

Parental Alcohol Use and Brain Volumes in Early- and Late-Onset Alcoholics

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Background: Studies have shown that alcoholics have smaller brain volumes than non-alcoholic cohorts, but an effect of family history (FH) of heavy drinking on brain volume has not been demonstrated. We examined the relationship between an FH of heavy drinking and both brain shrinkage as measured by the ratio of brain volumes to intracranial volume (ICV) as well as maximal brain growth as measured by ICV in early-onset and late-onset alcoholics.

Methods: With T1-weighted resonance imaging, we measured ICV, brain volume, and white and gray matter volume in adult treatment-seeking late-onset and early-onset alcoholics with either a positive or a negative FH of heavy alcohol use, and in healthy control subjects. We also calculated brain shrinkage using a ratio of soft tissue volumes to ICV.

Results: The FH positive alcoholic patients had significantly smaller ICVs than FH negative patients, suggesting smaller premorbid brain growth. Brain shrinkage did not correlate with FH. Late-onset alcoholics showed a greater difference in ICV between FH positive and FH negative patients than early-onset alcoholics. Late-onset FH positive patients also had significantly lower IQ scores than late-onset FH negative patients, and IQ scores were correlated with ICV.

Conclusions: These data provide evidence that parental alcohol use might increase risk for alcoholism in offspring in part by a genetic and/or environmental effect that might be related to reduced brain growth.

Key Words: Alcoholism, brain volumes, family history, intracranial volume, IQ, magnetic resonance imaging, neurodevelopment

Children of alcoholics (COAs) are at greater risk of developing alcoholism than children from nonalcoholic families (Cotton 1979; Devor and Cloninger 1989; Sher 1991). Many factors contribute to this increased risk. In addition to inheriting genetic predisposition, COAs might suffer from both biological and psychological injury, stemming from poor diets, inadequate psychological support, unstable parental relationships, and gestational alcohol exposure due to maternal alcohol use, all of which could contribute to the development of alcoholism (Carrion *et al.* 2001; De Bellis *et al.* 1999; Rosso 1990; Welch-Carre 2005). However, except in the case of fetal alcohol syndrome (FAS), direct physical evidence for the effects of the putative genetic and environmental factors mediating the family transmission of alcoholism is lacking.

Many studies have shown that alcohol-dependent men and women have smaller brain volumes than their non-alcohol-dependent cohorts (Bjork *et al.* 2003; Jernigan *et al.* 1991; Pfefferbaum *et al.* 1992), but an effect of family history (FH) of heavy drinking on brain volume in alcoholism has not been demonstrated. It is widely believed that most of the difference in brain volume between alcoholics and non-alcoholics is due to ethanol neurotoxicity, which causes the alcoholic's brain to shrink with aging to a greater extent than the non-alcoholic's. If this is true, then an FH of heavy drinking could only contribute to differences in brain volume between alcoholics and non-alcoholics

by altering an individual's vulnerability to ethanol neurotoxicity or by causing alcoholics with an FH of heavy drinking to drink more than alcoholics without an FH. However, it is not clear that the difference in brain volume between alcoholics and non-alcoholics is due exclusively to ethanol neurotoxicity.

We and others have reported that alcoholics have smaller intra-cranial volumes (ICVs) than non-alcoholics (Bjork *et al.* 2003; Cardenas *et al.* 2005; Hommer 2003). These differences are around 2.5%, but they do not reach statistical significance. The small difference in ICV we observed between alcoholics and non-alcoholics suggested that there could be a subgroup of alcoholics, such as COAs, with considerably smaller ICV. Unlike brain volume itself, ICV is a valid measure of brain growth, because it is determined by skull growth, which occurs as the brain, meninges, and cerebrospinal fluid (CSF) space expand to their maximal size around puberty (Carmichael 1990). The ICV does not change as a function of neurodegeneration or aging like brain volume (Jenkins *et al.* 2000) and therefore is a useful estimate of the lifetime maximum volume of the brain (Blatter *et al.* 1995). Although ICV is highly heritable, it might also be influenced by environmental conditions (Baare *et al.* 2001), particularly when the environment is not ideal. There have been several animal studies demonstrating that gestational exposure to ethanol causes decreased size of craniofacial structures (Edwards and Dow-Edwards 1991), and a small head size is one of the diagnostic criteria for FAS (Mattson *et al.* 1996; Roebuck *et al.* 1998). Some COAs who are not formally diagnosed with FAS might have fetal alcohol effects that are more subtle and might include slight reductions in skull and brain size.

In this study, we used T1-weighted magnetic resonance imaging to measure ICV, cerebral volume, and white and gray matter volume in both healthy control subjects and in adult treatment-seeking alcoholics with and without a positive FH of heavy drinking. We also further analyzed ICV as well as soft tissue volumes within the FH positive alcoholics as a function of which parent was a heavy drinker (neither, mother, father, or both) in order to determine whether the alcohol use of each parent had a differential influence on brain growth and devel-

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opment. A study in rats by Abel (1993) demonstrated that even in alcohol-treated males who sired offspring, there was a significant increase in the number of “runts” or smaller than average offspring at birth compared with those sired by non-alcohol-treated males. We therefore hypothesize that a positive FH, even one limited to fathers alone, would be associated with smaller ICV but those alcoholics with a maternal FH of heavy drinking would be most severely affected.

In addition to premorbid differences in brain growth as indexed by ICV, we also examined whether an FH of heavy alcohol use was independently related to the amount of brain shrinkage that occurs throughout adulthood. A previous study by Cardenas *et al.* (2005) found a positive FH to be protective against brain shrinkage in heavy drinkers. In our study, brain shrinkage was inferred from the ratio of cerebral volume to total ICV. If FH does affect ICV, then the smaller absolute brain volumes observed in alcoholics might be a result of either greater brain shrinkage with age, smaller maximal brain growth, or both. Calculating a ratio of brain volume to ICV allows us to independently measure the contribution FH makes to brain shrinkage as well as brain growth.

Finally, many studies have shown a weak but consistent correlation between brain size and IQ (e.g., Andreasen *et al.* 1993; De Bellis *et al.* 1999; Willerman 1991), and several studies indicate that COAs tend to do more poorly academically than control children (Ervin *et al.* 1984), particularly in verbal skill (Gabrieli and Mednick 1983). These cognitive/reasoning deficits might be related to a reduction in brain size in COAs. If a positive FH is correlated with decreased brain sizes and general neurodevelopmental deficits, we would observe lower IQ scores in FH positive alcoholics. We conducted IQ tests to see whether ICV and a positive FH are accurate predictors of intelligence.

Methods and Materials

Participants

Alcohol-dependent patients were recruited from among all the patients consecutively admitted to the National Institute of Alcohol Abuse and Alcoholism (NIAAA) inpatient unit at the Clinical Center of the National Institutes of Health in Bethesda, Maryland between January 1995 and September 2004. Most patients lived in Montgomery County, Maryland or the greater Washington DC area. All participants were interviewed with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders. Information on recent and chronic alcohol use was obtained from structured research questionnaires. All subjects provided written informed consent to participate in the study, which was approved by the NIAAA Institutional Review Board.

All alcoholic patients met DSM-III-R criteria for alcohol dependence. We excluded patients who met the criteria for alcohol abuse but not alcohol dependence as well as those who had a history of delirium tremens or gross neurological disorders. In addition, we excluded patients who had an IQ < 80 or who demonstrated signs of dementia or Korsakoff's disease. Participants were not thiamine deficient at admission, and none of the subjects had a history of head injury requiring hospital stay. Patients were scanned 3 weeks after admission or, if they had been transferred from another hospital, at least 3 weeks from the last alcohol use.

Family history was assessed by administering an interviewer-completed Lifetime Drinking questionnaire after the patient had undergone several weeks of group therapy focused on alcohol-

ism. The FH of the participant was determined through the use of a rating instrument with six categories ranging from “does not drink” to “alcoholic.” If a patient rated his or her biological father or mother as a “heavy drinker,” “problem drinker,” or “alcoholic,” the patient was considered to have a positive FH. We further subdivided patients according to age of onset of alcohol dependence. Age of onset of alcoholism was defined as the age at which the patient first consumed 90 drinks in a one-month period. Early onset alcohol-dependent patients (EOAs) had an age of onset of alcoholism between the ages of 13 and 25 years, and late onset alcohol-dependent patients (LOAs) had an age of onset of alcoholism > 25 years of age. Average quantity (average number of drinks daily/drinking day) and frequency (number of drinking days/month) were also calculated over the 6-month period preceding admission. Years of heavy drinking was defined as the cumulative total contiguous or noncontiguous months during which the subject drank 90 drinks/month (note: because subjects often maintain this high a level of alcohol use for at least 12 consecutive months, months were summed into years). Patients were considered comorbid substance abusers if they met DSM-III or DSM-IV criteria for drug abuse or dependence with a substance other than alcohol at some point in their lives.

Healthy community-recruited male and female participants with no history of significant medical illness or psychiatric disorders were included for comparison. Most control participants were also drawn from the Montgomery County, Maryland and greater Washington DC area. All participants were assessed with the Structured Clinical Interview for either DSM-III-R or DSM-IV, which confirmed that each patient met criteria for alcohol dependence and that no comparison subject met criteria for a psychiatric disorder.

Magnetic Resonance Imaging Scan Acquisition and Analysis

Participants were scanned with 1.5-T MRI (GE Medical Systems, Milwaukee, Wisconsin) with a fast spoiled-GRASS (FSPGR) sequence. A gapless series of high-contrast, 2-mm-thick, T1-weighted coronal images (repetition time 25 msec, inversion time 5 msec, and echo time 16 msec) was obtained. Images were acquired with a 256×256 matrix with a 240×240 mm field of view. Each volumetric brain consisted of 124 coronal slices with voxel size of $.9375 \times .9375 \times 2.0$ mm.

Intracranial tissue margins were marked manually on coronal sections with a hand-driven cursor. The ICV included the cerebrum and CSF spaces covering the cortex but excluded the cerebellum and CSF of the posterior fossa. Inter-rater reliability for manual identification of the ICV of 10 randomly selected magnetic resonance imaging volumes was high (intra-class correlation = .97). Next, brain tissue was automatically segmented into gray matter, white matter, sulcal CSF, and ventricular CSF with a previously described computerized method (Momenan 1997) that used voxel intensity to perform a K-means clustering procedure. Cerebral brain volume was calculated by adding the white and gray matter volumes. Brain shrinkage was inferred by calculating the ratio of cerebral volume, gray volume, and white volume to total ICV.

Intelligence (IQ)

The IQ was estimated with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) vocabulary and block design tests (Wechsler 1981). The IQ data was available for 203 alcoholic participants. The vocabulary test measured verbal intelligence, and the block design tested visuospatial abilities by requiring the

Table 1. Demographic Characteristics of Study Groups

Variable	Late Onset Alcoholics (<i>n</i> = 102)	Early Onset Alcoholics (<i>n</i> = 129)	Control Subjects (<i>n</i> = 114)
Age			
Mean (SD)	43.90 (8.48)	36.98 (8.65)	34.63 (10.13)
Range	28–67	20–64	20–63
Gender			
Male	51	104	54
Female	51	25	60
Education			
Mean Yrs	14.92 (2.62)	13.79 (2.55)	16.92 (2.72)
Height (cm)	169.34 (9.26)	172.51 (8.52)	168.08 (13.64)
Ethnicity			
Caucasian	83	105	83
Black	17	18	16
Hispanic	1	3	7
Asian	1	0	6
Other	0	3	2
Family History			
FH–	38	47	114
FH+	64	82	0
Mother	12	12	
Father	35	42	
Both	17	28	

FH, family history.

subject to create geometric designs with blocks. These two subtests have previously been used as a “short-form” of the WAIS-R to estimate IQ (Silverstein 1983), and results of the short form significantly correlate with scores of the Full Scale test (Silverstein 1985). Age-corrected scaled scores were used to calculate estimated IQs.

Statistical Analyses

Data distributions were examined for normality. We used a general linear model (GLM) to examine the independent variables of gender, height, age, FH, age of onset of alcoholism, and all possible interactions on the dependent variables of ICV, brain volumes, and brain shrinkage as measured by the brain volume/ICV ratio (package JMP-SAS; SAS Institute, Cary, North Carolina). We also used a GLM to test the independent variables of ICV, level of education, age, FH, and age of onset as well as all interactions on IQ scores. When an interaction was observed, we conducted post hoc simple-effects analyses with a Student *t* test. All significance testing was two-tailed with $\alpha = .05$. In our first analysis, we divided patients into two groups, FH positive and FH negative, according to responses on the lifetime drinking history interview, and within those two groups, we divided patients into LOAs and EOAs. When we found a significant FH

Table 3. Psychiatric Diagnoses of Study Groups

Total No. Lifetime Disorders	Early-Onset		Late-Onset	
	FH–	FH+	FH–	FH+
Mood				
0	13%	27%	14%	14%
1	53%	31%	32%	46%
2	28%	35%	40%	33%
3	4%	6%	13%	6%
Mean (SD)	1.30 (2.58)	1.27 (3.02)	1.54 (2.89)	1.49 (1.92)
Anxiety				
0	55%	53%	67%	55%
1	30%	32%	19%	35%
2	13%	12%	8%	7%
3	2%	2%	5%	2%
Mean (SD)	.62 (0.83)	.64 (1.12)	.51 (.90)	.62 (1.17)
Axis II				
0	10.5%	14.8%	40%	21.8%
1	19.1%	13.6%	10.8%	21.8%
2	8.5%	11.1%	8%	18.2%
3	12.8%	9.9%	16.2%	9.1%
4	10.6%	7.4%	5.4%	10.9%
>4	38.5%	43.2%	19.6%	18.2%
Mean (SD)	3.62 (.80)	4.0 (.80)	2.41 (.87)	2.25 (.85)

FH, family history.

effect, we conducted a secondary analysis where we divided patients into four groups, depending on which parent was the heavy drinker (neither, mother, father, or both). In this secondary analysis, because of smaller sample sizes, we did not divide patients into LOAs and EOAs.

Results

Participant characteristics are described in Table 1. We did not find any main effects of age of onset or FH on the quantity or frequency of drinking during the 6 months preceding hospital stay (Table 2). There were no differences in the quantity or frequency of drinking between men and women when we controlled for body size, but women had a later average age of onset than men [$F = 4.69$, $p = .03$].

Psychiatric history is summarized in Table 3. Early-onset alcoholics had a greater number of total Axis II disorders than LOAs [$F = 18.05$, $p < .001$], but there were no differences in total number of mood or anxiety disorders. There was no effect of FH on psychiatric diagnoses or on the percentage of comorbid drug abusers. Early-onset alcoholics were significantly more likely than LOAs to have abused drugs other than alcohol [$F = 29.08$, $p < .0001$].

Table 2. Drinking Behavior and Co-Morbid Drug Abuse of Study Groups

	Early-Onset		Late-Onset	
	FH–	FH+	FH–	FH+
Mean Age of Onset (SD)	18.98 (2.49)	19.32 (2.87)	33.76 (7.45)	33.03 (7.47)
Range	14–24	13–24	25–55	25–59
Mean Quantity Consumed	14.87 (6.87)	13.46 (7.3)	11.23 (5.87)	11.69 (7.07)
Mean Drinking Frequency	26.08 (6.94)	21.9 (10.98)	24.34 (8.85)	25.37 (8.13)
Mean Years of Heavy Drinking	15.07 (7.94)	13.04 (7.19)	8.65 (6.59)	8.79 (6.81)
% Comorbid Drug Abusers	72%	71%	39%	48%

FH, family history.

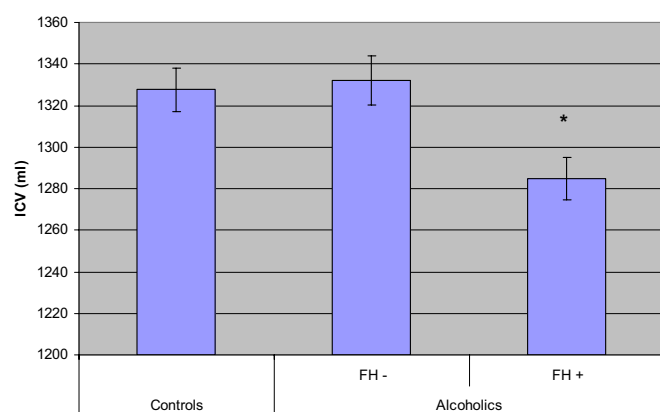


Figure 1. Adjusted means of intracranial volume (ICV) in control subjects and alcoholic patients. We found a significant difference in ICV among healthy control subjects, family history (FH) positive, and FH negative alcoholic patients [$F(2,356) = 6.52, p = .0017$]. Post hoc Student *t* tests demonstrated a significant difference between control subjects and FH positive alcoholic patients. * Significant difference ($p < .05$) from controls.

Intracranial Volume

We found a significant difference in ICV among healthy control subjects, FH positive, and FH negative alcohol-dependent patients [$F(2,356) = 6.52, p = .0017$]. Post hoc Student *t* tests demonstrated a significant difference between control subjects and FH positive alcoholics ($p < .001$) but not between control subjects and FH negative alcoholics (Figure 1).

A Least Squares Fit model showed that gender, height, and FH as well as the interaction between FH and age of onset independently accounted for significant proportions of the variance in ICV (Table 4). We found a significant difference in ICV as a function of FH in both male and female alcoholics (Figure 2). We did not find significant differences between the ICVs of EOAs and LOAs. There was a significant interaction effect of FH \times age of onset [$F(2,356) = 5.209, p = .023$]. In post hoc simple effect tests, the ICVs of FH negative LOAs were significantly greater than the ICVs of FH positive LOAs ($p < .0001$). We did not find a significant difference in the ICV of FH positive compared with FH negative EOAs. Furthermore, we did not find a significant difference in ICV between EOAs and LOAs with a positive FH, but within FH negative subjects, LOAs had significantly larger ICVs than EOAs ($p = .02$) (Figure 3).

In the second analysis, we divided alcoholic patients into four groups, depending on which parent was a heavy drinker, again controlling for height, gender, and age. This model demonstrated a significant difference in ICV among the four groups [$F(3,242) = 4.521, p = .004$]. Pairwise post hoc *t* tests found that alcoholics with no FH had significantly larger ICVs than those with a

heavy-drinking father ($p = .0133$), a heavy-drinking mother ($p = .0104$), or two heavy-drinking parents ($p = .0037$). Moreover, FH negative men had larger ICVs than men with a heavy-drinking mother or father ($p < .05$). In contrast, among women, FH negative patients had larger ICVs than those with a heavy-drinking mother or both heavy-drinking parents ($p < .05$), but there was no difference between female patients with a heavy-drinking father and those who were FH negative (Figure 4).

Brain Shrinkage

We found no main effects of FH or of age of onset of alcoholism on brain shrinkage (the brain volume/ICV ratio) and no interaction between the two measures (Table 5). Predictors of brain shrinkage included age [$F = 57.67, p < .0001$], gender [$F = 15.11, p = .0001$], and years of heavy drinking [$F = 5.02, p = .02$]. Age of onset of alcoholism did not significantly correlate with brain shrinkage in either men or women. Female alcoholics experienced significantly lower ratios of brain volume/ICV (indicating greater shrinkage) than men. There were no significant interactions between gender and either FH or age of onset. When we examined selective shrinkage of gray and white matter volumes, we found similar results, but both FH positive and FH negative alcoholics had greater brain shrinkage than healthy control subjects [$F(1,356) = 69.75, p < .0001$].

Estimated IQ

Total IQ scores were predicted significantly and independently by ICV, level of education, and FH but not by gender, age, or age of onset (see Table 6). When examined separately, block design and vocabulary scores were both predicted by age. However, vocabulary significantly increased with age, whereas block design score decreased. In addition to age, vocabulary score was also predicted by ICV, education, and FH. In contrast, block design score was not predicted by ICV but was predicted by education and FH.

There was a significant interaction between the age of onset and parental drinking in both performance (block design) IQ and total IQ. For total IQ, post hoc Student *t* tests indicated that FH positive LOAs had significantly lower scores than FH negative LOAs, but there was no significant difference between any of these measures in EOAs as a function of FH (Figure 5). In addition, FH negative LOAs scored significantly higher than FH positive EOAs. In block design score, the same pattern emerged, with FH positive LOAs scoring significantly lower than FH negative LOAs but no difference in the scores of EOAs as a function of FH.

Analyses conducted with patients divided into four groups again demonstrated that total IQ scores differed significantly as a function of FH [$F(3,203) = 5.11, p = .002$] (Figure 6). Post hoc Student *t* tests indicated that FH negative patients had signifi-

Table 4. Factors Affecting Brain Volume Measures in Alcoholic Patients

	r^2	Gender		Height		Age		Family History		Age of Onset		Family History \times Age of Onset	
		F	p	F	p	F	p	F	p	F	p	F	p
ICV	3.33	20.277	<.0001	11.884	.001	.01	.92	13.232	<.0001	.379	.539	5.209	.023
Brain/ICV	.30	5.692	.0179	.0176	.8945	61.337	<.001	2.119	.1469	.001	.979	.765	.383
Gray/ICV	.39	1.557	.213	2.639	.105	105.748	<.001	1.674	.197	.1194	.729	1.716	.191
White/ICV	.19	9.917	.002	2.245	.135	13.427	<.001	1.81	.179	.106	.744	.209	.647

The value of r^2 equals the amount of variance explained by all of the factors (gender, height, age, family history, and age of onset) included in the model. ICV, intracranial volume.

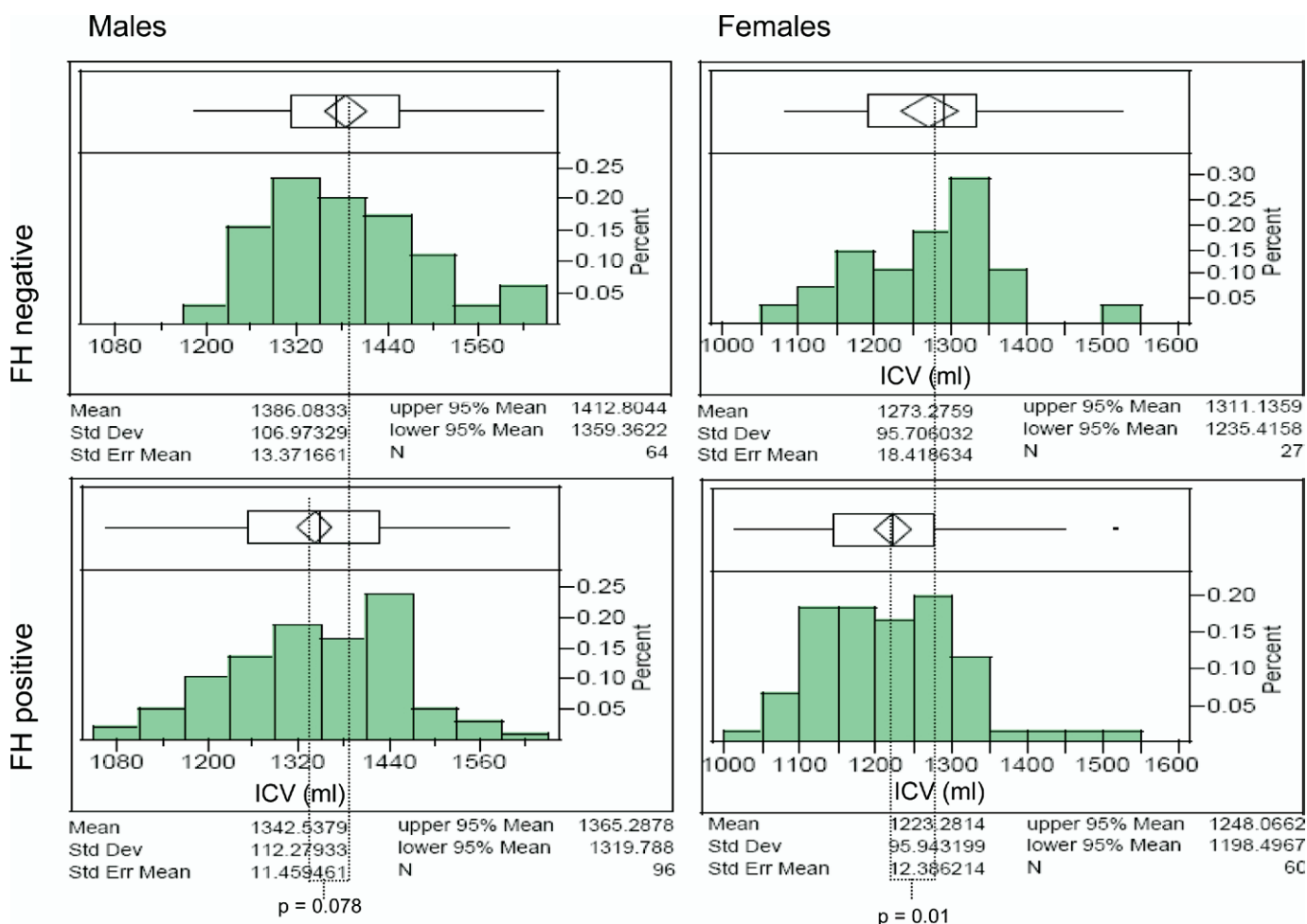


Figure 2. Intracranial volumes (ICVs) of male and female alcoholic patients. The rectangular box above each distribution shows the middle half of the data. The solid line within the box represents the median value. The whiskers that extend out from the box show the tails of the distribution, and any points outside of the whiskers are possible outliers. The solid line connecting the family history (FH)+ and FH– panels represents the mean value for each cell.

cantly higher scores than the FH positive patients. The FH negative patients had higher block design scores, but the difference did not reach significance. In vocabulary scores, there was a significant difference as a function of FH [$F(3,203) = 4.48$, $p = .005$], and Student t tests indicated that FH negative patients had higher scores than FH positive patients ($p = .014$).

Discussion

The main finding of this paper is that adult alcoholics with a positive FH of heavy drinking have significantly smaller ICVs than alcoholics from non-alcoholic or non-heavy-drinking families when we controlled for age, gender, and height. Brain shrinkage as measured by the ratio of brain volumes/ICV was not affected by FH. Only maximal brain and skull growth as measured by ICV was affected by FH. Family history did not correlate with drinking behavior of the alcoholics themselves. Although drinking patterns might have varied throughout the lifetimes of the patients, there were no significant differences in the frequency of drinking, the quantity of drinking, total years of heavy drinking, or the age of onset of heavy drinking between the patients with a positive FH and those without. This suggests that differences in ICV between FH positive and negative alcoholics are not the result of different drinking patterns. Also,

because the mean age of onset of heavy drinking, even for the EOAs, was more than 2 SDs greater than the age at which ICV growth typically ends, it is unlikely that heavy drinking contributed to differences in ICV. Less skull growth might have functional consequences in that there is a correlation between IQ and brain size (Andreasen *et al.* 1993; De Bellis *et al.* 1999). We found that FH positive patients had significantly lower IQ scores than patients with no parental drinking and that ICV weakly but significantly predicted both total IQ and vocabulary score.

The relationship between ICV and intelligence should be interpreted cautiously. Although ICV is highly heritable with an h^2 (the proportion of phenotypic variation that can be attributed to genetic causes) of about .9 (Baare *et al.* 2001), ICV might be influenced by environmental factors as well. In fact, recent studies of the heritability of IQ have found that h^2 is highest when environment is optimal but is considerably lower when estimated in populations enjoying less than ideal environments (Turkheimer *et al.* 2003). Because ICV predicts IQ, it might show a similar pattern. In addition, it seems likely that alcoholics, in general, are raised in less than optimal environments. Thus, an h^2 of .9 for ICV might be an overestimate in alcoholic populations. However, the mechanisms by which environment affects ICV are uncertain.

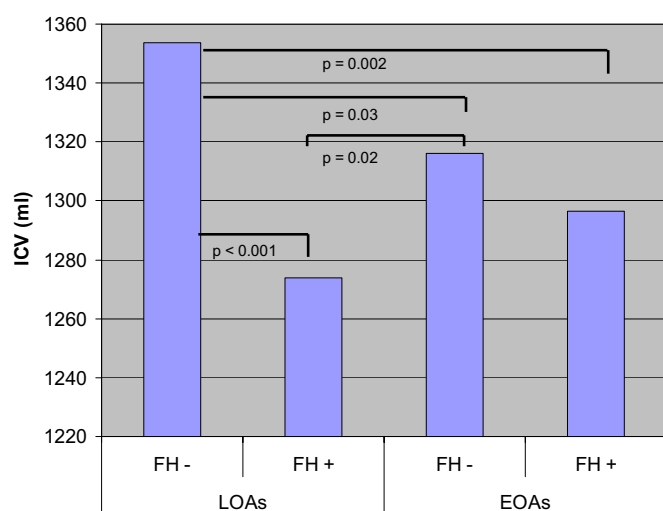


Figure 3. Adjusted means of intracranial volume in late onset alcohol-dependent patients (LOAs) and early onset alcohol-dependent patients (EOAs). We found a significant effect of family history (FH) [$F = 13.23$, $p < .0001$] and an interaction between FH and age of onset [$F = 5.209$, $p = .023$]. Bars indicate significant results of a Student t test among the four groups.

Many studies have found that living in an enriched environment positively influences central nervous system growth and development (van Praag *et al.* 2000), whereas other studies have described the effects of stress on brain growth, which indicate that increased cortisol and catecholamine concentrations can modulate neuronal migration, differentiation, and synaptic proliferation in the developing brain (Lauder 1988; Sapolsky 1990; Sapolsky *et al.* 1986; Todd 1992). In both human (Sapolsky 1996; Sapolsky *et al.* 1986) and non-human primates (Uno *et al.* 1989),

elevated levels of stress hormones such as catecholamines and cortisol can affect brain growth by accelerating loss of neurons (Swaab *et al.* 2005) or by delaying myelination (Dunlop 1997). Children of alcoholics might experience this stress during a particularly crucial developmental stage. Between the ages of 6 months and 3 years, myelination increases dramatically and continues to increase into the 3rd decade of life, and grey matter and limbic structures increase in volume throughout this time (Sowell *et al.* 1999). Therefore, the stress of growing up in an alcoholic home might affect brain growth and development and correlate with increased risk for alcoholism during adulthood. DeBellis *et al.* (1999) found that in maltreated children with post-traumatic stress disorder, cortisol and catecholamine concentrations correlated with the duration of maltreatment. In a subsequent study, they also found that decreased ICV was associated with the duration of maltreatment, and they propose that traumatic childhood experiences might adversely influence brain development. This is consistent with the measured heritability of ICV being lower in a more adverse environment. Although in the current study it is not known whether children of heavy drinkers have experienced abuse or neglect, it is likely that they grew up in a more stressful environment than children of non-drinking parents. Most likely, genetics and environment both contribute to the smaller ICV observed in FH positive alcoholics.

A surprising finding in the study was that the brain volumes of LOAs showed a greater effect of parental alcohol use than those of EOAs. This is, in large part, due to the FH negative EOAs having significantly smaller ICVs than the FH negative LOAs. This difference in ICV among FH negative alcoholic groups might be related to greater severity of alcoholism among the EOAs. In a clinical setting, EOAs often have more psychopathology and poorer global functioning regardless of whether their parent is a heavy drinker (von Knorring *et al.* 1987). The EOAs in our

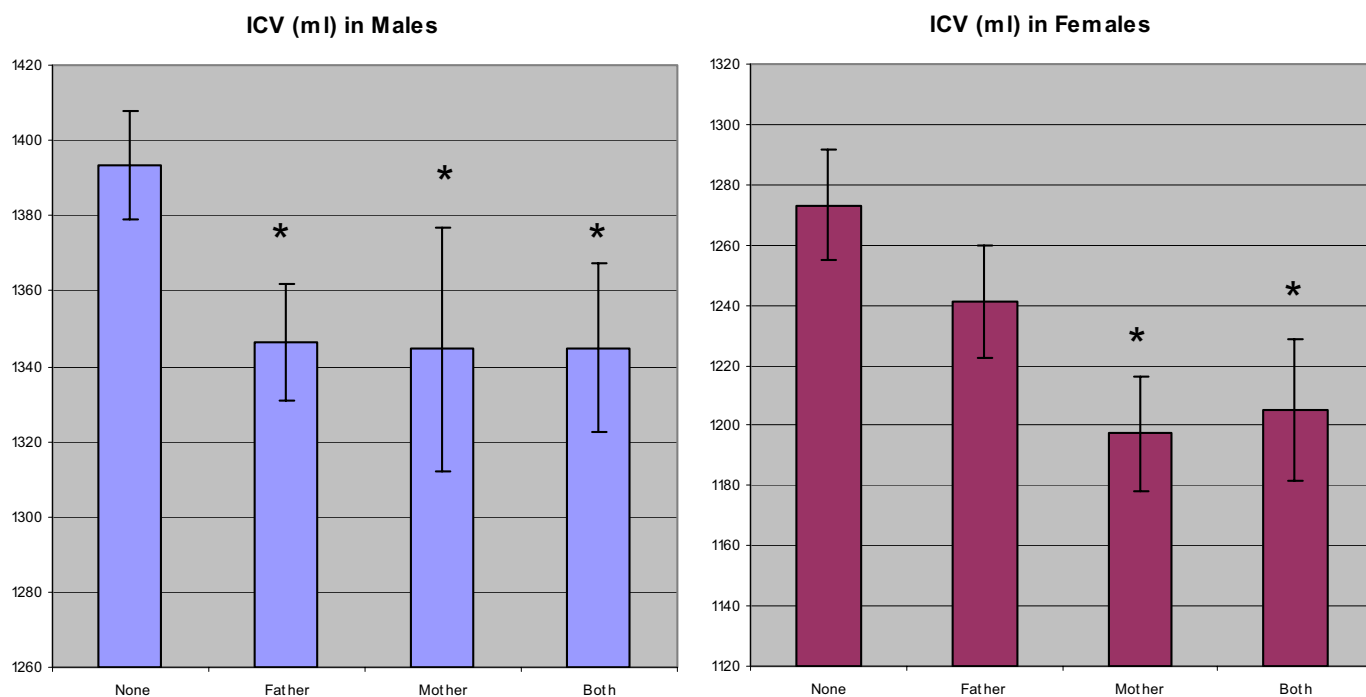


Figure 4. Adjusted means of intracranial volume (ICV) in alcoholic patients. We generated adjusted means for ICV after co-varying for gender and height. The ICVs of family history (FH) negative patients were significantly larger than those of FH positive patients. *Mean is significantly different from "none."

Table 5. ICV and Brain Shrinkage Values in Healthy Control Subjects and Alcoholic Patients

	Control Subjects		FH–		FH+	
	Mean	SD	Mean	SD	Mean	SD
ICV	1323.89	129.65	1349.89	113.14	1296.48 ^a	121.28
Brain/ICV	.824 ^a	.028	.790	.032	.796	.034
Gray/ICV	.441 ^a	.021	.419	.020	.423	.021
White/ICV	.382 ^a	.035	.371	.016	.372	.017

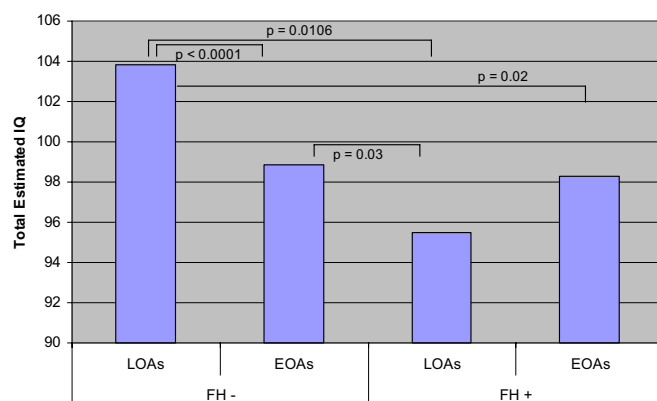
ICV, intracranial volume; FH, family history.

^aSignificant difference ($p < .05$) from the other two groups.

sample had significantly higher rates of comorbid drug abuse and dependence than the LOAs as well as a considerably higher incidence of Axis II personality disorders. In a previous study with a subset of patients of the current study, EOAs scored higher on measures of impulsivity and aggression (Bjork *et al.* 2004). This more pathological, higher-severity group might not manifest the effects of FH as clearly as other factors underpinning severe psychiatric comorbidity. We did not find, consistent with this explanation, significant differences in ICV between FH positive and negative EOAs.

The LOAs, in contrast, tend to have higher scores in global functioning, and alcoholism often manifests in the absence of other disorders. They have few if any social complications, few legal difficulties, and rarely act out violently while intoxicated (von Knorring *et al.* 1987). Perhaps the differences between LOAs with and without parental heavy drinking are magnified because of the lack of other confounding factors in this “cleaner” population. Further studies are required to more thoroughly understand this effect. However, our results challenge the assumption that the genetic contribution to alcoholism necessarily manifests early in life. These data indicate that both genetics and early life environment might have profound implications that might not surface until adulthood.

We also found that, among women, maternal drinking seemed to influence ICV more than paternal drinking. This makes sense, because the mother was probably the principal caretaker of the child and more likely to influence the child's nutrition, social surroundings, and intellectual environment than the father. In addition, we have no way of assessing whether the heavy-drinking mothers drank while pregnant. Although none of our participants were diagnosed with FAS, patients might have had subtle fetal alcohol effects. We did not find differences between the effects of maternal and paternal drinking on ICV in the men in our study, suggesting that at least among men fetal alcohol effects cannot explain the smaller ICV among FH positive alcoholics. We also report larger effect size for FH on ICV among the women in our sample compared with the men, perhaps owing to the more selective effect of maternal drinking on

**Figure 5.** Estimated IQ Scores of EOAs and LOAs by FH. We found a significant effect of FH [$F = 11.202, p = .001$] and an interaction between FH and age of onset [$F = 8.85, p = .003$]. Bars indicate significant results of a Student *t* test among the four groups. Abbreviations as in Figure 3.

women. This suggests that women might be particularly vulnerable to either prenatal alcohol effects or postnatal environmental effects.

We found no difference in brain shrinkage between EOAs and LOAs when we controlled for age, gender, and years of heavy drinking. Brain shrinkage is independently correlated with the duration of heavy drinking after controlling for age (Bjork *et al.* 2003), but it seems that the time at which the drinking is initiated does not affect this process. The brains of LOAs seem to be just as susceptible to atrophy as those of younger alcoholics, which provides additional evidence that ICV reflects pre-morbid brain growth that is not sensitive to individual differences in the patient's drinking behavior. Even within the alcoholics who began heavy drinking before the age of 21 ($n = 85$), age of onset of alcoholism did not significantly predict brain shrinkage in either men or women. We also found that, as in previous work (Hommer 2001), women are more susceptible to alcohol-induced brain shrinkage at similar alcoholism severity.

We did not find a main effect of FH on brain shrinkage, indicating that brain shrinkage occurs as a result of heavy drinking regardless of FH status. This finding contrasts with a previous study by Cardenas *et al.* (2005), which reported that a positive FH of alcoholism was protective against brain shrinkage. However, although the Cardenas study also looked at the effects of FH of alcoholism on brain atrophy, their methods and study population differed considerably from ours. Their primary measure of brain shrinkage was % CSF, whereas ours was a ratio of brain volume to ICV. They measured the four lobes of the brain, whereas we measured total gray matter and total white matter. In addition, their population was non-treatment-seeking and they drank considerably less than our population. Therefore, their

Table 6. Factors Affecting Estimated IQ in Alcoholic Patients

	r^2	ICV		Education		Age		Family History		Age of Onset		Family History × Age of Onset	
		Complete Model		Complete Model		Complete Model		Complete Model		Complete Model		Complete Model	
		F	p	F	p	F	p	F	p	F	p	F	p
Total Estimated IQ	.27	4.389	.038	22.587	<.0001	2.087	.151	7.62	.007	.163	.163	4.85	.029
Vocabulary IQ	.35	4.025	.042	27.158	<.0001	4.271	.041	5.857	.017	.070	.792	1.596	.208
Block IQ	.19	.398	.529	6.344	.013	14.839	.0002	3.993	.049	.854	.357	5.646	.019

The value of r^2 equals the amount of variance explained by all of the factors (intracranial volume [ICV], education, age, family history, and age of onset) included in the model.

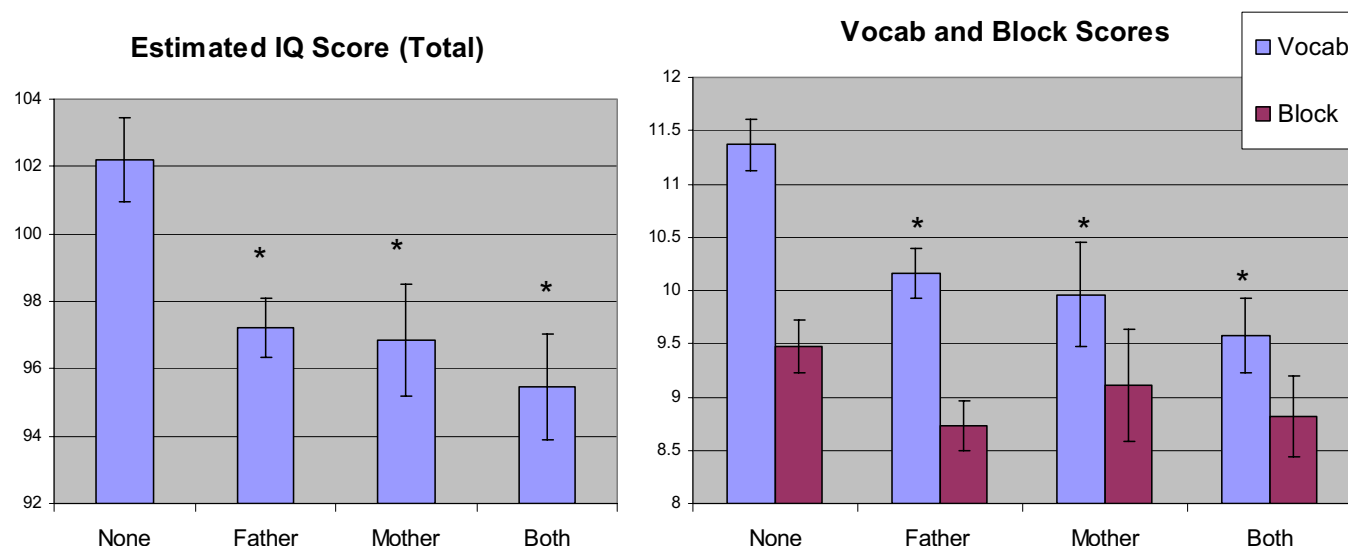


Figure 6. Estimated IQ scores of alcoholic patients. **(Left)** Family history (FH) negative patients had significantly higher scores than FH positive patients. **(Right)** FH negative patients had significantly higher vocabulary scores than FH positive patients. *Mean is significantly different from “none.” Vocab, vocabulary.

findings that FH might be protective might only be valid to a certain alcoholism severity.

Estimated IQ

We found, consistent with Gabrielli and Mednick (1983), a significant effect of FH on estimated IQ after controlling for gender, age, and education level. Gabrielli and Mednick demonstrated that children at high risk for alcoholism had lowered verbal ability, suggesting that the lower IQs observed in alcoholics might exist before the onset of alcoholism. Because ICV is set before the onset of alcoholism, this is consistent with our finding that a lower vocabulary score is associated with smaller ICV (although, it should be noted, ICV is a fairly weak predictor of IQ when education, FH, and age of onset are taken into account). Block score results were not as strongly correlated with either education or FH as vocabulary results. Several studies have examined the effect of parental neglect on IQ. Cognitive, language, and intellectual impairments are frequently observed in abused and neglected children (Augoustinos 1987; Kolko 1992), and the effects might reach adulthood. In a study of adult survivors of child abuse, Perez and Widom (1994) reported lower IQ and decreased reading ability in the abused group compared with control subjects.

Interestingly, we found that a positive FH affected the IQ scores of the LOAs but not of the EOAs. Again, this might be explained by the greater psychopathology of the EOAs mitigating the effect of FH on IQ through a ceiling effect. The FH negative LOAs had significantly higher IQ scores than FH negative EOAs, but in the FH positive patients, both EOAs and LOAs had similar low IQ scores.

Finally, we found that EOAs had significantly higher numbers of axis II disorders than LOAs, which has been shown in many clinical samples of alcoholics (Hallman *et al.* 1996; von Knorring *et al.* 1987). There was no main effect of FH, suggesting that parental heavy drinking does not influence the psychiatric diagnoses of adult alcoholics.

A limitation of this study was the reliance on patients' reports of parental heavy drinking as well as use of an in-house interview instrument that did allow for a formal diagnosis of

alcohol abuse or dependence. However, by the time of the interview, patients had undergone weeks of educational alcoholism therapy sessions that directly and indirectly clarify what constitutes problematic levels of drinking. In contrast, our classification of FH positive patients as having a “heavy drinking” parent underscores the strength of the relationship between parental drinking and ICV. Even if the heavy-drinking parents would not have been diagnosed with alcohol dependence, patients raised by parents with a general pattern of heavy drinking are still affected.

An additional limitation of this study is the absence of data collected about aspects of parental lifestyles other than drinking that might have contributed to smaller ICVs of offspring, such as comorbid drug abuse or socioeconomic status. We were also unable to assess maternal drinking during pregnancy. We also cannot say how well FH, ICV, and IQ will predict the development of alcoholism. These are risk factors, but as with any risk factor, they do not determine that a person will develop the condition but rather increase the likelihood that they will. To answer the question of how selective risk factors predict alcoholism, we would need to select FH positive subjects on the basis of low IQ or small ICV and see whether they have a higher rate of alcoholism.

Future research could more precisely study how the amount of parental drinking affects brain volumes of COAs before they are old enough to develop alcoholism themselves. Subsequent studies could also examine brain volumes of healthy control subjects with alcohol-dependent parents, in order to determine whether smaller ICV is a more specific risk factor for the development of alcoholism than FH. Finally, more in-depth psychosocial interviewing could more directly assess parental factors on both structural development and behavioral consequences in COAs.

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