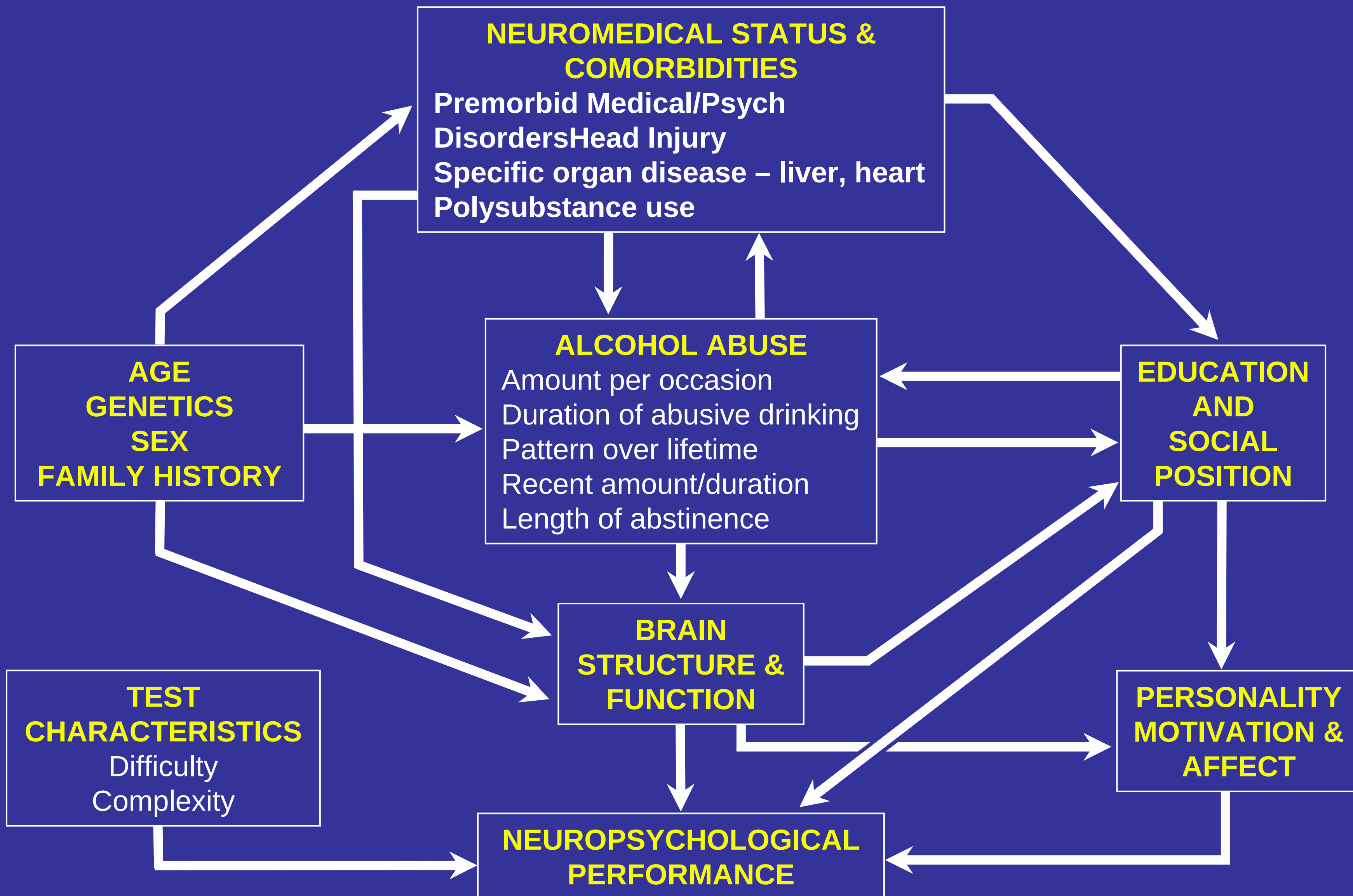
ALCOHOL AND THE BRAIN:

Igor Grant, MD

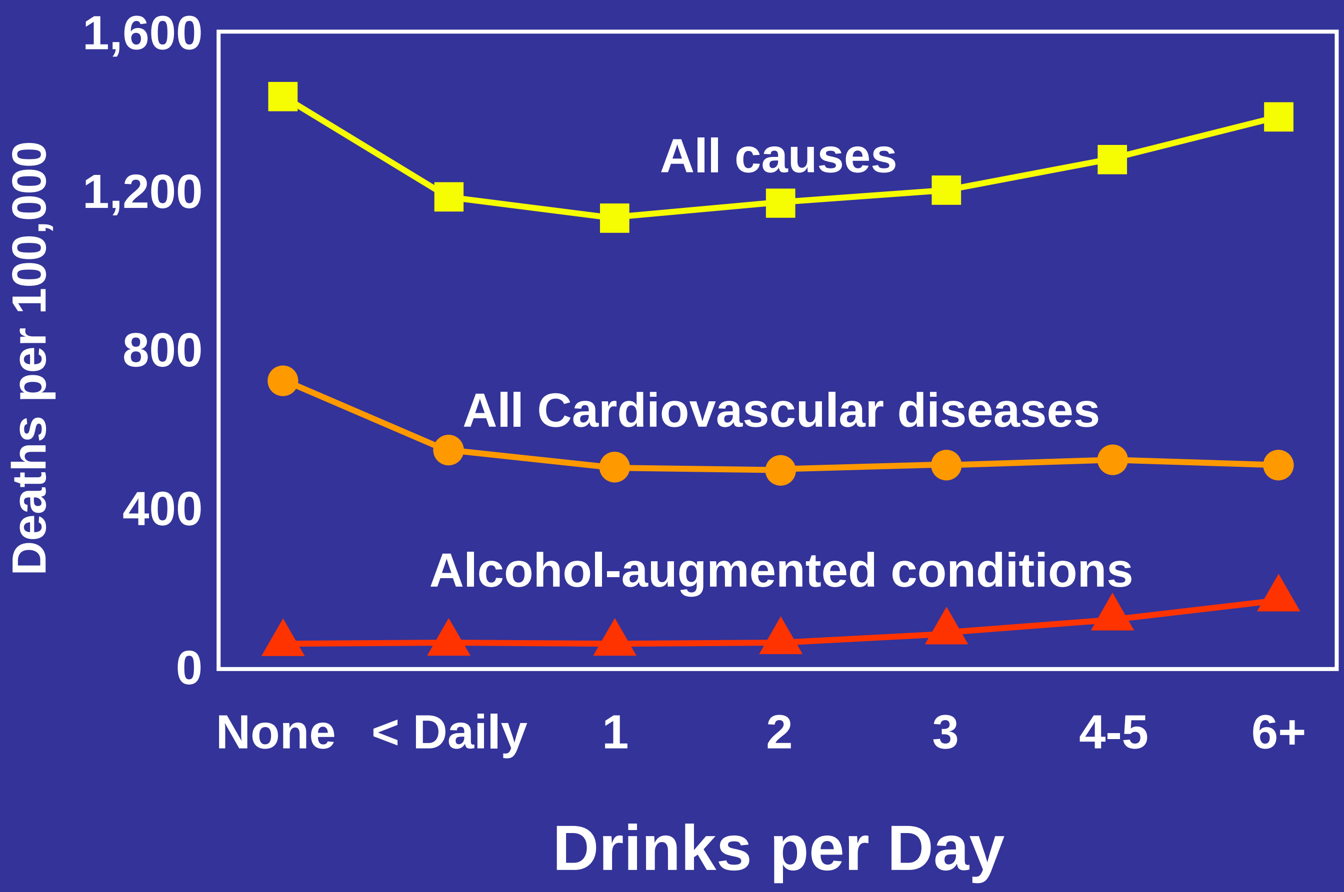
VA San Diego
Alcohol Study

VARIABLES TO CONSIDER IN ANY CAUSAL MODEL OF ALCOHOL ASSOCIATED NEUROPSYCHOLOGICAL DEFICIT



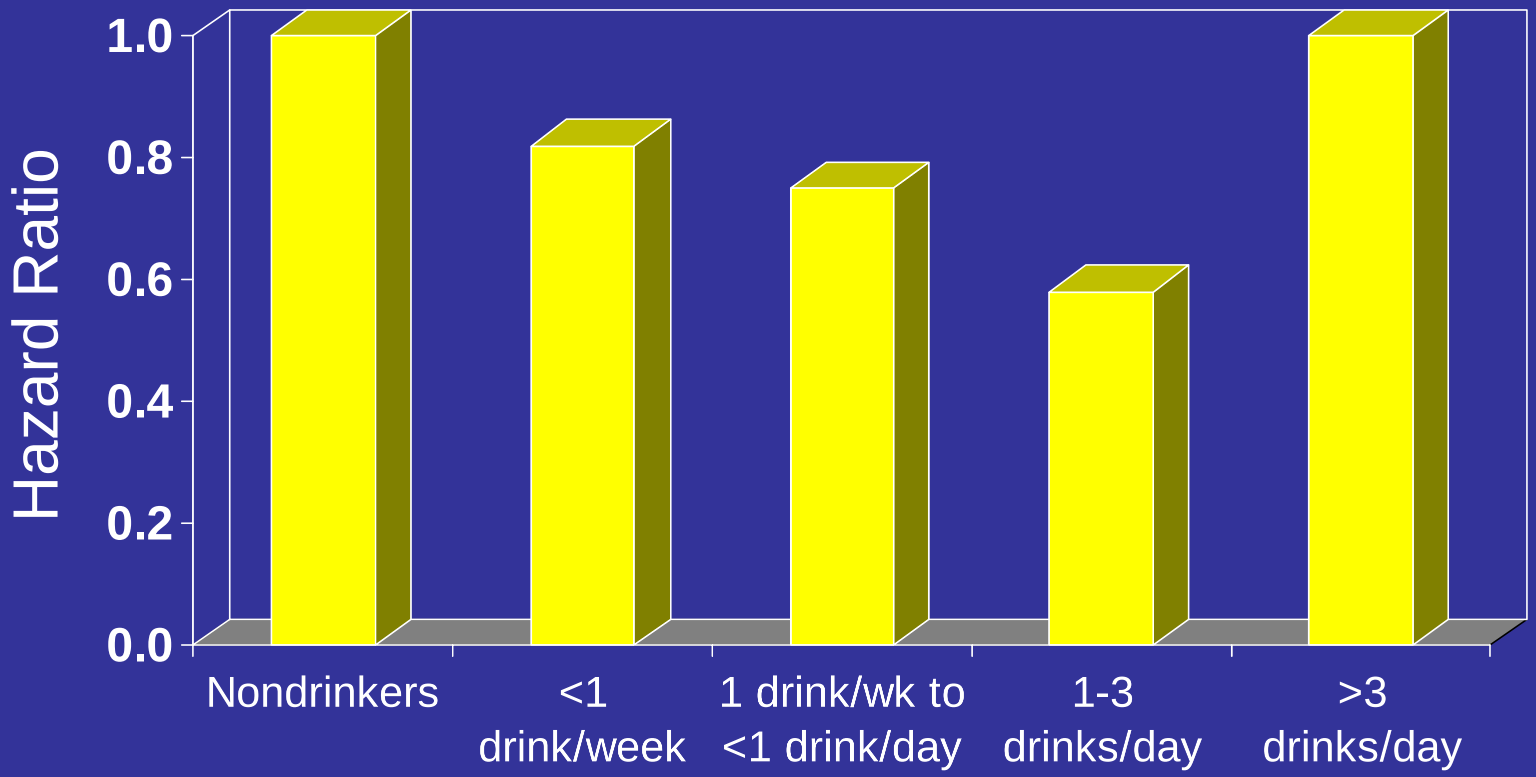
"THE GOOD"

Fewer Deaths in Moderate Drinkers



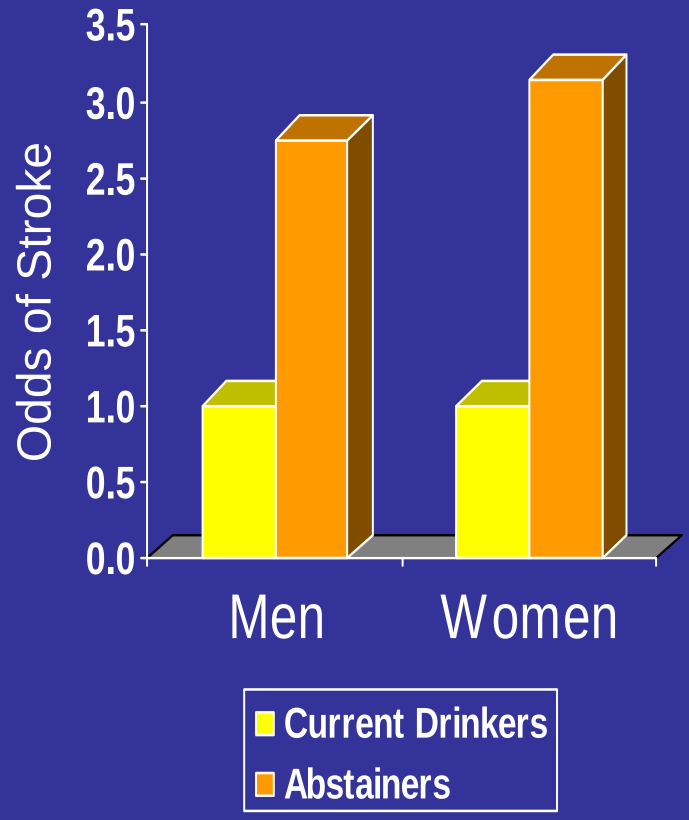
Thun, et al., NEJM, 1997

"Light to moderate alcohol consumption is associated with a lower risk of developing dementia" (Letenneur, 2007)



Ruitenberg, et al., Lancet, 2002

Moderate Alcohol Use Related to Lower Risk of Stroke and Blood Pressure

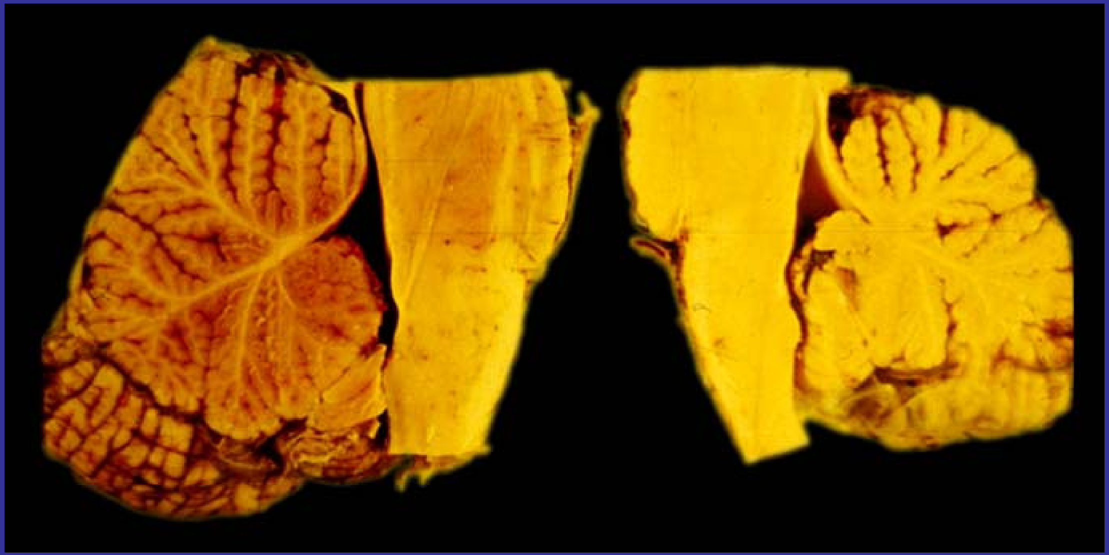


Rodgers, et al., Stroke, 1993

Gillman, et al., Hypertension, 1995

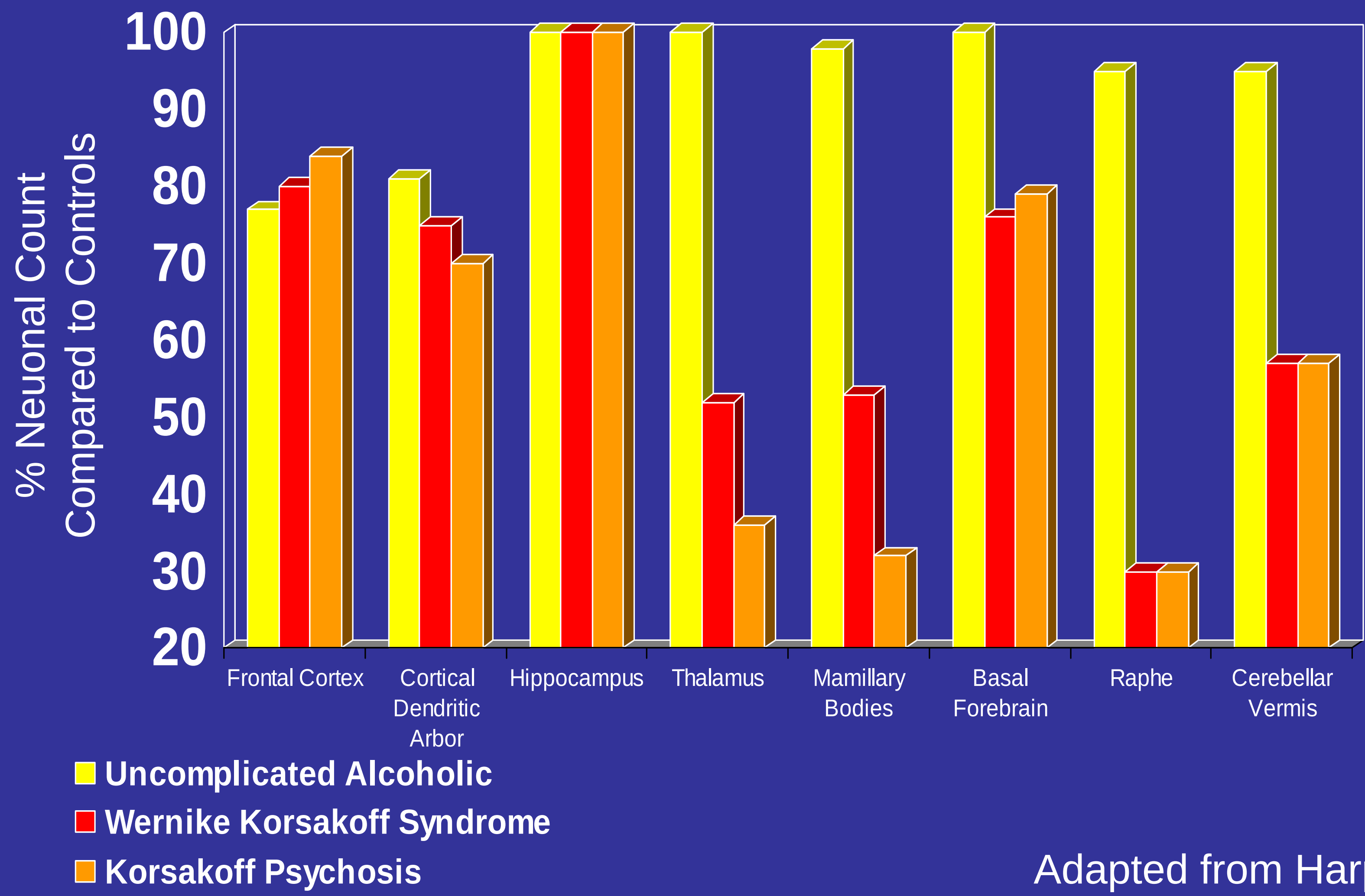
"THE BAD"

Ventricular Dilatation



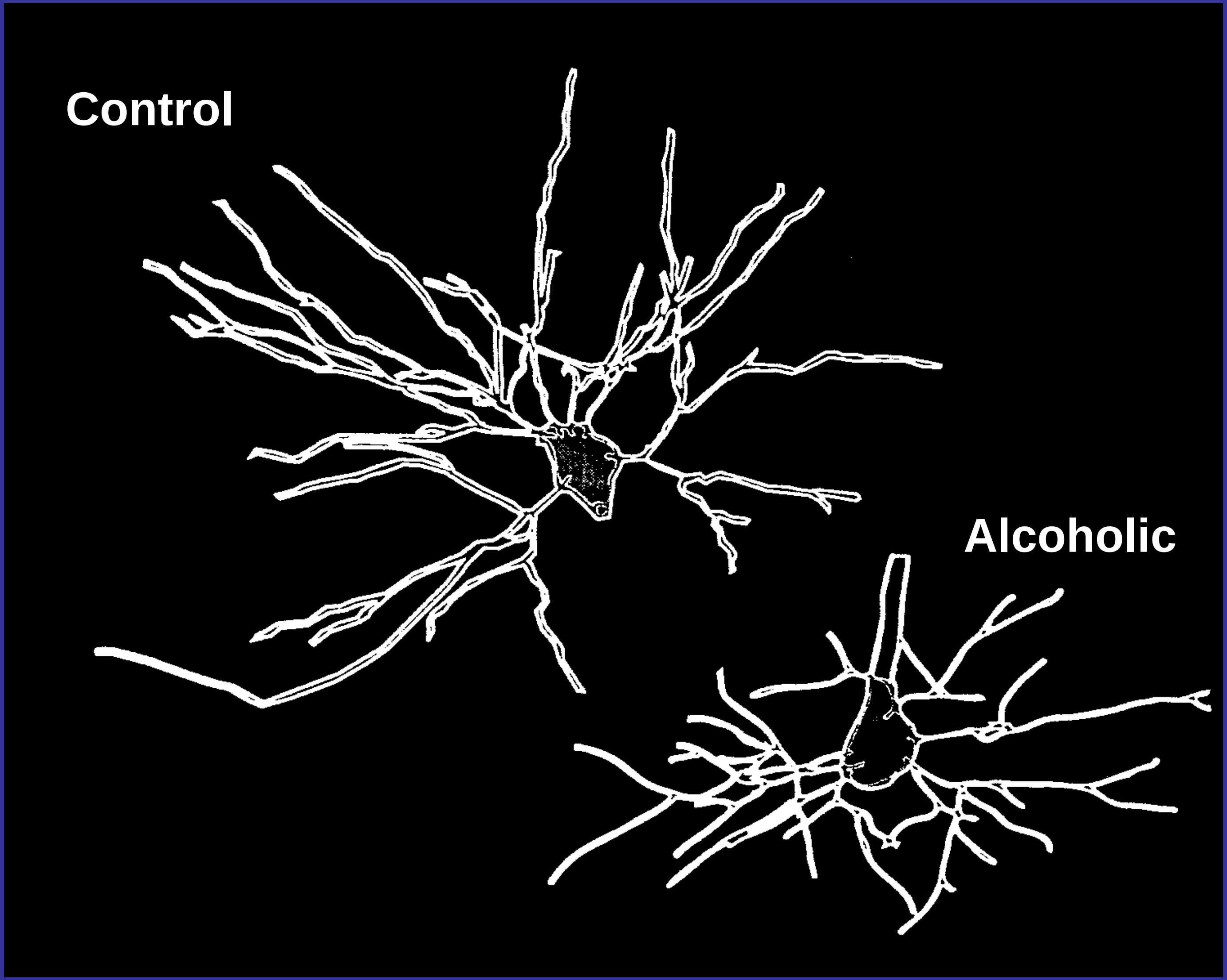
Cerebellar Atrophy

Neuropathology of Alcoholism



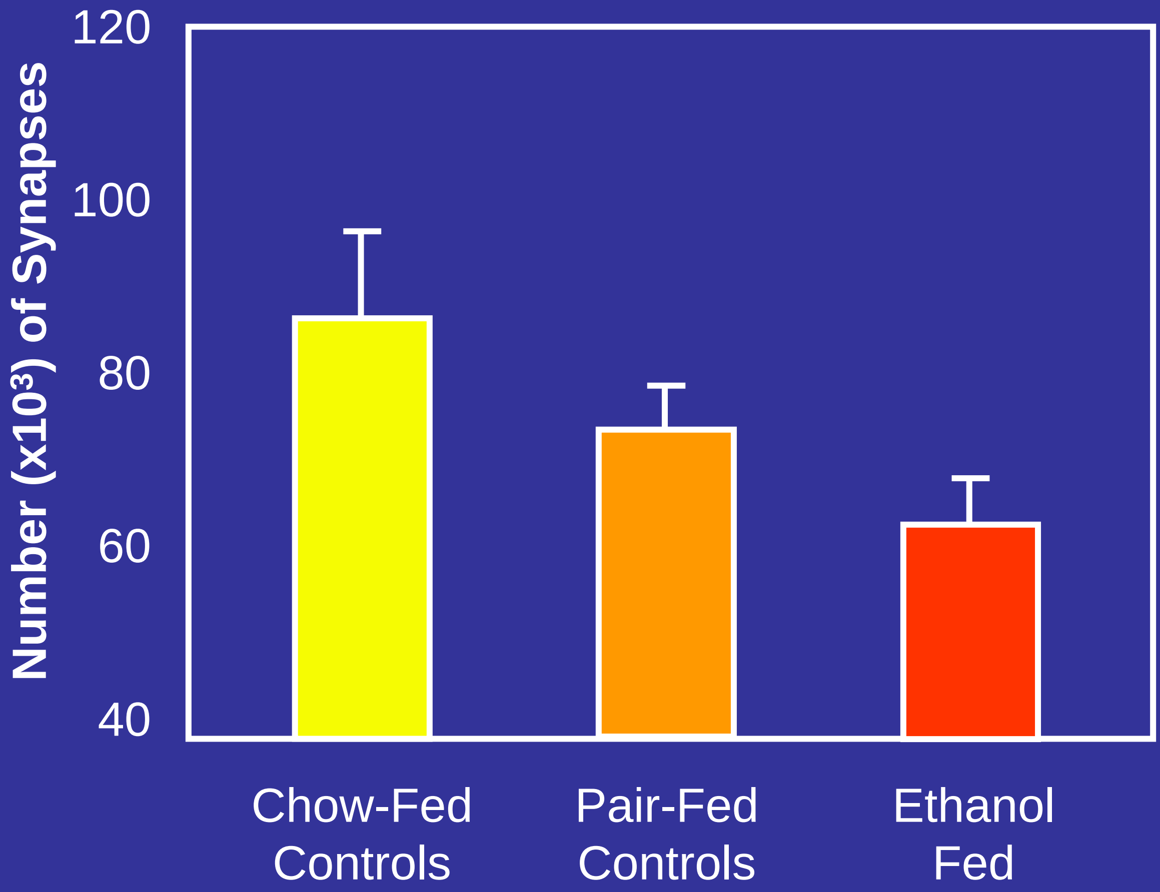
Adapted from Harper, et al.,
Prog in Neuro-Psychopharm and Biol Psych 2003

Less Dendritic Arborization of Layer III Pyramidal Neurons From Superior Frontal Cortex in Alcoholics



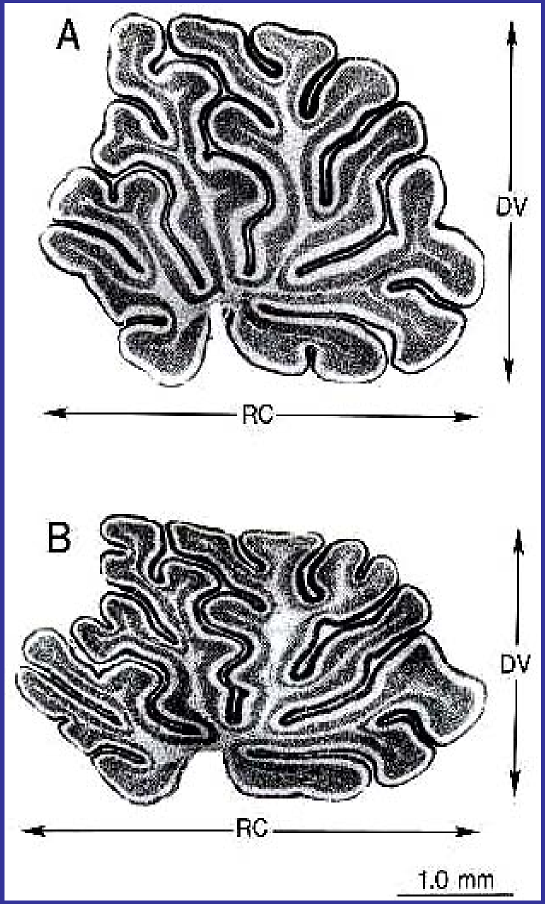
Harper & Corbett, J Neurol Neurosurg Psychiatry, 1990

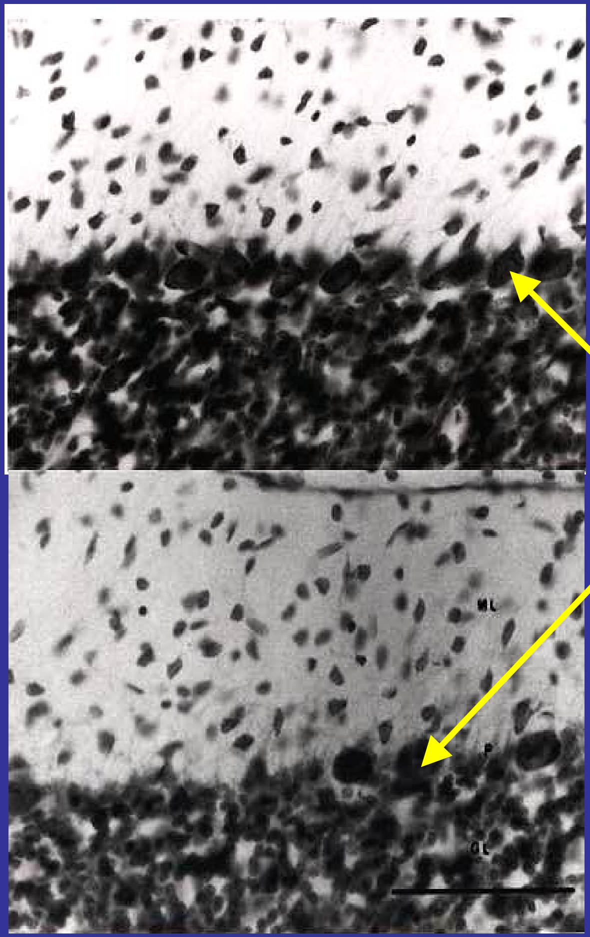
Lower Synapses per Purkinje Neuron in Ethanol-Fed Rats



Crews, et al., ACER, 2004

Alcohol and the Cerebellum

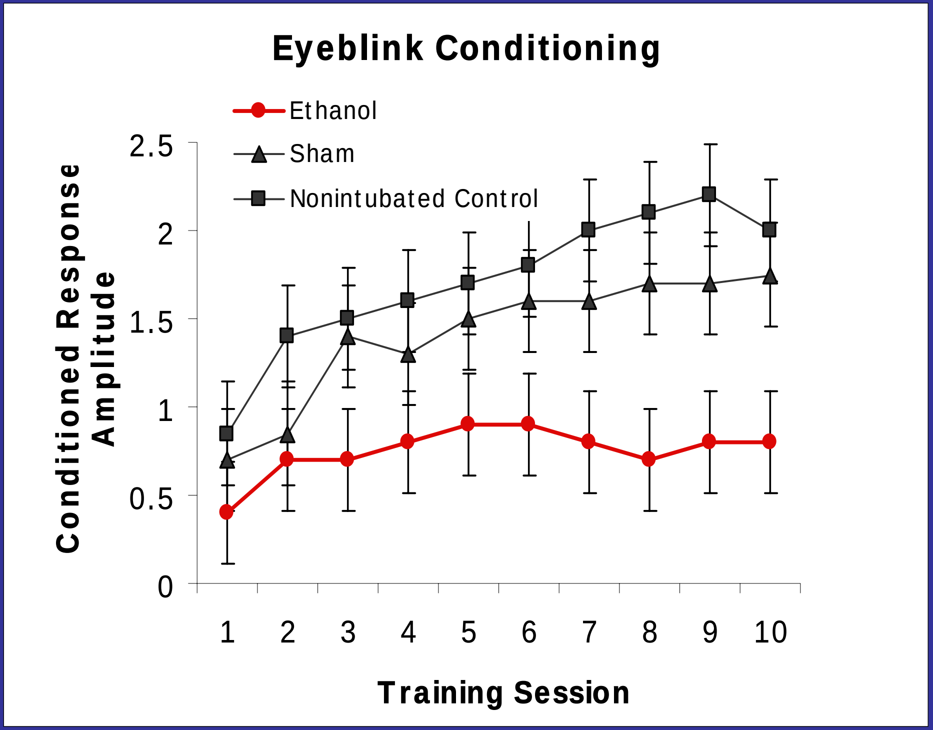


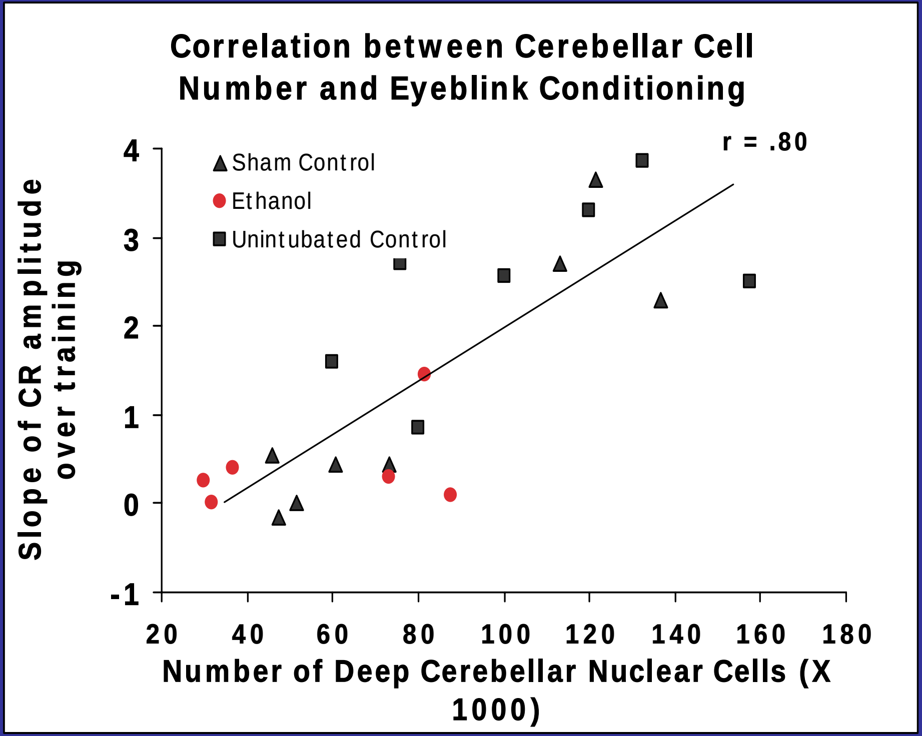


Purkinje Cell Layer

Pictures courtesy of James West

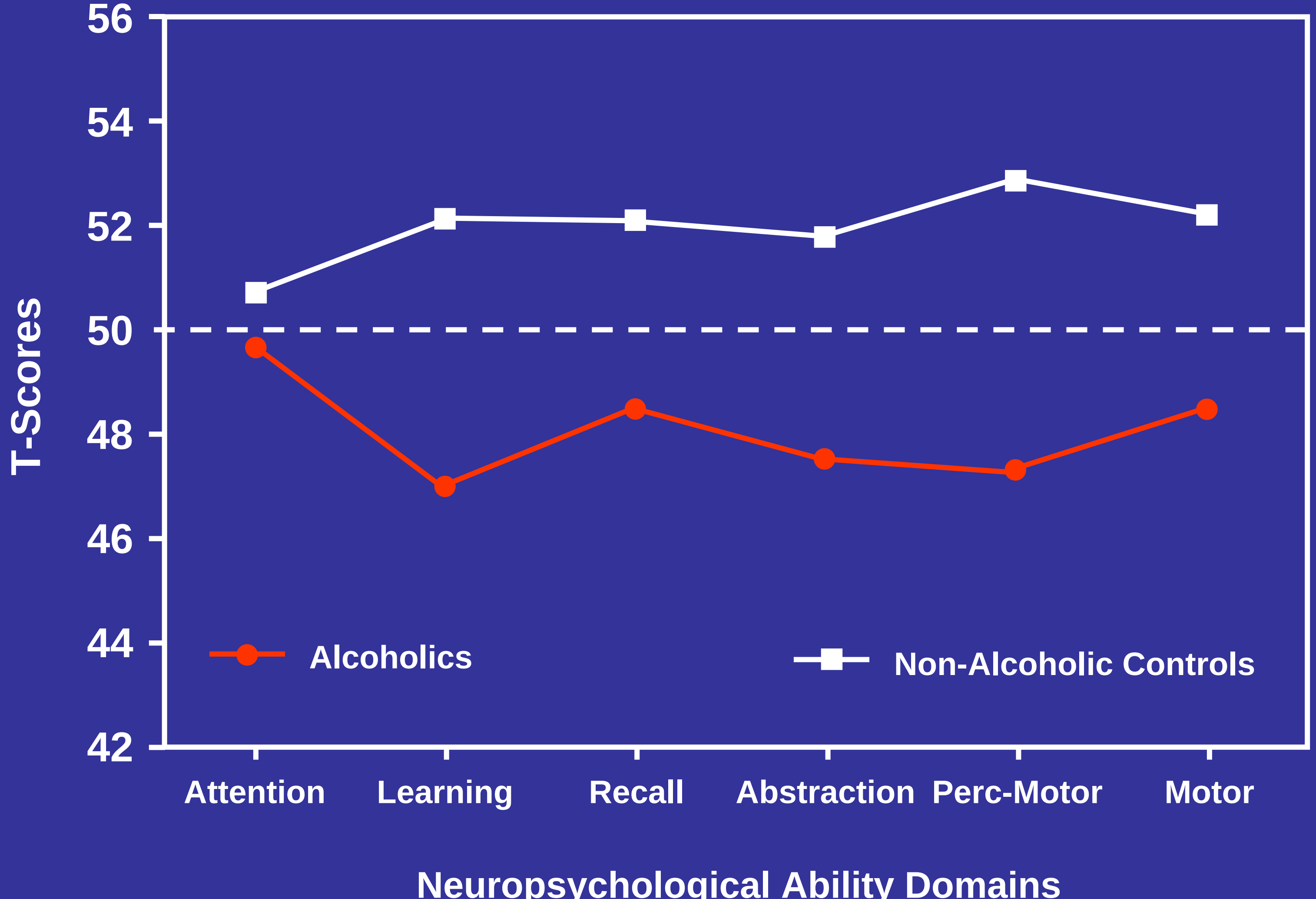
Eyeblink conditioning deficits are correlated with cerebellar damage





Adapted from Green et al., Brain Research, 2002

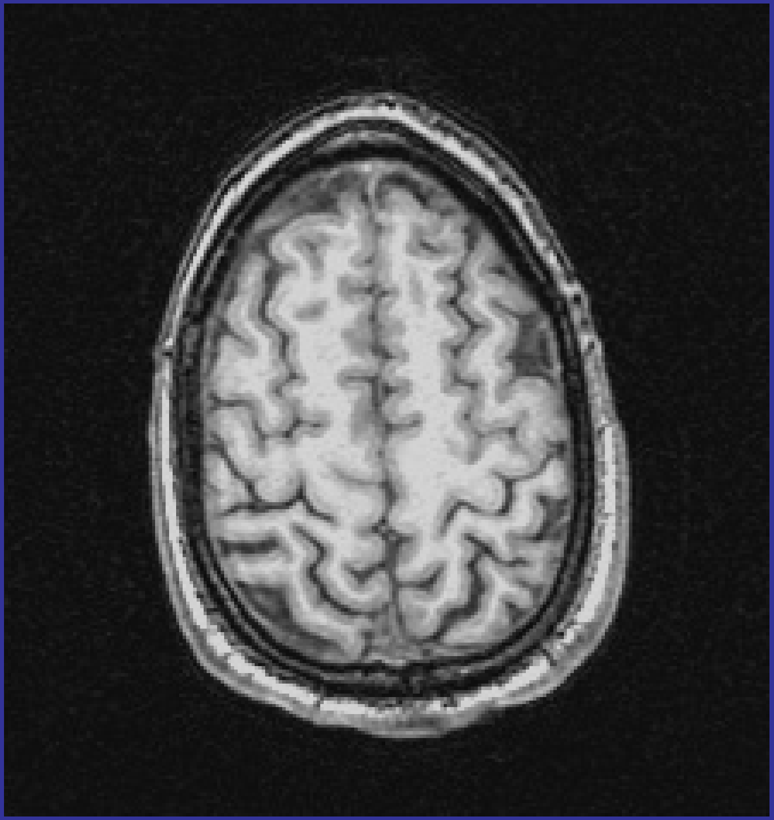
Impaired NP Performance in Alcoholics



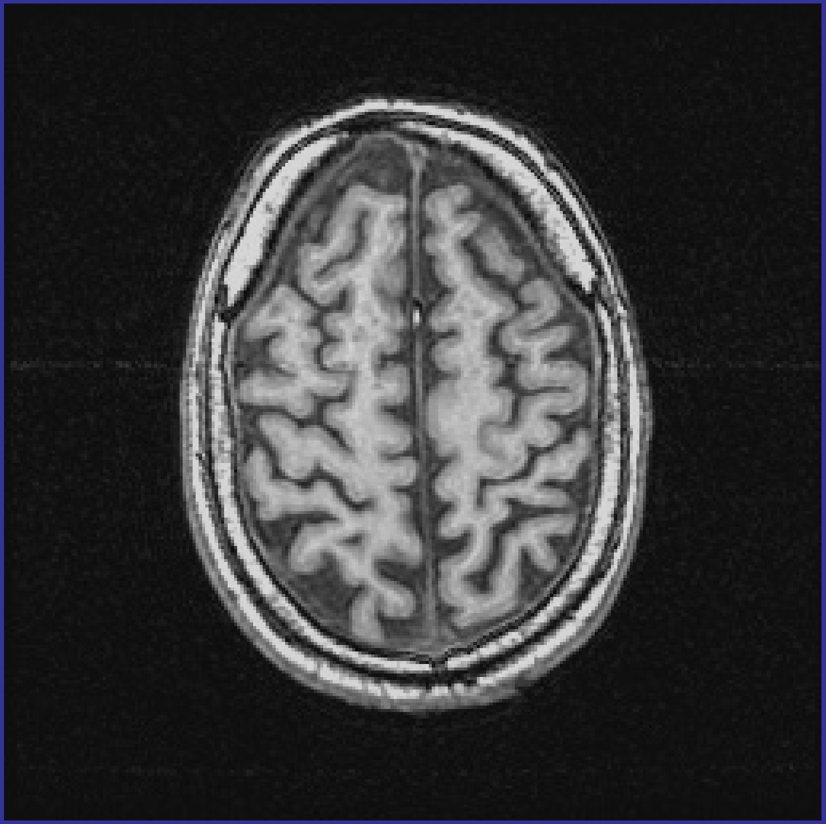
VA San Diego
Alcohol Study

Rourke & Grant, 1996

Sulcal Dilatation on Brain MRI in Recently Detox Alcoholics



Healthy Control

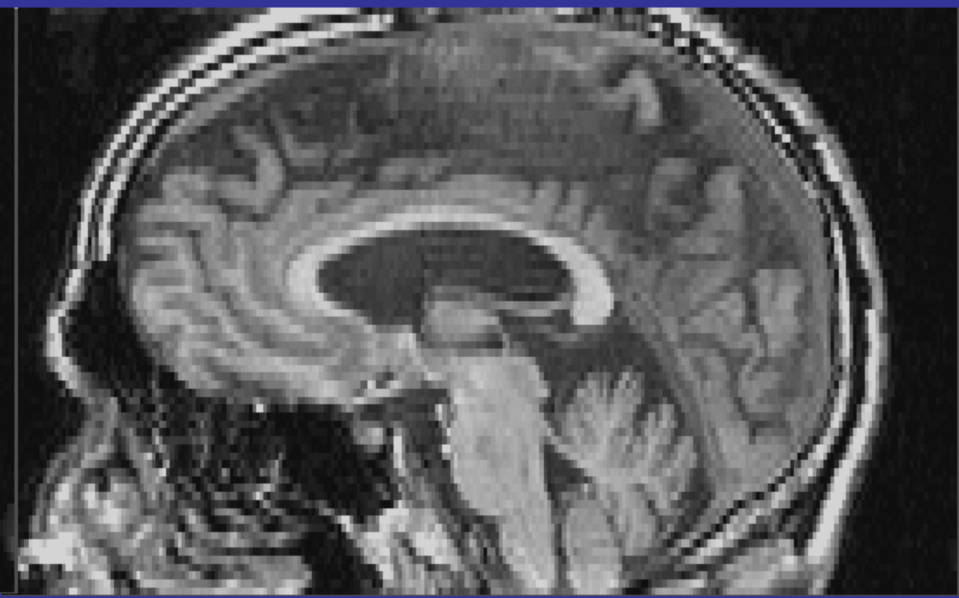


Alcoholic

VA San Diego
Alcohol Study

Brain Abnormalities on MRI in Recently Detox Alcoholics

47 y/o Healthy Control



47 y/o Recently Detoxified Alcoholic

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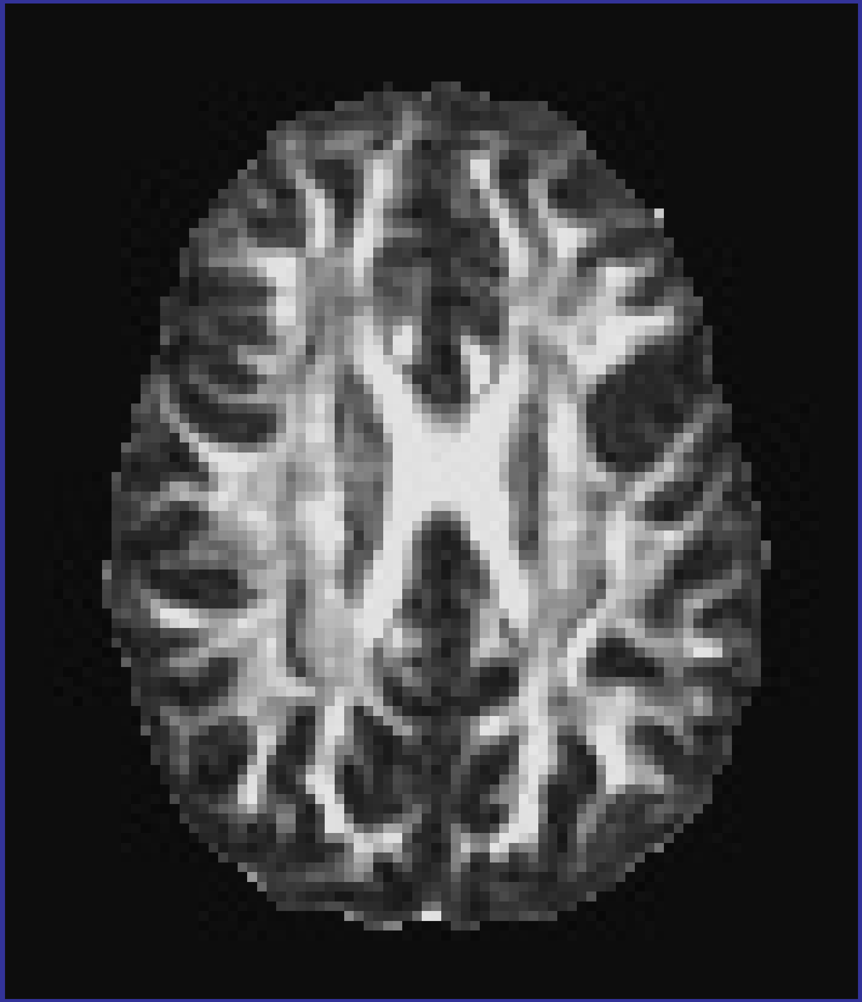
Alcohol Study

Diffusion Tensor Imaging



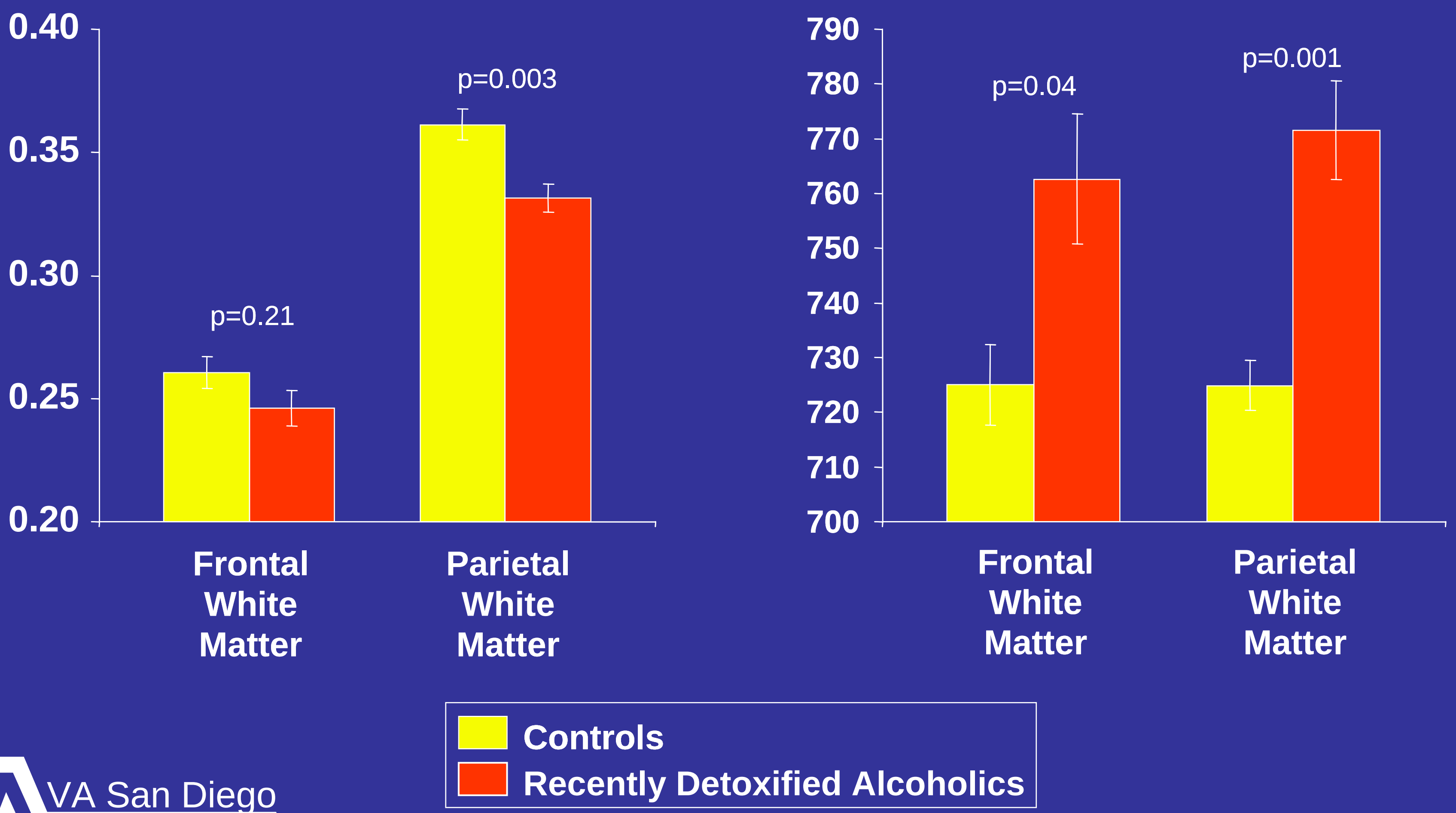
VA San Diego
Alcohol Study

Taylor, et al., 2006

Microstructural Cerebral Disruption in Alcoholics Detected with DTI

Fractional Anisotropy

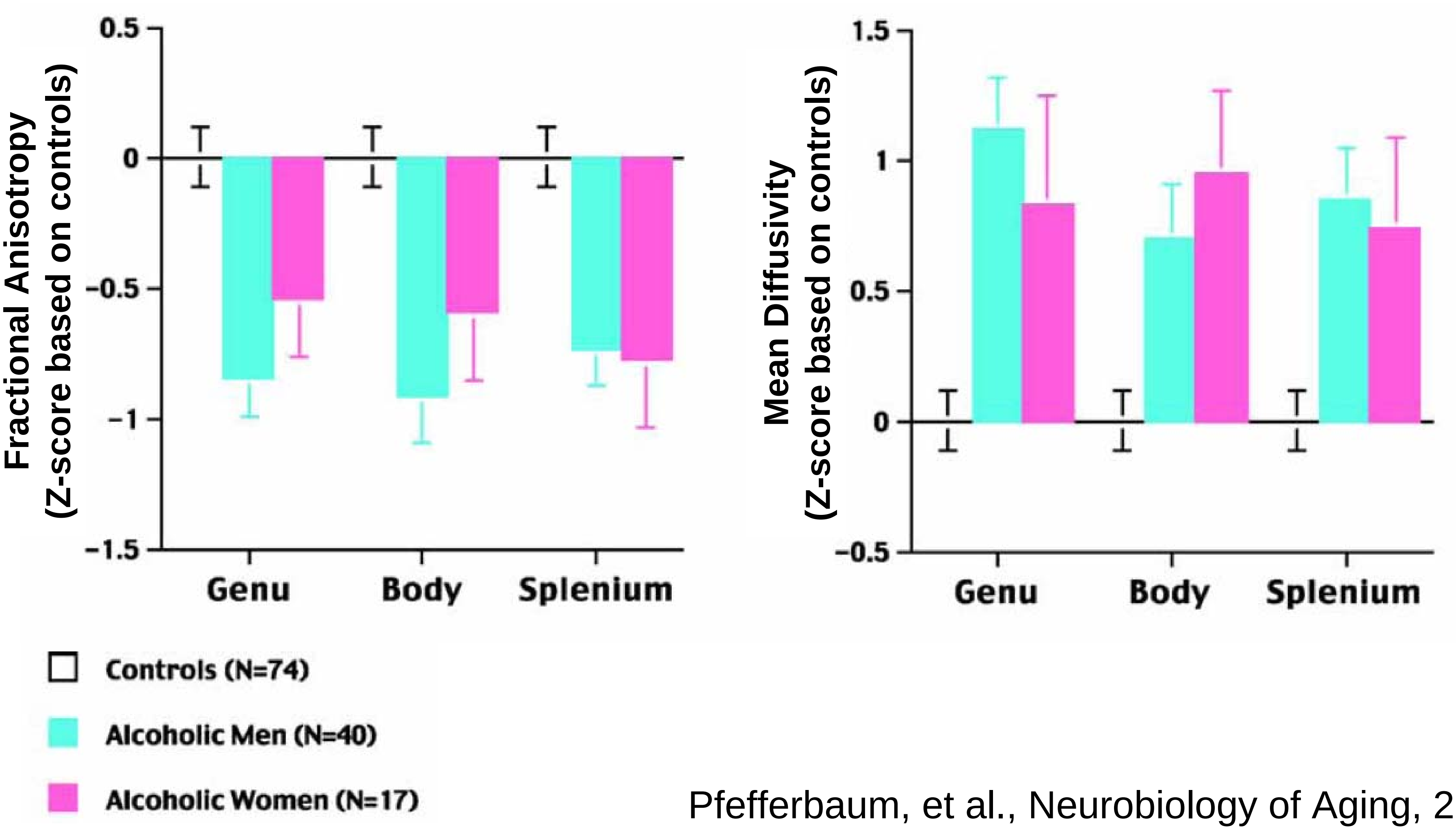
Average Diffusion Coefficient



VA San Diego
Alcohol Study

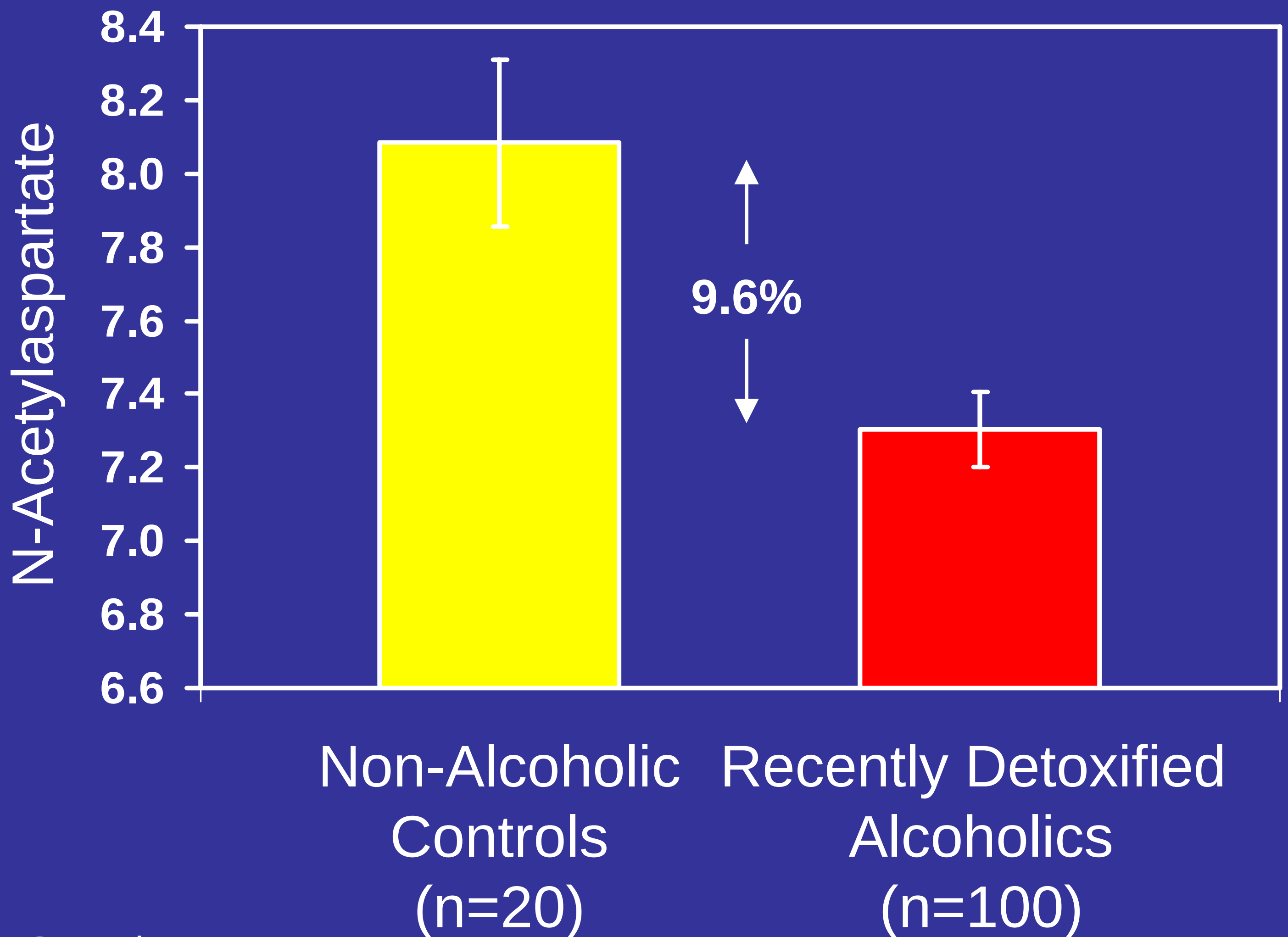
Taylor, et al., 2006

DTI of Corpus Callosum in Alcoholics



Pfefferbaum, et al., Neurobiology of Aging, 2007

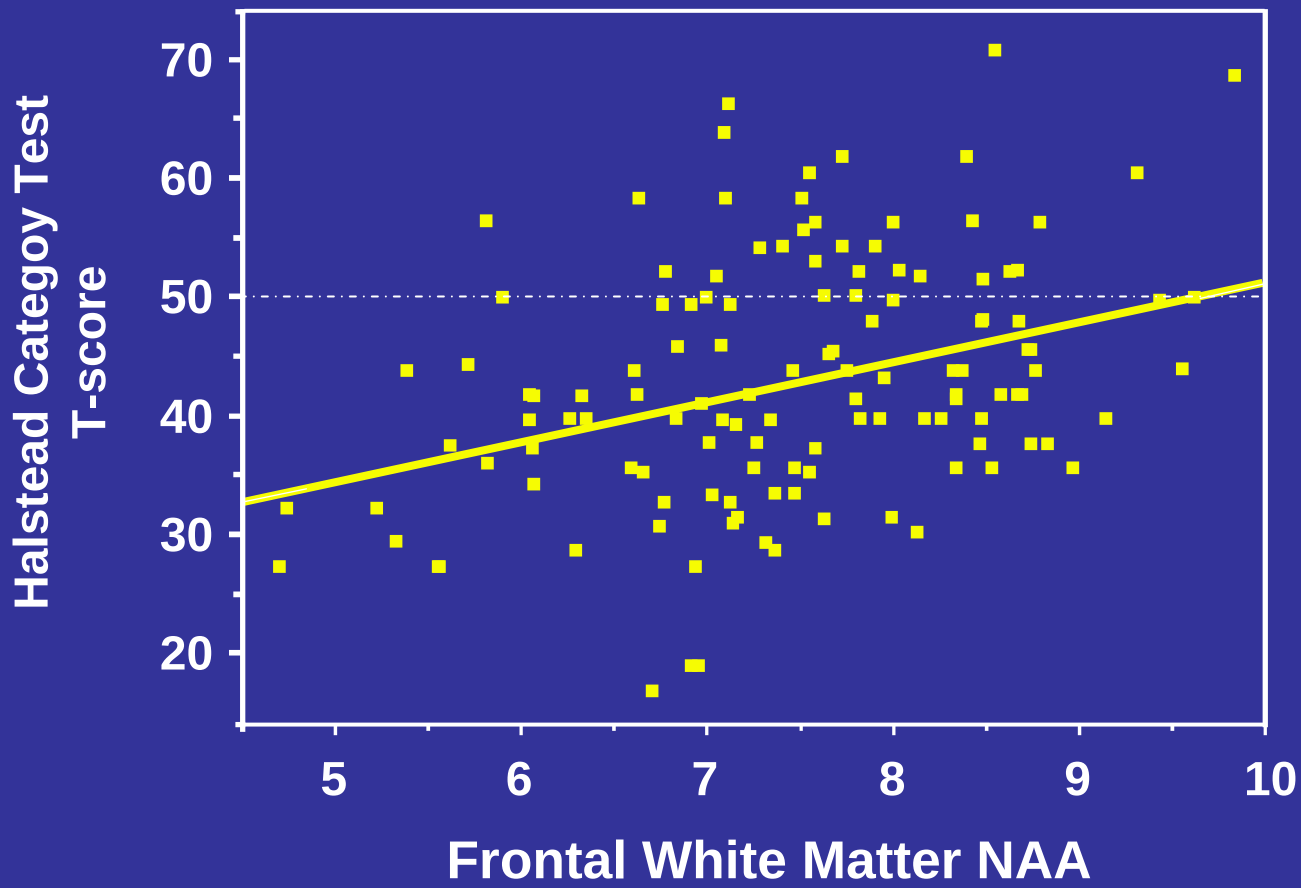
Lower Frontal White Matter NAA in Recently Detoxified Alcoholics



VA San Diego
Alcohol Study

Taylor, et al, 2004

Lower Frontal White Matter NAA Predicts Poorer Executive Functioning in Recently Detoxified Alcoholics



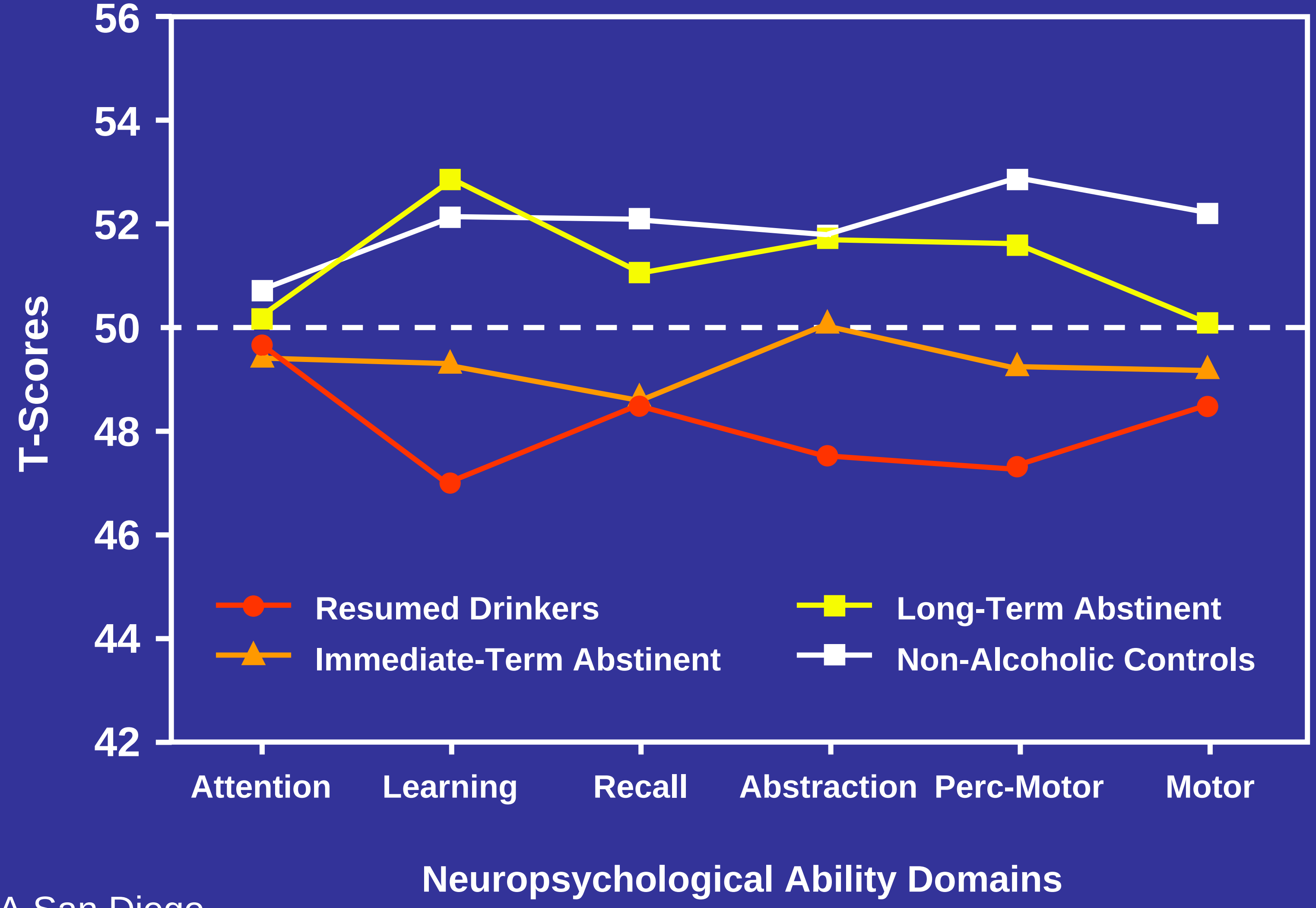
r = 0.31
p = .001

VA San Diego
Alcohol Study

Taylor, et al, 2004

How permanent is the alcohol-induced neuronal injury?

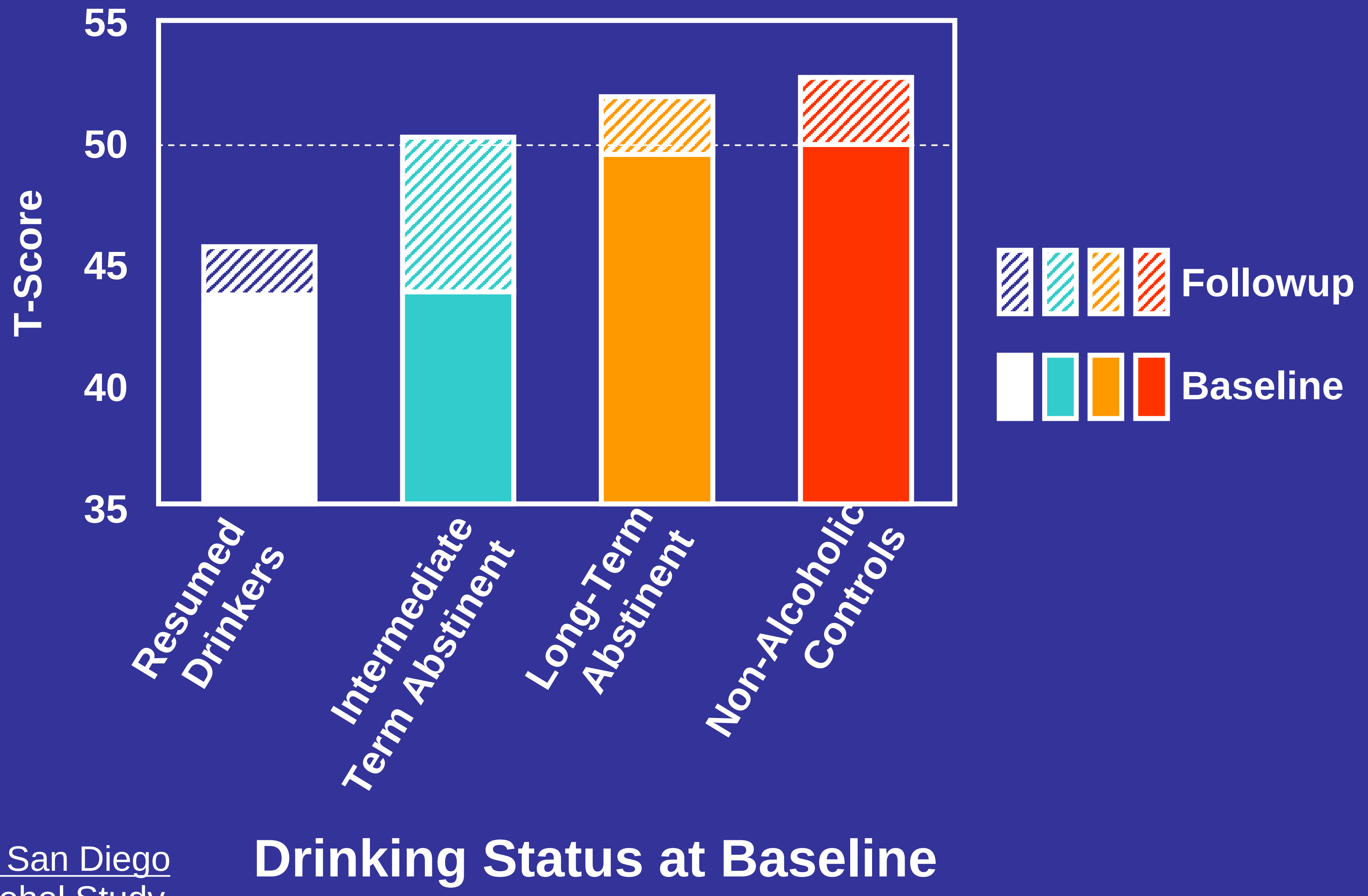
Follow-up NP Performance



VA San Diego
Alcohol Study

Rourke & Grant, 1996

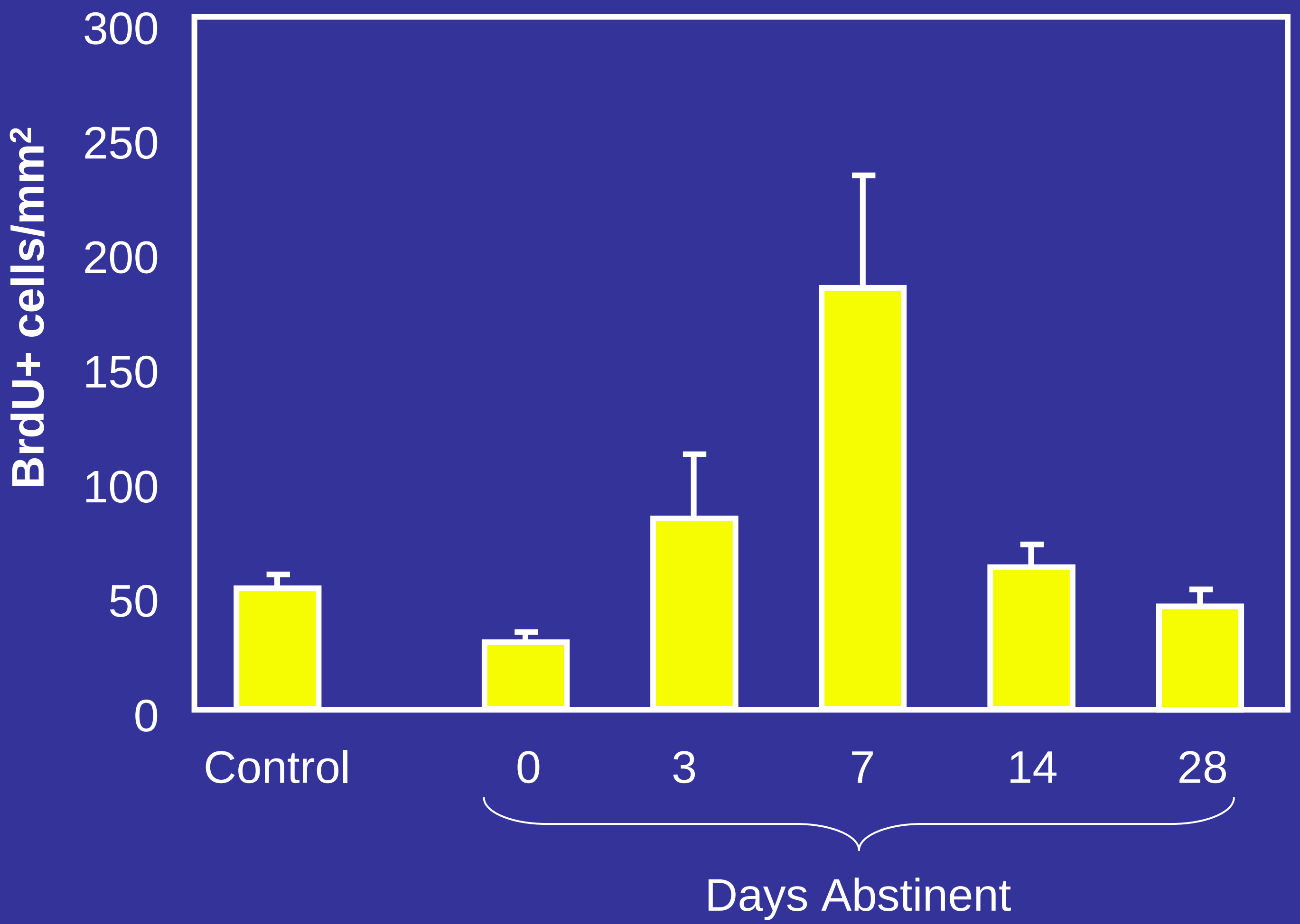
Practice Effect and True NP Improvement in Relation to Length of Abstinence



VA San Diego
Alcohol Study

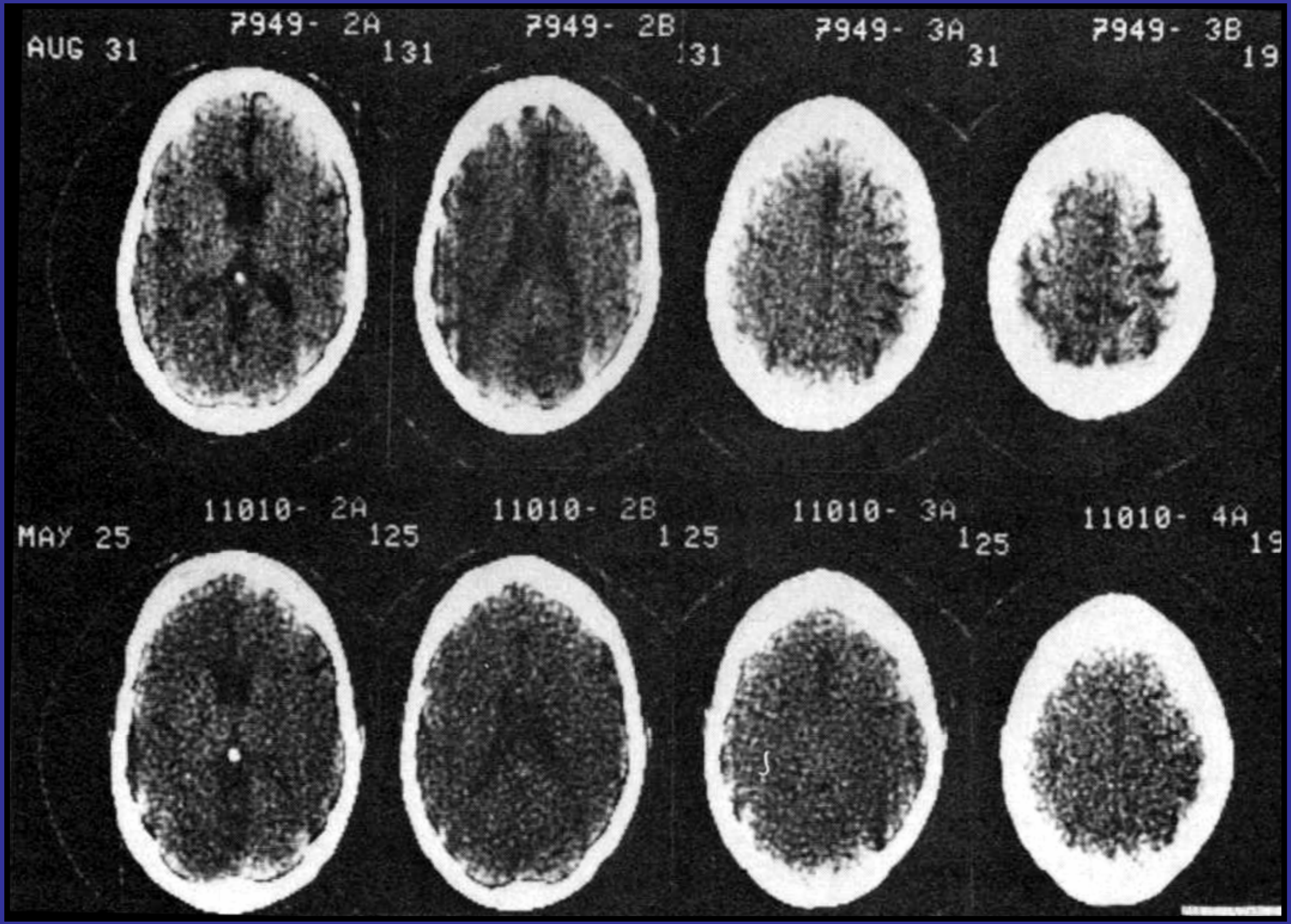
Rourke & Grant, 1999

Alcohol-Induced Reduction in Rat Hippocampal Neuron Proliferation Normalizes with Abstinence



Nixon & Crews, J Neurosci, 2004

Reversible cerebral atrophy in recently abstinent 35-year-old alcoholic



Carlen, et al., Science, 1978

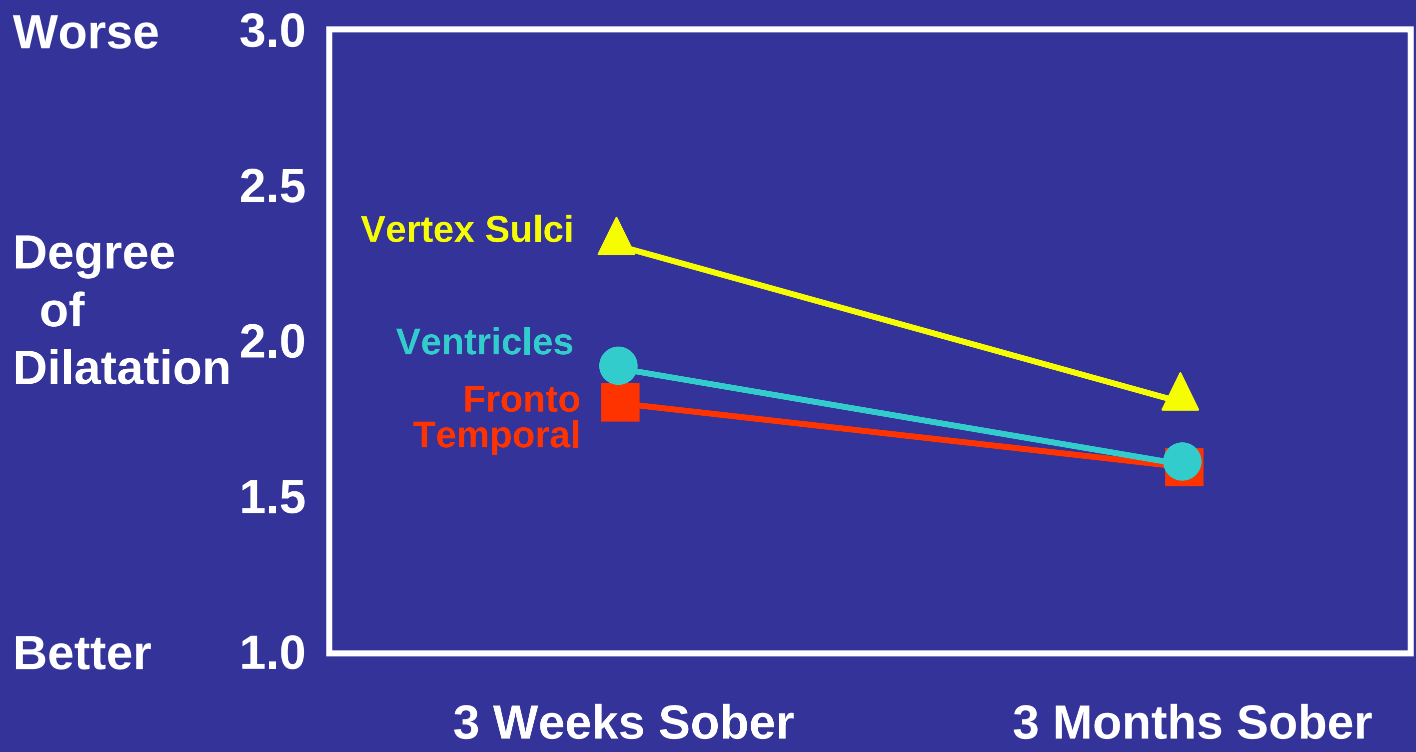
CT Improvement with 2 years Abstinence

Baseline

2 Years Abstinent

Markman, et al., Liver Transplantation, 2000

Improved CT with Three Months Sobriety



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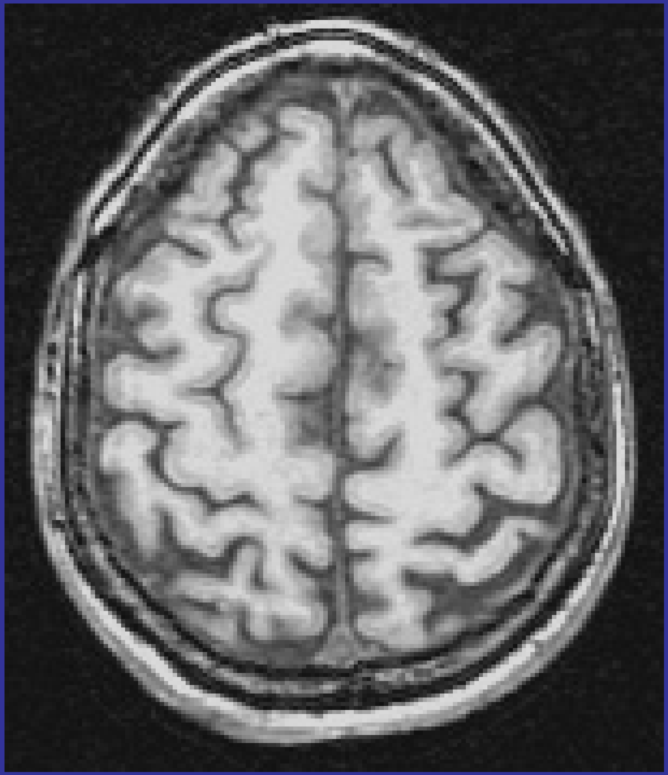
Alcohol Study

Brain MRI Improvement with Abstinence



During Treatment

1 ½ Years Later

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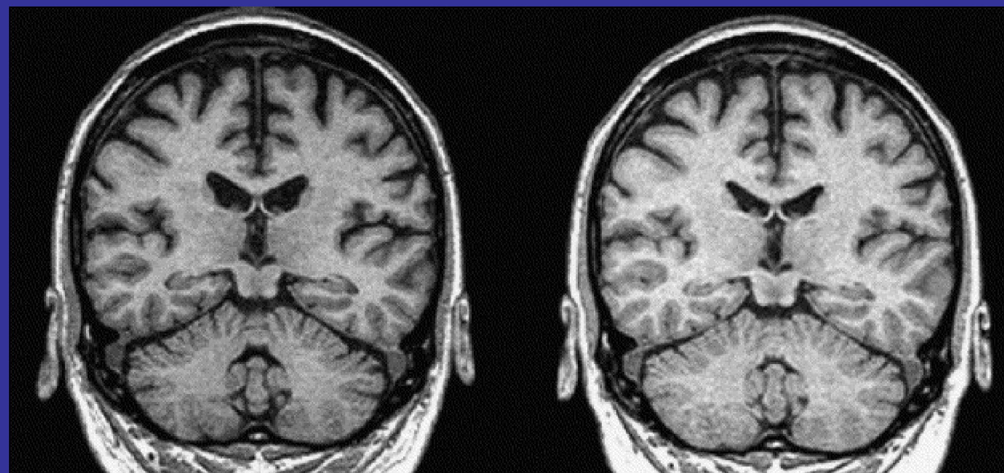
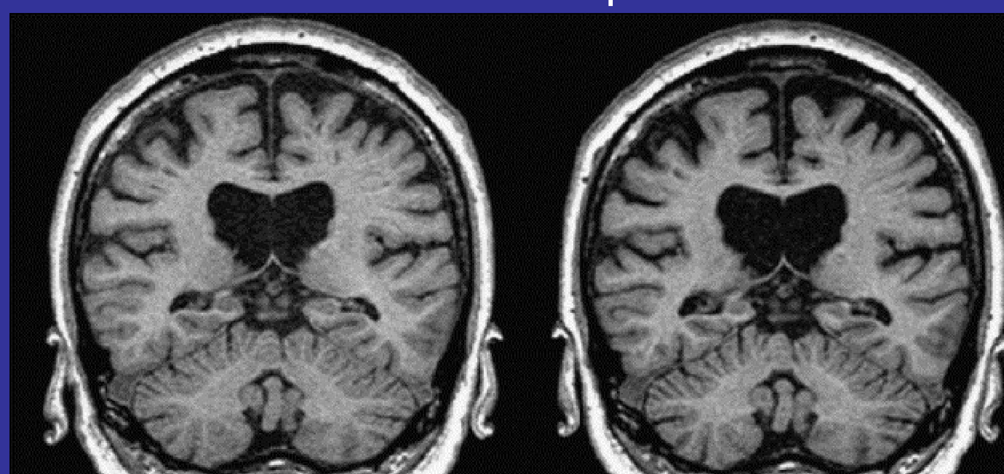
Alcohol Study

MR Improvement with Abstinence

Baseline 8 Months Abstinent

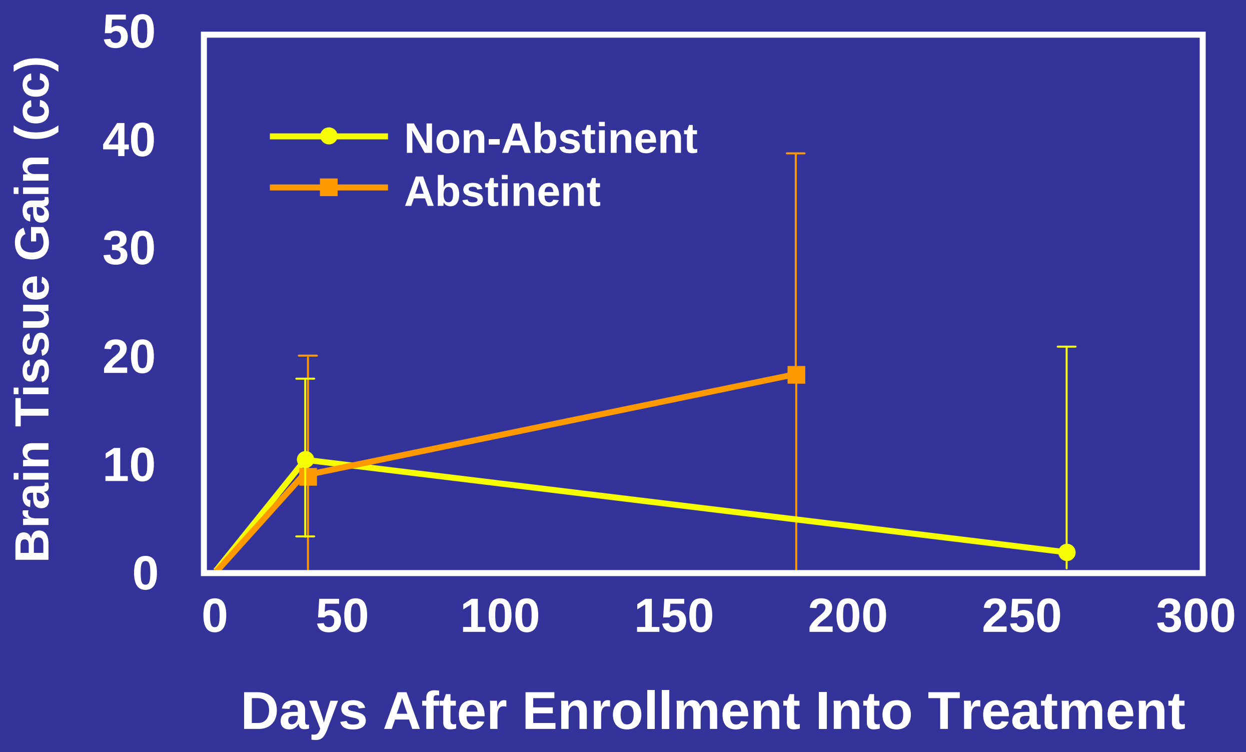


Baseline Relapsed after 10 months



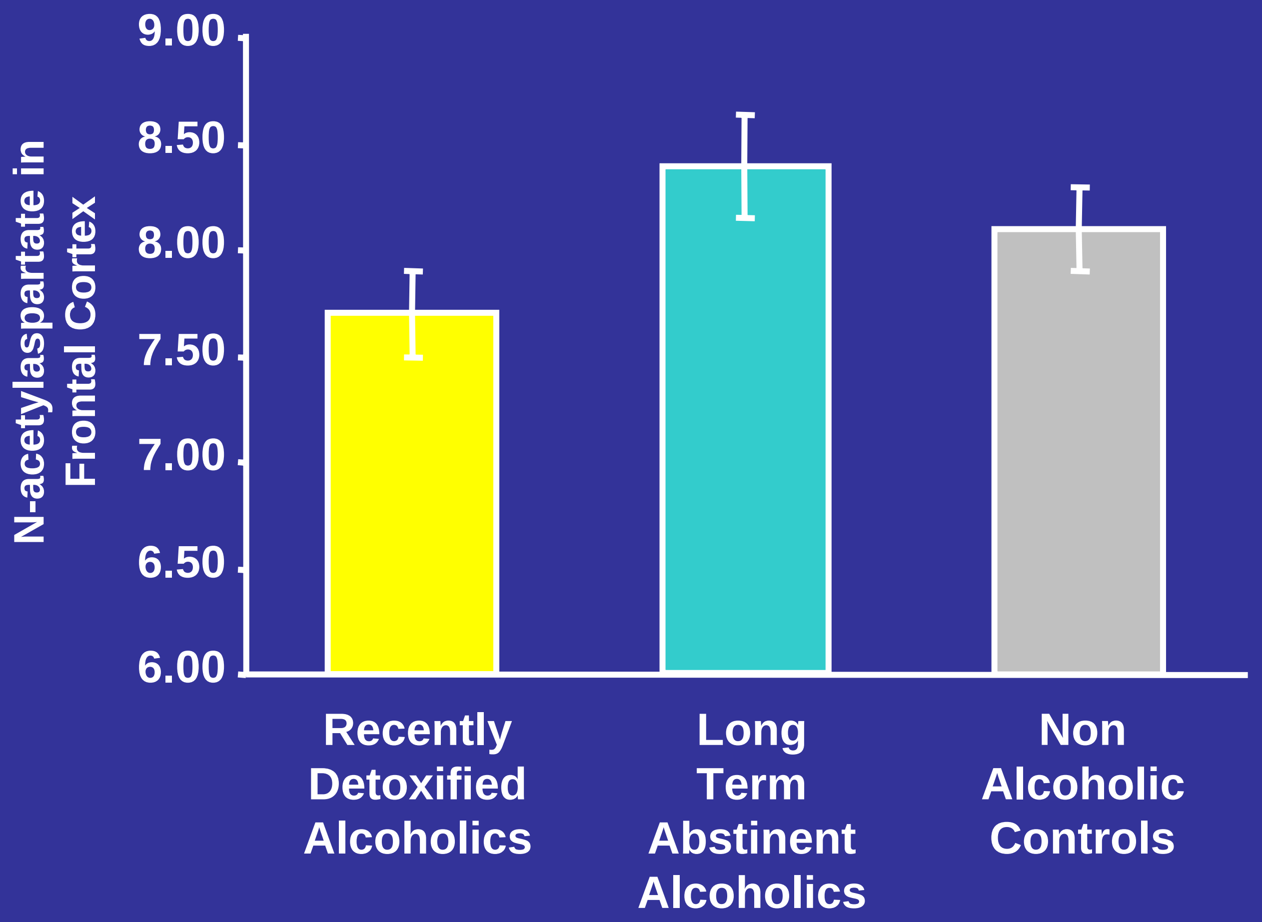
Gazdzinski, et al, Drug and Alcohol Dependence, 2005

MR Brain Volume Gain with Long-term Abstinence



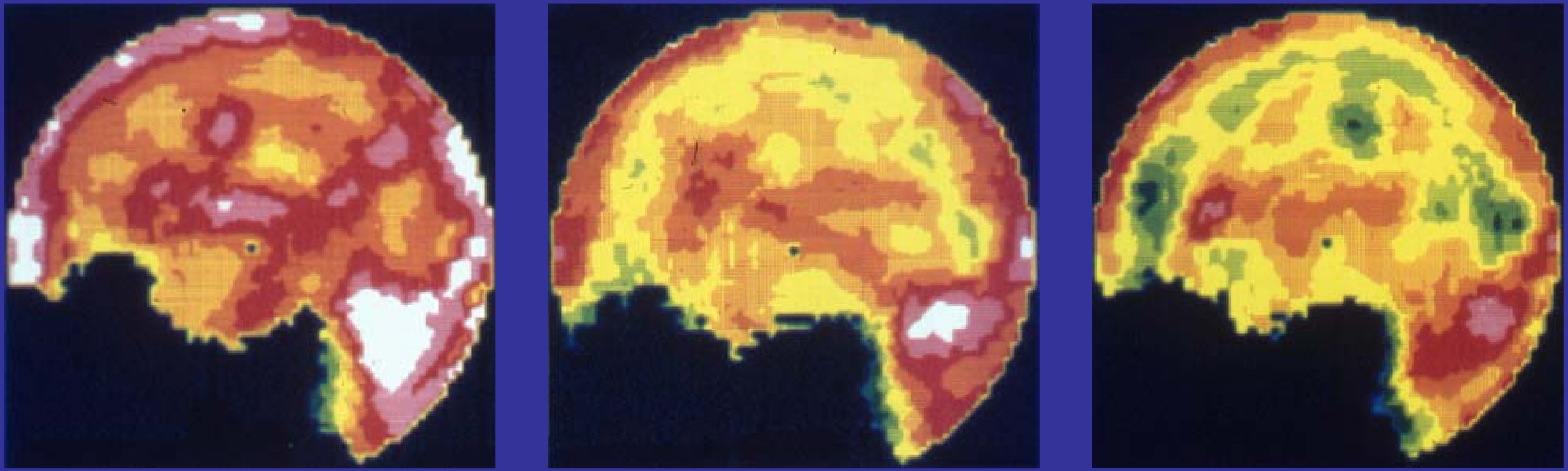
Gazdzinski, et al, Drug and Alcohol Dependence, 2005

Evidence for Improved NAA with Abstinence



Schweinsburg, et al, 2004

Decreased Cerebral Blood Flow in Alcoholics and Partial Recovery after Abstinence



Non-alcoholic Controls

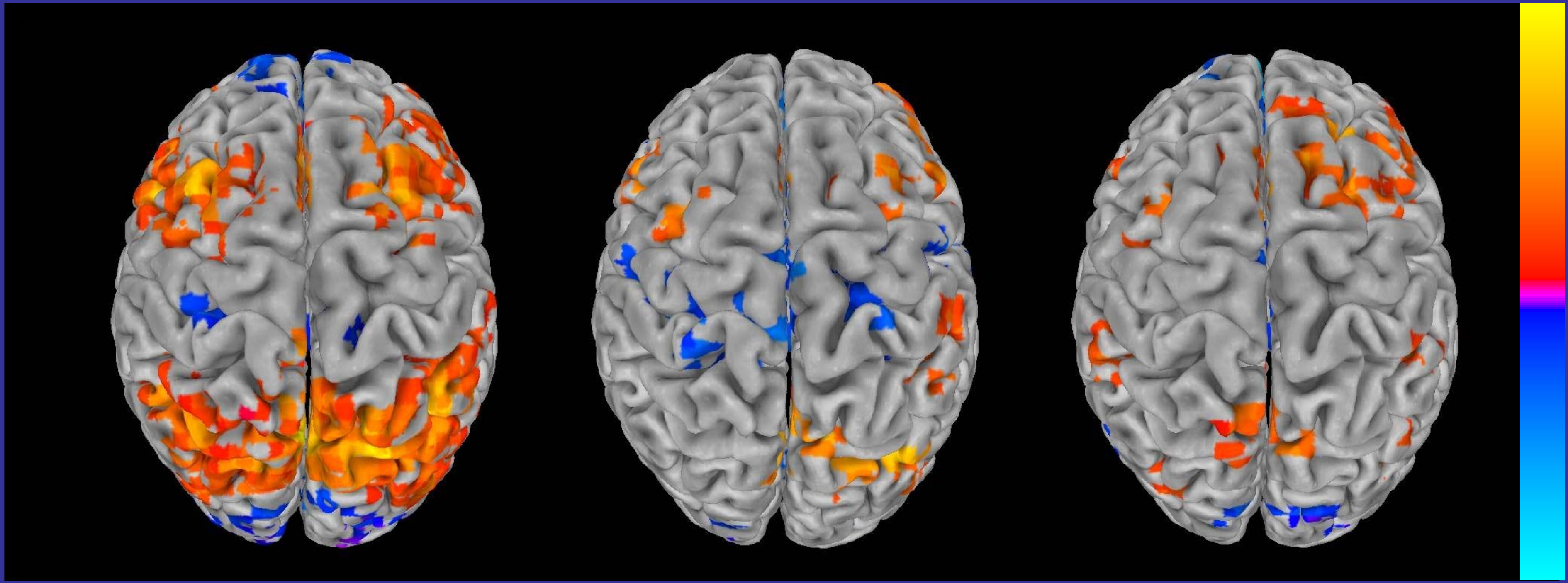
Long-term Abstinent Alcoholics

Recently Detoxified Alcoholics

VA San Diego
Alcohol Study

Alhassoon, et al., 1998

Increased Bold Response during Spatial Working Memory in Alcoholics with Recovery after Abstinence



Recently Detoxified **Long-term Abstinent** **Control**

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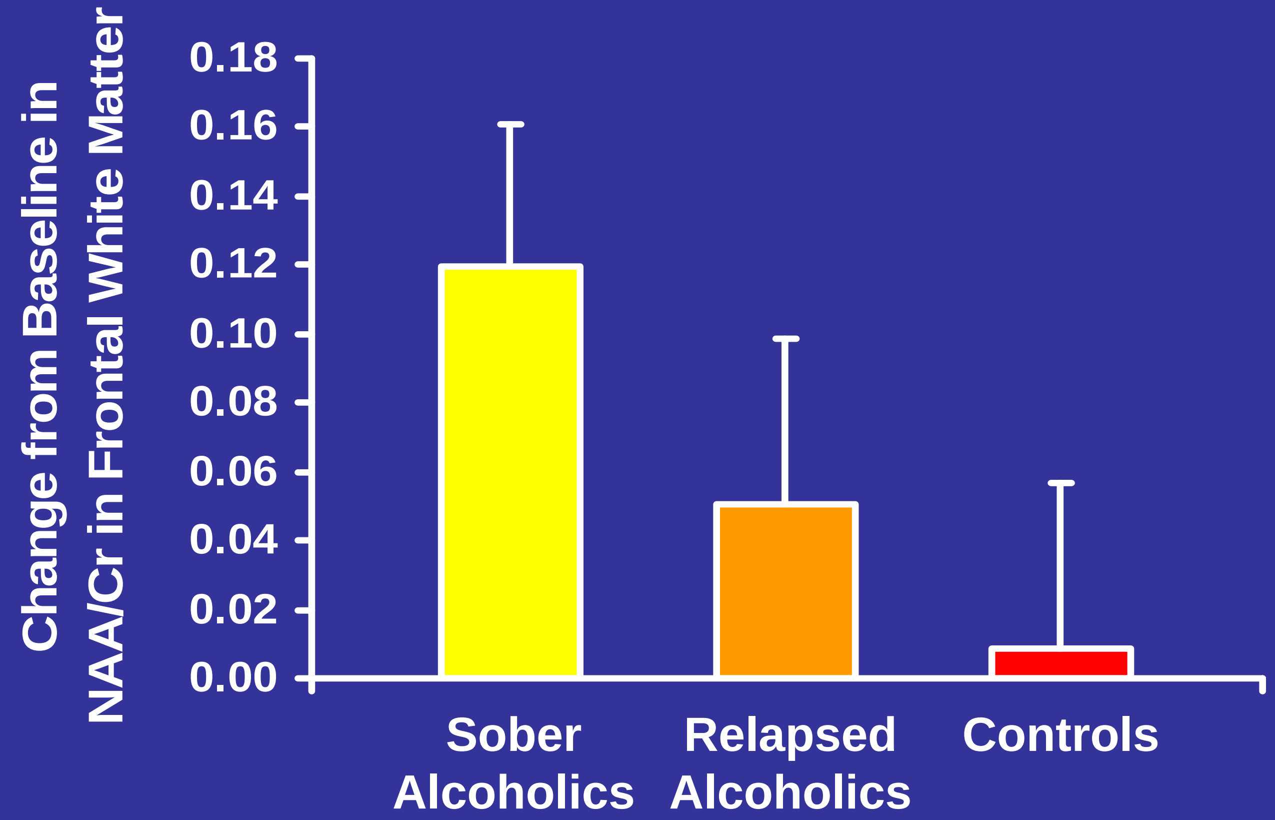
Alcohol Study

Schweinsburg, et al, 2004

Greater Frontal White Matter NAA/Cr Improvement with Long-Term Abstinence (2-Year followup)

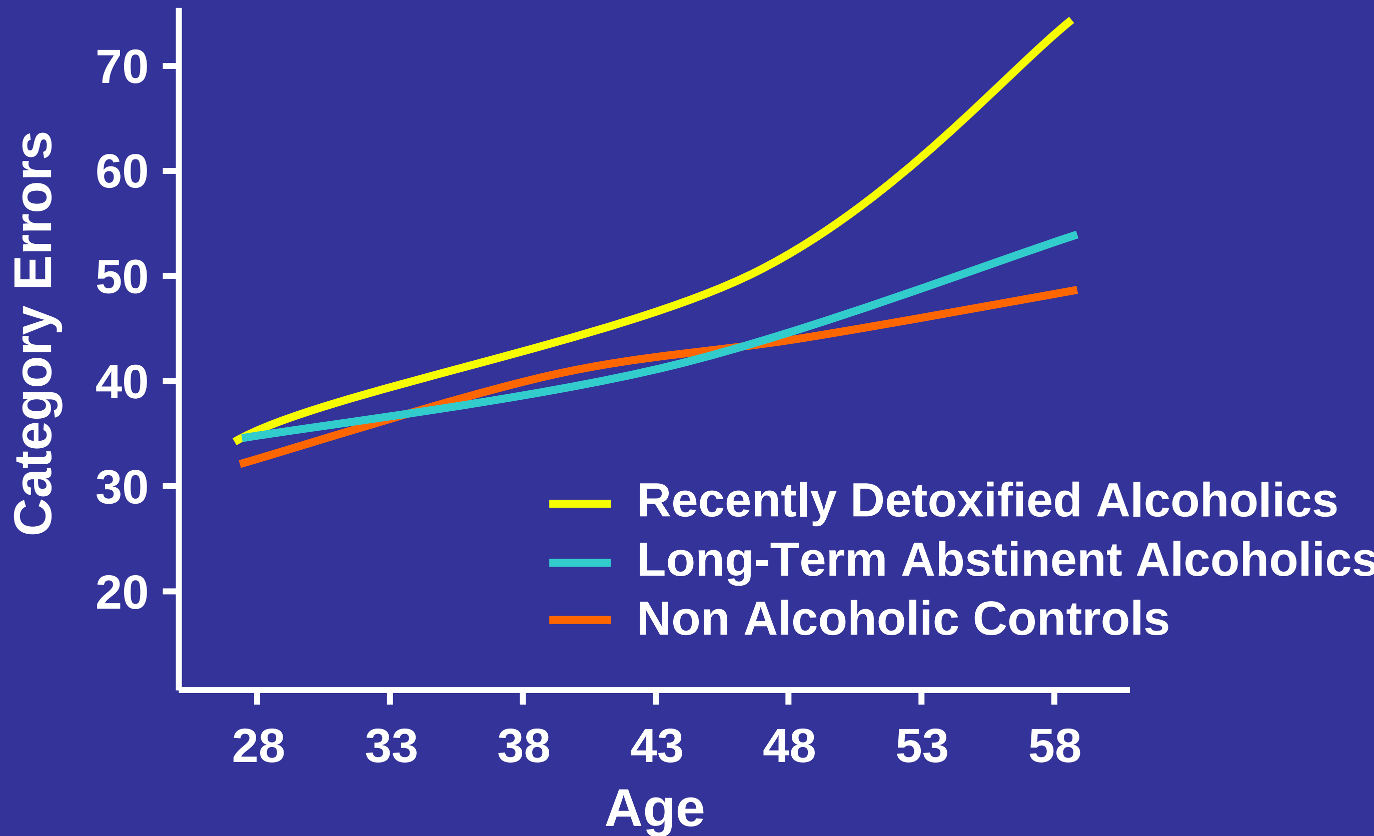


VA San Diego
Alcohol Study

Taylor, et al., 2004

What factors moderate alcoholism associated neurocognitive impairment and improvement?

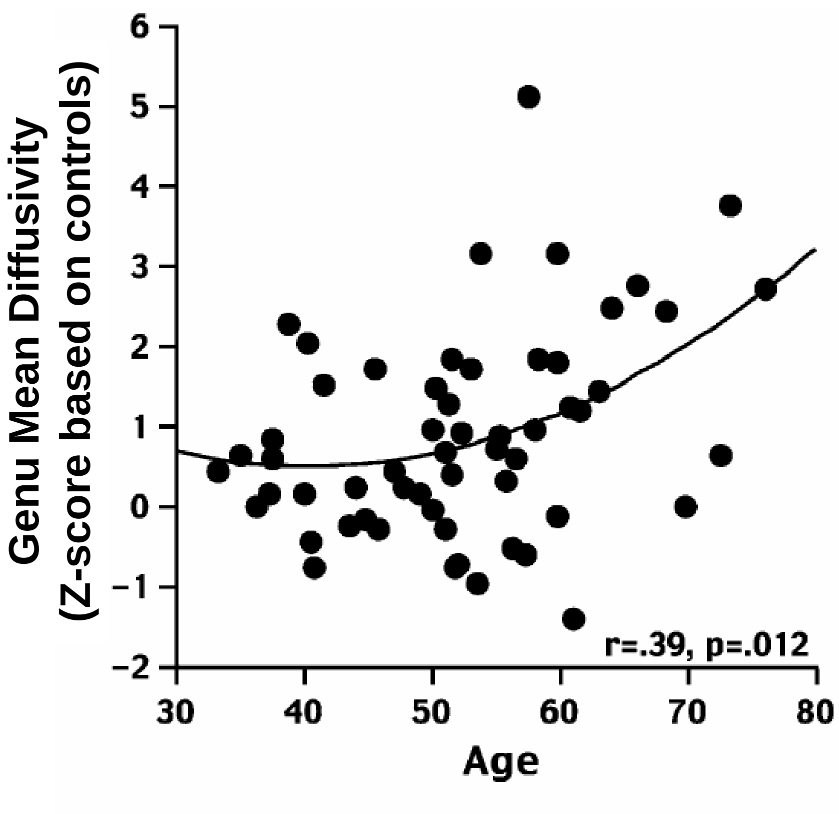
Differentially Poorer Category Test Performance is Associated with Age in Recently Detoxified Alcoholics

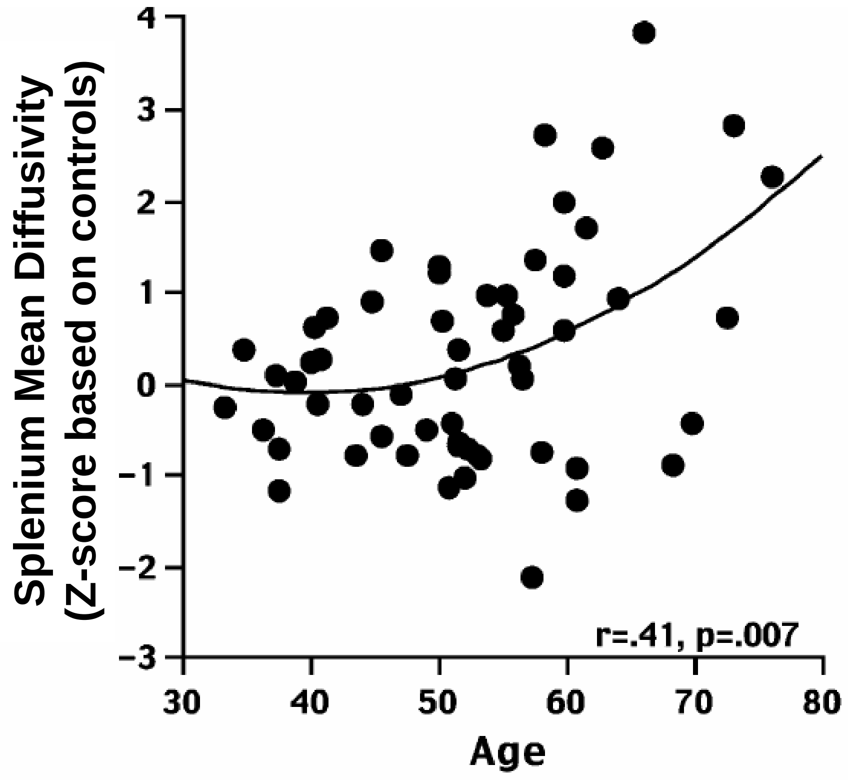


VA San Diego
Alcohol Study

Rourke & Grant, 1996

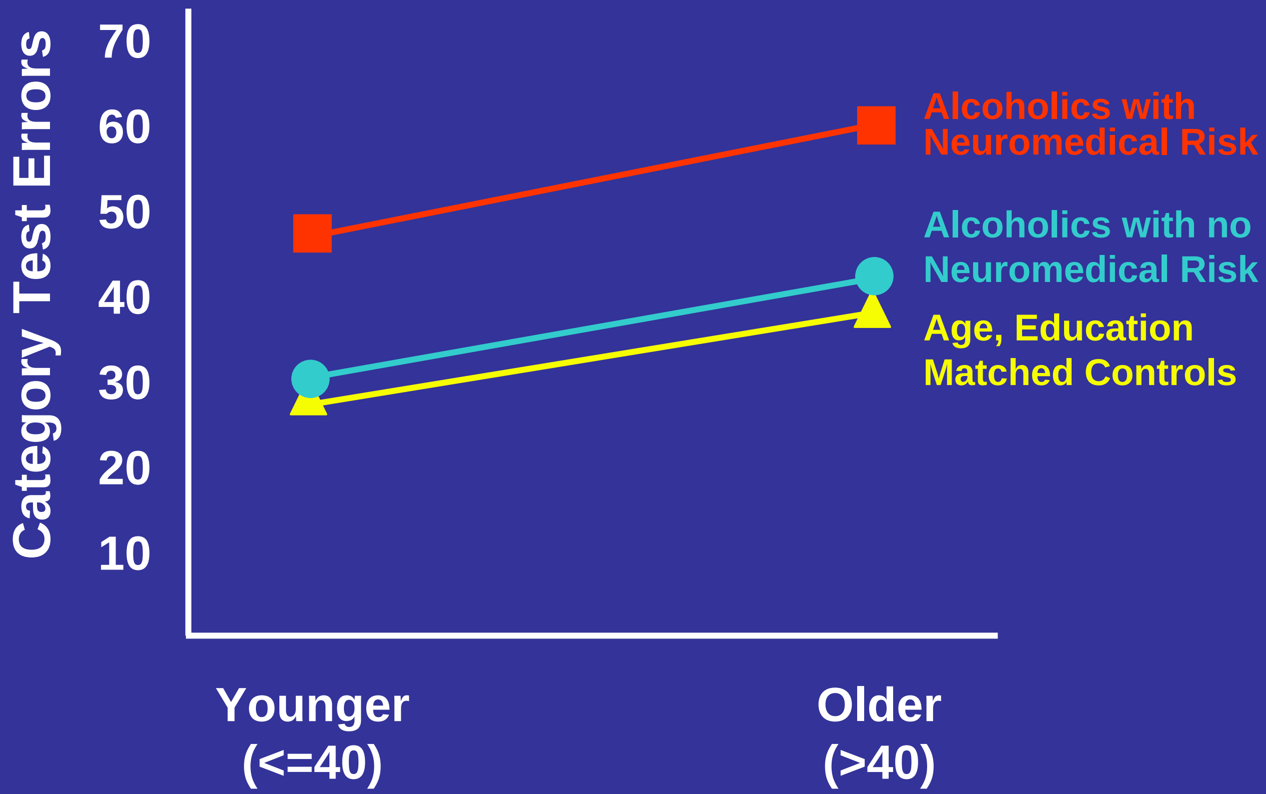
Impact of Age on Mean Diffusivity in Corpus Callosum in Alcoholics





Pfefferbaum, et al., Neurobiology of Aging, 2007

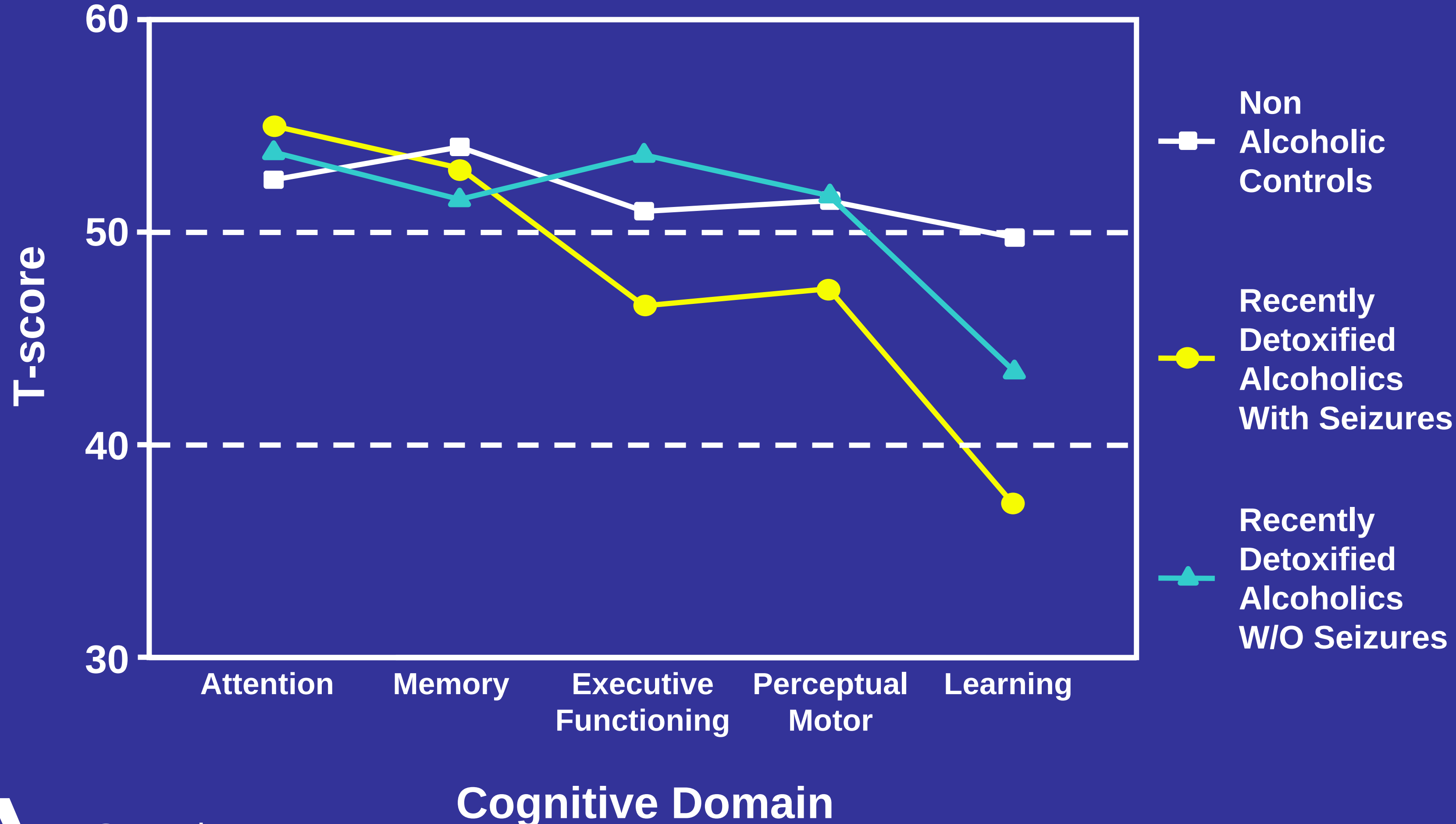
Poorer Category Test Performance in Alcoholics with Neuromedical Risk



VA San Diego
Alcohol Study

Rourke & Grant, 1996

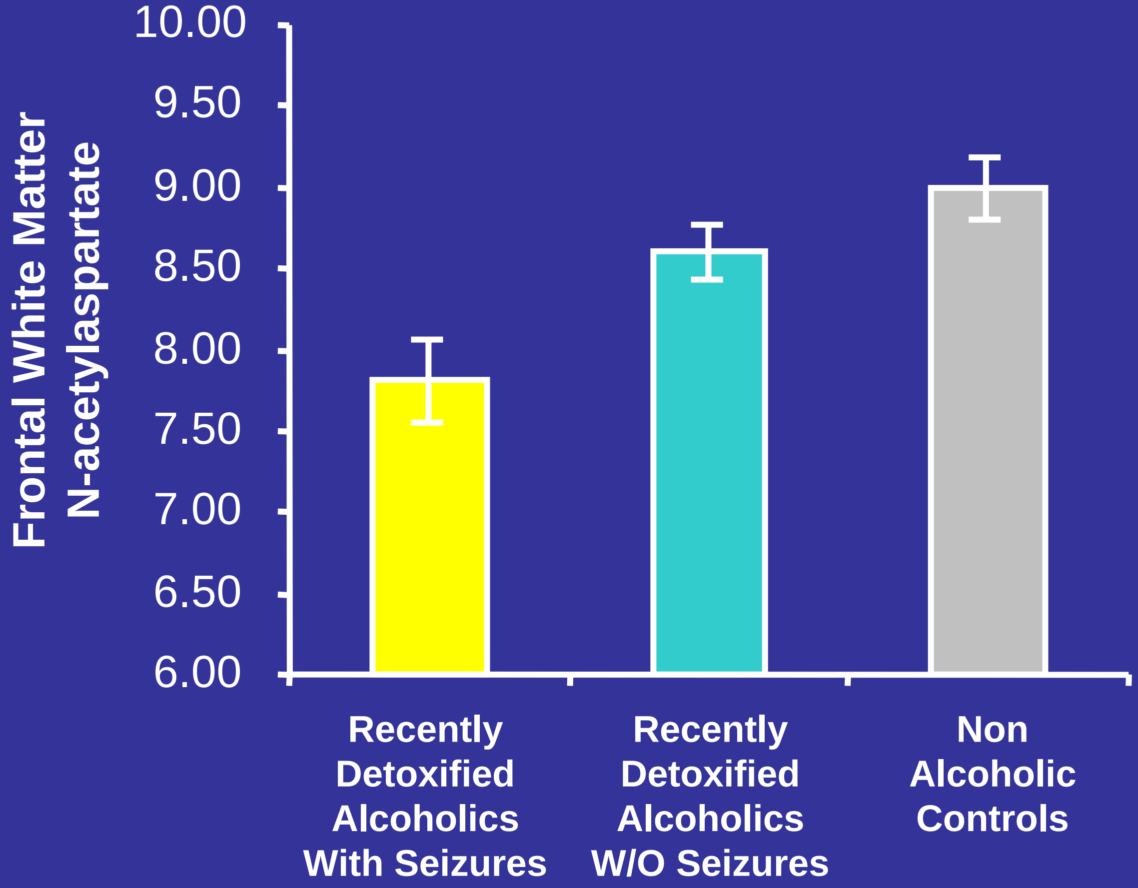
Alcohol Withdrawal Seizures Associated with Greater NP Deficits



VA San Diego
Alcohol Study

Schweinsburg, et al, 2002

Alcohol Withdrawal Seizures Associated with Greater Brain Injury



VA San Diego
Alcohol Study

Schweinsburg, et al, 2002

Factors Related to Changes in NP Performance Among Alcoholics

	Neurobehavioral Performance			
	Improved	Unchanged	Worse	p-value
Age	43.6	43.7	49.6	.05
Education	13.4	12.9	12.3	NS
Interim Medical Risk Score*	1.5	1.9	3.5	.001

*Includes learning disability, head injury, toxic reaction, neurological, anoxic, and sickness risks

VA San Diego
Alcohol Study

Grant, et al., 1984

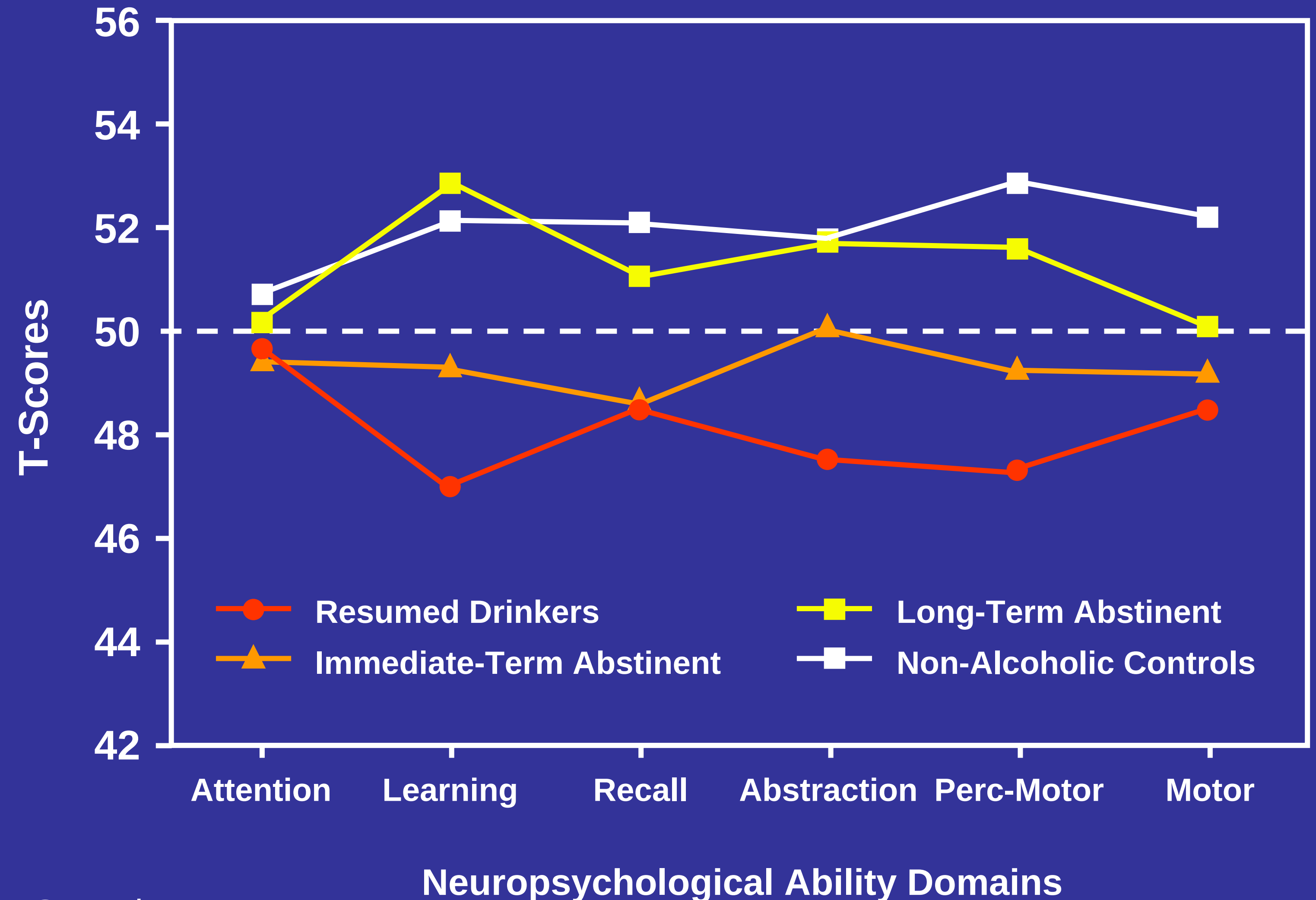
Interim Drinking Rather than Lifetime Consumption Predicts NP Change at Followup

	Neurobehavioral Performance			
	Improved	Unchanged	Worse	p-value
Grams ethanol per week during interim	87.7	139.6	462.4	.001
Grams ethanol per drinking week during interim	136.5	282.7	681.8	.01
Total ethanol (kg) during interim	8.7	23.1	68.0	.02
Years of Alcoholism	11.4	14.7	17.6	NS
Lifetime average weekly ethanol (g) in drinking years	681.4	875.5	739.4	NS

VA San Diego
Alcohol Study

Grant, et al., 1984

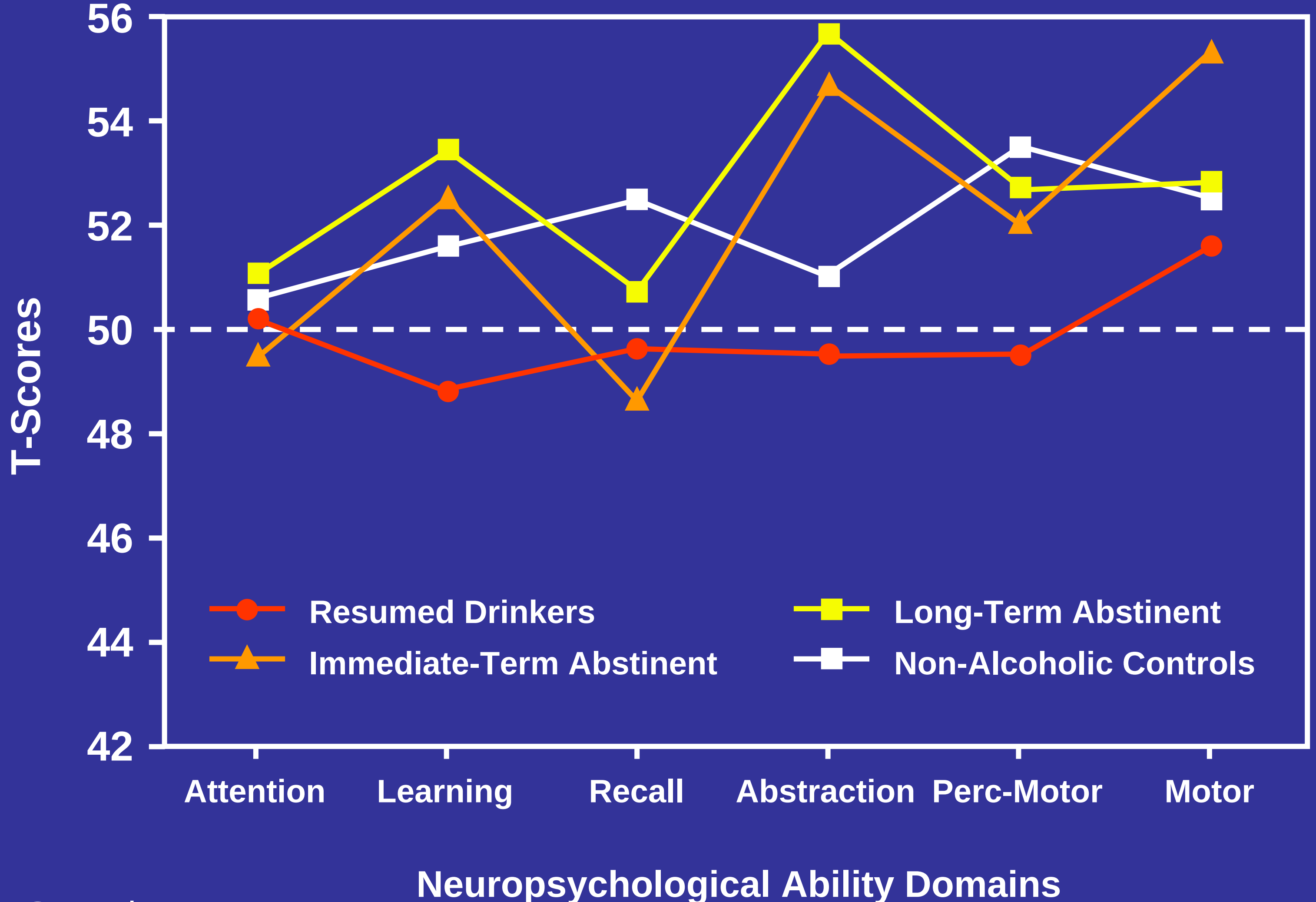
Follow-up NP Performance



VA San Diego
Alcohol Study

Rourke & Grant, 1996

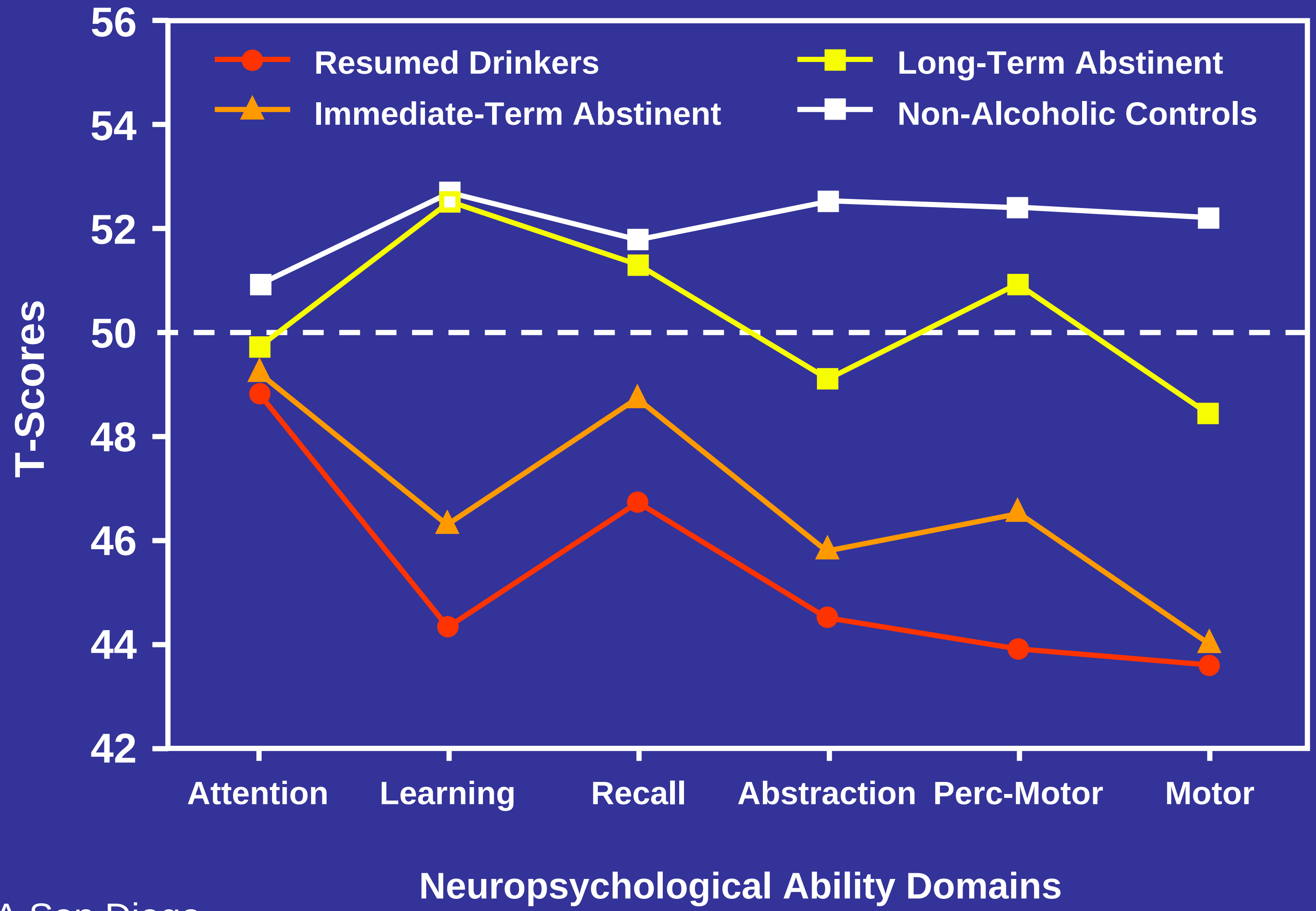
Follow-up NP Performance (YOUNGER ONLY)



VA San Diego
Alcohol Study

Rourke & Grant, 1996

Follow-up NP Performance (OLDER ONLY)

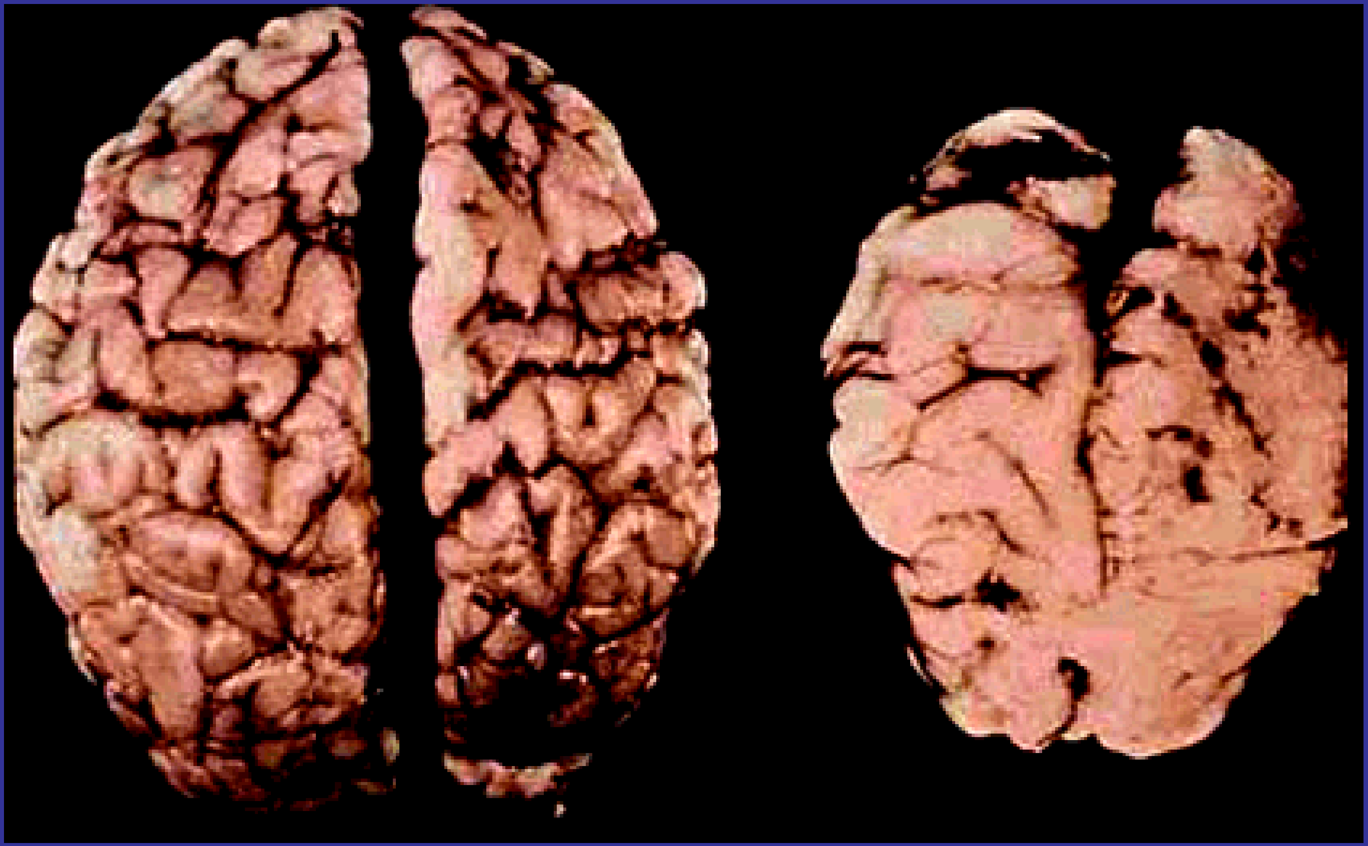


VA San Diego
Alcohol Study

Rourke & Grant, 1996

Alcohol Effects on Development

"THE UGLY"



Normal Infant

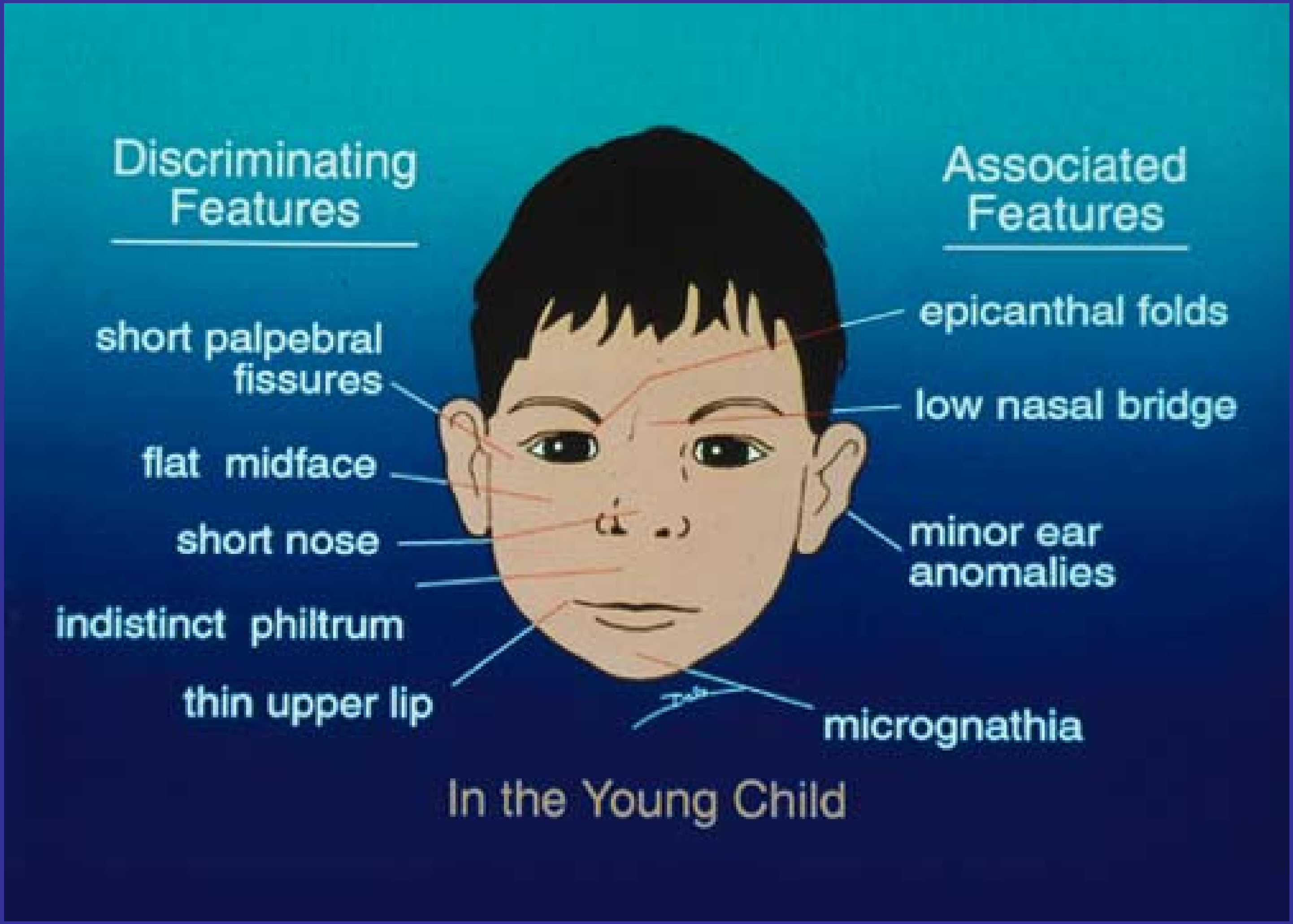
Fetal Alcohol Syndrome

Fetal Alcohol Syndrome

- Specific pattern of facial features
- Pre- and/or postnatal growth deficiency
- Evidence of central nervous system dysfunction

Photo courtesy of Teresa Kellerman

Features of Fetal Alcohol Syndrome



Streissguth 1994

FAS – Only the tip of the iceberg

- Fetal alcohol syndrome
- Fetal alcohol effects ARND/ARBD*
- Appear normal but clinical suspect

*Alcohol related neurodevelopment disorder/alcohol related birth defects

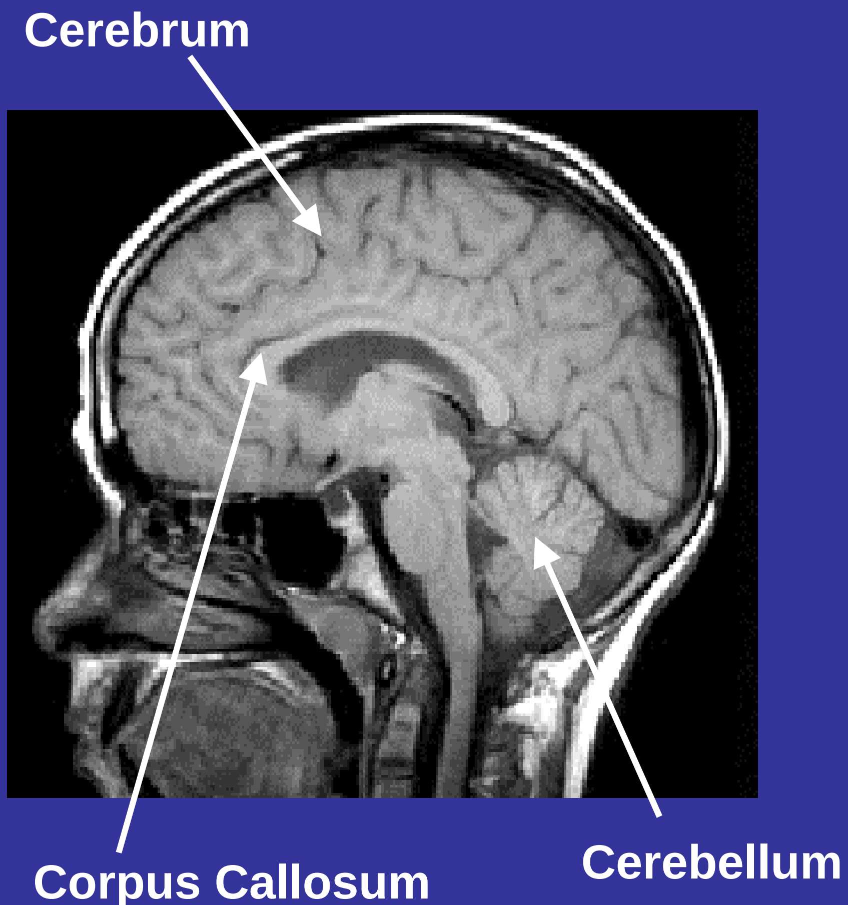
Adapted from Streissguth

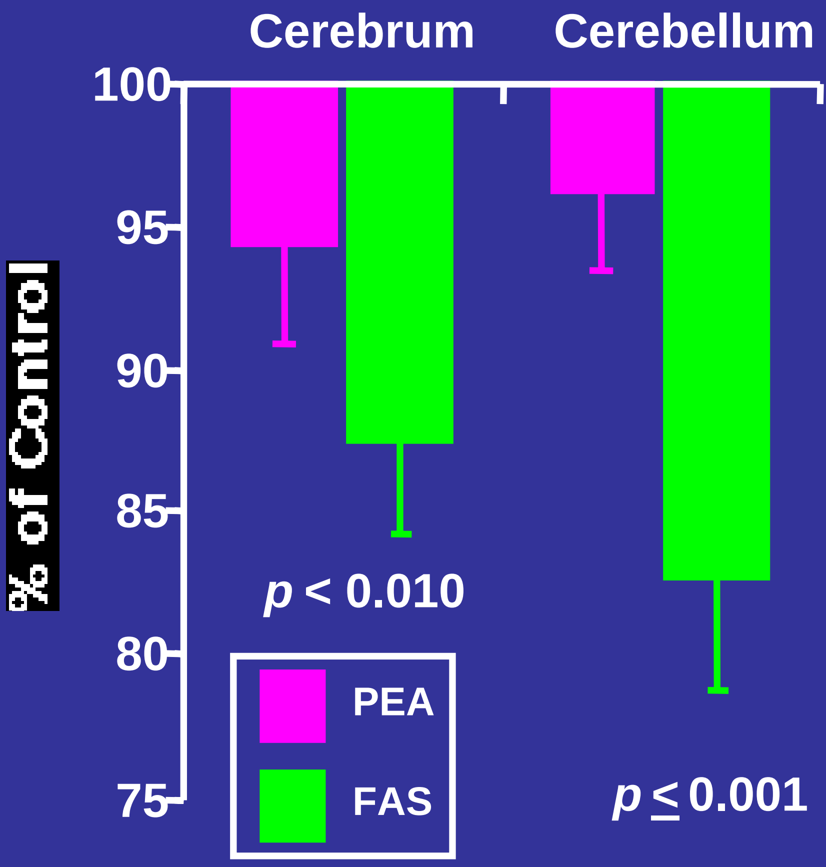
Prevalence of FAS (rates per 1000)

Alaska	0.2	non AI/AN
	3	AI/AN
Aberdeen	2.7	AI/AN
BDMP	0.7	
Atlanta	0.1	
	0.3	FAS pFAS
IOM	0 .5 - 2.0	
	2 - 8.5	AI/AN

Seattle	2.8-3.1
Cleveland	4.6
Roubaix	1.3-4.8
Seattle FASD	9.1
school study	3.1
South Africa	4.1
Western Cape	7.4
FAS and PFAS	8.9

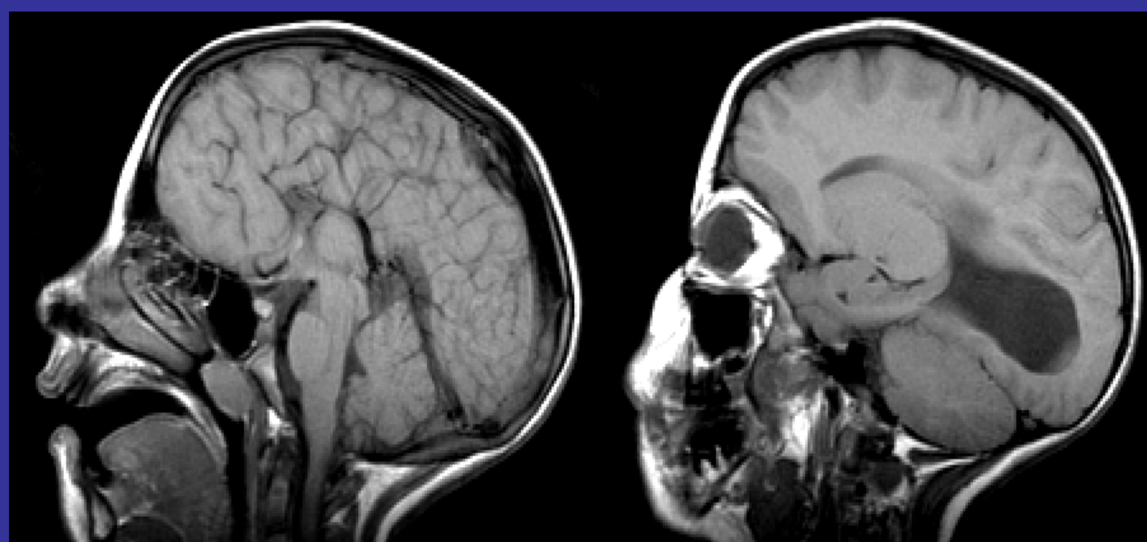
Change in Brain Size





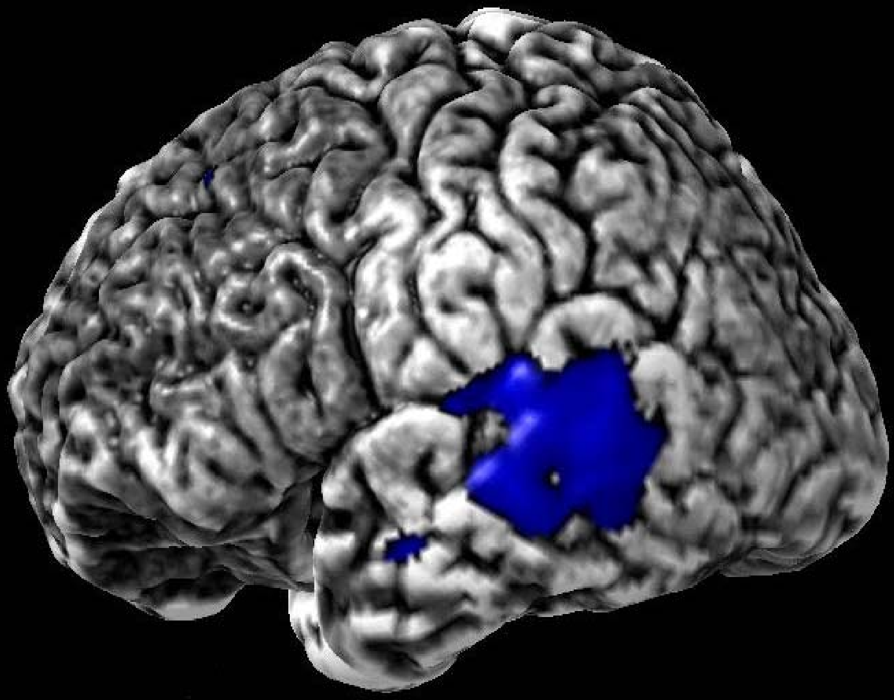
Mattson et al., Neurotoxicology and Teratology, 1994

Corpus Callosum Abnormalities

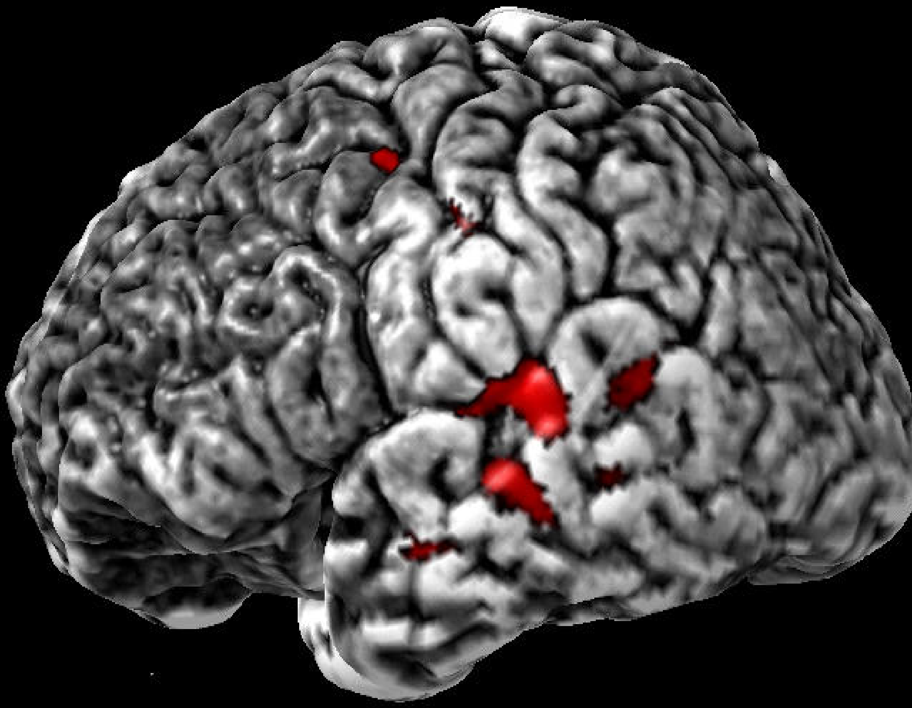


Mattson, et al., 1994; Mattson & Riley, 1995; Riley et al., 1995

Brain Mapping in PAE



Gray Matter Density Increase



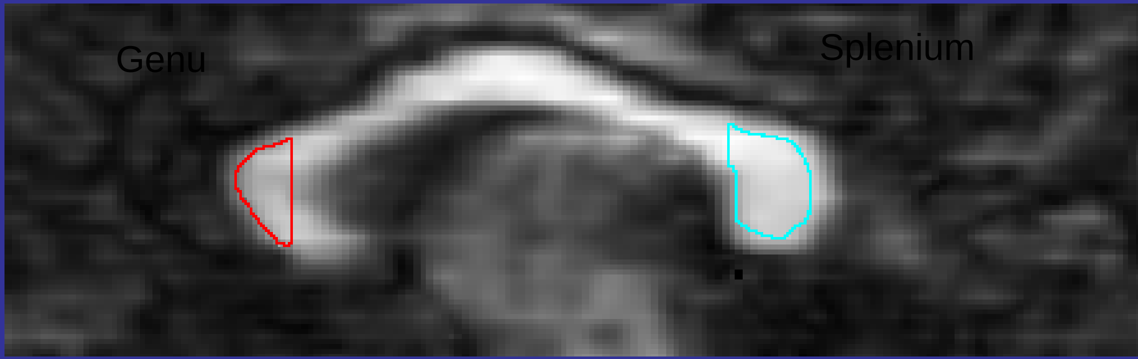
White Matter Density Decrease

Sowell et al., Neuroreport, 2001

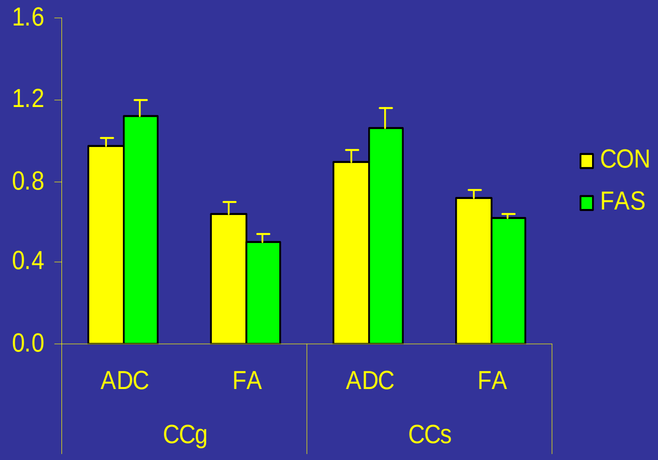
Prenatal Alcohol Exposure and White Matter in the Corpus Callosum of Young Adults

CORPUS CALLOSUM

Diffusion Tension Image. Midsagittal slice, demonstrating the regions of interest of the genu (CCg) and the splenium (CCs) of corpus callosum.



Comparison of ADC and FA in corpus callosum of adults with FAS and Controls demonstrating decreased integrity of white matter in alcohol-exposed individuals

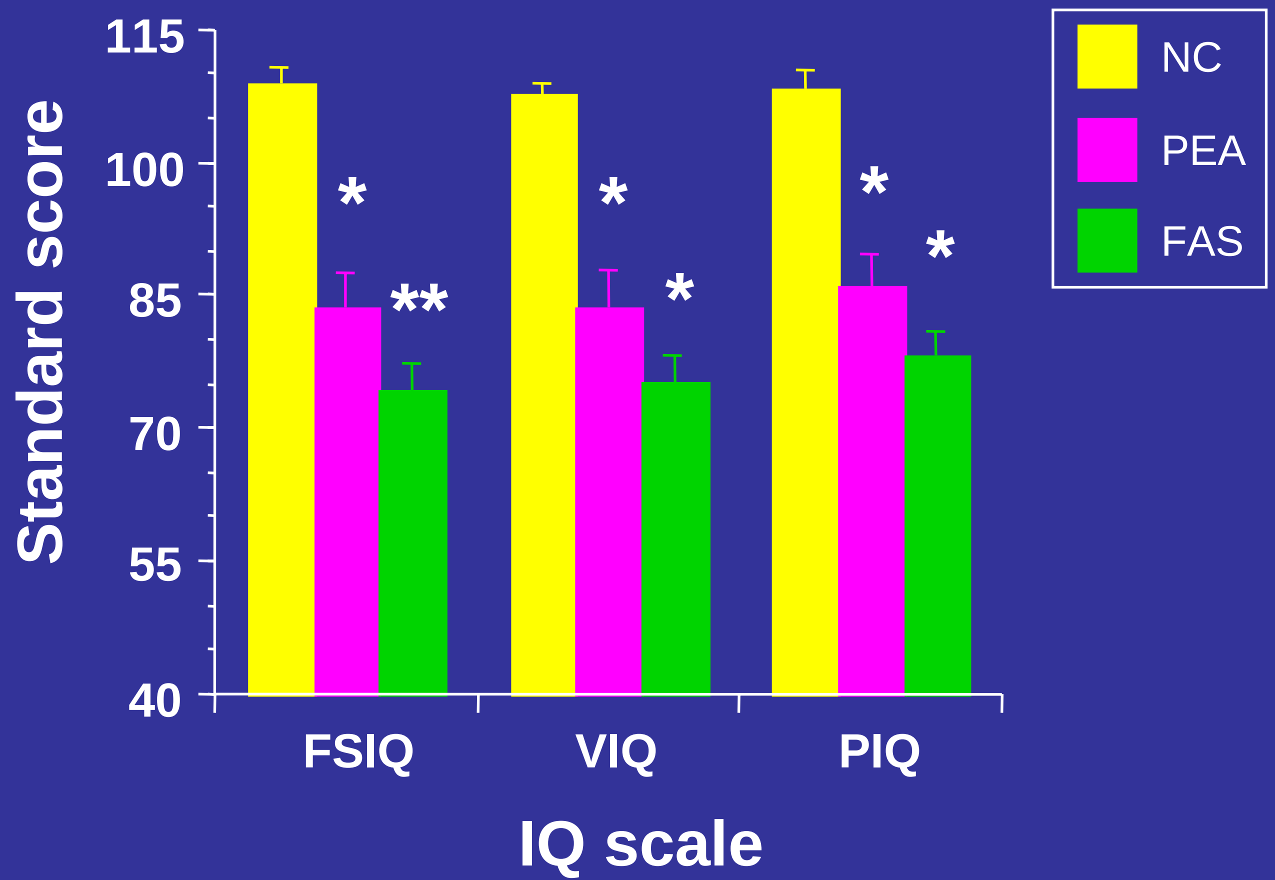


ADC=Apparent Diffusion Coefficient

FA= Fractional Anisotropy

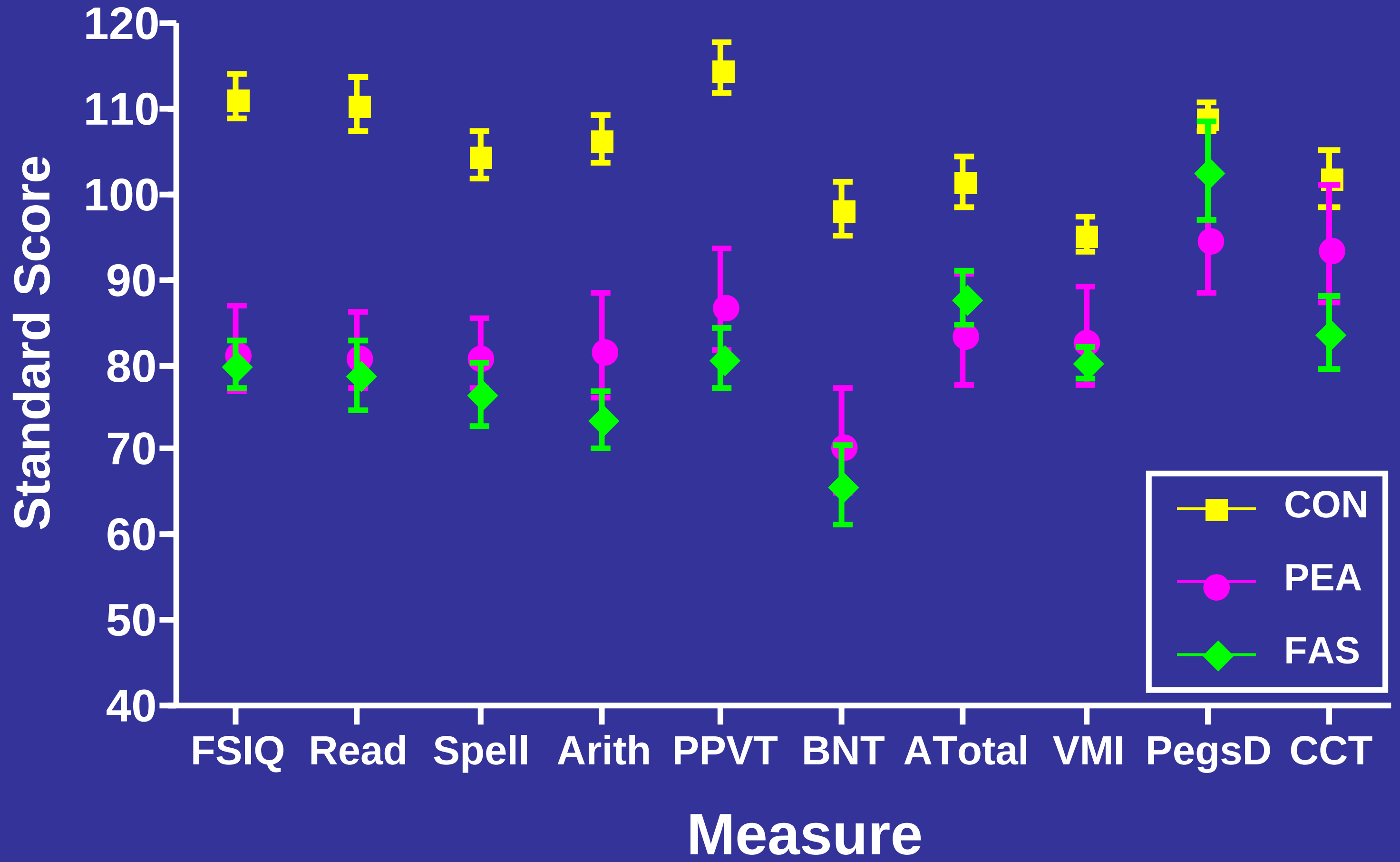
(From Ma, et al, 2005, ACER)

General Intellectual Performance



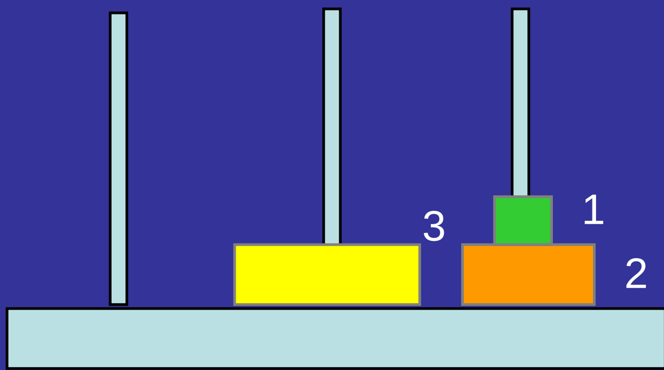
Mattson, J. of Pediatrics, 1997

Neuropsychological Performance

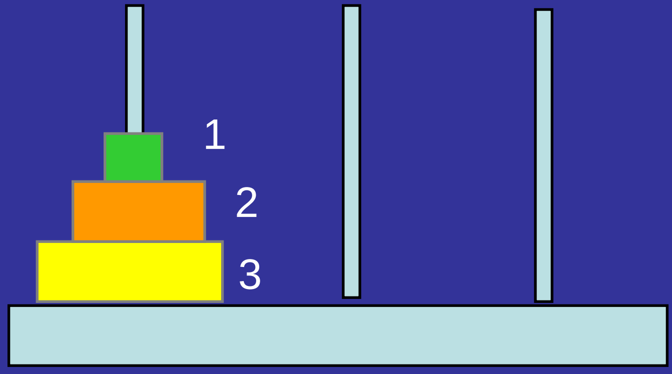


Mattson, et al., Neuropsychology, 1998

Executive Functioning Deficits

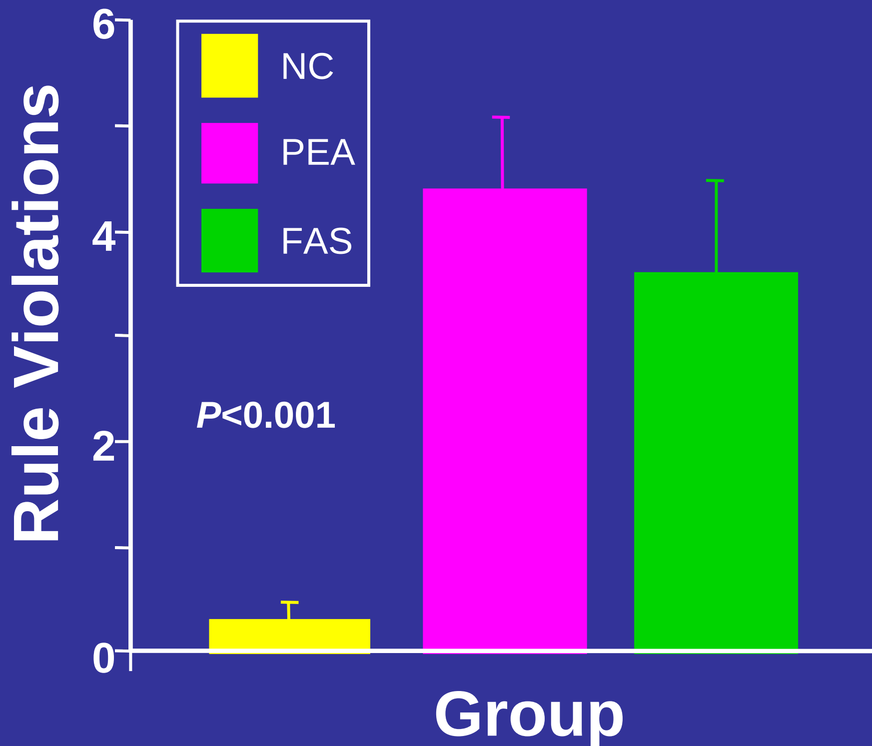


Starting position



Ending position

Move only one piece at a time using one hand and never place a big piece on top of a little piece



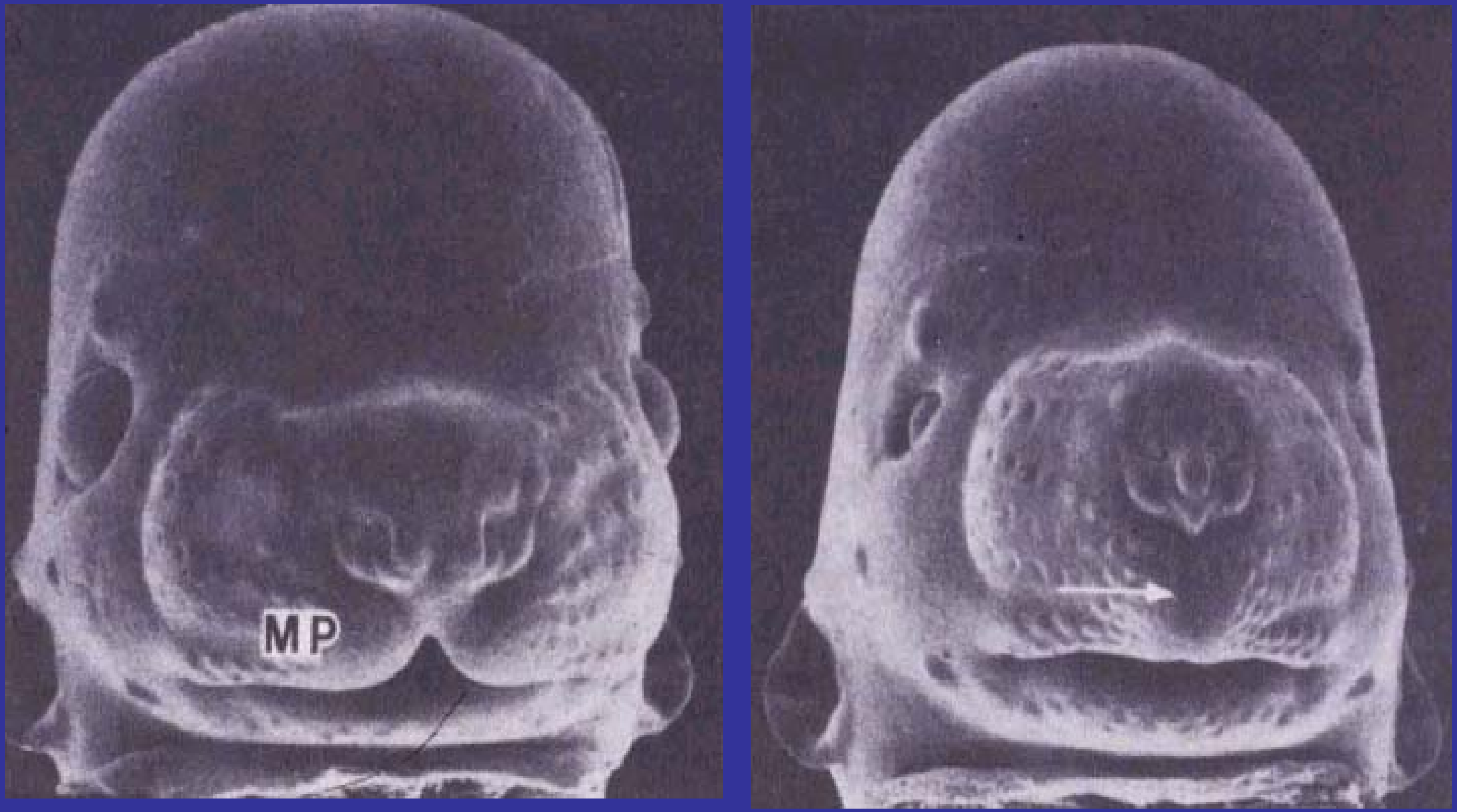
Mattson, et al., ACER, 1999

Animal models – Example of the comparability of effects

- Growth retardation
- Facial characteristics
- Heart, skeletal defects
- Microcephaly
- Reductions in basal ganglia and cerebellar volumes
- Callosal anomalies
- Hyperactivity, attentional problems
- Inhibitory deficits
- Impaired learning
- Perseveration errors
- Feeding difficulties
- Gait anomalies
- Hearing anomalies

Driscoll, et al., Neurotoxicology and Teratology 1990; Samson, Alcohol and Brain Development, 1986

Facial features of FAS in the mouse

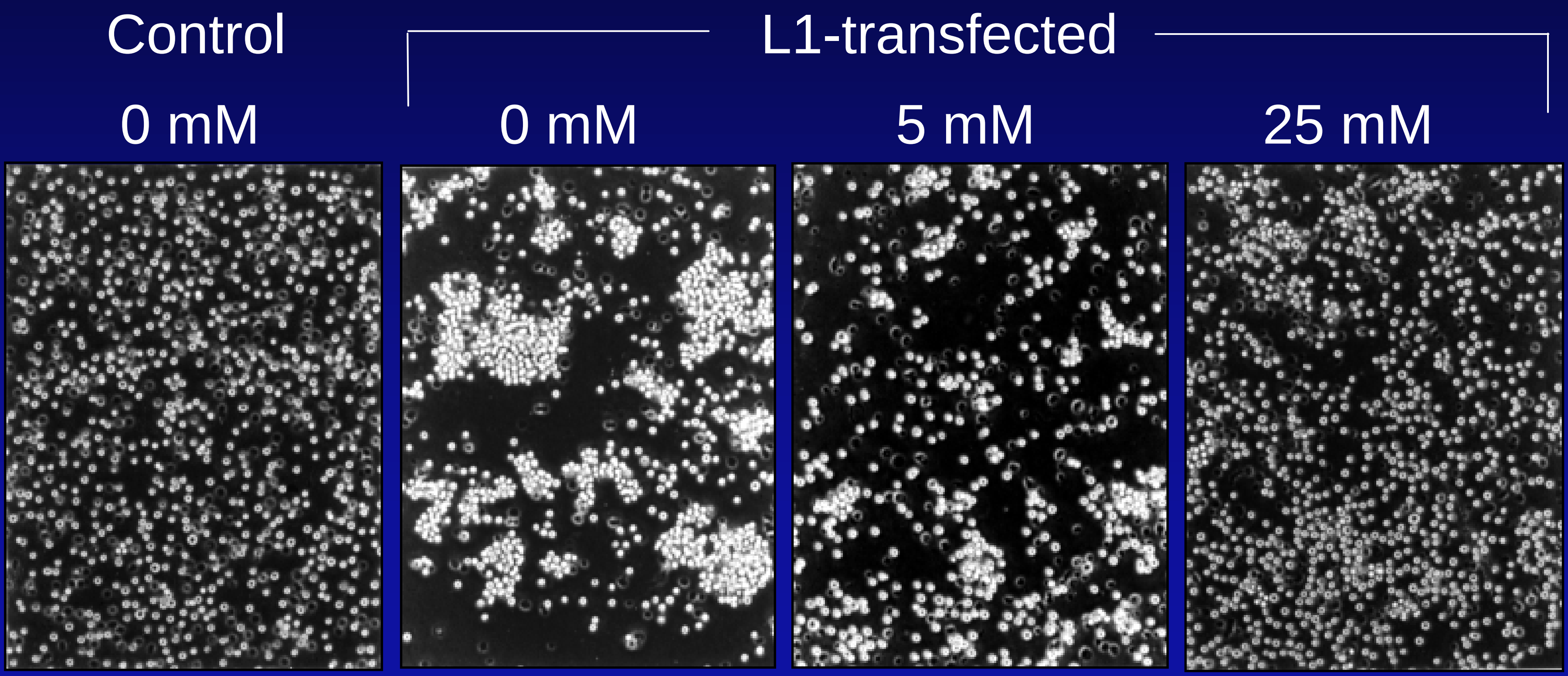


Adapted from Sulik & Johnston, Scanning Electron Microscopy, 1982

Possible mechanisms for alcohol's effects

- Impaired progression through cell cycle
- Impaired glia development - migration, neurotropic factor production, myelination
- Impaired cell adhesion
- Alterations in cell membranes
- Altered production of or responsiveness to factor that regulate growth, cell division, or cell survival
- Altered regulation of intracellular calcium
- Increased production of free radicals

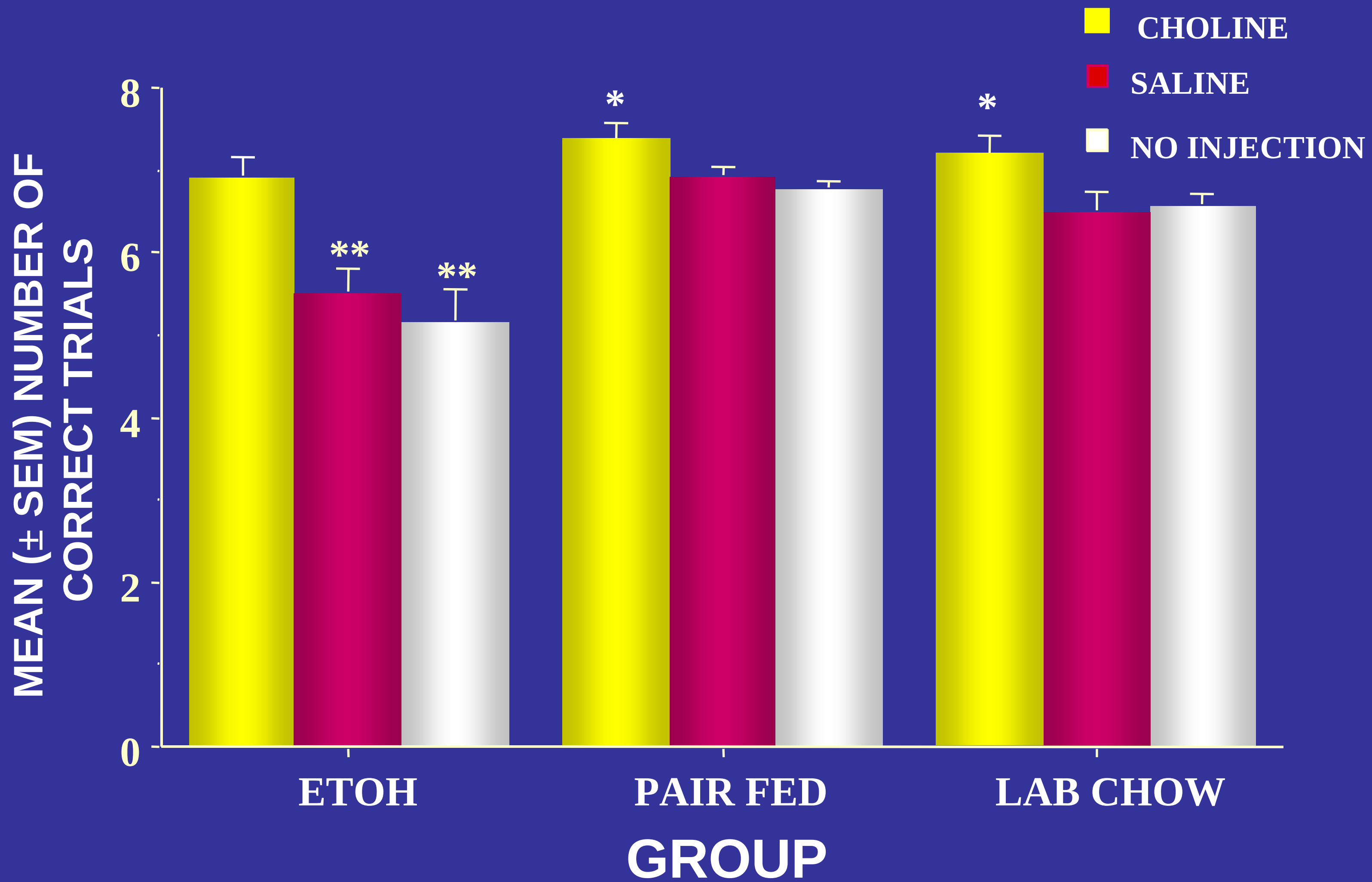
Ethanol inhibits cell adhesion in L1-transfected mouse L cells.



Courtesy of Michael Charness from Ramanathan et al., 1996

Can effects of prenatal alcohol exposure be mitigated?

Choline supplementation after prenatal alcohol mitigates learning deficits in rats



Adapted from Thomas et al, Neurotoxicology and Teratology, 2000

Conclusions

- Alcohol effects on brain depend on host factors, developmental stage, and conditions of use
- Moderate exposure to alcohol may have health benefits, including reduced CNS disease
- Drinking in alcoholic range induces brain structural and functional deficits
- Abstinence is associated with recovery in brain; recover best in younger, and those without neuromedical morbidities

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