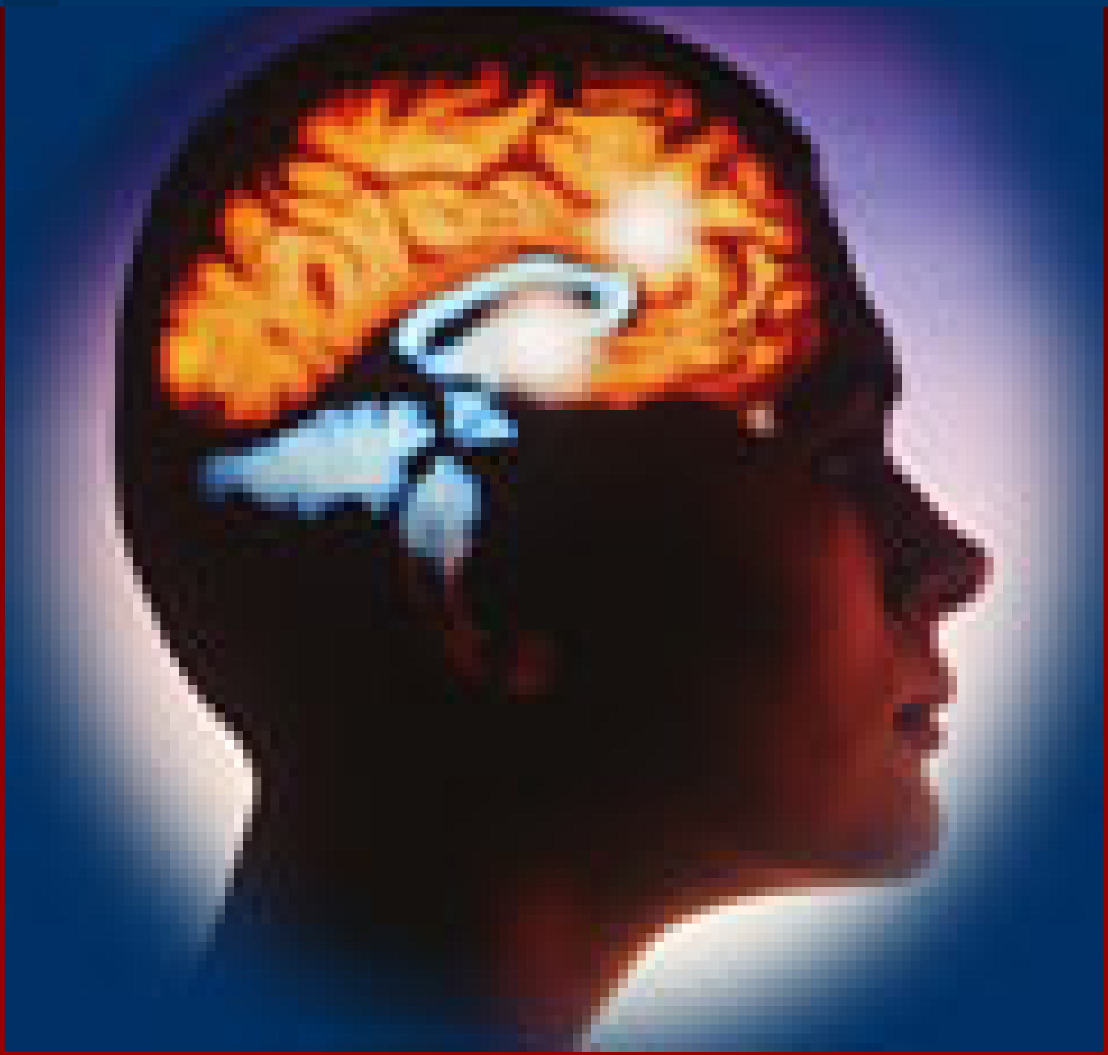
CTNA



Methodology of Magnetic Resonance Spectroscopy: MRS

Graeme Mason, Ph.D.

Depts. of Psychiatry and Diagnostic Radiology
Yale University, New Haven, CT

Welcome to New Haven

Overview

What is MRS?

What is Spectroscopic Imaging?

What is Image Segmentation?

What is ^{13}C MRS?

Overview

What is MRS?

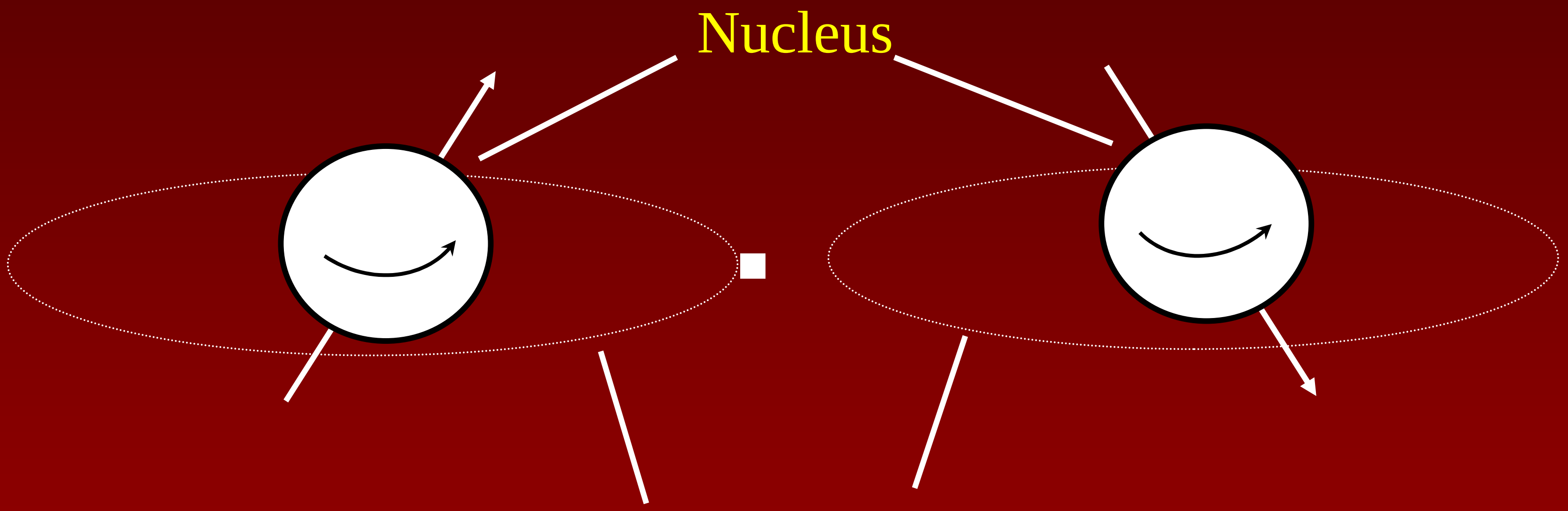
What is Spectroscopic Imaging?

What is Image Segmentation?

What is ^{13}C MRS?

Methods: What is MRS?

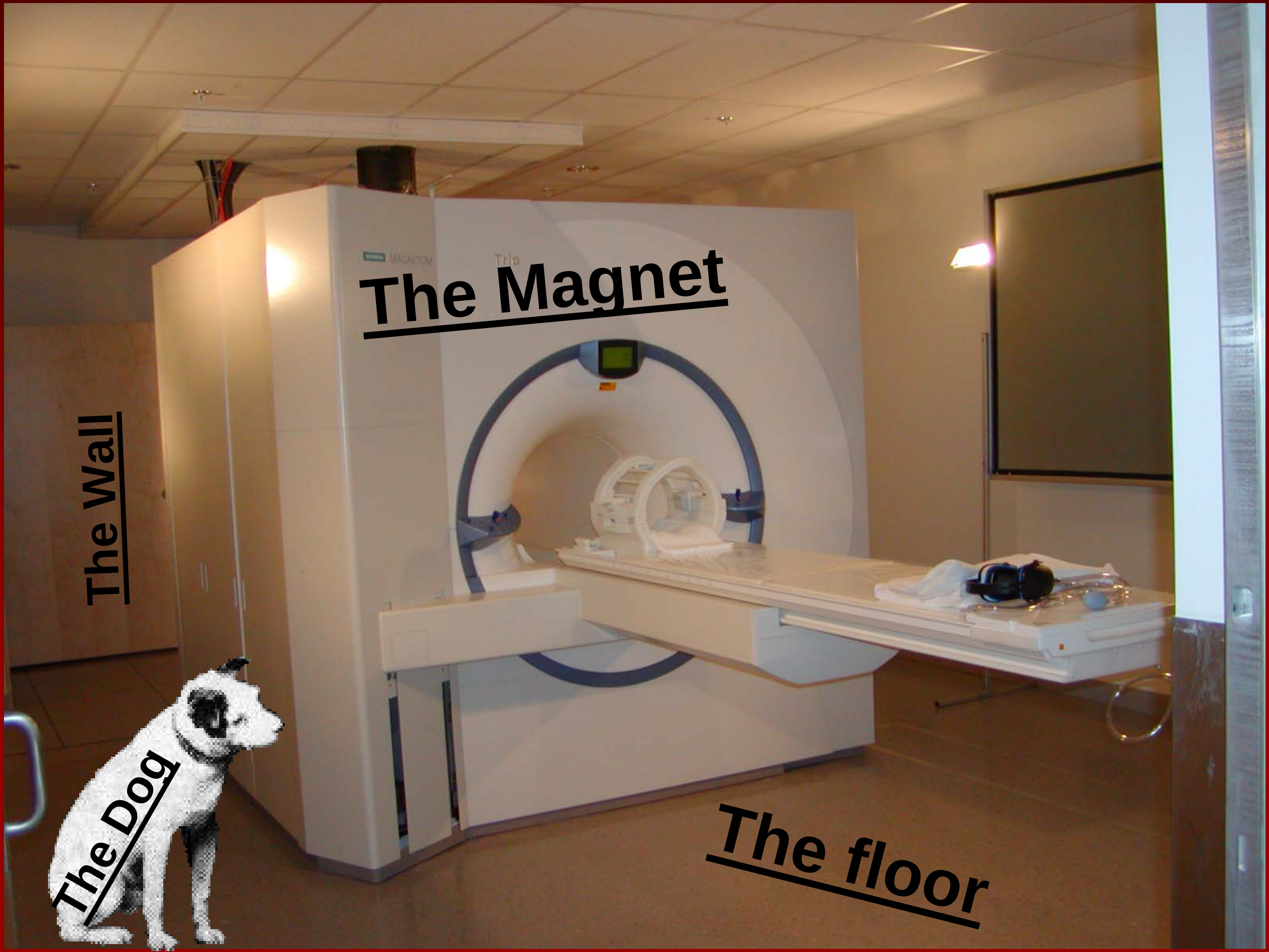
Nuclear Magnetic Resonance Spectroscopy



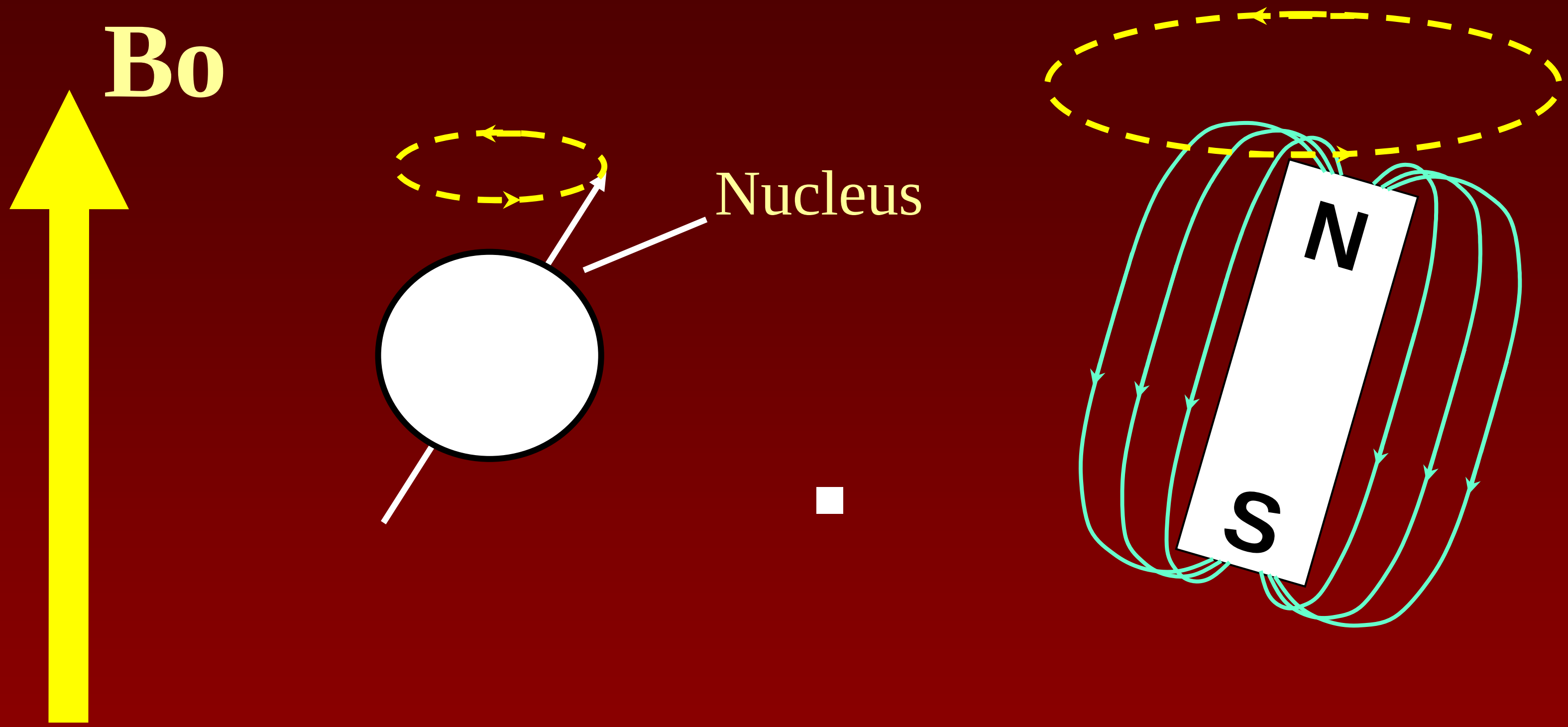
Spin of nucleus is either 'up' or 'down'.

Methods: What is MRS?

Subject lies inside a large magnet to orient the spins.



Rotating Magnetic Dipole



In a large magnetic field (scanner magnet), the magnetic dipole precesses about the axis of the large field with a frequency $\nu = \gamma B_o/2\pi$.

Only nuclei with *spin* can be detected with MRS.

Some NMR-Visible Nuclei

^{1}H – water, lipids, amino acids, many other metabolites
$\gamma = 2.67 \times 10^4$ radians/sec/Gauss

^{13}C - amino acids, neurotransmitters, glucose, lipids, acetate
$\gamma = 0.67 \times 10^4$ radians/sec/Gauss

^{15}N - metabolism of ammonia, amino acids

^{19}F - pharmacokinetics of fluoxetine and fluvoxamine

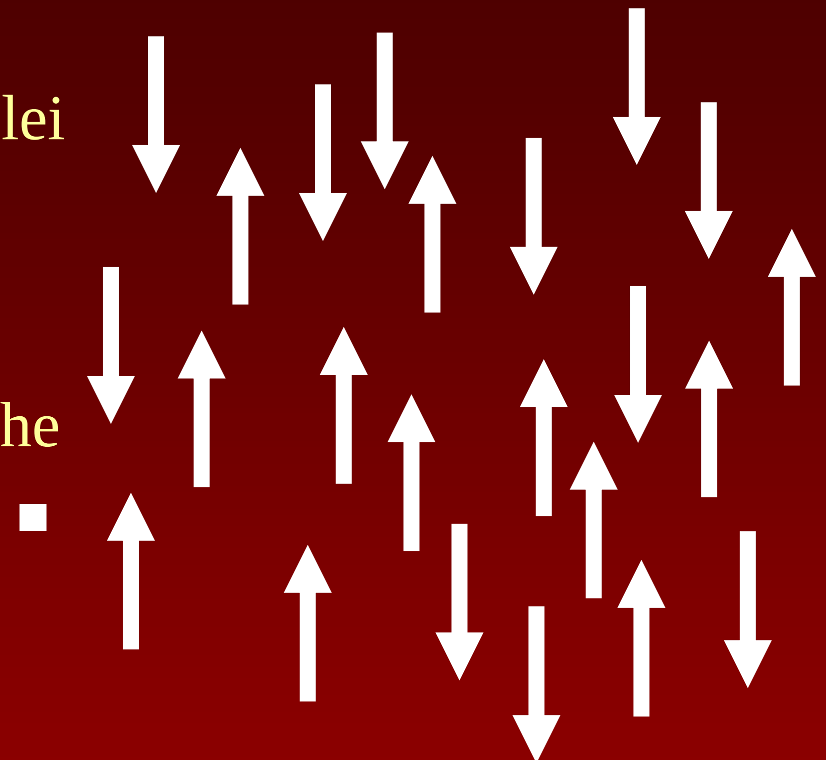
^{23}Na - effects of hypoxia, challenges to Na pumps

^{2}H - metabolism of fats

^{7}Li - pharmacokinetics of lithium

Transition from Quantum to Classical Mechanics

1.5 mM GABA, 13.5 cc voxel
contains 2.4 x 10^{22} hydrogen nuclei
for GABA detection



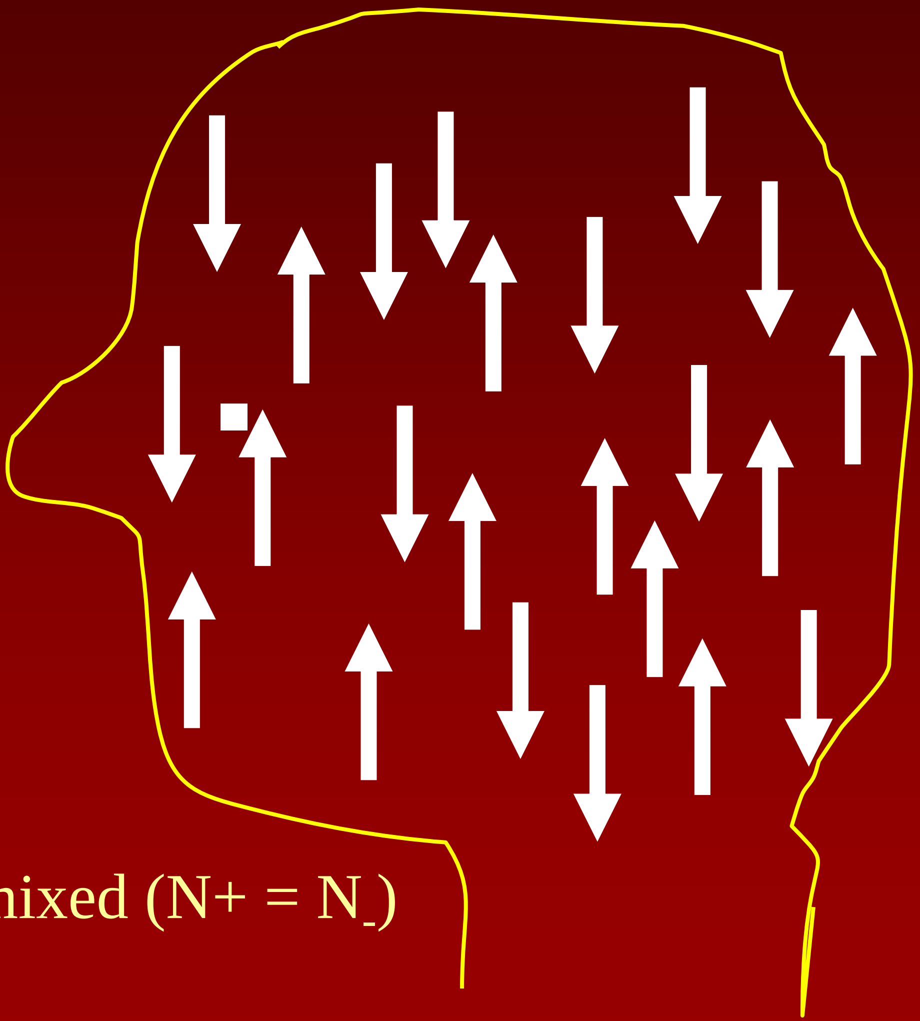
The large number of particles
allows a meaningful analysis of the
behavior of the whole group.

Boltzmann distribution:
$N_+/N_- = \exp(-\gamma h B_o / 2\pi kT)$

approximated as
$N_+/N- = 1 - \gamma h B_o / 2\pi kT$

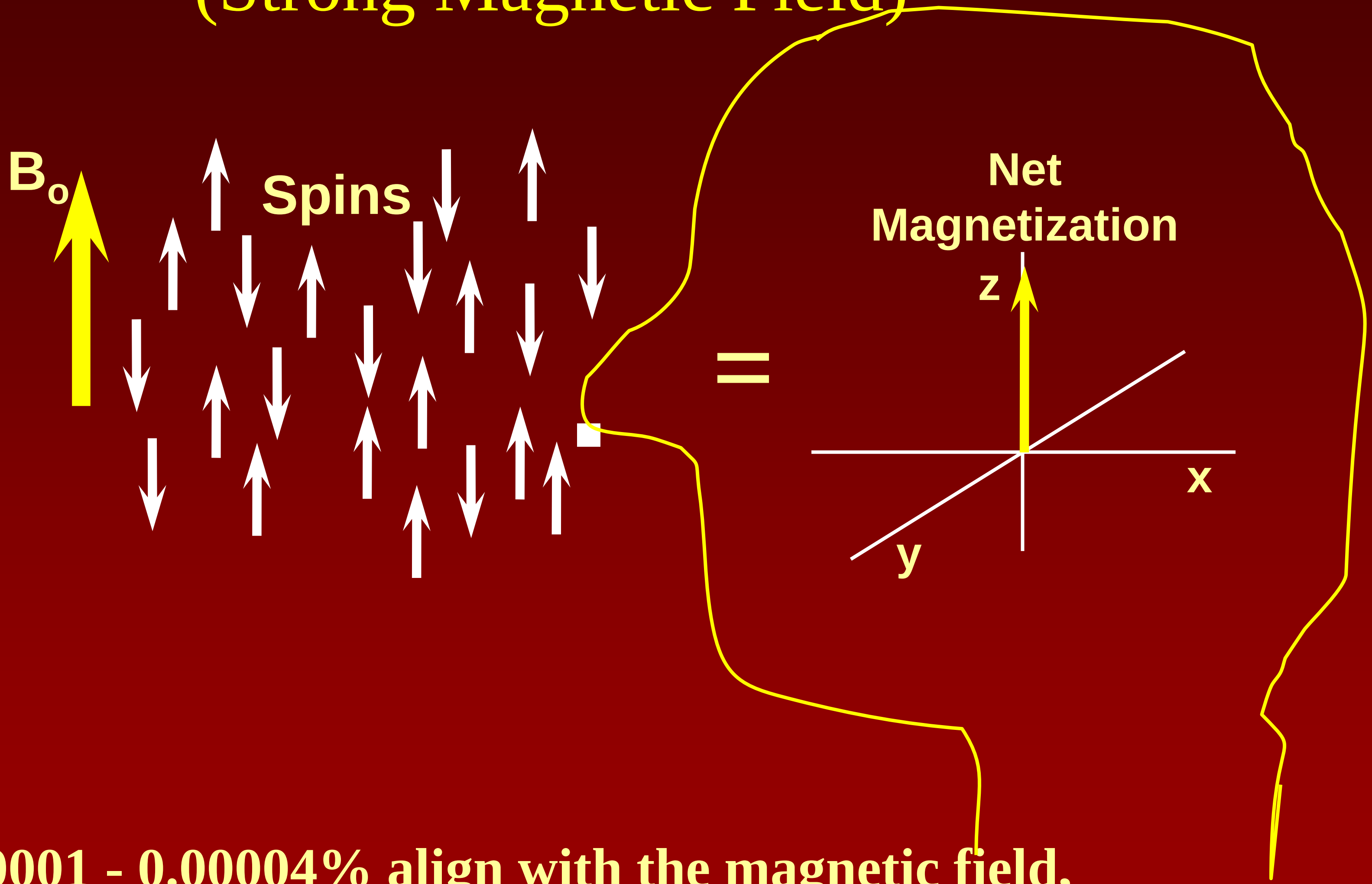
N_+ minus N- is the net magnetization:

Spin Orientation in a Head (Outside the Scanner)



Spins evenly mixed ($N_+ = N_-$)

Inside Scanner
(Strong Magnetic Field)

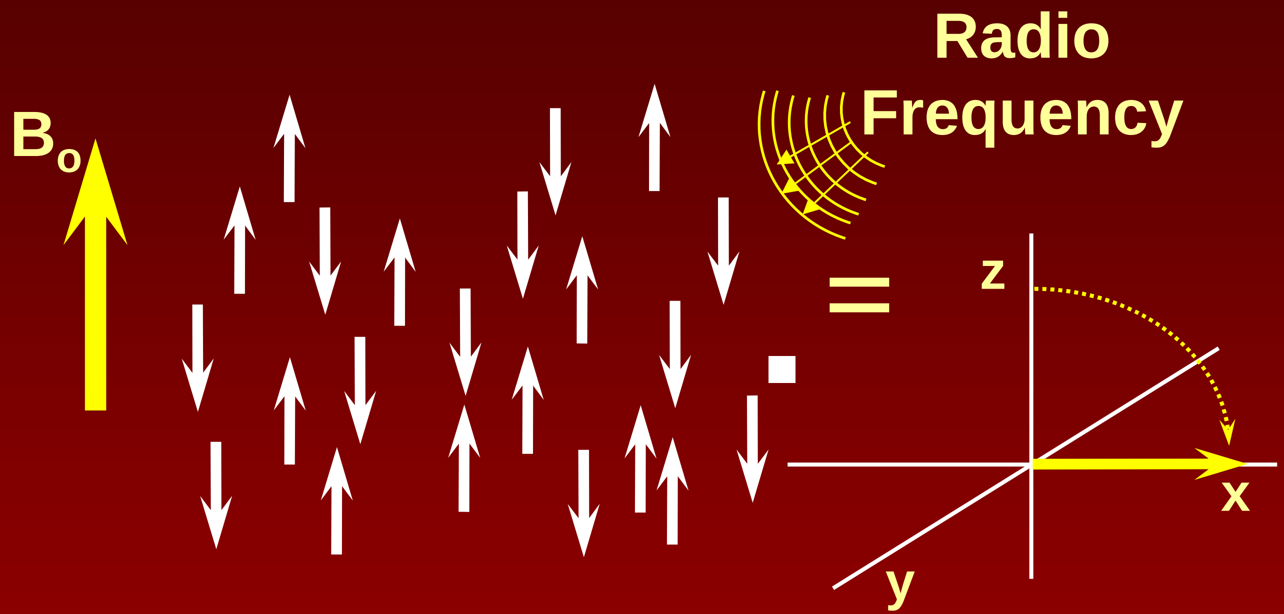


0.00001 - 0.00004% align with the magnetic field, creating net magnetization in the head.

What is MRS?

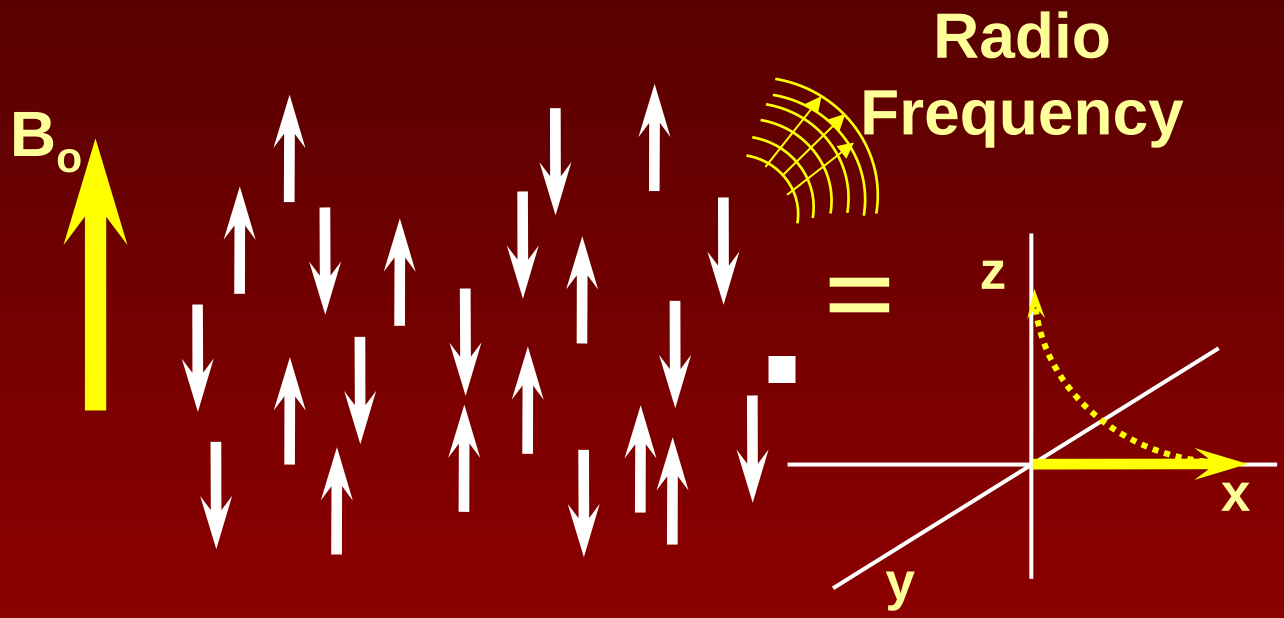
Subject lies inside a large magnet to orient the spins.

Radio Frequency Energy Applied



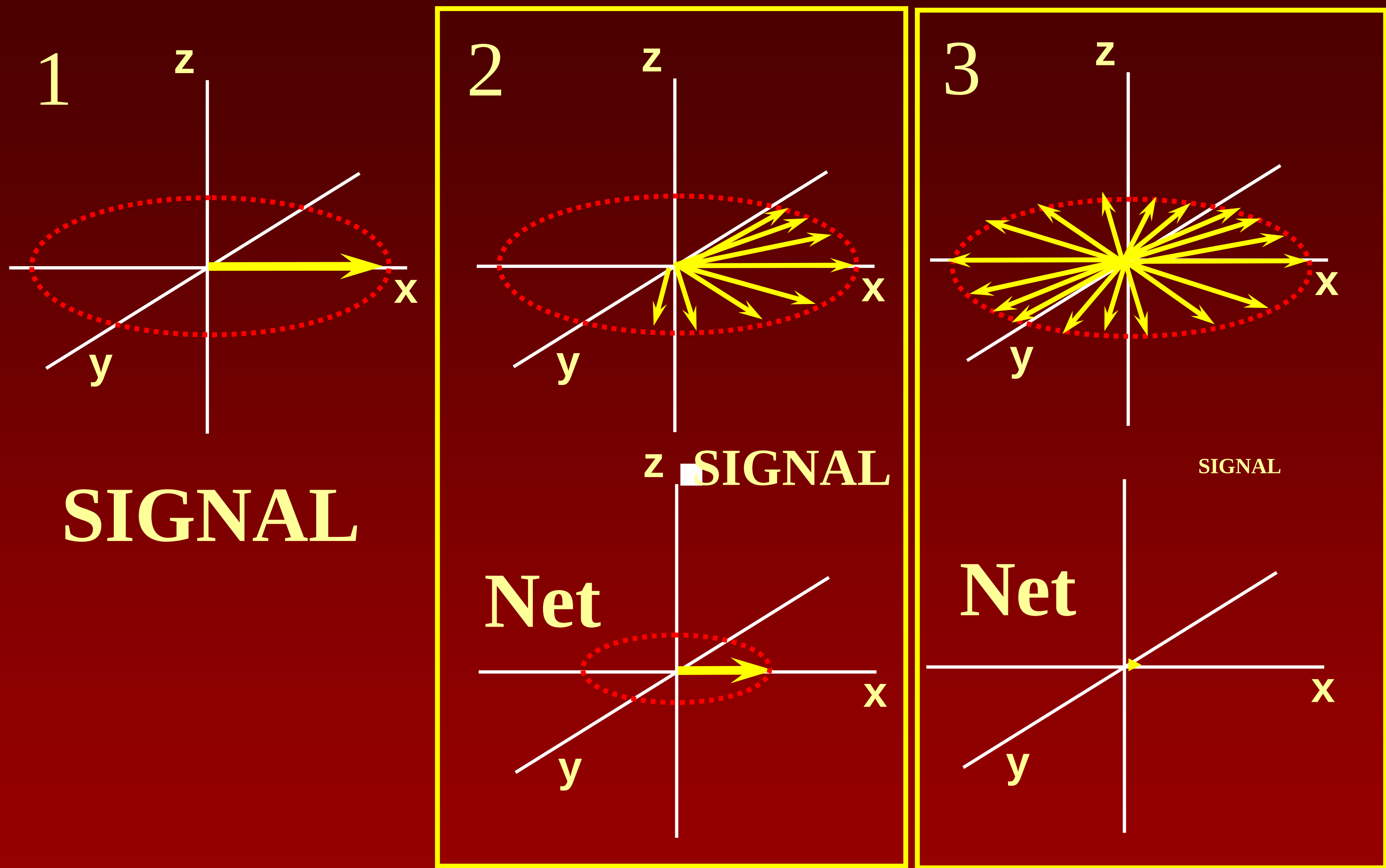
The net magnetization is altered by the application of energy at the proper frequency.

Longitudinal (T_1) Relaxation



The magnetization returns to its original orientation at a rate governed by the exponential constant T_1.

Transverse (T_2) Relaxation



Phase coherence is lost as the spins dephase due to microscopic magnetic field inhomogeneity.

MRS Frequencies Distinguish Chemicals: Sources of Differences in NMR Frequencies

1. Nucleus and Magnetic Field Strength (MHz)

Nucleus:

Example: ^{13}C frequency ≈ 25% ^{1}H frequency

Magnetic Field Strength:

For ^{1}H, 42.6MHz x field strength (Tesla)

Examples:

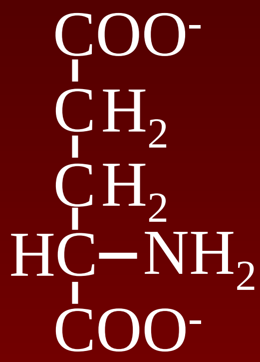
a. 1.5T = 63.9 MHz

b. 2.1T = 89.4 MHz (~public radio - Bridgeport)

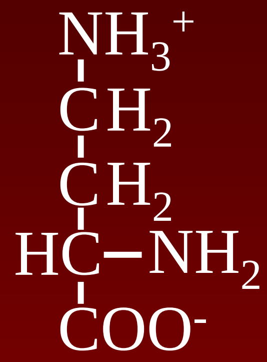
c. 4 T = 170 MHz

Sources of Differences in NMR Frequencies

2. Molecular identity (Hz to thousands of Hz)



Glutamate



Glutamine

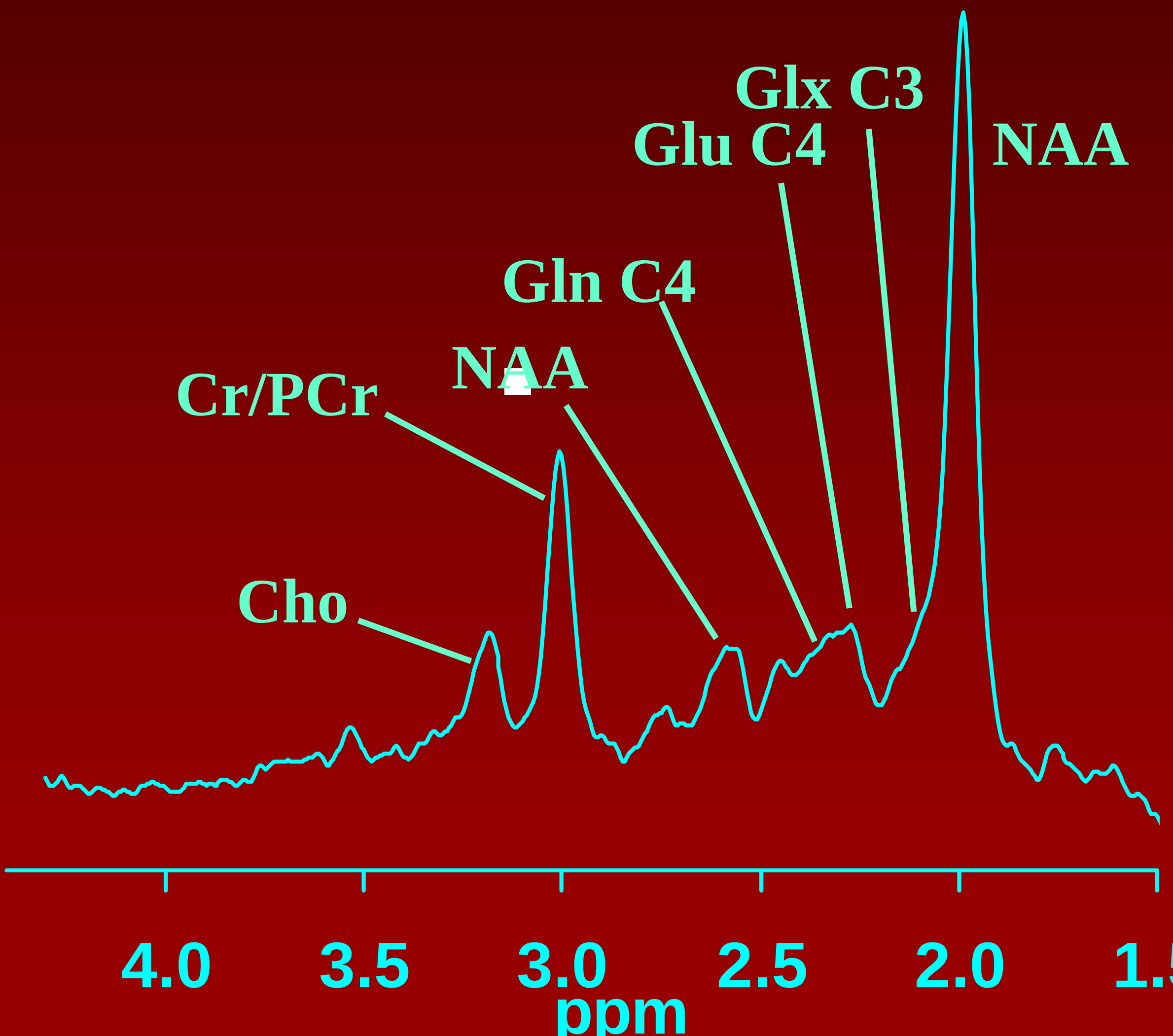
- Different molecules respond with slightly different frequencies.

- At 2.1T, glutamate responds at 89,633,931 Hz
  glutamine responds at 89,633,940 Hz

3. J-coupling: (Hz to hundreds of Hz) (used for GABA editing)

MRS

MRS of the human brain: chemicals separated by frequency



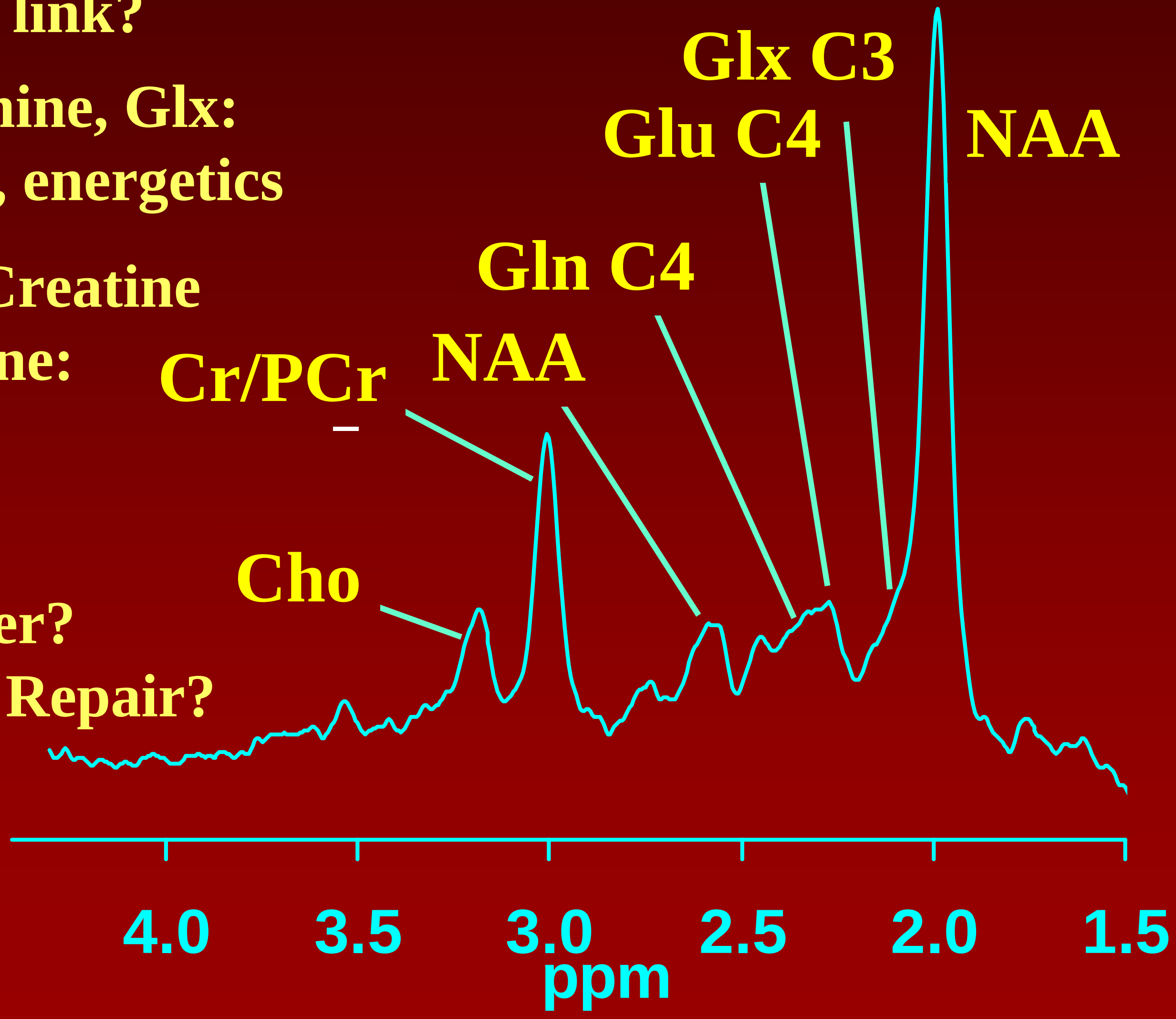
MRS: Significance

N-AcetylAspartate: neuronal viability, energetic link?

Glutamate, Glutamine, Glx: neurotransmission, energetics

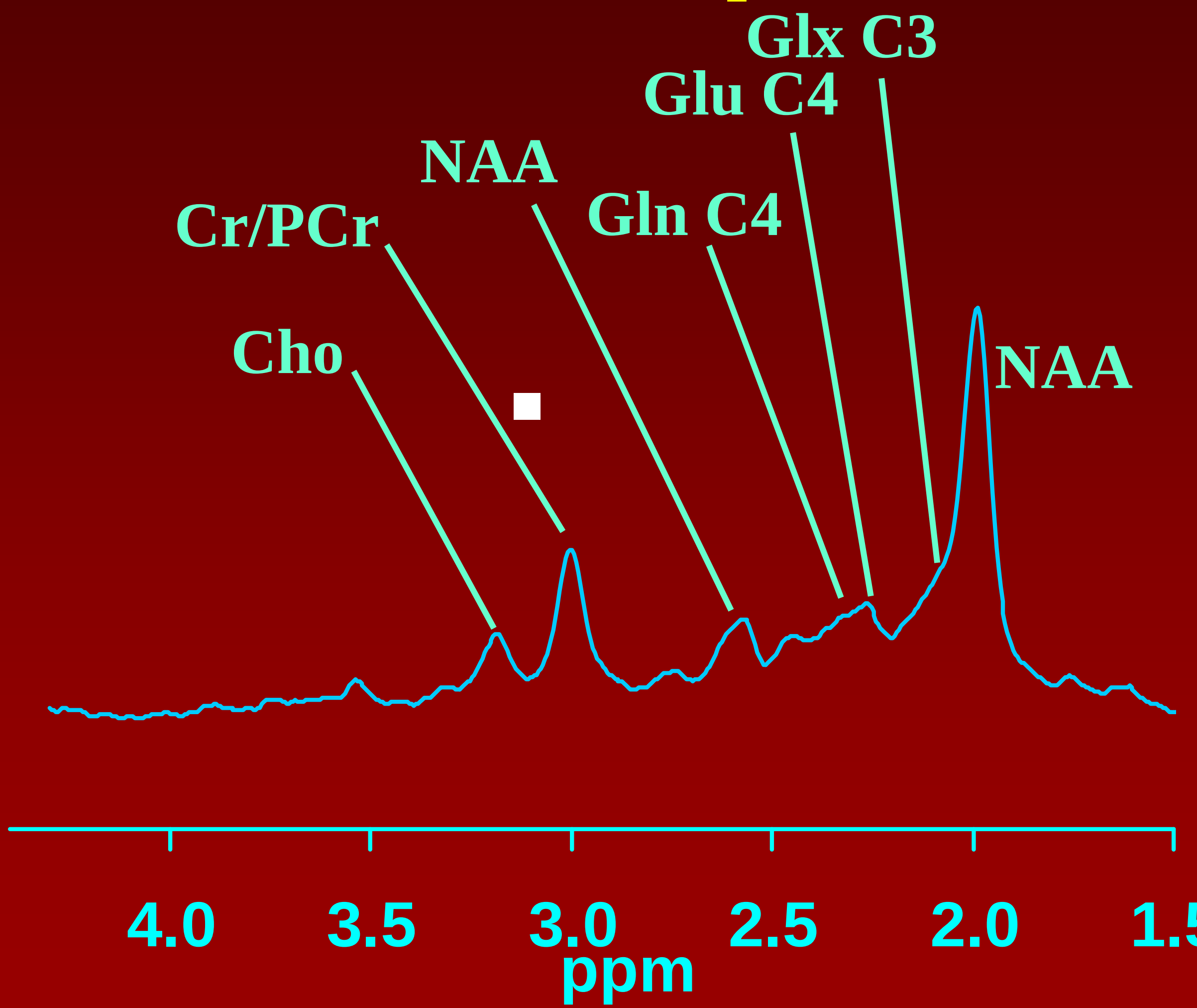
Cr/PCr: Total of Creatine and Phosphocreatine: Largely inert

Choline:
Membrane Turnover?
Cell Damage? Cell Repair?



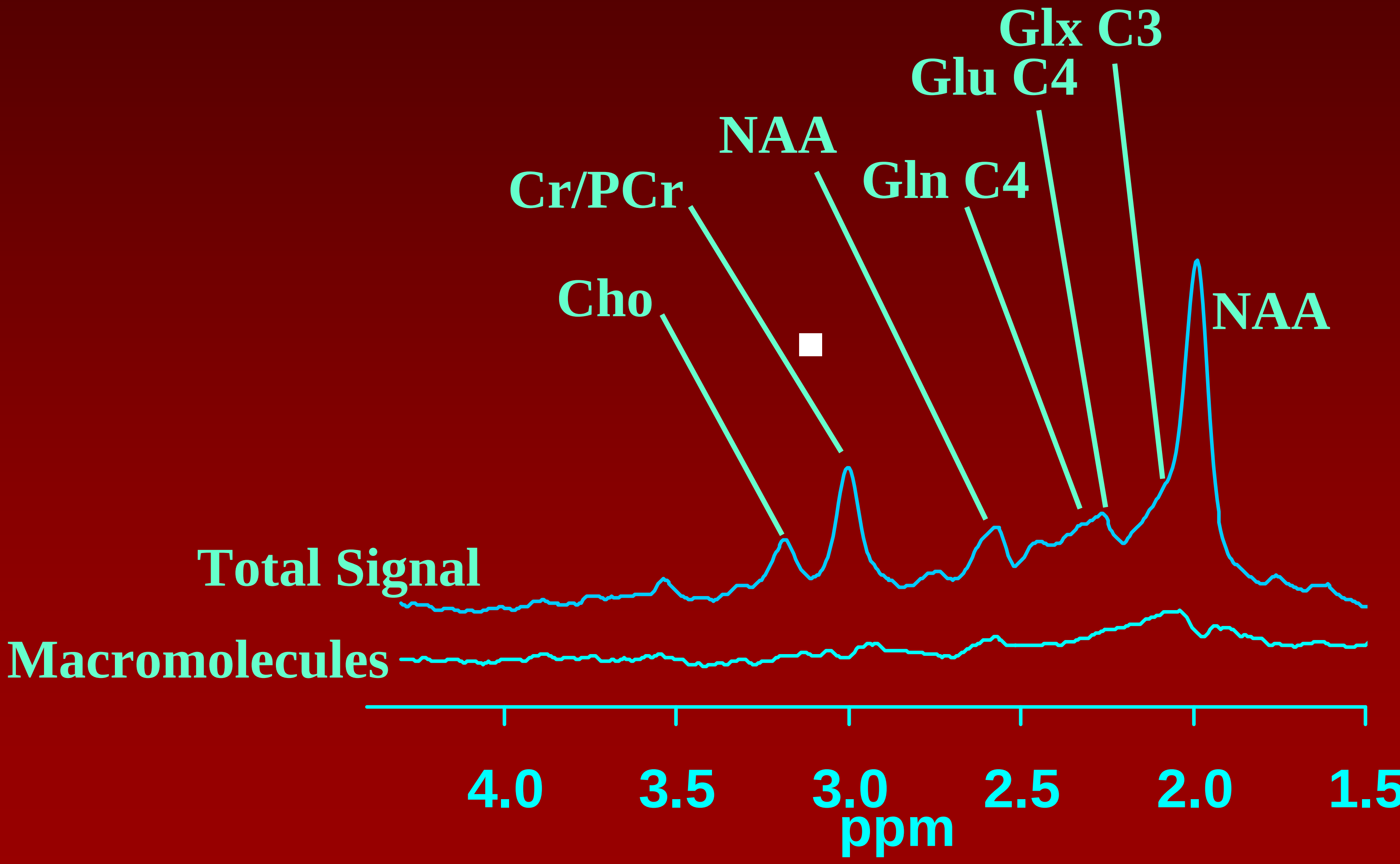
MRS

Short-echo measurement of glutamate, N-acetylaspartate, and other metabolite: What else is present?



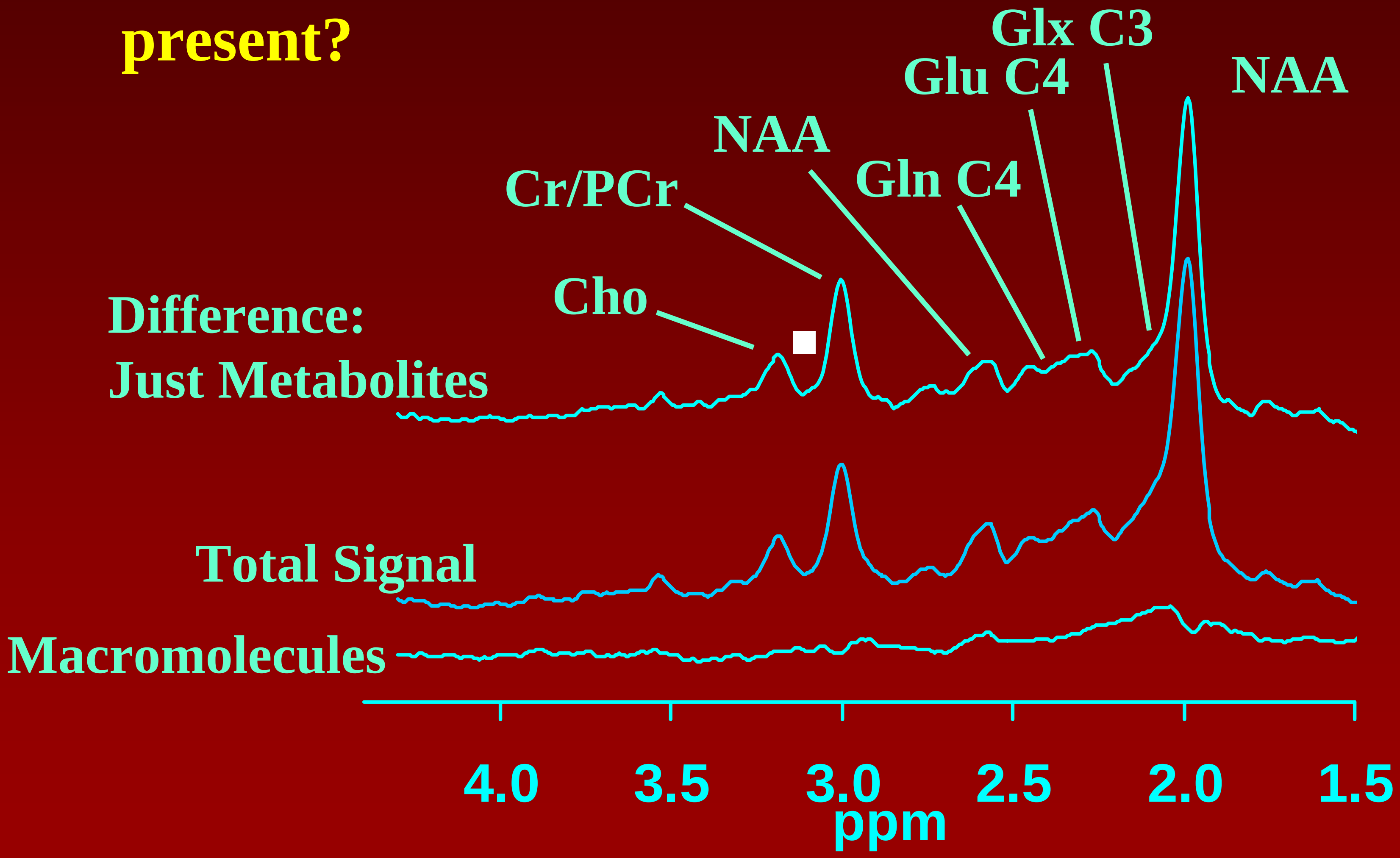
MRS

Short-echo measurement of glutamate, N-acetylaspartate, and other metabolite: Macromolecules in baseline



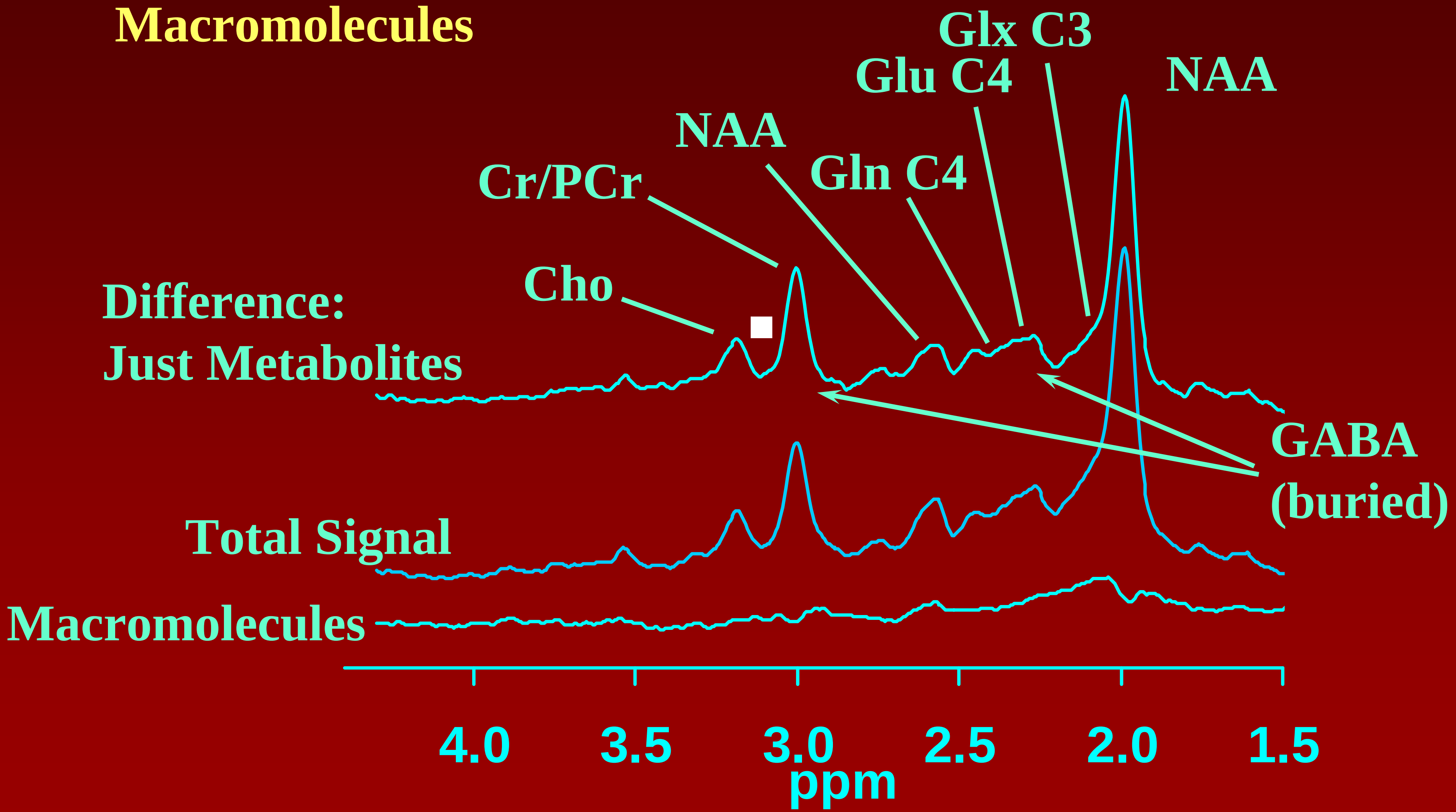
MRS

Short-echo measurement of glutamate, N-acetylaspartate, and other metabolite: Macromolecules out. What else is present?



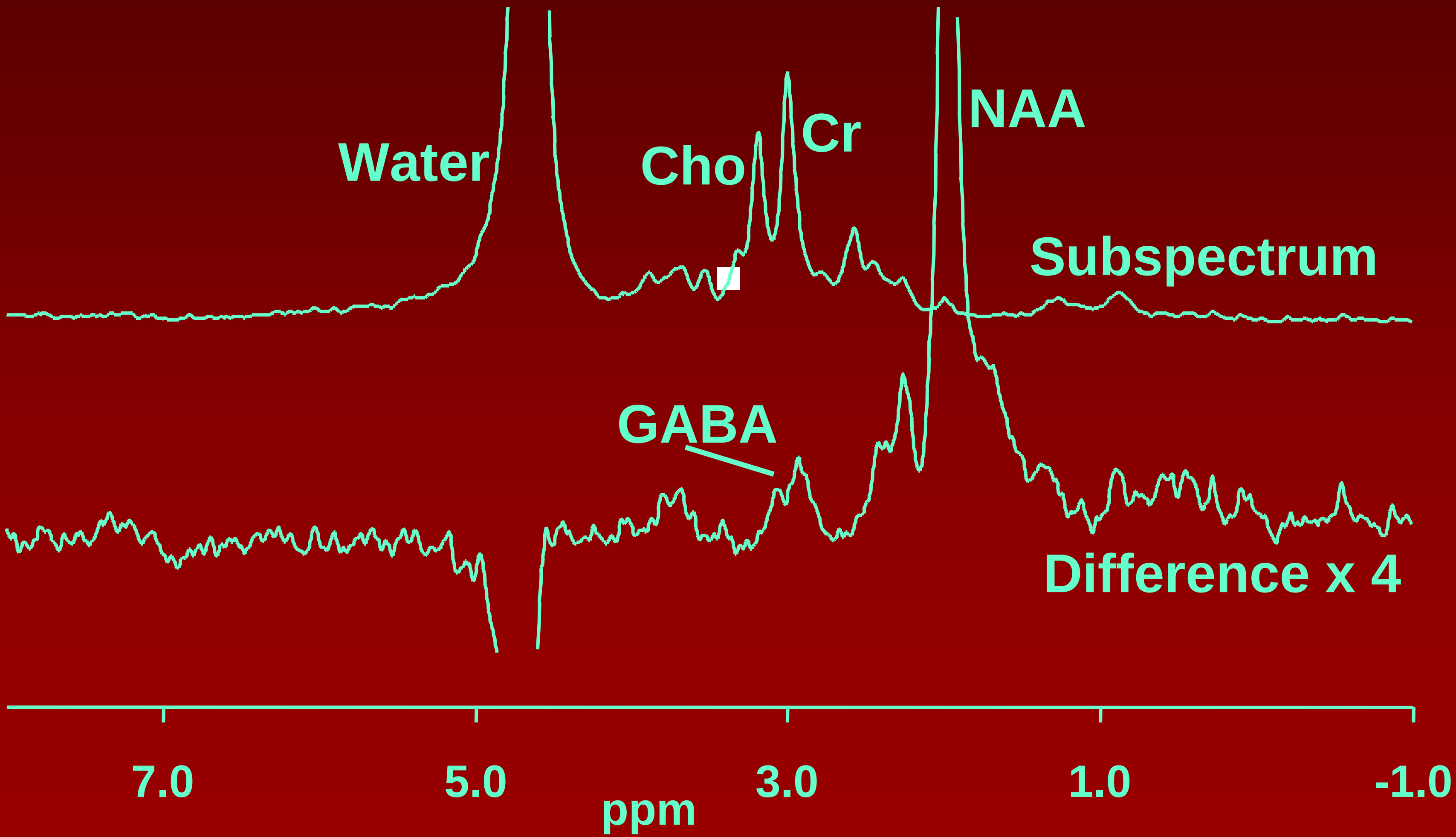
MRS

Short-echo measurement of glutamate, N-acetylaspartate, and other metabolite: Measurement and Removal of Macromolecules



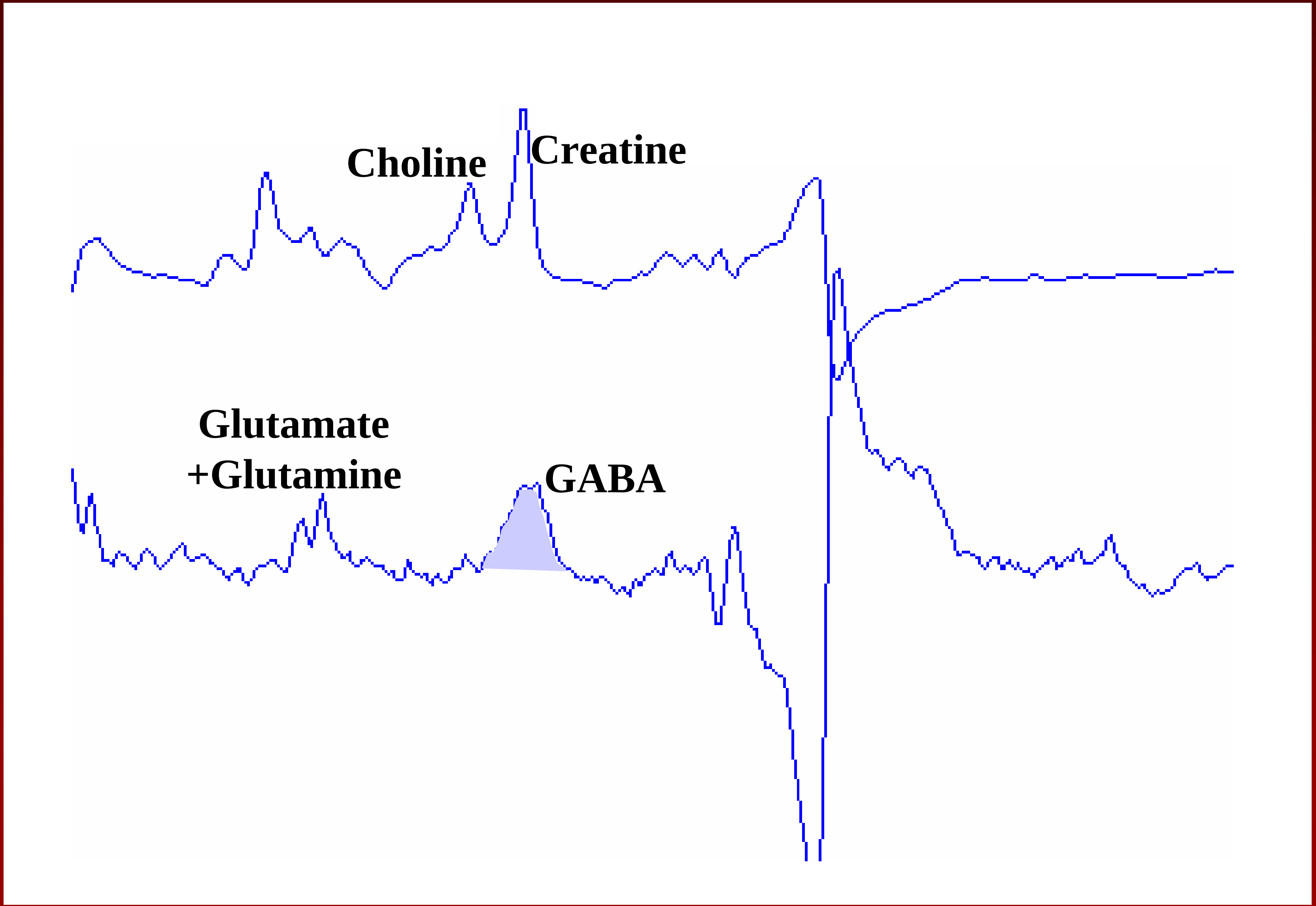
MRS

[1]H MRS measurement of GABA, Bruker 2.1T MR scanner, 13-22 cc occipital voxel: J-editing difference method

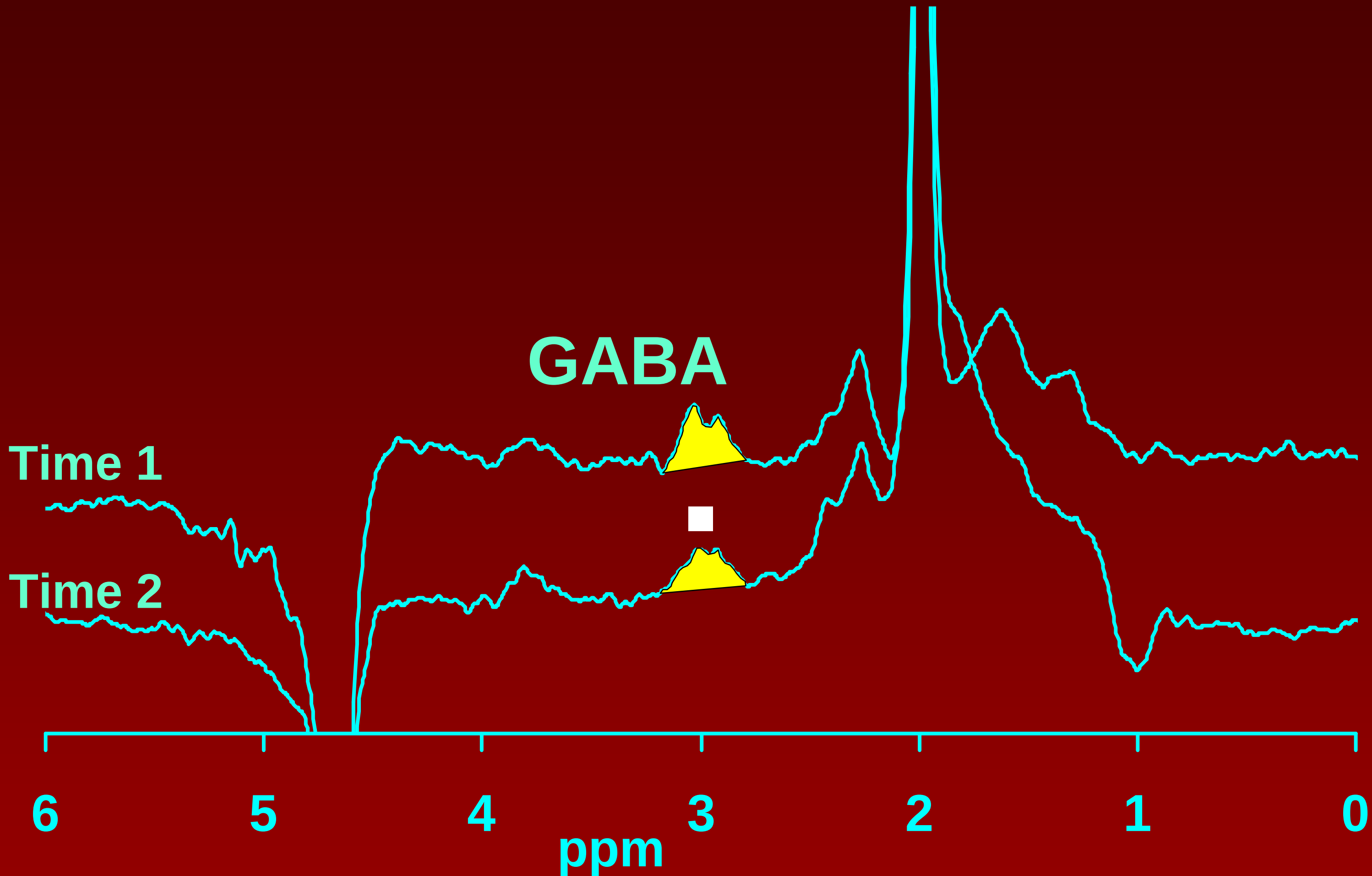


GABA Editing

- 8 cc at 4T.

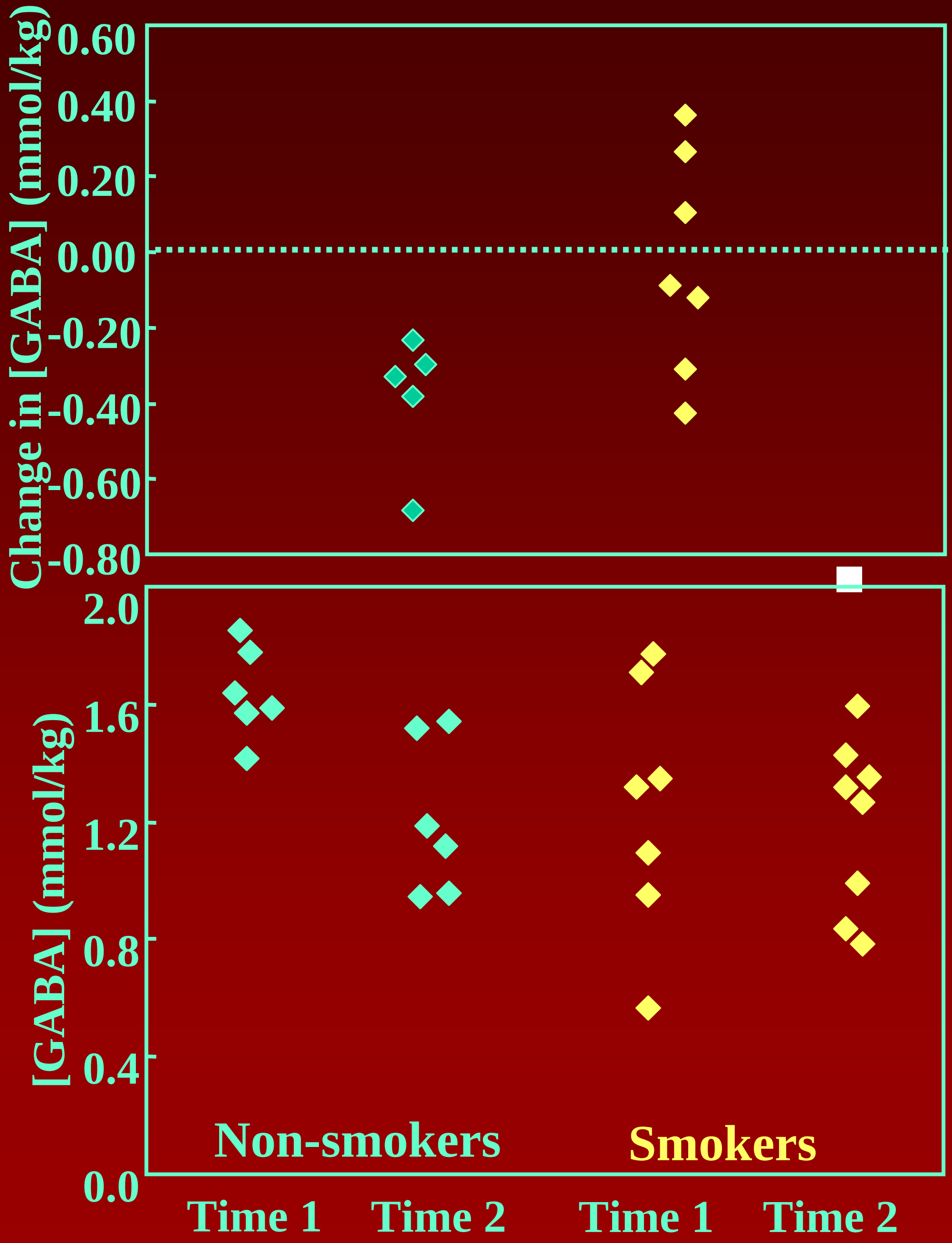


GABA in One Alcohol-Dependent Subject



Spectra of cortical GABA obtained in one subject at one week and one month of sobriety. GABA was reduced at one month.

Effects of 1 Month of Sobriety on GABA



- Changes in GABA levels with sobriety depended on smoking ($p = 0.03$).
- GABA in non-smokers fell by 0.39 ± 0.18 mmol/kg ($p = 0.004$), but GABA in smokers did not ($p = 0.75$).
- GABA in non-smokers at time 1 differed from the non-smokers' GABA at time 2 ($p = 0.03$).

Overview

What is MRS?

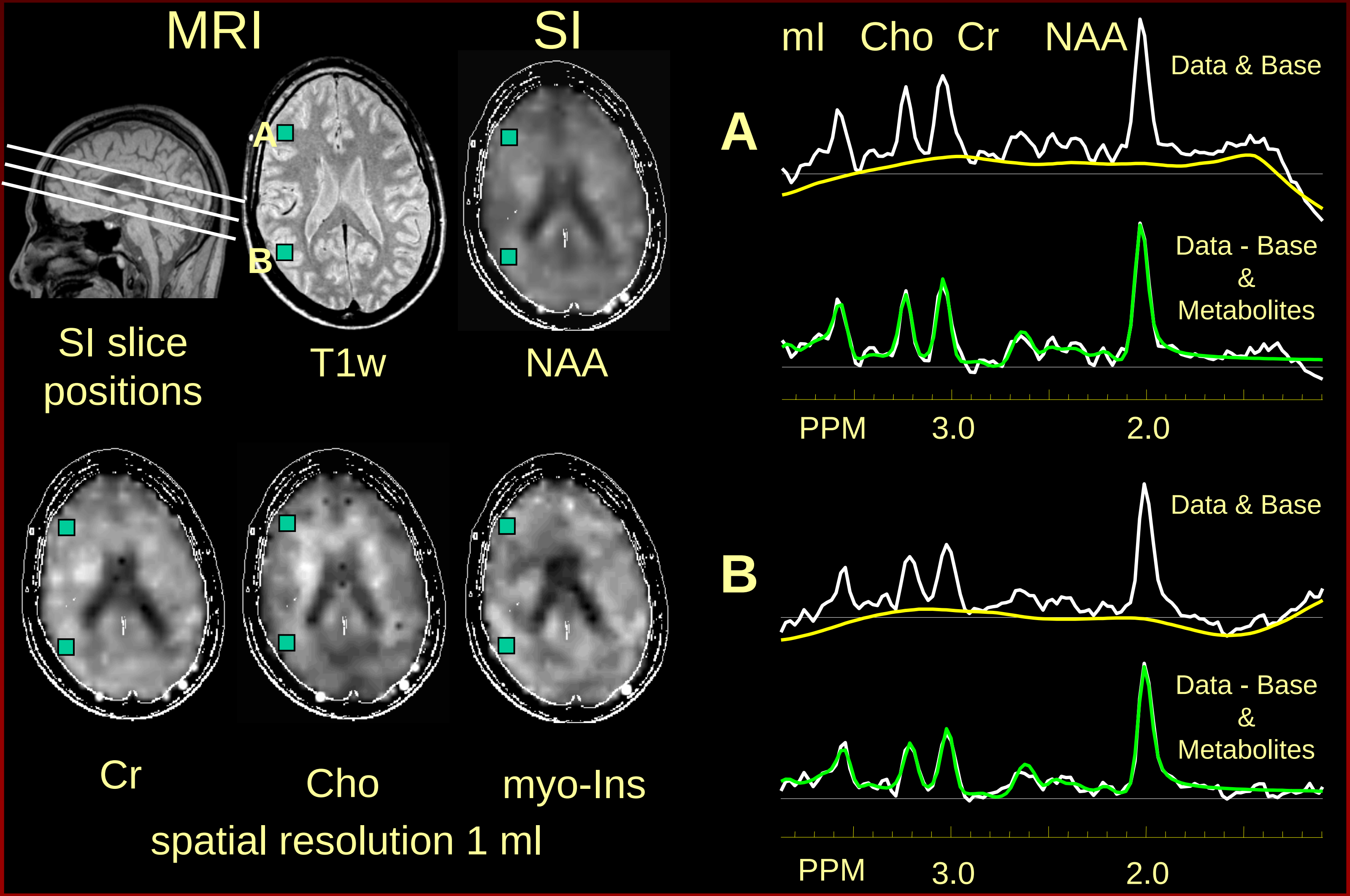
What is Spectroscopic Imaging?

What is Image Segmentation?

What is ^{13}C MRS?

^{1}H MR Spectroscopic Imaging TE = 25 ms

Metabolite Distribution and Quantification



Soher B et al. MRI 2000

Overview

What is MRS?

What is Spectroscopic Imaging?

▪

What is Image Segmentation?

What is ^{13}C MRS?

Image Segmentation

Creating images to quantify GM, WM, and CSF

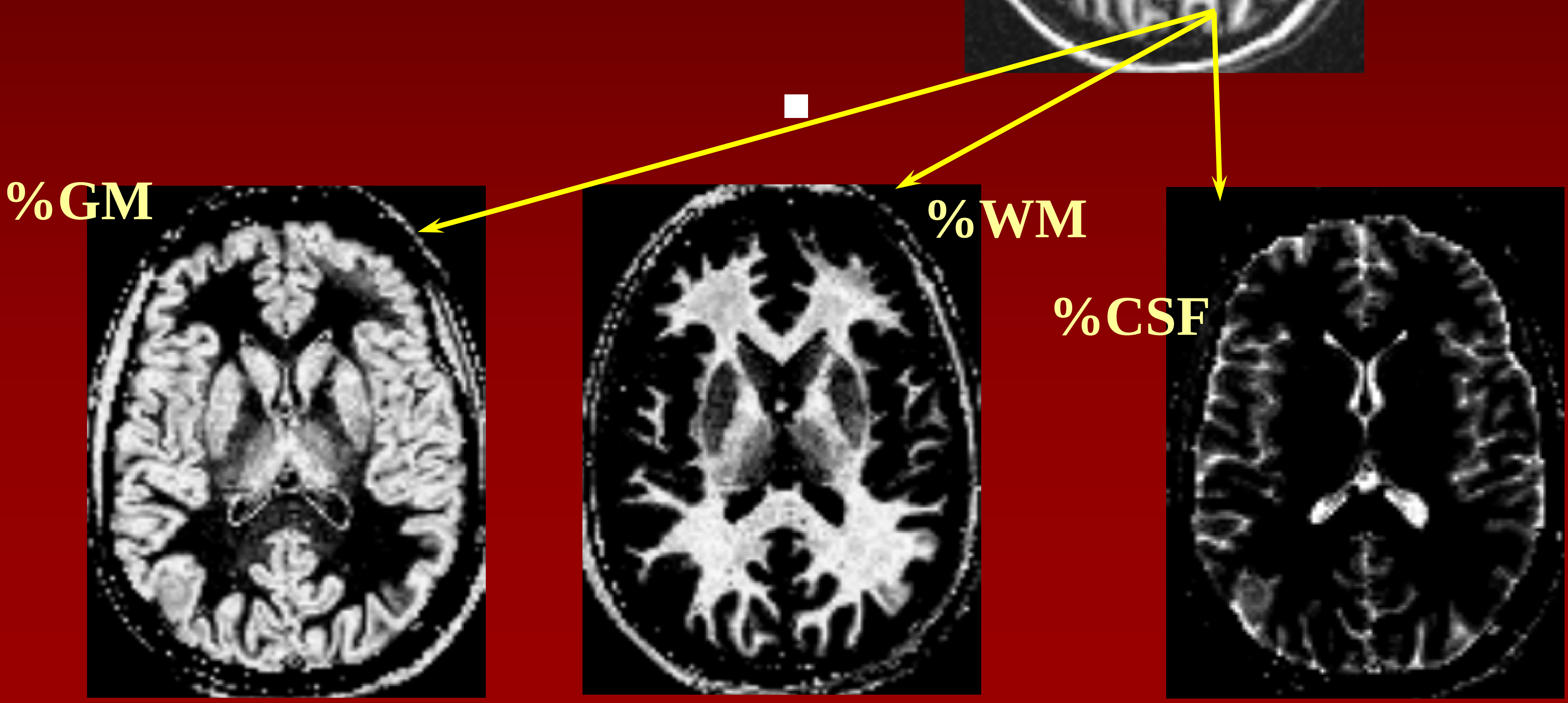
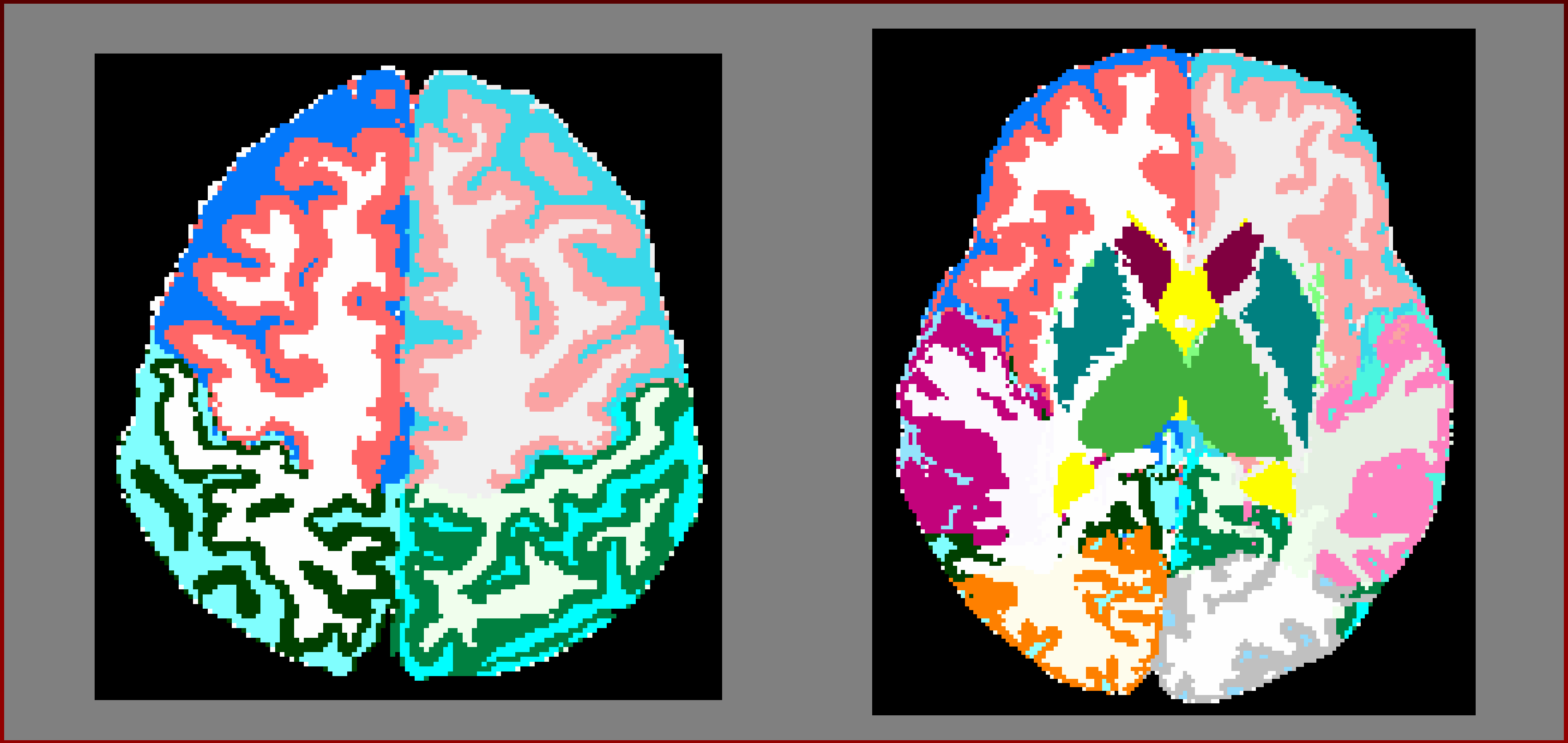


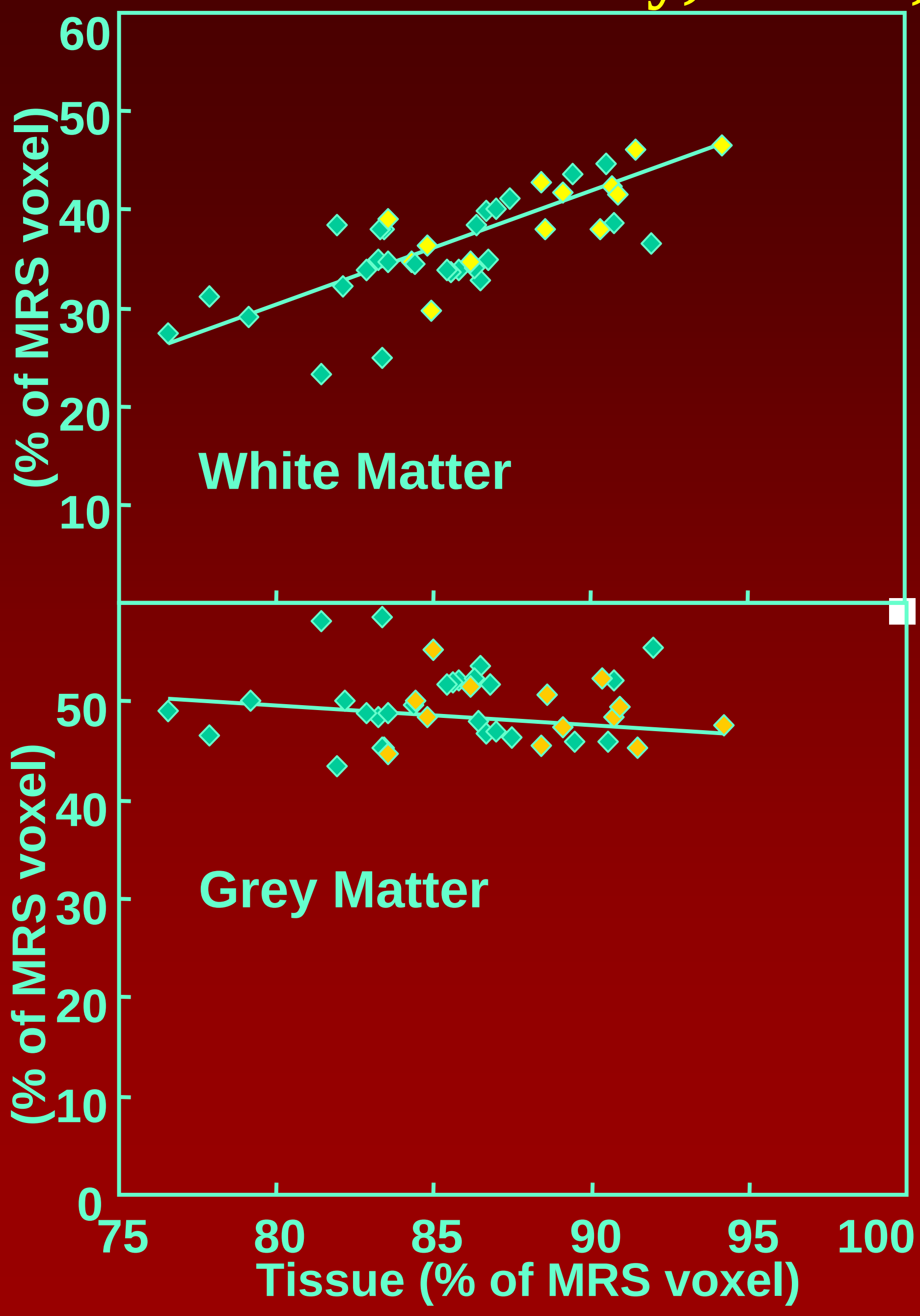
Image Segmentation



Volumes expressed as % of intracranial volume (ICV)

Meyerhoff, ICANA 2004

Correlations of Gray, White, and Total Tissue Volumes in Alcoholism



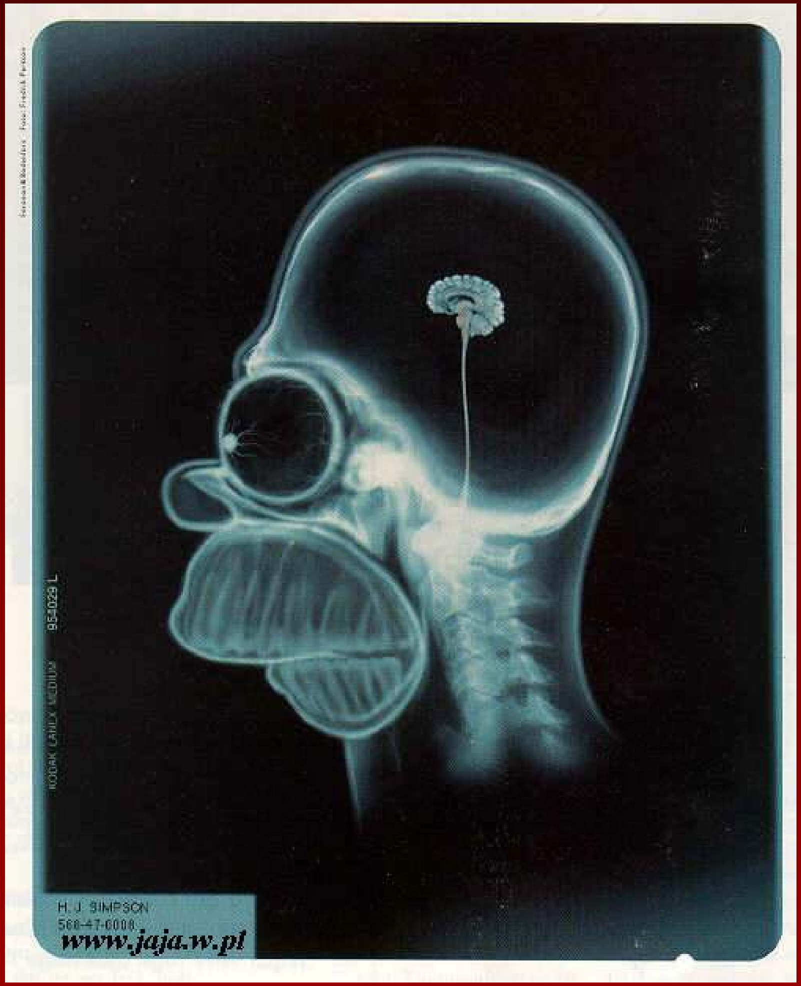
- Across timepoints, there was a significant correlation between white matter content in the voxel and the total solid tissue ($p < 0.0005$), but not between grey matter and solid tissue ($p = 0.36$).

- Significance: long-term improvements in occipital tissue composition are primarily from white matter.

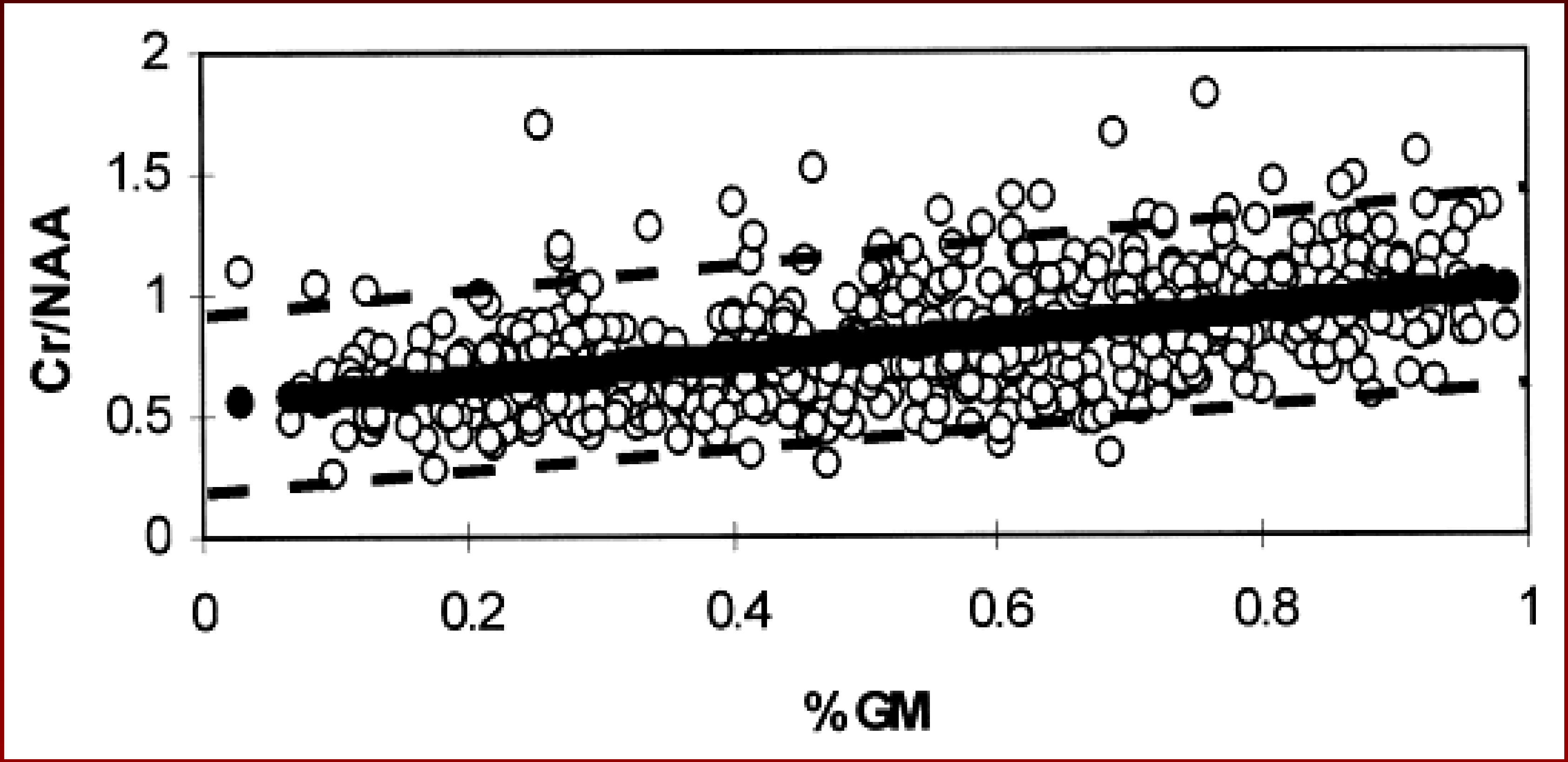
◆ Short-term sober subjects

◆ Long-term sober subjects

Alcohol-Related Brain Atrophy



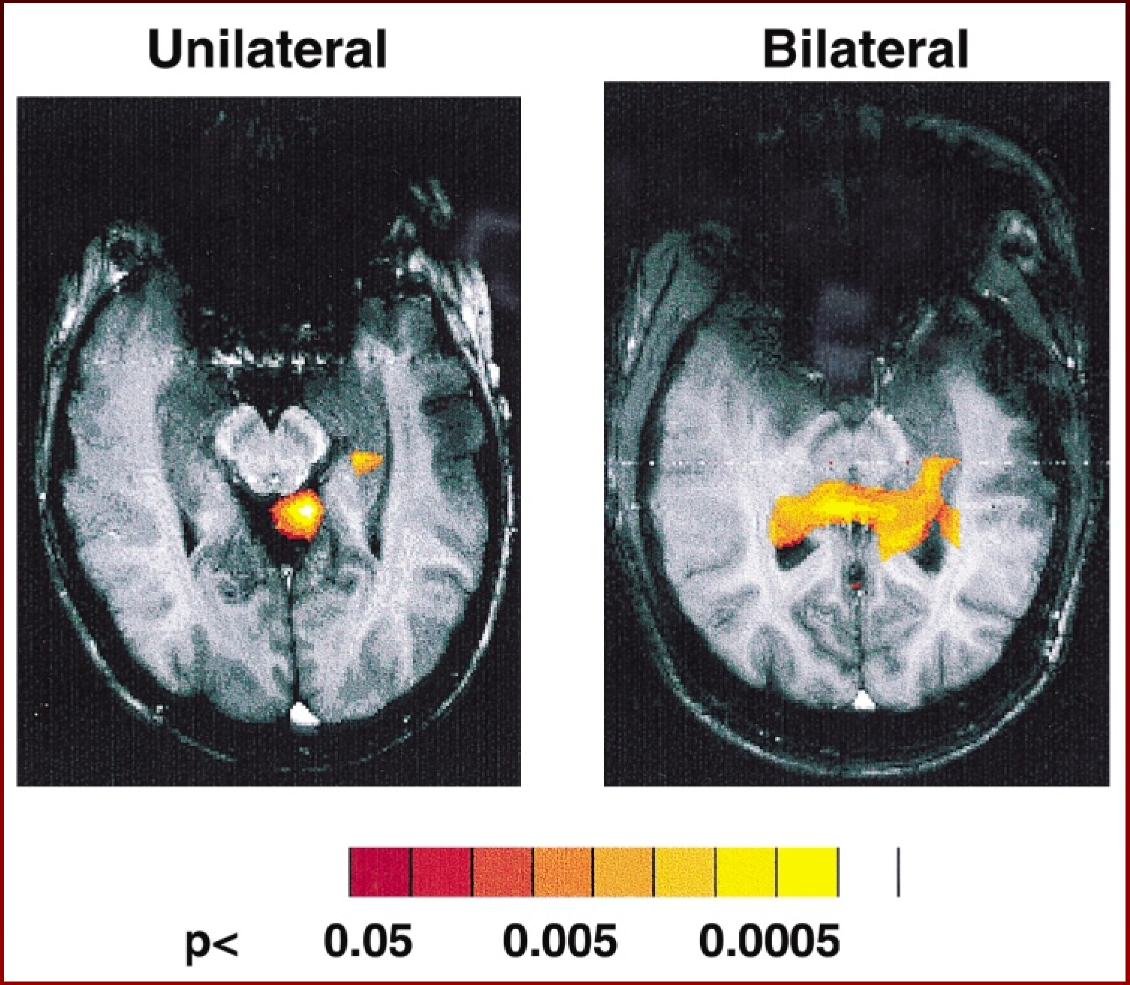
How Can Segmented Data Be Useful?



When pure tissue is not accessible, regression analysis can be used to estimate concentrations in pure tissue.

Chu et al., *Magn Reson Med*, 2000

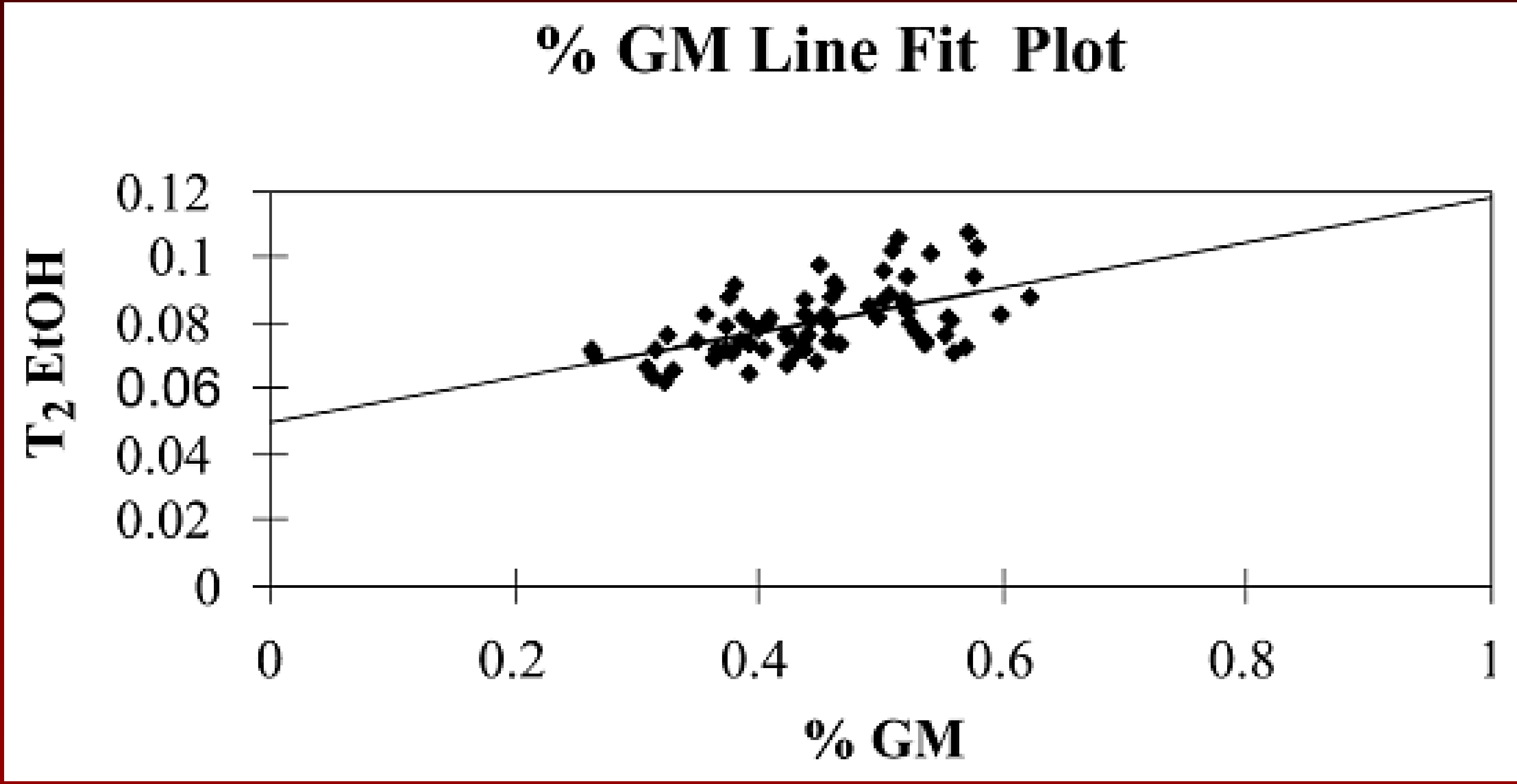
How Can Segmented Data Be Useful?



A disease state can be examined with MRSI and image segmentation. Statistically abnormal pixels can be highlighted.

Chu et al., *Magn Reson Med*, 2000

How Can Segmented Data Be Useful?



When pure tissue is not accessible, regression analysis can be used to estimate T2 effects in pure tissue.

Sammi et al., *Magn Reson Med*, 2000

Overview

What is MRS?

What is Spectroscopic Imaging?

What is Image Segmentation?

What is ^{13}C MRS?

^{13}C MRS:
Rates of Metabolism and Neurotransmission, Clear Resolution of Glutamate and Glutamine

- ^{13}C → non-radioactive isotope of carbon.

- 1% natural abundance means low background.

- No isotope effect on metabolism.

- Natural labeled substrates in blood yield MRS-detectable products in glutamate, glutamine, and other compounds in the brain.

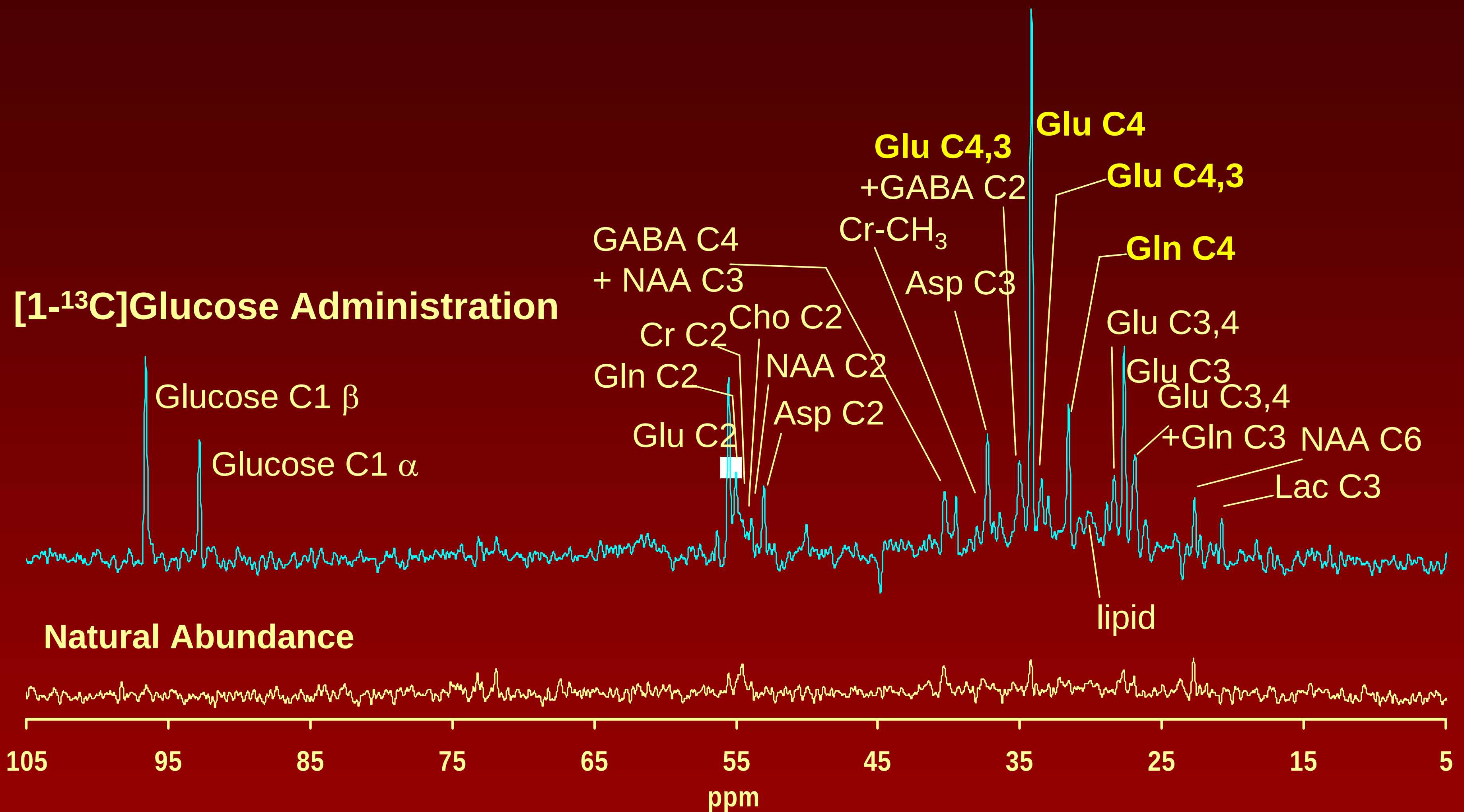
^{13}C Isotopic Labeling

[4-^{13}C]Glutamate **[4-^{13}C]Glutamine**

[1-^{13}C]Glucose

Time courses of labeling yield rates of metabolic pathways.

A ^{13}C NMR Spectrum of a Human Brain *in Vivo*



140 cc voxel, 45 min accumulation

Isotopic Flow

Yellow Dye

Hana, Maui

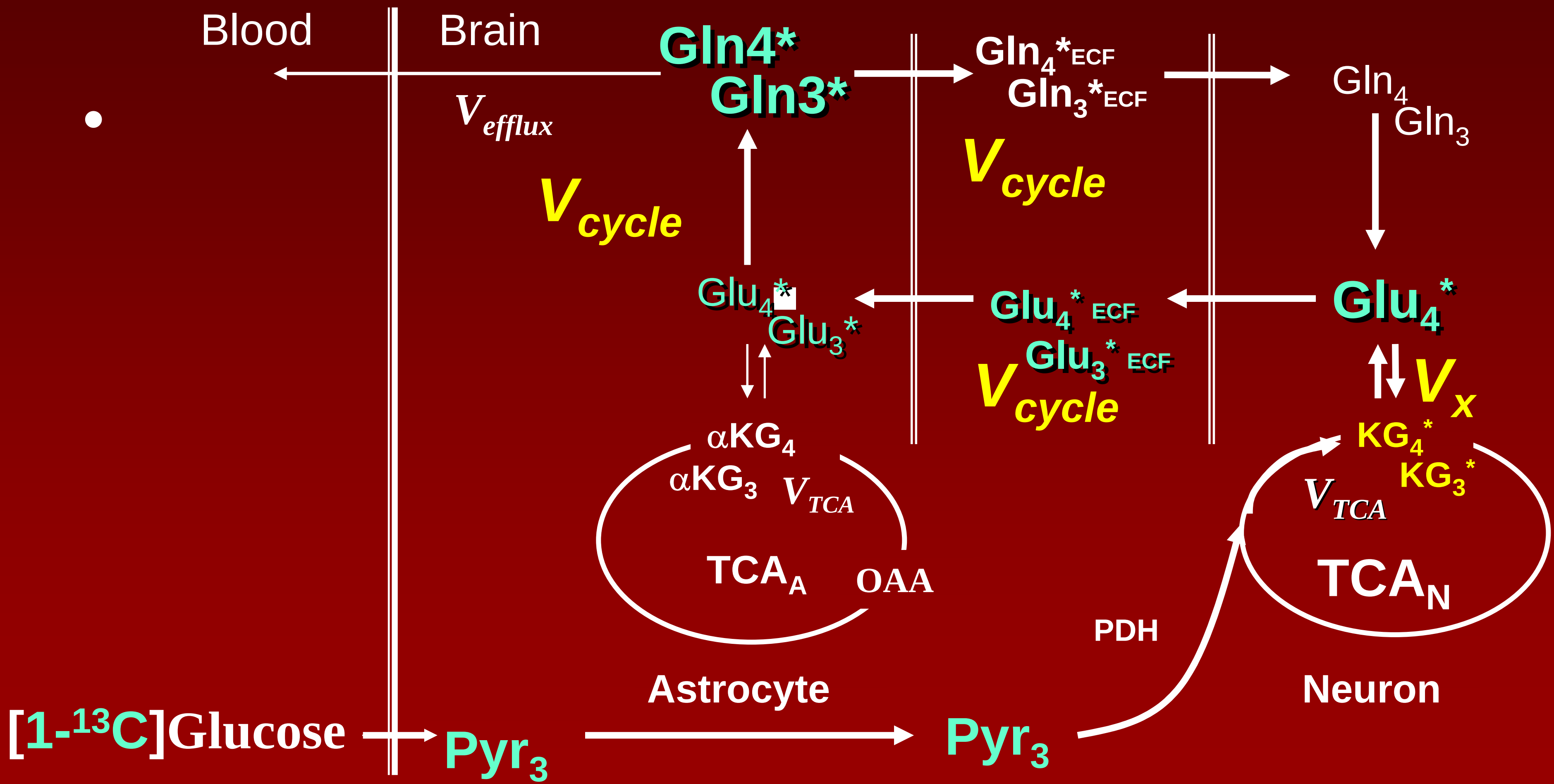
Glucose → Lactate → Glutamate → Glutamine

▪

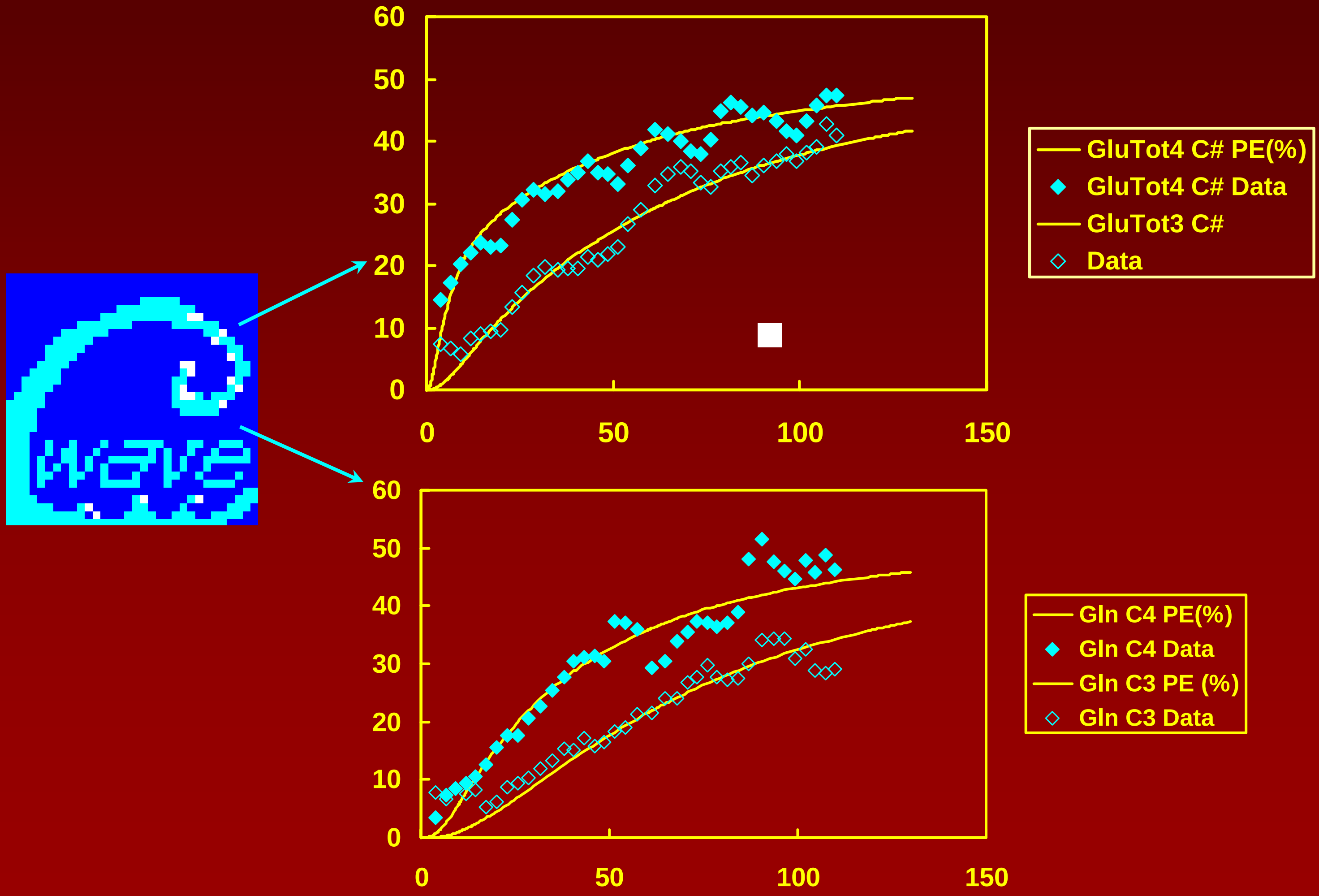
•Faster flow → more rapid appearance of dye at each pool

•Precursor pools “trap” dye temporarily

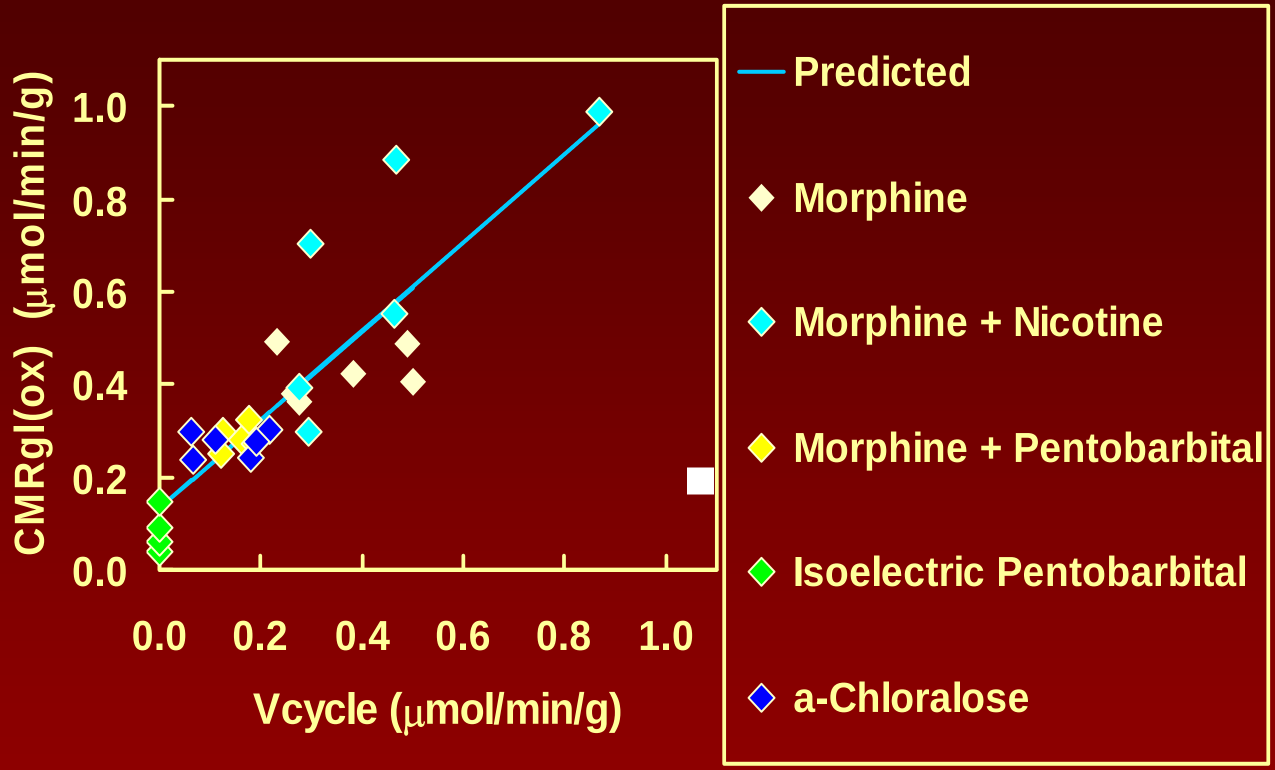
^{13}C Labeling of Neuronal Glutamate & Astroglial Gln by Glutamate/Glutamine Cycle



^{13}C Labeling of Neuronal Glutamate & Astroglial Gln by Glutamate/Glutamine Cycle: V_X, V_{tca}, V_{cycle}



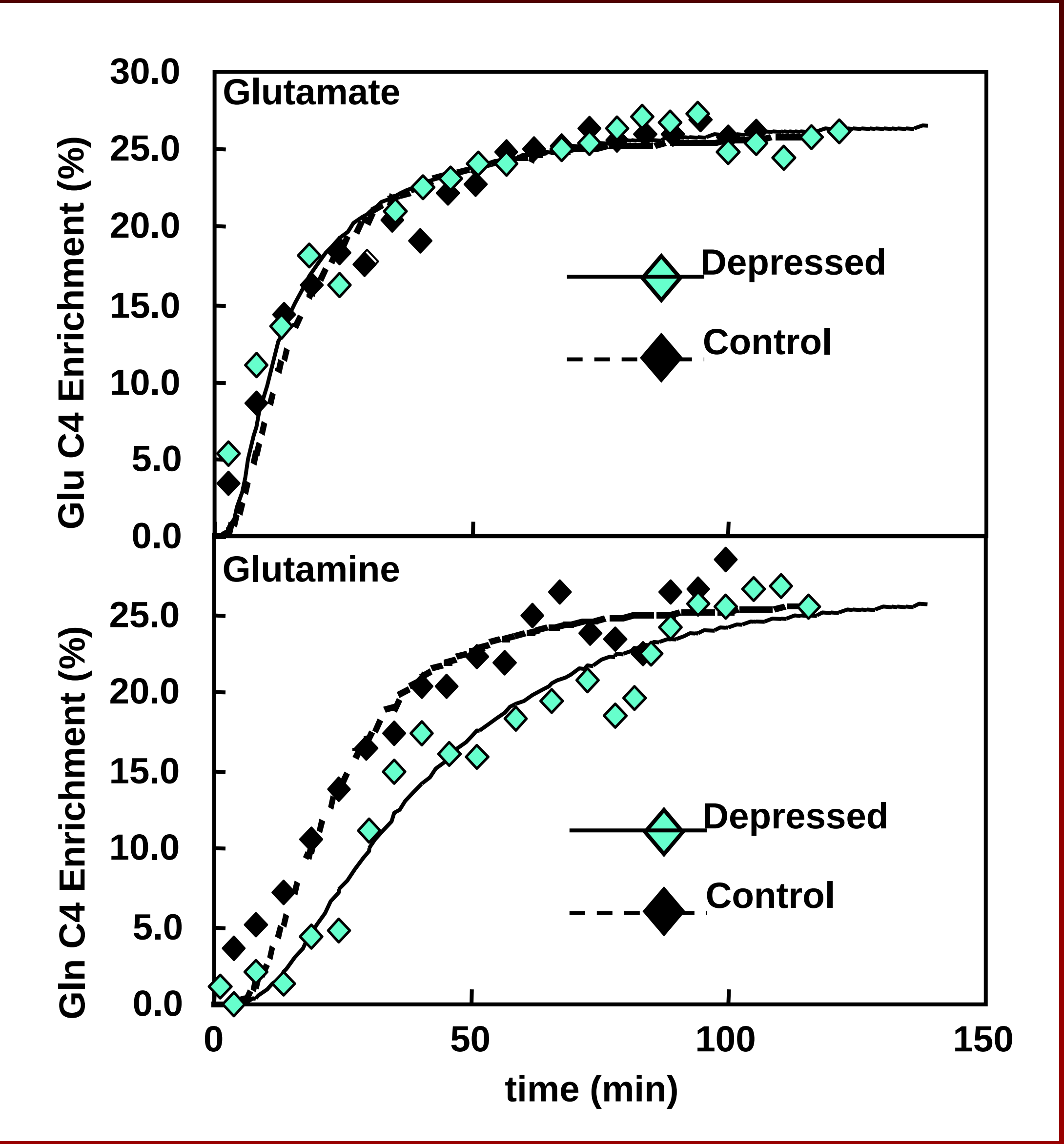
Determining a Relationship Between Glutamate Release and Glucose Oxidation



$CMRgl(ox) = 0.13 + 0.96Vcycle$, $R^2 = 0.74$

~1:1 relationship between changes in glucose oxidation and glutamate-glutamine neurotransmitter cycling

^{13}C MR Time Courses of Glu and Gln in Individual Patients and Controls



No difference in oxidative metabolism.

Glutamate-glutamine cycling is reduced in depression.

^{13}C MRS Application to Human Disease: Measurement of NAA *Synthesis* in Canavan Disease

Journal of Neurochemistry, 2001, 77, 347–350

RAPID COMMUNICATION

Direct determination of the *N*-acetyl-L-aspartate synthesis rate in the human brain by ^{13}C MRS and [1-^{13}C]glucose infusion

Angel Moreno,*·† Brian D. Ross* and Stefan Blüml*·†

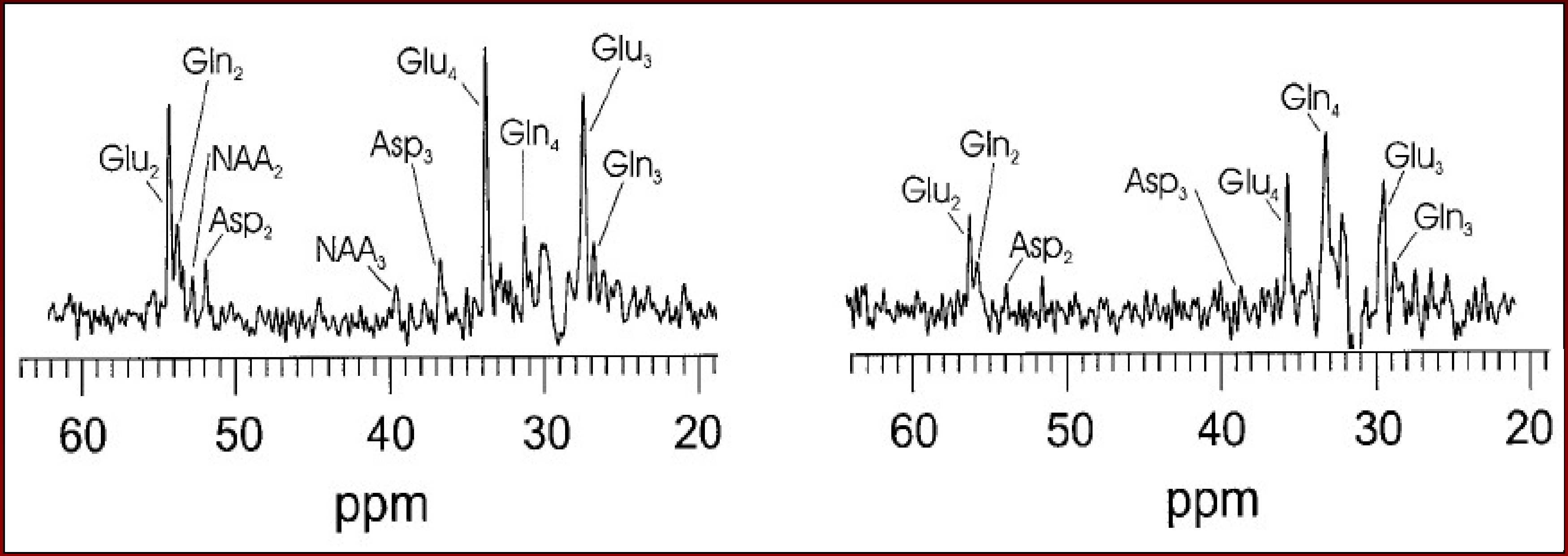
**Huntington Medical Research Institutes, Pasadena, California USA*
†Rudi Schulte Research Institute, Santa Barbara, California, USA

Abstract
A non-invasive ^{13}C magnetic resonance spectroscopy (MRS) technique is described for the determination of the *N*-acetyl-L-aspartate (NAA) synthesis rate, V_{NAA}, in the human brain *in vivo*. In controls, the mean V_{NAA} was 9.2 ± 3.9 nmol/min/g. In Canavan disease, where [NAA] is increased ($p < 0.001$) and [aspartate] is deceased ($p < 0.001$), V_{NAA} was significantly reduced to 3.6 ± 0.1 nmol/min/g ($p < 0.001$). These rates are in close agreement with the activity of the biosynthetic enzyme measured *in vitro* in animals, and with the rate of urinary excretion of NAA in

consistent with the regulation of NAA synthesis by the activity of a single enzyme, L-aspartate-*N*-acetyltransferase, *in vivo*, and with its control in Canavan disease by limited substrate supply and/or product inhibition. The ^{13}C MRS technique provides the means for further determination of abnormal rates of neuronal NAA synthesis among neurological disorders in which low cerebral [NAA] has been identified.
Keywords: ^{13}C MRS, [1-^{13}C]glucose infusion, Canavan disease, humans, *N*-acetyl-L-aspartate synthesis.
J. Neurochem. (2001) **77**, 347–350.

Moreno et al., *J Neurochem*, 2001

^{13}C MRS Application to Human Disease
Grading of Hepatic Encephalopathy



Blüml et al., *Magn Reson Med*, 2001

Overview

What is MRS?

What is Spectroscopic Imaging?

What is Image Segmentation?

What is ^{13}C MRS?

Acknowledgements

Alcohol Studies
John Krystal (CTNA director)
Ismene Petrakis
Louis Trevisan
Elizabeth Ruff
Vladimir Coric
Ralitza Gueorguieva

MRS
Douglas Rothman (MRRC director)
Kevin Behar (GABA expertise, director mouse imaging program)
Robin de Graaf
Michael Appel
Nicola Sibson

Acknowledgements

NIAAA
Dept. Veterans Affairs

CTNA
NIAAA Center for the Translational Neuroscience Of Alcoholism

R01 AA 11321-01A2
I-P50 AA-12870-01
K02-AA13430-01