during successful inhibition in the left paracentral gyri and left superior parietal lobule. Maternal history and parental history of AUD findings were accounted for by a family history of substance use disorder in general. All effect sizes were relatively small.

Conclusions: Substance-naïve children with a parental family history of AUD exhibit greater neural activation in some regions of the fronto-basal ganglia and cerebellar networks when they successfully or unsuccessfully inhibit a response as compared to children with no such family history. This unique neural response pattern could reflect a compensatory response and may represent an inherent neurobiological vulnerability to risk-related behaviors in these youth which will be examined in future longitudinal analyses of this cohort.

Key Words: Response Inhibition, Functional Magnetic Resonance Imaging, Alcohol Use Disorder, Family History, Stop Signal Task.

LATE CHILDHOOD IS a vulnerable developmental period characterized by significant neural and cognitive changes (Crews et al., 2007; Spear, 2013). Important morphometric restructuring and functional neuromaturation

continue in parallel throughout this period (Tamnes et al., 2017). The resulting increased neural efficiency (de Graaf-Peters and Hadders-Algra, 2006) is thought to improve cognition, such as executive functions (Casey et al., 2005). Inhibitory control is one component of higher-order executive functions (Giedd et al., 1999; Gogtay et al., 2004). It is subserved by neural circuitry in the fronto-basal ganglia network (Koyama et al., 2017; Lopez-Caneda et al., 2014), which includes the prefrontal (PFC) and inferior frontal cortices (IFC), the presupplementary motor area, basal ganglia, and primary motor cortex (Aron, 2011). Typically developing children exhibit progressive reductions in neural network activation across the medial and lateral parts of the PFC and age-related increases in the IFC and insula that are associated with improved inhibitory control performance (Casey et al., 1997; Somerville et al., 2011; Tamm et al., 2002). Therefore, functional differences in fronto-basal ganglia network development may be related to an inherent

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neurobiological vulnerability in the cognitive control network and thus difficulty suppressing maladaptive behaviors. This in turn may promote risky actions, such as excessive alcohol use (Casey et al., 2008; Shulman et al., 2016; Steinberg, 2010).

The onset of alcohol use typically occurs during adolescence when the brain continues to undergo critical development. In the United States (US), 24% of high school students have consumed alcohol (more than just a few sips) by age 14, and 59% have done so by age 18 (Johnston et al., 2019). Of particular concern, approximately 4% and 14% of US high school students aged 14 and 18 years, respectively, have engaged in binge drinking (i.e., the consumption of 5+ drinks in a row) in the past 2 weeks (Johnston et al., 2019). These statistics are concerning because excessive alcohol use during adolescence is associated with a myriad of negative consequences including alcohol and substance use disorders (AUD, SUD; Dwyer-Lindgren et al., 2018), and other mental health problems (Pompili et al., 2010; Teesson et al., 2010; Welsh et al., 2017). Alcohol use during adolescence has also been associated with alterations in brain structure and function, including aberrant activation patterns during response inhibition tasks (for review, see Lees et al., 2020; Lees et al., 2019; Squeglia and Cservenka, 2017; Squeglia and Gray, 2016), as well as poorer test performance across cognitive domains, with executive functions and memory being the most vulnerable (Gould, 2010; Lees et al., 2019). Recent longitudinal neuroimaging studies have begun investigating, and have shown, that underlying neural vulnerabilities of response inhibition in substance-naïve children appear to contribute to earlier initiation and problematic progression of alcohol use during adolescence (Squeglia and Cservenka, 2017).

Vulnerability for early alcohol initiation is heightened among individuals with a positive family history (FH+) of AUD, particularly among those with a FH+ first-degree relative (Dawson et al., 1992). FH+ has been associated with earlier initiation and greater magnitude of alcohol use, a 3- to 5-fold increased likelihood of developing an AUD (Cotton, 1979; McCaul et al., 1990), and a heightened likelihood of experiencing alcohol-related problems in adolescence (Lieb et al., 2002), when compared to family history negative (FH-) youth. FH+ risk is thought to be driven at least partially by deficits in motor response inhibition (Sher et al., 2005; Tarter et al., 2003). Emerging research has aimed to uncover the neurobiological markers that may increase risk for early alcohol use and AUD in FH+ youth aged between 8 and 19 years who are largely substance-naïve (Squeglia and Cservenka, 2017). Preliminary functional magnetic resonance imaging (fMRI) research, utilizing the Go/NoGo Task, suggests that FH+ youth may have altered development of the fronto-basal ganglia network. Some studies have reported reduced activation among FH+ youth in the right ventral and lateral parts of the PFC (Koyama et al., 2017), and the fronto-parietal regions (Schweinsburg et al., 2004),

while others have reported greater activation among FH+ youth in the ventral caudate (Heitzeg et al., 2010) and frontal regions (Acheson et al., 2014b), when compared to FH- youth. Furthermore, longitudinal research has suggested that alcohol-naïve FH+ youth show increasing anterior cingulate activity over time, while their FH- peers showed the expected reduction in fronto-striatal response to the Go/NoGo Task (Hardee et al., 2014). These fMRI studies highlight that FH+ youth consistently show altered brain activity during response inhibition tasks compared to their FH- peers.

To date, motor response inhibition fMRI studies examining FH+ substance-naïve youth have been restricted to small sample sizes with mostly Caucasian adolescents. This has not allowed for adequate examination of response inhibition as related to: (i) the mother and father's independent heritable influence of AUD history on their child's neurobiological development or (ii) variability as related to demographic and genetic differences, such as race/ethnicity and sex. Previous neuropsychological research has reported differential effects of paternal and maternal AUD on offspring cognition and impulsivity (Corte and Becherer, 2007; Ozkaragoz et al., 1997), yet how this translates to neural activation during response inhibition remains unknown. Furthermore, differences in alcohol use behaviors by race/ethnicity and sex have been documented (Flewelling et al., 2004; Johnston et al., 2019); however, comparisons of these groups on neurobiological predictors of alcohol use remain limited. More nuanced understanding of neural functioning in FH+ (mother, father, both parents) individuals from diverse backgrounds will advance our understanding of the underlying biological vulnerabilities to alcohol-related problems, and will inform early intervention strategies.

In the present study, we sought to examine neural activation to a motor response inhibition Stop Signal Task (SST) in parental FH+/- substance-naïve youth aged 9 to 10 years enrolled in the Adolescent Brain Cognitive Development (ABCD) Study (Auchter et al., 2018; Garavan et al., 2018; Volkow et al., 2018). The stop-signal paradigm probes neural networks reflective of motor response inhibition, similar to the Go/NoGo Task, but requires greater inhibitory control (Nee et al., 2007). We investigated maternal, paternal, and parental (both mother and father) FH of AUD. By drawing on the large ABCD dataset, we were also able to explore differential ethnicity effects and sex interactions, and adjust for in utero exposure to alcohol for the first time. It was hypothesized that FH+ youth would show altered activity in regions known to be involved in SST performance, particularly in fronto-basal ganglia network regions (Cieslik et al., 2015), when compared to FH- youth. We also anticipated that youth with 2 parents reporting a history of AUD would show greater genetic liability and thus increased vulnerability resulting in greater neural response deviation than youth with 1 FH+ parent or FH- youth (Khemiri et al., 2020).

MATERIALS AND METHODS

This study used baseline cross-sectional data from the ABCD Data Release 2.0.1. The ABCD study is a 10-year longitudinal study across 21 US-based sites, recruiting 11,878 participants, and funded by the National Institutes of Health (Volkow et al., 2018). A total of 6,898 participants had valid parental history, demographic, and fMRI SST data following quality control processing (Fig. 1). The Institutional Review Board at the University of California, San Diego, approved all aspects of this study for the ABCD consortium.

Recruitment

A detailed account of the recruitment strategy has been previously published (Garavan et al., 2018). The ABCD study primarily utilized a probability sample recruited through schools, where school selection was based on sex, race and ethnicity, socioeconomic status, and urbanicity. Interested participants and their families completed a brief eligibility interview over the phone to ensure interested youth were 9 to 10 years old and had no MRI contraindications (i.e., irremovable metal in body).

Procedure

Youth and their parent/guardian presented for study session(s) at their local research site to complete the baseline visit. Parents/guardians provided written consent while the child provided written assent. Youth and their parent/guardian were in separate, private rooms during study participation to maintain confidentiality of their survey responses. The baseline measures included questionnaires, neurocognitive testing, biological samples, and an MRI scan (Lisdahl et al., 2018; Luciana et al., 2018; Uban et al., 2018). Study assessment was completed over an 8-hour research session (or two 4-hour sessions). Parents and youth were compensated financially and with prizes for their time.

Family History of Alcohol Use Disorders

Full descriptions of ABCD environmental, health, and mental health questionnaires are described elsewhere (Barch et al., 2018;

Lisdahl et al., 2018; Zucker et al., 2018). The parent/guardian completed a 15-minute modified version of the Family History Assessment Module Screener (FHAM-S; Rice et al., 1995). Parents/guardians reported on the presence or absence of a range of mental health symptoms including those associated with AUD in all first- and second-degree blood relatives of the youth, including biological siblings, parents, grandparents, aunts, and uncles. Only parental history of alcohol and drug use problems were of interest for the current study (Cservenka, 2016).

Covariates

Covariates were chosen based on prior evidence of an association with the outcomes (Table 1). Standard ABCD demographic covariates included race, age, sex, and parental education. Substance-related covariates included parental retrospective report of maternal alcohol use during pregnancy (yes/no), as reported in the modified Developmental History Questionnaire (Kessler et al., 2009a; Kessler et al., 2009b; Merikangas et al., 2009). Youth emotional and behavioral covariates included internalizing, externalizing, and total behavioral problems from the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2013).

fMRI Stop Signal Task

Full task information has been described previously (Casey et al., 2018). The SST measures domains of motor response inhibition and impulsivity, showing child/adolescent-specific and substance use effects (Smith et al., 2014; Whelan et al., 2012). The SST requires participants to withhold or interrupt a motor response to a “Go” stimulus when it is followed unpredictably by a signal to stop. Participants completed 2 sets, each containing 180 trials. Each trial began with the presentation of a leftward or rightward pointing arrow, and participants were instructed to indicate the direction, responding quickly and accurately via a 2-button response panel. Thirty of the trials were “Stop” trials where the leftward or rightward facing arrow was followed by an up-right arrow, indicating to participants to stop their prepotent “Go” response. To ensure that there were approximately 50% successful and 50% unsuccessful inhibition trials for Stop trials, a tracking algorithm varied the interval of trials (see Casey et al., 2018 for further details). Mean beta weights for correct stop contrasts (correct stop contrasted with correct go) and failed stop contrasts (incorrect stop contrasted with correct go) were used in all analyses to compare neural response differences to both successful and unsuccessful inhibition trials.

Imaging Data Acquisition and Processing

Full MRI and fMRI acquisition and scanning parameters are described elsewhere (Casey et al., 2018). All scans were uploaded to a shared server that was processed by the Data Analytics and Information Core (DAIC) of ABCD, to maintain consistency across methodology and ensure quality. Details on data processing are described by Hagler and colleagues (2018). All parcellations based on the Desikan-Killiany Atlas were examined (68 cortical and 30 subcortical regions). Only participants whose SST task scans met all quality checks by DAIC were used in analyses. There was no significant difference in the number of FH– (81%) and FH+ youth (80%) who provided useable, high-quality SST fMRI data.

Data Analysis

Differences in demographic and behavioral variables between the FH+/- for AUD (none, father, mother, both parents) were determined using χ^2 tests for categorical data and ANOVAs for

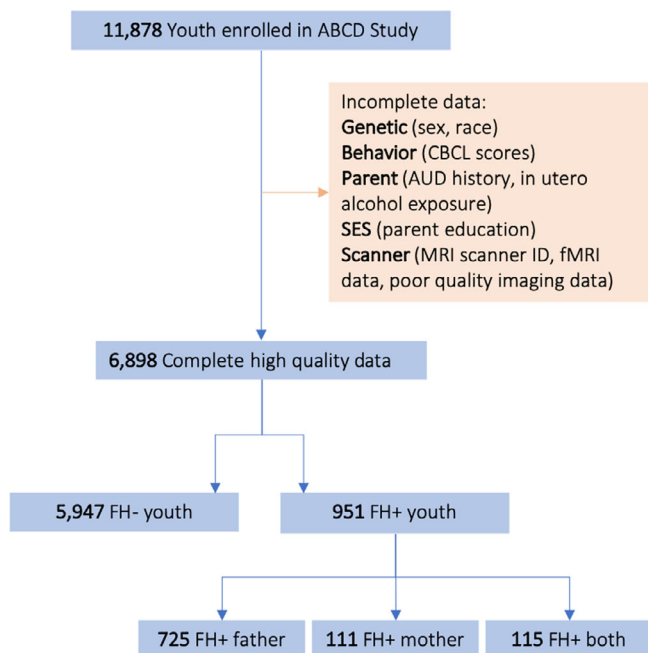


Fig. 1. Selection of the ABCD cohort for analyses.

Table 1. Demographic Characteristics of Sample at Baseline, *N* = 6,898

	FH– n=5947	FH+ n=951		
		Father n = 725	Mother n = 111	Both n = 115
Age (mean [SD])	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)
Race (%) ^{a,c,d}				
White	55.7	53.2	54.1	50.4
Hispanic	19.6	23.2	16.2	11.3
Black	13.3	11.2	17.1	13.0
Asian	2.0	0.4	0.0	0.9
Other	9.4	12.0	12.6	24.4
Sex (%)				
Female	48.4	50.3	50.5	45.2
Male	51.6	49.7	49.6	54.8
Highest Parent Education (%) ^{a,b,c,d,f}				
<HS Diploma	5.0	5.2	9.0	7.0
HS Dip/GED	10.0	11.5	9.9	18.3
Some College	27.8	40.0	40.5	43.5
Bachelor	30.8	25.0	24.3	16.5
Post Grad	26.4	17.9	16.2	14.8
In utero alcohol exposure (%) ^{a,b,c,d,e,f}				
Not exposed	76.0	67.6	61.3	39.1
Exposed	24.0	32.4	38.7	60.9
FH of SUD (%) ^{a,b,c,d,e,f}				
FH–	95.3	63.5	64.0	41.7
FH+ Father	3.5	31.7	8.1	11.3
FH+ Mother	0.7	1.2	21.6	5.2
FH+ Both	0.5	3.4	6.3	41.7
Internalizing (T-score [SD]) ^{a,c,d,e}	47.8 (10.4)	50.7 (10.8)	48.8 (11.7)	52.6 (11.6)
Externalizing (T-score [SD]) ^{a,b,c,d,e,f}	44.8 (9.8)	47.4 (10.4)	46.4 (10.8)	50.7 (11.4)
Total problems (T-score [SD]) ^{a,c,d,e,f}	44.9 (10.9)	47.8 (11.4)	46.3 (11.7)	51.2 (12.8)

No significant group differences between youth of FH+ mothers vs FH+ fathers.

^aFH– youth ≠ FH+ youth, *p* < .05

^bFH– youth ≠ youth of FH + mothers, *p* < 0.05

^cFH– youth ≠ youth of FH + fathers, *p* < 0.05

^dFH– youth ≠ youth of FH + both parents, *p* < 0.05

^eYouth of FH + mothers ≠ youth of FH + both parents, *p* < 0.05

^fYouth of FH + fathers ≠ youth of FH + both parents, *p* < 0.05

continuous variables. First, a series of generalized additive mixed models (GAMM) were conducted to examine the association between parental FH+/- and neural activation during correct stop and failed stop contrasts in the SST task, using the *GAMM4* package in R, version 3.5.3. Covariates included race/ethnicity, age, sex, parental education, in utero alcohol exposure, total emotional/behavioral problems, externalizing symptoms, and internalizing symptoms, as well as nesting of subjects by scanner. Participants with missing data for any of these variables were excluded from analyses. This series of models were then repeated to examine family history × sex interactions. Next, a series of main effect and sex interaction GAMMs were conducted for significant regions and contrasts, with participants grouped by race/ethnicity to account for the heterogeneity of socioeconomic and social covariates (e.g., income, youth education) within ethnic groups across FH+/- (i.e., FH– vs. FH+ for Asian, Black, Hispanic, White). All covariates, besides race/ethnicity, were included in this pass. Finally, sensitivity analyses were conducted to determine whether results were specific to parental FH of AUD or whether they were influenced by other substance use problems. Analyses described above were repeated for significant brain regions with parental FH of SUD included as an additional covariate. In all analyses, the false discovery rate (FDR) was used to correct for multiple comparisons and the adjusted *p*-values are reported (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001).

Table 2. Behavioral Data for the Stop Signal Task, *N* = 6,898

	FH– n=5947	FH + n=951		
		Father n = 725	Mother n = 111	Both n = 115
Mean Go RT (ms mean [SD])	472.5 (82.2)	468.8 (78.4)	470.1 (74.7)	467.5 (88.0)
Mean Stop RT (ms mean [SD])	301.5 (79.6)	302.3 (79.3)	290.3 (73.9)	298.0 (75.5)
Correct Go (%) ^{a,b,c,d}	81.4	80.7	82.8	77.0
Correct Stop (%)	50.8	50.7	51.7	50.9
Failed Stop (%)	45.4	45.3	43.7	45.2

No significant group differences: FH– youth vs youth of FH + mothers, FH– youth vs youth of FH + fathers, youth of FH + mothers vs FH + fathers.

^aFH– youth ≠ FH + youth, *p* < 0.05

^bFH– youth ≠ youth of FH + both parents, *p* < 0.05

^cYouth of FH + mothers ≠ youth of FH + both parents, *p* < 0.05

^dYouth of FH + fathers ≠ youth of FH + both parents, *p* < 0.05

RESULTS

Participant Characteristics

Demographic characteristics of FH– and FH+ youth are provided in Table 1. Of 6,898 participants, 951 youth (13.8%) were FH+ for parental AUD: 725 youth had a FH+ father, 111 had a FH+ mother, and 115 had 2 FH+ parents. In terms of parent-reported in utero alcohol exposure, 24.0% of FH–, and 32.4%, 38.7%, and 60.9% of youth with a FH+ father, mother, and both parents were exposed, respectively. There were relatively high rates of cooccurring alcohol and substance use problems among parents: 31.7%, 21.6%, and 41.7% of FH+ AUD father-only, mother-only, and both parents also reported a SUD history, respectively. Youth with 2 FH+ parents had the highest internalizing, externalizing, and total problems on the CBCL, compared to youth with 1 FH+ parent or FH– youth. Participants in all groups scored similarly on SST performance, besides youth with 2 FH+ parents who had a lower correct go rate than other groups (Table 2).

Between-Group Family History Findings. Table 3 and Fig. 2 present brain regions exhibiting significantly greater activation for correct stop and failed stop contrasts among FH+ compared to FH– youth, when controlling for relevant covariates. Children with FH+ mothers had greater activation for failed stop contrasts in the right cerebellum compared to FH– youth ($R^2 = 0.003$). FH+ fathers had greater neural activation for correct stop contrasts in the right medial orbital frontal cortex compared to FH– youth ($R^2 = 0.001$). For children with 2 FH+ parents, greater neural activation for correct stop contrasts was observed in the left paracentral lobule ($R^2 = 0.002$) and left superior parietal lobule ($R^2 = 0.048$; Fig. 3). No significant between-group differences were observed for any other ROI. A family history \times sex interaction was observed in the right cerebellum ($B = 0.288$, $SE = 0.055$, $p < 0.001$, $R^2 = 0.003$). Female youth of FH+ mothers exhibited significantly greater activation than FH– female youth for the failed stop contrast ($p < 0.001$), while no significant difference was observed between male youth of FH+ mothers compared to FH– parents in the cerebellum. No other significant interactions were observed. The results for FH+ fathers remained significant during sensitivity analyses when FH of SUD was included as an additional covariate; however, the results for FH+

mothers (main effect and family history \times sex interaction) and 2 FH+ parents were no longer significant.

Ethnicity Findings. Demographic characteristics for each ethnic group are provided. Between-group analyses for all regions that showed significant group differences for correct stop and failed stop contrasts were rerun separately for each ethnic group, as summarized in Table 4. When controlling for relevant covariates, Hispanic youth with FH+ mothers exhibited significantly greater activation for failed stop contrasts in the right cerebellum compared to FH– Hispanic youth ($R^2 = 0.034$). Hispanic youth with FH+ fathers exhibited significantly greater activation for correct stop contrasts in the right medial orbital frontal lobe compared to FH– Hispanic youth ($R^2 = 0.009$). White youth with 2 FH+ parents exhibited greater activation in the left paracentral lobule ($R^2 = 0.001$) and left superior parietal lobule ($R^2 = 0.003$), when compared to White FH– youth for correct stop contrasts.

FH+ mother \times sex interactions were driven by Hispanic families: Female Hispanic youth with FH+ mothers exhibited significantly greater activation than FH– female Hispanic youth in the right cerebellum ($p < 0.001$) for failed stop contrasts. No significant differences were observed among FH+ and FH– male Hispanic youth in the cerebellum, or for any other ethnicity. During sensitivity analyses when FH of SUD was included as an additional covariate, the results remained significant for Hispanic families (main effects and FH \times sex interaction), while the results did not remain significant for White families. No significant between-group differences were observed for Asian or Black youth.

DISCUSSION

Leveraging a large multisite US sample, this study compared neural response in substance-naïve youth aged 9 to 10 years with and without parental FH of AUD during a response inhibition task. Overall, substance-naïve youth with a FH+ mother had significantly greater neural activation for the failed stop contrast in the right cerebellum compared to FH– youth. Exploration of sex interactions demonstrated that this effect was driven by activation differences in young females. Youth with a FH+ father had significantly greater neural response as compared to FH– youth for the

Table 3. Brain Regions Exhibiting Greater Activation in FH+ Compared to FH– Youth for the Correct Stop vs. Correct Go Contrast, After Controlling for Relevant Covariates. There Were No Significant Differences Between Groups for the Incorrect Stop vs. Correct Go Contrast. $N = 6,898$

FH + parent	Contrast	Region	B (SE)	p	R^2	AIC	BIC
Mother	Failed stop vs correct go	Cerebellum, R	0.288 (.055)	<0.001	0.0033	7234.6	7371.4
Father	Correct stop vs correct go	Medial orbital frontal, R	0.083 (.025)	0.034	0.0013	13007.9	13144.7
Both	Correct stop vs correct go	Paracentral, L	0.058 (.017)	0.029	0.0016	–4262.3	–4125.6
		Superior parietal, L	0.063 (.019)	0.048	0.0019	–2518.8	–2382.0

L: left; R: right. Only regions where the model passed the FDR correction are presented.

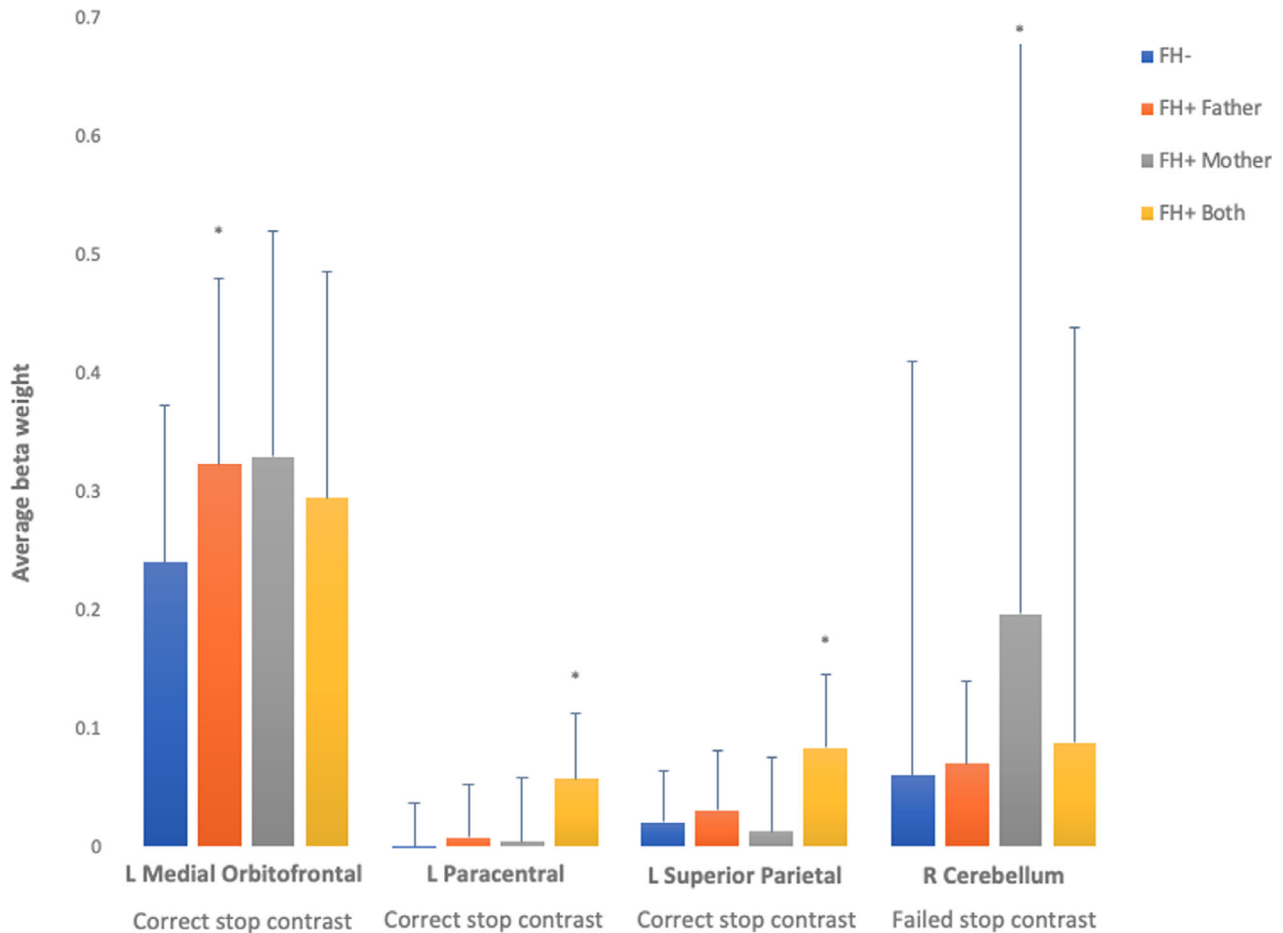


Fig. 2. Summary of brain parcellations exhibiting significantly greater activation in FH+ vs. FH– youth. Blue = greater activation among FH+ vs. FH– youth during failed stop contrast. Red = greater activation among FH+ vs. FH– youth during correct stop contrast. OFC = orbitofrontal cortex.

successful stop contrast in the right medial orbital frontal gyrus. Youth with 2 FH+ parents demonstrated greater neural response for the successful stop contrast in the left paracentral and left superior parietal lobule compared to FH– youth. Sensitivity analyses demonstrated activation differences observed among youth with FH+ mothers or 2 FH+ parents were accounted for by FH of SUD effects. Neural activation profiles differed for each ethnic group; greater response for female youth with FH+ mothers and greater response for youth with FH+ fathers were driven by Hispanic families, while greater response for youth with 2 FH+ parents was driven by White families. Only effects observed among Hispanic families were robust to inclusion of FH of SUD as an additional covariate. Between-group effect sizes were very small.

Our findings align with previous research and suggest that greater activation in FH+ youth aged 9 to 10 years occurs in some regions of the fronto-basal ganglia network (i.e., PFC, supplementary motor area) during successful response inhibition (Acheson et al., 2014a; Acheson et al., 2014b; DeVito et al., 2013; Silveri et al., 2011). Greater activation was also observed in parts of the default network (left superior

parietal lobule), which is involved in diverse cognitive operations, including aspects of attention, visuospatial processing, and executive functioning (Johns, 2014; Koenigs et al., 2009). Greater neural activation in the cerebellum during failed response inhibition has been previously reported among FH+ youth (Acheson et al., 2014b). Observed effects were small which is consistent with previous research in this age group (Acheson et al., 2014b). Other studies have reported larger effect sizes (Acheson et al., 2014a) and have also reported increased fronto-basal ganglia network activation during failed response inhibition contrasts for FH+ individuals (Heitzeg et al., 2010; Jamadar et al., 2012). However, these smaller, less diverse study samples included adolescents and adults who had initiated substance use. Therefore, these findings may reflect an altered neural response pattern that is more characteristic of a later stage of neurodevelopment among FH+ individuals.

To the best of our knowledge, no previous study has investigated the association between FH of AUD and neural activation during response inhibition using a family-based design, stratified by race/ethnicity. Drawing on the large ABCD dataset meant we were uniquely positioned to explore

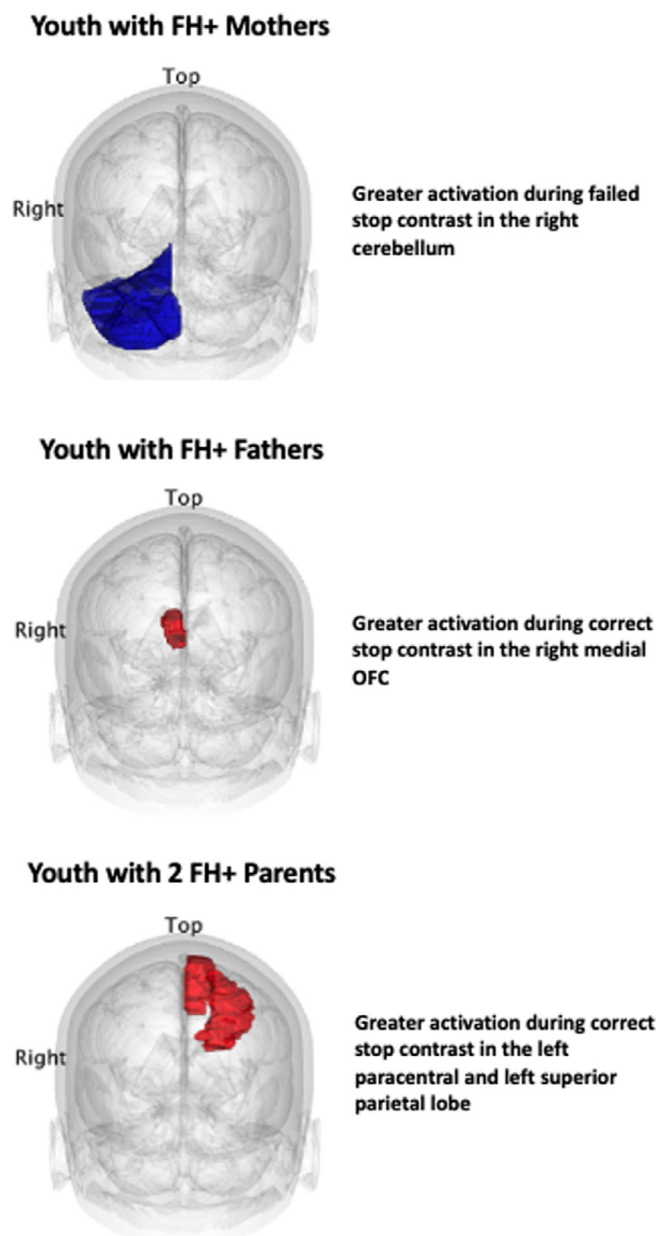


Fig. 3. Significantly greater neural activation for correct stop contrast (correct stop vs. correct go) observed in youth with fathers or both parents exhibiting a history of alcohol use problems, compared to FH– youth. Significantly greater neural activation for failed stop contrast (failed stop vs. correct go) observed in youth with mothers exhibiting a history of alcohol use problems, compared to FH– youth. $n = 6,898$. $*p(\text{FDR}) < 0.05$

these effects, allowing us to better understand phenotypic mechanisms of FH of AUD. We found that both paternal and parental AUD when compared to FH– were associated with greater activation across portions of the fronto-basal ganglia network. This was not observed in youth with a maternal FH of AUD. Interestingly, maternal FH of AUD was associated with activation differences in the cerebellum of young females. Previous studies have reported weaker fronto-cerebellar connectivity in FH+ youth (Cservenka, 2016) and in adults with AUDs (Sullivan et al., 2003).

Altered cerebellar activation has been associated with reward processing and risky decision making in FH+ youth (Cservenka, 2016), although whether these neurofunctional differences increase risk for excessive alcohol use remains unknown. Future prospective investigations of this cohort should explore how connectivity within and between the fronto-basal ganglia and cerebellar networks confers risk to uptake, and escalation, of alcohol use. While we hypothesized that youth with 2 FH+ parents would show greater deviations than youth with 1 FH+ parent, our findings suggest that maternal and paternal AUD potentially confer differential risk to offspring neurofunction in the fronto-basal ganglia network. Previous research has reported that paternal AUD is associated with poorer response inhibition, impulsivity, and externalizing problems, such as alcohol use, in offspring (Corte and Becherer, 2007; Grekin et al., 2005; Ozkaragoz et al., 1997); however, the neural mechanisms of this differential risk remain unknown. The null fronto-basal ganglia network findings for maternal AUD may also be partly due to adjustment for in utero alcohol exposure (39% of FH+ mothers reported alcohol use during pregnancy), which is known to impact offspring brain development (Lees et al., Under review). It is important to note that given the lower frequency of FH+ mothers compared to FH+ fathers in the ABCD study, analyses examining a maternal effect had lower statistical power and this may have yielded less reliable estimates, as observed by similar average beta weights with larger standard errors in the medial orbital frontal gyrus (Fig. 3).

Neural activation to response inhibition in FH+ youth also appears to vary across racial/ethnic groups. Race and ethnicity variables may be a proxy for more meaningful factors, such as level of acculturation, quality of education, socioeconomic status, and racial socialization, which may be contributing to differences in neurofunction (Manly, 2006). Genetic and other biological variants associated with different racial and ethnic backgrounds (e.g., aldehyde dehydrogenase 2 deficiency) can also induce pronounced effects on alcohol consumption, which may also be contributing to the observed findings (Edenberg, 2007). Further neuroimaging research is required in a diverse ethnic population to investigate mechanisms underlying differential parental risk for altered offspring neurodevelopmental trajectories.

Patterns of greater activation in FH+ youth may reflect heightened processing effort and energy utilization throughout the fronto-basal ganglia network to successfully inhibit prepotent responses, which is more automatic and less effortful for FH– youth. Greater neural response may reflect a developmental lag in functional organization to some extent, given the lack of findings in the ventrolateral PFC, a key region for developmental changes in inhibition-related neural response (Aron et al., 2007; Braet et al., 2009). Previous research suggests that altered white matter integrity may also contribute to neural response differences via decreased neural efficiency and the need for recruitment of more neural resources (thus resulting in greater neural response;

Table 4. Brain Regions Exhibiting Greater Activation in FH+ Compared to FH– Youth for the Correct Stop vs. Correct Go Contrast When Ethnicity Groups Were Analyzed Separately, After Controlling for Relevant Covariates. *N* = 6,898

FH + Parent	Contrast	Region	Asian <i>N</i> = 122		Black <i>N</i> = 908		Hispanic <i>N</i> = 1363		White <i>N</i> = 3819	
			<i>B</i> (SE)	<i>p</i>	<i>B</i> (SE)	<i>p</i>	<i>B</i> (SE)	<i>p</i>	<i>B</i> (SE)	<i>p</i>
Mother	Failed stop vs correct go	Cerebellum, R	NA		−0.108 (0.109)	1.000	0.928 (0.132)	<0.001	−0.003 (0.042)	1.000
Father	Correct stop vs correct go	Medial orbital frontal, R	−0.074 (0.232)	1.000	0.187 (0.118)	0.339	0.181 (0.048)	<0.001	0.056 (0.024)	0.083
Both	Correct stop vs correct go	Paracentral, L	−0.111 (0.142)	1.000	0.061 (0.060)	0.937	0.064 (0.057)	0.810	0.052 (0.020)	0.023
		Superior parietal, L	−0.094 (0.172)	1.000	0.086 (0.070)	0.674	0.078 (0.064)	0.665	0.063 (0.023)	0.018

L: left; R: right. Reference group for analyses was FH– youth who identified as 1 of the 4 ethnicities. Youth identifying as ‘other’ race/ethnicity were not included in these analyses. FDR-corrected *p*-values are presented. NA = fixed-effect model matrix is rank deficient. *N* = total number of participants for each racial category.

Burzynska et al., 2013; Zhu et al., 2015). Greater recruitment of inhibitory control regions in FH+ youth may therefore reflect an altered neurodevelopmental trajectory of the fronto-basal ganglia network, creating an inherent neurobiological vulnerability, which affects their ability to suppress behavior. Examining the developmental trajectories of neural responses during cognitive control in this cohort when multiple waves of data are available, and correlating these to risk-related behaviors that change between childhood and adolescence (i.e. uptake of alcohol), may help identify patterns of brain activity that predict the onset of heavy alcohol use in FH+ youth.

There are several limitations to this study. Firstly, information on FH of AUD or SUD, as well as in utero alcohol exposure, may have been underreported or imprecisely recalled. Self-report data on substance use can be influenced by social stigma, desirability bias, and fear of intervention by child protection or social services (Johnson and Fendrich, 2005; Stone, 2015). Effects of reporting influenced by social stigma can also significantly vary by race/ethnicity (Garland and Bumphus, 2012; Kulesza et al., 2016). The effects of underreporting and imprecise recollection of substance use resulting in FH of AUD misclassification would likely attenuate the observed association toward the null. Potentially, this means the reported associations are smaller in magnitude than the true effects. Secondly, despite the large sample size, there were relatively few cases of youth with FH+ mother or 2 FH+ parents. The small sample size of youth with FH+ mothers or 2 FH+ parents resulted in wider variance in neural responses and may underestimate the true impact. This was also evident when we conducted analyses for separate race/ethnicity. The ABCD cohort has a smaller proportion of Asian and Black families relative to White and Hispanic, and this resulted in very small FH+ samples of Asian and Black youth. The low statistical power may yield less reliable estimates for these cases. The current study was uniquely positioned to separately explore maternal and paternal AUD on youth neurofunction; however, the effects of second- and third-degree relatives with AUD (i.e., FH+

density) should be further explored in future studies. Finally, as this study utilized observational and cross-sectional data, it remains unclear how greater forebrain activations may relate to risk for developing substance use disorders. Altered and/or delayed development of regions of the fronto-basal ganglia and cerebellar networks could be a risk factor and potential mechanistic target for intervention. However, we observed very small effect sizes in a small portion of the fronto-basal ganglia network, and this may limit applicability of neural responses to inhibitory control in late childhood as a clinically relevant marker of later alcohol use outcomes. Larger effect sizes in more regions have been observed with older cohorts (Acheson et al., 2014a) and may reflect a more advanced stage of altered neurodevelopment in FH+ individuals. Longitudinal analyses in the ABCD cohort are necessary to address these issues.

In conclusion, substance-naïve children aged 9 to 10 years with parental FH of AUD exhibited greater neural activation in some regions of the fronto-basal ganglia and cerebellar networks when successfully or unsuccessfully inhibiting a response during the SST compared to FH– youth, although effect sizes were very small. These youth are part of the longitudinal ABCD study, and as they reach adolescence, we will investigate how elevated activation during response inhibition at baseline predicts later uptake of risk-related behaviors.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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