

# Smoking Impairs Recovery from Alcohol: New Evidence

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## Outline

- **Background**
- **Cross-sectional MR studies**
  - 1-week abstinence
  - Smoking and non-smoking recovering alcoholics (RA)
  - Effects of alcohol dependence and chronic smoking on brain structure, neurochemistry and blood flow.
- **Longitudinal MR spectroscopic imaging and neurocognitive studies**
  - Over 1 month of abstinence
  - Smoking and non-smoking RA
  - Effects of smoking on brain neurochemistry and neurocognition
- **Conclusions and implications**

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## Background

- **Chronic, heavy alcohol consumption is associated with abnormalities in:**
  - brain structure
  - neurometabolism
  - regional cerebral blood flow
  - neurocognition
- **The most frequently used substances among the alcohol dependent are tobacco products:**
  - 80% of alcohol-dependent individuals are cigarette smokers (50-90% are nicotine dep.)
  - 70-90% seeking treatment for alcohol use disorders in North America are heavy smokers

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## Background II



- **Drinking AND smoking - Why?**
  - Nicotine and alcohol potentiate each others rewarding properties
  - Paired use of nicotine and alcohol produce classical conditioned cue reactivity
  - Nicotine counteracts the adverse effects of alcohol on cognition and motor incoordination
  - Genetic susceptibility

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## The Big Question

Does chronic cigarette smoking contribute to the brain abnormalities linked to chronic alcohol-dependence?



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## Alcohol-Induced Brain Injury

3D MRI

57 year old alcoholic



ca. 1866 kg  
ca. 160,000 drinks

57 year old social drinker



ca. 60 kg  
ca. 5000 drinks

Lifetime alcohol consumption

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Sullivan, NIAAA Monograph 2000

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## Alcohol-Induced Brain Injury

MRI (T1-weighted image)



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Hommer et al., 2001

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## Alcohol-Induced Brain Injury

CT and MRI



- Cortical gray matter (GM) and white matter (WM) atrophy, especially frontal lobes
- Enlarged sulci and ventricles
- Reduced volume and other abnormalities of subcortical structures
- Gender differences ?
  - conflicting results
- Effects of smoking *not* considered

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## Smoking-Induced Brain Injury (No hx Alcohol Use Disorders)



- **CT** (Hayee et al., 2003)
  - Greater brain atrophy > 50 years
- **MRI** (Brody et al., 2004)
  - Smaller cortical GM volumes and densities in the prefrontal cortex
  - Smaller left anterior cingulate volume
  - Lower GM densities in the right cerebellum
  - Same areas affected by alcoholism

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## Neuropsychological Findings in Chronic Smokers



- **Memory** (Hill et al., 2003)
- **Working memory** (Ernst, 2001)
- **Executive functions** (Razani et al., 2004)
- **Psychomotor speed & cognitive flexibility** (Kalmijn et al., 2002)
- **General intellectual abilities** (Deary et al., 2003)
- **Abnormal decline in cognition** (Ott et al., 2004)
- **Increased risk for various forms of dementia – AD** (Launer et al., 1999; Ott et al., 1998)
- **Greater incidence of mood disorders** (Gilman & Abraham, 2001)

**Dysfunction in above cognitive abilities - same as attributed to alcohol dependence**

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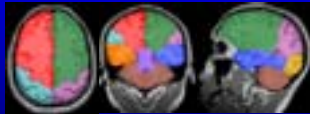
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## Volumetric MRI



Alcohol Clin Exp Res, Aug. 2005

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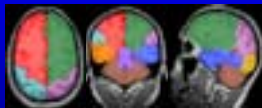
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## Volumetric MRI

Automated Segmentation of MR Images

Standard clinical 1.5T MRI



CSF



Gray matter



White matter



Studholme C, Song E et al. 2002

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## Volumetric MRI

### Participants

- **Male RA studied 6 ± 2 days after last drink**
  - DSM-IV alcohol dependence (all with physiologic dependence)
  - No history of other drug dependence, and neurologic or psychiatric disorders (except unipolar mood disorders)
- **Retrospective smoking classification**
  - Non-smoking recovering alcoholics (nsRA)
  - Actively smoking recovering alcoholics (sRA)
  - Non-smoking light drinkers (nsLD)
  - Actively smoking light drinkers (sLD)

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## Volumetric MRI

### Demographics

	nsLD n = 23	sLD n = 7	nsRA n = 13	sRA n = 24
Age	47.5 ± 6.0	38.1 ± 8.7	49.8 ± 9.7	49.4 ± 8.3
Education	16.6 ± 2.4	15.8 ± 1.3	13.7 ± 2.5	13.4 ± 2.4
Lifetime mean [dri/mo]	14 ± 14	16 ± 18	200 ± 120	290 ± 120

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## Volumetric MRI

### Smoking Characteristics

- **sRA**

		range
– Fagerstrom	5.5 ± 1.9	2 - 10
– Cigarettes per day	21 ± 8	5 - 35
– Smoking Duration (yrs)	23 ± 13	2 - 44
– Pack years	26 ± 19	1 - 70
- **sLD**
  - 86% (6 of 7) smoked daily or nearly every day
  - 14% (1 of 7) smoked 1 – 2 times per week

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## Volumetric MRI

### Gray Matter z-scores

Region	nsLD n = 23	sLD n = 7	nsRA n = 13	sRA n = 24
Frontal	0.0 ± 1.0	-0.59 ± 0.57	-0.06 ± 0.84	-0.33 ± 0.83
Parietal	0.0 ± 1.0	-0.39 ± 0.57	-0.46 ± 0.69	-0.90 ± 0.66
Temporal	0.0 ± 1.0	-0.67 ± 0.81	-0.33 ± 1.06	-0.83 ± 0.98
Occipital	0.0 ± 1.0	-0.51 ± 0.51	-0.07 ± 0.65	-0.66 ± 0.92

Alcohol effects: RA < LD

Parietal GM p = .001  
Temporal GM p = .04

Smoking effects: smoke < non-smoke

Parietal GM p = .05  
Temporal GM p = .04  
Occipital GM p = .02

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## Volumetric MRI

### WM volumes

- Alcohol effects: RA < LD

- Frontal WM p = .03
- Parietal WM p = .002

- Smoking effects: Smokers > Non-smokers !!

- Temporal WM p = .005
- Frontal WM p = .08

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## Volumetric MRI

### Relationships Between Neurocognition and Regional Volumes

- nsRA

- Visuospatial learning & visuospatial memory

- Occipital WM r > 0.69 p < .009
- Temporal WM r > 0.76 p < .002

- Visuomotor scanning speed/incidental learning

- Frontal WM r = 0.76 p = .001

- sRA

- NO significant relationships

- Not due to a restriction of range

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### Possible Mechanisms for Brain Volumetric Changes in Smokers

- **GM and WM**
  - Cigarette Smoke → *direct* adverse effects on brain tissue through chronic exposure to noxious agents
  - Cigarette Smoke → *indirect* adverse effects
    - Cerebrovascular compromise
    - Mild hypoxia ?
  - Mechanisms independent or in concert

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### Possible Mechanisms for Volumetric Increases in Lobar WM of Smokers

- Minor cytotoxic swelling
- Minor vasogenic swelling
- Mild inflammatory state 2° to oxidative stress/damage
- Mechanisms independent or in concert

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### Volumetric MRI: Summary and Implications

- **Smoking may compound alcohol-induced volume loss in GM:** Greater risk for future cognitive decline?
  - Greater than normal atrophy (irrespective of etiology) related to greater risk for cognitive decline with age
- **Smoking may be associated with increases in temporal WM volume:** Premorbid? Pathological?
- **Smoking in RA appears to modulate structure-function relationships:** Pathological? Persistent?

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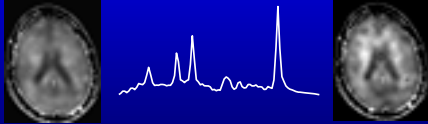
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# Quantitative MR Spectroscopic Imaging (MRSI)



Alcohol Clin Exp Res, Dec. 2004

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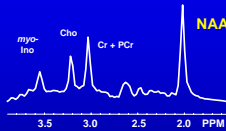
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## Quantitative MRSI

<sup>1</sup>H MRSI Metabolites I



Peak integral proportional to metabolite concentration !

### N-acetylaspartate (NAA):

- Marker of neuronal integrity
  - Grey Matter: neuronal density, cell body size
  - White matter: axonal integrity
- Possible marker of mitochondrial function (i.e., ATP synthesis)
- Osmolyte ?

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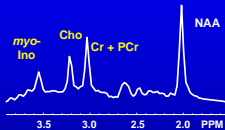
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## Quantitative MRSI

<sup>1</sup>H MRSI Metabolites II



Peak integral proportional to metabolite concentration !

- **Choline-containing compounds (Cho):**  
Membrane synthesis/turnover (membranes, myelin)
- **Creatine-containing compounds (Cr):**  
High-energy metabolites, osmolyte
- **Myo-Inositol (ml):**  
Osmolyte, putative marker of astrocytes

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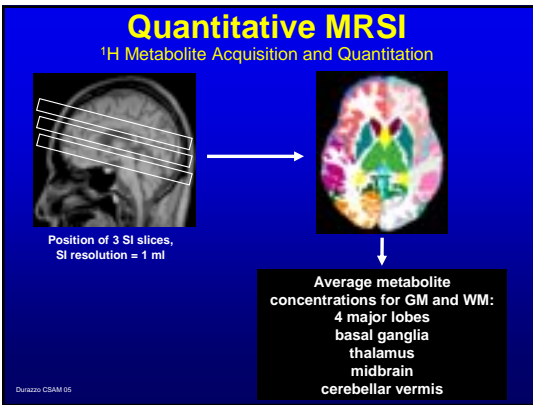
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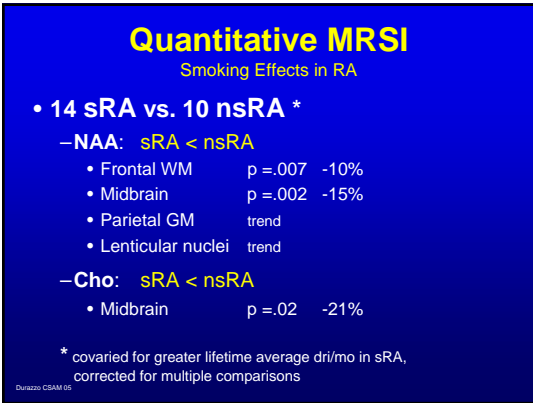
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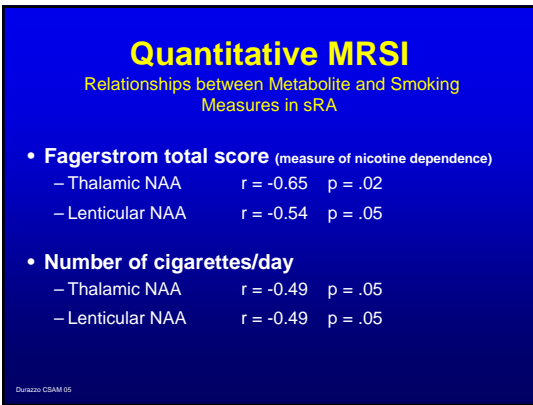
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## Quantitative MRSI

Relationships between Metabolite Levels and Neurocognition

- **nsRA**

- **Cerebellar vermis NAA**

- Visuospatial learning  $r = 0.72$   $p = .02$
    - Visuospatial memory  $r = 0.71$   $p = .02$

- **sRA**

- **Cerebellar vermis NAA**

- Visuomotor scanning speed/  
incidental learning  $r = 0.59$   $p = .05$

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## Possible Mechanisms of Lower Metabolite Levels in sRA

- Same as those for GM volume changes
  - Direct and indirect effects of smoking

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## Quantitative MRSI

Summary and Implications

- **Lower NAA frontal WM and midbrain in sRA**

- Premorbid ?
  - Greater deficiencies in executive functions ?
  - Less able to integrate treatment during early recovery ?

- **Greater metabolite abnormalities in midbrain of sRA**

- Potential alterations of function of midbrain tissue (e.g., VTA) that is part of the "Reward" pathway

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## Longitudinal Metabolite Changes Over 1 Month of Abstinence from Alcohol

	nsRA n = 11	sRA n = 14
• <b>NAA</b>		
• Frontal GM	6% ↑	5% ↑
• Frontal WM	8% ↑	6% ↓
• Parietal WM		6% ↓
• Occipital WM		
• <b>Cho</b>		
• Frontal GM	14% ↑	8% ↑
• Parietal GM	12% ↑	
• Frontal WM	16% ↑	11% ↑
• Parietal WM	17% ↑	
• Temporal WM	7% ↑	
• Occipital WM	13% ↑	

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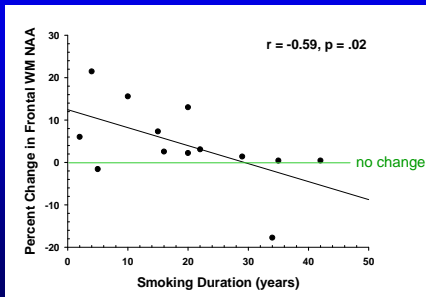
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## Smoking Duration vs. Frontal WM NAA Change Over 1 Month in sRA



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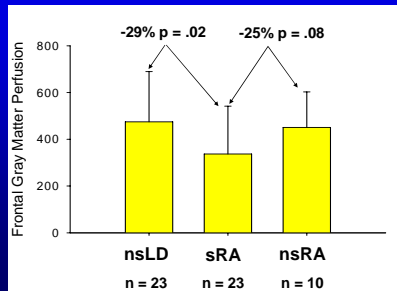
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## Frontal GM Perfusion (Blood Flow) 1-week abstinent RA



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## Neurocognition

### 1-month Abstinent RA

- **Longitudinal** (Over 1 month of abstinence)
  - nsRA: Improving visuospatial learning and working memory
  - sRA: No recovery of visuospatial learning or working memory over 1 month
- **Cross-sectional** (At 1 month of abstinence)
  - nsRA > sRA in auditory-verbal learning and memory, processing speed.

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## Summary and Implications I

- Preliminary results
- **Cross-sectional**: 1-week abstinent RA, chronic cigarette smoking may compound alcohol-induced abnormalities in brain:
  - structure
  - neurochemistry
  - perfusion (blood flow)
- Chronic smoking may modulate relationships between MR-based neurobiological measures and neurocognition

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## Summary and Implications II

- **Longitudinal**: smoking during short-term abstinence may interfere with recovery of:
  - regional NAA (neuronal integrity) and Cho (membrane synthesis/turnover)
  - visuospatial memory and working memory
- Chronic smoking in previous studies of RA may have:
  - accounted for a portion of the brain injury and cognitive deficits attributed solely to excessive alcohol
  - modulated relationships between neurobiological and neurocognitive measures

**53% of our RA were smokers !!**

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## Summary and Implications III

- If smoking in RA modulates brain structure, biochemistry and blood flow
  - smokers may respond differently to pharmacological interventions for AUD than non-smokers
- Concurrent participation in a smoking cessation program advised ?
  - pharmacological intervention should target both smoking and drinking (e.g., naltrexone, acamprosate, topiramate, perhaps selective nicotinic antagonists) ?

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- Derek Flenniken: data base management expertise
- The study participants, who made this research possible.

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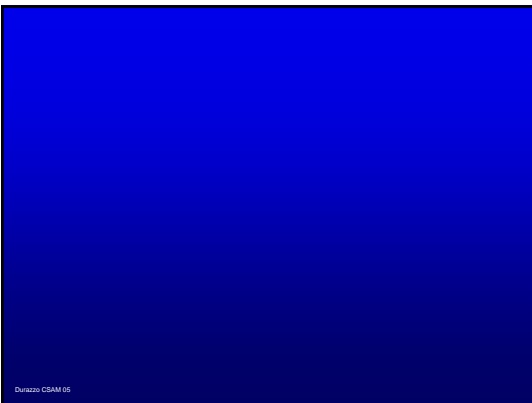
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