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Does family history of alcohol use disorder relate to differences in regional brain volumes? A descriptive review with new data

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Abstract

Background.—Differences in regional brain volumes as a function of family history (FH) of alcohol use disorder (AUD) have been reported, and it has been suggested that these differences might index genetic risk for AUD. However, results have been inconsistent. The aims of the current study were 1) to provide an updated descriptive review of the existing literature; and 2) to examine the association of FH with indices of subcortical volumes and cortical thickness in a sample of youth recruited based on FH status.

Methods.—To address aim 1, a literature search located fifteen published studies comprising 1735 participants. Studies were characterized according to population, analytic methods, regions of interest (ROIs), and primary findings. To address the second aim, we examined volumetric and cortical thickness in a sample of 69 youth (mean age = 19.71 years, $SD = 0.79$) recruited based on FH status and matched on drinking variables. Associations of sex and alcohol use with volumetric outcomes were also examined.

Results.—Our descriptive review revealed an inconsistent pattern of results with respect to the presence, direction, and regional specificity of volumetric differences across FH groups. The most consistent finding, significantly smaller amygdala volumes in FH+ participants, was not replicated in all studies. In the current sample of youth, measures of subcortical volumes and cortical thickness did not significantly differ as a function of FH, sex, or their interaction.

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Conclusions.—Evidence for FH group differences in regional brain volumes is inconsistent, and the current study failed to detect any group differences. Further research is needed to confirm the reproducibility of FH group differences and implications for AUD risk.

Keywords

genetic risk; neuroimaging; structural fMRI; regional brain volumes

Introduction

A family history (FH) of alcohol use disorder (AUD) is a robust risk factor for hazardous drinking (e.g., Hawkins et al., 1992; Hill et al., 2000) and the development of AUD (Chassin et al., 2004). A positive FH of AUD (FH+), though understood to reflect both genetic and environmental risk, is often used as a proxy for genetic risk (Cloninger et al., 1981). Increasingly, structural and functional magnetic resonance imaging (MRI) has been used to examine brain-based markers of AUD risk in FH+ individuals compared to FH negative (FH−) individuals (Cservenka, 2016).

Investigations into the relationships between FH and structural outcomes in those with or without AUD have been primarily underscored by two observations. First, those with an AUD appear to have differences in regional brain volumes compared to those without (Welch et al., 2013). A recent meta-analysis by Yang and colleagues (2016) highlighted widespread gray matter reductions in corticostriatal limbic regions in those with AUD compared to controls. The extent to which these group differences are pre-existing and represent elevated genetic risk (i.e., such as that conferred by FH+), rather than a consequence of prolonged exposure to the neurotoxic effects of alcohol, is not fully understood. To address confounds related to alcohol exposure, researchers have also investigated regional brain volume differences in younger and/or alcohol-naïve samples, with some studies reporting gray matter structural differences as a function of FH (e.g., Benegal et al., 2007; Henderson et al., 2018).

Second, among the potential explanations for FH group differences in young samples, it has been hypothesized that FH+ individuals experience a neurodevelopmental delay compared to their FH− peers (Hill et al., 2001). Perhaps consistent with this idea, numerous studies have shown reduced language abilities, visuospatial skills, and domains of executive functioning and affective processing among FH+ compared to FH− peers (reviewed in Squeglia and Cservenka, 2017). These observations have informed the hypothesis that FH+ individuals might reach age-specific neurodevelopmental milestones at a later time than their FH− peers. To date, the developmental delay hypothesis, as it relates to FH group differences in structural outcomes, has only been tested with cross-sectional analyses.

Overall, there remain a modest number of studies examining differences in volumetric outcomes as a function of FH. Among published studies, findings appear to be inconsistent. The primary aims of this study were 1) to provide an updated descriptive review of studies examining the relationship between FH and structural outcomes; and 2) report new data from a sample of youth selected based on FH status by way of targeted recruitment of FH+ and FH− groups. Concerning the latter aim, we focused on *a priori* ROIs selected based on

prior studies, and controlled for selected factors representing potential confounds. Specifically, substance use, childhood adversity, and psychiatric status data were collected to ensure that FH groups did not systematically differ on key variables that have previously been demonstrated to co-vary with regional brain volume.

Materials and Methods

Literature Review

For the descriptive literature review, we identified studies that reported on structural imaging outcomes as a function of FH status. Eligibility criteria included: (1) publication in a peer-reviewed journal; (2) analyses included FH+ and FH– group comparisons of cortical, subcortical, or cerebellar regions using structural MRI; and (3) written in English. Exclusion criteria included: (1) explicit comparison of groups with fetal alcohol exposure; and (2) analyses solely employed diffusion tensor imaging (DTI). Citations within eligible articles were used to identify additional articles. The search resulted in a total of fifteen articles comprising 1735 participants. Information extracted from the manuscripts included: ROIs, sample characteristics, FH status definition and assessment methods, segmentation methods, family wise error (FWE) corrections, covariates, and primary results reported.

Current Sample

Participants.—Participants (n = 69) between the ages of 19–21 years old were recruited from the community and local universities by way of posters, online postings, and handouts for participation as part of a research study that involved laboratory alcohol administration sessions and, for a subset of participants, neuroimaging sessions. Because we sought a sample stratified on FH status, recruitment included separate advertisements tailored to FH+ and FH– groups. Primary eligibility criteria included: age 19–21 years old; consumption of 5 or 4 standard drinks (for men and women, respectively) at least once in the past month; right handedness; meeting criteria for FH+ or FH– group membership (see Family History below); no current or past attempts to reduce alcohol intake; no current or past treatment for alcohol related problems; no current medication or medical condition contraindicating alcohol consumption; Fagerström test of Nicotine Dependence (Heatherton et al., 1991) total score < 6; and a brief Michigan Alcohol Screening Test (Pokorny et al., 1972) score < 10. Exclusion criteria included: any neurological condition or history of psychosis or manic episodes; currently receiving treatment for a psychiatric illness; head injury with accompanying loss of consciousness greater than 10 minutes; history of withdrawal from alcohol; positive urine drug screen test for any illicit substance other than cannabis; significant skin flushing immediately after consuming alcohol; and other criteria related to MRI safety. Eligibility criteria were confirmed during phone screening and a baseline interview session.

Study Procedures.—Participation in the study included the completion of interview sessions, intravenous alcohol administration sessions, and two MRI scans (see Hendershot et al., 2017; Strang et al., 2015, for a detailed overview). Structural data presented here are derived from the first MRI scan; for three participants, the T1-weighted images from the second scan were used for analyses due to poor image quality from the first scan.

Measures

Family History Assessment Module (FHAM).—The FHAM is a brief semi-structured interview used to assess for a family history of alcohol use disorders (Rice et al., 1995). Participants were queried about the presence of alcohol-related problems in any of their biological first- or second-degree relatives; the presence of alcohol dependence was established using Feighner criteria (Rice et al., 1995). The psychometric properties of the FHAM have been established in previous reports (e.g., Rice et al., 1995, Slutske et al., 1996).

Timeline Followback (TLFB).—The TLFB is a semi-structured interview that was used to assess past 90-day alcohol, cigarette, and substance consumption (Sobell & Sobell, 1992). Test-retest reliability of a 90-day TLFB has been previously reported to range between 0.77 and 1.00, depending on the outcome studied (Carey et al., 2004). Main outcomes from the TLFB included: number of days alcohol was consumed; total number of drinks; average number of drinks per drinking episode; maximum number of drinks consumed on one occasion; and number of heavy drinking episodes.

Rutgers Alcohol Problem Index (RAPI).—The RAPI is a 23-item self-report measure that was used to assess past-year self-reported history of alcohol-related problems (White & Labouvie, 1989). White and Labouvie (1989) reported an internal consistency of 0.92 for the RAPI. In the current study the Cronbach's alpha was 0.83. The total RAPI score served as the main outcome.

Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).—Frequency of illicit substance use during a typical week was further assessed with the World Health Organization's Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST; Humeniuk et al., 2008). The ASSIST was used as it provides an estimate of a typical pattern of weekly substance use that was used to ensure FH groups did not systematically differ on their reported illicit substance consumption.

Childhood Trauma Questionnaire – Short Form (CTQ-SF).—The CTQ-SF is a 25-item self-report measure that was used to assess childhood maltreatment (Bernstein et al., 2003). Convergent validity of the CTQ-SF was initially demonstrated by Bernstein and colleagues (2003). The CTQ-SF has good internal consistency (range of Cronbach's alpha estimates: 0.70 to 0.93; Paivio and Cramer, 2004). The internal consistency (Cronbach's alpha) of the CTQ-SF in the current sample was low at 0.52, which is likely a reflection of the use of the total score rather than the subscale scores. CTQ total scores, rather than subscale scores, were used in the present study.

Mini International Neuropsychiatric Interview (MINI).—The MINI was used to assess current and past psychiatric history including major depressive episodes, bipolar disorder, social anxiety disorder, generalized anxiety disorder, panic disorder, agoraphobia, specific phobia, obsessive-compulsive disorder, and psychosis (Lecrubier et al., 1997). In an initial study, the MINI was documented to have acceptable levels of inter-rater reliability (kappa range: 0.79 to 1.00) as well as validity demonstrated by convergence in diagnoses

obtained by both the MINI and the Structured Clinical Interview for DSM-III (kappa range: 0.43 to 0.90; Sheehan et al., 1997).

Centre for Epidemiologic Studies – Depression Scale (CES-D).—The CES-D is a widely used 20-item self-report inventory of depression symptomology (Radloff, 1977). The CES-D has good internal consistency (Cronbach's alpha range: 0.84 to 0.90), and the criterion and convergent validity of the scale has been established using clinician ratings and other measures of depression symptomology (Radloff, 1977). The Cronbach's alpha for the CES-D was 0.72 in the current sample. The total CES-D score was used for the current study to ensure groups did not differ on severity of depression symptomology reported.

World Health Organization Adult Attention-Deficit Hyperactive-Disorder (ADHD) Self-Report Scale (ASRS).—The ASRS is an 18-item self-report measure that was administered to gain information concerning ADHD symptomology (Kessler et al., 2005), which was not assessed in the MINI. Studies have generally supported the internal consistency and convergent validity of the ASRS (Adler et al., 2006; Kessler et al., 2007). Cronbach alpha for the ASRS was 0.87 in the current sample. A count of the total 'positive' number of symptoms endorsed served as the main outcome.

Conduct Disorder (CD) Symptomology.—CD symptomology was assessed using item content from the SCID-II Personality Questionnaire (SCID-II PQ; First, 1997), which was not fully assessed in the MINI. Participants were required to respond "Yes" or "No" to 15 questions with content related to the DSM-IV Conduct Disorder criteria. Data were analyzed on a continuum rather than as dichotomous diagnoses. Cronbach's alpha was 0.69 in the current sample. A count of the total number of symptoms endorsed served as the primary outcome.

Family History.—To qualify for the FH+ group, participants were required to report, at minimum, (a) alcohol dependence in their father or (b) a multigenerational (two generations) paternal history of alcohol dependence. This use of family history criteria (i.e., focus on paternal lineage) is similar to other research groups examining functional differences between FH+ and FH– groups in functional MRI (fMRI) and cognitive studies (e.g., Kareken et al., 2010; Pihl et al., 1990). Individuals who reported maternal alcohol problems or dependence were excluded to control for pre-existing neuroanatomical and functional differences observed in individuals exposed to alcohol in utero (Norman et al., 2009; Nuñez et al., 2011). To qualify for the FH– group, individuals were required to report no first- or second-degree biological relatives with a history of alcohol problems or dependence. Individuals who did not meet criteria for either group (e.g., mother only; maternal aunt only) were placed in a family history undetermined group and were excluded from participating in the study.

MRI Acquisition and Analysis.—Structural MRI data collection was incorporated into a larger protocol that included functional imaging with alcohol administration (Strang et al., 2015). T1-weighted MRI scan data were collected on a 3.0T General Electric MR750 scanner (Milwaukee, WI, USA) equipped with an eight-channel headcoil. The T1-weighted images were acquired with the following parameters: TR= 2300 ms.; TE = 2.74 ms; flip

angle = 8°; 200 sagittal slices; 256 × 256 matrix; slice thickness = 0.9 mm, no gap; total acquisition time = 4 minutes 12 seconds.

Automatic segmentation of subcortical structures and parcellation of cortical structures was completed using Freesurfer (<https://surfer.nmr.mgh.harvard.edu>). Technical details of the procedures used are described elsewhere (e.g., Dale et al., 1999; Fischl & Dale, 2000; Fischl et al., 2002, 2004a, 2004b). The automated process includes: motion correction and averaging (Reuter et al., 2010), removal of non-brain tissue (Segonne et al., 2004), Talairach transformation, segmentation of subcortical regions and parcellation of cortical regions (Fischl et al., 2002, 2004a, 2004b), intensity normalization (Sled et al., 1998), tessellation of gray and white matter (Segonne et al., 2007), and surface deformation to ensure that segmentation boundaries are placed at optimal locations (e.g., Dale et al., 1999). This automated analysis pipeline has good test-retest reliability (Han et al., 2006; Reuter et al., 2012) and comparable accuracy relative to hand-drawn estimates of neuroanatomical volumes (e.g., Desikan et al., 2006; Fischl et al., 2002, 2004b; Morey et al., 2009).

Visual data quality checks were completed in a multi-step process in accordance with the FreeSurfer automatic segmentation and parcellation analysis pipelines. First, the automatic skull strip process was checked. Of note, skull stripping was considered erroneous only if the pial boundary produced by FreeSurfer extended into the skull (i.e., the skull was coded as cortex). Second, the pial and cortical labeling was checked. Embedded within this step was an intensity normalization check. Third, an ‘inflated’ surface of each individual subject’s brain was inspected; this step primarily complemented step two. The fourth and fifth steps in the data quality check were comprised of checking the parcellation and segmentation of each subject’s brain, respectively.

Regions of Interest. Six ROIs were identified *a priori*; these include: (a) hippocampus; (b) amygdala; (c) accumbens area; (d) inferior frontal cortex (IFC); (e) orbitofrontal cortex (OFC); and (f) middle frontal cortex (MFC). ROIs were selected based on previous research and theoretical importance for AUD risk. The hippocampus, amygdala, and accumbens area are structures thought to be involved in the associations between alcohol consumption and its rewarding effects, immediate reinforcing effects of alcohol, and immediate rewarding processes, respectively (Adinoff, 2004; Koob and Volkow, 2010). The OFC is part of the brain’s reward system, based on the extensive connections it shares with the limbic system and nucleus accumbens (Goldstein and Volkow, 2002; Koob and Volkow, 2010). The MFC and IFC may contribute to inhibitory control (Verbruggen and Logan, 2008), a construct implicated as a risk factor for AUD (Rubio et al., 2008).

Cortical thickness was selected as the primary cortical outcome. As noted by Henderson and colleagues (2018), this approach is warranted since there has been little exploration of this outcome in the context of FH group differences to date. Moreover, cortical thickness in the MFC and OFC are related to impulsivity (Schilling et al., 2012) and MFC thickness is correlated with substance use outcomes (Holmes et al., 2016). ROIs were examined as total, rather than lateralized, volume and thickness, to reduce the number of statistical comparisons. Subcortical volumes were calculated as the average of both hemispheric volumes, congruent with previous approaches (e.g., Dager et al., 2015). Cortical thickness

estimates were obtained by calculating the weighted thickness average (weighted by surface area) of each constituent area (Fischl, 2010). Specifically, this included calculating weighted mean thicknesses in the pars opercularis, pars orbitalis, and pars triangularis areas for the IFC, the rostral and caudal middle frontal areas for the MFC, and the medial and lateral orbitofrontal areas for the OFC. Figure 1 depicts the cortical regions examined based on aggregation of these constituent areas.

Data Analysis.—Key demographic and psychiatric variables were compared between the FH+ and FH− groups using t-tests or chi-square tests of independence, as appropriate. Any factors differing between groups were entered as covariates. Normality of subcortical volumes (corrected by estimated total intracranial volume) and cortical thicknesses (uncorrected) was checked using Shapiro-Wilks and Kolmogorov-Smirnov tests; all subcortical volumes and cortical thicknesses met the assumption of normality (all p 's > 0.05). The distribution of volume estimates was additionally visually examined using histograms and P-P plots (Field, 2014). Univariate outliers were identified by computing Z scores for all subcortical volumes and cortical thicknesses; any Z -score > 3 was identified as an outlier (Tabachnick and Fidell, 2013). Univariate outliers were winsorized to 3 standard deviations (Field, 2014). This procedure was used for one participant's total accumbens area volume. Univariate outliers were also identified and winsorized in the RAPI ($n = 1$); TLFB number of drinks and maximum drinks ($n = 2$); and the CES-D ($n = 1$). In all cases, these transformation procedures did not alter any of the significance values for any of the statistical tests.

Hierarchical regression analyses were used to test the association of FH with structural outcomes. Subcortical ROIs were analyzed as a ratio to ICV, and ICV was included as a covariate in cortical thickness analyses, to control for naturally occurring differences in brain size (Giedd et al., 1996). In all hierarchical regressions, the first step included age, biological sex, number of drinks consumed in the past 90 days, and RAPI score, as predictors. The number of drinks consumed in the past 90 days was included in the baseline regression model to control for the potential effects of recent alcohol exposure. The RAPI score was included as a baseline predictor since the FH groups significantly differed on their reported alcohol-related problems (see Results). FH was included as a predictor in the second step. An interaction term of FH and sex (FH*sex) was included in the third step to test the possibility that FH and sex interact to predict ROI outcomes. To control the risk of inflated Type-I error rates due to the number of comparisons, a Bonferroni-type correction was applied to the α level for each omnibus comparison (Tabachnick and Fidell, 2013). As such, the criterion alpha level (α) for significance was set *a priori* to 0.008 for all results.

Results

Literature Review

Study Characteristics.—Descriptive findings of the literature review are presented in Table 5. Fifteen studies were identified and met eligibility for inclusion in the current review. The final reviewed studies included 1735 participants ($n = 898$ female), with an age range of 9–85 years old. There was extensive heterogeneity in sample characteristics, which included:

adolescents with limited alcohol use (e.g., Cservenka et al., 2015; Hanson et al., 2010; Squeglia et al., 2015); adolescents with alcohol use disorders (e.g., Hill et al., 2001, 2007); alcohol naïve participants (e.g., Benegal et al., 2007; Venkatasubramanian et al., 2007), and adults with lifetime alcohol use without a diagnosis of AUD (e.g., Dager et al., 2015).

A variety of segmentation methods were reported, including: SPM-2 and ImageJ ($n = 1$); FMRIB-FIRST ($n = 1$); FreeSurfer ($n = 3$); manual tracing ($n = 1$); IMAGE and manual tracing ($n = 1$); BRAINS2 ($n = 6$); SPM-5 ($n = 1$), and; Scion Image ($n = 1$). There was also divergence in the assessment of FH status with studies using the FHAM ($n = 3$); the SSAGA or FHAM ($n = 1$); the SSAGA and Family Interview for Genetic Studies ($n = 2$); the Diagnostic Interview Schedule ($n = 7$), and; the family tree method ($n = 1$). Assessment of FH status was unclear for one study. The majority of studies required FH+ participants to report at least one first-degree biological relative with AUD ($n = 13$). One study required participants to report a first- or second-degree relative with AUD and one study included an unclear definition of FH+ status.

Three research groups accounted for the majority ($n = 12$) of the published studies, and some studies reported on the same or similar cohorts. The majority of studies reviewed ($n = 14$) corrected for variations in intracranial volumes (ICV); for one study, it was unclear whether any correction for ICV was made. There was variability in the consideration of potential confounds. A small number of studies ($n = 5$) matched socioeconomic status (SES) between FH groups, achieved non-significant SES FH group differences ($n = 3$), or controlled for SES ($n = 3$) and four studies did not measure SES. Five studies specifically excluded individuals with psychiatric co-morbidities. Only two studies controlled for the effect of early life stress on the relationship between FH status and regional brain volumes. Notably, only 3 studies explicitly reported correcting for family-wise error rates to control for multiple comparisons.

Study Findings.—A summary of study characteristics, ROIs investigated, and study outcomes is presented in Table 5 and Table 6. Most published studies reported examining differences in amygdala volume between FH groups. Dager and colleagues (2015) observed significantly smaller amygdala volumes in FH+ as compared to FH– individuals, which is notable given the large sample size and correction for multiple comparisons. Hill and colleagues (2013a) similarly documented significantly smaller total, right, and left amygdalar volumes in the FH+ group as compared to the FH– group. Other studies have corroborated these findings (Benegal et al. 2007; Hill et al., 2001); however, other groups reported no differences in amygdalar volumes between FH groups (Cservenka et al., 2015; Sjoerds et al., 2013).

Similar discrepancies have been noted in studies of the relationship between FH status and hippocampal and cerebellar volumes. Benegal and colleagues (2007) documented reduced bilateral hippocampal volume in FH+ compared to FH– participants, whereas Hanson et al. (2010) observed increased hippocampal volume in FH+ males as compared to FH– males. Additionally, Hanson and colleagues (2010) found that hippocampal volume was not predictive of substance use at follow-up. In a comprehensive study, Dager et al. (2015) reported no significant differences in hippocampal volume between FH+ and FH–

individuals, similar to previous null findings (Hill et al., 2001). Regarding the relationship between cerebellar volume and FH status, one study (Hill et al., 2007) reported that FH+ individuals had greater grey matter volume compared to their FH– counterparts, but did not differ significantly in total cerebellar volume. In a subsequent study (Hill et al., 2011) FH+ individuals had greater grey and total cerebellar volume compared to FH– individuals, but did not significantly differ in cerebellar white matter volume. In a more recent study, FH+ individuals had greater total, grey, and white matter cerebellar volumes compared to their FH– peers (Hill et al., 2016). In contrast, Benegal and colleagues (2007) reported an opposite relationship, where FH+ participants had significantly smaller total cerebellar volume compared to the FH– cohort.

Other cortical and subcortical regions have been studied comparatively less. Three studies have investigated the relationship between caudate volume and FH status and all have documented a non-significant relationship (Benegal et al., 2007; Dager et al., 2015; Hill et al., 2013b). Disparate results have been documented for the NAcc and OFC. Squeglia and colleagues (2015) did not document any difference in NAcc volume between FH+ and FH– participants whereas Cservenka et al. (2015) observed a positive correlation between family history density (FHD) and left NAcc volume, in females only. Similarly, Squeglia and colleagues (2015) did not observe any significant differences in OFC volume in FH+ compared to FH– participants, whereas Henderson and colleagues (2018) reported significantly thinner right OFC in FH+ compared to FH– participants. Hill and colleagues (2009) reported that FH+ participants had smaller left/right asymmetry in OFC volume compared to their FH– peers, in contrast to Henderson and colleagues (2018) who did not observe significant differences in asymmetry between FH groups.

Several other regions have been investigated in one or two studies. Sjoerds and colleagues (2013) found no differences in superior frontal cortex, medial frontal cortex, or cingulate volume in FH+ and FH– participants, but noted that FH+ participants had significantly smaller parahippocampal cortex volumes. Similarly, Dager et al. (2015) reported that FH+ and FH– participants did not differ in thalamus, globus pallidus, putamen, or ventral diencephalon volume. In contrast, Benegal and colleagues (2007) reported significantly smaller superior frontal gyrus, cingulate, thalamus, and parahippocampal gyrus volumes in FH+ participants compared to FH– participants. Finally, Venkatasubramanian et al. (2007) observed smaller total corpus callosum, genu, and isthmus volumes in FH+ compared to FH– participants.

Association of age with structural outcomes.—Reflecting the theory that FH groups might differ due to a neurodevelopmental lag, seven of the identified studies tested for age effects, and/or an interaction between subject age and FH status. Benegal and colleagues (2007) observed a positive correlation between amygdala, hippocampus, and caudate volume with age, and a negative correlation between the cerebral and prefrontal cortical volumes with age. However, this pattern was observed across all participants and was not specific to the FH+ group. Henderson and colleagues (2018) documented an age-by-FH status interaction in right postcentral gyrus and right lateral and medial OFC thickness. Henderson and colleagues noted that this interaction was largely attributable to FH group differences in the youngest cohort (13–14 years-old), where FH– subjects had significantly greater

thickness in these areas compared to their FH+ peers. Hill and colleagues (2001) demonstrated that maturational delays in visual P300 amplitudes were associated with smaller right amygdala volumes in the FH+ group, reflecting possible evidence of a neuromaturational lag. In a subsequent study, Hill and colleagues (2007) compared regression slopes of cerebellar volume regressed on age in FH+ compared to FH– subjects and found that FH– individuals had steeper negative slopes compared to FH+ individuals. Relatedly, Hill and colleagues (2009) found no effect of age on right/left OFC ratios in females, but found that these right/left OFC ratios significantly increased with age in FH+ males only. Hill and colleagues (2011) documented a similar sex-by-development interaction where FH– males, compared to FH+ males, reached peak cerebellum volume at an earlier age; this relationship was not statistically significant in females. Finally, Venkatasubramanian and colleagues (2007) observed that in participants younger than 15 years old, FH+ individuals had smaller total corpus callosum, genu, and isthmus volume compared to FH– individuals. In participants older than 15 years old, only the isthmus volume was smaller in the FH+ participants compared to FH– participants.

Association of FH with Structural Outcomes in the Current Sample

Characteristics.—Table 1 provides information on descriptive characteristics of the sample. FH groups did not significantly differ on age, race, education, student status, ADHD symptom count, childhood stress, conduct disorder symptom count, number of years of regular drinking, number of binge episodes in their self-reported heaviest year of drinking, or past 12-month use of marijuana, sedatives, cocaine, stimulants, methamphetamine, inhalants, street opioids, or prescription opioids. Despite not differing significantly on alcohol consumption variables, participants in the FH+ group reported significantly more alcohol-related problems on the RAPI ($M = 11.00$, $SD = 7.46$) compared to FH– participants ($M = 6.30$, $SD = 5.58$). Based on this finding, RAPI score was included as a covariate in all baseline regression models.

FH, Sex, and ROI Outcomes.—Results of the hierarchical regression analyses for the subcortical and cortical ROIs are presented in Tables 2 and 3, respectively, and descriptive statistics for each ROI can be found in Table 4. In all models, age and RAPI score did not significantly predict regional brain volumes. Biological sex was a significant predictor of hippocampal volume ($p = 0.048$), unadjusted, with females having slightly larger hippocampus to ICV ratios ($M = 0.57$, $SD = 0.04$) compared to males ($M = 0.56$, $SD = 0.04$). Sex did not predict any other regional brain volumes and this finding did not survive correction. Although not surviving alpha correction, the number of drinks consumed in the past 90 days negatively predicted OFG thickness ($p = 0.019$) as did the estimated ICV ($p = 0.046$). These effects appeared to account for the significant baseline regression model for the OFC, which accounted for 16.3% of the observed variance in OFG thickness ($p = 0.042$). The number of drinks in the past 90 days and estimated ICV did not significantly predict any other regional brain volumes. For all ROIs, inclusion of FH and the interaction term between FH and sex did not significantly increase the amount of variance accounted for in the regression model, indicating no significant associations of FH status with regional volumes or differential associations as a function of sex. Finally, while our primary analyses focused on bilateral outcomes, exploratory analyses confirmed that the FH groups also did not differ

significantly on any lateralized cortical or subcortical outcomes (all p 's > 0.1, uncorrected, data not shown).

Discussion

The present study investigated the relationship between FH and regional brain volumes by way of an updated literature review and examination of structural MRI data in a sample of youth recruited based on FH status. Fifteen studies were identified as part of the literature review. Among these studies, there was minimal evidence for a reliable pattern of differences in regional brain volumes between FH groups. In the current sample of young adults, there were no FH group differences in any of the structural outcomes examined. An advantage of the new data analyzed in this study was the ability to control for variables that may also influence regional brain volume, such as recent alcohol consumption, early environmental stress, and current psychopathology.

Regarding inconsistent findings within the identified literature, several factors can be considered. First, the heterogeneity of alcohol consumption and other sample characteristics between studies warrants consideration. Young adulthood is a critical time of neuronal maturation and cognitive development (Paus, 2005), during which time the brain may be particularly vulnerable to the adverse effects of external stressors like alcohol (Lubman et al., 2007). Considering that regional brain volume differences are hypothesized to represent risk markers to engage in hazardous alcohol use, researchers often examine these differences in young, alcohol-naïve, samples. By examining alcohol-naïve individuals, potential confounds related to neurotoxic effects of alcohol are avoided (e.g., Jacobus and Tapert, 2013). While the neurotoxic effects of alcohol on the brain have been documented in animal studies, with both short- and long-term exposure to alcohol associated with structural changes in the rat brain (e.g., Crews et al., 2004, 2005; Sripathirathan et al., 2009), there is inconsistent evidence of the nature of structural changes in the human brain after exposure to alcohol. A negative correlation has been observed between alcohol consumption indices and total cerebral volume (TCBV; Paul et al., 2008), prefrontal cortex (PFC) volume (De Bellis et al., 2005), left middle and superior frontal gyri (Yang et al. 2016), and cerebellar grey and white matter volume (Lisdahl et al., 2013). Other studies, however, have not documented significant correlations between alcohol consumption and structural outcomes (e.g., De Bellis et al., 2000; Medina et al., 2007; Medina et al., 2008; Squeglia et al., 2014). Within the identified studies, there did not appear to be any systematic difference in significant findings between those studies with alcohol naïve samples and those with alcohol-exposed samples, suggesting that alcohol exposure alone cannot wholly explain the discrepancies identified.

Additionally, studies comparing FH+ and FH- participants on regional brain volumes have not ubiquitously controlled for environmental factors that could relate to both FH status and regional brain volumes. FH+ children may be at a higher risk of experiencing a greater amount of adverse childhood experiences than their FH- peers (Anda et al., 2002), which may be associated with differences in regional brain volumes. For example, Teicher and colleagues (2012) observed that a history of childhood maltreatment was negatively correlated with hippocampal volume in a sample of young adults. Considering that

environmental adversity may be related to neurodevelopment and FH concurrently, addressing indicators of adversity (e.g., childhood maltreatment) is potentially important in studies examining the association between FH and regional brain volumes.

Another consideration in interpreting the discrepant findings is the neurodevelopmental delay hypothesis, which predicts that that FH+ individuals should demonstrate a neurodevelopmental lag when compared to their FH– counterparts. Initial cross-sectional data suggest that FH+ individuals may have longer time to reach regional brain maturation than their FH– peers (e.g., Hill et al., 2007; Hill et al., 2011). Notably, many findings of a neuromaturational lag in regional brain development have yet to be replicated. Further, disparate results have been reported for those regions (i.e., amygdala, cerebellum) that have been investigated in more than one study. Regarding the present data, the FH–age interaction was not tested due to the restricted age range of this sample. Critically, studies examining the delay hypothesis with respect to structural outcomes to date have relied on cross-sectional analyses, precluding a direct test of the hypothesis.

Methodological differences also warrant consideration for discrepancies noted in the literature. At the level of the MRI scan, differences in hardware specifications, hardware imperfections, and image distortions can create artefacts in volumetric outcomes and can, more generally, create spurious differences between groups (Jovicich et al., 2006). Beyond the level of data collection at the scanner automatic segmentation pipelines, such as FreeSurfer, FSL, and SPM, are potentially accompanied with error that can result in artefacts in both segmentation and parcellation procedures (Klauschen et al., 2009). That is, there is error associated with automatic processing procedures that may result in decreased accuracy of ROI outcomes as compared to hand-drawn estimates (Wenger et al., 2014). In the context of such a small research base (i.e., 15 studies) this additional potential error in data collection and analysis may contribute to the issue of the reproducibility of findings.

The lack of a consistent relationship between FH status and structural outcomes might also viewed within the broader issue of reproducibility. Replicability of findings has been increasingly discussed in relation to inflated rates of Type I errors and false-positive findings (e.g., Pashler and Wagenmakers, 2012). Ionnadis (2005) outlined factors that contribute to false positives including: (a) a small literature base supporting the field of research; (b) small effect sizes; and (c) heterogeneity in study design, operationalization of variables, and analytical approaches. **Within the literature identified here, these factors were evident: there** was notable heterogeneity of FH status definition and in the samples characteristics (e.g., alcohol consumption rates, alcohol-related problems, and co-morbid psychopathology). Notably, only 20% of the identified studies statistically corrected for error inflation, which is critical in imaging research to maintain adequate control of FWE rates (Bennett et al., 2009). However, while one parsimonious explanation of inconsistencies in the reviewed findings is the general lack of replicable group differences in structural outcomes, an alternate explanation concerns Type II errors due to a potentially small effect size and small sample sizes in some studies, a possibility that cannot conclusively be ruled out.

Limitations of the current research must be considered. First, the reviewed literature only encompassed structural differences between FH groups and is exclusive of white matter integrity (e.g., diffusion tensor imaging) or functional outcomes (e.g., fMRI). Therefore, conclusions about differences other than regional brain volume are outside the scope of this paper. Second, the use of non-alcohol naïve samples, including the new data reported here, potentially obfuscates interpretation of any FH group differences in regional brain volume, given that it might not be possible to entirely disentangle the neurotoxic effects of alcohol from pre-existing group differences. Third, the developmental delay hypothesis does not explicitly specify whether the lag in development is transient (i.e., FH+ individuals eventually reach the same peak development as FH– individuals) or permanent (i.e., FH+ individuals never reach the same peak development as FH– individuals). This specificity has significant implications for interpreting FH group differences across the lifespan; however, there is currently insufficient data to determine the trajectory of the hypothesized delay. Ongoing prospective cohort studies such as the Adolescent Brain Cognitive Development study (Casey et al., 2018) and the National Consortium on Alcohol and NeuroDevelopment in Adolescence (Brown et al., 2015) will be important for providing a more rigorous test of the developmental delay hypothesis.

Overall, the present review suggests there is insufficient evidence to conclude a reliable relationship between a family history of AUD and regional brain volumes. While the most parsimonious conclusion may be that there is no relationship between regional brain volumes and FH status, additional research is needed to verify this conclusion. In addition to the need for further work to replicate reported findings, future work could focus on the development of a theoretical framework that specifies how regional brain volumes are expected to co-vary with FH status, to develop *a priori* hypotheses on this basis, and to investigate these theoretical predictors in large samples with prospective data collection. An example of one such framework is the developmental delay hypothesis, whereby FH+ individuals lag behind their FH– peers with regards to neural development. Prospective data collection will be imperative for future study designs to parse between-group and within-person variability in hypothesized atypical development, and to address the developmental lag hypothesis as it relates to structural outcomes. Within such a theoretical framework, research could also begin to specify clinical and functional correlates of regional brain volume differences (e.g., personality or cognitive traits) in order to clarify any implications of FH–related structural differences for alcohol consumption and AUD risk.

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Figure 1. Composite regions of interest (ROIs) for cortical thickness analyses: middle frontal cortex (rostral and caudal middle frontal areas, *top left*); inferior frontal cortex (pars opercularis, pars orbitalis, and pars triangularis, *top right*); orbitofrontal cortex (medial orbitofrontal cortex, *bottom left*, and lateral orbitofrontal cortex, *bottom right*).

Table 1.

Descriptive characteristics of the sample by family history status (n = 69).

	<i>df</i>	<i>t</i>	χ^2	<i>p</i>	FH status	
					FH+	FH–
Age ^a	67	–1.636		0.106	19.57 (0.80)	19.88 (0.75)
Sex (% female)	1		0.198	0.657	48.7	51.3
Race (% white)	1		1.865	0.172	75.0	59.5
Education (% post-secondary)	1		0.198	0.657	40.6	45.9
Student (% student)	2		0.404	0.525	84.4	78.4
ASRS Total ^a	67	–0.556		0.580	5.06 (3.75)	4.59 (3.24)
CES-D Total ^a	63	–0.234		0.654	10.54 (7.68)	10.11 (7.00)
CTQ Total ^a	67	0.168		0.867	34.95 (7.58)	35.30 (9.35)
Conduct Disorder Symptom count ^a	67	–0.741		0.461	1.47 (2.14)	1.16 (1.24)
90-Day TLFB ^a						
Days alcohol consumed	67	0.714		0.478	20.19 (7.45)	22.54 (17.3)
Total number of drinks	67	0.607		0.546	100.35 (45.1)	110.4 (84.01)
Maximum number of drinks	67	–1.444		0.113	11.8 (5.60)	10.1 (3.88)
Average number of drinks consumed	67	0.296		0.768	4.97 (1.59)	5.1 (1.89)
Total number of heavy drinking episodes	67	1.176		0.244	11.22 (5.87)	14.05 (12.49)
RAPI total score ^a	67	–3.05		0.004	10.68 (6.38)	6.30 (5.58)
ASSIST: Marijuana ^b	1		0.867	0.352	37.5	27.0
ASSIST: Sedatives ^b	1		0.878	0.349	0.00	2.7

Note. ASRS = Attention deficit hyperactive disorder (ADHD) self-report Scale; CES-D = Centre for Epidemiologic Studies – Depression Scale; data were missing for 4 participants. CTQ = Childhood Trauma Questionnaire; RAPI = Rutgers Alcohol Problem Index; ASSIST = Alcohol, Smoking, and Substance Involvement Screening Test. TLFB = Timeline followback.

^aDescriptive value presented as mean (standard deviation).

^bDescriptive value presented as percent reporting at least weekly use

Table 2.

Hierarchical regression results for subcortical volumes.

ROI	Step and Variable	b	SE _b	β	<i>t</i>	95% CI [LL, UL]	<i>R</i> ²	<i>F</i>	<i>p</i>
Hippocampus	Step 1						0.078	1.347	0.262
	Age	−0.004	0.006	−0.083	−0.682	[−0.018, 0.010]			0.498
	Sex ^a	−0.020	0.010	−0.244	−2.015	[−0.04, −0.001]			0.048
	90-Day SD	−4.9*10 ^{−5}	0.0001	−0.080	−0.617	[−0.0002, 7.2*10 ^{−6}]			0.540
	RAPI	0.0001	0.001	0.020	0.159	[−0.001, 0.002]			0.874
	Step 2						0.010	0.661	0.419
	FH ^a	0.009	0.011	0.110	0.813	[−0.13, 0.032]			0.419
	Step 3						0.001	0.046	0.830
	FH*Sex	−0.005	0.021	−0.043	−0.215	[−0.046, 0.039]			0.830
Amygdala	Step 1						0.014	0.221	0.926
	Age	−0.002	0.003	−0.079	−0.631	[−0.008, 0.003]			0.530
	Sex ^a	−0.003	0.005	−0.078	−0.625	[−0.014, 0.007]			0.534
	90-Day SD	−3.7*10 ^{−6}	0.00004	−0.012	−0.09	[−8.1*10 ^{−5} , 9.2*10 ^{−5}]			0.929
	RAPI	0.0001	0.0004	0.033	0.249	[−0.001, 0.001]			0.804
	Step 2						0.008	0.530	0.469
	FH ^a	0.004	0.006	0.102	0.728	[−0.007, 0.016]			0.469
	Step 3						0.0002	0.016	0.901
	FH*Sex	0.001	0.011	0.026	0.125	[−0.021, 0.021]			0.901
Accumbens Area	Step 1						0.078	1.347	0.262
	Age	−0.002	0.002	−0.140	−1.153	[−0.006, 0.001]			0.253
	Sex ^a	−0.004	0.003	−0.193	−1.596	[−0.01, 0.0004]			0.115
	90-Day SD	−1.5*10 ^{−6}	0.00002	−0.009	−0.070	[−3.5*10 ^{−5} , 3.15*10 ^{−5}]			0.945
	RAPI	−0.0002	0.0002	−0.141	−1.099	[−0.001, 0.0002]			0.276
	Step 2						0.044	3.159	0.080
	FH ^a	−0.005	0.003	−0.236	−1.778	[−0.012, 0.001]			0.080
	Step 3						0.004	0.249	0.620
	FH*Sex	0.003	0.006	0.097	0.499	[−0.008, 0.014]			0.620

Note: 90-Day SD = total number of reported standard drinks (SD) consumed in the past 90 days. RAPI = total Rutgers Alcohol Problem Index score. FH = family history. FH*Sex = family history by sex interaction term. 95% CI = Bias-corrected and accelerated 95% 5000 bootstrapped sample confidence interval; values presented as [lower-level, upper-level].

^a dummy-coded variable.

Table 3.

Hierarchical regression results for cortical thickness.

ROI	Step and Variable	b	SE _b	β	t	95% CI [LL, UL]	R ²	F	p
IFG	Step 1						0.060	0.806	0.549
	Age	−0.002	0.015	−0.016	−0.128	[−0.034, 0.033]			0.898
	Sex ^a	0.016	0.026	0.088	0.610	[−0.037, 0.062]			0.544
	90-Day SD	−0.0003	0.0002	−0.249	−1.881	[−0.001, −3.3*10 ^{−5}]			0.065
	RAPI	0.001	0.002	0.094	0.722	[−0.002, 0.005]			0.473
	ICV	1.3*10 ^{−8}	9.1*10 ^{−8}	0.021	0.146	[−1.7*10 ^{−7} , 2.1*10 ⁷]			0.884
	Step 2						0.011	0.760	0.387
	FH ^a	0.022	0.025	0.120	0.872	[−0.031, 0.079]			0.387
	Step 3						0.009	0.591	0.445
	FH*Sex	0.036	0.047	0.155	0.769	[−0.048, 0.115]			0.445
MFG	Step 1						0.068	0.914	0.478
	Age	0.001	0.013	0.006	0.048	[−0.027, 0.029]			0.962
	Sex ^a	0.031	0.024	0.182	1.274	[−0.017, 0.070]			0.207
	90-Day SD	−0.0002	0.0002	−0.143	−1.085	[−0.001, 9.2*10 ^{−5}]			0.282
	RAPI	−0.001	0.002	−0.143	−1.085	[−0.004, 0.003]			0.282
	ICV	3.2*10 ^{−8}	8.3*10 ^{−8}	0.057	0.394	[−1.6*10 ^{−7} , 2.4*10 ^{−7}]			0.695
	Step 2						0.001	0.046	0.831
	FH ^a	0.005	0.023	0.030	0.214	[−0.039, 0.049]			0.831
	Step 3						0.003	0.199	0.657
	FH*Sex	0.019	0.043	0.090	0.446	[−0.059, 0.100]			0.657
OFG	Step 1						0.163	2.459	0.042
	Age	−0.011	0.018	−0.071	−0.588	[−0.045, 0.023]			0.559
	Sex ^a	0.052	0.033	0.217	1.599	[−0.019, 0.023]			0.115
	90-Day SD	−0.001	0.0002	−0.301	−2.414	[−0.001, 6.4*10 ^{−6}]			0.019
	RAPI	0.002	0.002	0.082	0.667	[−0.002, 0.006]			0.507
	ICV	−2.3*10 ^{−7}	1.1*10 ^{−7}	−0.280	−2.034	[−4.4*10 ^{−7} , 9.9*10 ^{−9}]			0.046
	Step 2						0.014	1.057	0.308
	FH ^a	−0.032	0.031	−0.133	−1.028	[−0.095, 0.036]			0.308
	Step 3						0.004	0.278	0.600
	FH*Sex	0.030	0.058	0.100	0.527	[−0.069, 0.120]			0.600

Note: IFG = inferior frontal gyrus weighted average; MFG = middle frontal gyrus weighted average; OFG = orbitofrontal gyrus weighted average. 90-Day SD = number of standard drinks (SD) consumed in the past 90 days. RAPI = total Rutgers Alcohol Problem Index score. FH = family

history. FH*Sex = family history by sex interaction term. 95% CI = Bias-corrected and accelerated 95% 5000 bootstrapped sample confidence interval; values presented as [lower-level, upper-level]. ICV = total intracranial volume.

^a dummy-coded variable.

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Table 4.

Descriptive statistics of regions of interest stratified by family history status (n = 69).

	FH status			
	FH+		FH–	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Hippocampus	0.57	0.04	0.56	0.04
Amygdala	0.22	0.02	0.22	0.02
Accumbens area	0.09	0.01	0.10	0.01
Orbitofrontal gyrus	2.67	0.10	2.69	0.13
Inferior frontal gyrus	2.66	0.10	2.64	0.09
Middle frontal gyrus	2.48	0.09	2.48	0.08

Note. Values represent average volume (subcortical regions) and thickness (cortical regions) of both hemispheres. Hippocampus, amygdala, and accumbens area presented as ratios to intracranial volume.

Table 5.

Summary of studies included in the descriptive review.

Study	ROIs	Sample	FH definition and assessment	Segmentation Method	FWE Correction	Covariates	Results
Benegal et al. (2007) ^a	Cerebral volume, prefrontal gray matter, hippocampus, amygdala, and caudate nuclei	N = 41 (<i>n</i> = 0 female). Mean age = 15.55 years (range: 9–23 years). All participants were alcohol naïve.	FH+ (<i>n</i> = 20): at least one parent and more than 2 first-degree relatives with AUD. FH– (<i>n</i> = 21): no first-degree relatives with an AUD. Alcohol dependence in the parent was assessed in an in-person interview using the SSAGA. The Family Interview for Genetic Studies (FigS; Maxwell, 1992) was used to determine the presence of alcohol dependence in additional first-degree relatives.	SPM-2 and ImageJ (manual tracing for ROI-based analyses)	FDR (<i>p</i> < 0.05)	Cerebral Volume (ROI-based analyses)	SPM Analyses: FH+ participants had significantly smaller left superior frontal gyrus, parahippocampal gyrus, amygdala, cingulate gyrus, thalamus and right parahippocampal gyrus, amygdala, cingulate gyrus, thalamus, cerebellum, and superior frontal gyrus. ROI Analyses: FH+ individuals had significantly smaller left and right amygdala and hippocampus volume. Groups did not differ on caudate or prefrontal cortex volume.
Cservenka et al. (2015) ^b	NAcc and amygdala.	N = 140 (<i>n</i> = 65 female). Mean age = 14.31 years (range: 12–16 years). Participants had limited lifetime alcohol use.	FH+ (<i>n</i> = 78): at least one first-degree biological relative or more than 1 biological relative on the same side with an AUD. FHM (<i>n</i> = 62): at most one second-degree biological relative or two biological relatives on different sides with an AUD. FH was assessed using the FHAM.	FMRIB-FIRST (subcortical volumes were analyzed as a ratio to ICV)	none reported	none	There was a positive relationship between FHD and left NAcc volume in females only. No other differences were reported.
Dager et al. (2015) ^a	Hippocampus, amygdala, globus pallidus, caudate, putamen, and ventral diencephalon	N = 364 (<i>n</i> = 263 female). Mean age = 44.58 years (range: 18–85 years). Varied levels of lifetime alcohol use.	FH+ (<i>n</i> = 137): participants reported at least one first-degree relative with AUD. FH– (<i>n</i> = 227): no family history of AUD. Assessment of FH status unclear.	FreeSurfer (average volume across both hemispheres was the main outcome variable)	FDR (<i>p</i> < 0.05)	Age, sex, ICV	FH+ participants had smaller amygdala volumes compared to FH– participants. No other group differences were found.
Hanson et al. (2010) ^b	Hippocampus	N = 30 (<i>n</i> = 10 females). Mean age = 13.55 years (range: 12–14 years). Limited lifetime alcohol	Definition of FH+ (<i>n</i> = 15) versus FH– (<i>n</i> = 15) unclear. FH was assessed using the FHAM.	Manual Tracing. (hippocampal volumes were analyzed as a ratio to ICV)	none reported	Tracer	FH+ males had larger left hippocampal volumes than FH– males; this difference was not significant in females. No differences in right hippocampi were observed.

Study	ROIs	Sample	FH definition and assessment	Segmentation Method	FWE Correction	Covariates	Results
Henderson et al. (2018)	Cortical thickness	$N = 188$ ($n = 96$ females). Mean age = 15.48 years (range: 13 to 18 years). Limited lifetime alcohol use.	FH+ ($n = 93$) participants had at least one biological parent with a history of AUD. FH- ($n = 95$) participants had both parents screen negative for a history of AUD. FH status was assessed using in-person interview (SSAGA) or informant interview (FHAM).	FreeSurfer	none reported	Gender	FH+ participants had significantly thinner right frontal, parietal and left parietal lobes compared to FH- participants. FH+ participants also had significantly thinner cortices in the right pars triangularis and left superior parietal. There was an age by FH status interaction in the right post central gyrus, right lateral OFC and MFC, with the youngest FH+ participants demonstrating significant differences from age-matched FH- participants in these areas.
Hill et al. (2001) ^b	Cerebral gray and white matter, hippocampal, and amygdalar volume	$N = 34$ ($n = 0$ females). Mean age = 17.4 years (range not reported). 18.2% of FHP Participants met DSM-III criteria for AUD or SUD.	FH+ ($n = 17$) participants had at least two adult brothers with AUD. FH- ($n = 17$) participants (low-risk) did not have any family with any Axis-I psychopathology. FH status was assessed using in-person Diagnostic Interview Schedule (DIS) data for all living first- and second-degree relatives.	IMAGE (manual tracing of amygdala and hippocampus)	none reported	Past month alcohol use	FH+ participants had significantly smaller right amygdala volume compared to FH- participants.
Hill et al. (2007) ^a	Cerebellum	$N = 33$ ($n = 0$ females). Mean age = 17.55 years (range not reported). 29.4% of the FHP Participants met DSM-III criteria for alcohol or drug dependence.	FH+ ($n = 17$). FH- ($n = 16$). See Hill et al. (2001) for definition and assessment of FH status.	Neural Net program of BRAINS2.	none reported	ICV	Uncorrected cerebellar volumes were not statistically different between FH+ and FH- participants. FH+ participants had significantly greater grey cerebellar matter. FH- participants had a significantly steeper regression slope of age-related decline in grey matter compared to FH+ participants.
Hill et al. (2009) ^b	OFC	$N = 107$ ($n = 50$ females). Mean age = 17.6 years (range not reported).	FH+ ($n = 63$). FH- ($n = 44$). See Hill et al. (2001) for definition and assessment of FH status.	BRAINS2 (OFC volume analyzed as a ratio to ICV)	none reported	Age, prior SUD diagnosis, handedness	The ratio of right to left OFC was greater in FH- compared to FH+ participants. This remained significant after removal of cases with anxiety, depression, or past

Study	ROIs	Sample	FH definition and assessment	Segmentation Method	FWE Correction	Covariates	Results
Hill et al. (2011) ^b	Cerebellum	<i>N</i> = 131 (<i>n</i> = 66 females). Mean age = 18.06 years (range not reported). Varied levels of alcohol use.	FH+ (<i>n</i> = 71). FH- (<i>n</i> = 60). See Hill et al. (2001) for the definition and assessment of FH status.	BRAINS2 (cerebellar Volume corrected for ICV)	none reported	Age, ICV	SUD. There were significant effects of FH on total, grey, and white volume. There were interactions between FH and sex for both total and white volume. Only FH+ male participants demonstrated increased R/L OFC ratio with age.
Hill et al. (2013a) ^a	Amygdala	<i>N</i> = 129 (<i>n</i> = 65 females). Mean age = 17.99 years (range not reported). Varied levels of alcohol use.	FH+ (<i>n</i> = 71). FH- (<i>n</i> = 58). See Hill et al. (2001) for the definition and assessment of FH status.	BRAINS2	none reported	ICV, gender	Compared to FH- individuals, FH+ participants had significantly smaller total, right, and left amygdalar volume.
Hill et al. (2013b) ^a	Caudate	<i>N</i> = 130 (<i>n</i> = 65 females). Mean age = 17.88 years (range not reported). Varied levels of alcohol use.	FH+ (<i>n</i> = 59). FH- (<i>n</i> = 71). See Hill et al. (2001) for the definition and assessment of FH status.	BRAINS2	none reported	age, yearly alcohol consumption, ICV	No differences in caudate volume were noted between FH groups. There was no interaction between FH and sex in predicting caudate volume.
Hill et al. (2016)	Cerebellum	<i>N</i> = 131 (<i>n</i> = 65 females). Mean age = 18.46 years (range 8–29 years). Varied levels of alcohol use.	FH+ (<i>n</i> = 72). FH- (<i>n</i> = 59). See Hill et al. (2001) for the definition and assessment of FH status.	BRAINS2	none reported	gender, age, prior SUD diagnosis	FH+ participants had greater total cerebellar volume, gray and white matter in the corpus medullar and inferior posterior lobes compared to FH- participants. FH+ participants had greater left and right inferior posterior, and total bilateral volume, and

Study	ROIs	Sample	FH definition and assessment	Segmentation Method	FWE Correction	Covariates	Results
Sjoerds et al. (2013) ^c	Superior frontal gyrus, medial frontal gyrus, parahippocampal gyrus, amygdala, and cingulate gyrus	$N = 143$ ($n = 102$ females). Mean age = 38.12 years (range: not reported). Varied levels of alcohol use.	FH+ ($n = 36$): at least one first-degree relative with a history of AUD. FH- ($n = 107$): no family members with a history of AUD. FH was assessed using the family tree method.	SPM5	Small Volume Correction ($p < 0.05$)	age, gender, total gray matter volume, scan location	bilateral corpus medullar volumes. FH- participants had significantly smaller right parahippocampal gray matter volume compared to FH+ participants. This difference remained significant after controlling for childhood adversity, familial anxiety and depression, and current major depressive episode and anxiety diagnosis status. No other significant differences were reported.
Squeglia et al. (2015) ^a	OFC, NAcc	$N = 94$ ($n = 51$ females). Mean age = 13.58 years (range: 12–14 years). Limited (<2 drinking days) lifetime alcohol use.	FH+ ($n = 49$): one or more first- or second-degree relatives with a history of AUD. FH- ($n = 45$): no history of AUD in first- and second-degree relatives. FH was assessed using the FHAM.	FreeSurfer	none reported	ICV	FH+ and FH- groups did not differ on right or left NAcc or OFC volumes.
Venkatasubramanian et al. (2007) ^a	Corpus callosum (rostrum, genu, rostral body, anterior mid body, posterior mid body, isthmus, splenium)	$N = 40$ ($n = 0$ females). Mean age = 15.8 years (range: 9–25 years). Participants were alcohol-naïve.	FH+ ($n = 20$). FH- ($n = 20$). See Benegal et al. (2007) for the definition and assessment of FH status.	Scion Image	none reported	age, ICV	In subjects younger than 15 ($n = 19$): FH+ subjects had significantly smaller corpus callosum total, genu, and isthmus volumes compared to FH- participants. In subjects older than 15 ($n = 21$): FH+ subjects had significantly smaller isthmus volumes only.

Table 6.

Study findings by region of interest.

ROI (# studies)	Effect of FH on Volume			
	FH+ > FH-	FH+ < FH-	FH+ = FH-	FH*Sex Interaction Other
Amygdala (6)		Benegal et al (2007) ^a Dager et al (2015) Hill et al (2001) Hill et al (2013a)	Cervenka et al (2015) ^a Sjoerds et al (2013)	
Cerebellum (4)	Hill et al (2007) - grey Hill et al (2011) - total, grey Hill et al (2016) - total, grey, white	Benegal et al (2007) ^a - total	Hill et al (2007) - total Hill et al (2011) - white	
Hippocampus (4)		Benegal et al (2007) ^a	Dager et al (2015) Hill et al (2001)	Hanson et al (2010) ^a
OFC (3)		Henderson et al (2018) ^a	Squeglia et al (2015) ^a	Hill et al. (2009) - greater L:R asymmetry in FH-
Caudate (3)			Benegal et al (2007) ^a Dager et al (2015) Hill et al (2013b)	
Parahippocampal gyrus (2)		Benegal et al (2007) ^a Sjoerds et al (2013)		
Superior Frontal Gyrus (2)		Benegal et al (2007) ^a	Sjoerds et al (2013)	
Cingulate (2)		Benegal et al (2007) ^a	Sjoerds et al (2013)	
Thalamus (2)		Benegal et al (2007) ^a	Dager et al (2015)	

ROI (# studies)	Effect of FH on Volume				Other
	FH+ > FH−	FH+ < FH−	FH+ = FH−	FH*Sex Interaction	
Nacc (2)			Squeglia et al (2015) ^a	Cservenka et al (2015) ^a	
Medial Frontal Gyrus (1)			Sjoerds et al (2013)		
Globus Pallidus (1)			Dager et al (2015)		
Putamen (1)			Dager et al (2015)		
Ventral Diencephalon (1)			Dager et al (2015)		
Corpus Callosum (1)		Venkatashubramanian et al (2007) ^a			

^a alcohol-naïve sample