ALCOHOL AND THE BRAIN:

THE GOOD
THE BAD
THE UGLY

Igor Grant, MD

VA San Diego
Alcohol Study
VARIABLES TO CONSIDER IN ANY CAUSAL MODEL OF ALCOHOL ASSOCIATED NEUROPSYCHOLOGICAL DEFICIT

**NEUROMEDICAL STATUS & COMORBIDITIES**
- Premorbid Medical/Psych Disorders
- Head Injury
- Specific organ disease – liver, heart
- Polysubstance use

**ALCOHOL ABUSE**
- Amount per occasion
- Duration of abusive drinking
- Pattern over lifetime
- Recent amount/duration
- Length of abstinence

**AGE**
- Genetics
- Sex
- Family History

**TEST CHARACTERISTICS**
- Difficulty
- Complexity

**BRAIN STRUCTURE & FUNCTION**

**NEUROPSYCHOLOGICAL PERFORMANCE**

**EDUCATION AND SOCIAL POSITION**

**PERSONALITY MOTIVATION & AFFECT**
“THE GOOD”
Fewer Deaths in Moderate Drinkers

Deaths per 100,000

Drinks per Day

Thun, et al., NEJM, 1997
“Light to moderate alcohol consumption is associated with a lower risk of developing dementia” (Letenneur, 2007)
Moderate Alcohol Use Related to Lower Risk of Stroke and Blood Pressure

Odds of Stroke

Men

Women

Current Drinkers

Abstainers

Systolic Blood Pressure

None <1/day 1 to <2/day 2 to <3/day 3/day

Alcohol Consumption

Rodgers, et al., Stroke, 1993

Gillman, et al., Hypertension, 1995
“THE BAD”

Ventricular Dilatation

Cerebellar Atrophy

University of Alabama at Birmingham Department of Pathology
Neuropathology of Alcoholism

% Neuronal Count Compared to Controls

- Frontal Cortex
- Cortical Dendritic Arbor
- Hippocampus
- Thalamus
- Mamillary Bodies
- Basal Forebrain
- Raphe
- Cerebellar Vermis

Uncomplicated Alcoholic
Wernike Korsakoff Syndrome
Korsakoff Psychosis

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

T-Scores

Attention
Learning
Recall
Abstraction
Perc-Motor
Motor

Neuropsychological Ability Domains

Alcoholics Non-Alcoholic Controls

Rourke & Grant, 1996
Sulcal Dilatation on Brain MRI in Recently Detox Alcoholics

Healthy Control

Alcoholic
Brain Abnormalities on MRI in Recently Detox Alcoholics

47 y/o Healthy Control

47 y/o Recently Detoxified Alcoholic

VA San Diego Alcohol Study
Diffusion Tensor Imaging

Taylor, et al., 2006
Microstructural Cerebral Disruption in Alcoholics Detected with DTI

Fractional Anisotropy

Frontal White Matter

Parietal White Matter

p=0.21

p=0.003

Average Diffusion Coefficient

Frontal White Matter

Parietal White Matter

p=0.04

p=0.001

Controls

Recently Detoxified Alcoholics

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

Non-Alcoholic Controls (n=20)  Recently Detoxified Alcoholics (n=100)

Taylor, et al, 2004
Lower Frontal White Matter
NAA Predicts Poorer Executive Functioning
in Recently Detoxified Alcoholics

Alcohol Study
VA San Diego
Taylor, et al, 2004

$r = 0.31$
$p = .001$
How permanent is the alcohol-induced neuronal injury?
Follow-up NP Performance

T-Scores

Neuropsychological Ability Domains

- Attention
- Learning
- Recall
- Abstraction
- Perc-Motor
- Motor

- Resumed Drinkers
- Immediate-Term Abstinent
- Long-Term Abstinent
- Non-Alcoholic Controls

VA San Diego Alcohol Study

Rourke & Grant, 1996
Practice Effect and True NP Improvement in Relation to Length of Abstinence

Drinking Status at Baseline

Resumed Drinkers
Intermediate Term Abstinent
Long-Term Abstinent
Non-Alcoholic Controls

Followup
Baseline

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

CT Improvement with 2 years Abstinence

Baseline

2 Years Abstinent

Markman, et al., Liver Transplantation, 2000
Improved CT with Three Months Sobriety

Vertex Sulci
Ventricles
Fronto Temporal

Degree of Dilatation

Worse
3.0
2.5
2.0
1.5
1.0
Better

3 Weeks Sober
3 Months Sober

VA San Diego Alcohol Study
Brain MRI Improvement with Abstinence

During Treatment

1 ½ Years Later

VA San Diego Alcohol Study
MR Improvement with Abstinence

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

N-acetylaspartate in Frontal Cortex

- Recently Detoxified Alcoholics
- Long Term Abstinent Alcoholics
- Non Alcoholic Controls

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

Alhassoon, et al., 1998
Increased Bold Response during Spatial Working Memory in Alcoholics with Recovery after Abstinence

Schweinsburg, et al, 2004
Greater Frontal White Matter NAA/Cr Improvement with Long-Term Abstinence (2-Year followup)

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

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

- Alcoholics with Neuromedical Risk
- Alcoholics with no Neuromedical Risk
- Age, Education Matched Controls

Rourke & Grant, 1996
Alcohol Withdrawal Seizures Associated with Greater NP Deficits

Recently Detoxified Alcoholics With Seizures

Recently Detoxified Alcoholics W/O Seizures

Non Alcoholic Controls

Cognitive Domain

Schweinsburg, et al, 2002
Alcohol Withdrawal Seizures Associated with Greater Brain Injury

Recently Detoxified Alcoholics With Seizures
Recently Detoxified Alcoholics W/O Seizures
Non Alcoholic Controls

Frontal White Matter N-acetylaspartate

Schweinsburg, et al, 2002
## Factors Related to Changes in NP Performance Among Alcoholics

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worse</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>43.6</td>
<td>43.7</td>
<td>49.6</td>
<td>.05</td>
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<tr>
<td><strong>Education</strong></td>
<td>13.4</td>
<td>12.9</td>
<td>12.3</td>
<td>NS</td>
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<tr>
<td><strong>Interim Medical Risk Score</strong>*</td>
<td>1.5</td>
<td>1.9</td>
<td>3.5</td>
<td>.001</td>
</tr>
</tbody>
</table>

*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

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

Grant, et al., 1984
Follow-up NP Performance

T-Scores

Attention Learning Recall Abstraction Perc-Motor Motor

Resumed Drinkers Long-Term Abstinent Immediate-Term Abstinent Non-Alcoholic Controls

Neuropsychological Ability Domains

VA San Diego Alcohol Study

Rourke & Grant, 1996
Follow-up NP Performance (YOUNGER ONLY)

T-Scores

Attention | Learning | Recall | Abstraction | Perc-Motor | Motor

Follow-up NP Performance (YOUNGER ONLY)

- Resumed Drinkers
- Immediate-Term Abstinent
- Long-Term Abstinent
- Non-Alcoholic Controls

Neuropsychological Ability Domains

Rourke & Grant, 1996
Follow-up NP Performance (OLDER ONLY)

T-Scores

Attention | Learning | Recall | Abstraction | Perc-Motor | Motor
---|---|---|---|---|---
Resumed Drinkers | Long-Term Abstinent | Immediate-Term Abstinent | Non-Alcoholic Controls

Neuropsychological Ability Domains

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

Discriminating Features:
- short palpebral fissures
- flat midface
- short nose
- indistinct philtrum
- thin upper lip

Associated Features:
- epicanthal folds
- low nasal bridge
- minor ear anomalies
- micrognathia

In the Young Child

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)

<table>
<thead>
<tr>
<th>Location</th>
<th>Rate(s)</th>
<th>Population</th>
<th>Other Note(s)</th>
<th>Location</th>
<th>Rate(s)</th>
<th>Population</th>
<th>Other Note(s)</th>
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<tbody>
<tr>
<td>Alaska</td>
<td>0.2</td>
<td>non AI/AN</td>
<td></td>
<td>Seattle</td>
<td>2.8-3.1</td>
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<tr>
<td></td>
<td>3</td>
<td>AI/AN</td>
<td>FAS pFAS</td>
<td>Cleveland</td>
<td>4.6</td>
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<tr>
<td>Aberdeen</td>
<td>2.7</td>
<td>AI/AN</td>
<td>FAS pFAS</td>
<td>Roubaix</td>
<td>1.3-4.8</td>
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<tr>
<td>BDMP</td>
<td>0.7</td>
<td></td>
<td>FAS pFAS</td>
<td>Seattle FASD</td>
<td>9.1</td>
<td></td>
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<tr>
<td>Atlanta</td>
<td>0.1</td>
<td></td>
<td></td>
<td>school study</td>
<td>3.1</td>
<td></td>
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<tr>
<td></td>
<td>0.3</td>
<td>FAS pFAS</td>
<td>FAS and PFAS</td>
<td>South Africa</td>
<td>4.1</td>
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<tr>
<td>IOM</td>
<td>0.5 - 2.0</td>
<td>AI/AN</td>
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<td>Western Cape</td>
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<td></td>
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<tr>
<td></td>
<td>2 - 8.5</td>
<td>AI/AN</td>
<td></td>
<td>FAS and PFAS</td>
<td>8.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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.

(From Ma, et al, 2005, ACER)
General Intellectual Performance

Mattson, J. of Pediatrics, 1997
Neuropsychological Performance

Mattson, et al., Neuropsychology, 1998

<table>
<thead>
<tr>
<th>Measure</th>
<th>CON</th>
<th>PEA</th>
<th>FAS</th>
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<td>Read</td>
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<td>PPVT</td>
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<td>BNT</td>
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<td>VMI</td>
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<td>PegsD</td>
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<tr>
<td>CCT</td>
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</tbody>
</table>

Standard Score

Mattson, et al., Neuropsychology, 1998
Executive Functioning Deficits

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

Starting position

Ending position

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.

Control
0 mM

L1-transfected
0 mM
5 mM
25 mM

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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