



Brain Growth & Shrinkage in Alcoholism

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	Alcoholic Men (n = 176)	Alcoholic Women (n = 76)	Non-Alcoholic Men (n = 59)	Non-Alcoholic Women (n = 59)
Height (cm) ¹	175.5 ± 7.3	164.6 ± 5.8	174.6 ± 7.5	164.5 ± 6.6
Weight (kg) ²	81.8 ± 14.3	64.0 ± 12.9	79.9 ± 11.4	66.3 ± 12.6
Age (years) ³	39.4 ± 7.9	40.5 ± 7.8	35.5 ± 9.2	36.7 ± 8.0
Education (years) ⁴	14.1 ± 2.7	14.8 ± 2.6	16.8 ± 3.2	16.7 ± 2.3
Handedness ⁵ (% Right-handed)	84.8 %	89.1%	90.2%	88.4%
Cigarette Smoker ⁶ (current)	64.8%	54.0%	15.3%	14.6%

¹ Main effect for gender, $F(1,366) = 167.2$, $p < .00001$

² Main effect for gender, $F(1,366) = 100.1$, $p < .00001$

³ Main effect for diagnosis, $F(1,366) = 16.6$, $p < .0001$

⁴ Main effect for diagnosis, $F(1,366) = 51.2$, $p < .00001$

⁵ Diagnosis; Chi-square (1) = 1.01, ns

⁶ Diagnosis; Chi-square (1) = 73.7, $p < .00001$

	Alcoholic Men	Alcoholic Women	t test for independent samples; df =250
Age at onset (years)	23.4±7.4	28.4±9.0	t = -4.22, p =.0001
Years of heavy drinking	12.6±7.1	8.9±6.0	t = 3.79, p < .005
Lifetime ethanol consumption (kg)	590±473	458±442	t = 1.94, p = .05
Lifetime ethanol consumption adjusted for total body water (TBW) (ethanol kg/ TBW kg)	13.5±11.4	14.8±14.5	t = -0.75, ns
Days drinking during past 6 months	126 ± 59	140 ± 44	t = -1.69, ns
Ethanol consumption (kg) during past 6 months	26.1±18.7	23.5±14.1	t = 1.04, ns
Ethanol consumption over past 6 months adjusted for TBW (ethanol kg/ TBW kg)	0.59±0.43	0.76±0.48	t = -2.70, p = .01

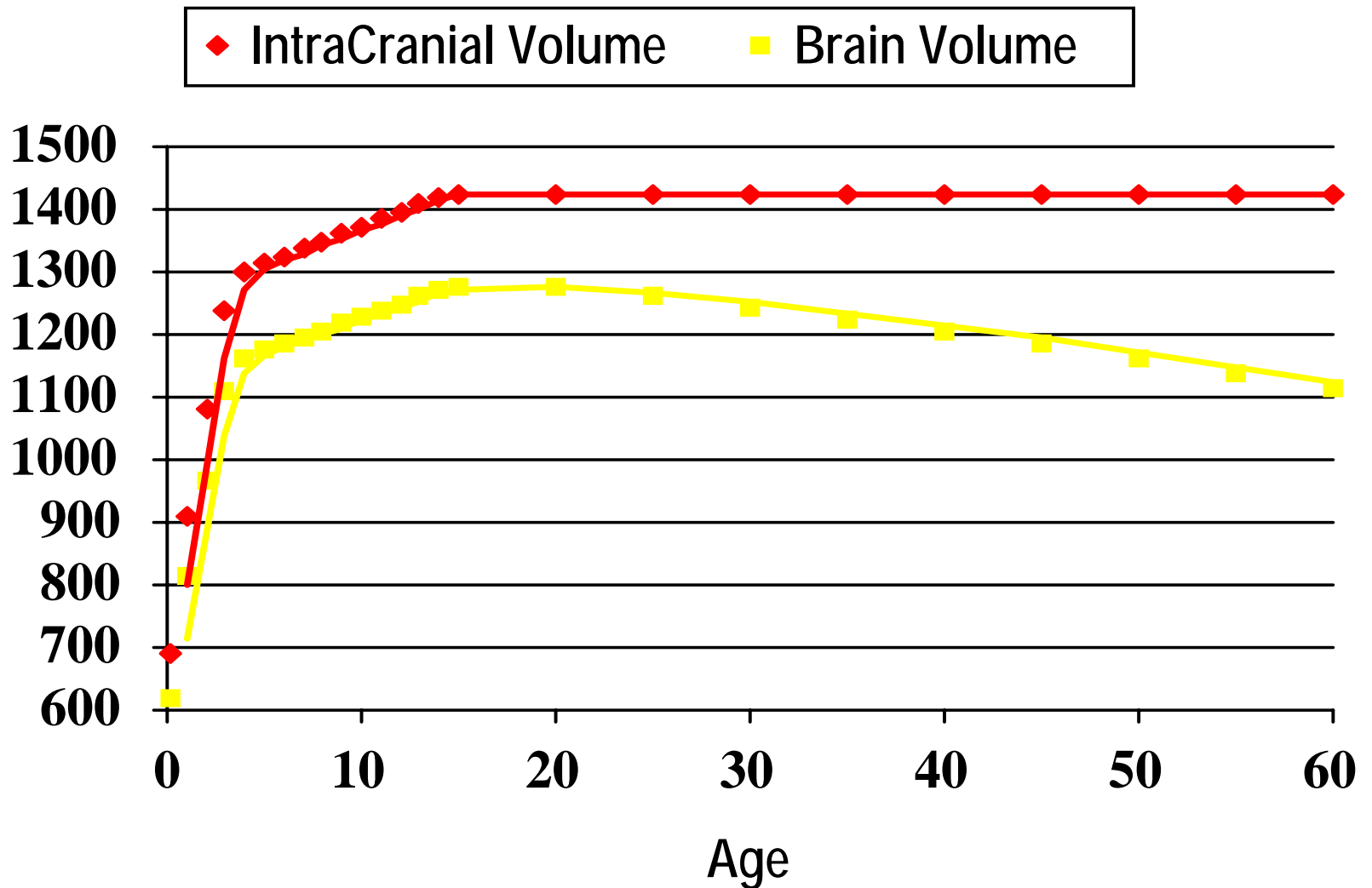
	Alcoholic Men	Alcoholic Women	Pearson Chi-square
Mood Disorder	79%	85%	$\chi^2(1)= 1.13, ns$
Anxiety Disorder	32%	49%	$\chi^2(1)= 5.84, p < .05$
Cluster B Personality Disorder	49%	40%	$\chi^2(1)= 1.67, ns$
Drug Dependence (other than alcohol)	60%	42%	$\chi^2(1)= 6.79, p < .01$
Maternal Alcohol Dependence or Abuse	21%	17%	$\chi^2(1)= 0.52, ns$
Paternal Alcohol Dependence or Abuse	46%	39%	$\chi^2(1)= 0.79, ns$

- Many studies have found that alcoholics have smaller brains than non-alcoholics
- How much of this difference is due to less brain growth before the onset of alcoholism?
- How much is due to brain shrinkage after the onset of alcoholism?

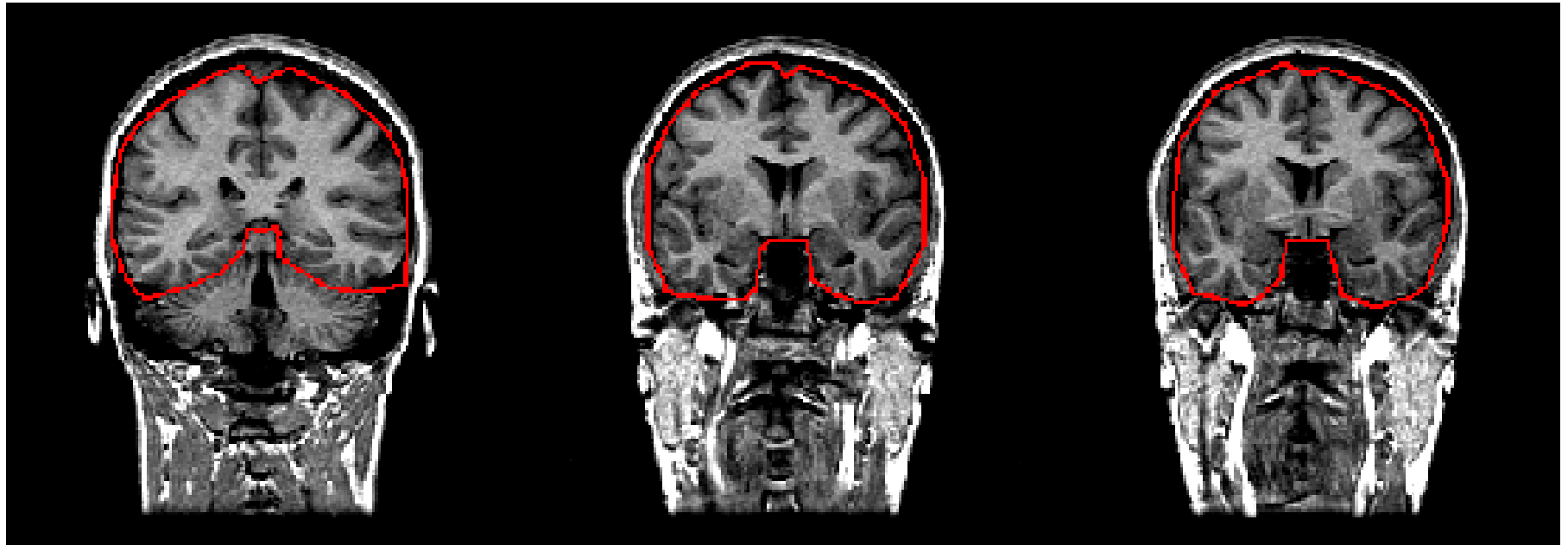
How to Distinguish Brain Growth from Brain Degeneration

- Maximal brain growth can be measured by skull size since skull size remains constant throughout life.
- Brain shrinkage can be measured by the ratio of brain volume to the rest of the inside of the skull.

ICV and Brain Volume

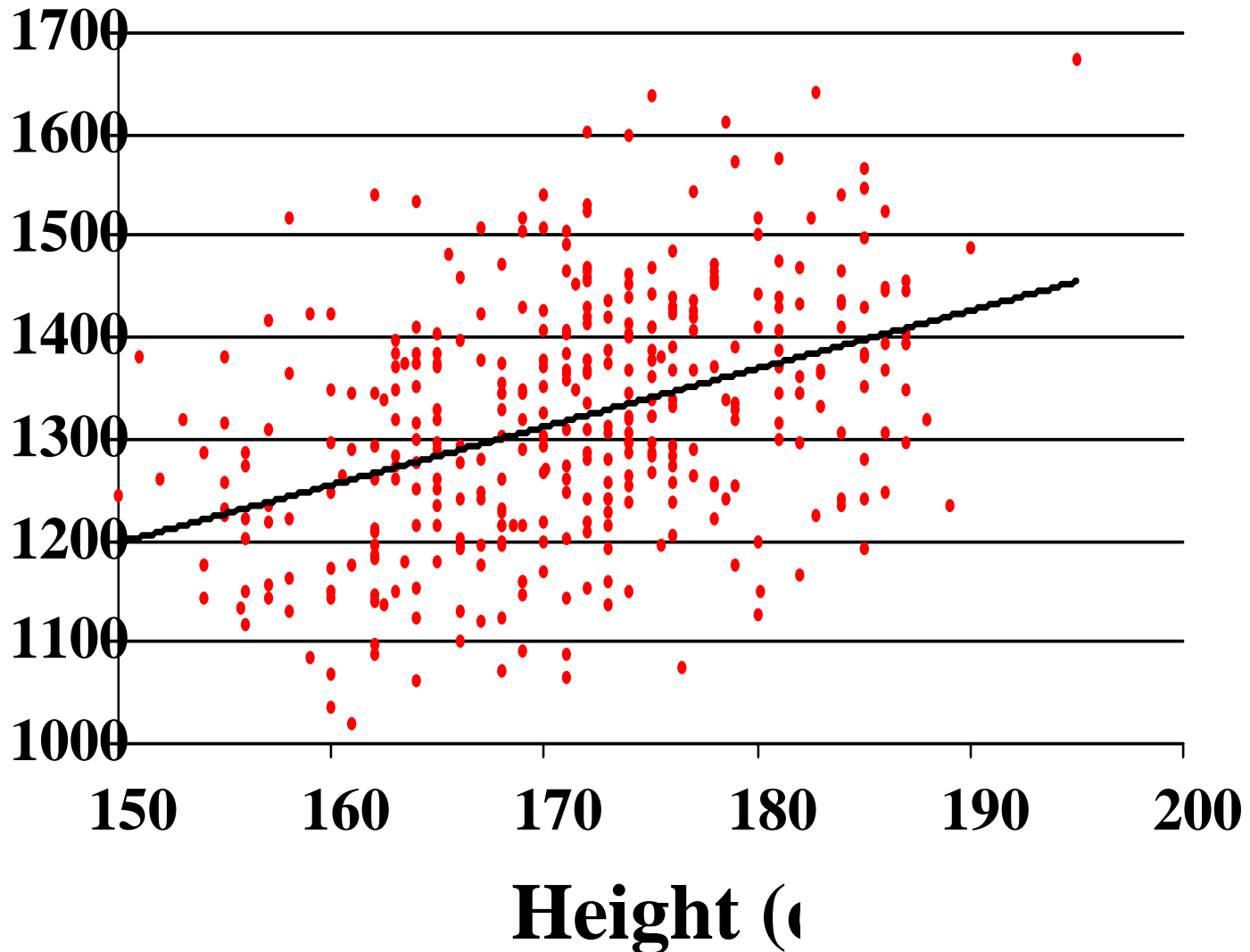


ICV is measured by outlining the inner table of the skull

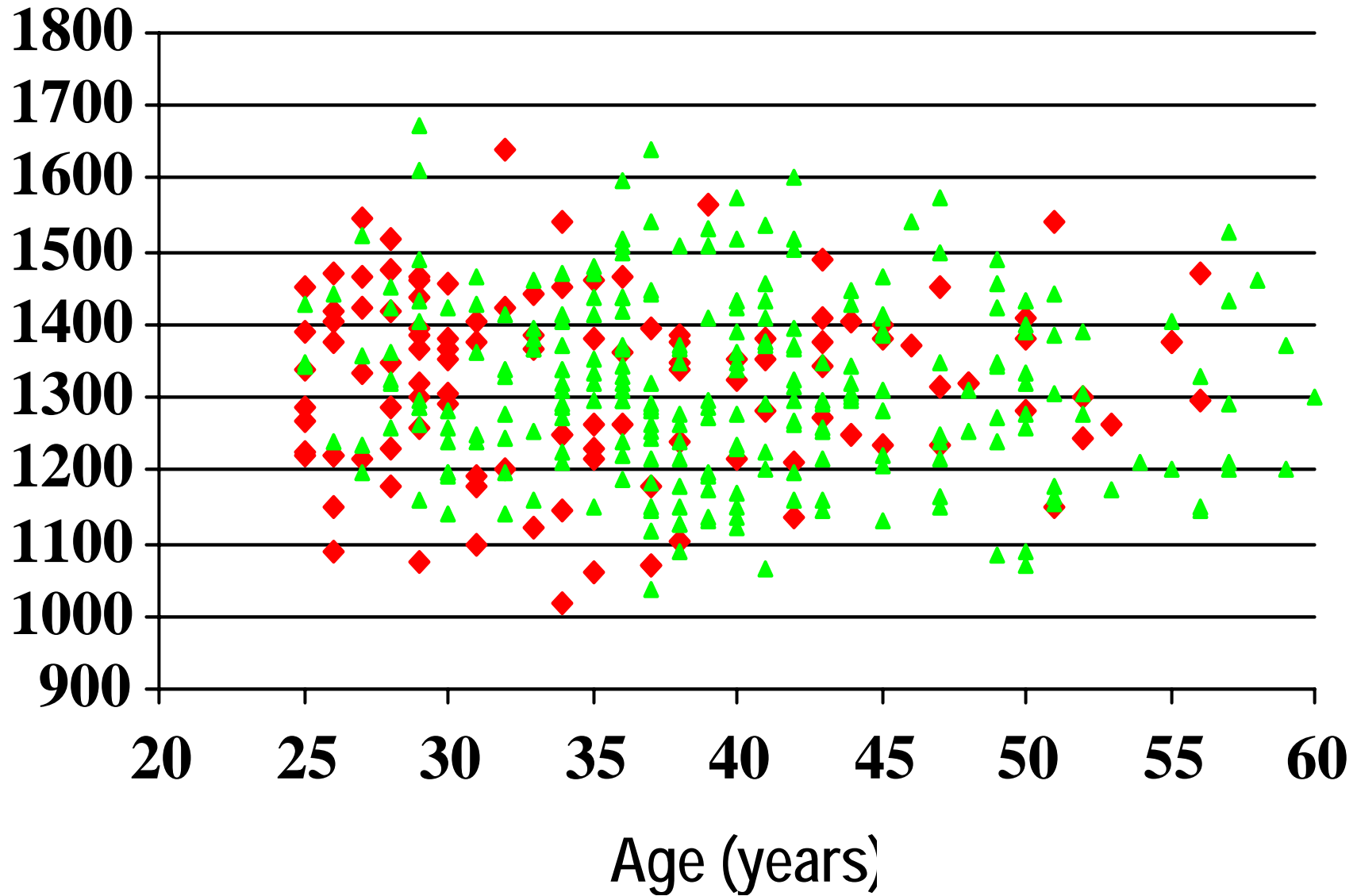


ICV is predicted by height

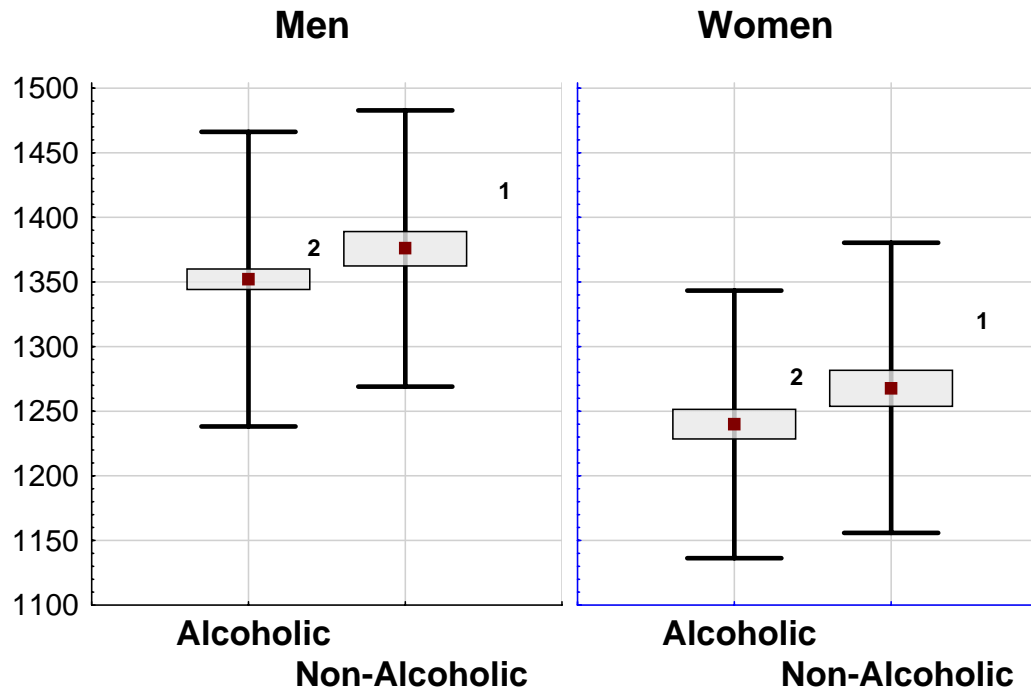
$r = .40, p < .001$



◆ Non-Alcoholics ▲ Alcoholics



Alcoholics have smaller ICV than non-Alcoholics



¹ Main effect for gender (co-varying for height), $F(1,365) = 24.7$, $p < .00001$

² Main effect for diagnosis (co-varying for height), $F(1,365) = 5.0$, $p < .05$

The smaller Intra-Cranial Volume among Alcoholics is not due to:

- Maternal alcohol abuse or dependence
- Paternal alcohol abuse or dependence
- Co-morbid psychiatric disorders
- Tobacco use
- Education

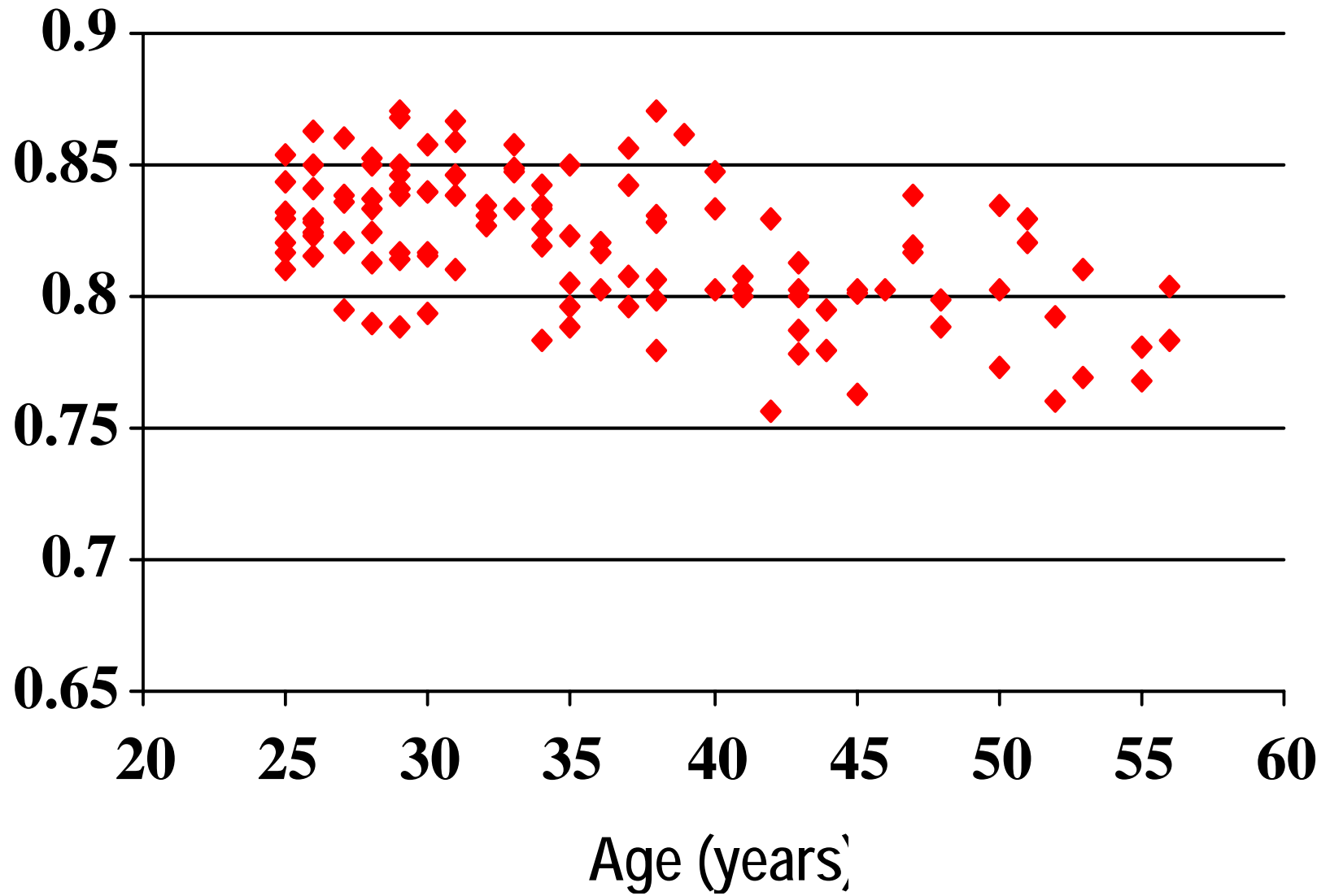
Education & Intra-Cranial Volume

1. Education is not significantly correlated with ICV among the non-alcoholics.
2. Education is correlated with ICV among the alcoholics.
3. Fewer years of education among the alcoholics can not be the cause of their smaller ICV because nearly all the alcoholics begin heavy drinking after the end of skull growth.

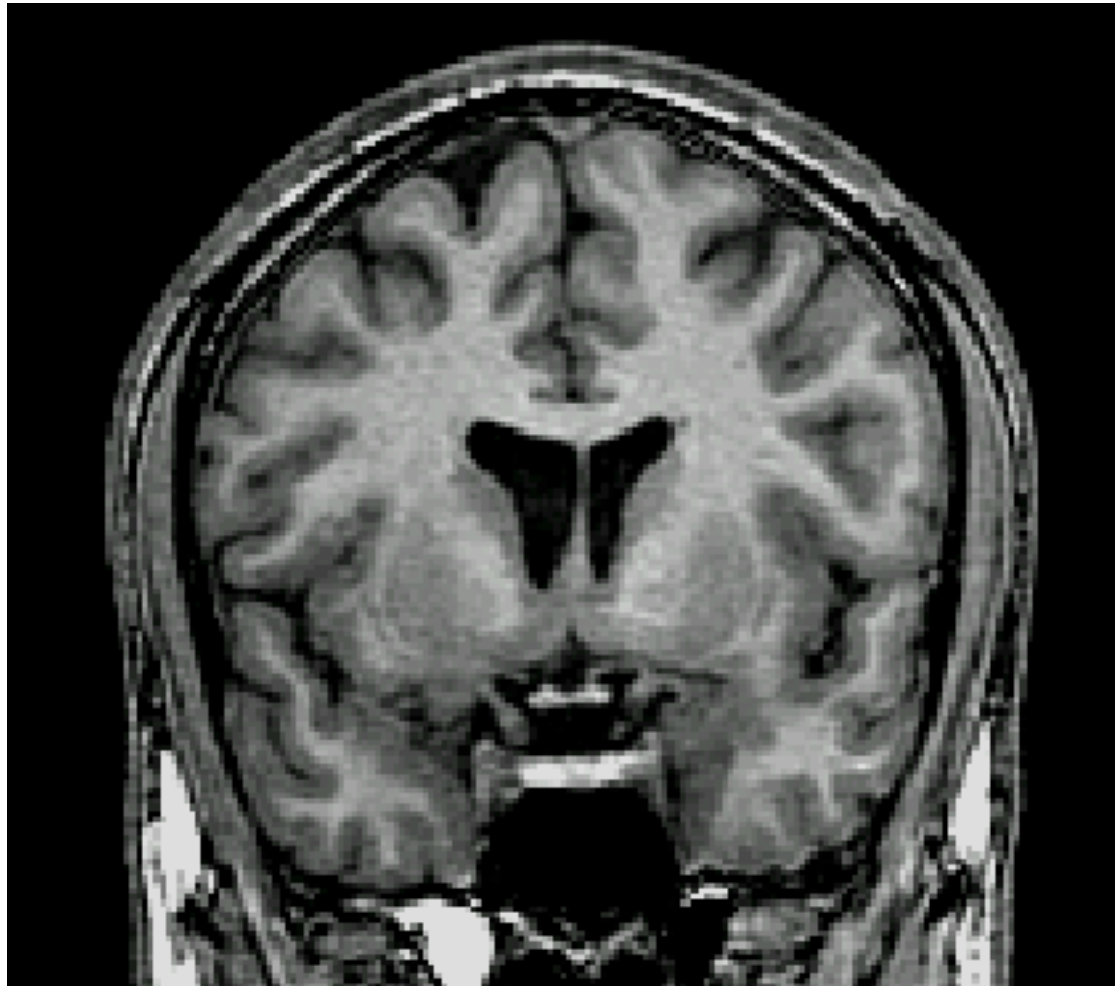
1. Alcoholics have smaller Intra-Cranial Volumes than non-Alcoholics
2. Less brain growth may be a risk factor for alcoholism
3. IVC is very heritable, but it is possible that environmental factor also contribute

Brain Shrinkage in Alcoholism

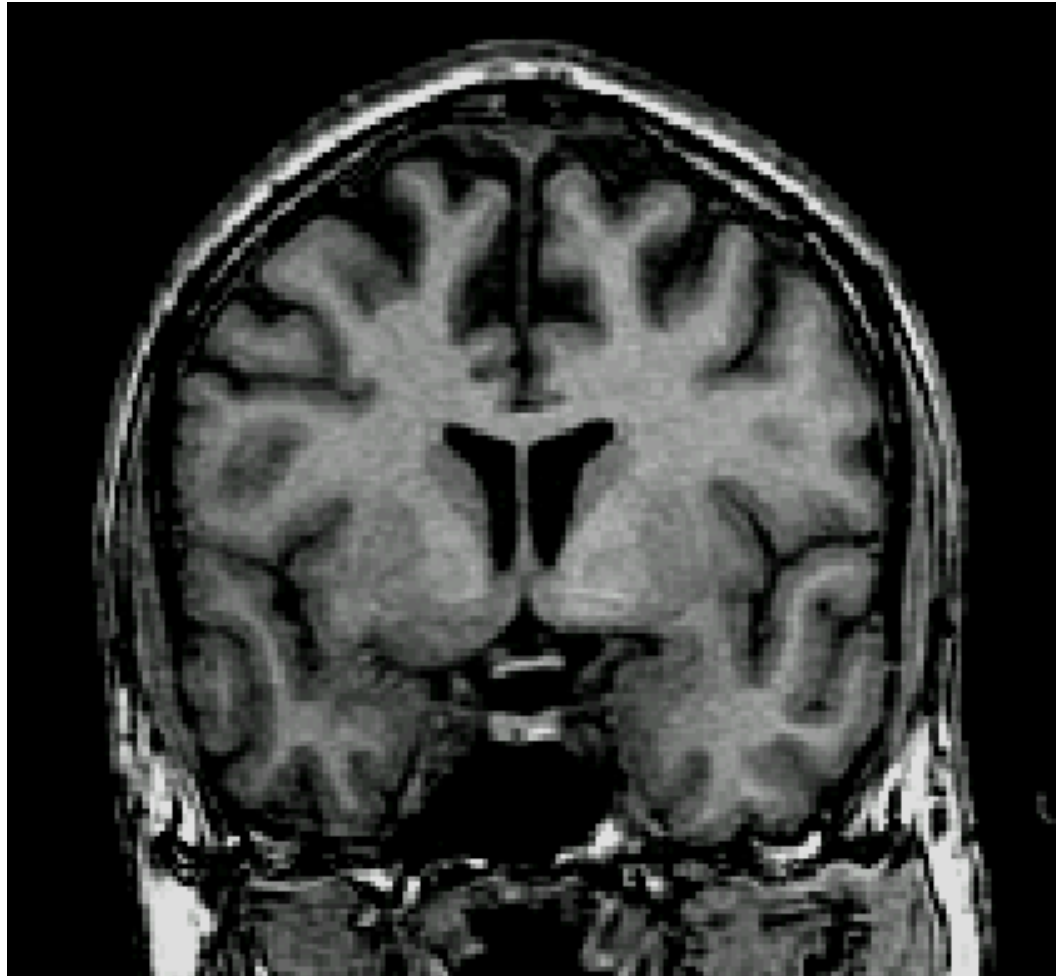
◆ Non-Alcoholics



ICV = 1471 cm³
Cerebral Volume = 1213 cm³
Ratio = .823



ICV = 1369 cm³
Cerebral Volume = 1072 cm³
Ratio = .783



ICV = 1599 cm³
Cerebral Volume = 1119 cm³
Ratio = .699

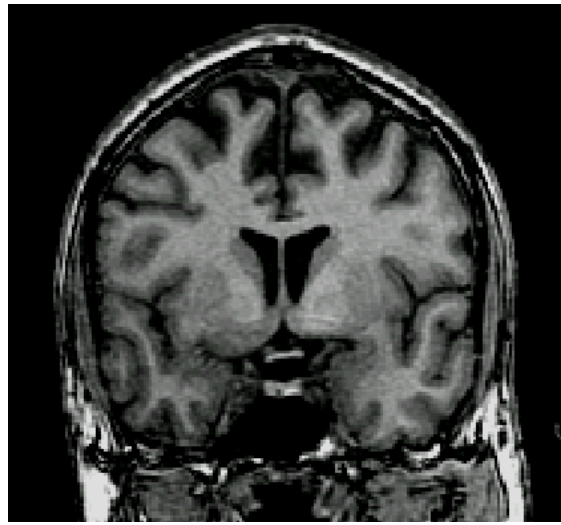
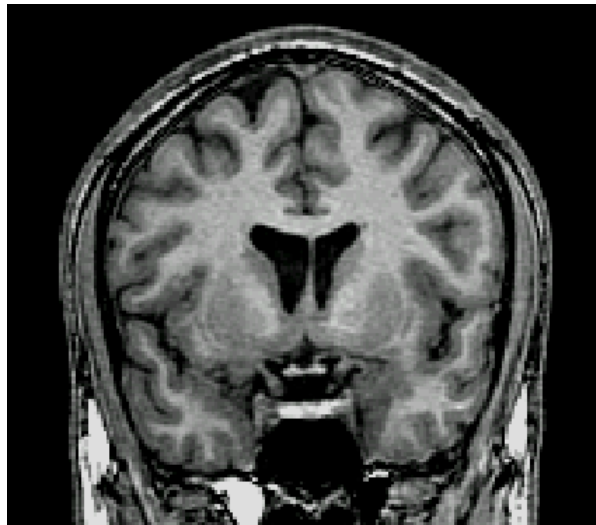


$$\frac{\text{Cerebral Volume}}{\text{IntraCranial Volume}} =$$

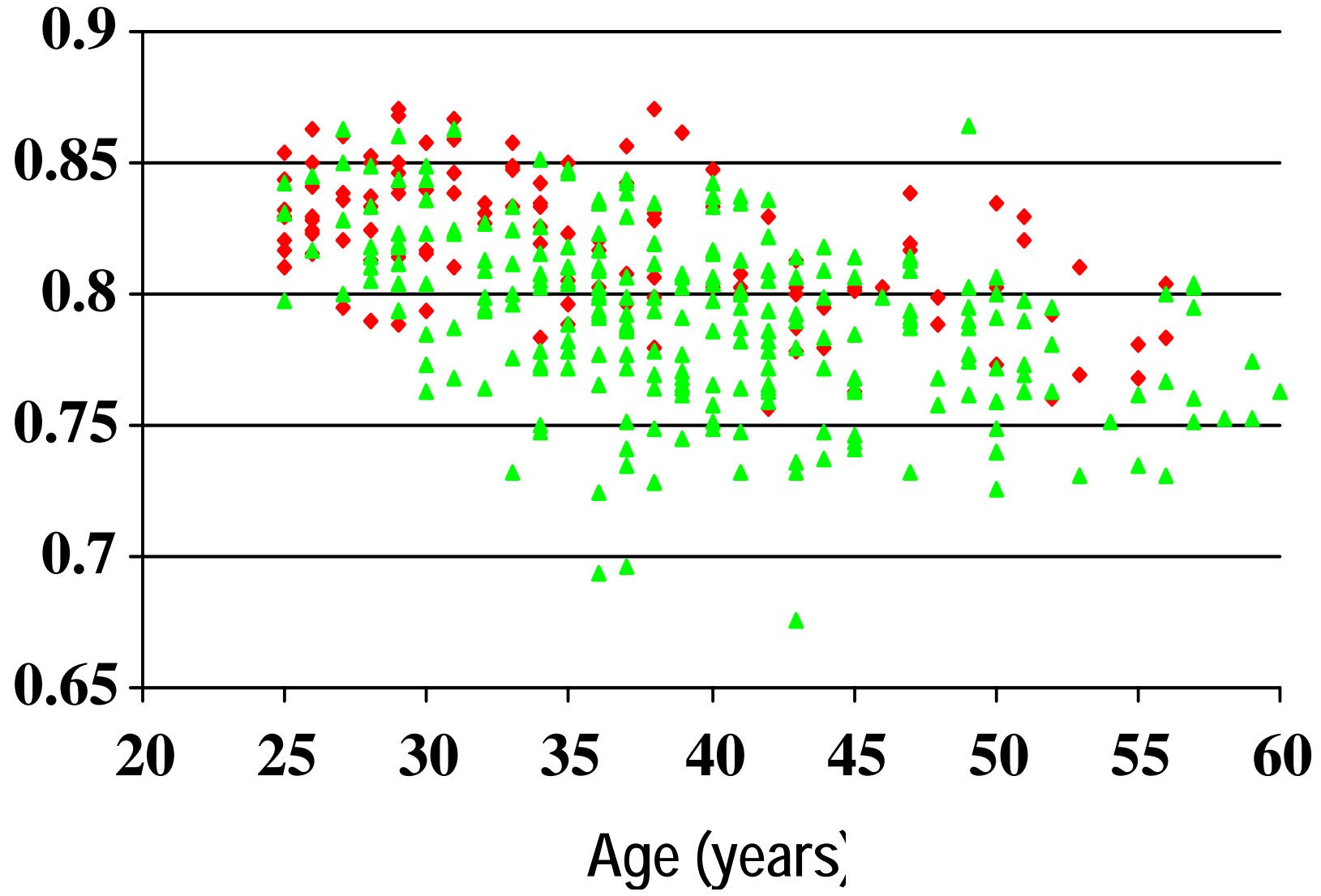
.823

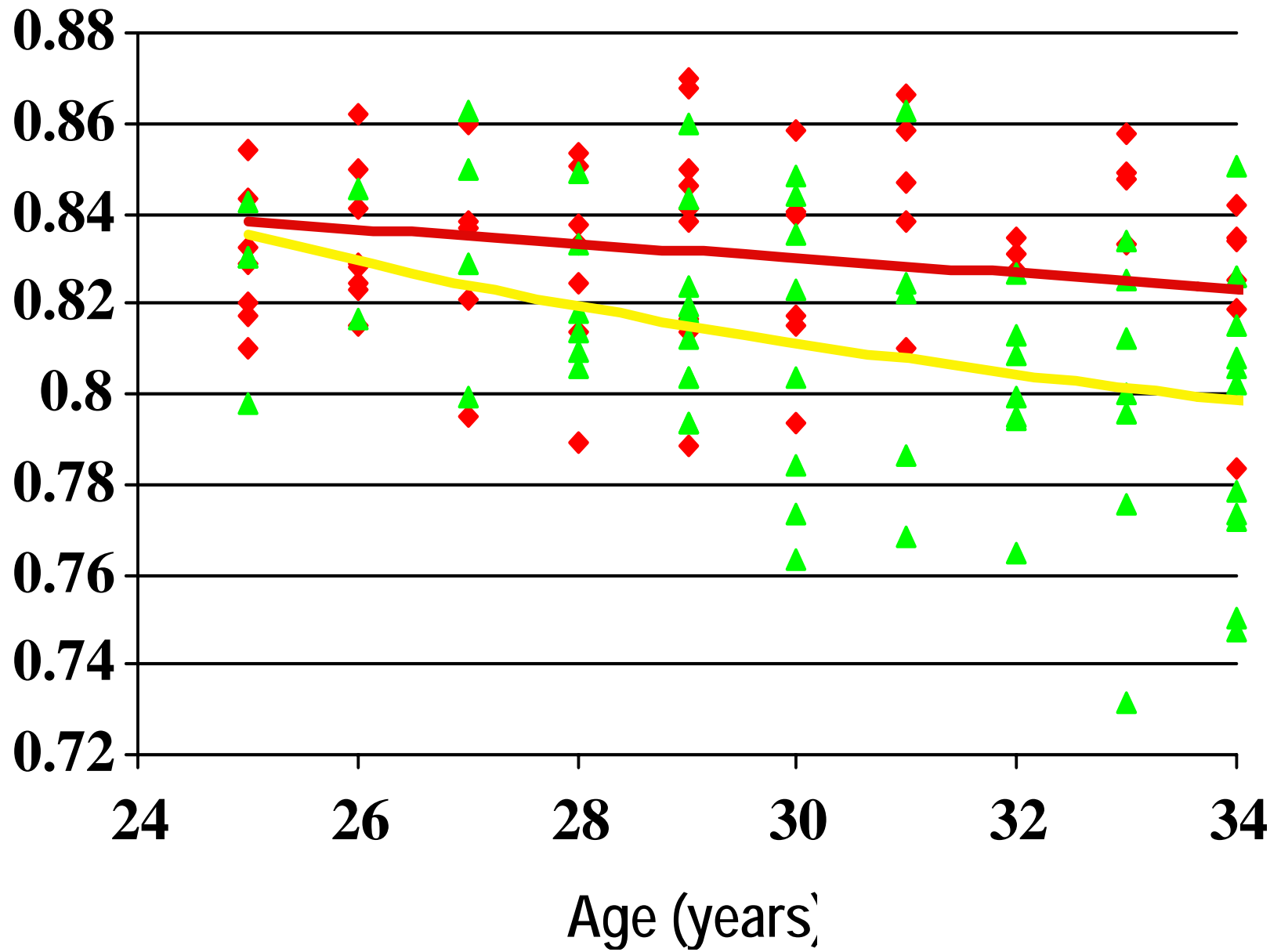
.783

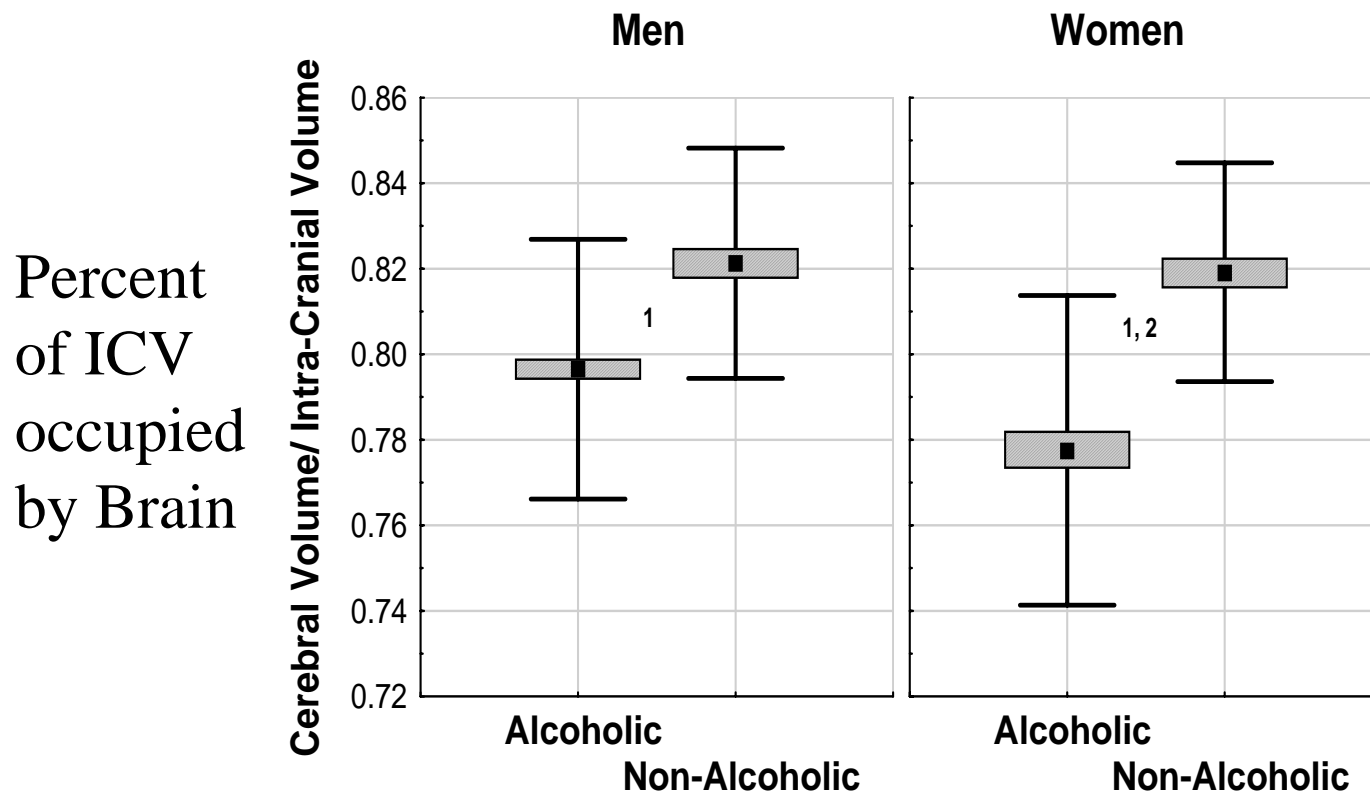
.699



◆ Non-Alcoholics ▲ Alcoholics







¹ Main effect for diagnosis (co-varying for age),
 $F(1,365) = 68.2, p < .00001$

² Interaction between diagnosis and gender (co-varying for age),
 $F(1,365) = 7.8, p < .005$

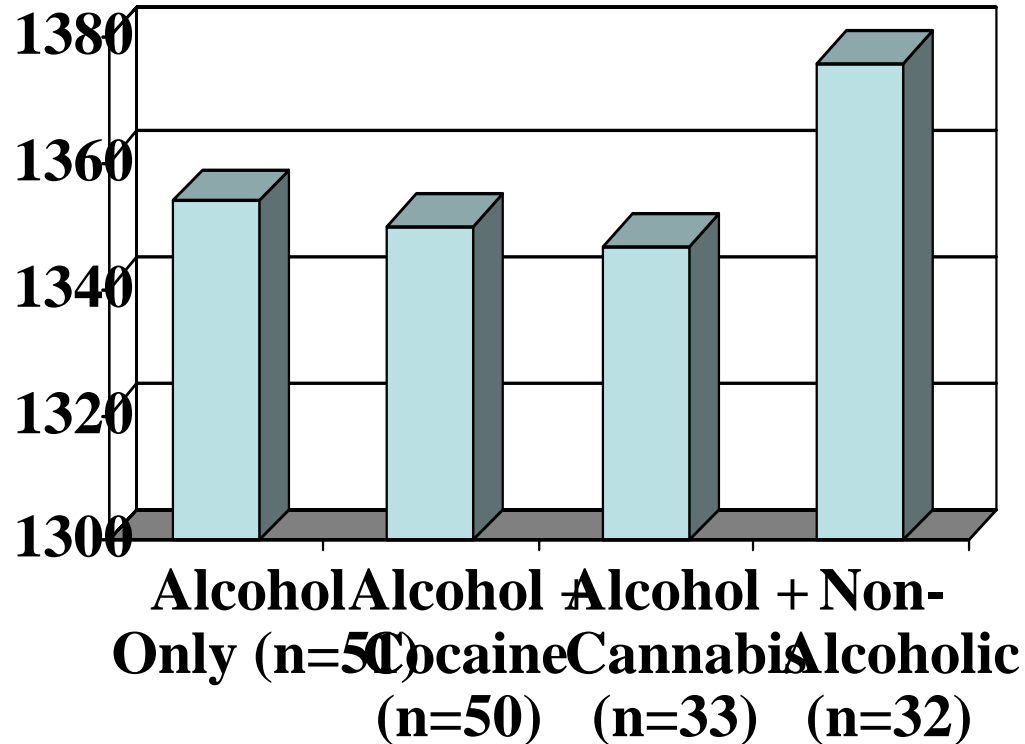
- Alcoholics have smaller Intra-Cranial Volumes than non-alcoholics
- Alcoholics have more brain shrinkage than non-Alcoholics
- Alcoholic women have greater shrinkage than alcoholic men
- Brain Shrinkage begins early in the course of alcoholism

Factors that may influence the amount of brain shrinkage in alcoholism

- Age
 - Yes
- Gender
 - Yes
- Psychiatric co-morbidity
 - No
- Other drug abuse
 - ?
- How much you drink
 - ?

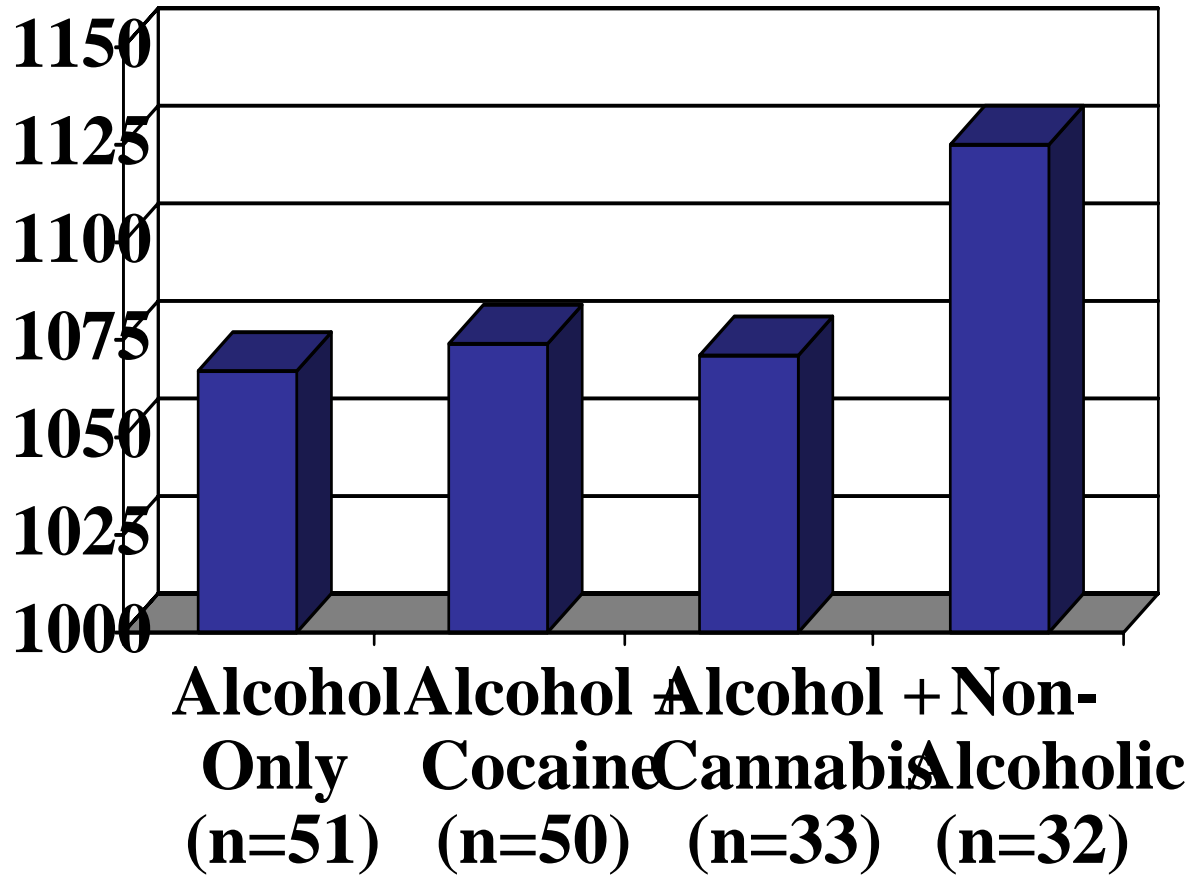
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IntraCranial Volu

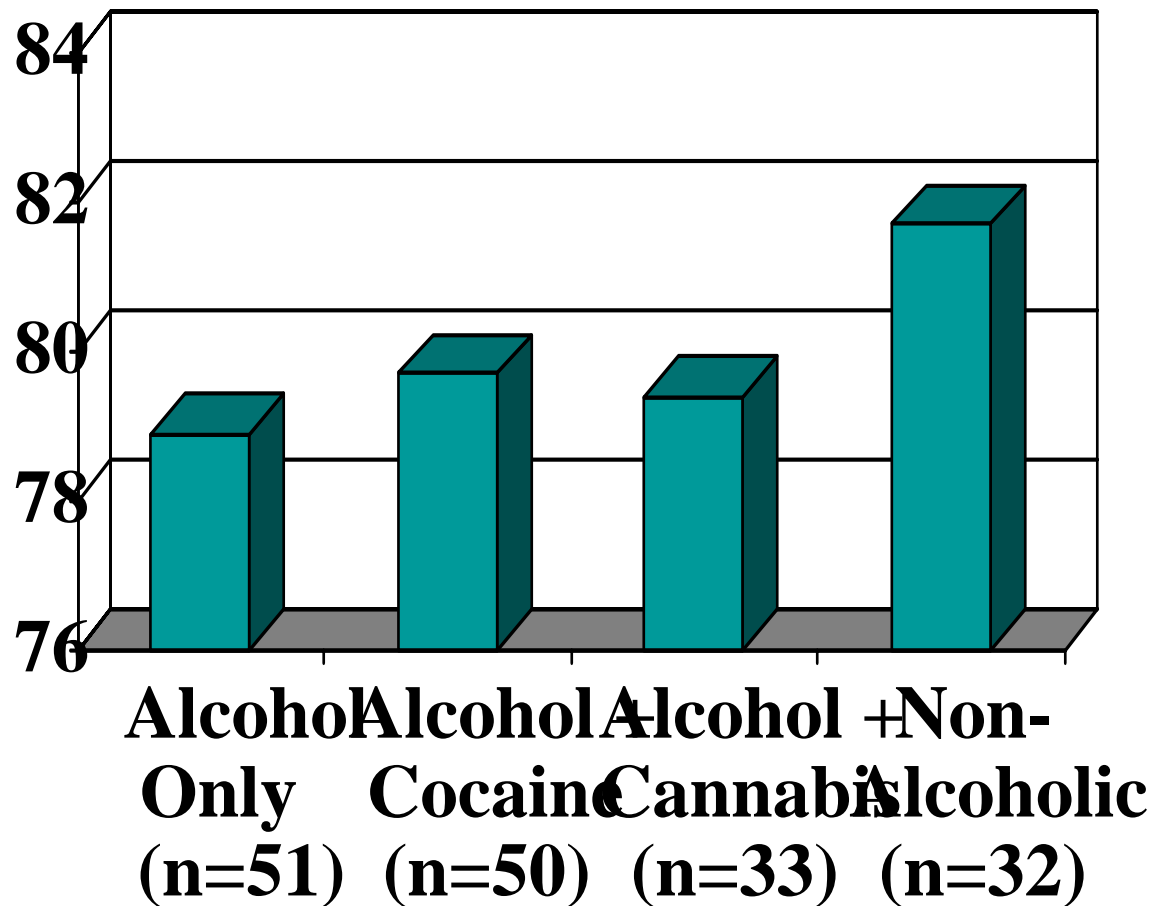


The subjects were all males between 30 and 50 years of age

Cerebral Volun



Percent of ICV o by Brain

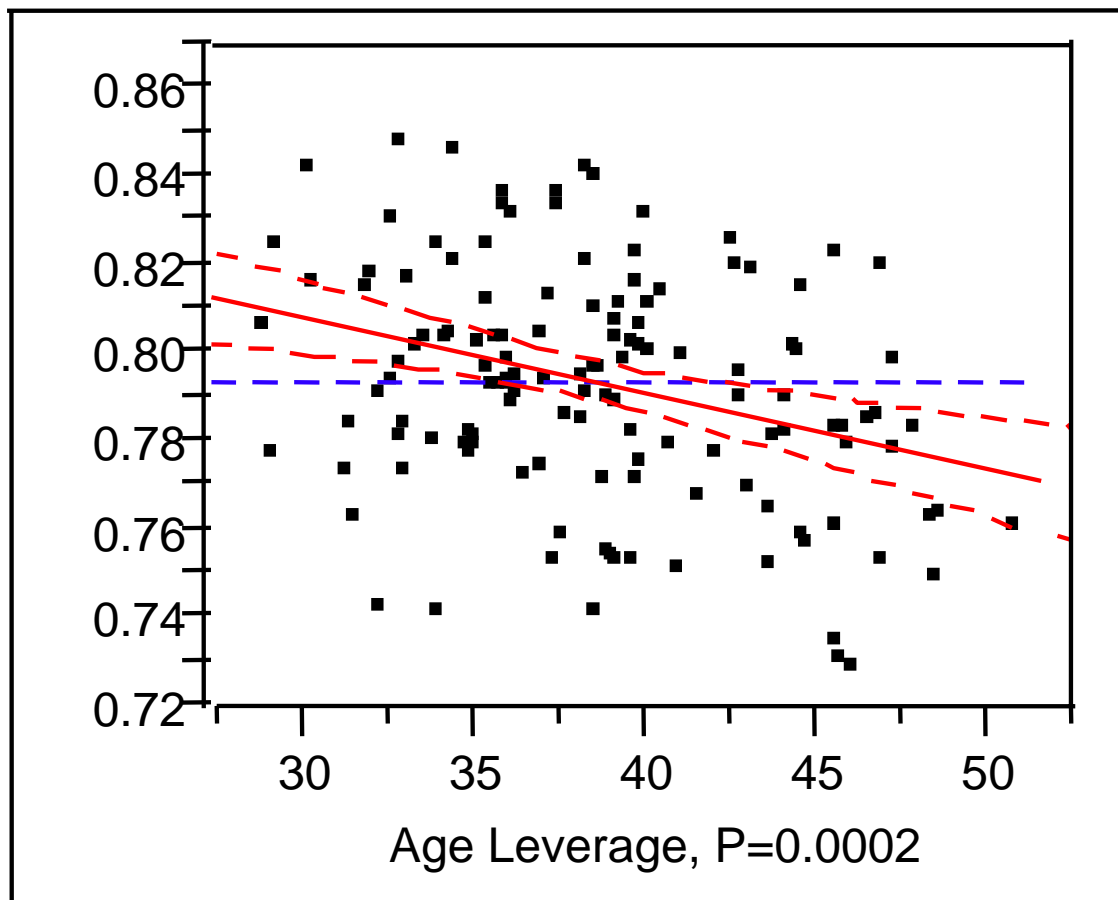


The present or absence of other substance abuse or dependence does not influence brain shrinkage among alcoholics.

Is cumulative alcohol exposure the most important factor other than age in determining brain shrinkage among alcoholics?

We performed multiple regressions with drinking history, age, co-morbid drug use as independent variables and brain shrinkage as the dependent variable.

Partial correlation between age and Brain Shrinkage (Cerebral Volume/ICV), $r = -.37$



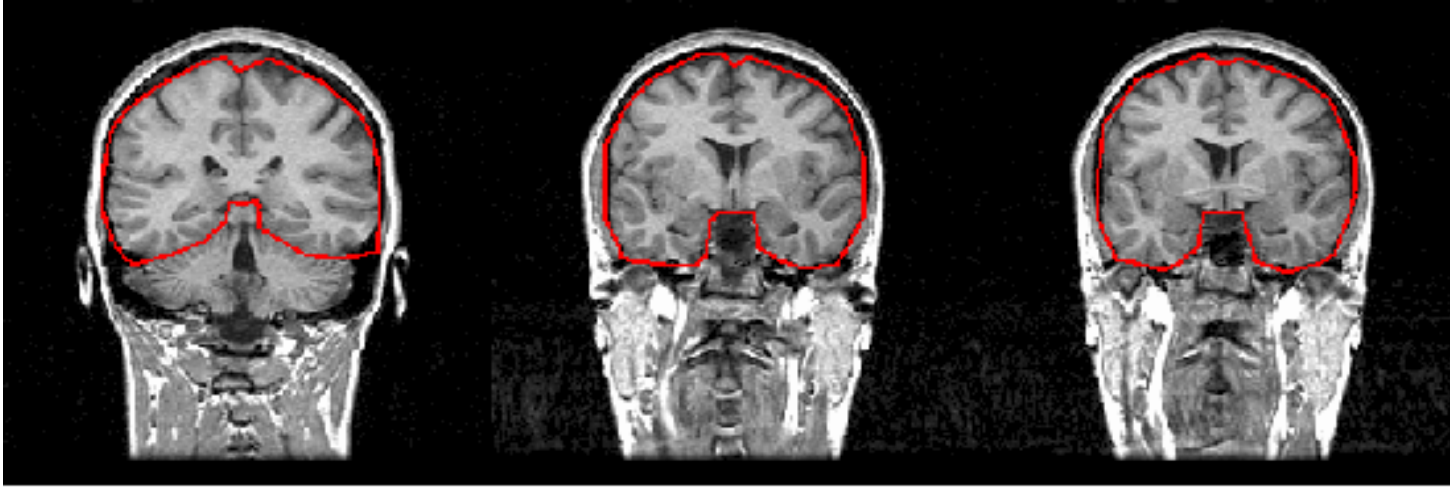
- Years of heavy drinking predicts brain shrinkage independently of age or drug use
- Estimated lifetime alcohol consumption does not.

Is Gray or White Matter more affected in Alcoholism?

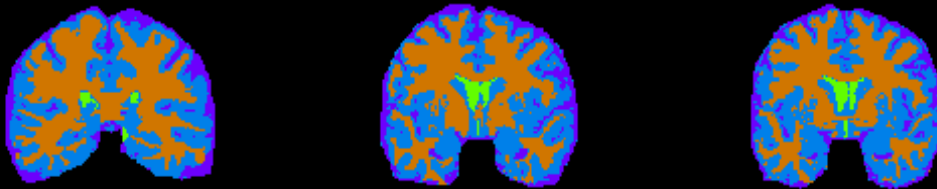
- Post mortem studies suggest gray matter is more affected.
- MRI studies suggest gray matter is more affected.
- We compared the ratio of gray to white matter volume. This removes contributions of ICV or cerebral volume.

Results of Automated Segmentation

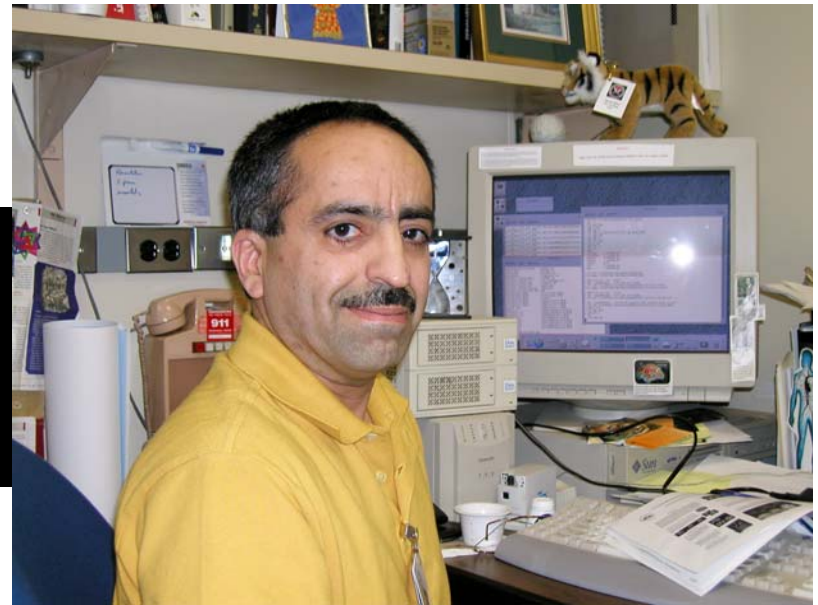
First inner table of the skull is outlined and cerebrum is separated from cerebellum.



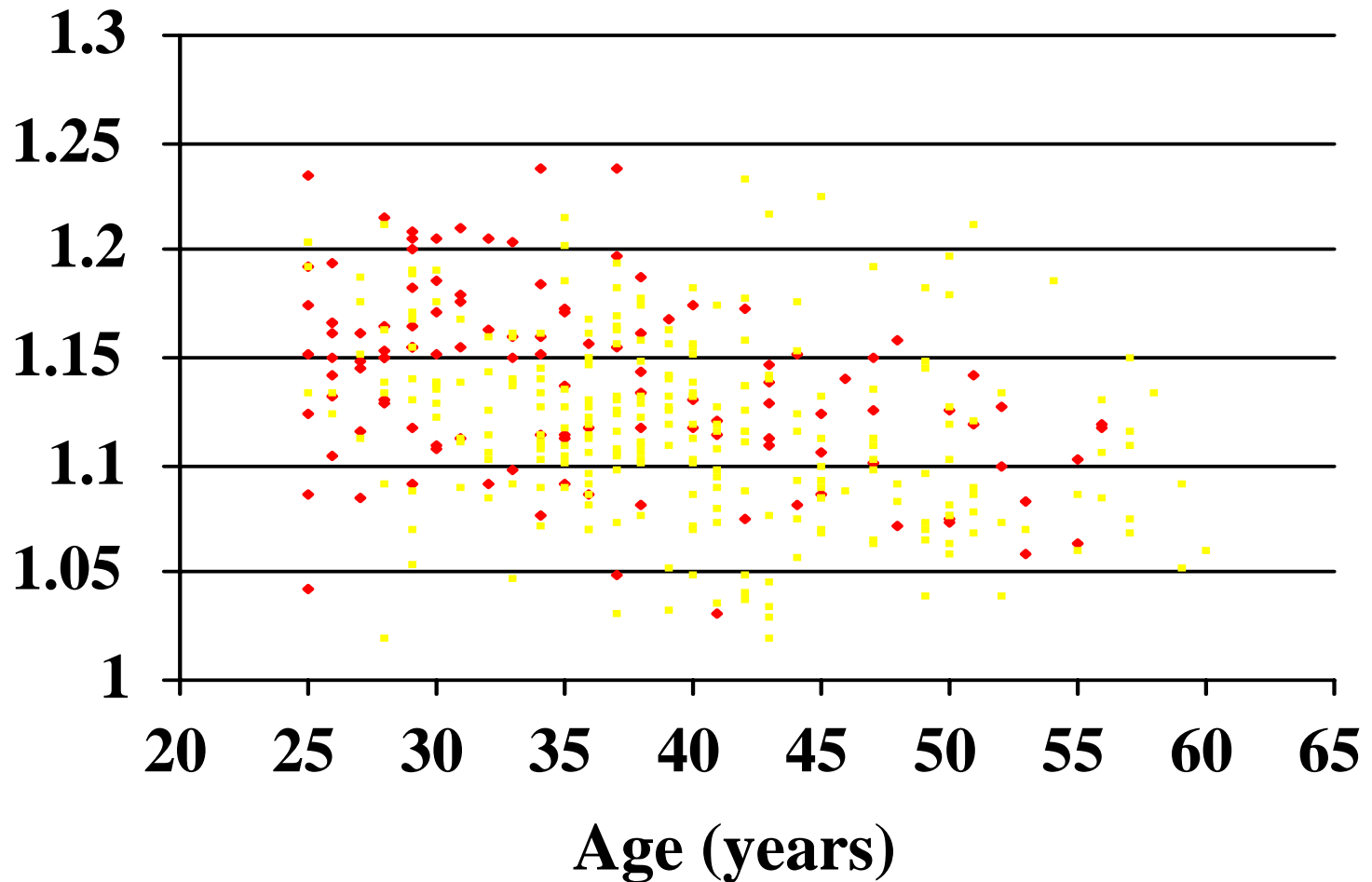
Then intracranial contents are segmented into Sulcal CSF (purple), Gray matter (blue), White matter (orange), and Ventricular CSF (green) and volumes calculated.



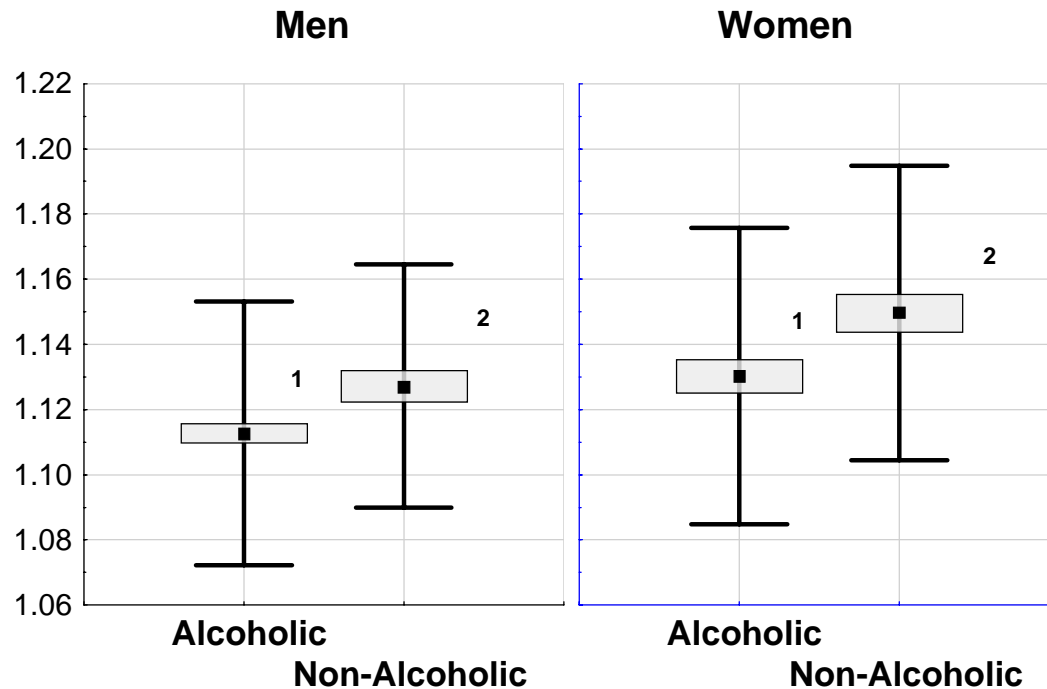
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Both Alcoholics and non-alcoholics lose gray matter as they age



Ratio of gray matter volume to white matter volume



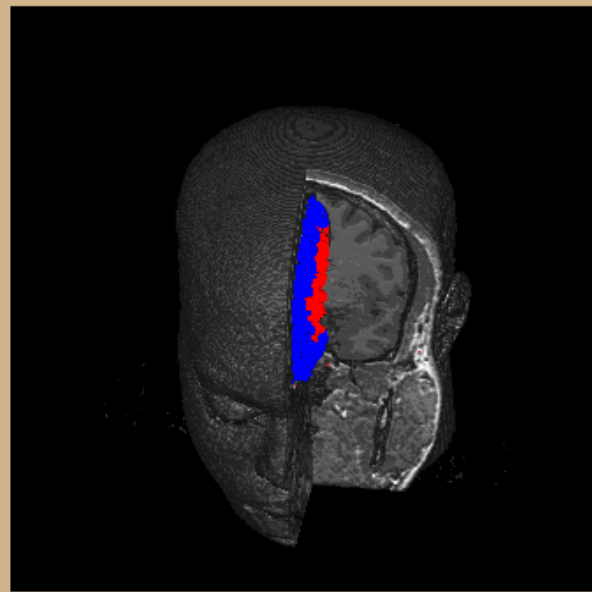
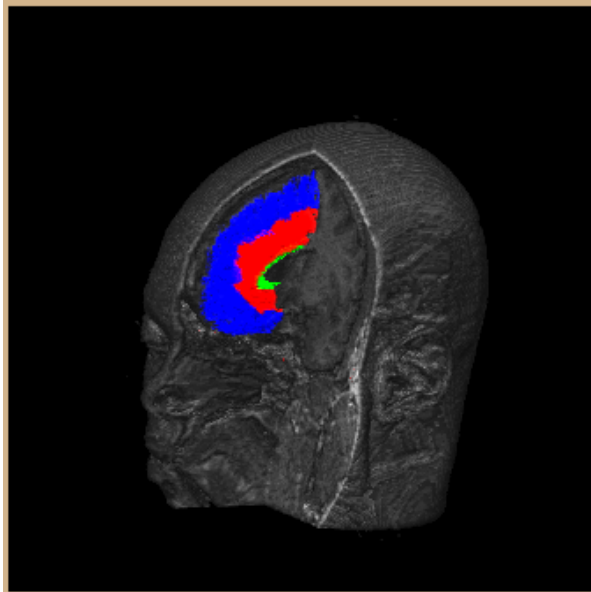
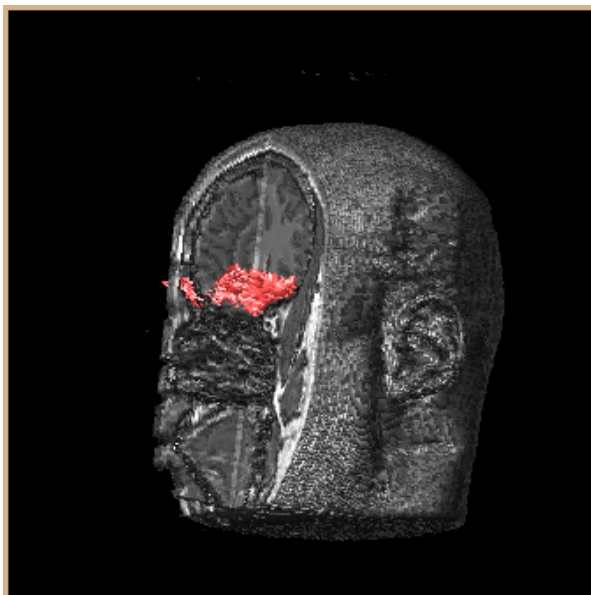
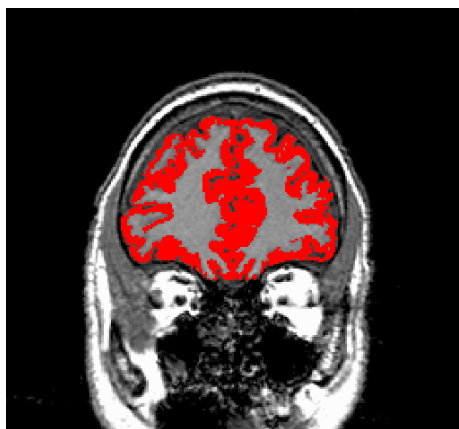
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 $F(1,365) = 24.2, p < .00001$

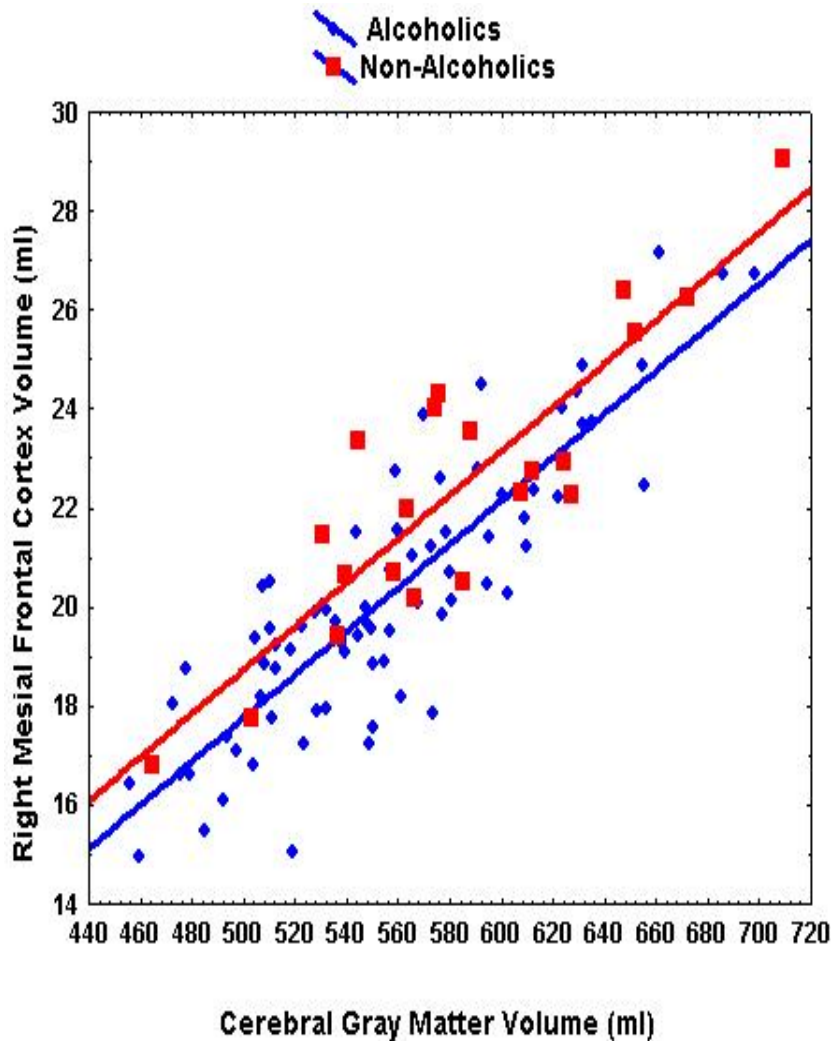
² Main effect for diagnosis (co-varying for age), $F(1,365) = 4.3, p < .05$

- Alcoholics lose proportionally more gray matter than white matter as they age.

Are some brain regions more affected by alcoholism or is the damage global and non-specific?

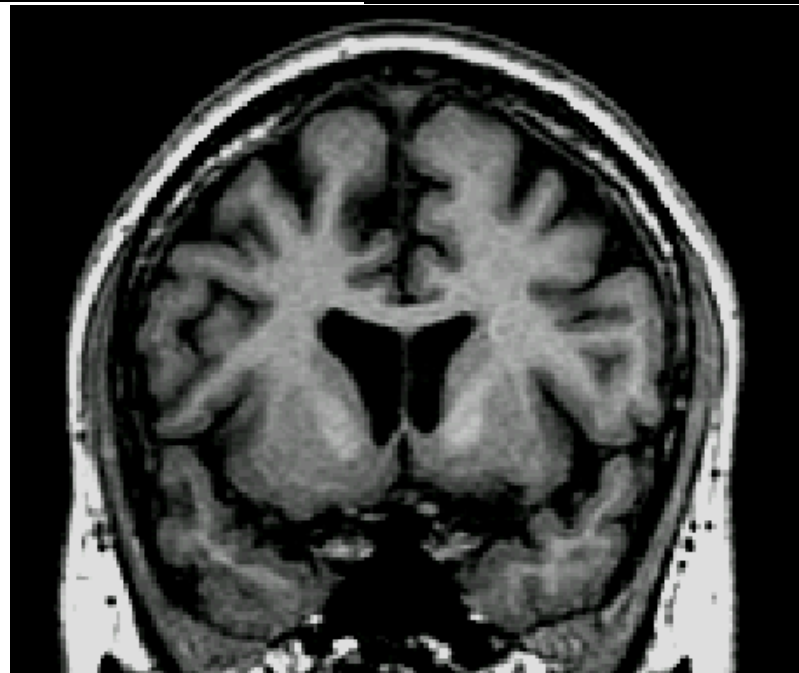
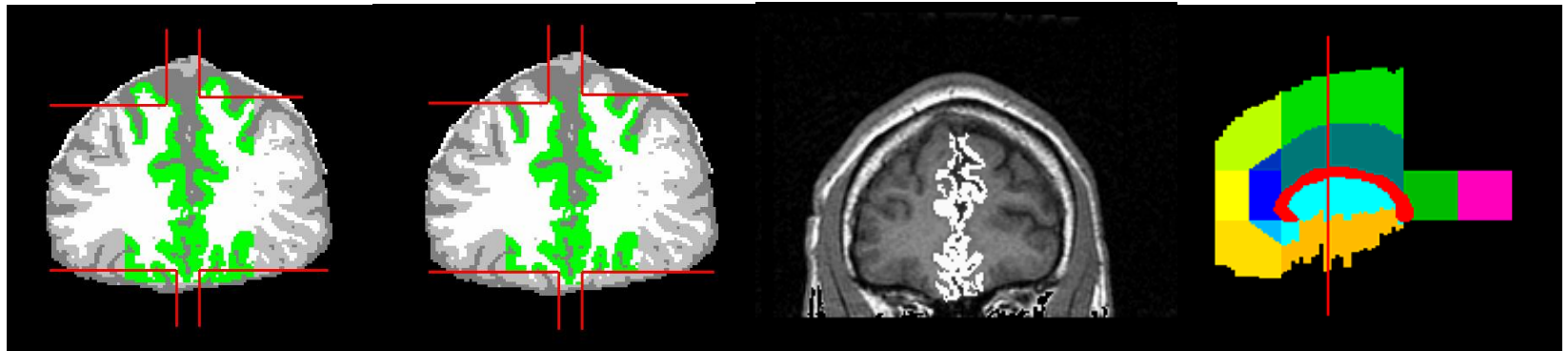
- We have previously shown there is shrinkage of hippocampus in alcoholism, but the reduction is proportional to overall brain shrinkage (Agartz et al, Arch Gen Psychiat. 56:356, 1999)
- Other investigators have suggested the frontal lobes are more vulnerable to alcoholism than other regions.





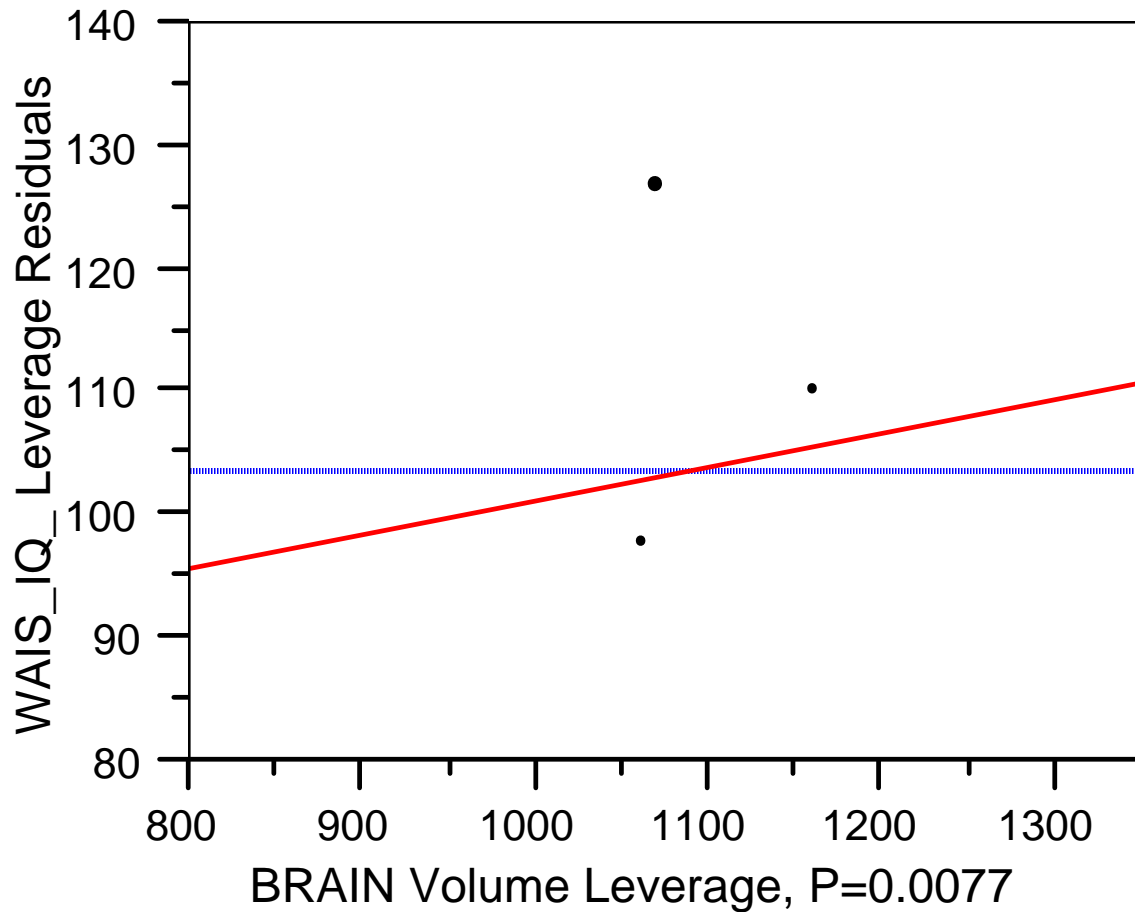
- When you co-vary for overall cortical volume only three regions of the frontal cortex are selectively affected in alcoholism.
- Right Mesial Frontal Cortex, $F(1,128) = 10.7, p < .002$
- Left Mesial Frontal Cortex, $F(1,128) = 4.7, p < .05$
- Left Dorso-Lateral Prefrontal Cortex, $F(1,128) = 6.9, p < .01$

Largest amount of cortex loss is in the outer half of the mesial frontal cortex



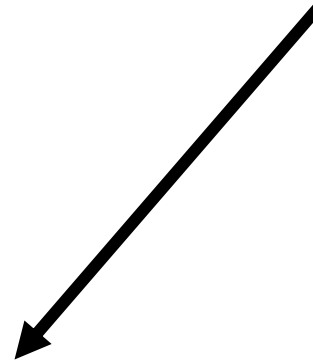
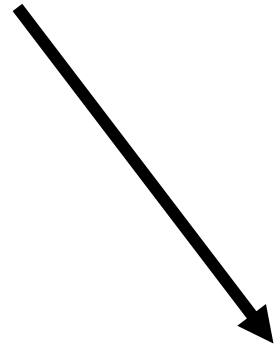
Structure and Function

Controlling for Age, Sex, and Education Brain Volume Predicts IQ among Alcoholics



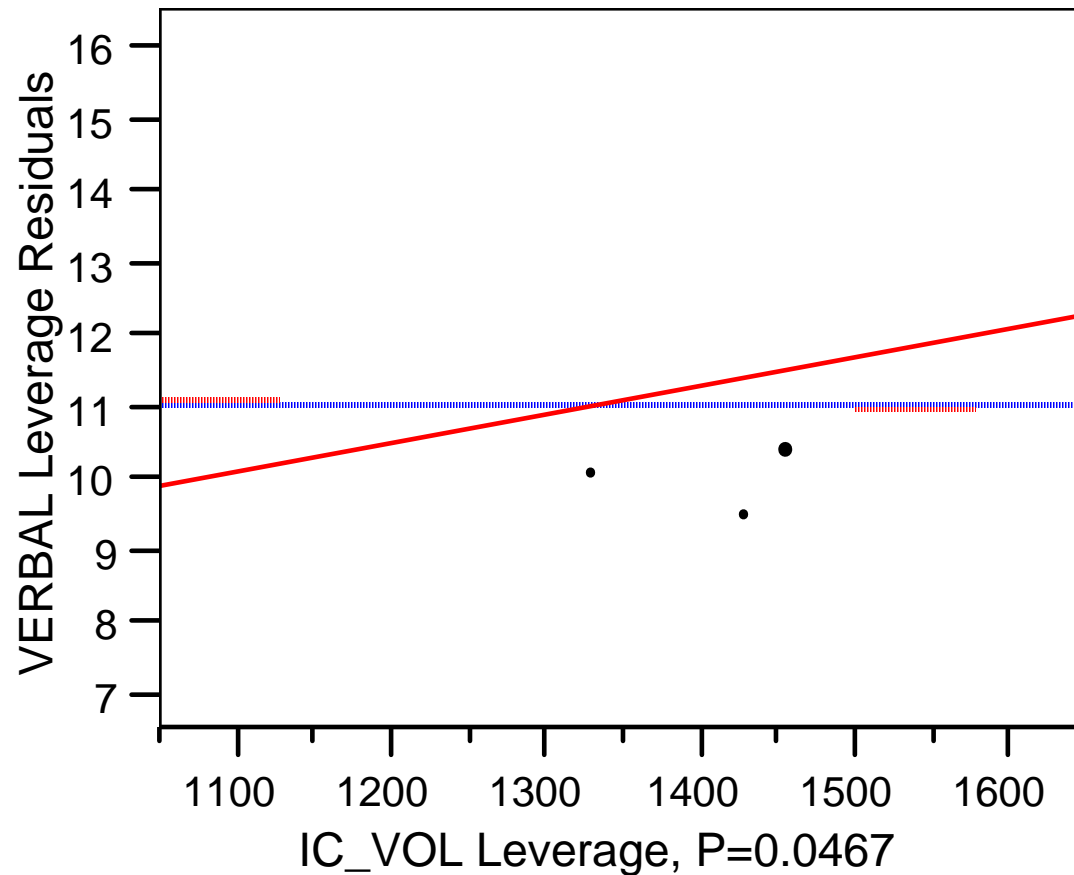
Verbal IQ

Performance IQ

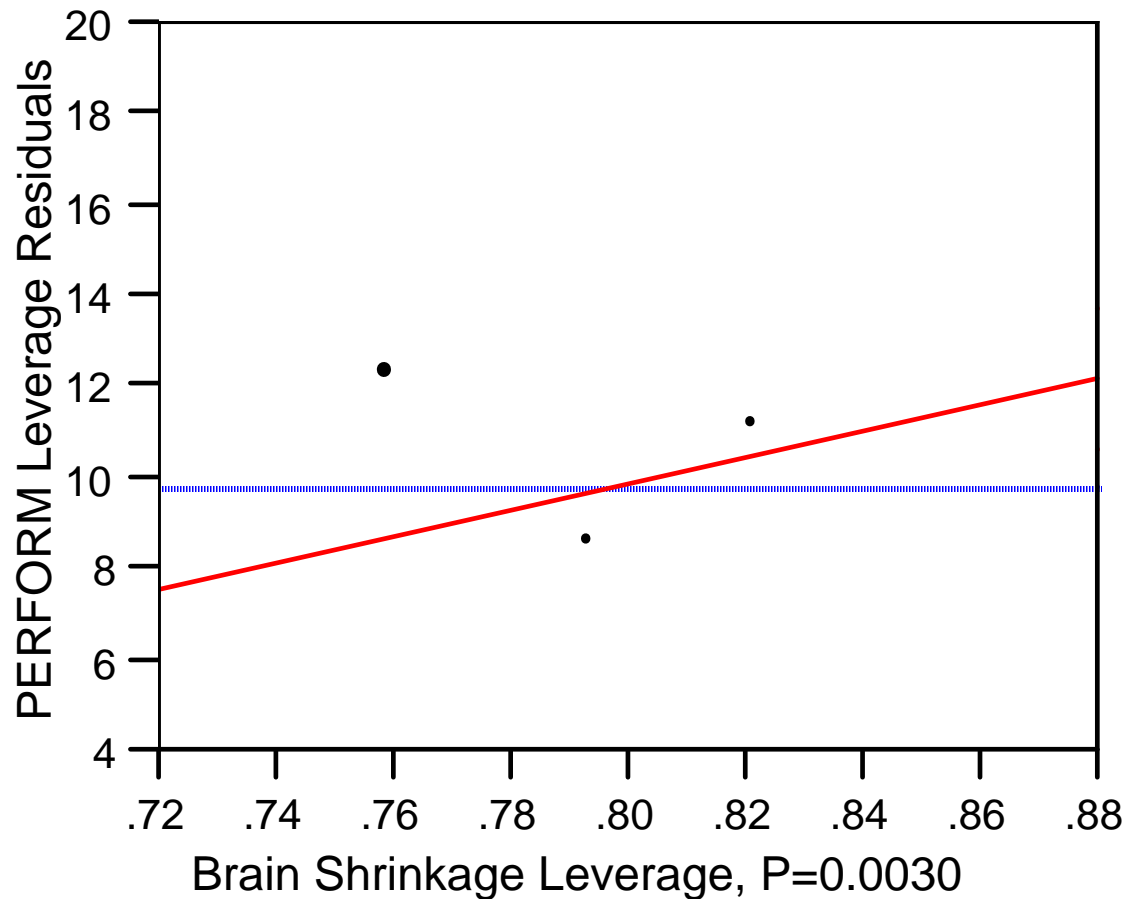


Full Scale IQ

Controlling for Age, Sex, and Education ICV (Brain Growth) Predicts Verbal IQ



Controlling for Age, Sex, and Education Brain Shrinkage Predicts Performance IQ



Summary

- Alcoholics have slightly smaller brains even before the onset of heavy drinking
- Alcoholic women have more brain shrinkage than alcoholic men
- The brain damage begins early in the course of alcoholism
- Gray matter is slightly more vulnerable than white matter in most alcoholics
- Co-morbid drug abuse or mood disorder does not increase brain shrinkage
- Years of heavy drinking predicts brain shrinkage independently of age
- The mesial frontal cortex and left dorso-lateral prefrontal cortex are selectively affected in alcoholism
- Maximal brain growth predicts verbal intelligence
- Brain shrinkage predicts performance IQ