Brain Abnormalities in Chronic Adult Alcoholics
Measured using Proton MR Spectroscopy

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Proton (1H) MRS

- **N-acetylaspartate (NAA)** (Neuronal Integrity)
- **Choline compounds** (Lipid Metabolism)
- **myo-Inositol** (Osmotic or Astrocyte Change)
- **Creatine + Phosphocreatine** (Cellular Energy Reserve)
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

- Frontal White Matter
- Frontal Gray Matter
- Right Thalamus
- Parietal White Matter
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?
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## Sample Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (in years)</th>
<th>Median Abstinence (range)</th>
<th>Median Alcoholism (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA (n=4)</td>
<td>48.7 (6.8)</td>
<td>41.5 days (27-44)</td>
<td>13.5 years (7-27)</td>
</tr>
<tr>
<td>LTA (n=5)</td>
<td>45.1 (7.0)</td>
<td>1.7 years (1.5-22.3)</td>
<td>10.0 years (5-16)</td>
</tr>
<tr>
<td>CON (n=5)</td>
<td>45.0 (8.3)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Group</td>
<td>Median Lifetime Alcohol Consumption (range)</td>
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<tr>
<td>RDA (n=4)</td>
<td>899 kg (412-1033)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTA (n=5)</td>
<td>701 kg (453-978)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON (n=5)</td>
<td>N/A</td>
<td></td>
<td></td>
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</table>
myo-Inositol

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Frontal Susceptibility Background

- Neuropsychological profile
  - Executive dysfunction in alcoholics

- Studies of brain volume demonstrating frontal susceptibility
  - Post mortem
  - Computed tomography
  - Magnetic resonance imaging
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<th>Age (in years)</th>
<th>Length of Abstinence (in days)</th>
<th>Alcoholism (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA (n=37)</td>
<td>40.4 (9.8)</td>
<td>27.9 (11.0)</td>
<td>15.1 (7.9)</td>
</tr>
<tr>
<td>CON (n=15)</td>
<td>38.0 (7.6)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Group</td>
<td>Lifetime Ethanol Consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>RDA (n=37)</td>
<td>1012.5 kg (537.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CON (n=15)</td>
<td>37.5 kg (31.3)</td>
<td></td>
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</tbody>
</table>
Recently Detoxified Alcoholics

Healthy Controls

Conclusions

♦ Frontal specific ↓ in white matter NAA
  • Neuronal injury or death
    – Oxidative stress
    – Excitotoxic injury

♦ Non-specific ↑ in myo-Inositol
  • Astrocytosis
  • Osmotic stress
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Alcohol Withdrawal and Brain Injury

♦ Seizure is a complication of alcohol withdrawal

♦ ↑ severity of withdrawal may be related to ↑ risk of brain injury
<table>
<thead>
<tr>
<th>Group</th>
<th>Age (in years)</th>
<th>Length of Abstinence (days)</th>
<th>Years of Alcoholism</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA-SEIZ (n=10)</td>
<td>39.8 (8.2)</td>
<td>24.4 (7.3)</td>
<td>17.7 (6.6)</td>
</tr>
<tr>
<td>RDA (n=16)</td>
<td>41.5 (3.7)</td>
<td>29.3 (11.0)</td>
<td>16.8 (5.0)</td>
</tr>
<tr>
<td>CON (n=10)</td>
<td>41.6 (4.9)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Sample Characteristics (Cont.)

<table>
<thead>
<tr>
<th>Group</th>
<th>Lifetime Ethanol Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDA-SEIZ (n=10)</td>
<td>1135.0 kg (474.1)</td>
</tr>
<tr>
<td>RDA (n=16)</td>
<td>961.3 kg (384.8)</td>
</tr>
<tr>
<td>CON (n=10)</td>
<td>56.0 (50.5)</td>
</tr>
</tbody>
</table>
Alcohol Withdrawal and Brain Injury

Frontal White Matter

Parietal White Matter

Recently Detoxified Alcoholic (RDA)

Alcohol Withdrawal and Brain Injury

Cognitive Domain

- Learning
- Perceptual
- Motor
- Executive Functioning
- Memory
- Attention

T-score (Marginal means)

CON  RDA-SEIZ  RDA

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<th>Alcoholism (in years)</th>
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<tbody>
<tr>
<td>RDA (n=74)</td>
<td>43.8 (8.9)</td>
<td>26.8 (8.7)</td>
<td>16.9 (8.3)</td>
</tr>
<tr>
<td>CON (n=15)</td>
<td>39.7 (7.8)</td>
<td>N/A</td>
<td>N/A</td>
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Early Aging in Alcoholics?

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<thead>
<tr>
<th>Group</th>
<th></th>
<th>Age (in years)</th>
<th>Length of Abstinence (days)</th>
<th>Length of Alcoholism (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholics</td>
<td>Males (n=17)</td>
<td>36.2 (5.8)</td>
<td>26.2 (11.1)</td>
<td>10.6 (4.8)</td>
</tr>
<tr>
<td></td>
<td>Females (n=8)</td>
<td>43.3 (7.9)</td>
<td>39.7 (20.1)</td>
<td>10.8 (4.1)</td>
</tr>
<tr>
<td>Controls</td>
<td>Males (n=13)</td>
<td>38.8 (10.0)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Females (n=12)</td>
<td>35.8 (8.3)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
## Sample Characteristics (cont.)

<table>
<thead>
<tr>
<th>Group</th>
<th>Lifetime Ethanol Consumption (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholics</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>668.2</td>
</tr>
<tr>
<td>(n=17)</td>
<td>(256.4)</td>
</tr>
<tr>
<td>Females</td>
<td>660.3</td>
</tr>
<tr>
<td>(n=8)</td>
<td>(235.4)</td>
</tr>
</tbody>
</table>
Differential Gender Effects?

Frontal White Matter

Frontal Gray Matter

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Worse NAA/Cr with Relapse

![Graph showing change in NAA/Cr with relapse and sobriety. The graph compares the change in NAA/Cr for sober and relapsed individuals. The bar for relapsed individuals shows a significant decrease compared to the sober group.]
Acknowledgements

Principal Investigators
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Michael J. Taylor, Ph.D.

Co-Investigators
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Brian Schweinsburg, B.A.

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