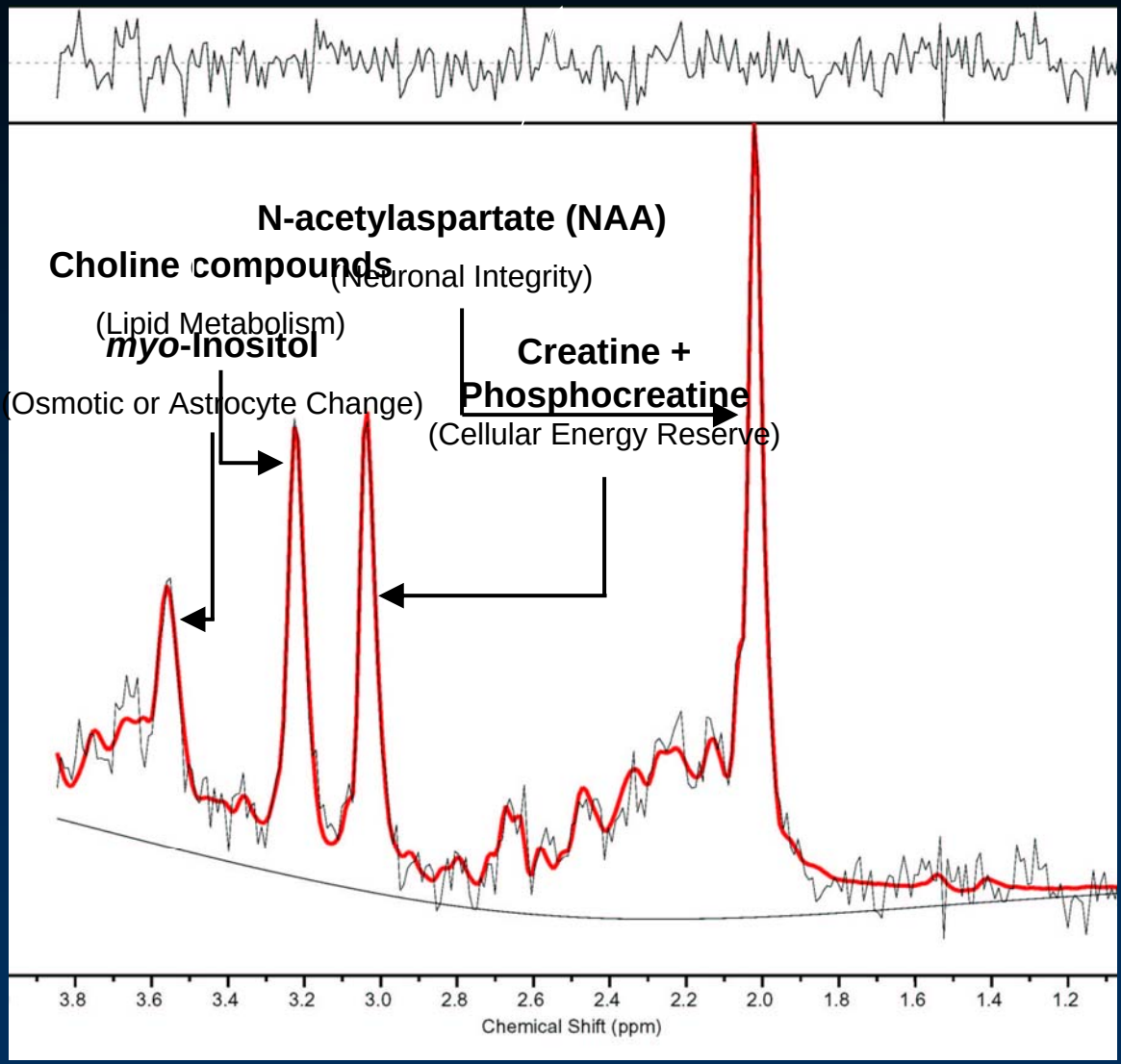
Brain Abnormalities in Chronic Adult Alcoholics Measured using Proton MR Spectroscopy

Michael J. Taylor, Ph.D.

VA San Diego Healthcare System
University of California, San Diego

Proton (1H) MRS



MRS findings in Alcoholics

↓ NAA/Cr in frontal lobes

(Fein, et al., 1994; Jagannathan, et al., 1996; Bendszus, et al., 2001)

May resolve with abstinence (Bendszus, et al., 2001)

↓ NAA/Cr in cerebellum

(Jagannathan, et al., 1996; Seitz, et al., 1999; Bendszus, et al., 2001)

May resolve with abstinence (Parks, et al., 2002; Bendszus, et al., 2001)

↓ Cho/Cr and ↓ Cho/NAA in cerebellum

(Bendszus, et al., 2001; Martin, et al., 1995)

May resolve with abstinence (Bendszus, et al., 2001; Martin, et al., 1995)

Definitions

- **Recently Detoxified Alcoholics**
  - Short term recovery (< 8 weeks) tested while inpatients in 28 day program
  - DSM-IV diagnosis of alcoholism
  - At least 6 drinks/day for most recent 5 year period

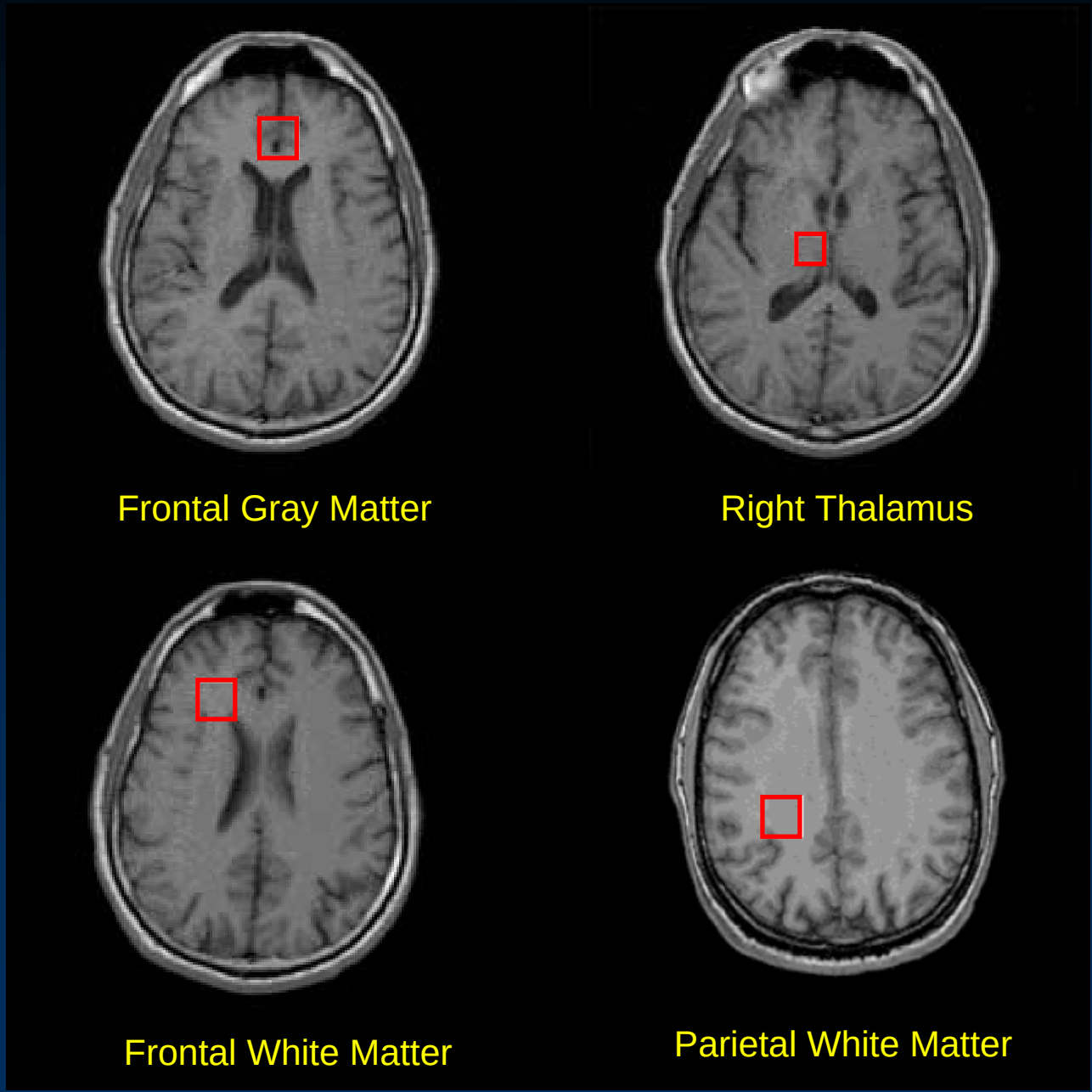
- **Long Term Abstinent Alcoholics**
  - Long term recovery (> 12 months)
  - DSM-IV diagnosis of alcoholism
  - At least 6 drinks/day for most recent 5 year drinking period

- **Non-Alcoholic Controls**
  - Individuals with no history of substance abuse or dependence

Exclusion Criteria

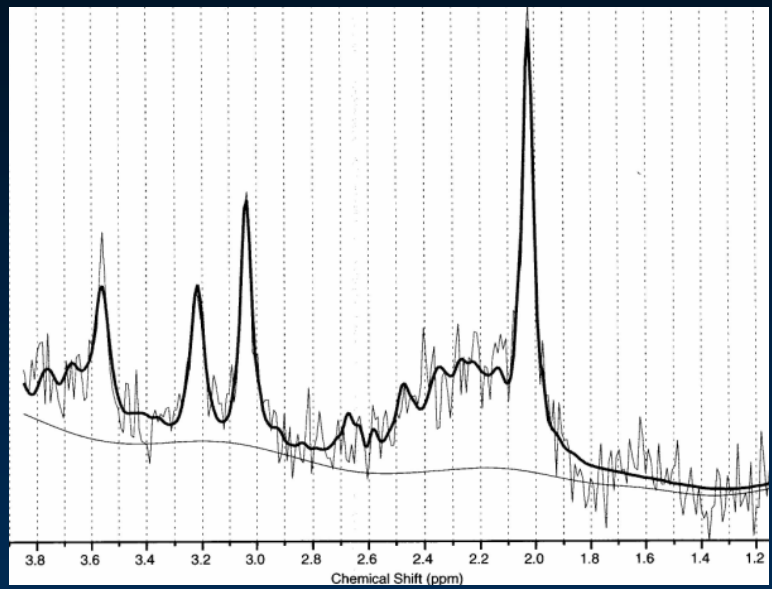
- Systemic disease (e.g., liver disease)
- Neurological disease
- DSM-IV diagnosis of substance abuse/dependence other than alcoholism
- DSM-IV Axis I diagnoses
- LOC > 15 minutes

MRS Regions of Interest



MRS Protocol

- Spectroscopy
  - PRESS
  - TE = 35 ms
  - TR = 3000 ms
  - Voxel size 20 x 20 x 20 (Caudate 15 x 15 x 15)
  - 64 acquisitions (Caudate 96 acquisitions)
- LCModel processing (Provencher, 1993)
- Partial Volume Corrections (Ernst, Kreis, & Ross, 1993)



Key Questions

- What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?
- Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?
- Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?
- Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?
- Do male and female alcoholics have different profiles of MRS visible metabolites?
- Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?

Key Questions

- **What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?**
- **Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?**
- **Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?**
- **Is Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?**
- **Do male and female alcoholics have different profiles of MRS visible metabolites?**
- **Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?**

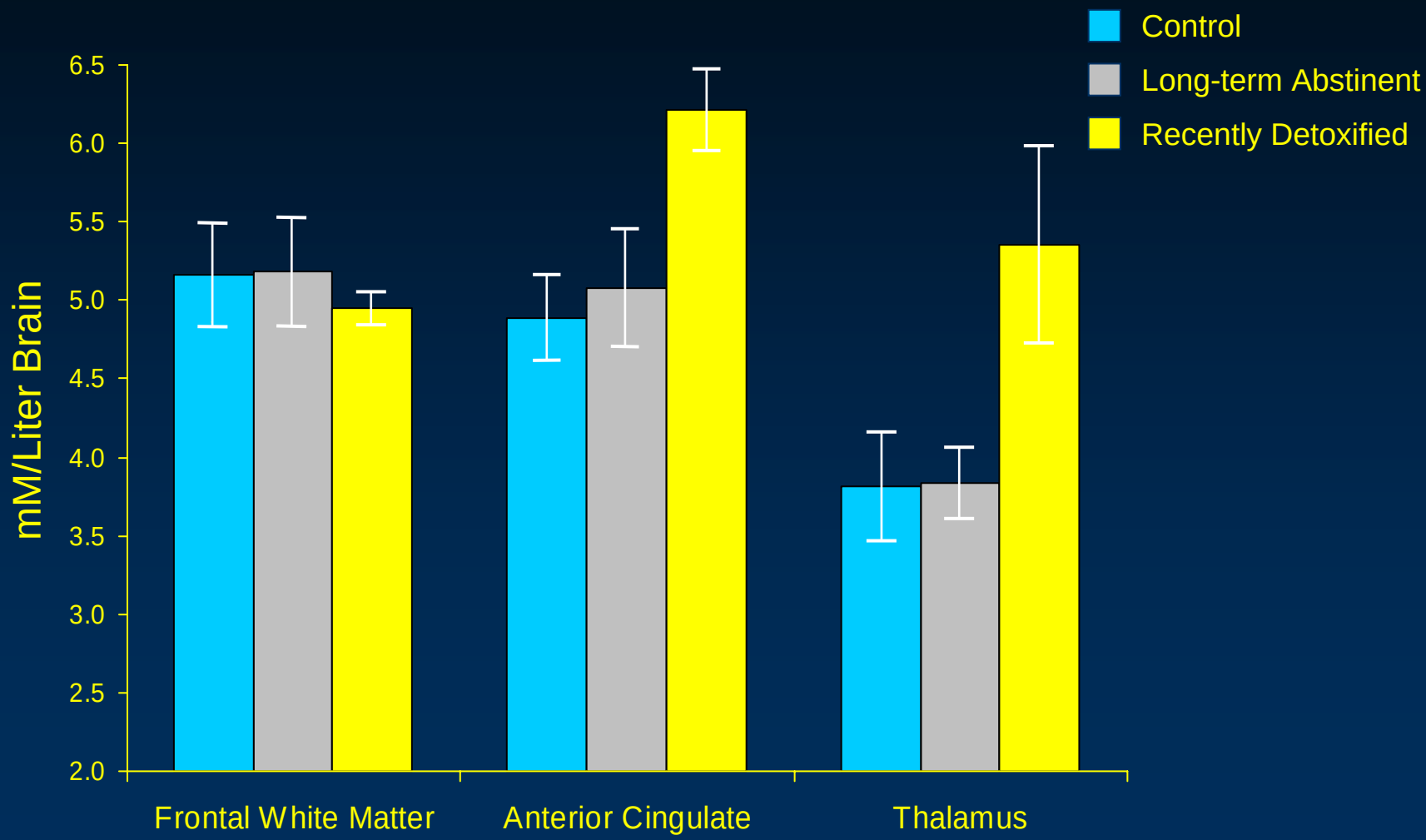
Sample Characteristics

Group	Age (in years)	Median Abstinence (range)	Median Alcoholism (range)
RDA (n=4)	48.7 (6.8)	41.5 days (27-44)	13.5 years (7-27)
LTA (n=5)	45.1 (7.0)	1.7 years (1.5-22.3)	10.0 years (5-16)
CON (n=5)	45.0 (8.3)	N/A	N/A

Sample Characteristics (Cont.)

Group	Median Lifetime Alcohol Consumption (range)
RDA (n=4)	899 kg (412-1033)
LTA (n=5)	701 kg (453-978)
CON (n=5)	N/A

myo-Inositol



Schweinsburg et al, (2000). Alcoholism, 24(5):699-705.

Key Questions

- What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?
- **Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?**
- Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?
- Is Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?
- Do male and female alcoholics have different profiles of MRS visible metabolites?
- Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?

Frontal Susceptibility Background

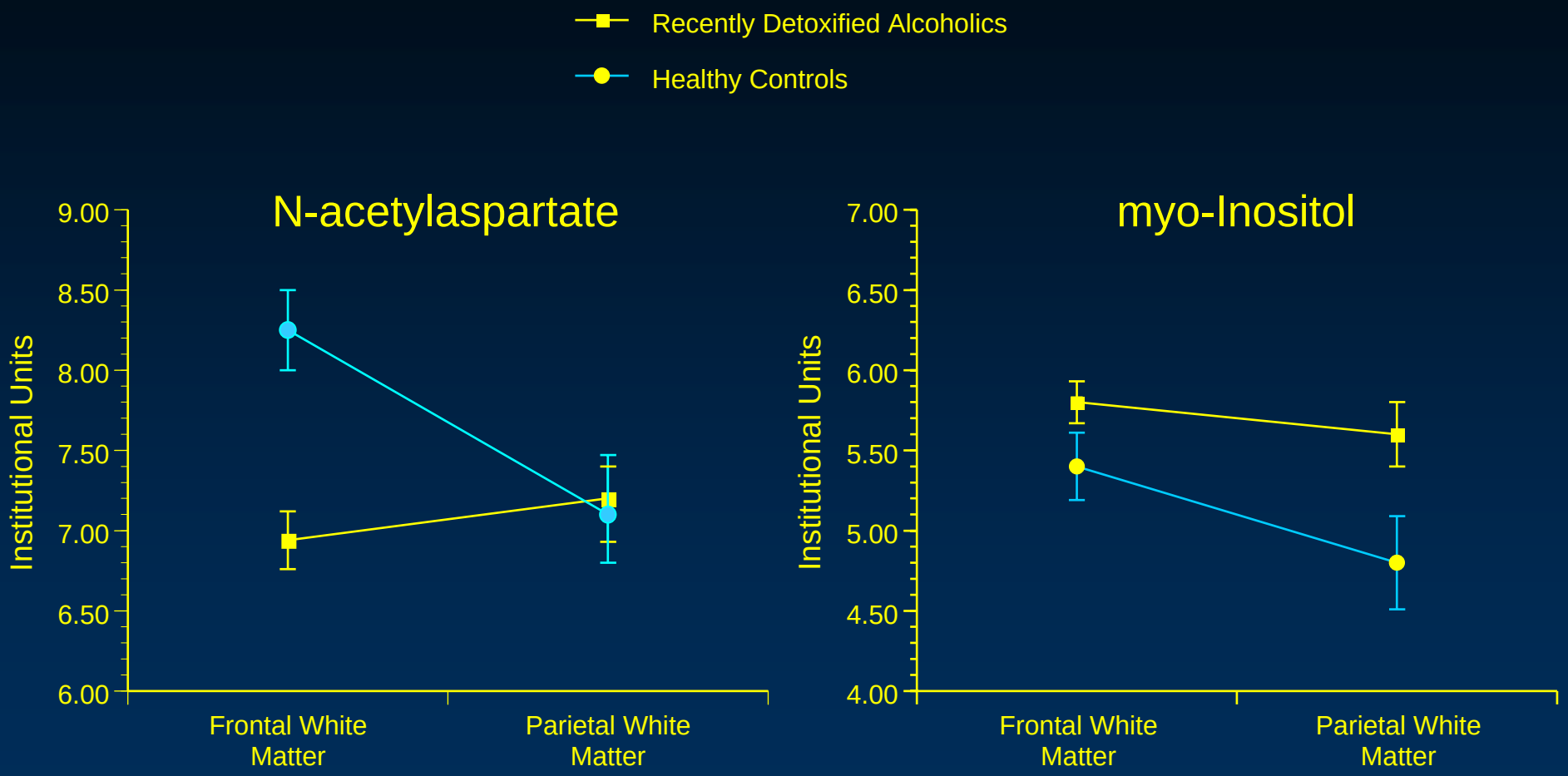
- Neuropsychological profile
  - Executive dysfunction in alcoholics
- Studies of brain volume demonstrating frontal susceptibility
  - Post mortem
  - Computed tomography
  - Magnetic resonance imaging

Sample Characteristics

Group	Age (in years)	Length of Abstinence (in days)	Alcoholism (in years)
RDA (n=37)	40.4 (9.8)	27.9 (11.0)	15.1 (7.9)
CON (n=15)	38.0 (7.6)	N/A	N/A

Sample Characteristics (Cont.)

Group	Lifetime Ethanol Consumption
RDA (n=37)	1012.5 kg (537.5)
CON (n=15)	37.5 kg (31.3)



Schweinsburg et al, (2001). Alcoholism, 25(6):924-34.

Conclusions

- Frontal specific ↓ in white matter NAA
  - Neuronal injury or death
    - Oxidative stress
    - Excitotoxic injury

- Non-specific ↑ in myo-Inositol
  - Astrocytosis
  - Osmotic stress

Key Questions

- What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?
- Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?
- **Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?**
- Is Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?
- Do male and female alcoholics have different profiles of MRS visible metabolites?
- Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?

Alcohol Withdrawal and Brain Injury

- Seizure is a complication of alcohol withdrawal
- ↑ severity of withdrawal may be related to ↑ risk of brain injury

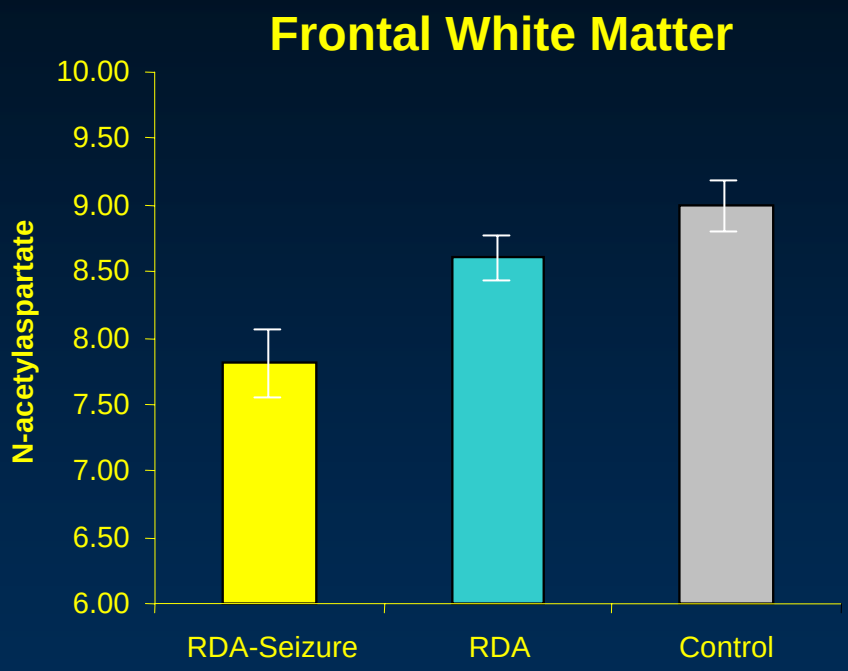
Sample Characteristics

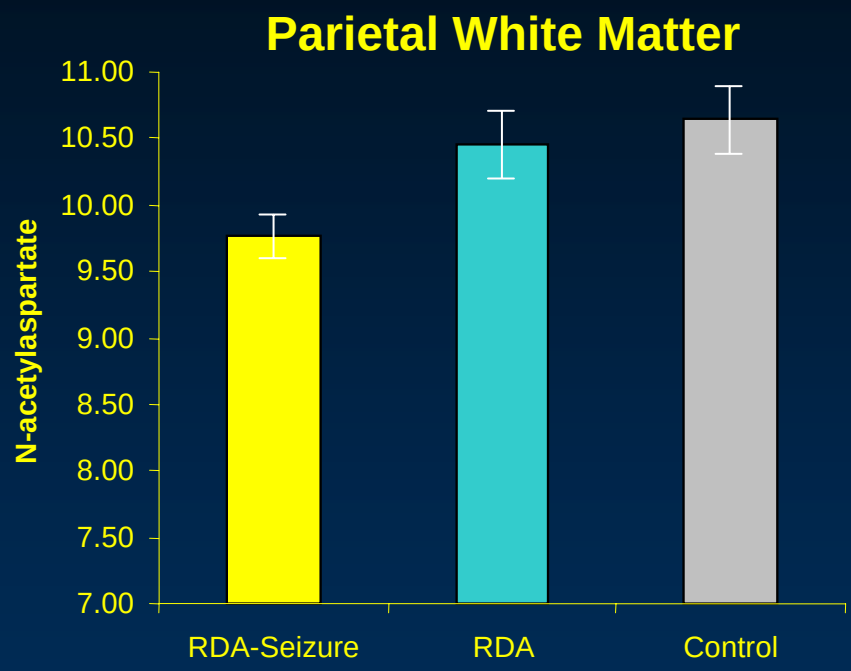
Group	Age (in years)	Length of Abstinence (days)	Years of Alcoholism
RDA-SEIZ (n=10)	39.8 (8.2)	24.4 (7.3)	17.7 (6.6)
RDA (n=16)	41.5 (3.7)	29.3 (11.0)	16.8 (5.0)
CON (n=10)	41.6 (4.9)	N/A	N/A

Sample Characteristics (Cont.)

Group	Lifetime Ethanol Consumption
RDA-SEIZ (n=10)	1135.0 kg (474.1)
RDA (n=16)	961.3 kg (384.8)
CON (n=10)	56.0 (50.5)

Alcohol Withdrawal and Brain Injury

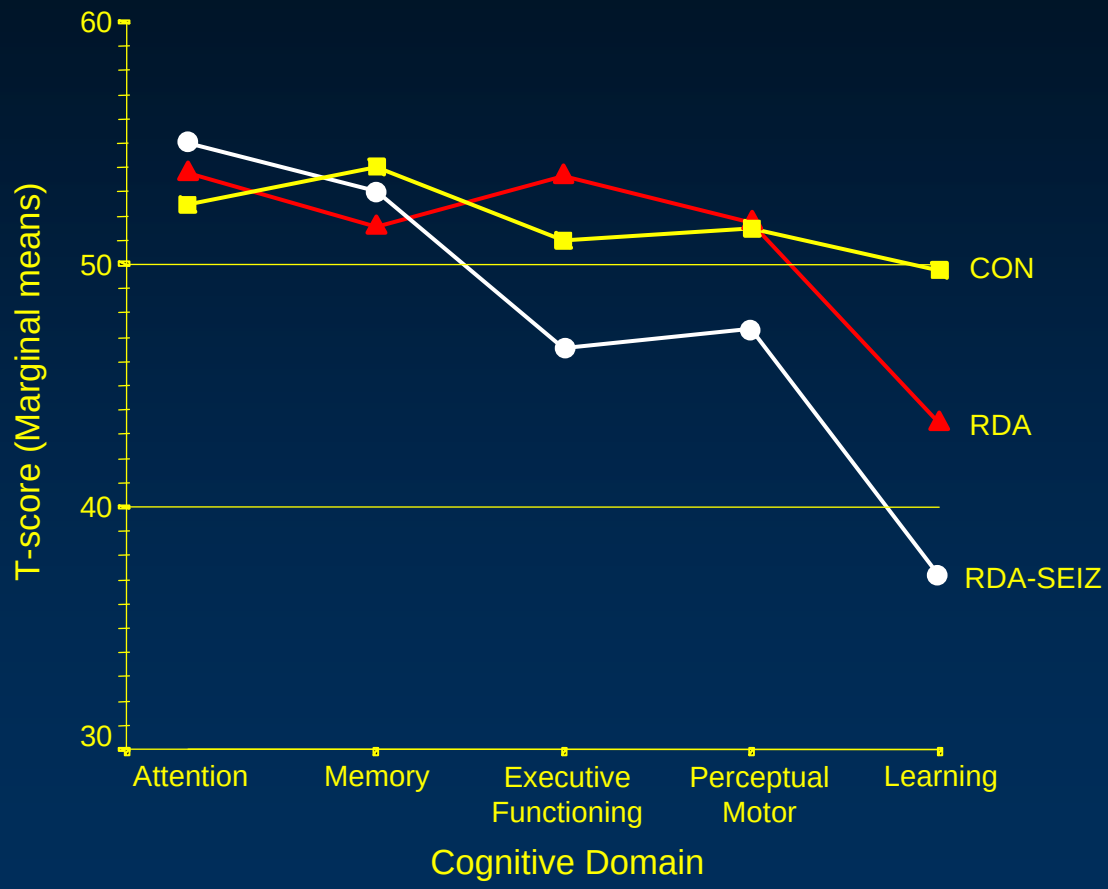




Recently Detoxified Alcoholic (RDA)

Schweinsburg et al, (in preparation).

Alcohol Withdrawal and Brain Injury



Schweinsburg et al, (in preparation).

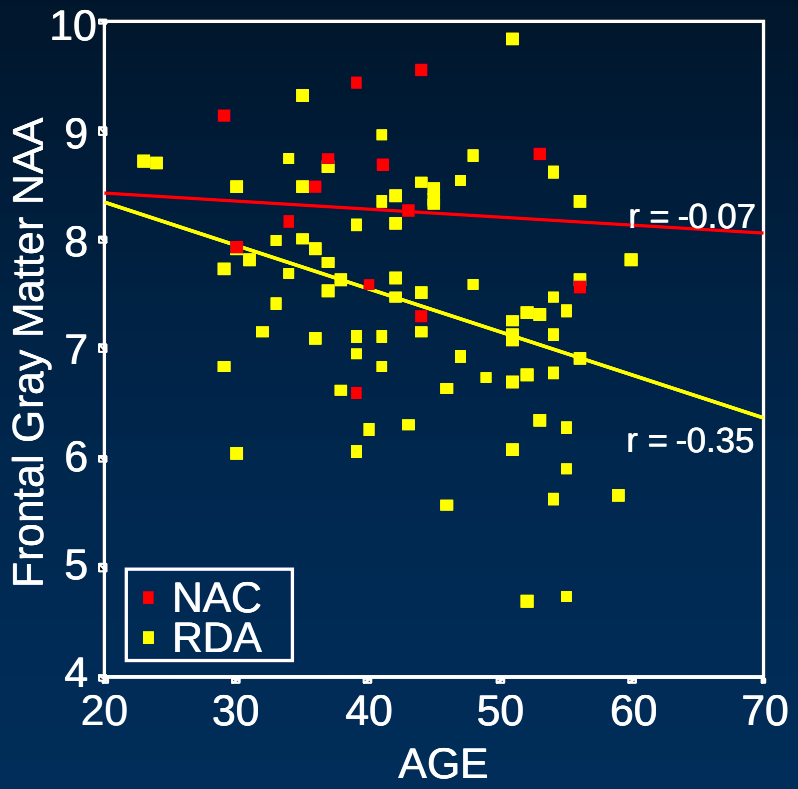
Key Questions

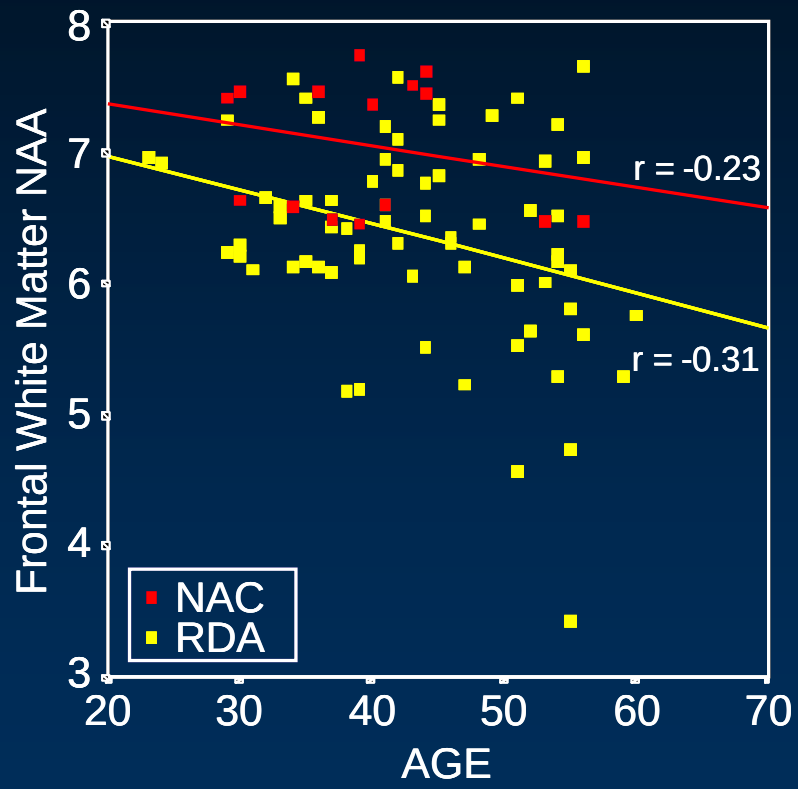
- What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?
- Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?
- Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?
- **Is Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?**
- Do male and female alcoholics have different profiles of MRS visible metabolites?
- Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?

Sample Characteristics

Group	Age (in years)	Length of Abstinence (in days)	Alcoholism (in years)
RDA (n=74)	43.8 (8.9)	26.8 (8.7)	16.9 (8.3)
CON (n=15)	39.7 (7.8)	N/A	N/A

Early Aging in Alcoholics?





Taylor et al, (2001). Alcoholism, 25(5):79 (abstract)

Key Questions

- What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?
- Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?
- Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?
- Is Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?
- **Do male and female alcoholics have different profiles of MRS visible metabolites?**
- Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?

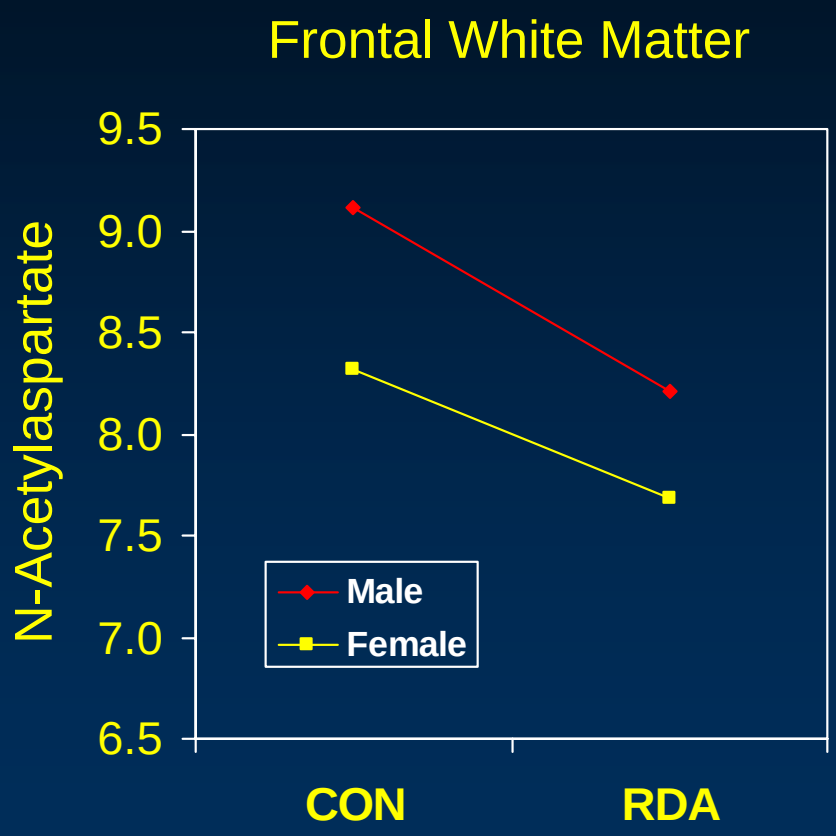
Sample Characteristics

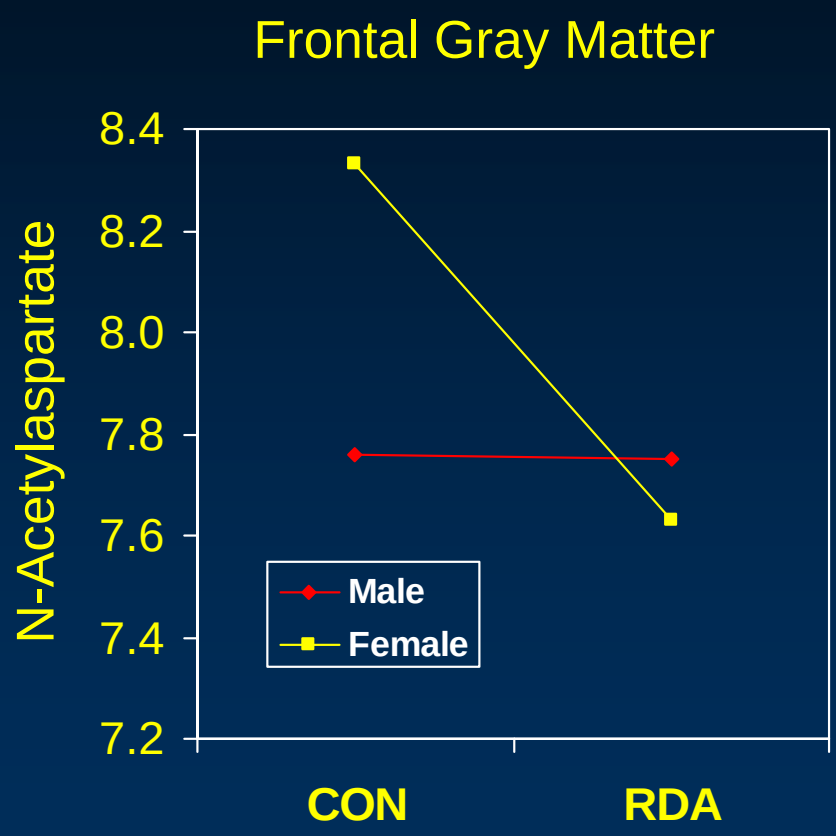
Group	Age (in years)	Length of Abstinence (days)	Length of Alcoholism (years)
Alcoholics			
Males (n=17)	36.2 (5.8)	26.2 (11.1)	10.6 (4.8)
Females (n=8)	43.3 (7.9)	39.7 (20.1)	10.8 (4.1)
Controls			
Males (n=13)	38.8 (10.0)	N/A	N/A
Females (n=12)	35.8 (8.3)	N/A	N/A

Sample Characteristics (cont.)

Group	Lifetime Ethanol Consumption (kg)
Alcoholics	
Males (n=17)	668.2 (256.4)
Females (n=8)	660.3 (235.4)

Differential Gender Effects?



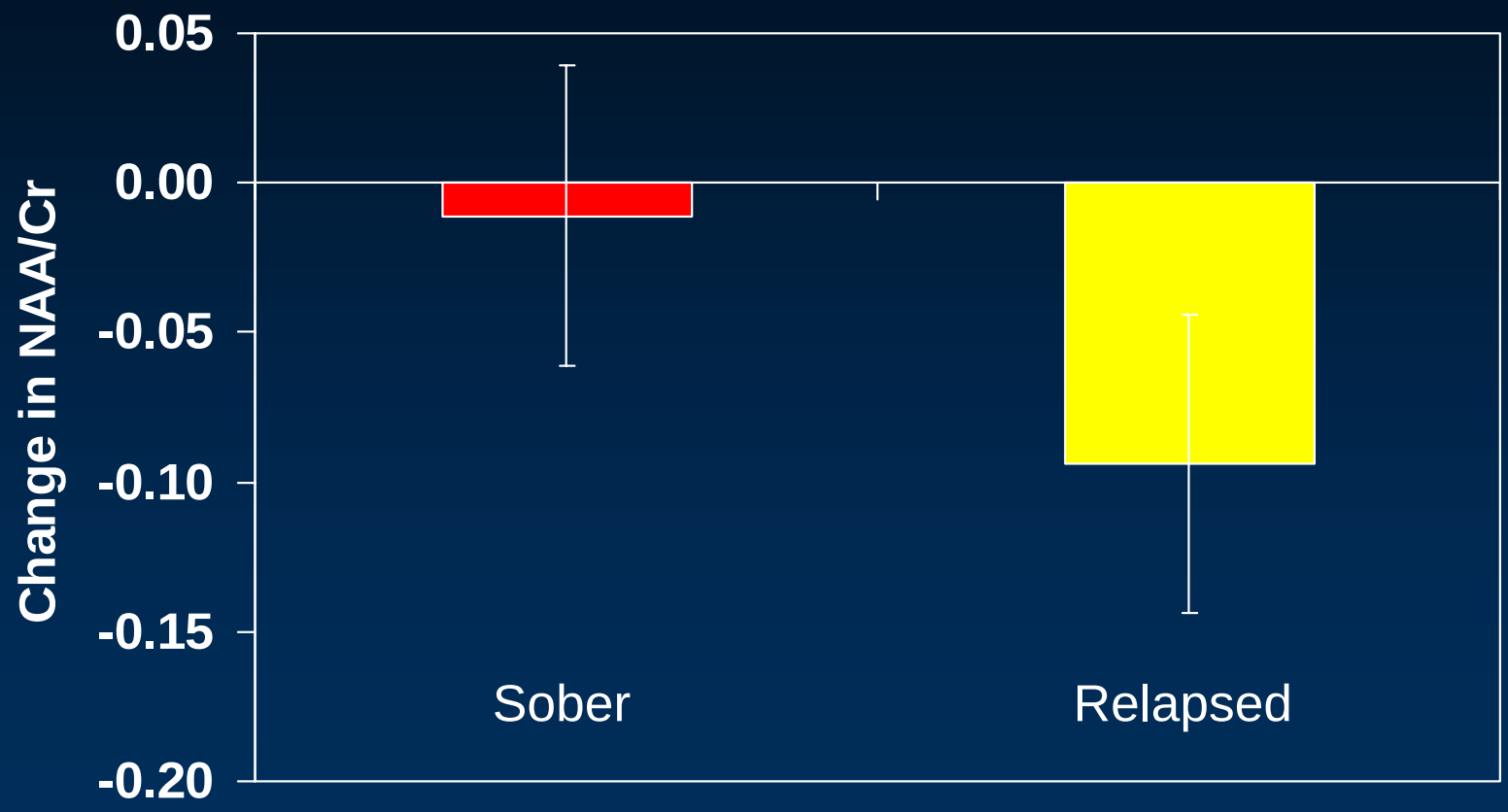


Schweinsburg et al, (2003). American Journal of Psychiatry, 160:1180-1183

Key Questions

- What Metabolic Abnormalities are Present in Short and Long-Term Alcoholics?
- Is Frontal Lobe White Matter More Susceptible to Alcohol-associated Metabolite Changes?
- Are Alcohol-withdrawal Seizures Associated with Greater CNS Involvement?
- Alcohol-associated Cerebral Metabolic Dysfunction Consistent with Early Aging?
- Do male and female alcoholics have different profiles of MRS visible metabolites?
- **Do Cerebral Metabolites Change Differentially Over Time in Sober vs. Relapsed Alcoholics?**

Worse NAA/Cr with Relapse



Acknowledgements

Principal Investigators
Igor Grant, M.D.
Michael J. Taylor, Ph.D.

Co-Investigators
Omar Alhassoon, Ph.D.
Gregory Brown, Ph.D.
Assawin Gongvatana, M.A.
Thomas Patterson, Ph.D.
Brian Schweinsburg, B.A.

Funded by VA Merit Review Grant SA325