MRI and MRSI Application in Neurodegeneration

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Magnetic Resonance Imaging(MRI) MR Spectroscopic Imaging(MRSI)

I. H-1 Magnetic Resonance Spectroscopic Imaging in Alzheimer's Disease, Multiple Sclerosis and Epilepsy

II. Micro Na-23 MRI and micro F-18 FDG-PET of cancer and apoptosis

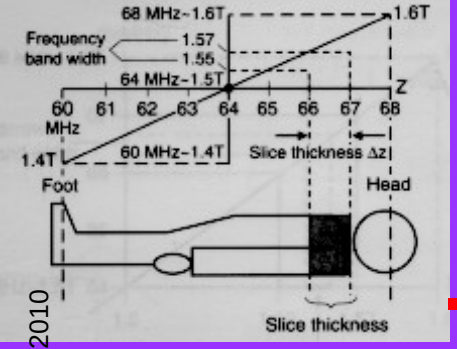
Neurodegeneration: AD,Epilepsy,MS

Hypothesis

MRI combined with MRSI characterize & define the disease better

MRI Imaging: Concepts

- **Proton spins resonate with RF pulse in high magnetic field: Slice imaging**
- **RF pulse sequences:** Spin-echo, Inversion recovery, Gradient echo, phase contrast, Time-of-flight(TOF) sequences
- **T1, T2, proton density weighting by TE, TR, TI etc.**
- **Data acquisition:** 2D slice, 3D volume imaging.
  $S(k_x,k_y,t)=\iint \Sigma\rho \,.e^{\gamma\Delta B_o \gamma \varnothing(r) + (TI-TR/T1)}$
- **Surface Rendering and Volume Rendering**
- **Manipulation and Analysis: Interactive MRI and MR Spectroscopic Imaging**



1.5 T MRI is Enough to Generate Brain Image

Nature Precedings : doi:10.1038/npre.2010.4317.1 : Posted 28 Mar 2010

AFFIRMATIVE Pulse Sequence

Anisotropic Diffusion Filtering

RF Inhomogeneity Correction
+
Intensity Normalization

Automatic Removal of Extrameningeal Tissues

3D Image Registration to
Standard Coordinate System

3D Phase-Contrast Flow Imaging

Flow Images:
1)Combination of MRA & Magnitude Image Data
2) Reslicing of Flow Images to Conform to MRI

RF Inhomogeneity Correction
+
Intensity Normalization

Automatic Removal of Extrameningeal Tissues

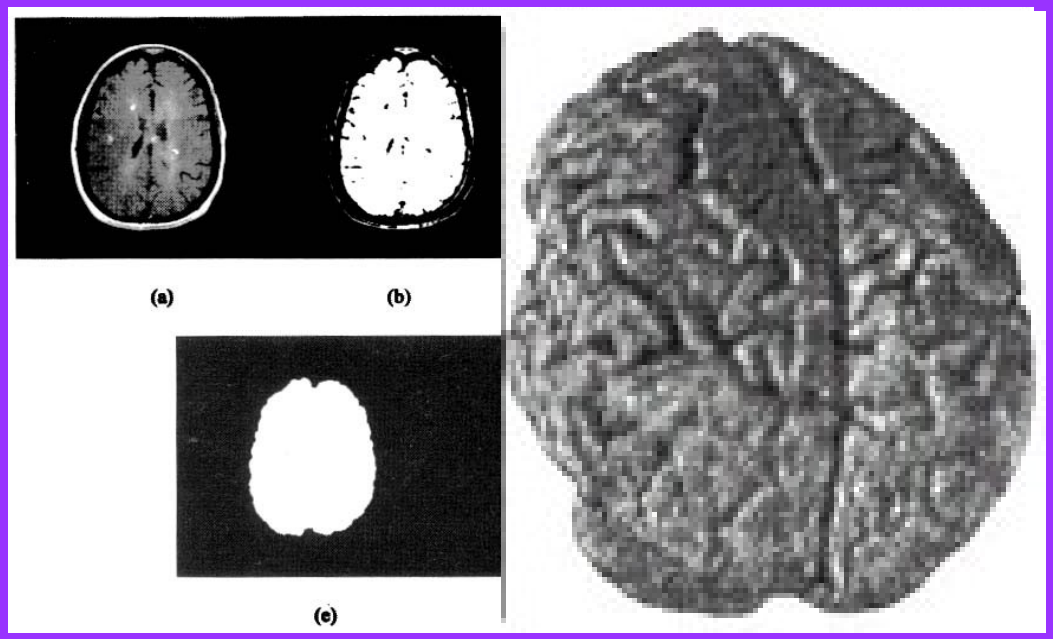
3D Image Registration to
Standard Coordinate System

Multi-Spectral Image Segmentation:
Feature Map #1: Late-Echo fast FLAIR/MTC
vs. Flow Image for Lesions
Feature Map #2: Early- vs. Late-Echo FSE
for GM, WM, and CSF
Removal of Flow Artifacts Based on MRI

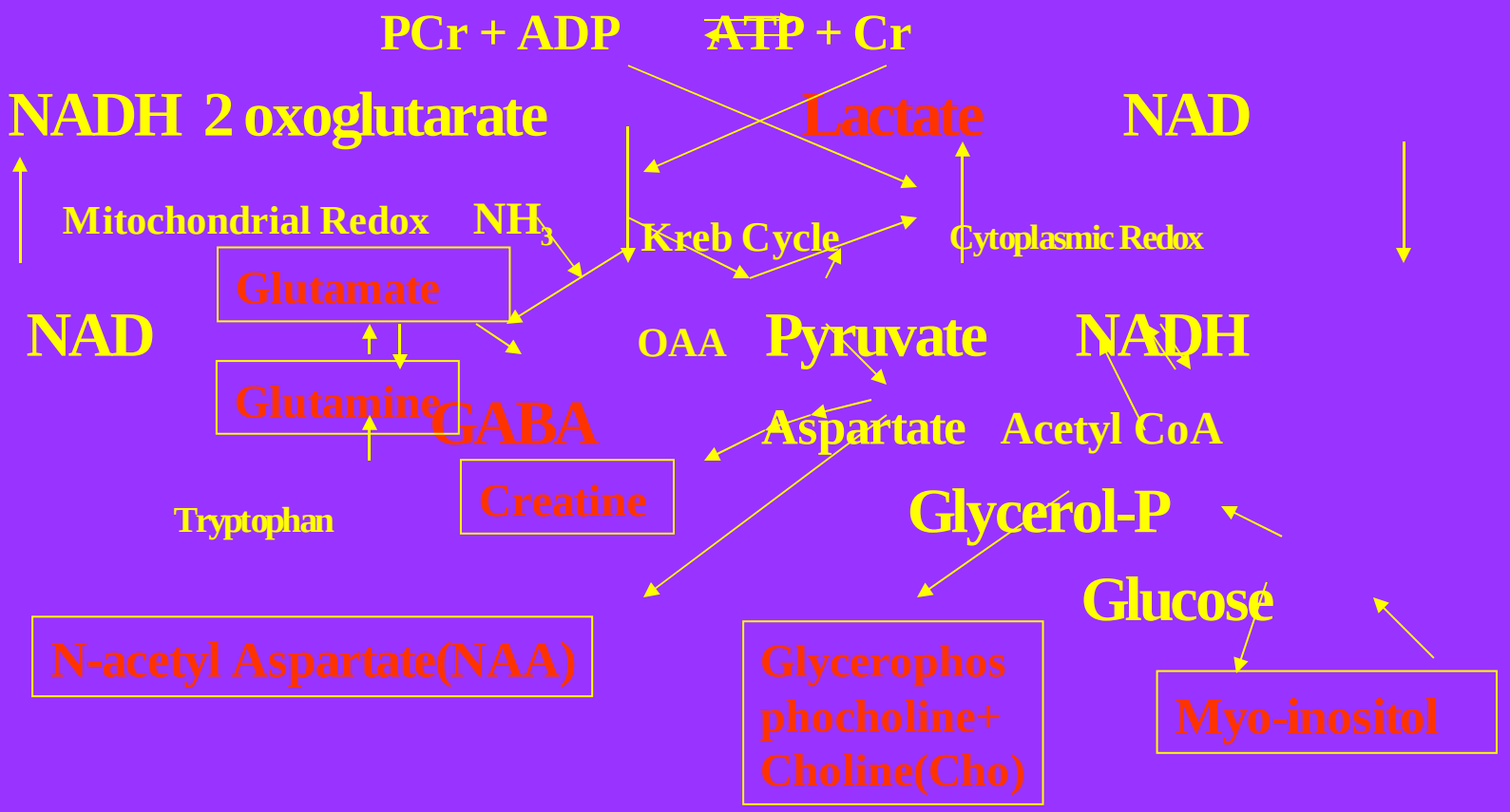
Volumetric Analysis

Brain Tissue Composition

- Cortex
- Sub-cortical
- Cingulate
- Ventricles
- Gyri and Sulci
- Frontal, Parietal, Temporal, Inter-hemispheric Fissure
- Distribution of gray matter, white matter and CSF as total content $\rho=(GM+WM+CSF)$



MR visible metabolites in brain



Metabolite signal= (MRI resolution x SRF x chemical shift profile) xH-1 density (MRSI resolution)

Proton Magnetic Resonance Spectroscopic Imaging(MRSI) Technique

- **Data Acquisition:**

-H-1 Multi Slice SI(MSSE) sequence-Metabolite maps

PE 36 diameter, FOV 280.280, (TE 25 TR 1800 TI 170)ms

-Stimulated (CHESS) SI sequence (STEAM)-Spectral map

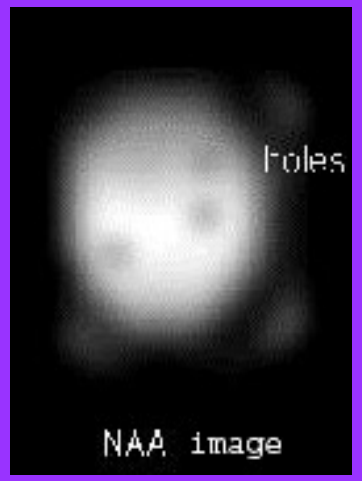
PE 32 x 32, TR/TE 1000/30, NEX 2, VOI 240 mm^2, ROI .75 x .75 x 1.5 cm^3

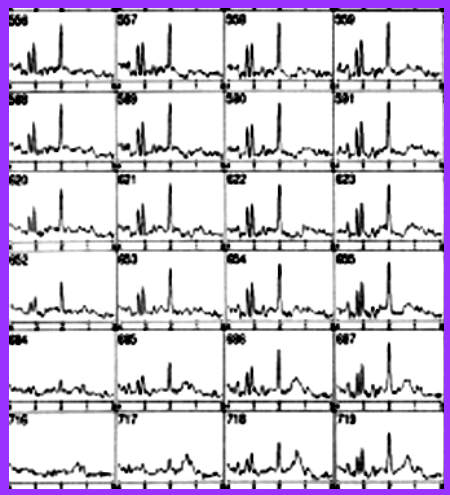
-Point-Resolved SI sequence (PRESS)-Single Spectrum

PE 24.24, FOV 210.210, (TE 25 TR 1800)ms, voxel 2.2 ml

Outer volume suppression for minimizing extrameningial lipids

Variable TR for reducing scan time





- **Image Postprocessing**

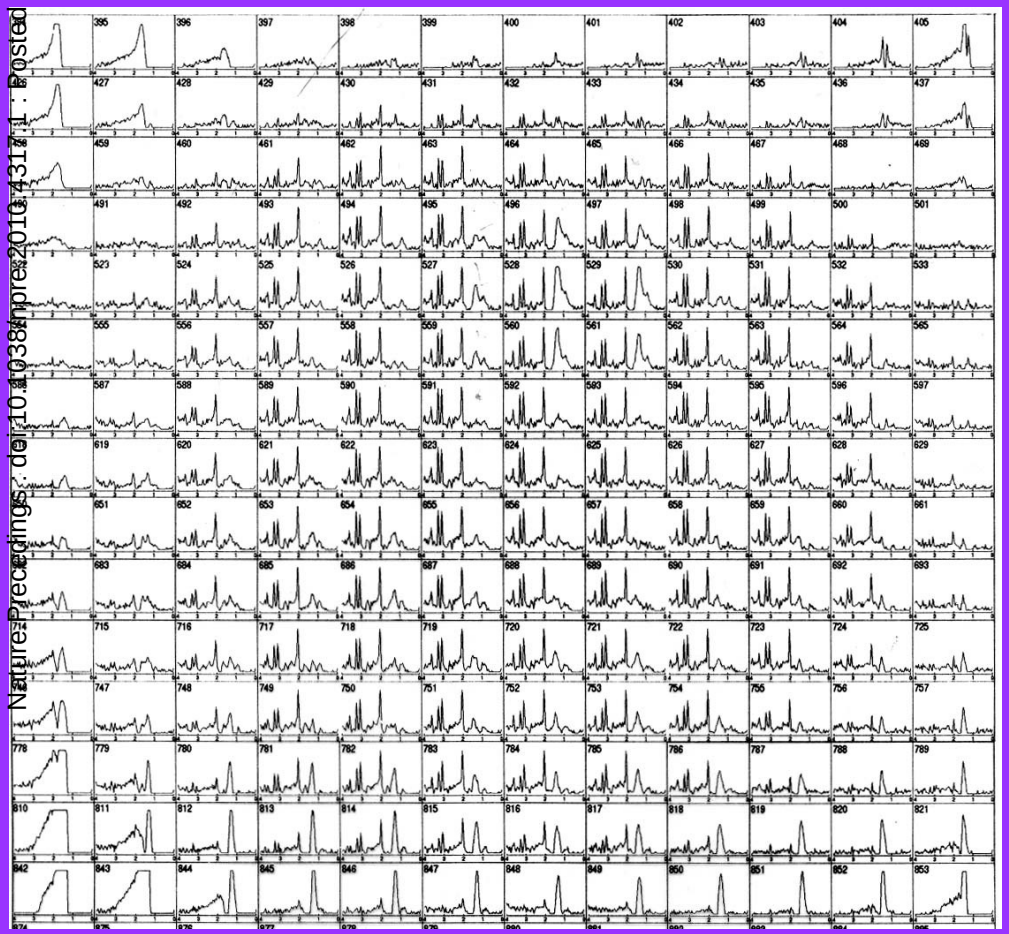
Segmentation, Co-registration (**MRIAP, Viewer**)

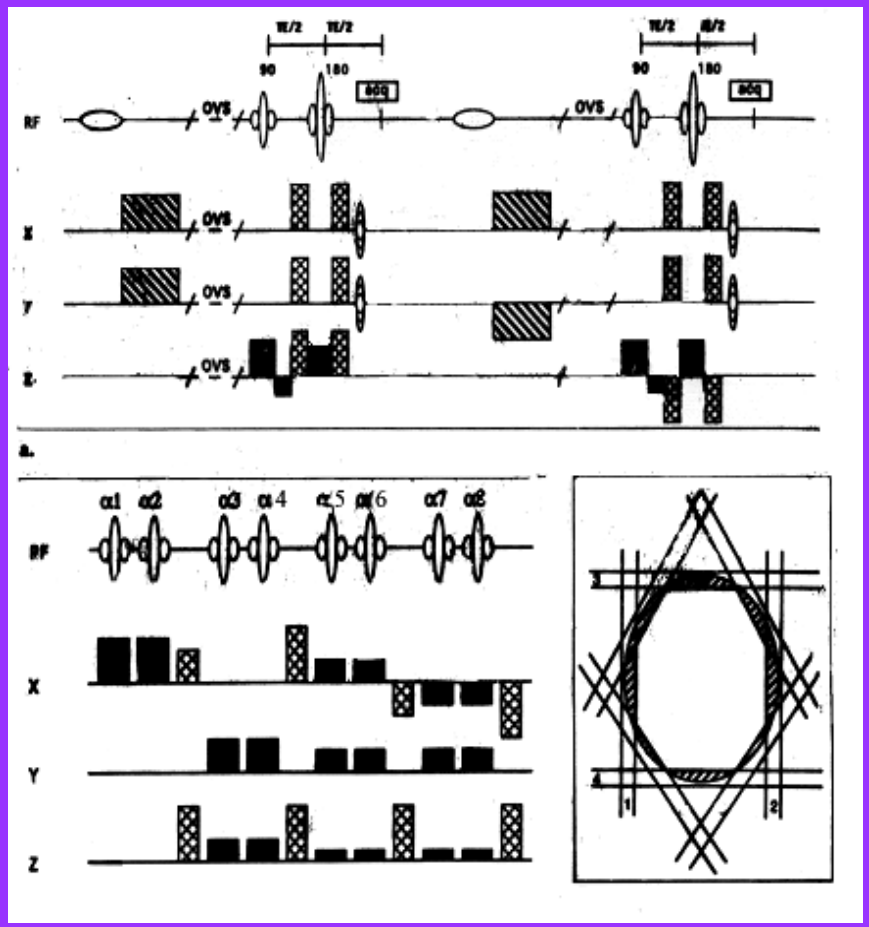
- Automatic Spectral Image Analysis software(**APSIP**)

-Metabolic map generation, Spectral analysis

- Interfacing MRSI with MRI (Co-analysis by **SID**)

Multi-slice octagonal VOI: STEAM Chemical Shift Imaging



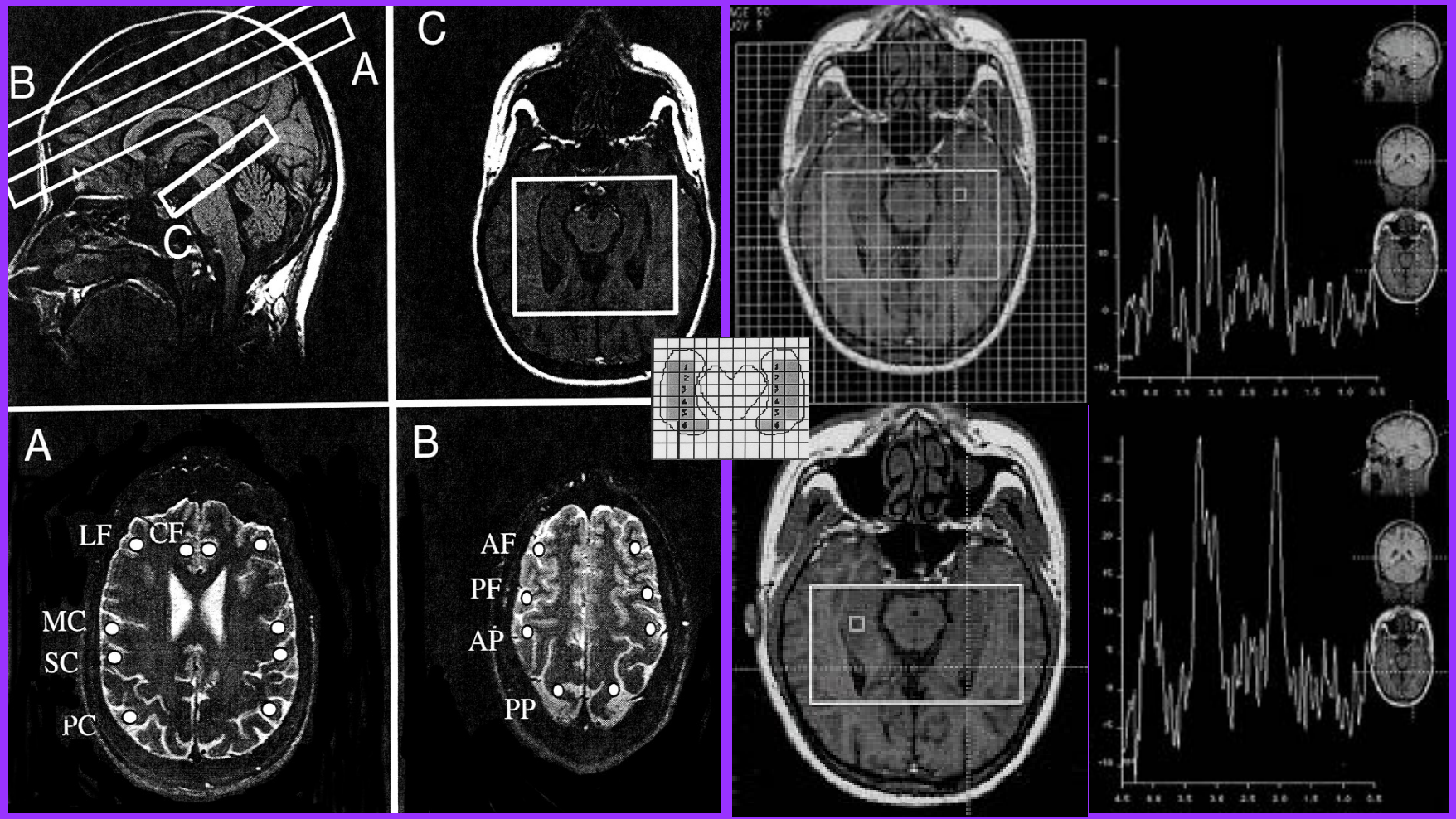


MRI+MRSI in Alzheimer's Disease (AD) and SIVD

1. AD is diffused cortical neurodegenerative disease

- Memory Loss is associated with Reduced NAA(Neuronal Loss) and Enhanced Choline (Inflammation,demyelination)
- Subcortical Ischemic Vascular Dementia
- MRI + MRSI define it better
- MRI offers visible hippocamcal changes (segmentation)
- MRSI offers localized neurochemical changes for lateralization, test for asymmetry (co-analysis)

H-1 MRSI + MRI predict Hippocampal Volumes and Neurometabolites in Alzheimer's Disease



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MRI and MRSI Image Post Processing and Analysis in AD vs SIVD

- **Image Post-Processing**:MRI-Ventricular dilatation, Sulcus widening, subcortical WMSH
- MSSI and CSI-Zero-filling, exponential line broadening(time domain), Gaussian Multiplication(spatial domain),Water suppression(digital filter+linear interpolation in FID), fat removal,FFT,Atrophy Correction
- Automated Spectral Analysis: Simulated parametric peak amplitude,phase,frequency(sinusoidal LG shape), FFT+Baseline Wavelet-LM Optimization Iterations Curve fits and metabolite concentrations
- **Statistics**:

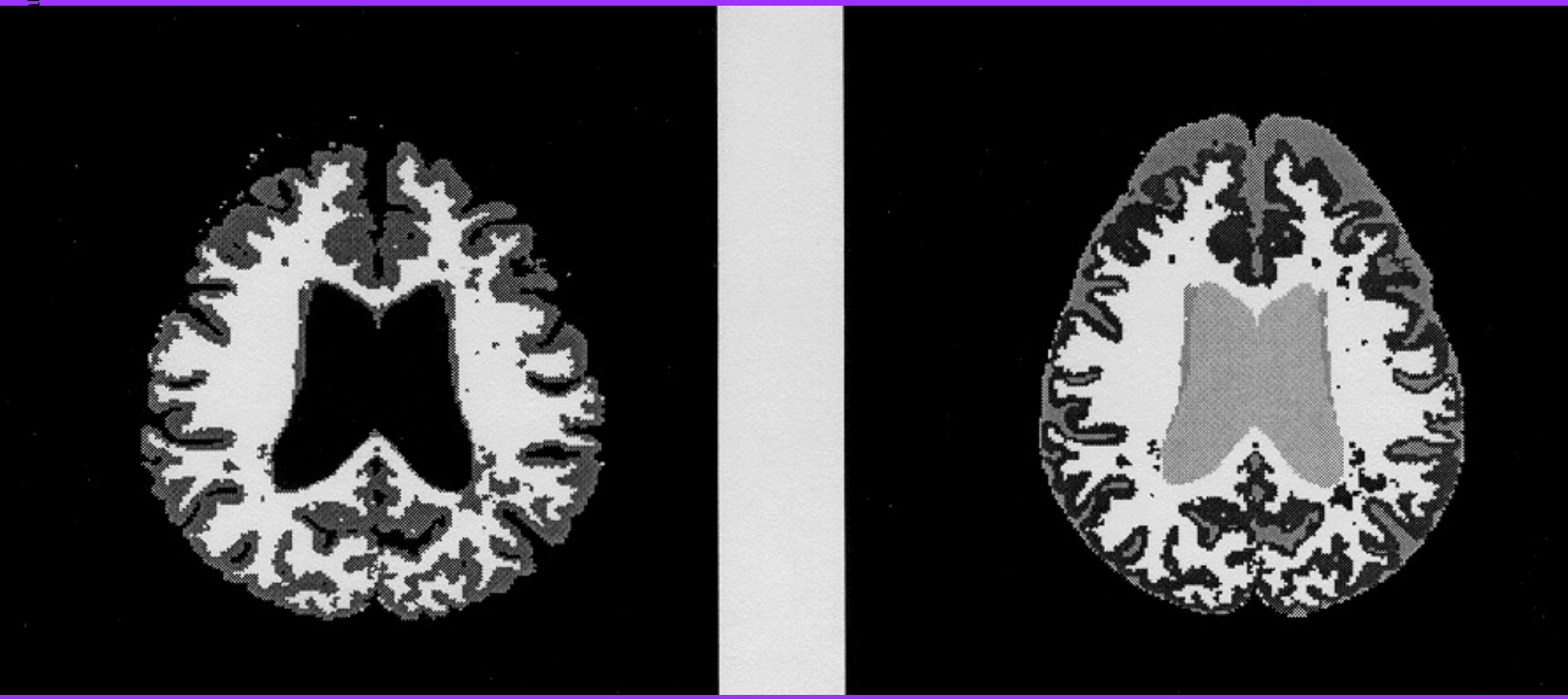
1. WM and GM(Frontal,Parietal) NAA/Cr,NAA/Cho, Cho/Cr): Control vs AD vs SIVD
2. Ventricular Dilatation,WMSH,Sulcus Widening, Hippocampal Volume: Control vs AD vs SIVD

4. Total(GM+WM) Metabolite Differences: AD vs Control and AD vs SIVD

MRI segmentation(1st step)

- Removal of extrameningial tissue and scalp
- Co-registration of DSE images with interleaved images(Wood Algorithm)
- 3D inhomogeneity correction
- Segmentation by K-means cluster analysis - tissue-seeds defined around pixel intensity histograms
- Automated edge detection for hippocampus area and hippocampus voluming

Tissue MRI segmentation
(supervised K-NN cluster method)

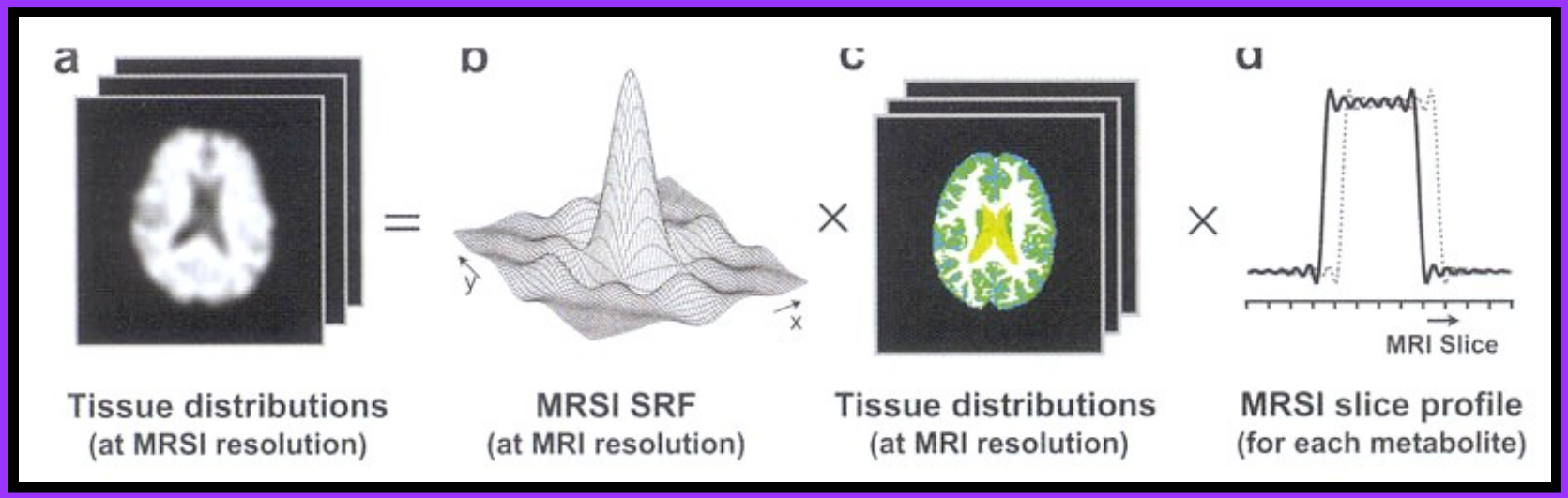


Sharma (2002) Adv.Segmentation Chap

MRSI post-processing(2nd step)

- Parametric Automated spectral peak editing
- *a priori information* of metabolites and voxel-by-voxel training data for tissue composition(CSF nulling)
- Point Spread Function and Chemical shift displacement(MRSI Resolution)
- Data Processing in the X, Y co-ordinates
- Co-registration and segmentation for serial scans

Resolution at MRI and MRSI slices: Multi-slice MR Spectroscopic Imaging Display(SID)

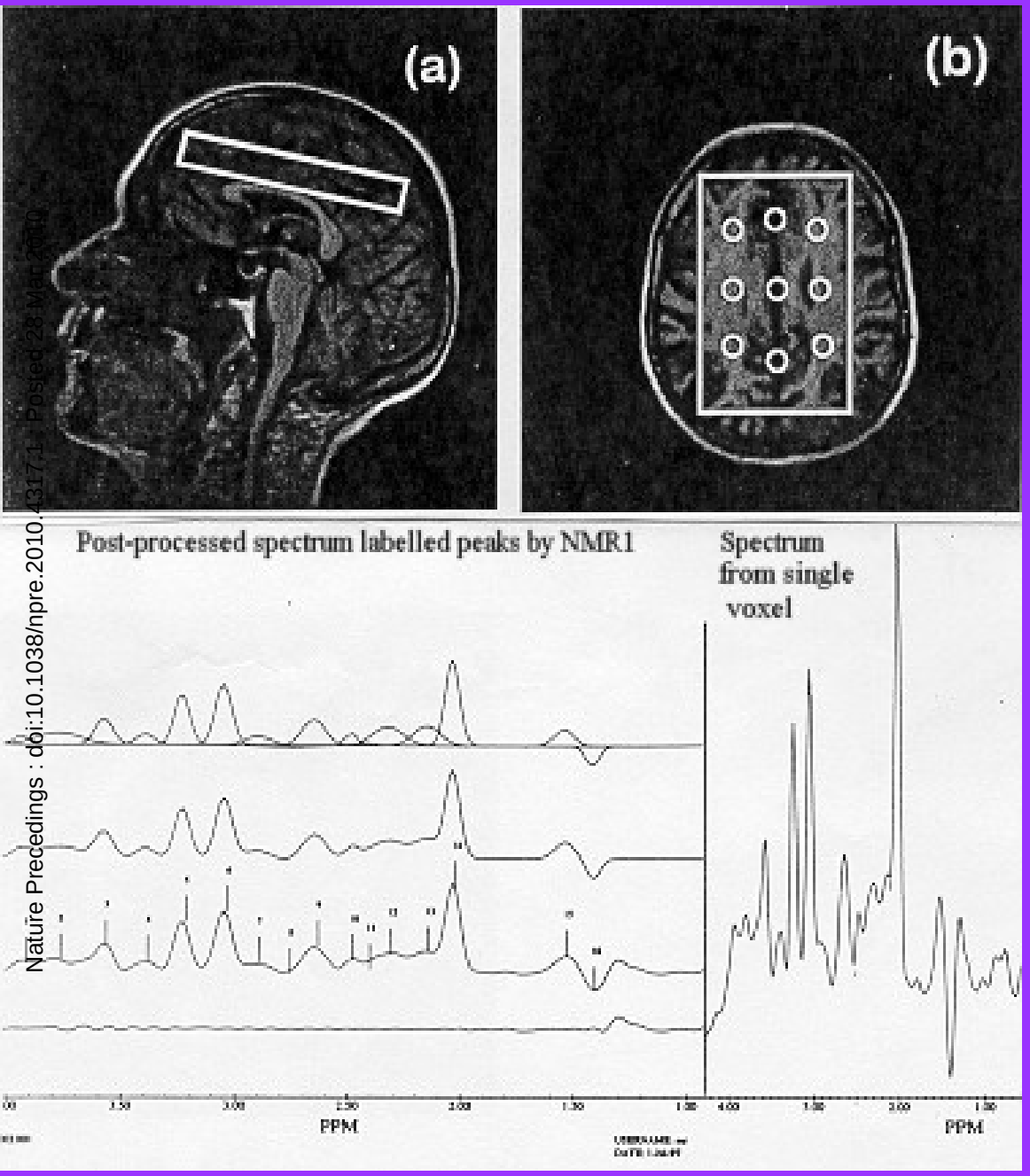


Effective tissue contribution in spectroscopic volume =

SRF x tissue distribution(MRI resolution) x MRSI Slice selective profile

MRSI: Spectra Post-processing (NMR-1 program) (Step 3)

- Deconvolution
- Gaussian apodization
- Zero-filling to matrix 32 x 32 x 1024 points
- Fourier Transformation
- Phase and baseline correction
- Peak editing and reference with phantom
- Iteration and curve-fitting



1.5 T MR Spectroscopy and Image Processing of Alzheimer's Disease

(a) Sagittal scout image
(b) Location of ROI voxels

Lower-left: Curve fitted spectrum
Lower-right: Metabolite peaks

Sharma(2002)Adv.Segmentation Chap7,187

MRI segmentation and co-analysis with H-1 MRSI (SID)(step 4)

- Tissue content ρ= GM + WM (from MRI)
- f=GM/(GM+WM)
- Co-registration of MRI with MRSI data
- Metabolite intensity correction for NAA,Cr and Cho as: $NAA^{corrected}=NAA/\rho$ (MRSI)
- CSF signal nulling
- 3D inhomogeneity correction by digital filter

Regional Differences of Metabolites in brain: AD

	Brain Region		
NAA [mM]	**Frontal**	**Medial**	**Posterior**
Gray Matter			
AD	8.59 ± 0.4	9.35 ± 0.3	9.43 ± 0.3
Control	10.04 ± 0.4	9.75 ± 0.4	10.52 ± 0.4
% Difference	- 14.4 *	- 4.1	- 10.3 *
White Matter			
AD	8.33 ± 0.3	9.70 ± 0.3	8.94 ± 0.2
Control	9.25 ± 0.2	9.63 ± 0.2	9.48 ± 0.3
% Difference	- 10.1 **	+ 0.7	- 5.7
Cr [mM]			
Gray Matter			
AD	8.52 ± 0.3	8.08 ± 0.2	8.11 ± 0.3
Control	8.70 ± 0.3	7.29 ± 0.3	8.15 ± 0.3
% Difference	- 2.0	+ 10.8	- 0.5
White Matter			
AD	6.39 ± 0.2	6.19 ± 0.2	6.72 ± 0.2
Control	6.52 ± 0.3	6.12 ± 0.2	6.74 ± 0.2
% Difference	- 2.1	+ 1.1	- 0.3
Cho [mM]			
Gray Matter			
AD	1.85 ± 0.09	1.55 ± 0.06	1.34 ± 0.07
Control	1.82 ± 0.07	1.56 ± 0.08	1.38 ± 0.07
% Difference	+ 1.7	- 0.7	- 3.2
White Matter			
AD	1.61 ± 0.07	1.49 ± 0.05	1.30 ± 0.05
Control	1.71 ± 0.08	1.55 ± 0.06	1.26 ± 0.04
% Difference	- 5.8	- 4.1	+ 3.1

*$p < 0.03$; ** $p < 0.003$; both by ANCOVA;

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MRI+MRSI Predicts Better Tissue Composition in AD

	AD	Control	% diff.
HP-volume(mm^3)			
Right	1982 ± 134	2884 ±102	31.1
Left	1868 ± 88	2943 ± 86	36.5
Ventricular CSF(%)	4.2 ± 0.3	2.8 ± 0.3	33.3
Sulcus CSF (%)	23.4 ± 2	18.2 ± 0.5	22.2
White Matter(%)	35.2 ± 0.9	38.1 ± 0.8	7.6
Cortical GM(%)	38.8 ± 1.1	42.2 ± 0.6	8.0
Subcortical GM(%)	1.2 ± 0.08	1.4 ± 0.03	n.s
TIV(cm^3)	1342 ± 5	1402 ± 52	n.s.

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MRSI: Metabolite* distribution and tissue content in AD

Metabolite	AD	Control	% Diff
NAA(mM)			
Right	7.55 ± 0.5	10.01±0.6	13.2
Left	7.61 ± 0.4	9.82 ±0.9	22.6
Cho(mM)			
Right	2.02 ± 0.7	2.08 ± 0.2	2.9
Left	2.04 ± 0.4	1.89 ± 0.5	7.4
Cr(mM)			
Right	7.02 ± 0.6	7.75 ± 0.5	9.4
Left	7.96 ± 0.6	7.49 ± 0.8	5.9

	AD	Control	% Diff
NAA/Cr			
Right	1.08 ±.06	1.39±.03	20.8
Left	0.96 ±.04	1.31±.02	26.7
NAA/Cho			
Right	3.74 ±.07	4.81±.09	22.2
Left	3.73 ±.03	5.1±.06	26.9
@ Tissue content ρ (%)			
Right	84 ± 3	98± 2	14.3
Left	87 ± 3	96 ± 3	0.93
Gray matter index (f)			
Right	0.45 ± 0.03	0.55 ± 0.05	18.2
Left	0.62 ± 0.02	0.62 ± 0.04	n.s.

*Atrophy corrected metabolite concentrations of NAA, Cho, and Cr and NAA/Cr and NAA/Cho ratios from right and left hippocampus in AD patients and control subjects.

@Tissue content ρ (in percent of the MRSI voxel volume) and gray matter index f of the MRSI voxels positioned at right and left hippocampus, characterizing MRSI partial volume effects.

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AD: Lateralization and Asymmetry

AD	Concordant	Discordant	non-lateralized
FDG-PET			
Asymmetry Index > 3	12	0	1
Hippocampus Volume			
AI > 8 %	10	0	3
T2			
AI > 4 %	9	0	4
NAA/(Cho+Cr)			
AI > 12 %	7	1	5
NAA			
AI > 12 %	7	0	6

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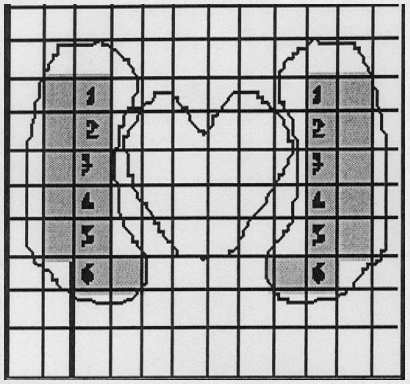
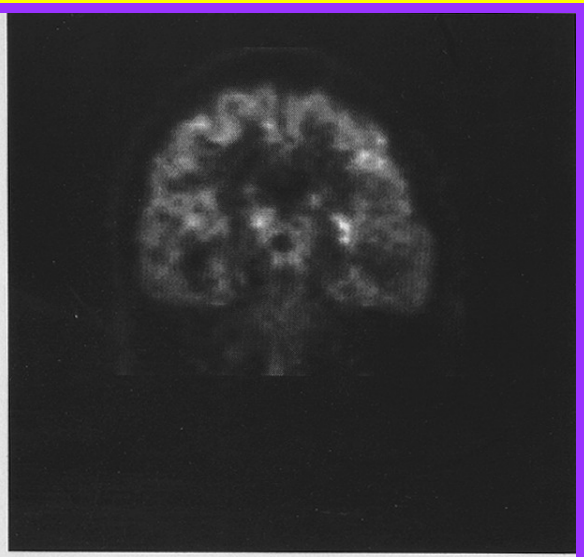
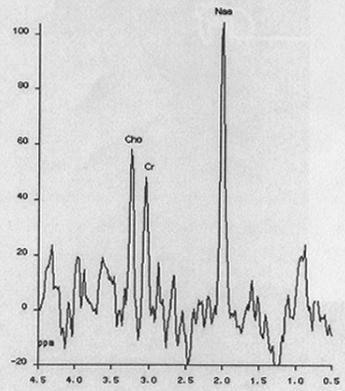
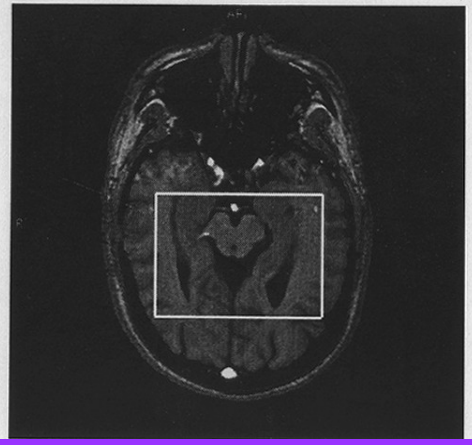
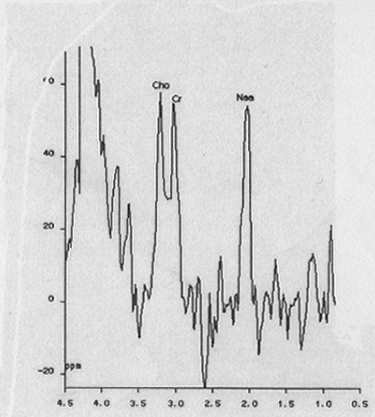
Lateralization of Hippocampus inAD: Reduced NAA and High Choline Peaks











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SIVD:Lateralization and Asymmetry

SIVD	Concordant	Discordant	Non-lateralized
FDG-PET Assymetry Index > 3	20	0	3
HV AI > 8 %	15	0	8
NAA/(Cho+Cr) AI > 12 %	14	1	8
NAA AI > 12 %	15	1	7

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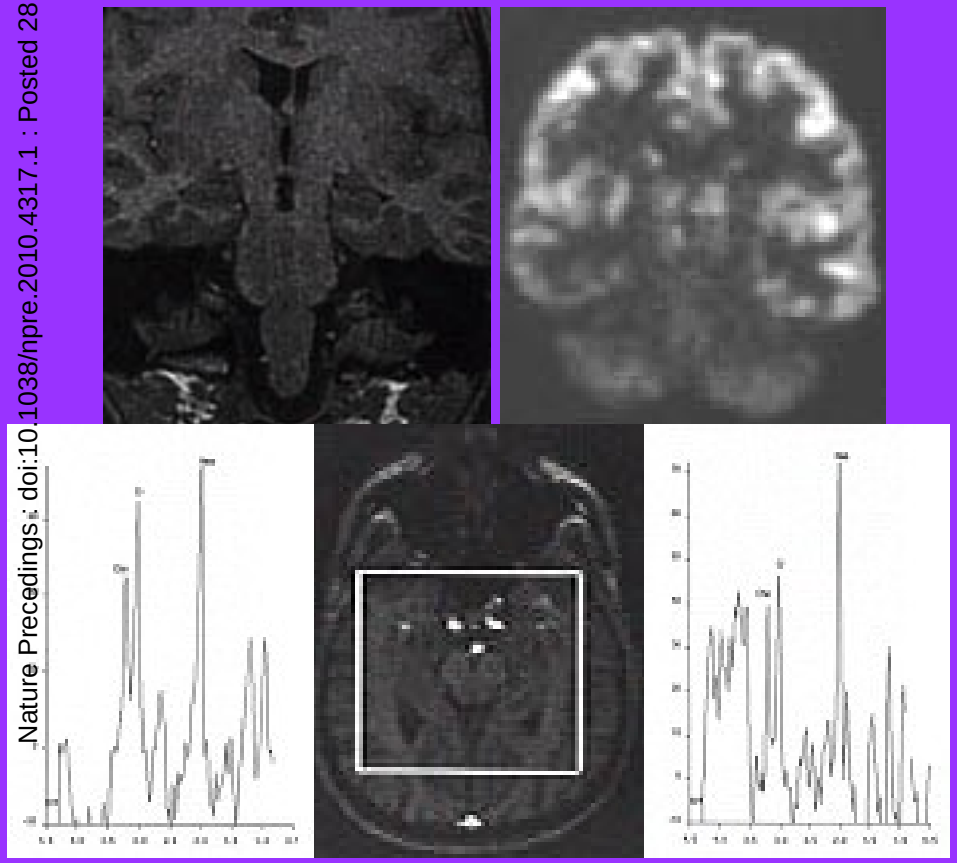
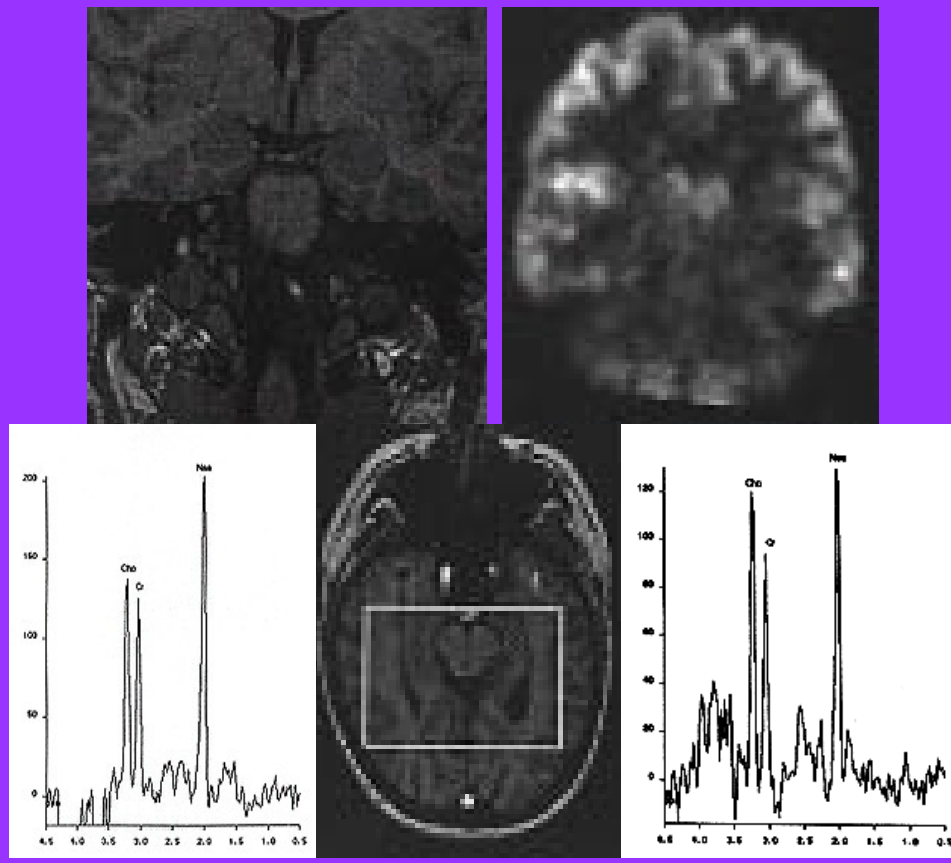
MRSI: Coronal T1 weighted images with MRS spectra (SIVD)





- Ipsilateral and contralateral differences in Choline peak

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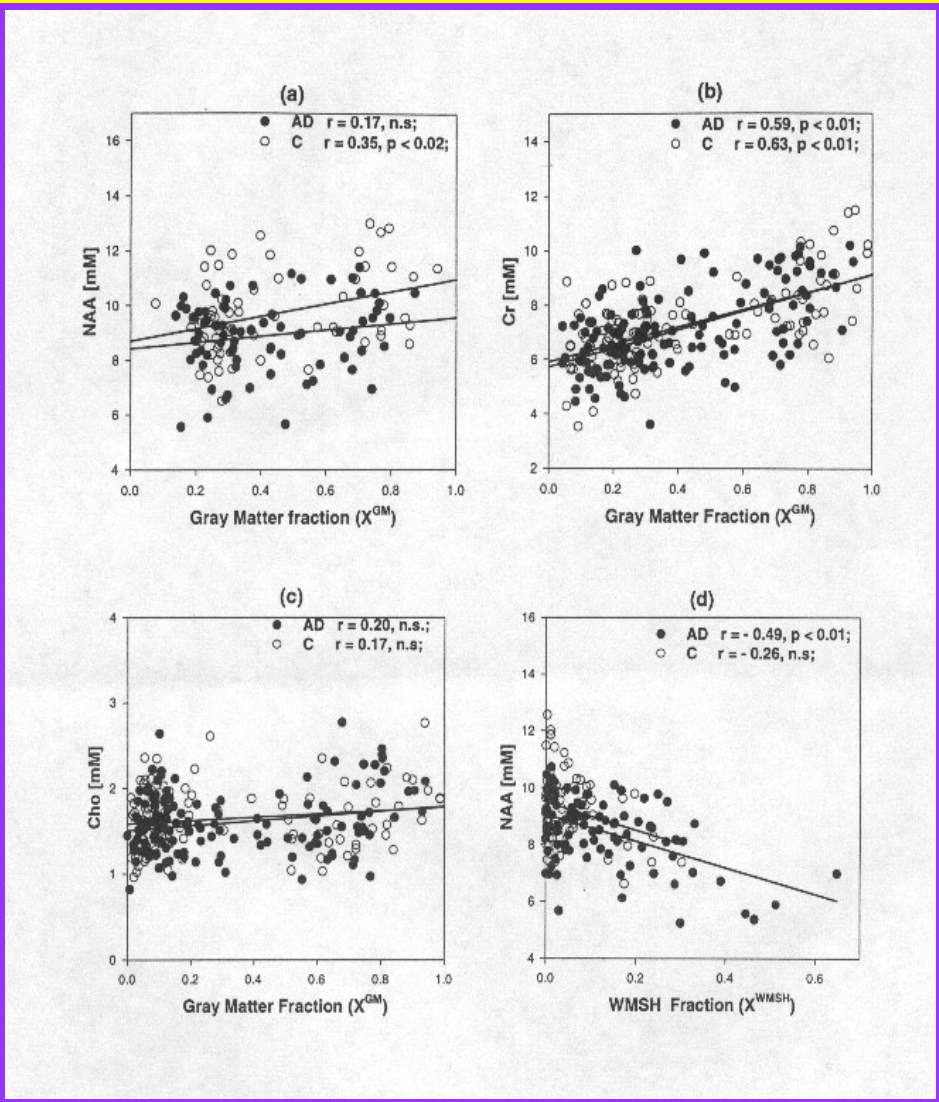
Regression Against Tissue Content and Histogram Analysis in AD

- **Regression analysis of $NAA^{corrected}$ as function of GM tissue fraction in each MRSI voxel.**

- **Histogram analysis of atrophy corrected NAA in parietal lobes (> 70 % GM) in AD**

Regression Analysis of Tissue Composition and Metabolites in AD



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Conclusion

- Metabolites measure optimum lateralization
- Decreased NAA for hippocampus atrophy
- Bilateral abnormalities by Asymmetry Index
- Lateralization and discordance of lobes:

  Atrophy; HV;T2; NAA; NAA/(Cho+Cr)
- Multi-slice MRI approach for Asymmetry Index
- MRI-defined two AD and SIVD disorders

Where we go from here?

Specific Aim 1:

Better spectral MRSI resolution

Specific Aim 2:

Amyloid proteins and CSF proteins

Specific Aim 3:

Dementia neuropsychological classification and metabolite regional differences and Source of NAA

Specific Aim 4:

Gene expression and regional metabolite

NAA/Cr+Cho ratio

Technique Development for Spectroscopic Imaging Display(SID)

- SNR enhancement, B_0 inhomogeneity, 1st/2nd order phase correction, minimization of operator interaction
- Parametric Automated spectral simulation
- *a priori information* of metabolites
- voxel-by-voxel training data for tissue composition(CSF nulling)
- Point Spread Function and peak-overlaps
- Data Processing in the X, Y co-ordinates
- Corregistration and segmentation
- Correction of lineshape variation due to T_2^*

MRI + MRSI: Epilepsy

- Neocortical Epilepsy
- Mesial Temoral Lobe Epilepsy
- Post-operative Mesial Lobe Epilepsy

MRI: DSE and MP-RAGE images

- Oblique axial Double Spin Echo(DSE) T2 weighted imaging at TR/TE1/TE2 300/20/80 ms; resolution 1 x 1.4 mm^2; 48 slices.

- 3D T1 weighted MP-RAGE acquisition TR/TI/TE 10/250/4 ms; flip angle 15; resolution 1 x 1 mm^2; 48 slices.

Combined (multisection FLASH + PRESS) MRSI in mTLE

- Unilateral mTLE (ipsilateral side)
- PRESS volume pre-selection on hippocampus(TR/TE=1800/140 ms; voxel 9 x 9 x 15 mm^3); circular K-space encoding of 24 points
- Multisection FLASH(TR/TE=1800/140 ms; voxel 8 x 8 x 15 mm^3); circular K-space encoding of 36 points

Epilepsy may be better classified by H-1 MRI + MRSI

- Neocortical Epilepsy
- Mesial Temporal Lobe Epilepsy(mTLE)
- Temporal Lobe Epilepsy(TLE)

by

- Ipsi- and contralateral localized changes
- Hippocampal Voluming
- PET and ectal EEG as clinical correlates of MRI and MRSI

Hippocampus Lateralization by MRSI

- **NAA, Choline, Creatine and their ratio: NAA/Cr, NAA/Cho, NAA/(Cho+Cr) in left vs right hippocampus lobes in Epilepsy**

- **Asymmetry Index =** $\dfrac{(M_{contra} - M_{ipsi})/(M_{contra} + M_{ipsi}) \times 100 \text{(patients)}}{(M_{left} - M_{right})/M_{left} + M_{right}) \times 100 \text{ (controls)}}$

M is metabolite concentration

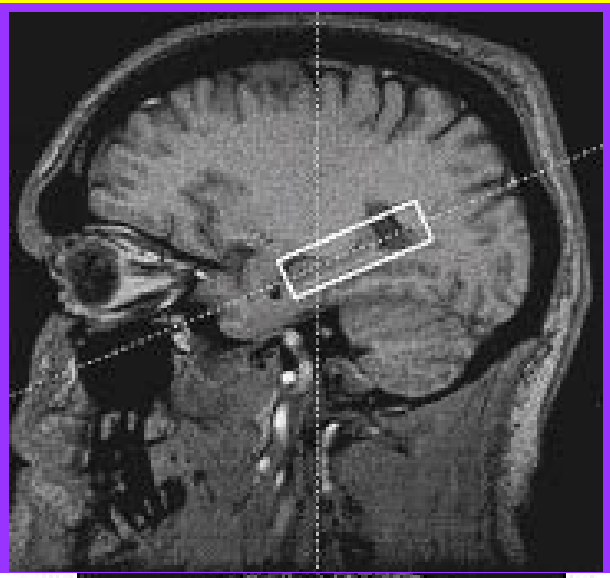
Criteria for Post-operative mTLE evaluation by H-1 MRI + MRSI:

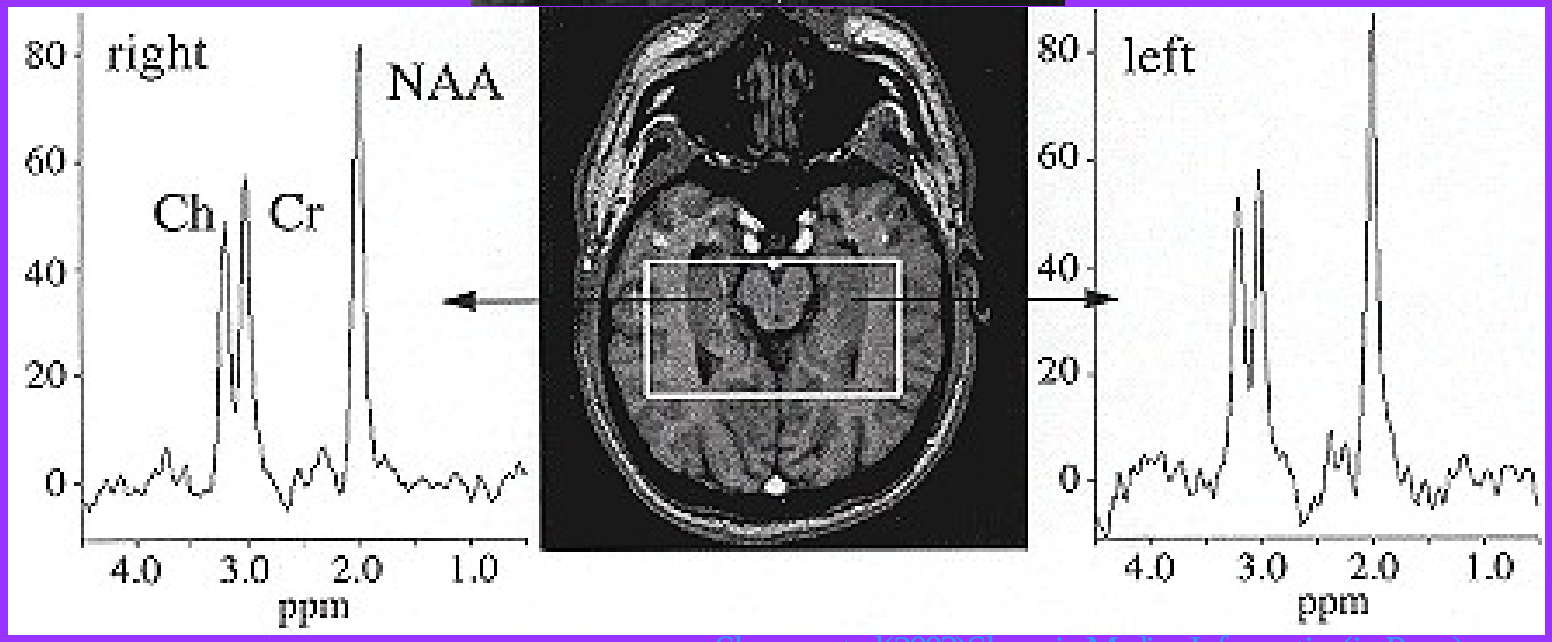
- Percent Hippocampal volume reduction
- Reduced NAA/Cr
- Reduced NAA/Cho
- % Gray matter + % White matter

Characteristic changes in:

- Temporal lobectomy - Class I
- Partial seizures - Class II
- Complex partial seizure - Class III

PRESS: H-1 MRS of Hippocampus





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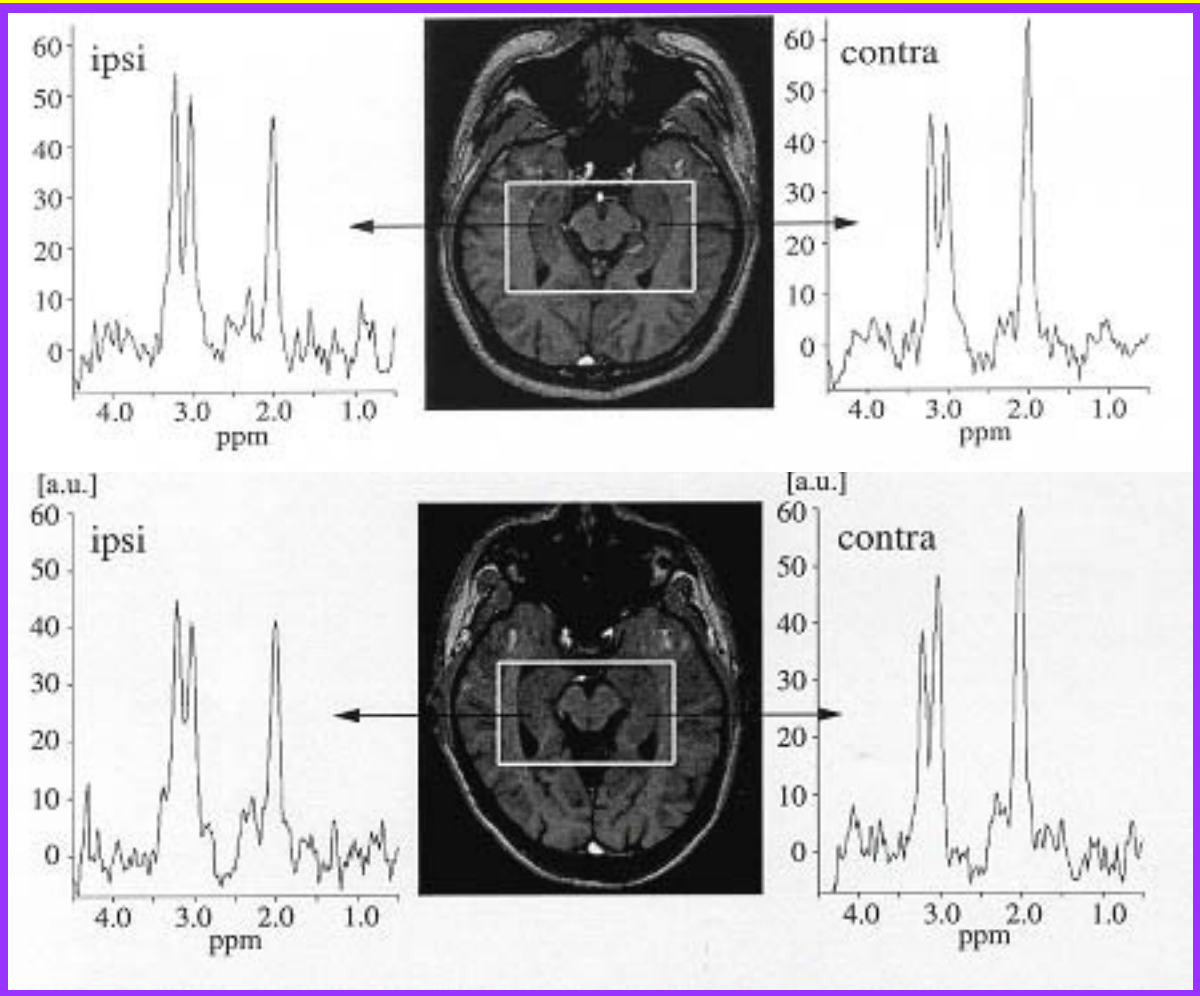
Transverse FLASH(Fast Low Angle Shot):

TLE ipsilateral vs. contralateral metabolites



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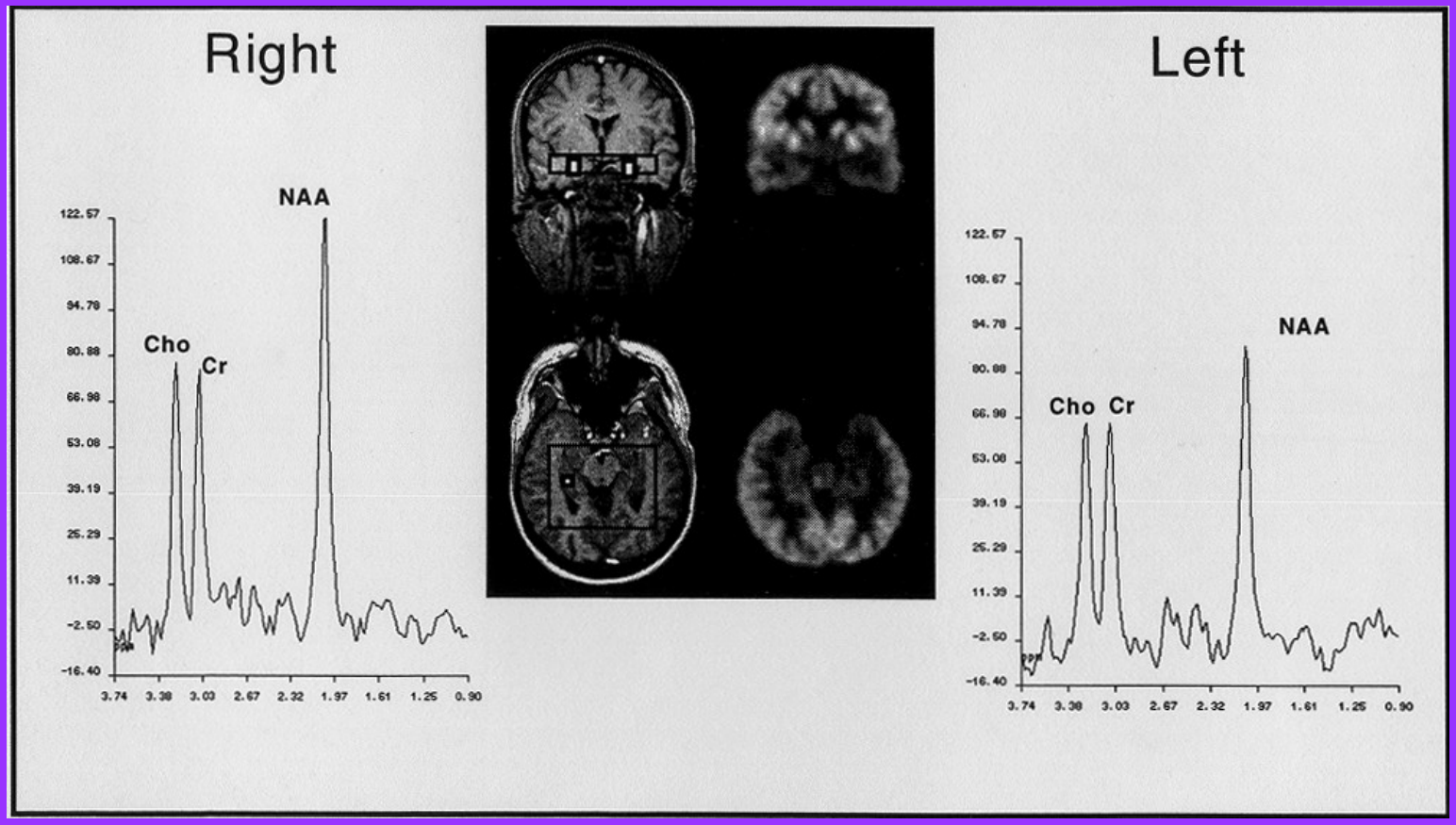
PRESS: Reduced NAA and Increased Cho in contralateral side



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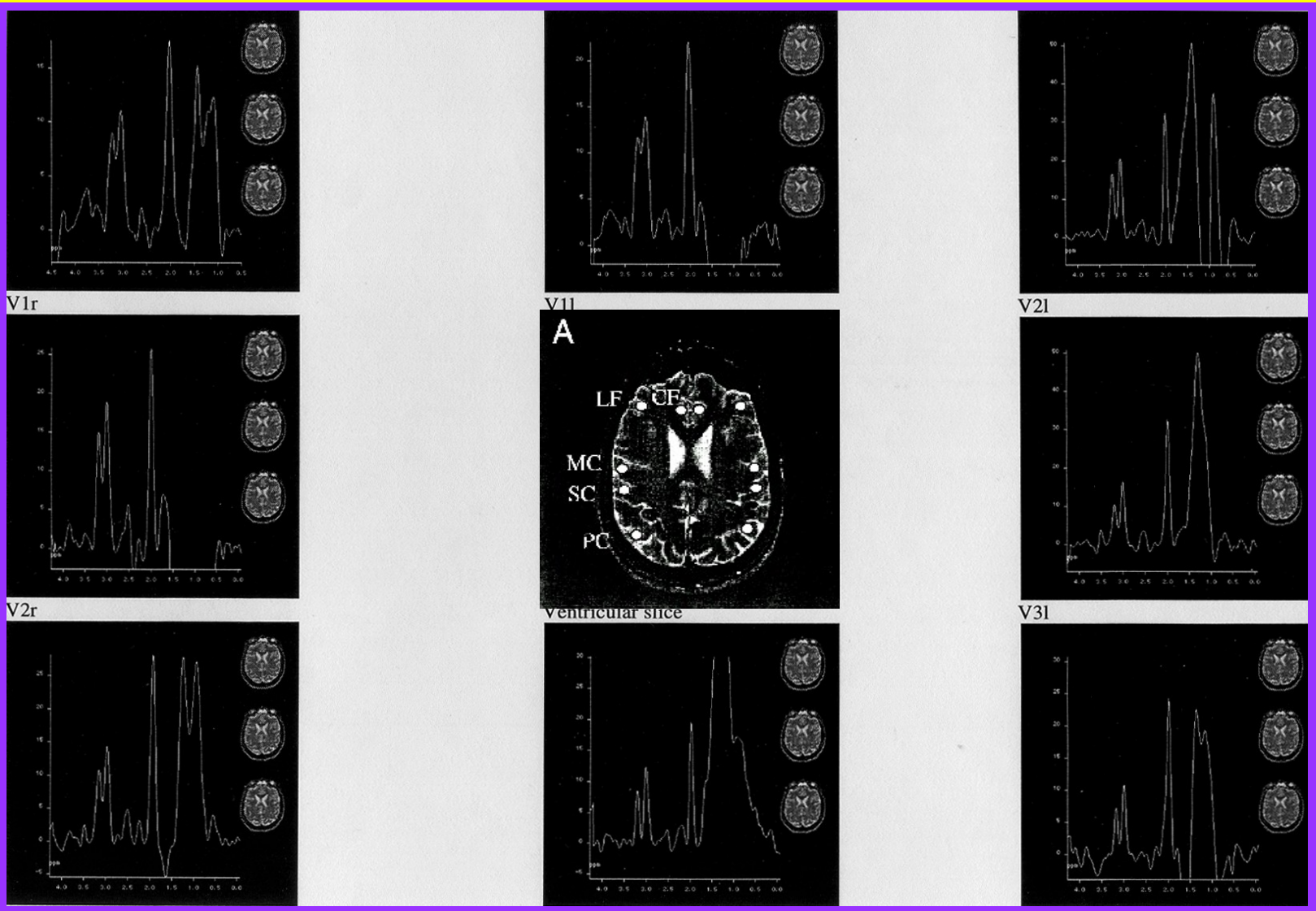
Voxelwise metabolite spectral peaks



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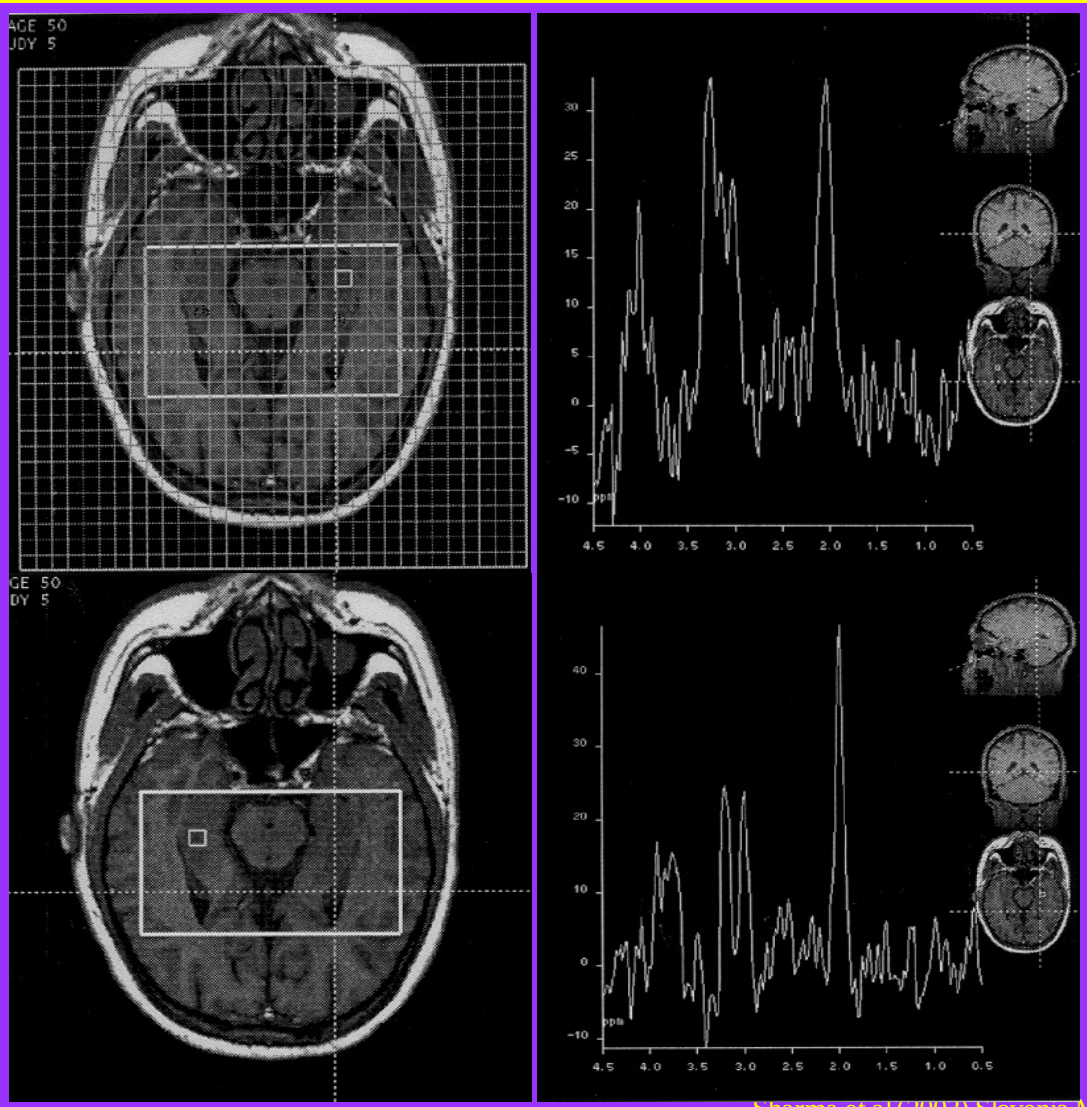
CSI: Metabolites in hippocampus left vs right lobes



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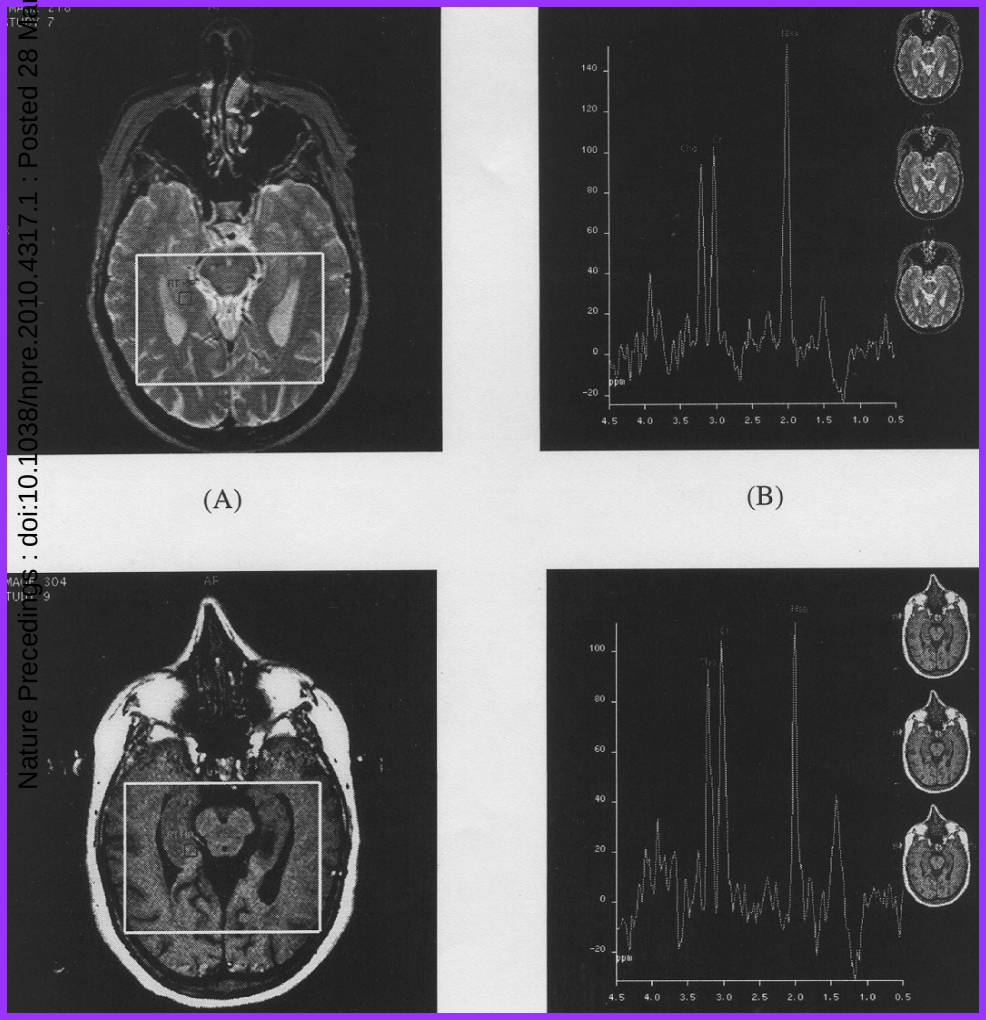
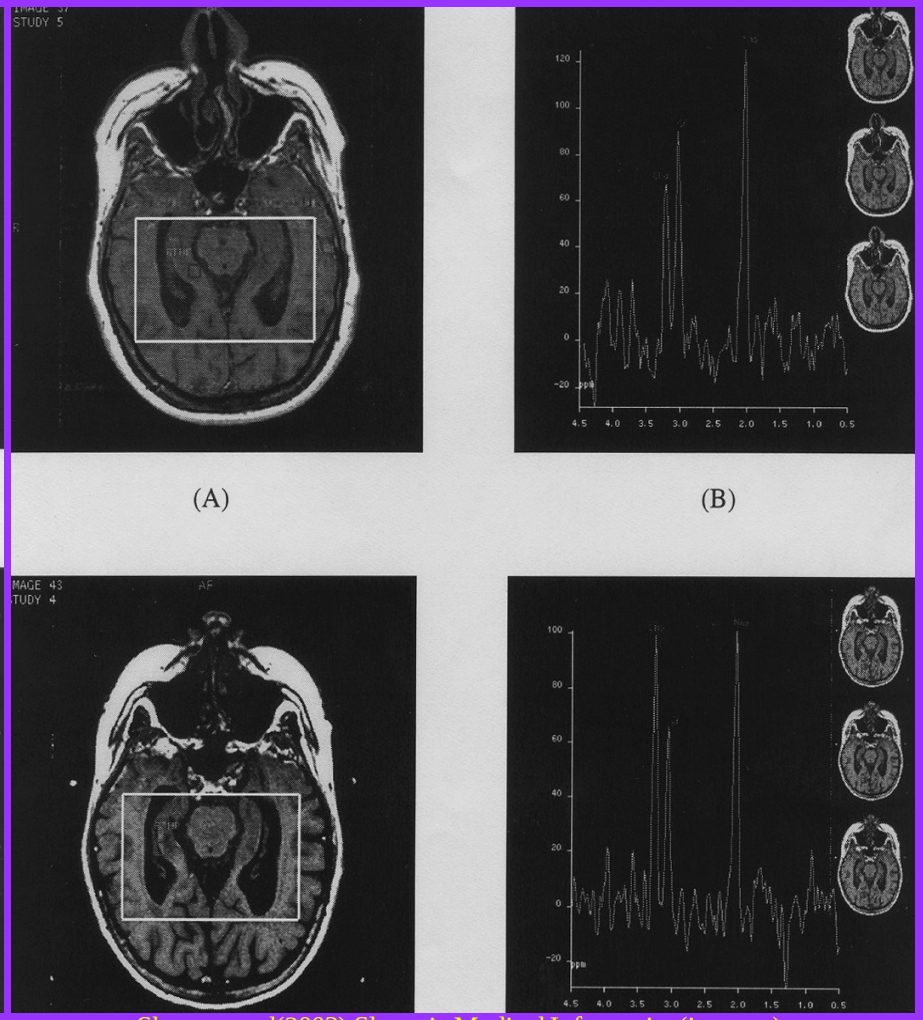
Hippocampus Volume Reduction and PRESS-MRS Lipids and Choline



(A) (B)



(A) (B)

Sharma et al(2003) Slovenia Medical Informatica(in press)

MRSI: Neuro-metabolites in Epilepsy

Subjects		NAA(mM)	NAA/(Cr+Cho)
Controls(n=16)		11.6 ±1.3	0.82 ± 0.06
NE(n=8/10)	Ipsilateral	12.3 ± 1.9	0.79 ± 0.1
	Contralateral	11.4 ± 2.7	0.78 ± 0.1
mTLE(n=23)	Ipsilateral	8.5 ± 1.3*	0.62 ± 0.1*
	Contralateral	9.6 ± 1.3*	0.72 ± 0.1*

Ipsi- and contralateral NAA concentrations and NAA/(Cr+Cho) ratios(mean ± SD) in the hippocampus of NE and mTLE patients in comparison with controls (p values comparison in patients with controls). *indicates p value 0.001.

Sharmaet al (2003) Slovenia Medical Informatica(in press)

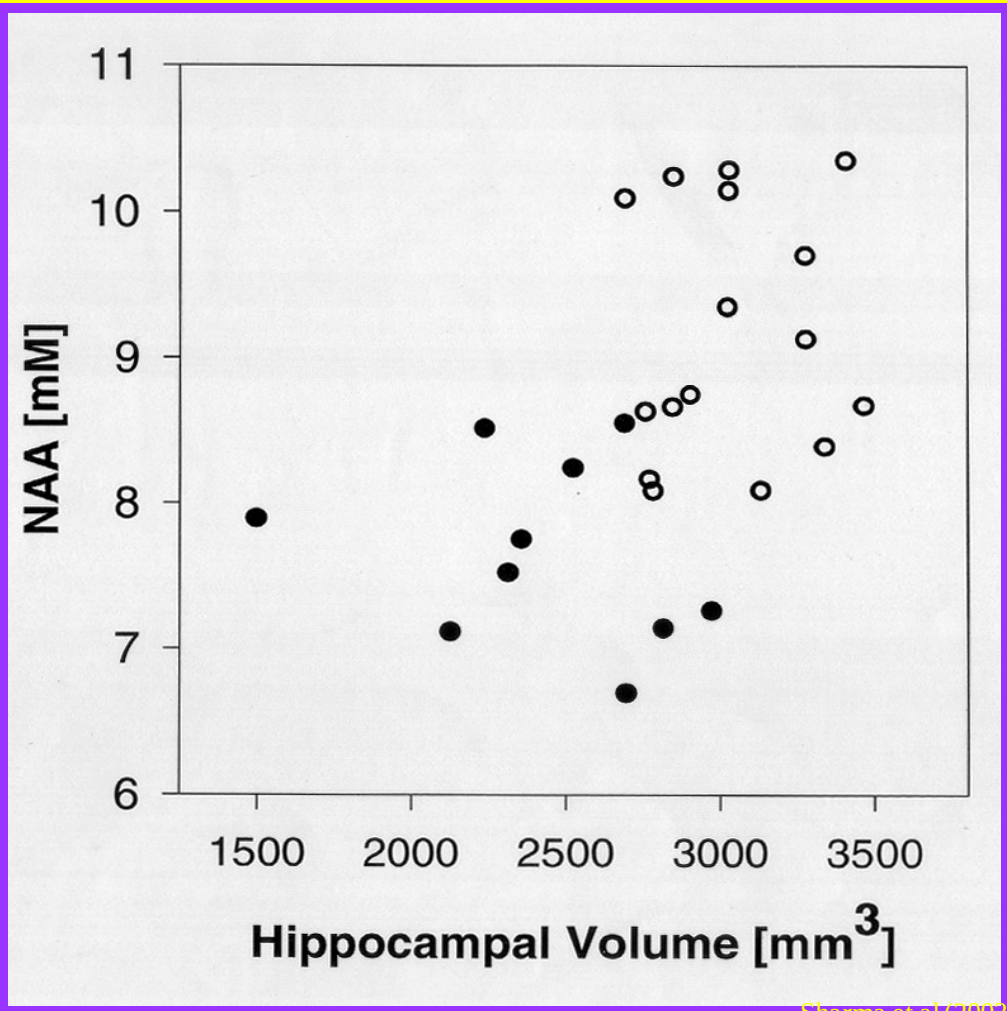
MRSI and Asymmetry Scores in Epilepsy

Subjects	Asymmetry (NAA)	Asymmetry NAA/(Cr+Cho)	absolute asymmetry NAA	absolute asymmetry NAA/(Cr+Cho)
Controls	4.85 ±0.2	6.25±0.63	5.65±3.15	4.75 ± 3.95
NE	7.8±4.6	8.01±1.2	6.8±5.71	6.75 ± 3.8
	n.s.	n.s.	n.s.	n.s.
mTLE	7.45 ± 2.27	7.4 ± 3.65	9.2 ± 6.4	9.07 ± 6.7
	(p <0.001)	(p <0.003)	(p <0.001)	(p <0.04)

- NAA and NAA/(Cr+Cho) Asymmetry Indices (mean ± SD) of NE and mTLE patients in comparison with controls (p values compared with controls).
- Absolute Asymmetry was independent of seizure focus

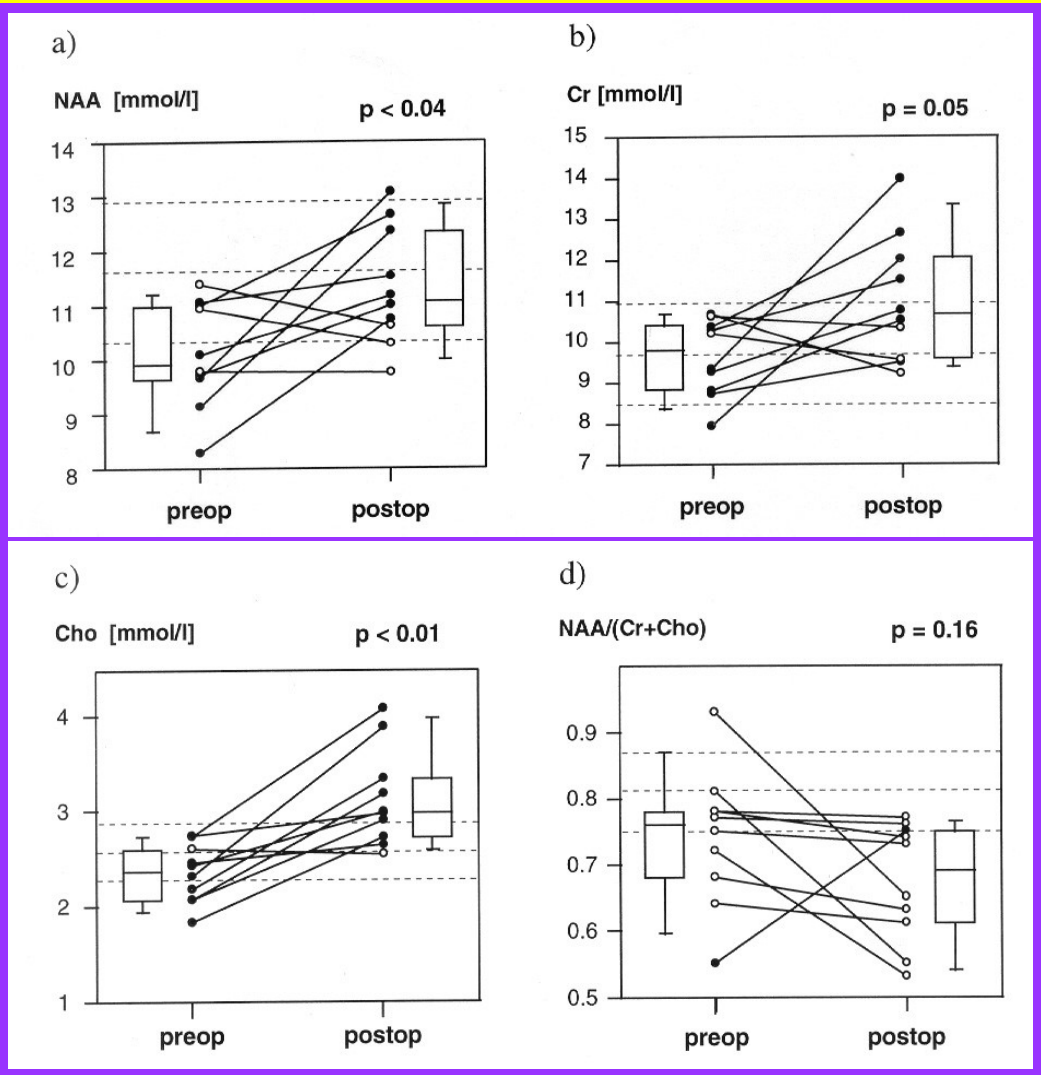
Sharma (2002) Slovenia Medical Informatica(in press)

MRSI: NAA and Hippocampus Volume in Epilepsy



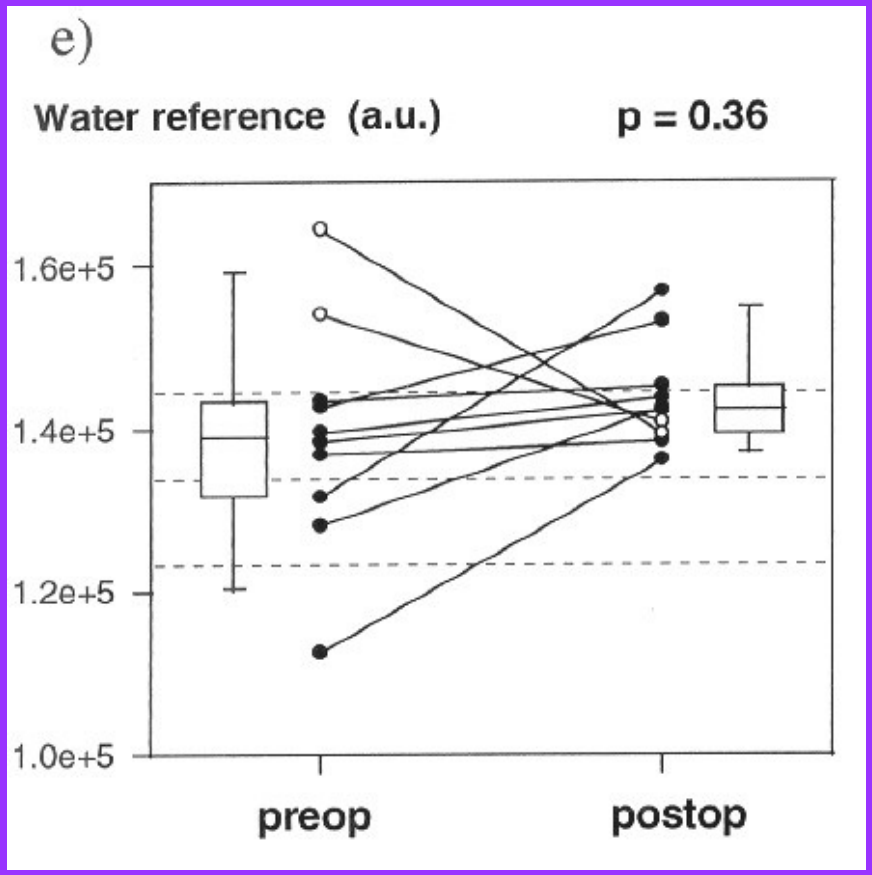
Sharma et al (2003) Slovenia Medical Informatica(in press)

MRSI: Metabolites in Pre-op vs post-op Epilepsy



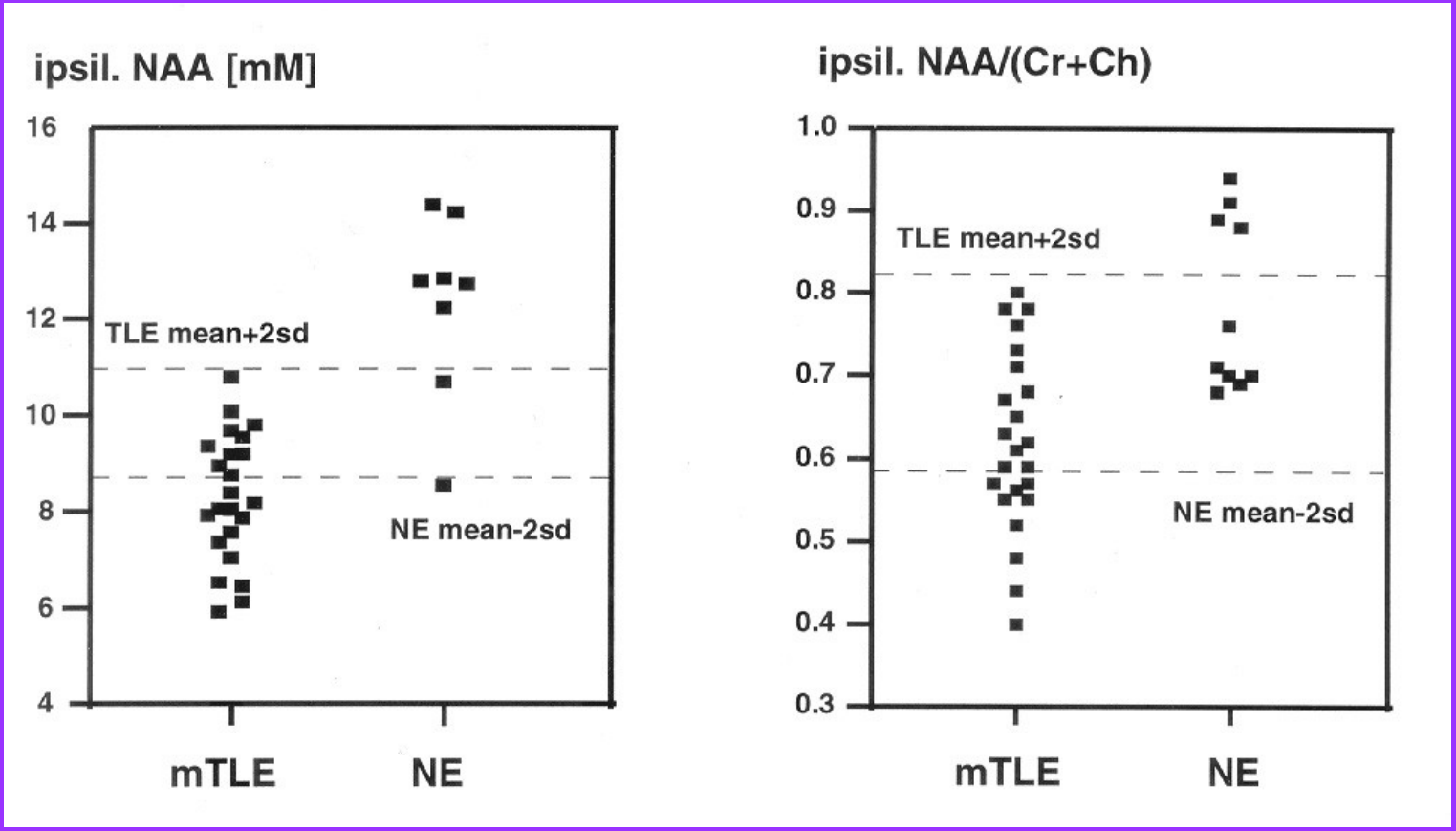
Sharma et al (2003) Slovenia Medical Informatica(in press)

MRSI: Water as internal reference for metabolites in Epilepsy



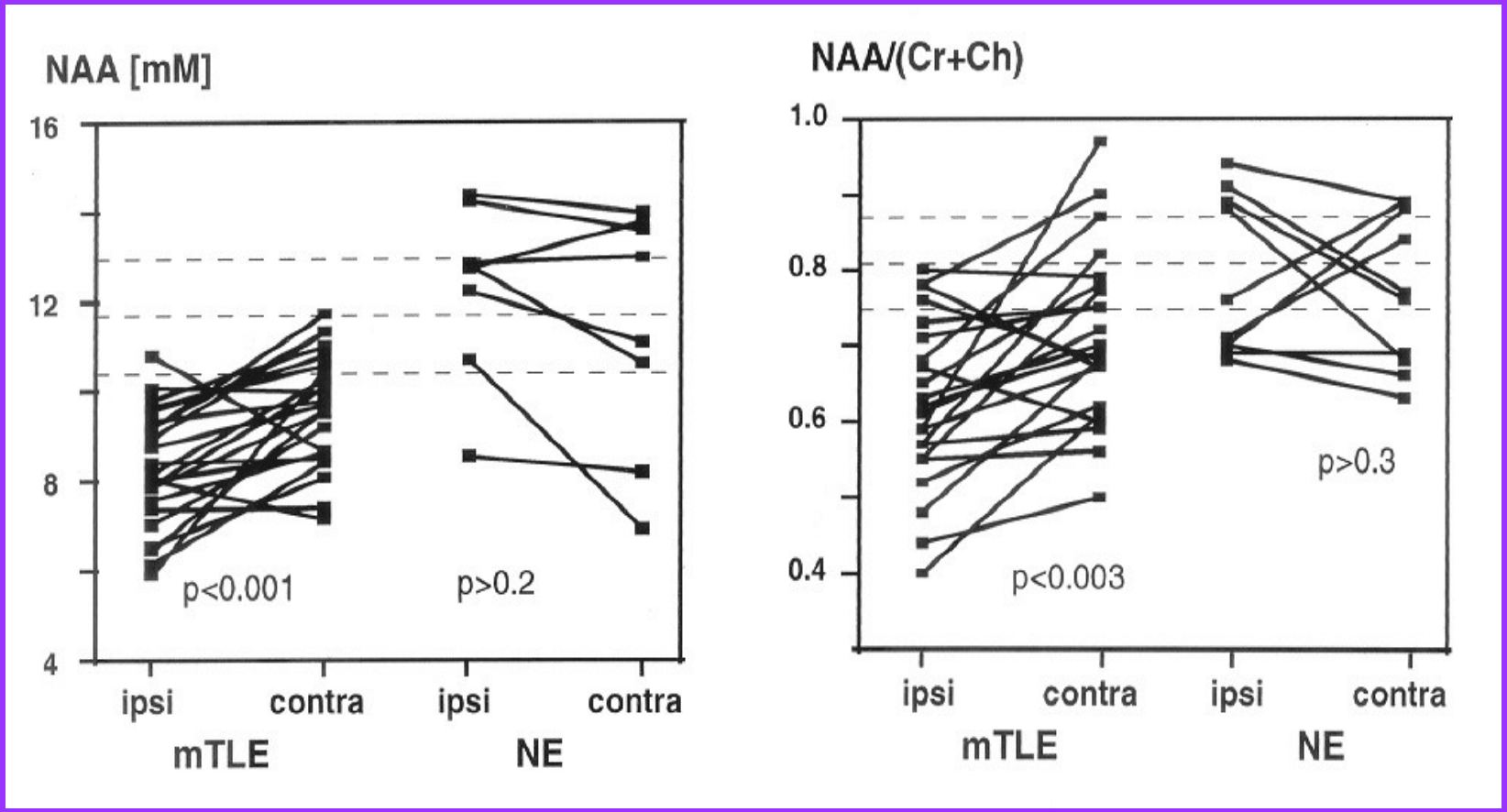
Sharma et al (2003) Slovenia Medical Informatica(in press)

MRSI: NAA and NAA/(Cr+Cho) in mTLE and NE Ipsilateral side



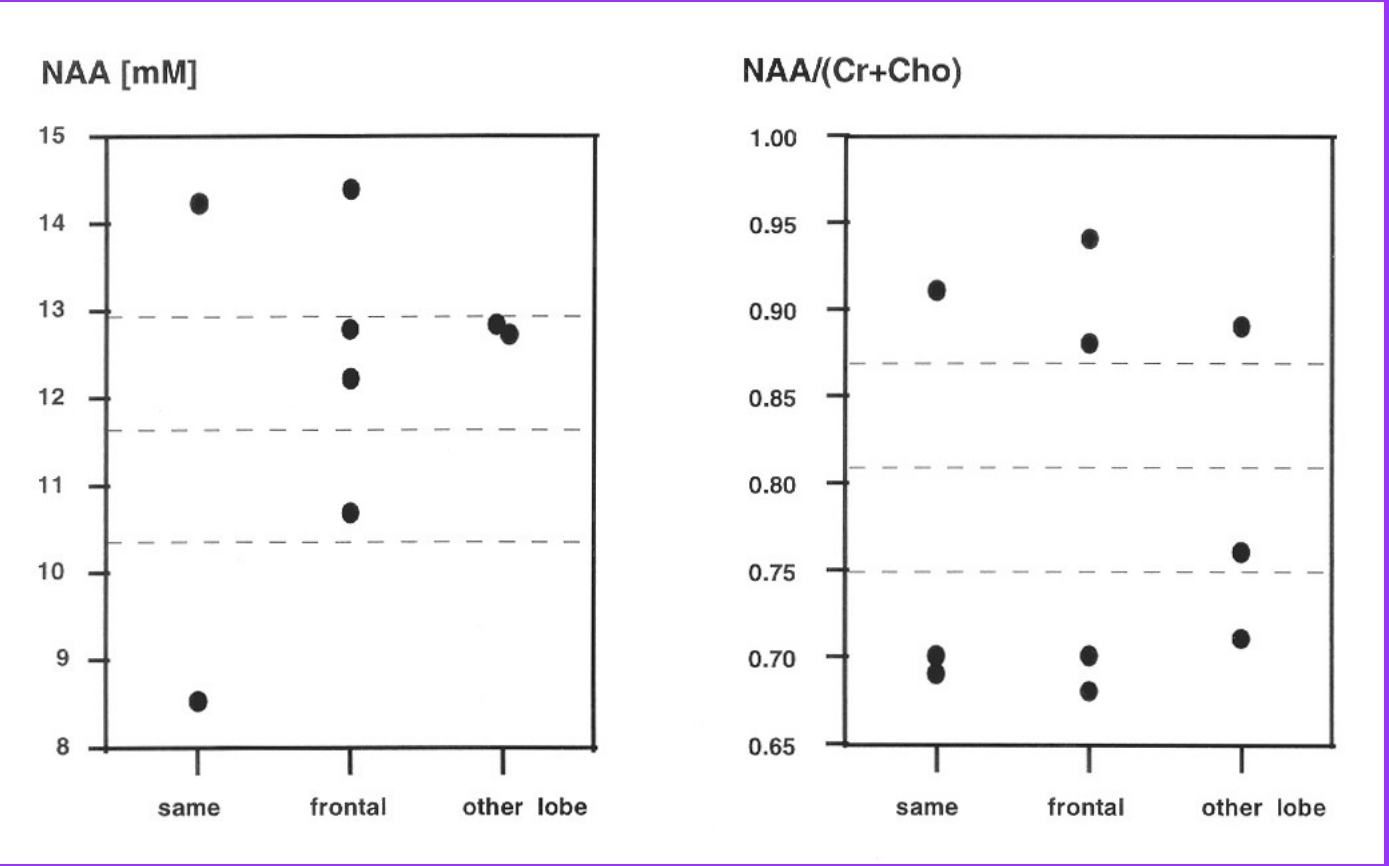
Sharma et al(2003) Slovenia Medical Informatica(in press)

MRSI: NAA and NAA/(Cr+Cho) differ in NE and mTLE in ipsi- and contra-lateral sides



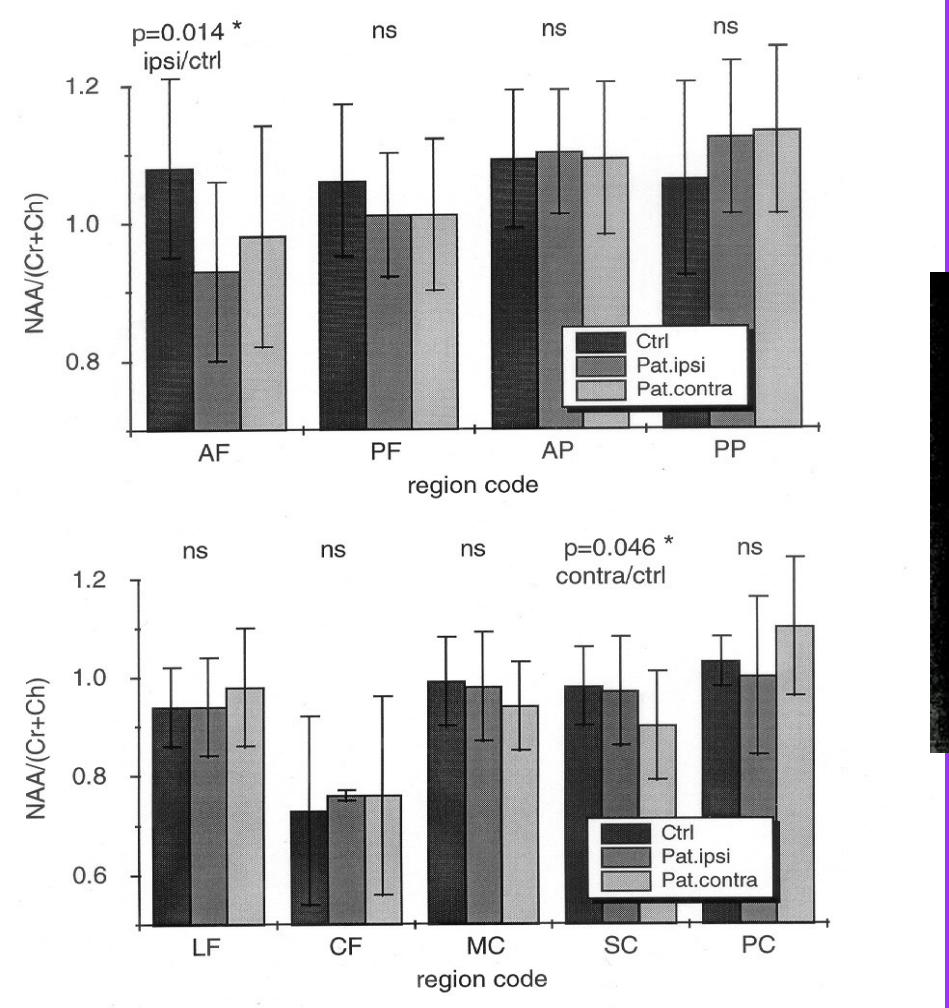
Sharma (2002) Slovenia Medical Informatica(in press)

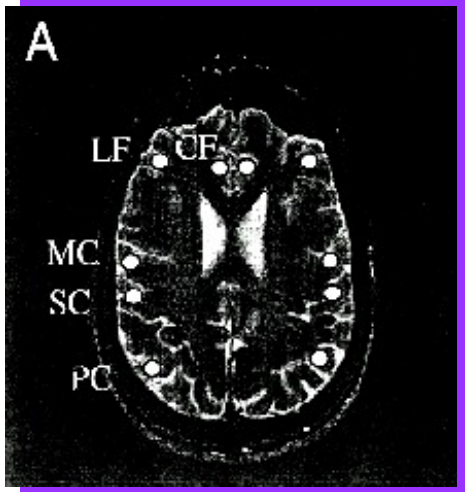
NAA, NAA/(Cr+Cho) in Frontal Lobe Epilepsy



Sharma (2002) Slovenia Medical Informatica(in

NAA/(Cr+Cho) in Control vs Epilepsy ipsi- and contra-lateral sides at different brain regions





Sharma et al (2003) Slovenia Medical Informatica(in press)

Conclusion

- Metabolites measure optimum lateralization
- Decreased NAA for hippocampus atrophy
- Bilateral abnormalities by Asymmetry Index
- Relationship of MRS peaks with post-op surgery seizure condition(bilateral abnormalities)
- Lateralization and discordance of lobes:
  Atrophy; HV;T2; NAA; NAA/(Cho+Cr)
- Assessment of seizure focus spread

From here where we go?

Specific Aim 1:

Absolute concentration of metabolites and 2D MR spectroscopy(COSY) information

Specific Aim 2:

Lateralization and discordance criteria

Specific Aim 3:

Sensitivity of the techniques by gradient correction, better Rf coil design

Specific Aim 4:

Alternative approach of FDG/PET and perfusion/diffusion weighted MRI

Specific Aim 5:

Robust software for registration-segmentation and hippocampus voluming

MRI and MRSI in Multiple Sclerosis

Introduction

- Multiple Sclerosis, a neurodegenerative disorder with relapsing remitting course is manifested as progressive lesions around ventricles.

  i. Blood-brain barrier altered--> demyelination of axon-->MS lesion enhancement(MRI-defined Perivenous inflammation)

  ii. Non-inflammatory, lipid rich WM and GM(No MS lesion)

- Serial MRI/MRSI data offers:

  1. MS lesion volumetry
  2. Brain GM and WM composition
  3. Comparison of H-1 MR metabolite images,
  4. *in vivo* H-1 MR spectral analysis in different regions of brain

Hypothesis

- **Mobile lipids release at the cost of NAA (without BBB breakdown) initially followed by amino acid release.**
- **Multiple Sclerosis may be non-inflammatory with lipid-rich Normal Appearing White Matter or Gray Matter (NAWM or NAGM)**

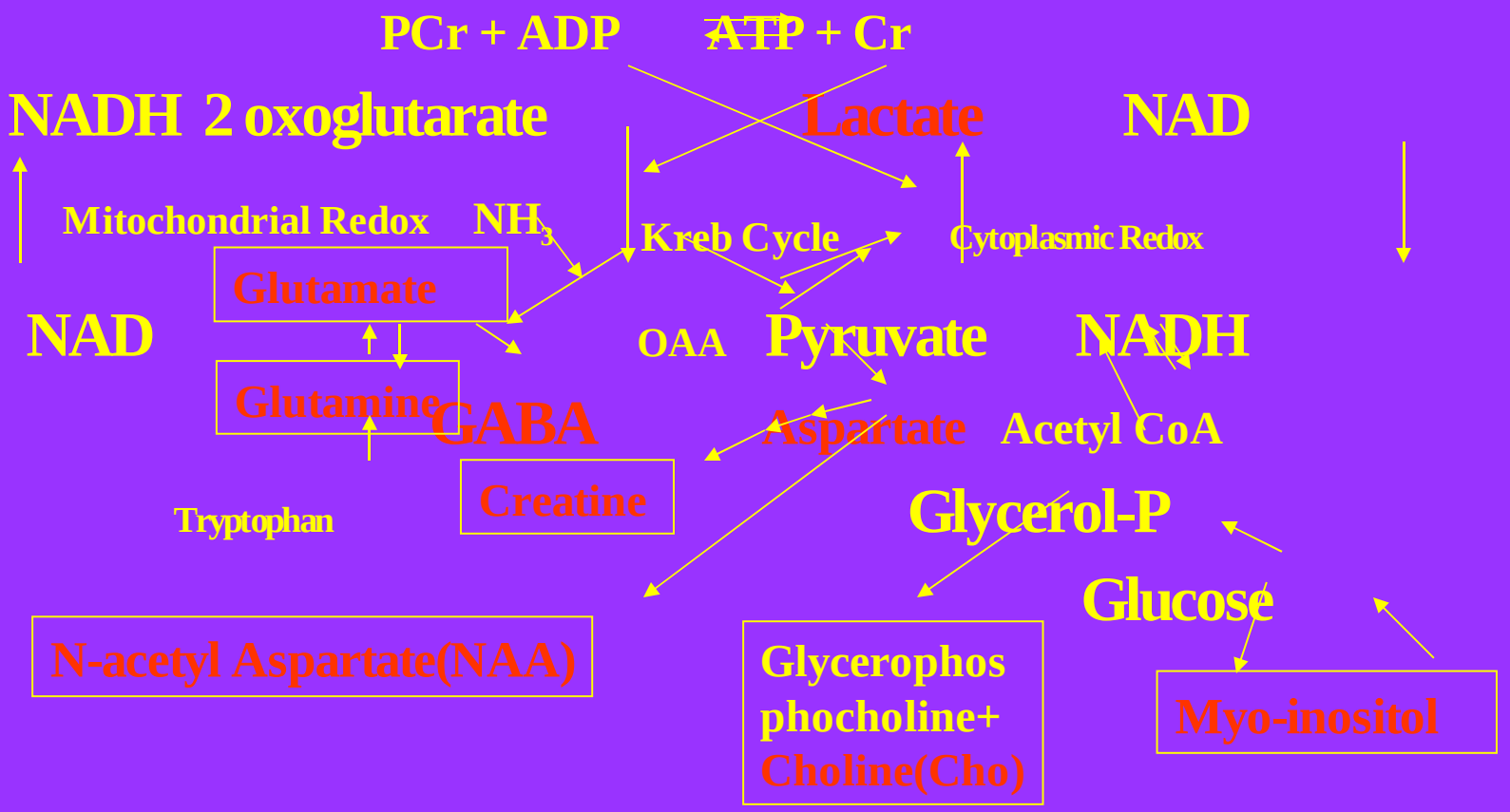
Approach of MRI/MRSI

- Brain and MS lesion tissue composition by MRI in serial scans:
  - Tissue segmentation:
    - Supervized and Automated Method:
      - MS lesion volumetry by 'seed growing algorithm'
      - Brain WM/GM feature-space (Perzen Window) volumetric analysis
      - Gd-lesion enhancement by saturation bands & Gradient dephasing
  - Tissue 3D Registration:
    - Intrahemispheric Fissure(IHF) and Edge-detection method:
      - Search window
      - Rotations about z and y axis
      - Spatial Transformation and Image reconstruction
- Regional metabolite differences by MRSI:
  - Metabolite image generation at TE=20 ms
  - Standardization of MR peaks (*a priori* information based parametric fitting)
  - Automated spectral analysis of all image voxels of MRSI data set in iterative manner (nonparametric baseline and parametric fitting of model metabolites)

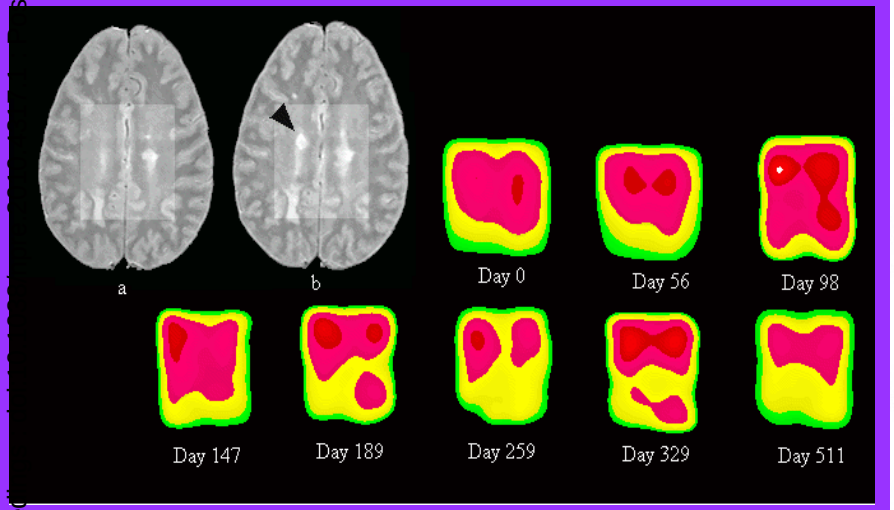
MRI+MRSI in Multiple sclerosis

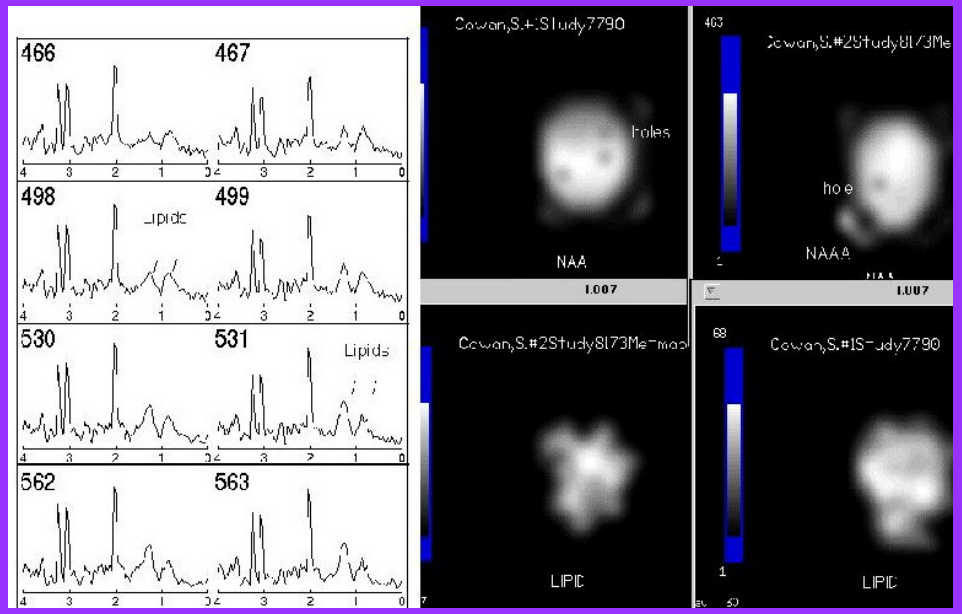
- Serial studies of multiple sclerosis(MS) lesion load(MRI)
- Serial brain metabolite imaging (Lipids)
- 1.5 T MR chemical shift imaging(CSI)
- MRI and MRSI Co-analysis

MR visible metabolites in brain



MRSI postprocessed metabolite NAA, Choline images in MS





- **Enhanced Mobile Lipids(doublet peak) and Choline associate with Reduced NAA**

MRSI: Lipids in serial MS lesions

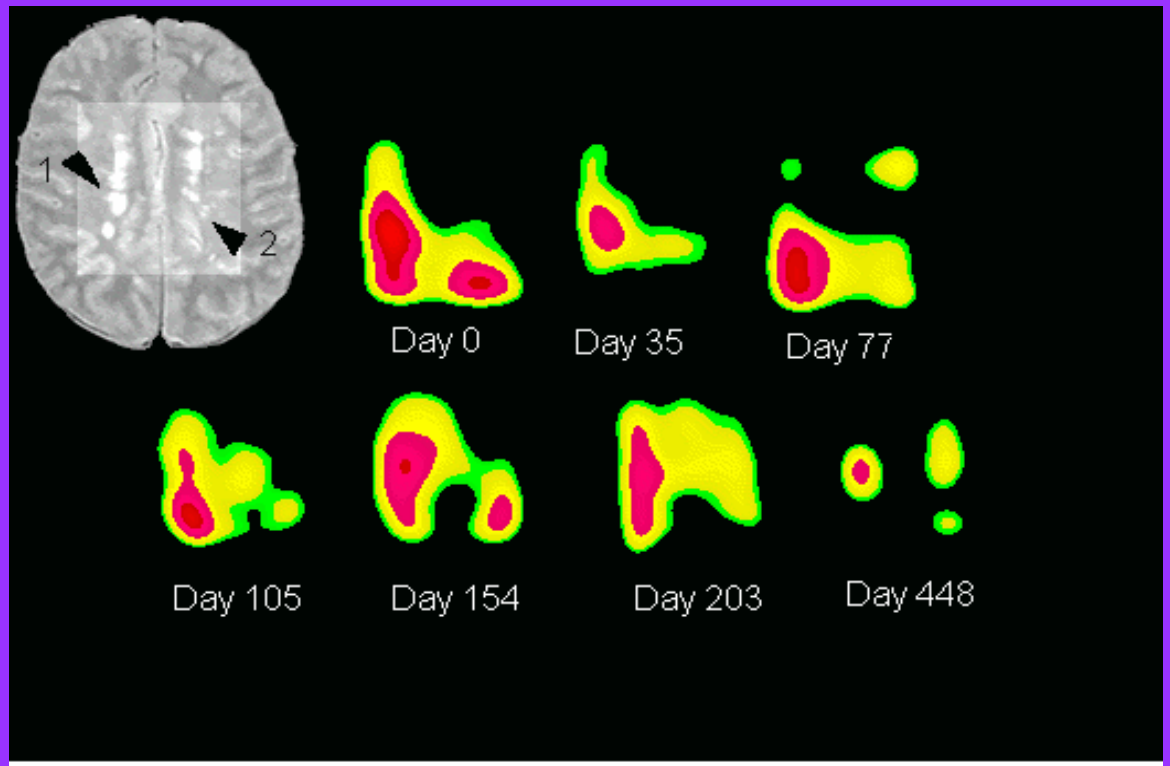
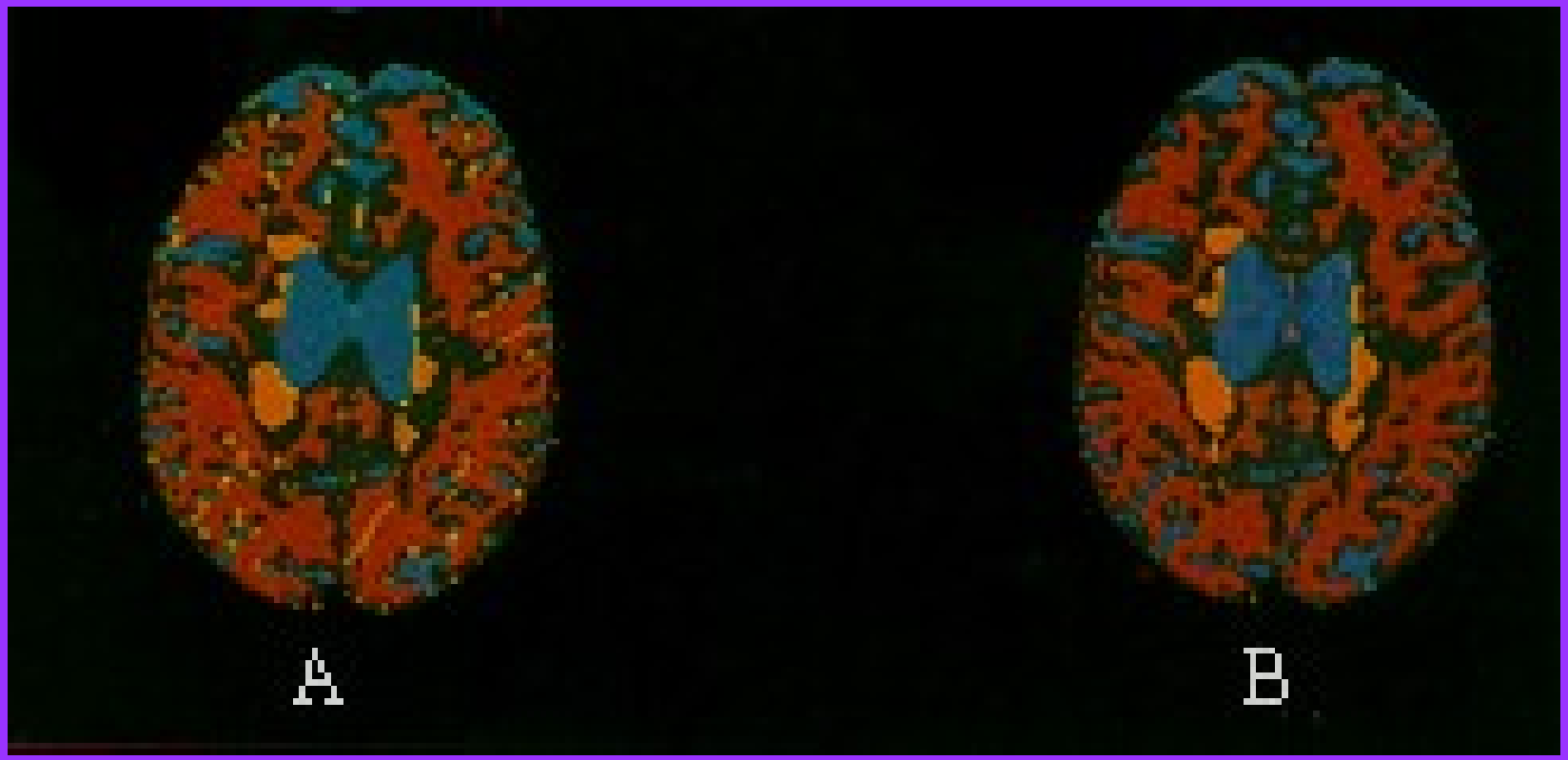


Figure 7: Spectroscopic VOI highlighted on 15 mm thick collapsed(left) slice image with arrowed enhancing lesions. Lipid distribution in lesions shown in time dependent manner. Note lipid images in NAWM(day 0) and later enhancing lesions(after 35days) and recovered later.

MRI+MRSI in MS

- RF inhomogeniety correction
- 3D image registration
- Metabolite concentrations and % tissue composition
- Automated segmentation of Gd-enhanced MS lesions
- Serial lipids and other metabolite changes in MS lesions
- Serial lesion volumetry
- GM seated MS lesions and NAGM vs NAWM

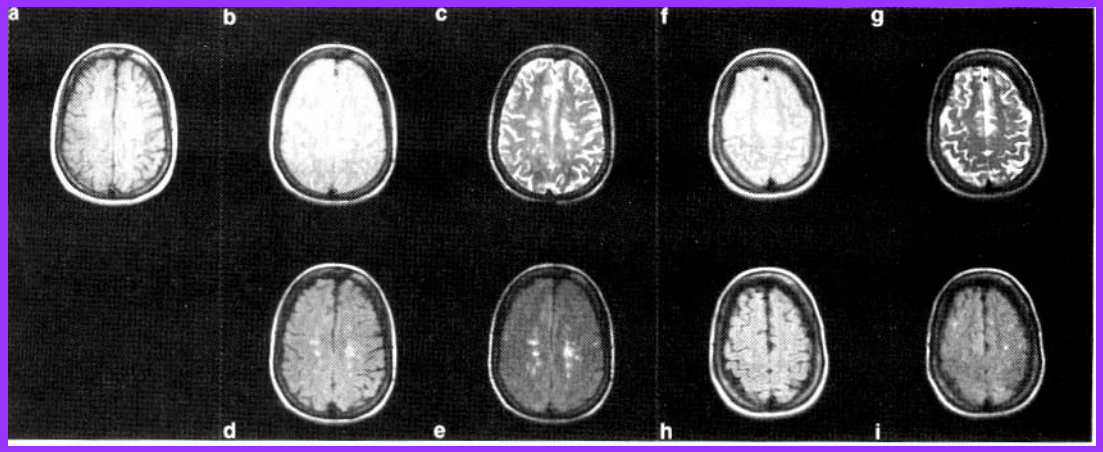
Step 1:Segmentation- Feature maps of different regions in MS brain



Automated segmentation of Gadolinium enhanced MS lesion

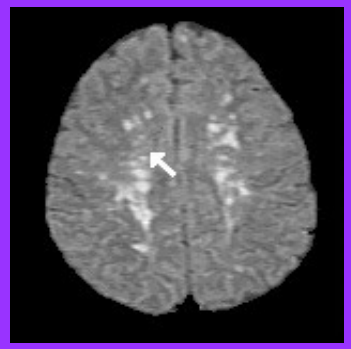
- a. Raw Image; b. Removal of scalp; c. CSF suppressed; d.WM+GM+CSF suppressed;
  e. Partial Volume Average Corrected

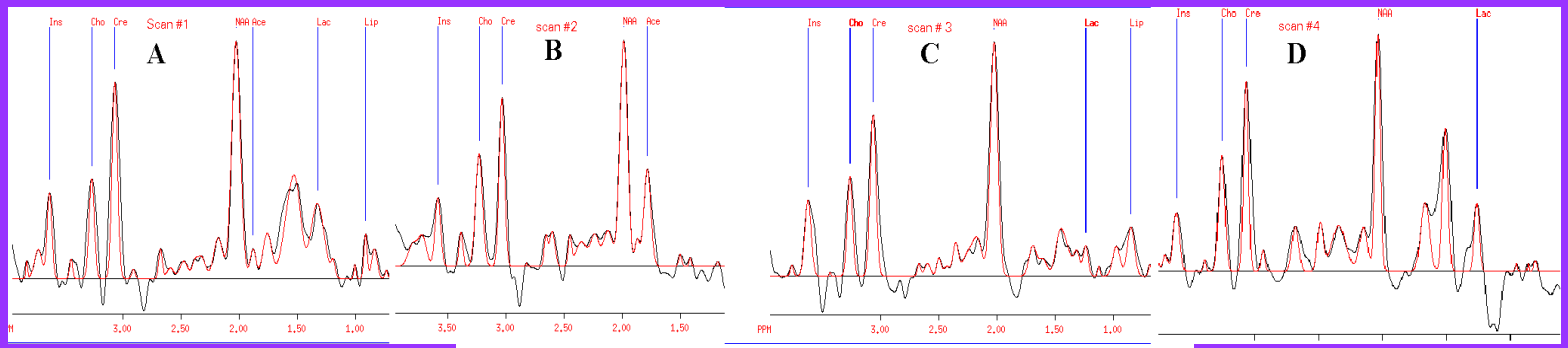
Step 2: Registration Technique

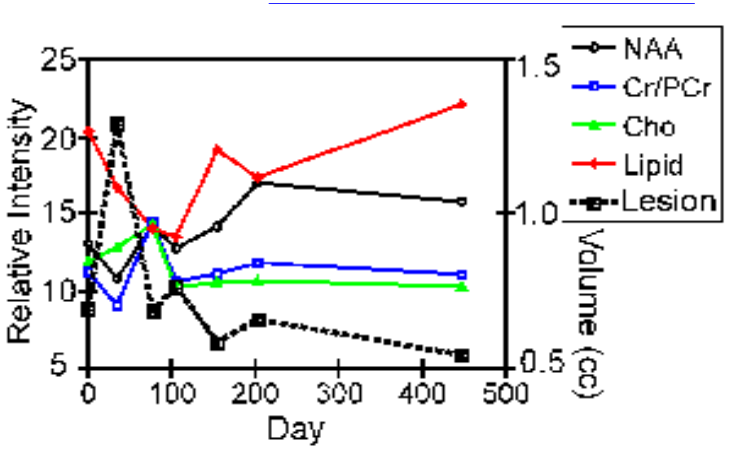


a. Post-contrast T1-w image; b-e. 4 FSE images with early and late echoes after registration; f-i. Same 4 images after registration

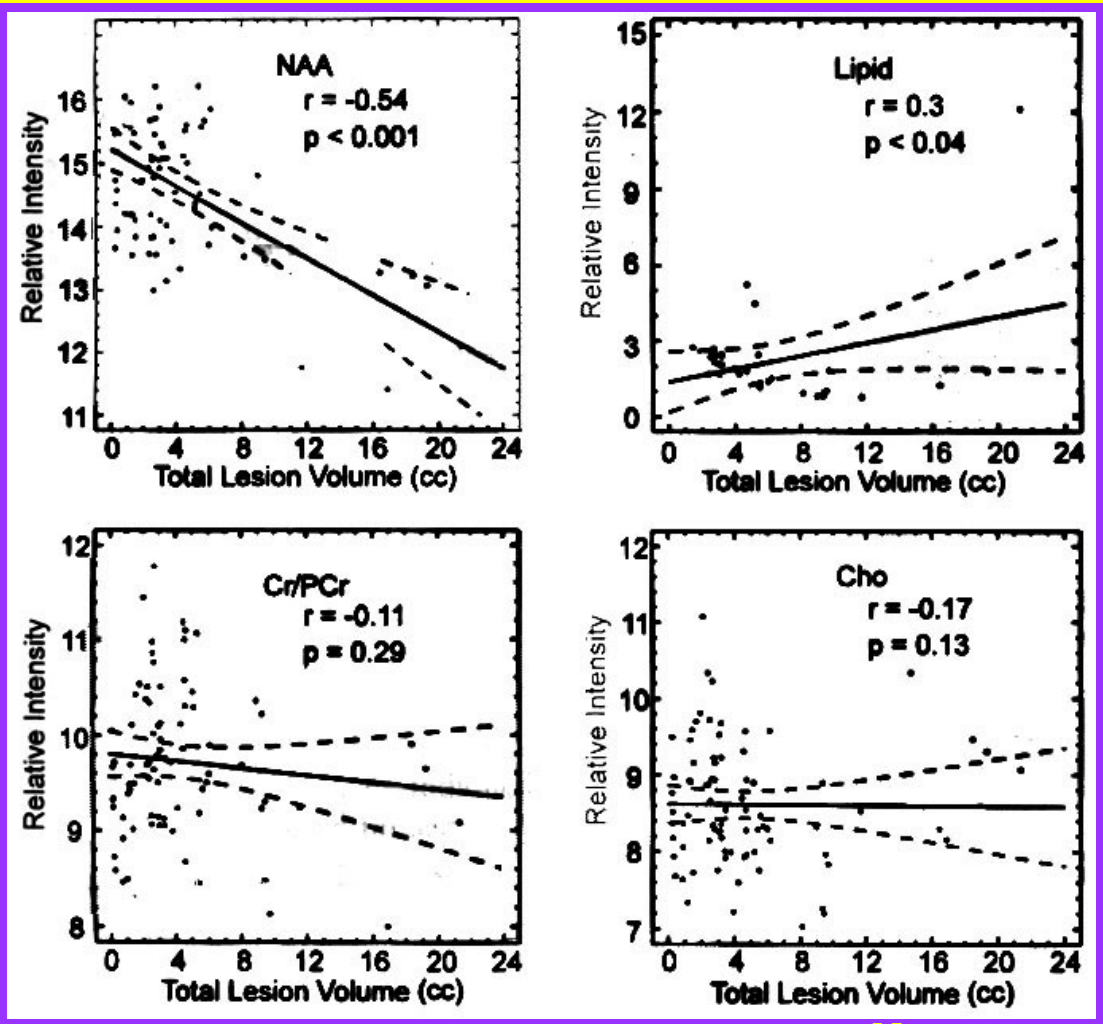
Time dependent metabolite changes in MS brain





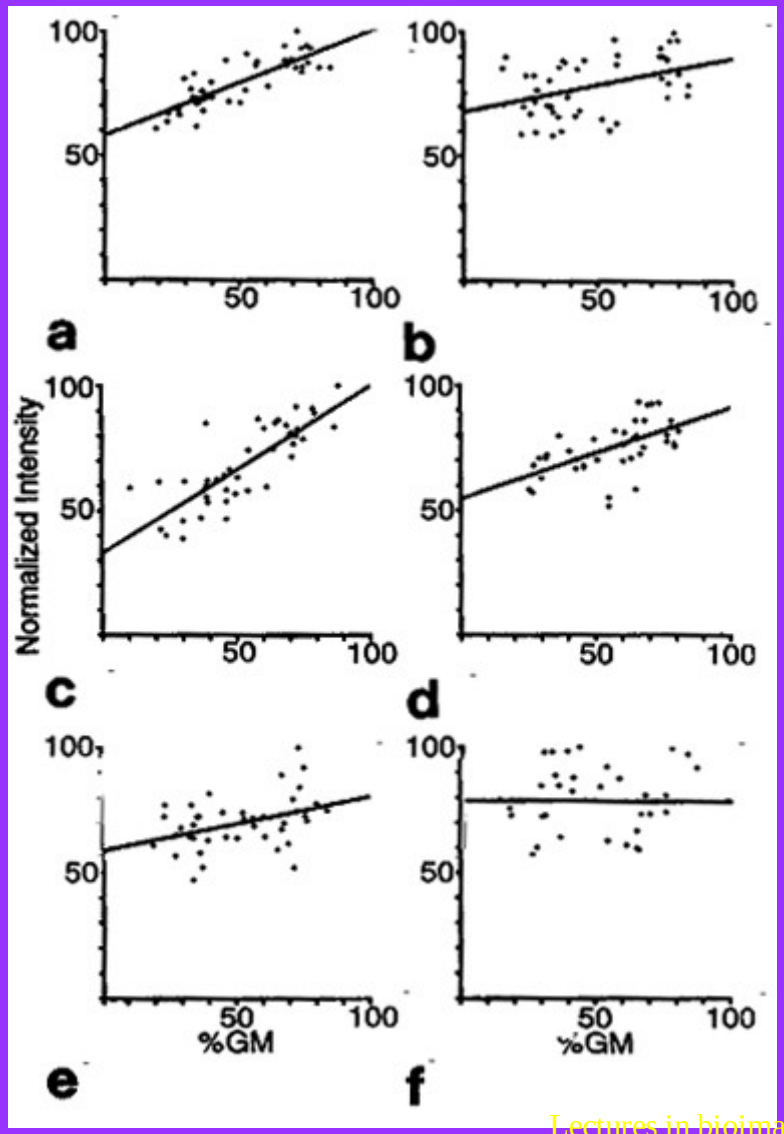


Regression Analysis:Metabolites and MS lesion Volumes



Narayana et al.(1998)MRM

Neurochemicals vs %GM in Normal Brain



- Scatter plots of neurochemical vs % GM for:
- NAA:

  a.(R=0.82,P <0.001);

  b.(R=0.42,P <0.003)
- Cr/PCr:

  c.(R=0.81,P <0.01;

  d.(R=0.56,P=0.001
- Cho:

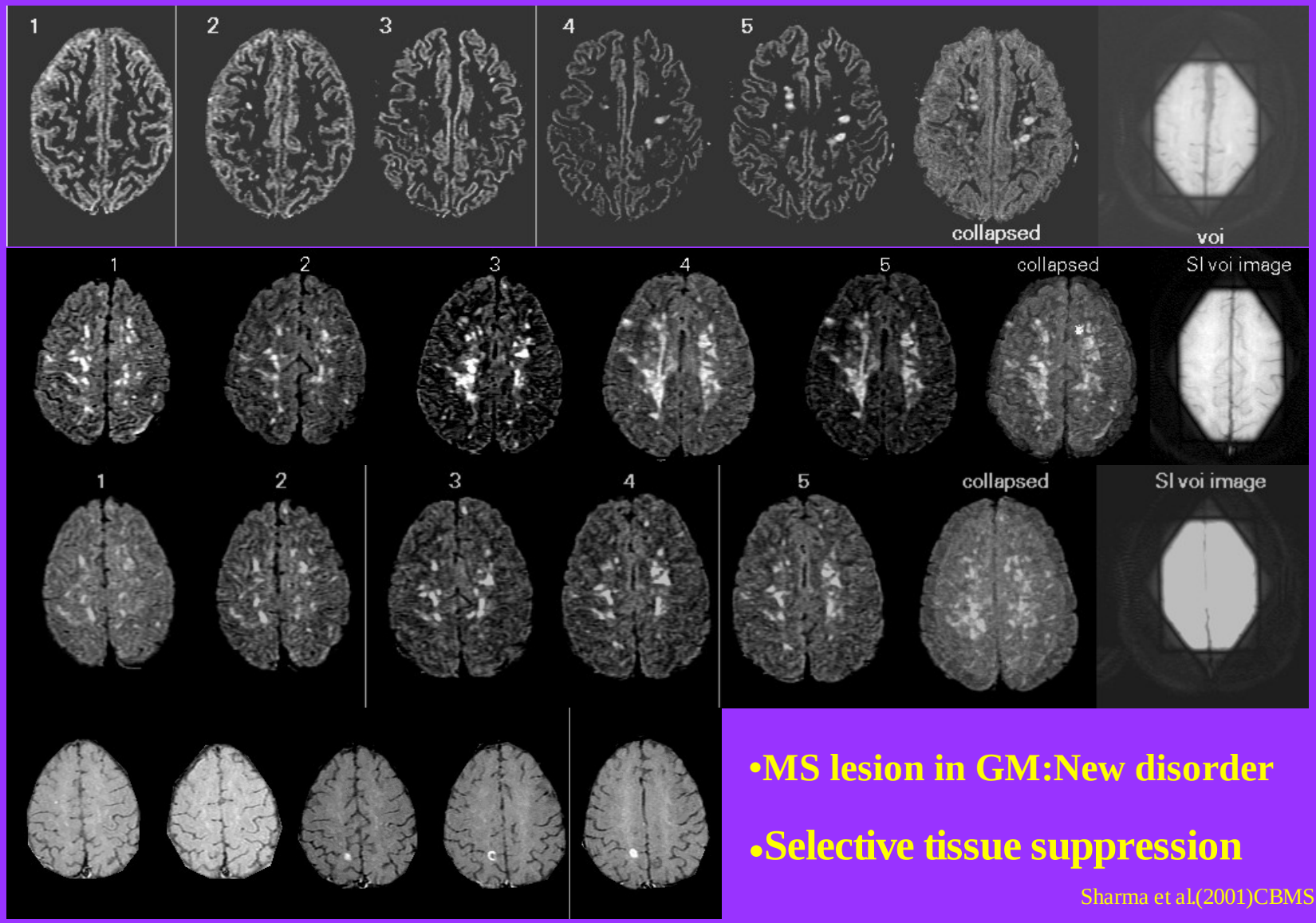
  e.(R= 0.4,P<0.009;

  f.(R=-0.01,P =0.994)

MS: Non-Inflammatory GM Lipid Disorder

- Multiple Sclerosis(MS) is known as demyelinating White Matter disorder
- Histology data suggests abnormal GM in MS
- Occasional presence of GM lesions on MRI

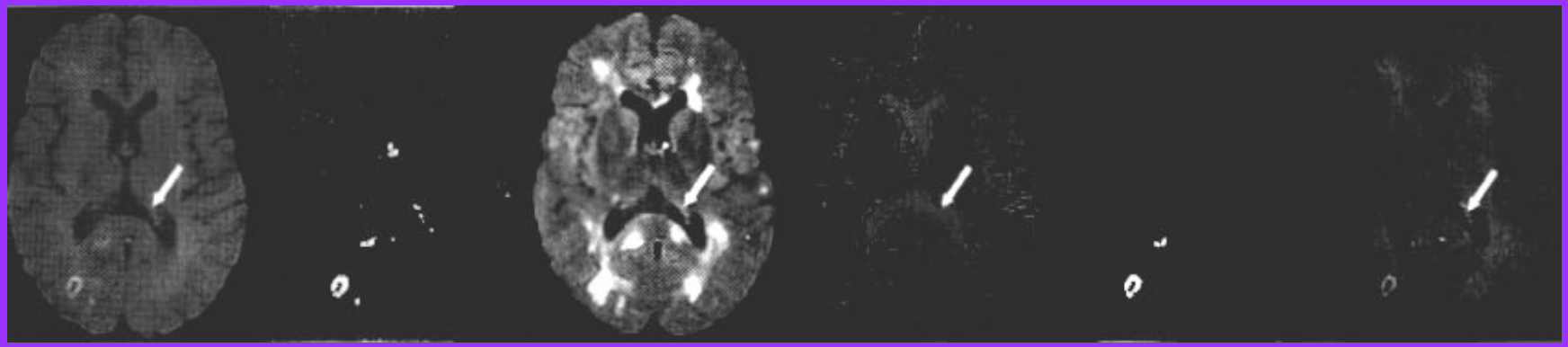
MS Lesion Showing Abnormal Metabolites in Pre- and Post-contrast GM and NAGM



- MS lesion in GM:New disorder
- Selective tissue suppression

Sharma et al.(2001)CBMS 13,87

Gd-Contrast enhancement on MR slice showing GM Lesion



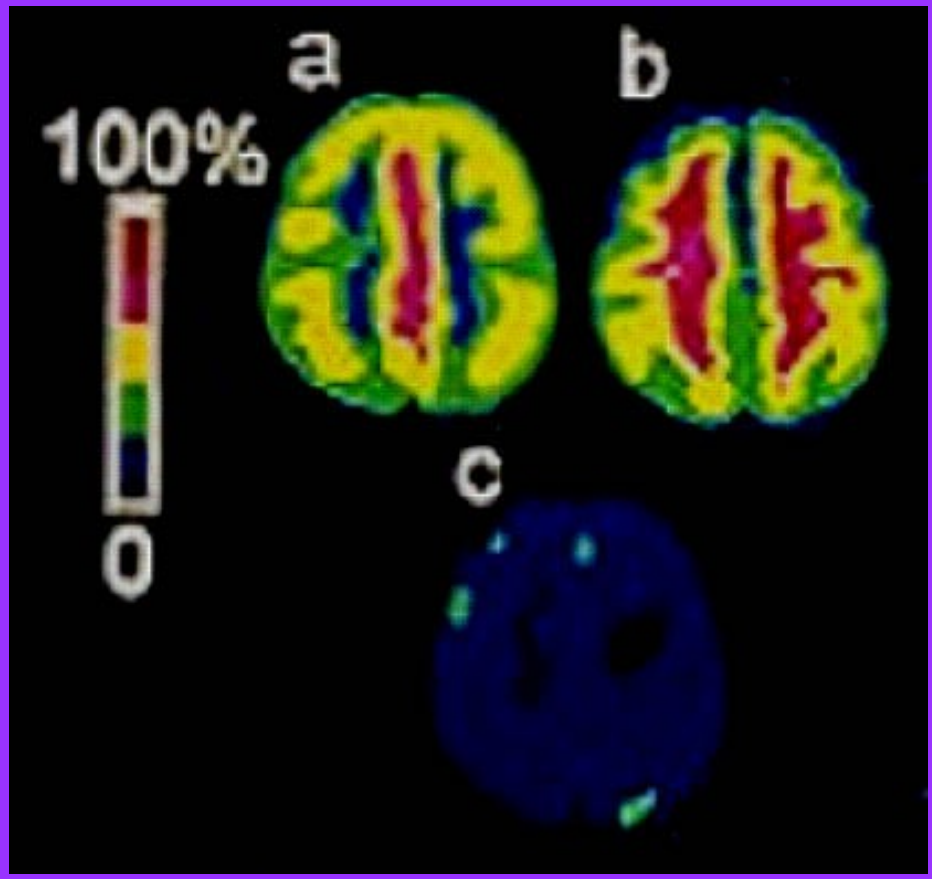
- GM+WM+CSF suppression visualize GM seated lesion after Post Gd- injection

Sharma et al.(2001) Multiple Sclerosis.7:221-226.

Selective Tissue Segmentation Method

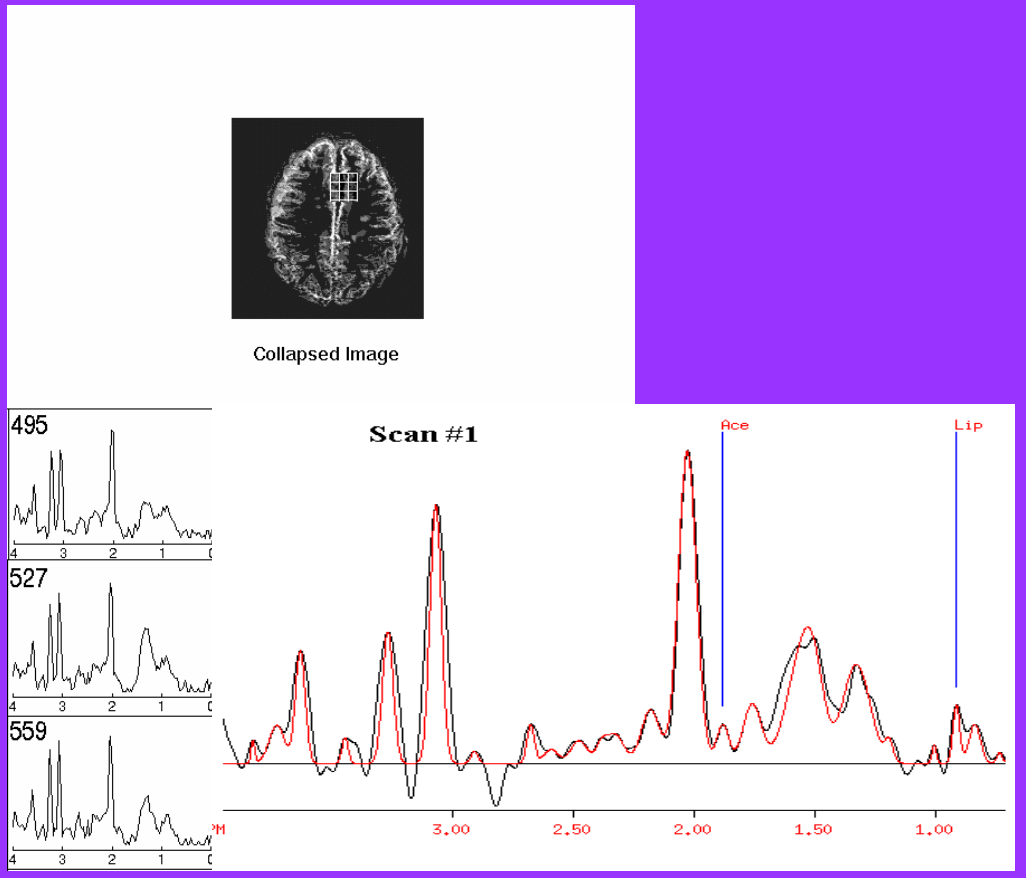
- Segmented images of GM(a); WM(b); CSF (c)

- 15 x 15 pixel^2 Gaussian-shaped filter with FWHM= 11 pixels applied



MS: Lipid and Lactate in NAGM

- MS Lesion not visible
- Lipid(doublet) and Lactate peaks



Distribution of lipid rich MS brain voxels in gray matter(GM) and normal Appearing Gray Matter(NAGM)

Voxels in different regions in brain hemisphere				
	Frontal	Parietal	Fronto-parietal	Mid-fissure
Left GM	16	5	6	
NAGM	29	14	7	
Right GM	18	5	8	210
NAGM	79	27	23	

Sharma et al.(2001) Multiple Sclerosis.7:221-226.

Percent Tissue Composition of Brain GM and NAGM Regions in MS

GM(n=65)	
%GM	82.41±22.36
%WM	10.2±16.7

NAGM(n=428)	
%GM	82.14±24.83
%WM	12.25±18.78

(Values shown as mean ± 2 S.D. after CSF correction)

Sharma et al.(2001) Multiple Sclerosis.7:221-226.

Absolute Concentrations of Metabolites in Spectroscopic Voxels in MS Patients

MS Patients:		
	GM(n=65)	NAGM(n=428)
NAA	10.02±3.95	10.8±4.6
Cr	8.39±3.16	6.73±1.36
Choline	6.43±2.96	3.76±1.19
Lipids	6.15±3.87	2.60±1.61

Normal Volunteers:No lipids		
	GM(n=50)	All types(n=75)
NAA	10.05±3.26	9.61±3.33
Cr	8.03±2.63	3.33±2.75
Cho	5.5±2.6	5.72±2.7

Sharma et al.(2001) Multiple Sclerosis.7:221-226.

Outcome of MRI+MRSI Co-analysis

- Quadruple Contrast images represent White matter and CSF suppression for clear MS lesion
- Cortical and subcortical lesions are normally MRI non-visible in GM
- MS lesion in GM represent strong peaks at 0.8-1.5 ppm(lipids and other metabolites)
- MS lesion rich GM represents 90 % GM and 10 % WM
- Neurochemical changes in GM and NAGM suggest membrane breakdown

CONCLUSION

- **Gray Matter and Normal Appearing Gray Matter in MS are abnormal on MRS**
- **Neurochemicals in MS lesion-rich GM suggest MRSI mesurement power for GM integrity**

Problem partly solved

- **Selective WM/GM suppression: (AFFIRMATIVE and QC pulse sequences)** MRM 37,94,102(1997)
- **Lesion Volume, metabolite image-generation (APSIP, Image Viewer and MRIAP)** MRM B, 106, 58(1995)

AFFIRMATIVE: Attenuation of Fluid by Fast Inversion Recovery with MAgnetization Transfer Imaging with Variable Echoes by FLAIR and MTC into spin echo

QC: Quadruple contrast;

APSIP: Automated Spectroscopic Imaging Program;

MRIAP: MR Image Analysis Program

Where we go from here?

Specific Aim 1:

Better spectral MRSI resolution

Specific Aim 2:

Amyloid proteins and CSF proteins,Demyelination, inflammation and metabolite regional differences

Specific Aim 3:

Source of NAA, amino acids, Gene expression and regional metabolite NAA/Cr+Cho ratio

Specific Aim 4:

MS Lesion serial characteristics

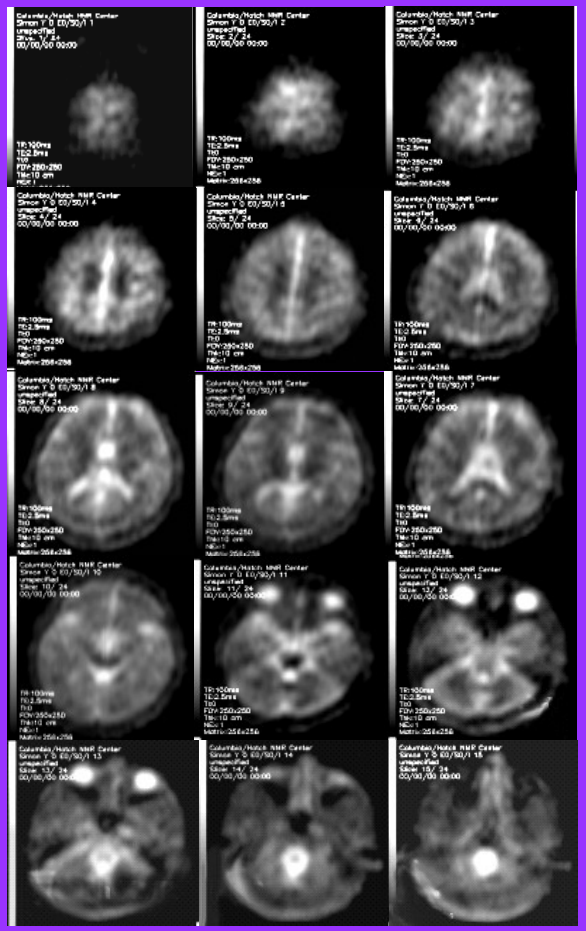
Sodium MRI Imaging

- **Brain**
- **Prostate and Breast Tumors for Chemosensitive effect**

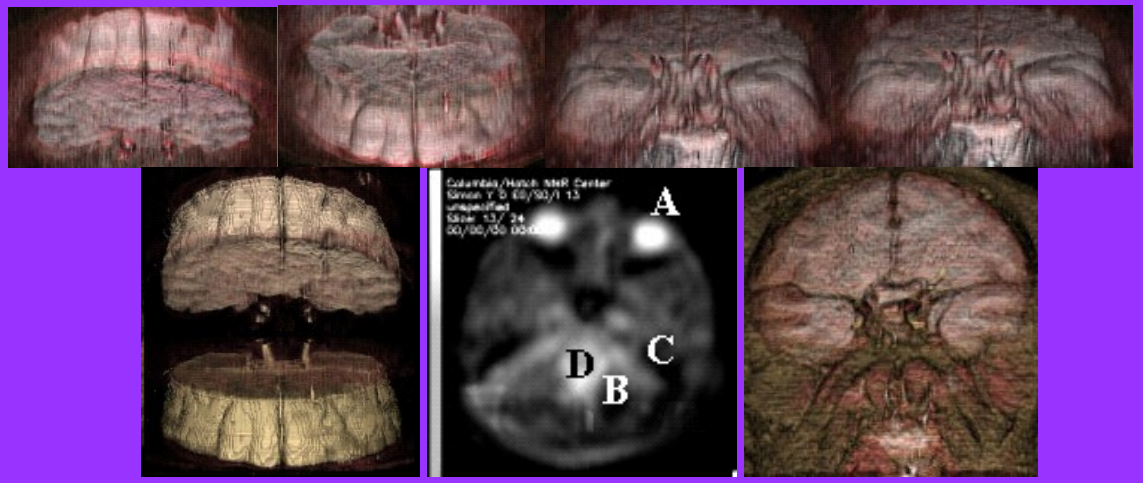
INTRODUCTION

- SQ, DQ, TQ, MQ MRI methods measure cellular sodium
- Inversion Recovery(IR) pulse sequence specifically alters null point of $[Na]_i$
- $[Na]_i$ is elevated during apoptosis due to membrane disrupted sodium pump
- High 18-FDG uptake in prostate tumor is due to elevated glycolysis in tumor

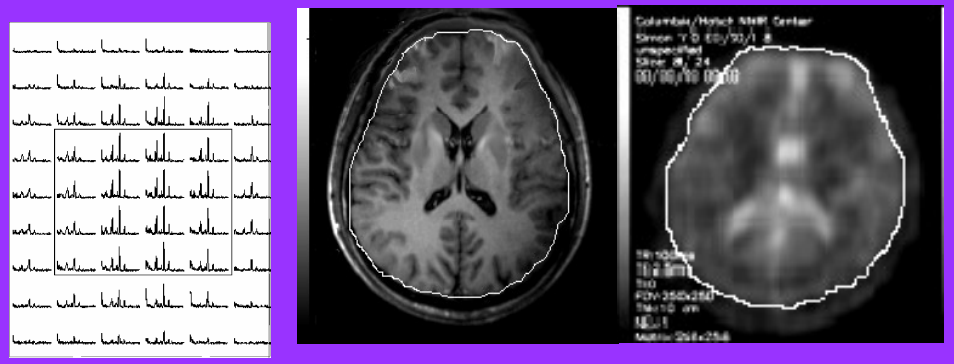
Hybrid Sodium-Proton MR spectroscopic imaging: Postprocessing



Sodium MRI images



Volume Rendered 3D Reconstructed images



Proton MRSI (left) and Sodium MRI(right)

Sharma(2003)JMS(communicated)

Where we go from here?

Specific Aim 1:

Better extracellular sodium suppression using variable inversion times (TI) and phase coherence

Specific Aim 2:

Intracellular sodium concentration by alternate methods AAS, EBCT, SBFI/FACT

Specific Aim 3:

Sodium gene expression and channels

Research Team

- **UCSF:**
  - **Peter Vermathen**
  - **Andrew Maudsley**
  - **Michael Weiner**
- **University of Texas Medical School, Houston**
  - **P.A.Narayana**
  - **Hong Yu**
  - **Jerry Wolinsky**
  - **Surjit Datta**

Columbia University & Albert Einstein COM, NYC

- **Richard Kline**
- **Paul Cannon**
- **R.K.Gupta**

MRSI in Multiple sclerosis: Techniques

- Serial studies of multiple sclerosis(MS) lesion load
- Serial brain metabolite imaging (Lipids)
- 1.5 T MR chemical shift imaging(CSI)
- Spectral analysis

Introduction

- H-1 gray matter- or white matter- and CSF-suppressed MRI images visualize the MS lesion
- MS lesion metabolite fingerprint and volumes suggest progression of MS
- MRSI may be tool for drug monitoring in MS

MRI+MRSI in MS:Technical Aspects

- RF inhomogeniety correction
- 3D image registration
- Metabolite concentrations and % tissue composition
- Automated segmentation of Gd-enhanced MS lesions
- Serial lipids and other metabolite changes in MS lesions and different regions
- Serial lesion volumetry
- GM seated MS lesions and NAGM vs NAWM

Problem partly solved

- **Selective WM/GM suppression: (AFFIRMATIVE and QC pulse sequences)** MRM 37,94,102(1997)
- **Lesion Volume, metabolite image-generation (APSIP and MRIAP)** (MRM B,106,58,1995)

AFFIRMATIVE: Attenuation of Fluid by Fast Inversion Recovery with MAgnetization Transfer Imaging with Variable Echoes by FLAIR and MTC into spin echo

QC: Quadruple contrast;

APSIP: Automated Spectroscopic Imaging Program;

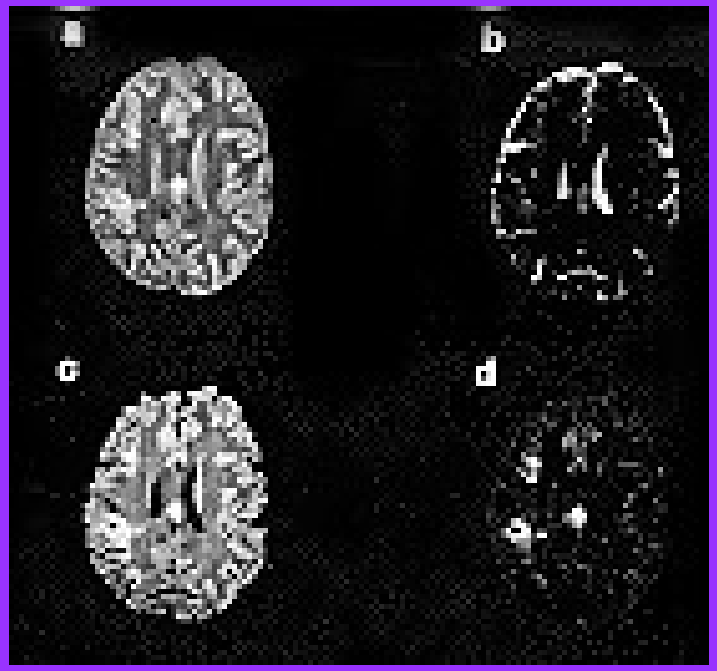
MRIAP: MR Image Analysis Program

Techniques used

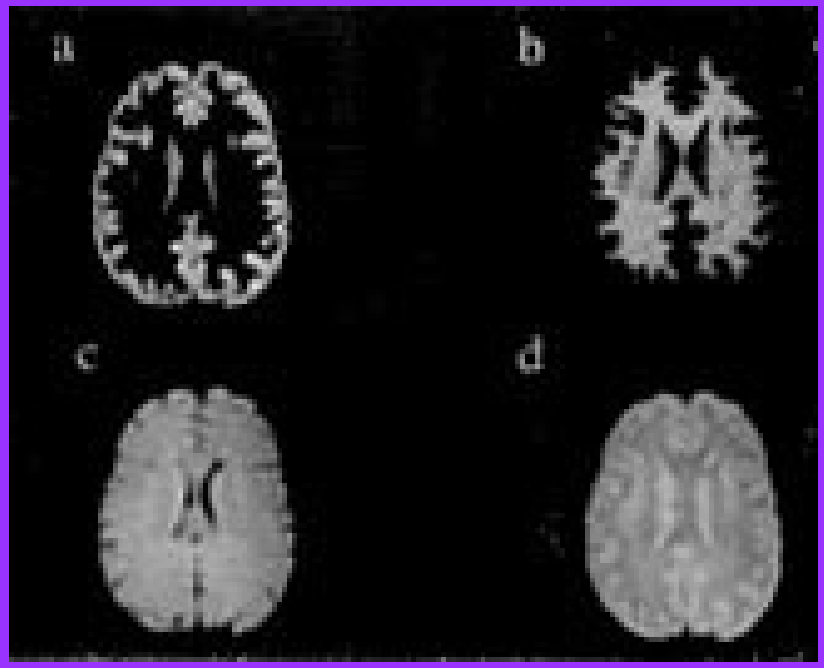
- MR sessions for imaging: Sagittal, Axial AFFIRMATIVE/QC, MRSI, Pre-/post Gd enahancement
- Image Processing: RF correction MRM 33,396(1995);
- 3D-MR Image registration JMRI 6,939(1996)
- Supervised segmentation(AFFIRMATIVE)
- Seed growing segmentation(QC images)
- Automated MS lesion segmentation MRM,39,935(1998)
- Serial H-1 MR spectroscopic Imaging + MS lesion voluming: VIEWER Ann Neurol,43,56(1998)

Two approaches to enhance MS lesion contrast

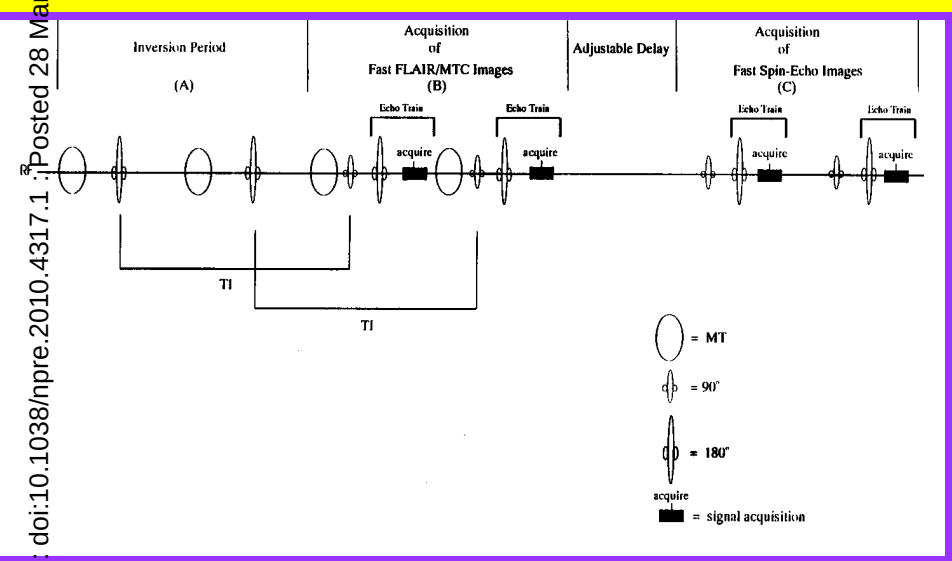
- AFFIR MATIVE

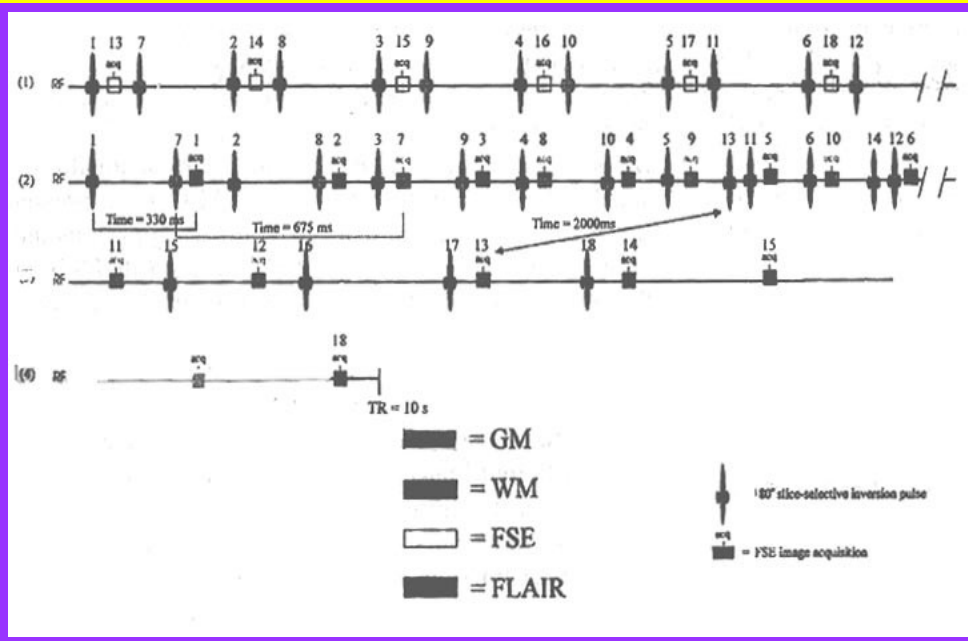


Quadruple Contrast



AF FIR MATI VE Pulse Sequence and Quadruple Pulse Sequence

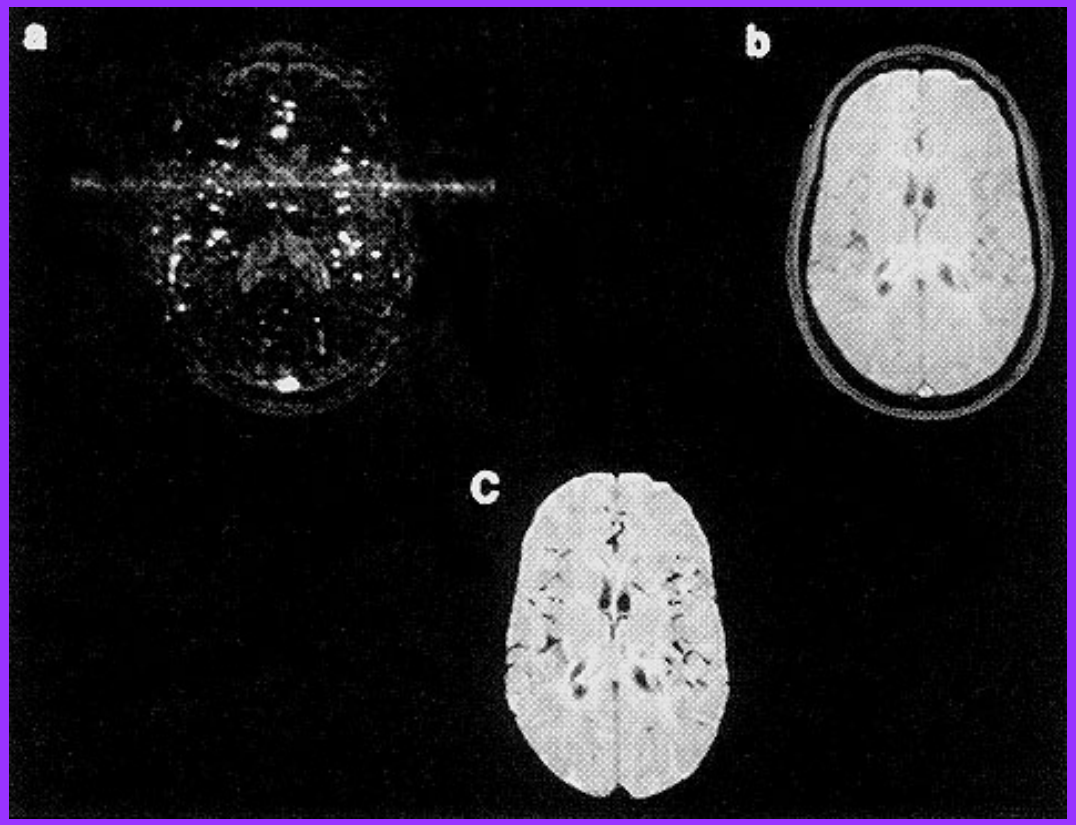




- Left: Fast SE + MT pulse at early and late echoes
- Right: 2 inversion pulses for selective suppression of GM, WM, CSF fractions

Suri et al(2002) Adv. Segmentation. Chapter 1,67

Phase-contrast Flow Images



- MRA image (a)
- Magnitude Image(b)
- Flow Image (c) without scalp
- Cerebro-vascular spins are visible (a)

Sharma et al(2003) communicated

Magnetic Resonance Image Analysis Package(MRIAP)

- Image Conversion
- Read/Modify Header
- Image Processing:
  - Anisotropic Diffusion Filter
  - Manual Editing:
    - Connectivity,line drawing, island removal,intensity thresholding, striping remained pixels
    - Automated Slice Editor
    - RF inhomogeneity correction
    - Flow Generation Image Generation
    - Image Set Recording
    - MR Angiography
- 3D Brain Registration
- Image Segmentation:

  -Seed growth/ manual editing

  -Supervised Segmentation: 2D feature

  map/multiple feature map segmentaion

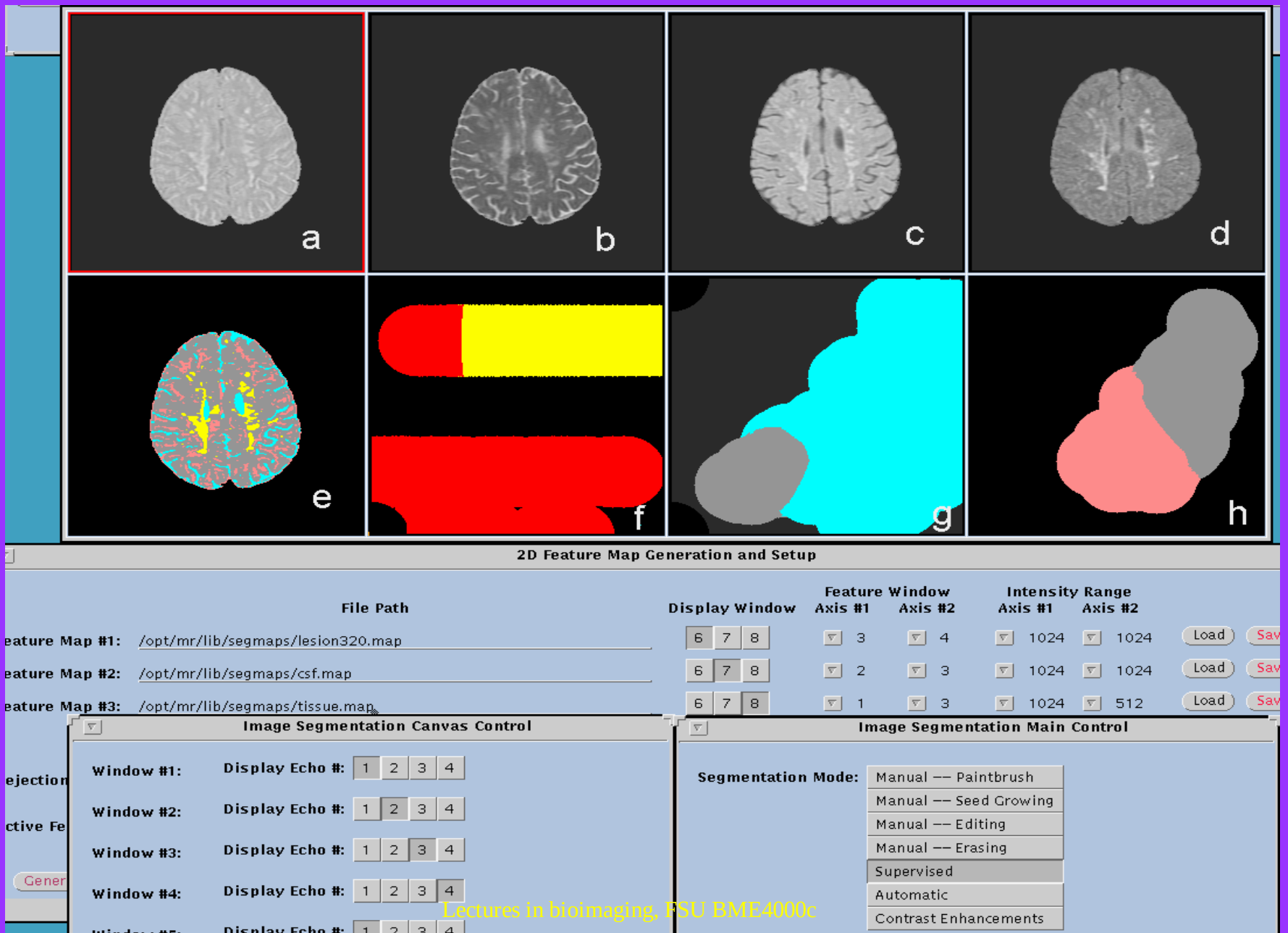
  -Automatic Segmentation

  -Lesion Contrast Enhancement
- Volumetric Analysis:

  -2D interactive

  -3D Automated lesion volumetry
- Multiple Display: SID

Magnetic Resonance Image Analysis Package



Lectures in bioimaging. FSU BME4000c

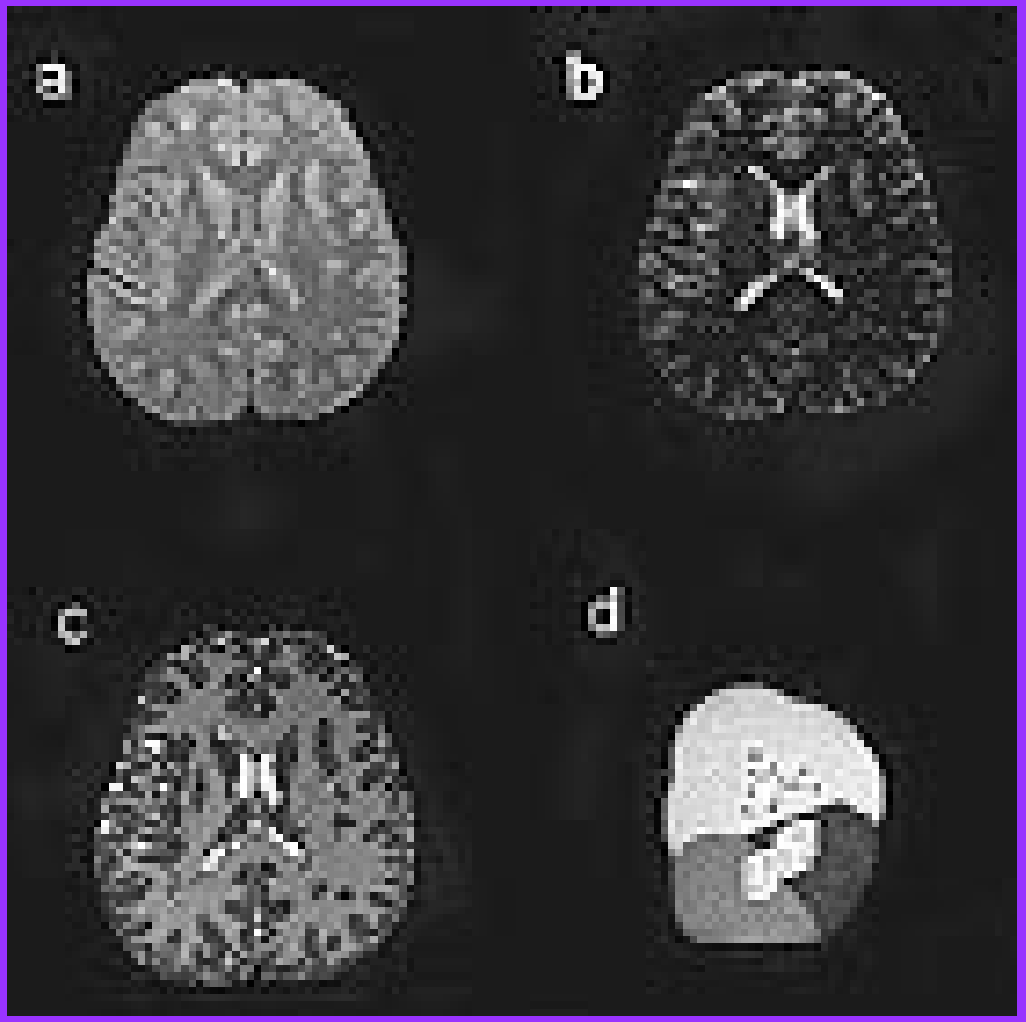
RF inhomogeneity Correction: Tissue Cluster Analysis

Normal axial brain images at TE=16 ms(a);

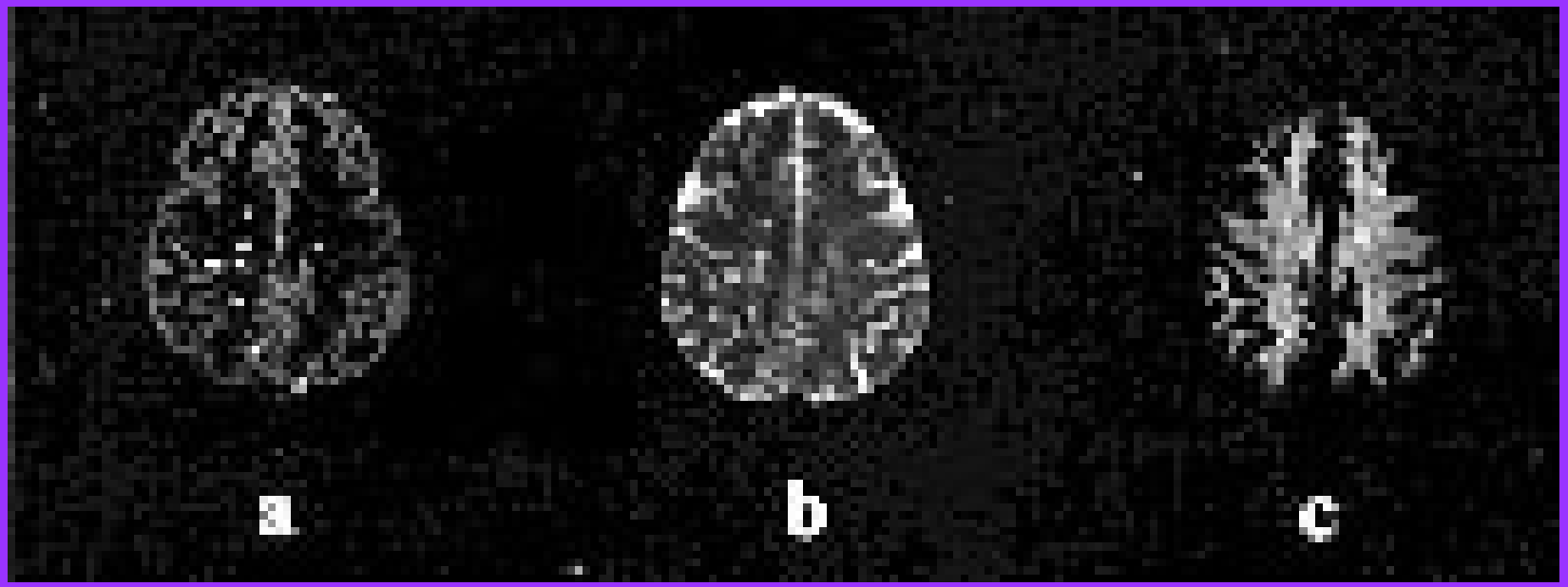
TE=80 ms(b);

Segmented image(c);

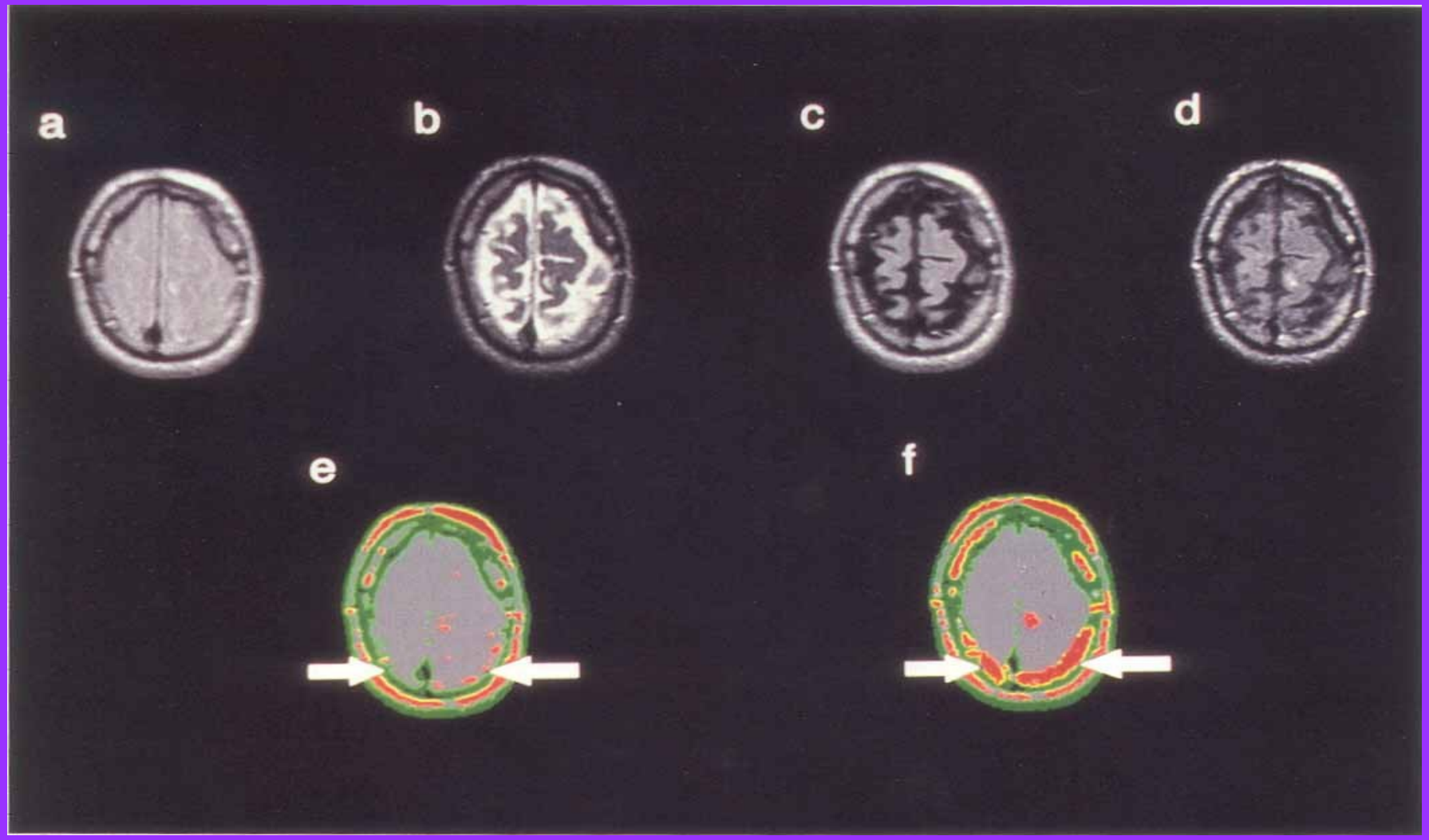
Tight clustering of feature map (d)



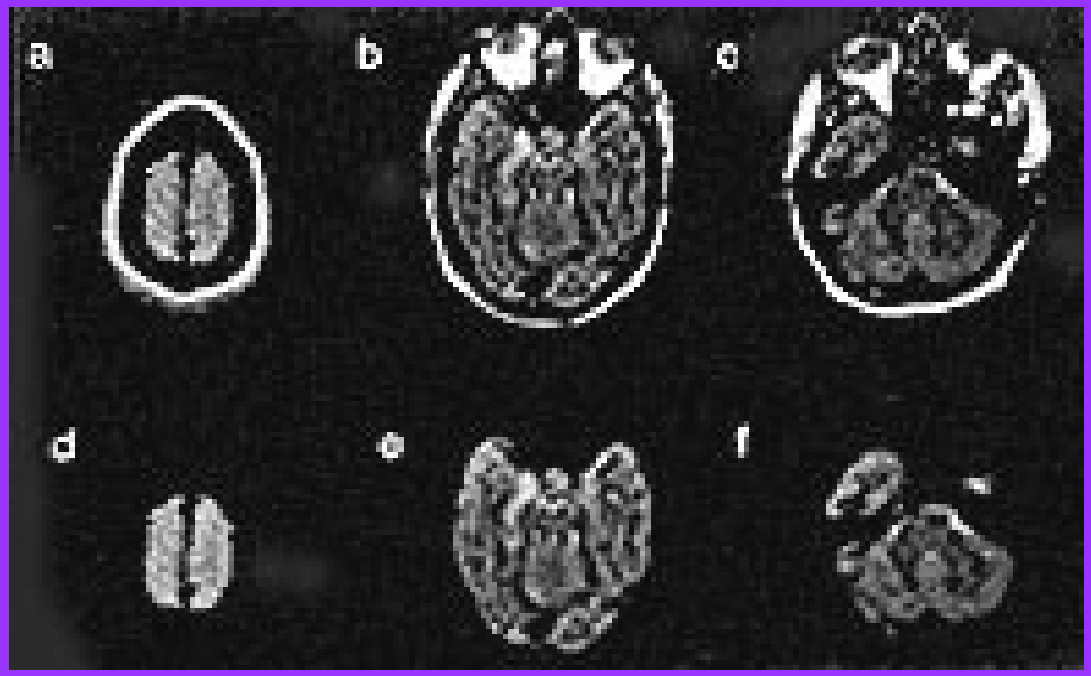
Selective Tissue Suppression Method



Extrameningial Tissue Removal by Connectivity Algorithm

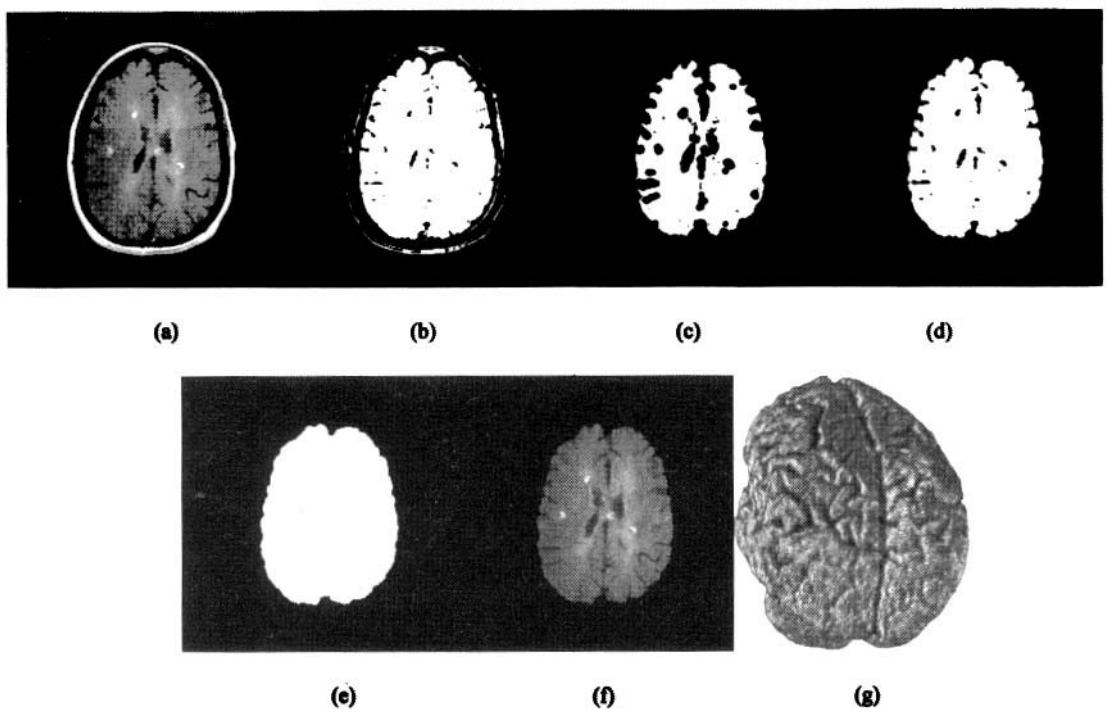


MR Images Prior to And Following Removal of Extrameningial Tissue



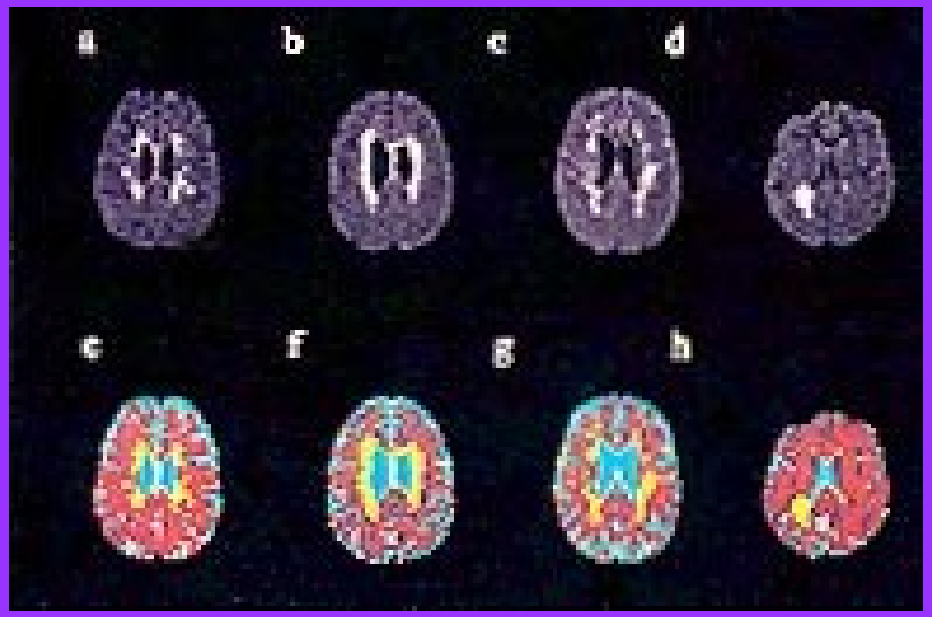
- Multispectral, nonparametric Perzen window classifies Extramengial Tissue
- Fluid attenuation and magnetization transfer contrast

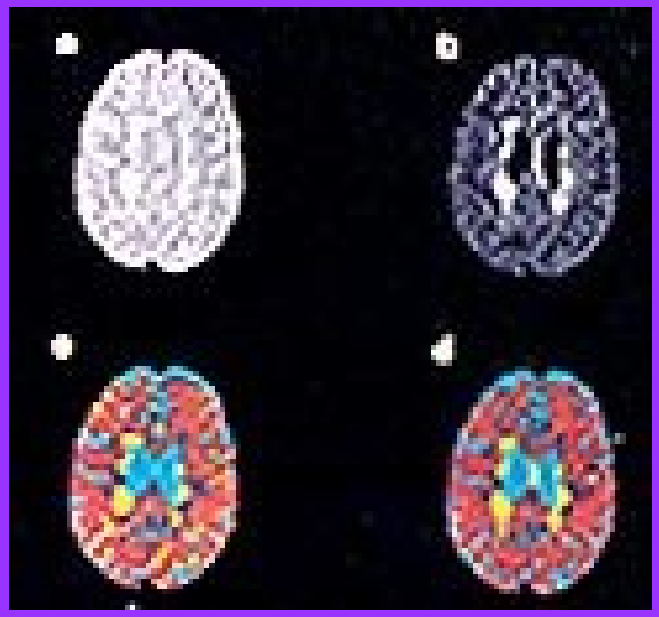
Segmentation in Brain



a.Raw image;b.Thresholding; c.Erosion;d.Dilatation; e.Closing f and g.Volume rendered images

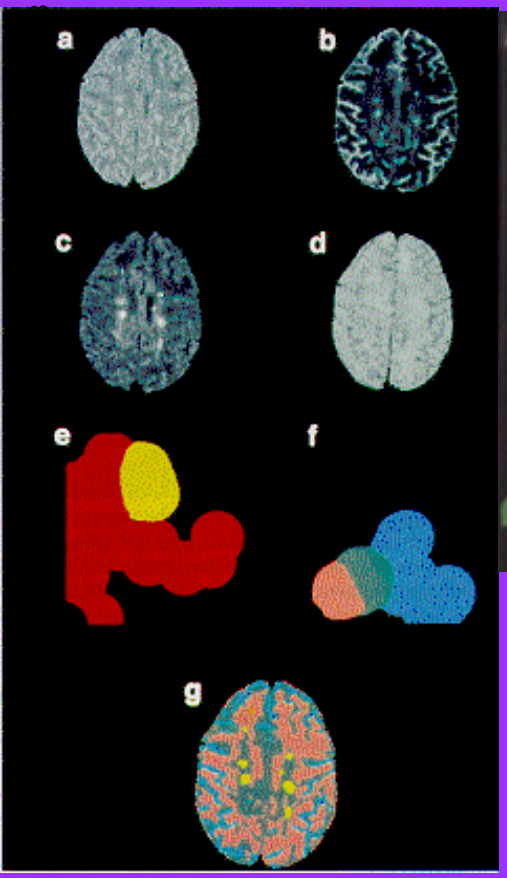
Automated Tissue Segmentation
(Perzen Non-parametric Method)

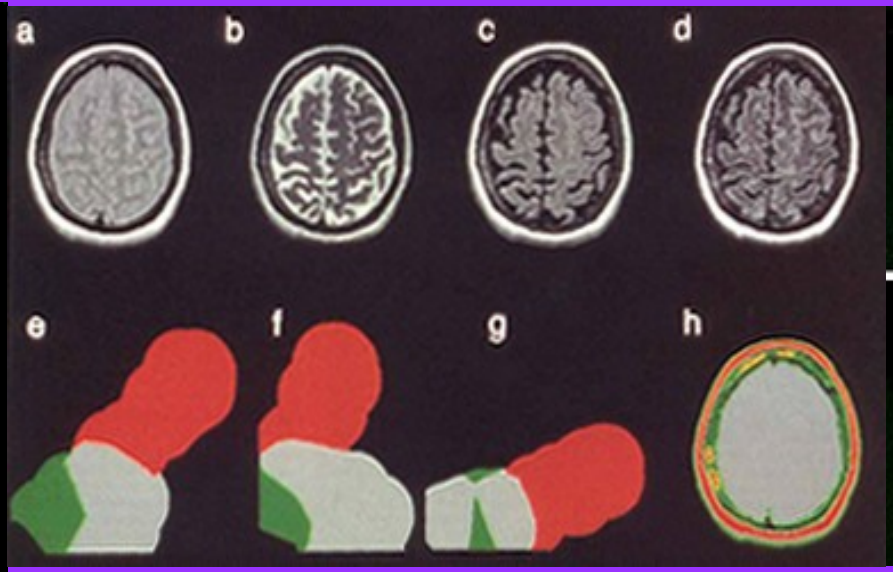


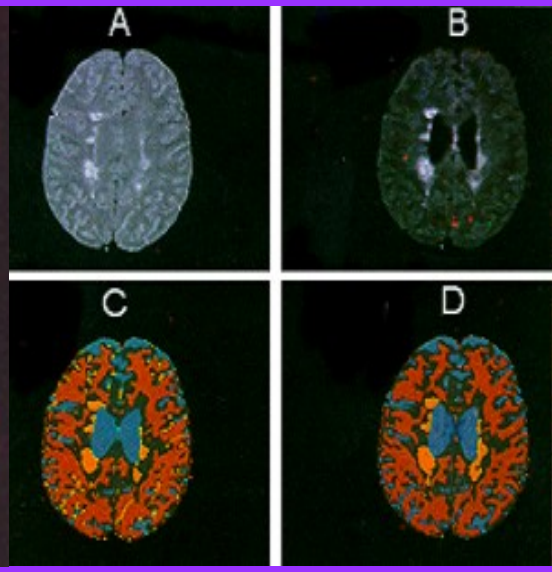


- MRI images at different level (top)
- Different color-coded tissues(GM,WM,CSF, lesion and non-lesion) by supervised training data-set

Non-Parametric Segmentation: (Perzen Window Feature Map Generation)

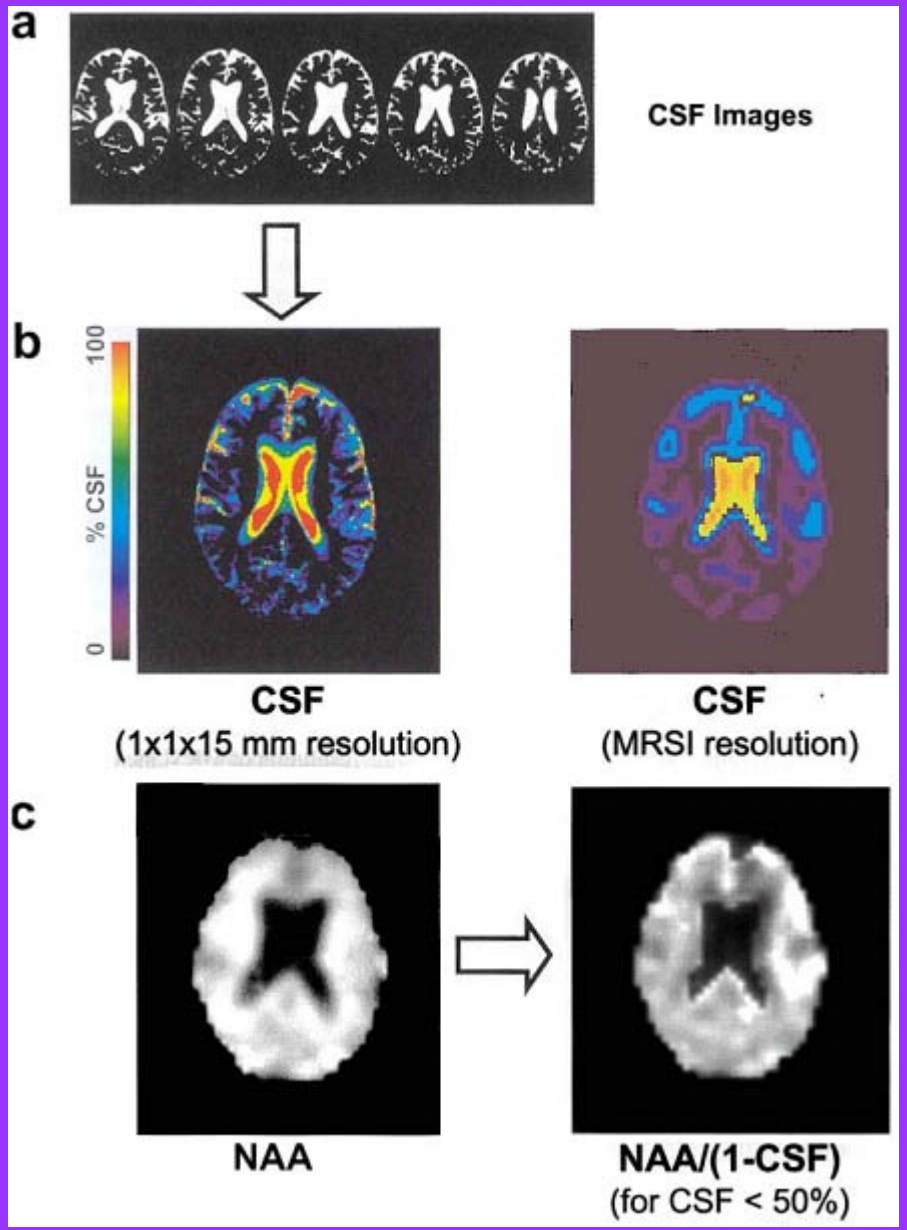






- AFFIRMATIVE Images and feature maps(Left)
- Quadruple contrast images and feature maps(on right)
- Dual Approach of false lesion minimization

Bedell & Narayana(1997) MRM 37:94

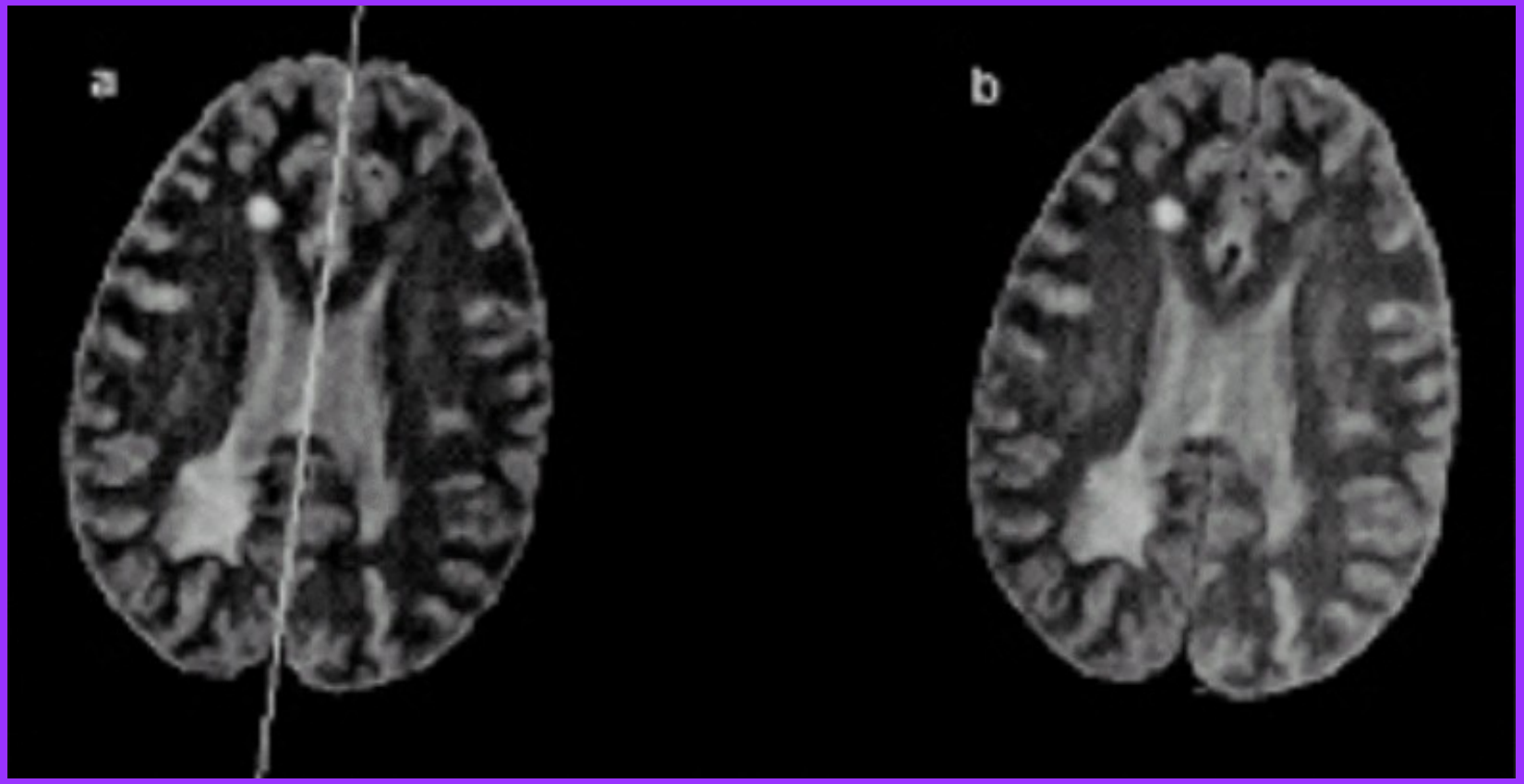


Effect of CSF Nulling

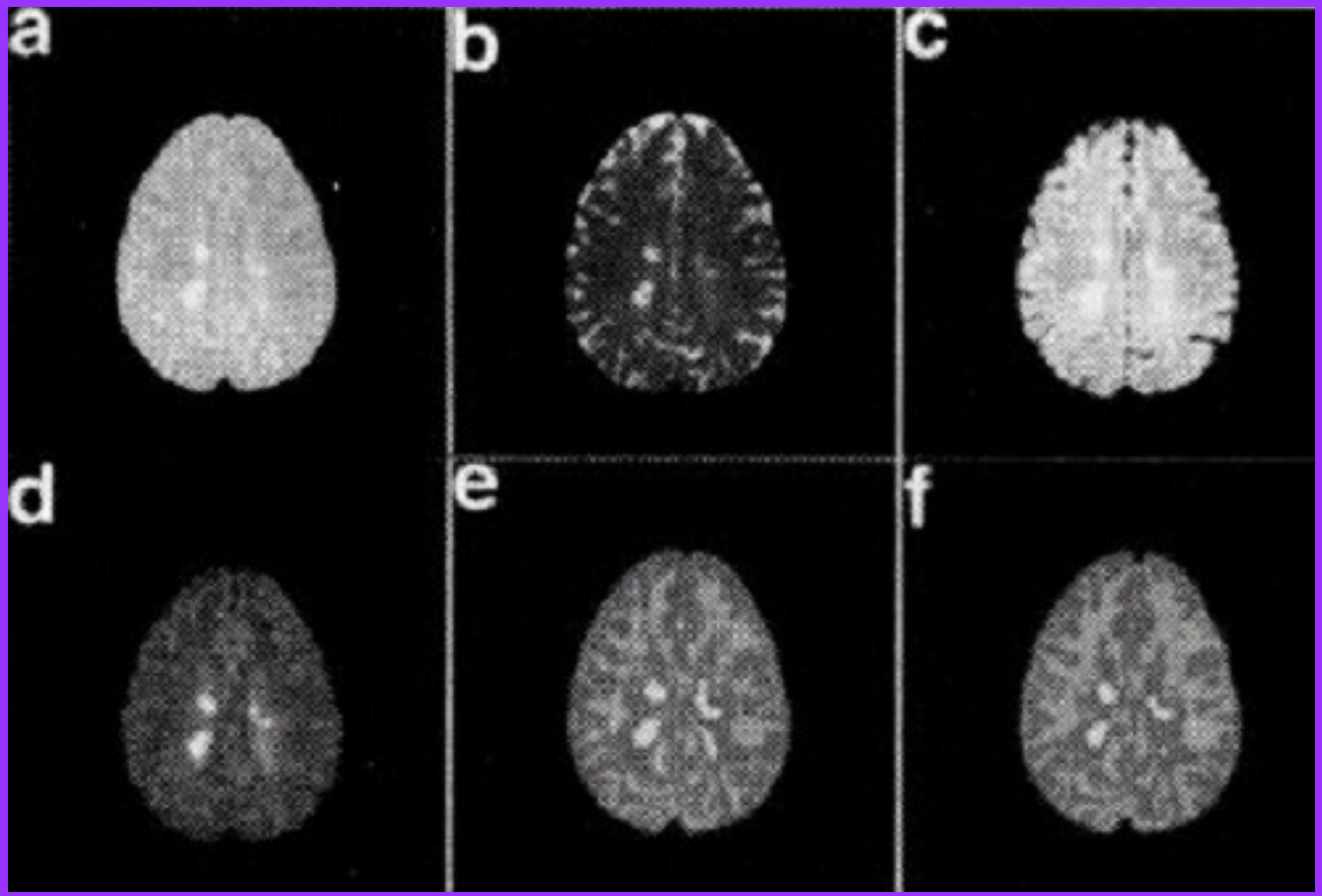
- CSF Minimization
- Atrophy Correction for NAA

Moudsley et al.(2002) MRSI Chap 14,169

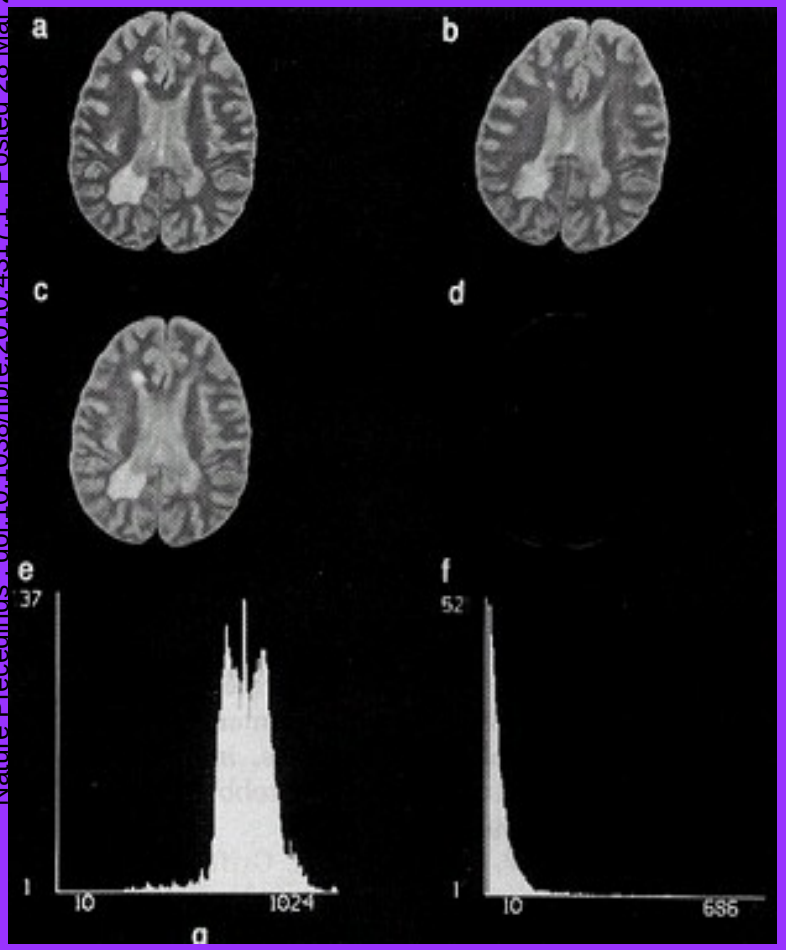
Registration: Interhemispheric Fissure Autosearch Method



The Effect of Histogram Normalization on Segmentation



3D Registration and histogram analysis



a. Axial T1 image of MS(a)

b. Computer Generated offsets

at 5° x 3° x 2° rotation in z,y,x axes(b)

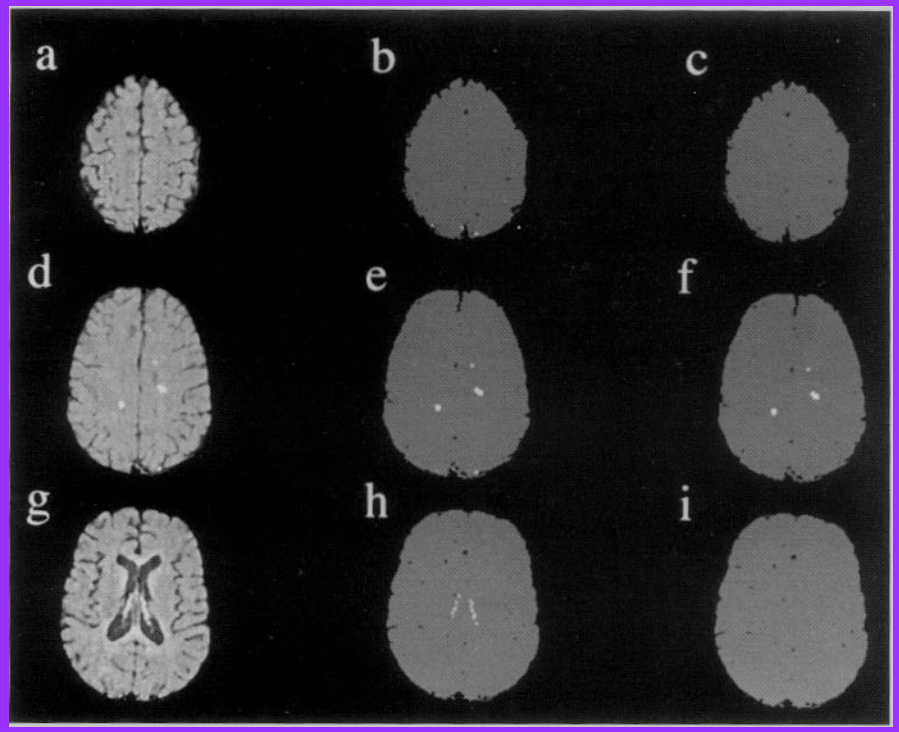
d. Registered image(c)

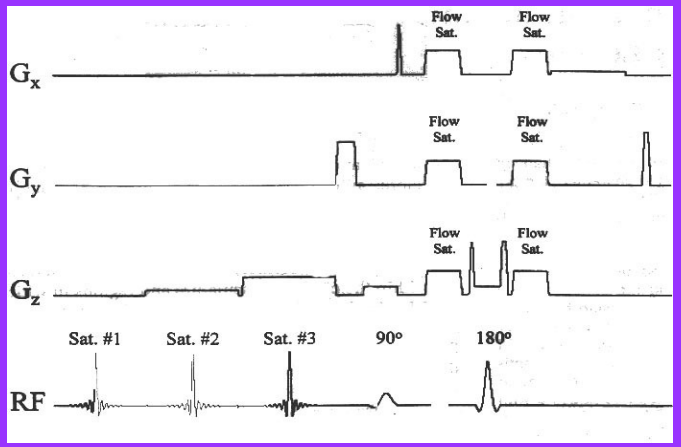
e. Subtracted image(d)

f. Histogram pixel value in image(e)

g. Histogram pixel value in image (f)

MS Lesion Gd-Enhancement





- Pre-contrast Images (1st column)
- Post-contrast (false positive 2nd column)
- Post-contrast (corrected 3rd column)

- Method: Saturation pulses and gradient dephasing Trapezoidal gradient waveforms select Gd-enhanced pixels.

Sharma et al.(2002) Adv.Segmentation. Chapter 5,179.

Delineation of Gd-contrast enhanced MS lesions

Top Row: GM+WM+CSF suppressed images

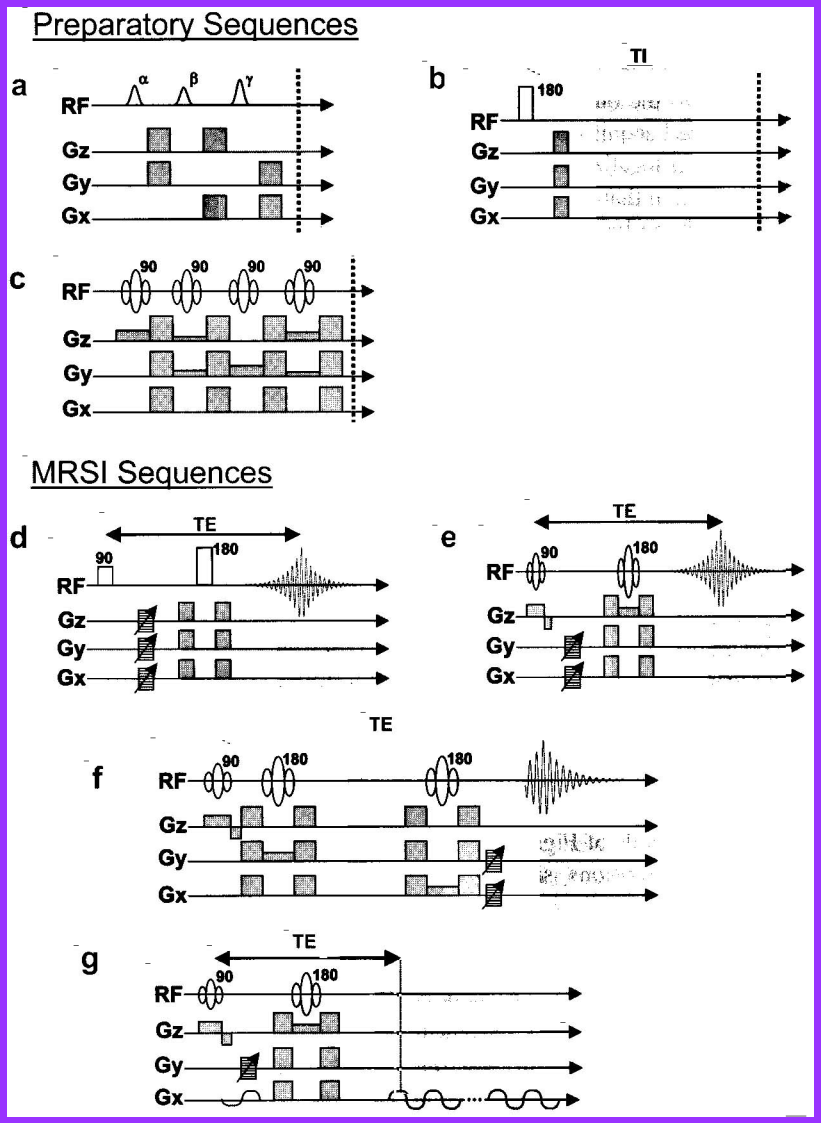
Bottom Row: Delineation of MS lesions

Connectivity Algorithm and Removal of Extrameningial Tissue

- Green lines represent the selective pixels separating out brain regions from optical nerve and other parts

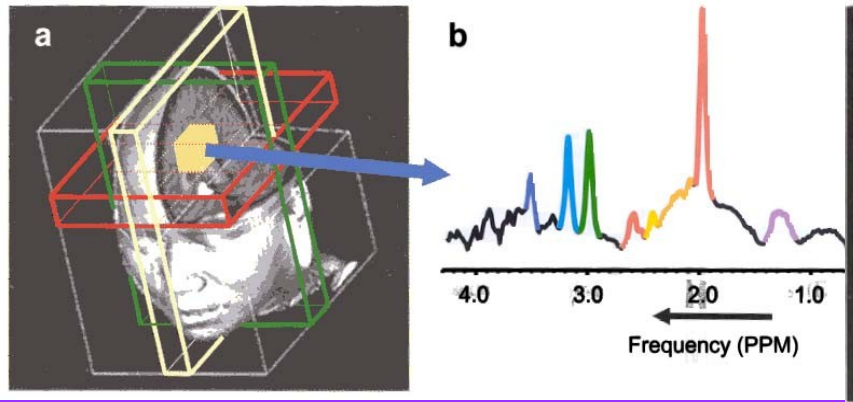
Sharma(2002) Adv.Segmentation Chap.7

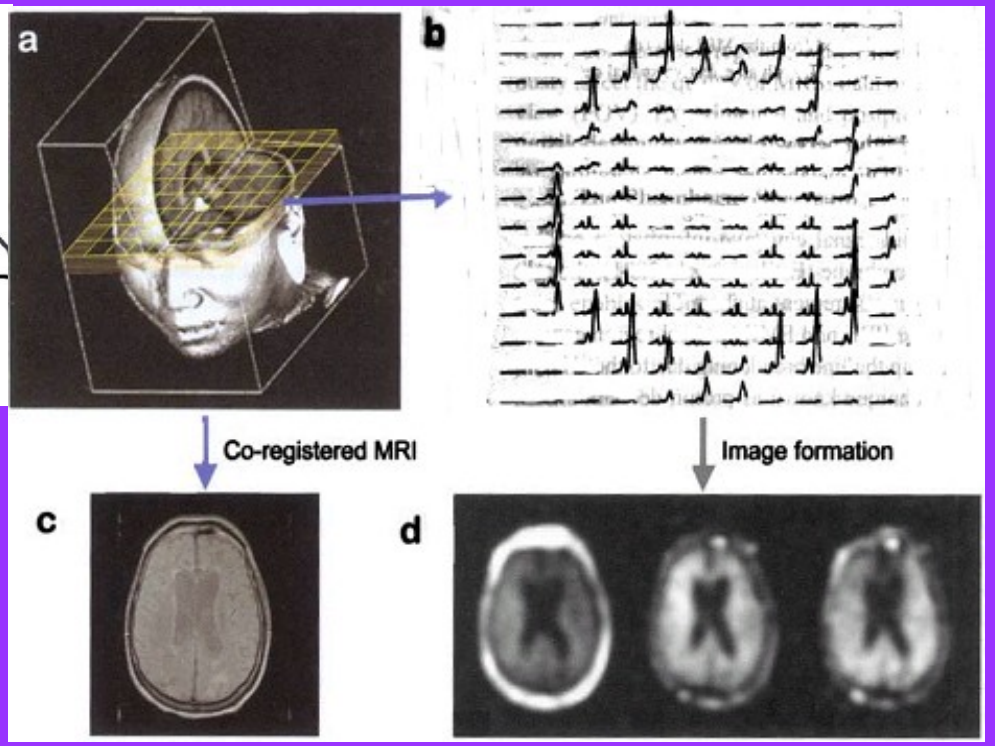
MRSI Pulse Sequences



- 90º and 180º RF Pulses applied with variable gradient sets
- Spectroscopic voxels are selected by use of fat saturation bands
- Protons of -CH3,-CH2 etc show chemical shift

MRSI Slice Selection: Metabolite Maps and CSI imaging





- Selective Single Voxel Spectroscopy(left)
- Single Plane Chemical Shift Imaging

Techniques Used in MRSI (APSIP package)

- For H-1Spectral model library for spectral simulation a priori information;
- Denoising algorithm for baseline smoothening
- Automated MRSI spectral fitting method:
  - Zero-filling, Object masking; Frequency shift(cross-correlation); iterative baseline and metabolite optimization(VOI), curve fitting

Spectroscopic Imaging and peaks: Data Processing

- **Spectroscopic VOI synthesis:**

  -masking "Octagonal OVS mask"

  -scanner co-ordinates selected

  -Pixel thickness and threshold fixed

  -Gray scale/color

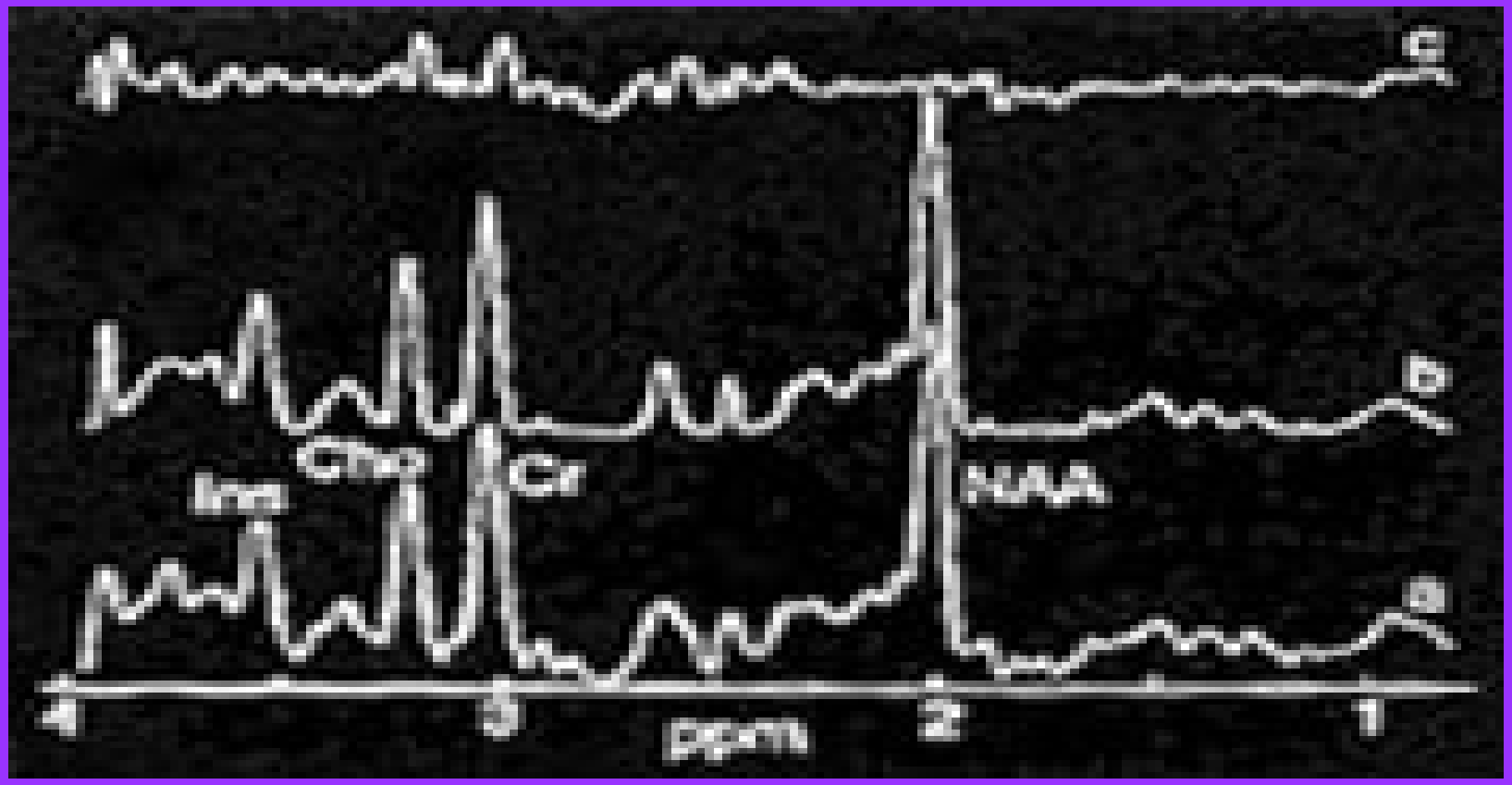
  -Grid and shift

- **Data Processing:**

  -APSIP(automated processing by SI program)

  -Steps: zero filling, DC baseline, spatial apodization, CSI 1D rotate, CSI flip, CSI 2D rotate, Bo autophase, water suppression, deconvolution coefficient, time apodization, FFT

Automated Processing for Spectroscopic Imaging Package



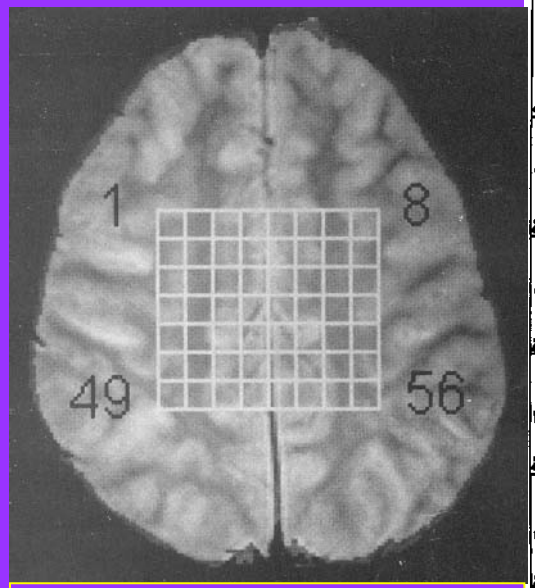
Autopsy MS lesion NMR spectral peaks

Chemical Shift (ppm)	Assignment Metabolite	Normal WM	MS lesion
0.8	lipid(-CH2)		
0.25			
1.00	lipid(-CH3)		0.68
1.20	triglycerides		1.88
1.33	lactate		2.25
1.4	alanine		1.80
1.5-1.55	leucine		2.5
1.6	??		
1.7	glutathione ??		0.6
1.8	GABA		0.5
1.9	acetate		--
2.02	N-acetyl aspartate (NAA)	10.8	6.3
2.1	NAA Glutamine (β methylene)		-
2.2,2.3,2.4	Glutamine/glutamate		5.5
2.7	Aspartate (β methylebne)		1.3
3.0	creatine/phosphocreatine(=N.methyl)	8.0	6.8
3.2	choline(-N(Methyl)3)	3.2	7.2
3.4	taurine(=_N.methylene)	0.4	0.45
3.6	myo-inositol	3.2	3.5

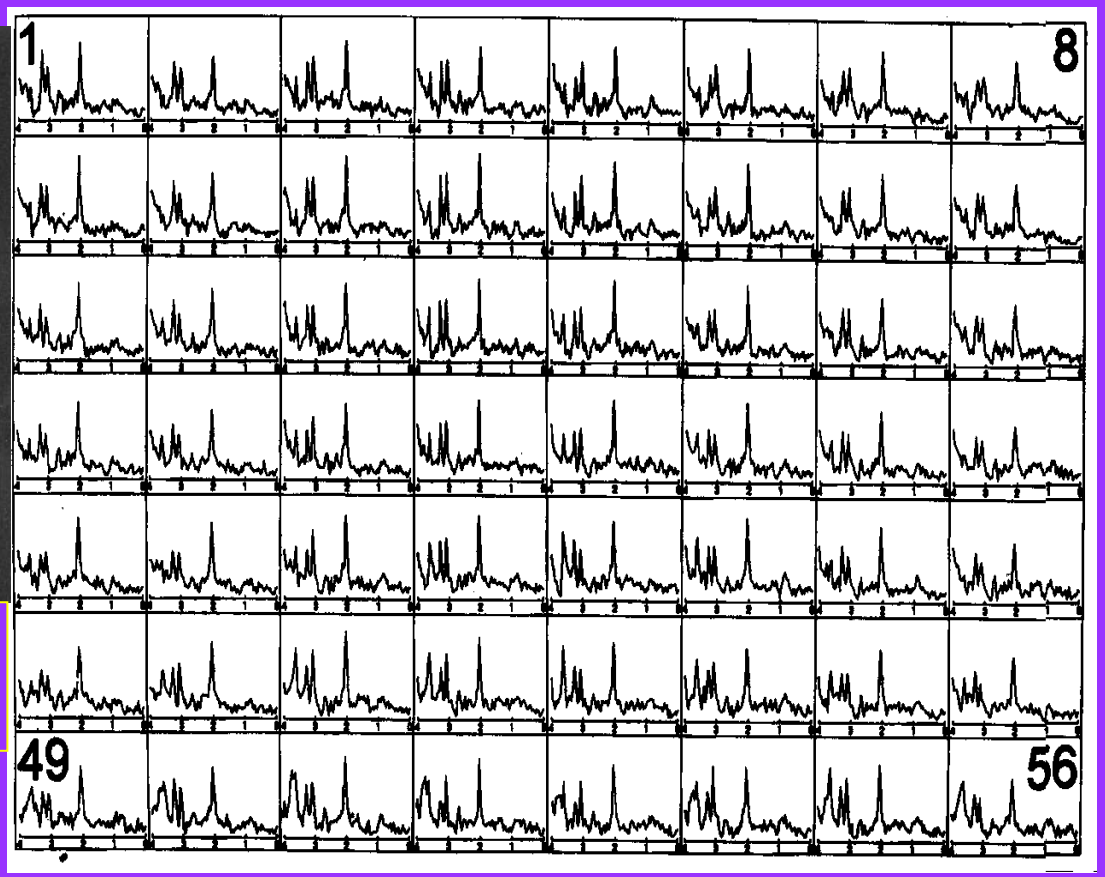
Objectives

- **Serial longitudinal studies of MS:**
  - **-lesion volumes**
  - **-Metabolies(NAA, Cr, Choline and lipids) at lesion, GM, WM sites**
  - **-Tissue(GM, WM) fractions**
  - **-Relationship with neuropsychological tests (MMSE and EDSS)**

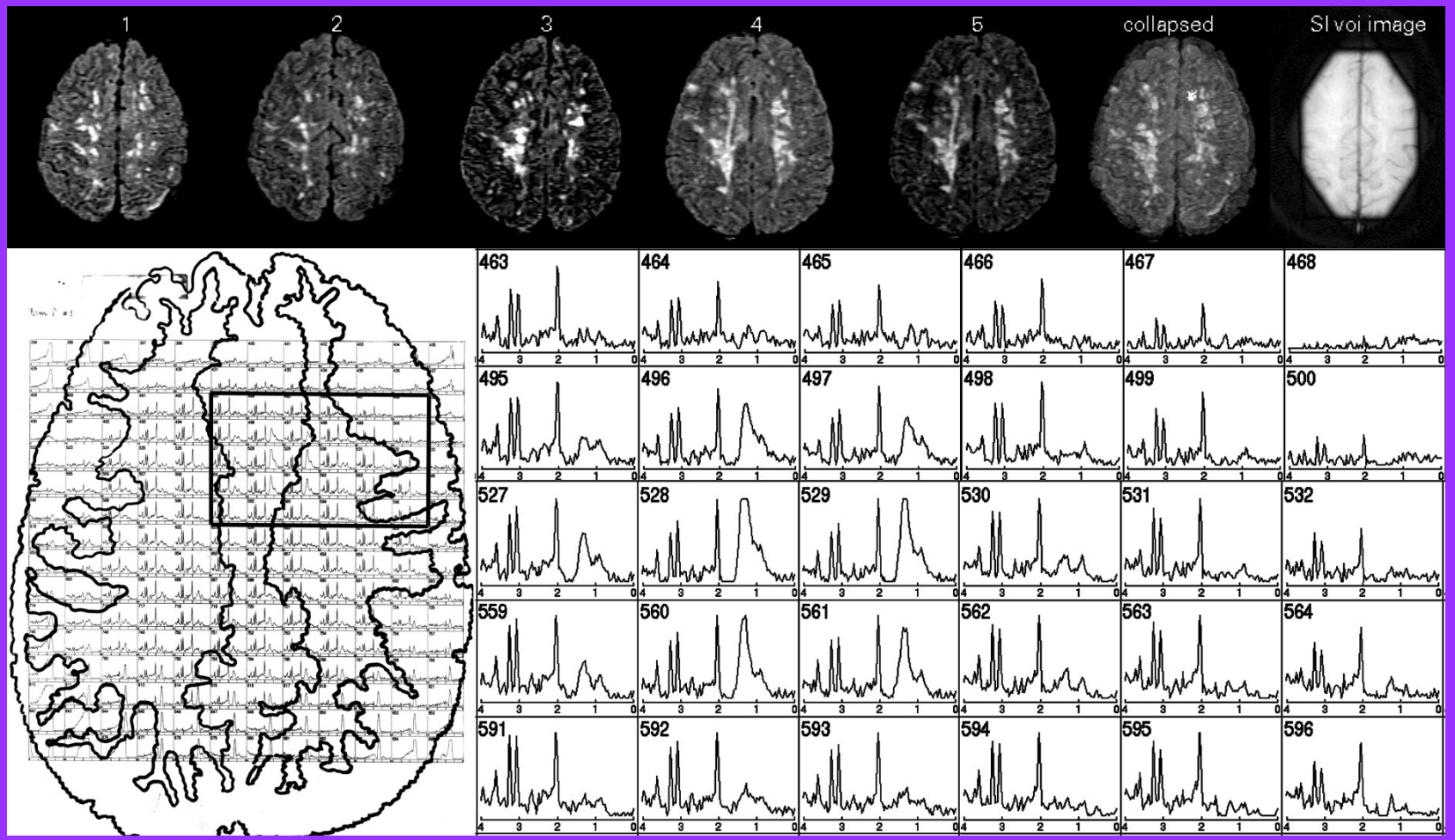
MRS metabolite peaks in Normal Volunteer



- NAA, Cr and Cho peaks visible



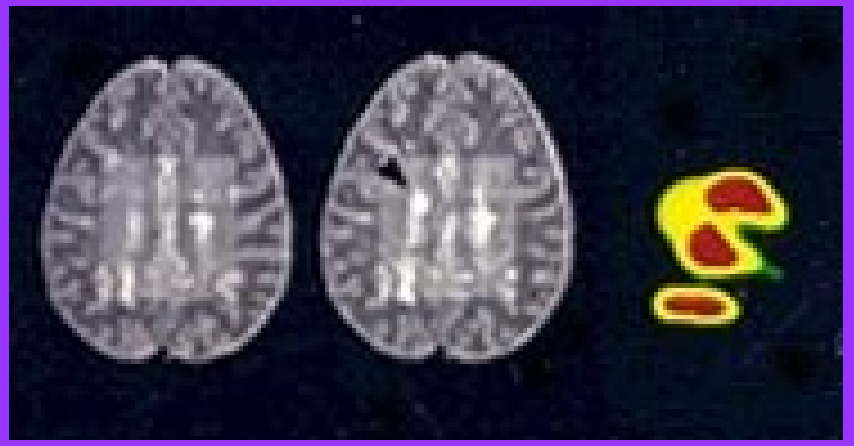
MS Lesions Showing Abnormal Metabolites in GM and NAGM After Post-Gd Contrast

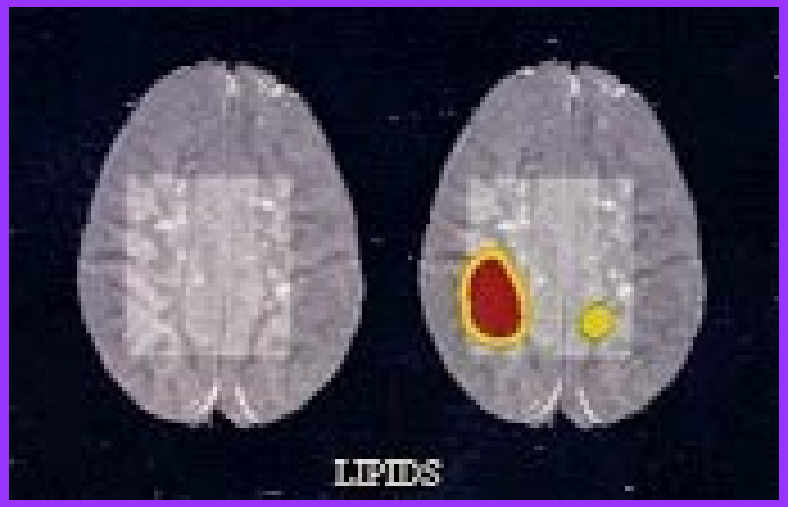


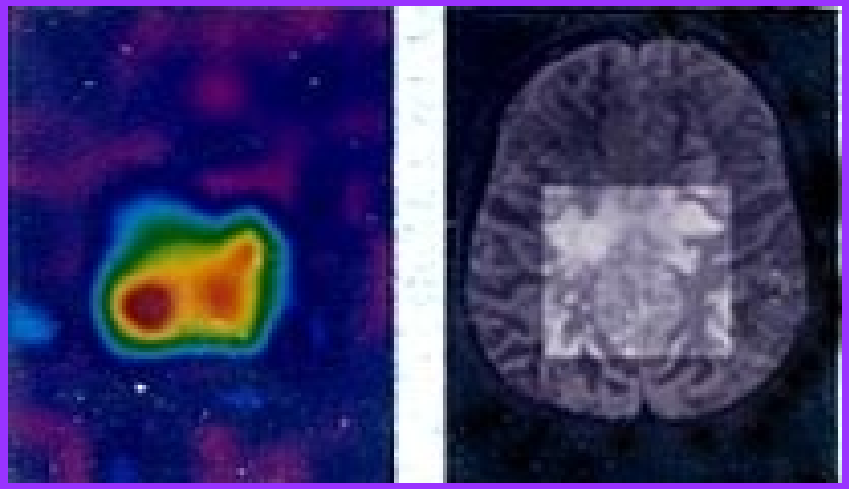
Sharma et al.(2000) IEEE CBMS Proc. 12,87

Lipids in MRI-defined MS lesions

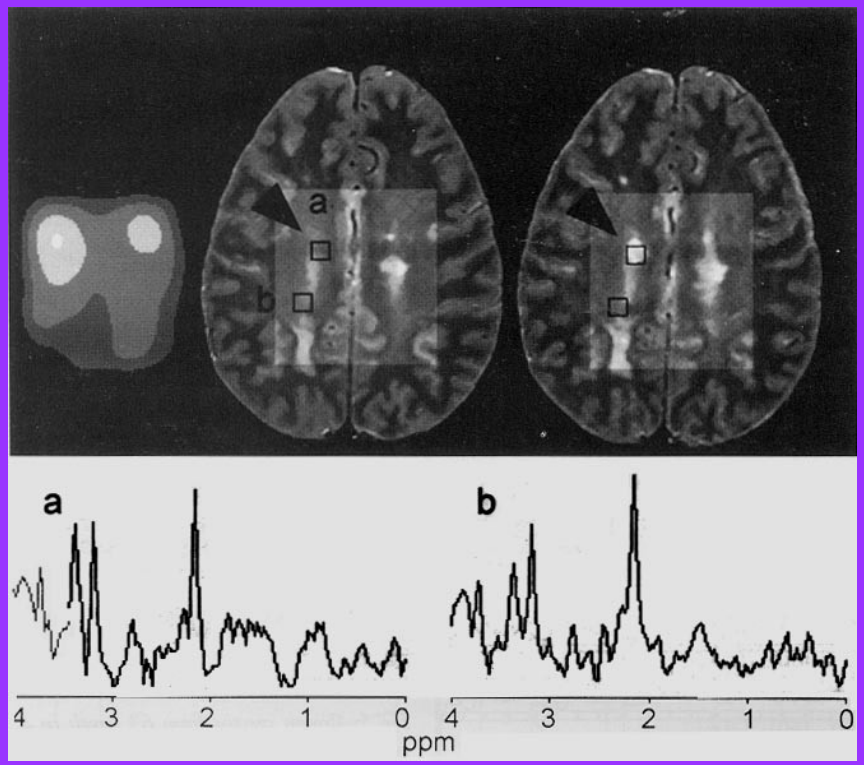
- MRI defined MS lesions
- Lipid metabolic maps (color-coded)
- Lateralization by lipids

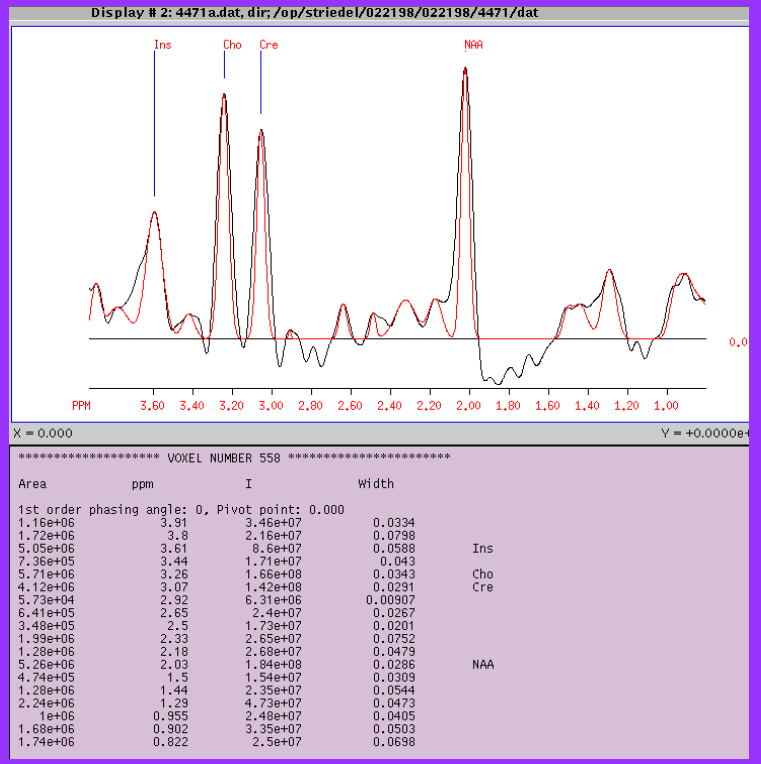




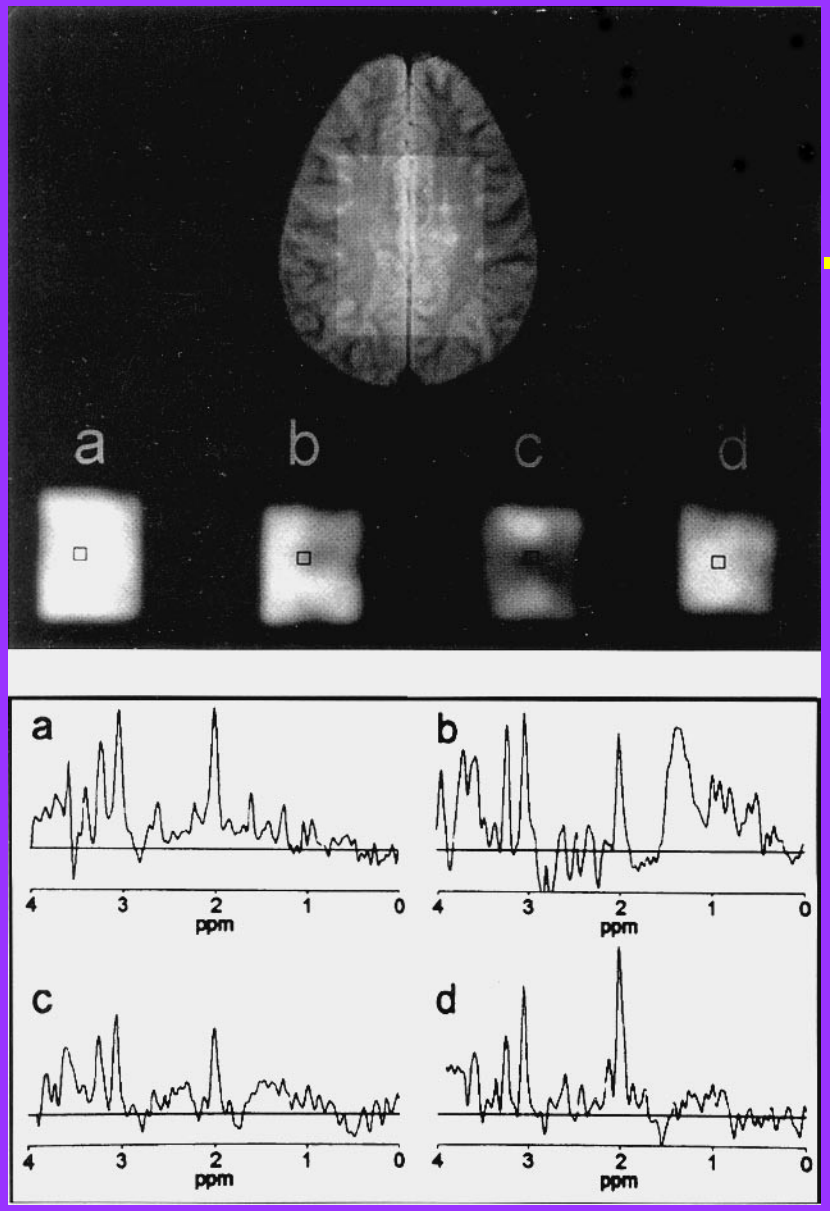


Serial MS study: choline peaks





- **Choline as inflammatory marker(perivenous inflammation)**
- **Related other lipids, amino-acids peaks**



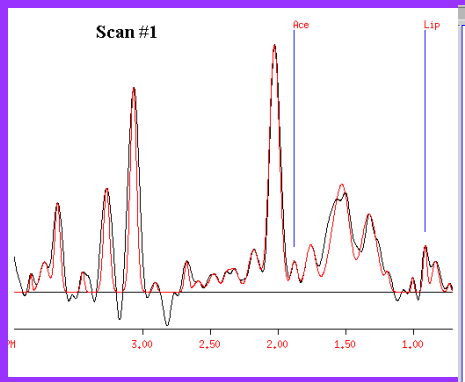
Serial Lipids in NAWM

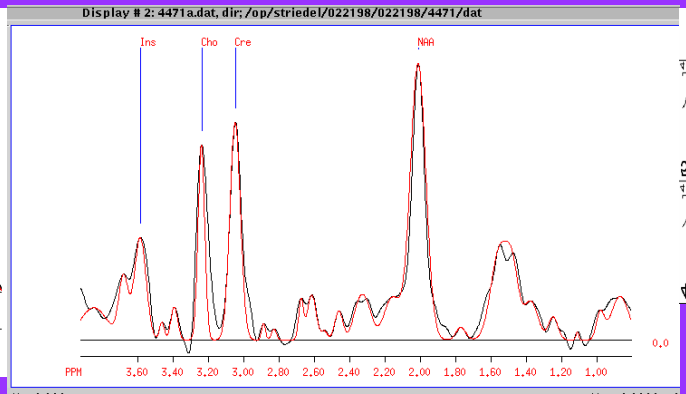
- No MRI-defined MS lesion
- Lipids as singlet and doublet peaks

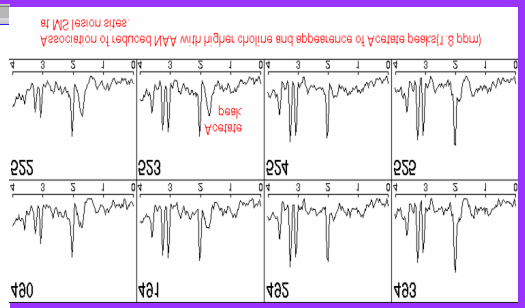
Where we go from here?

- Better spectral MRSI resolution
- New MR visible metabolite GABA, glutathione
- Amyloid proteins and CSF proteins
- Dementia classification and metabolite regional differences
- Source of NAA origin in different brain regions
- Gene expression and regional metabolite NAA/Cr+Cho ratio
- Relationship of neurochemicals with biochemical markers (Acetylcholine esterase)

Difficulty in Spectroscopy Peak Interpretation



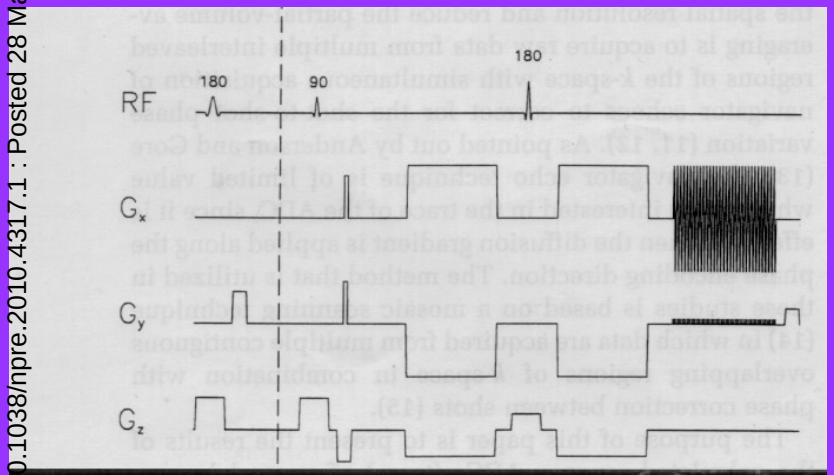


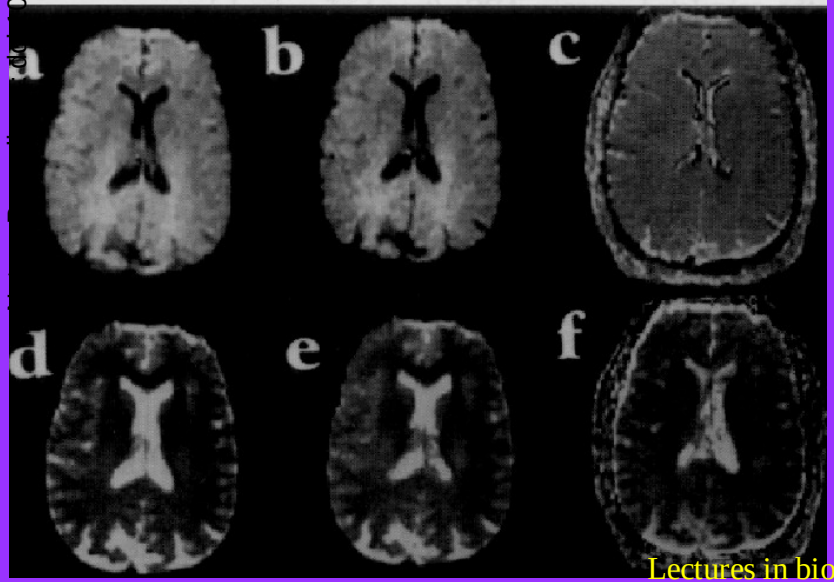


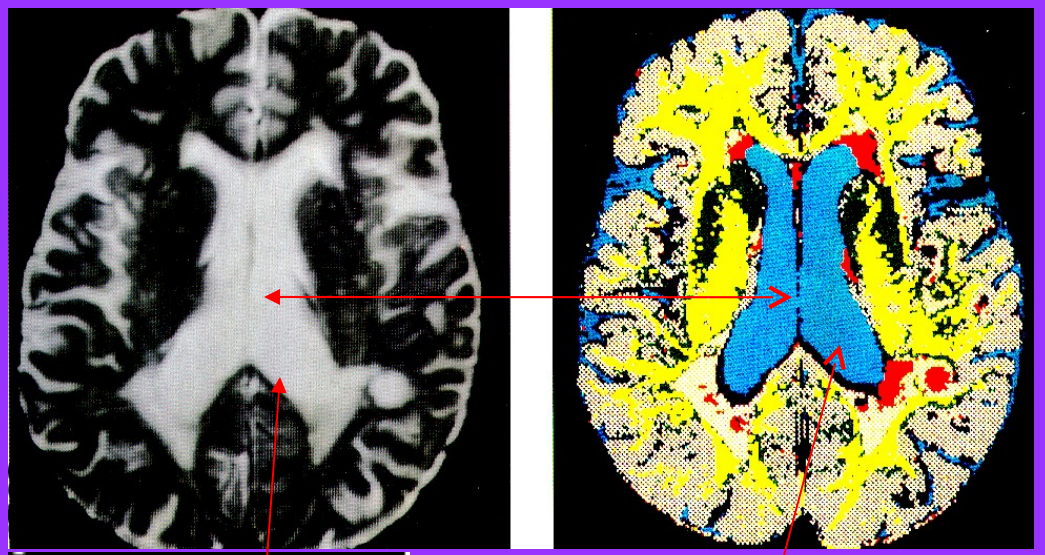
```
****************** VOXEL NUMBER 595 **********************

Area            ppm             I               Width

1st order phasing angle: 50, Pivot point: 4.760
2.44e+06          3.87          2.2e+07          0.111
1.56e+06           3.7         4.16e+07         0.0376
 3.3e+06          3.61         6.98e+07         0.0473        Ins
 2.3e+05          3.48          1.2e+07         0.0192
6.01e+05          3.41         2.24e+07         0.0268
3.55e+06          3.26         1.33e+08         0.0267        Cho
6.29e+06          3.06         1.48e+08         0.0425        Cre
1.74e+05           2.9         1.11e+07         0.0158
1.52e+05          2.84         7.58e+06           0.02
5.15e+05          2.69         2.68e+07         0.0192
1.09e+06          2.62         3.06e+07         0.0357
1.41e+05          2.55         5.93e+06         0.0238
6.36e+05          2.47         1.98e+07         0.0322
8.32e+05          2.36          1.8e+07         0.0461
1.08e+06          2.31         2.18e+07         0.0494
1.91e+06          2.16         2.87e+07         0.0665
1.17e+07          2.02         1.88e+08         0.0621        NAA
3.32e+05          1.77          8.6e+06         0.0386
4.22e+06          1.55         6.11e+07         0.0691
 1.9e+06          1.48         3.91e+07         0.0485
1.51e+06          1.37         2.62e+07         0.0575
5.88e+05          1.24         1.57e+07         0.0375
5.56e+04          1.11         5.54e+06           0.01
5.49e+05         0.975         1.78e+07         0.0308
2.13e+06         0.862         2.97e+07         0.0718
```

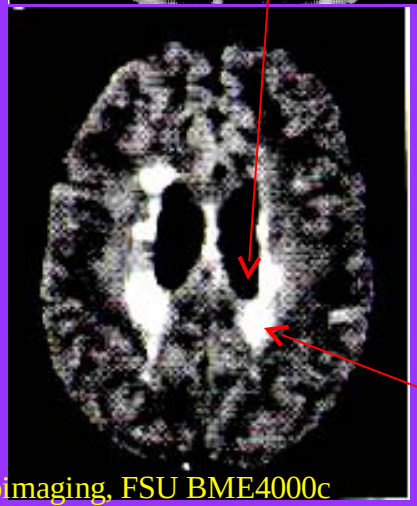
Nature Precedings : doi:10.1038/npre.2010.4317.1 : Posted 28 Mar 2010

Fast Imaging Technique: EPI Sequence and segmentation



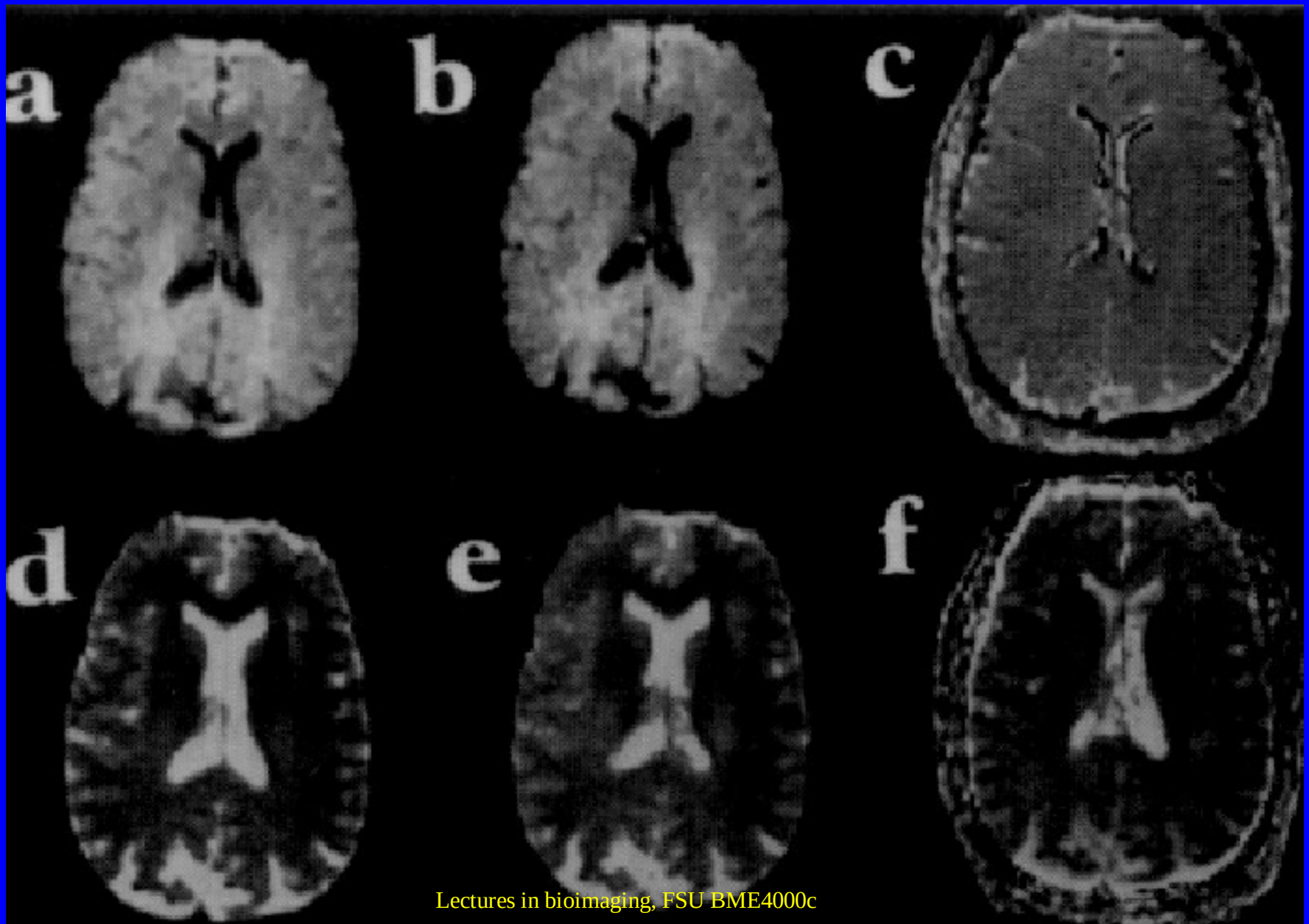




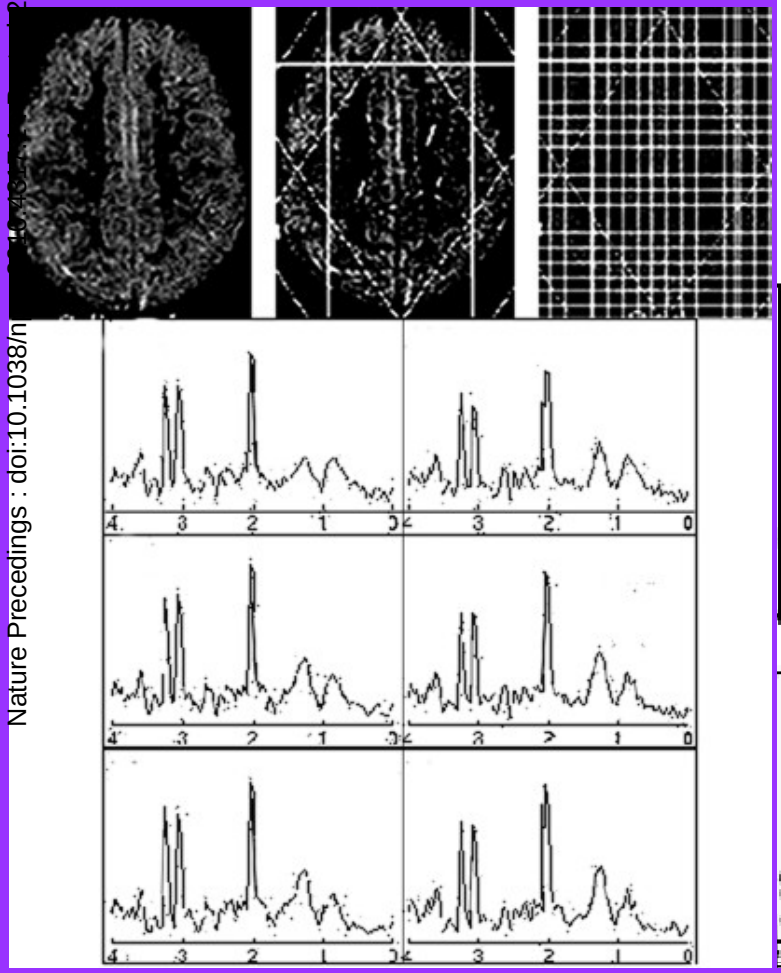


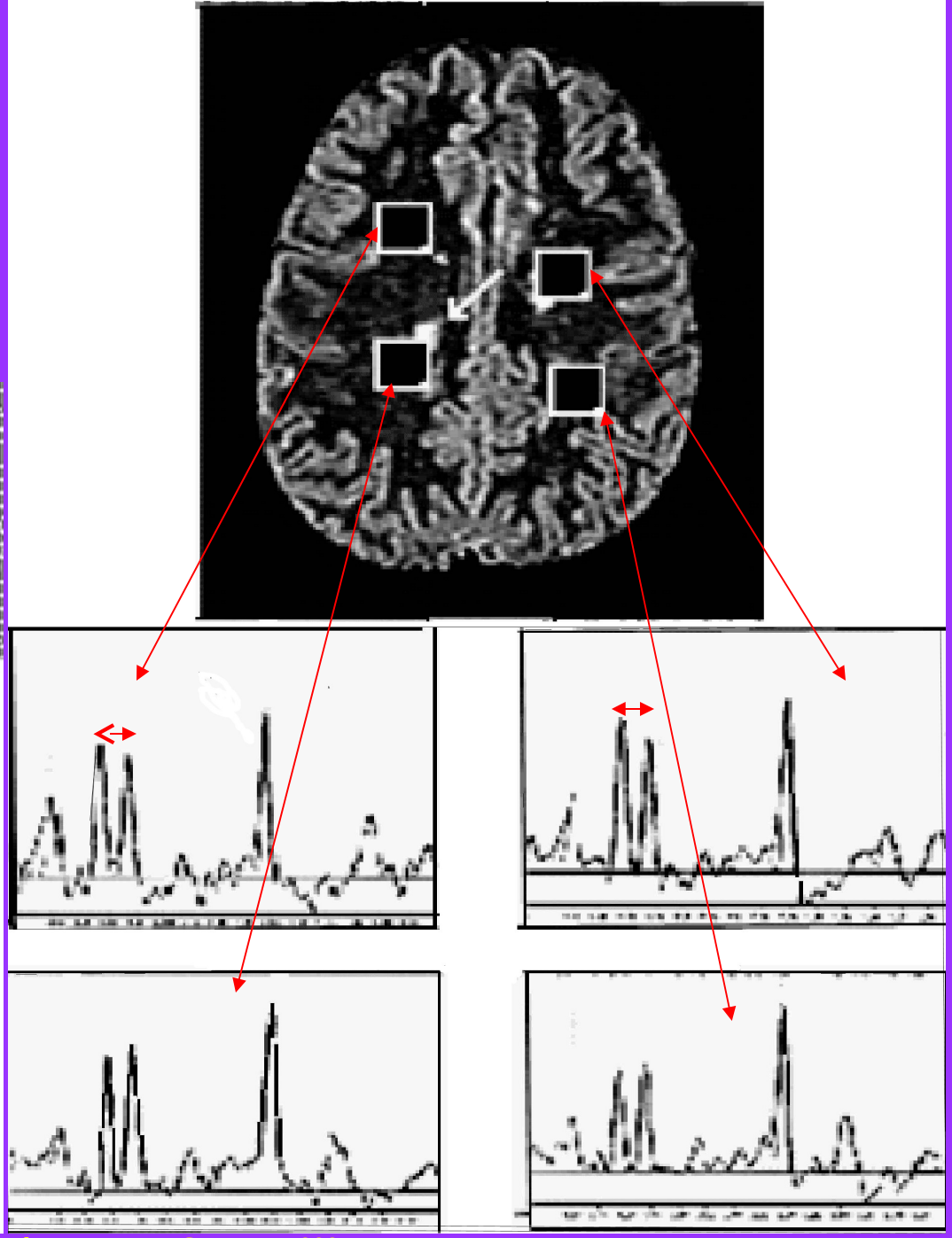
- Segmented color coded features of brain in different regions (MS lesions)

Echo Planar MR Images



MRSI: MS Lesions High Choline





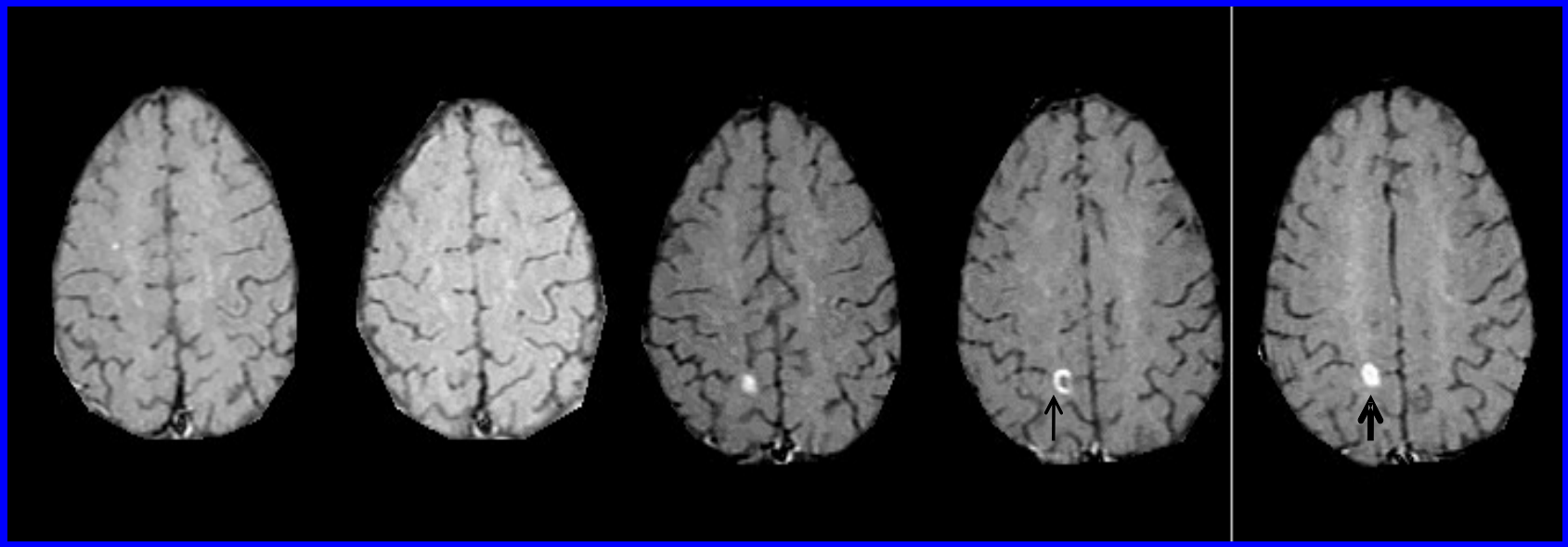
New Information on MS lesions METHODS

- False Lesion minimization by AFFIRMATIVE
- Gray Matter lesions
- CSF suppression by Quadruple Contrast sequences
- Single 15 mm MRSI slice
- 32 x 32 Phase encoding steps
- Spectroscopic voxel size 0.8 cc;TR=1000 ms, TE=30 ms

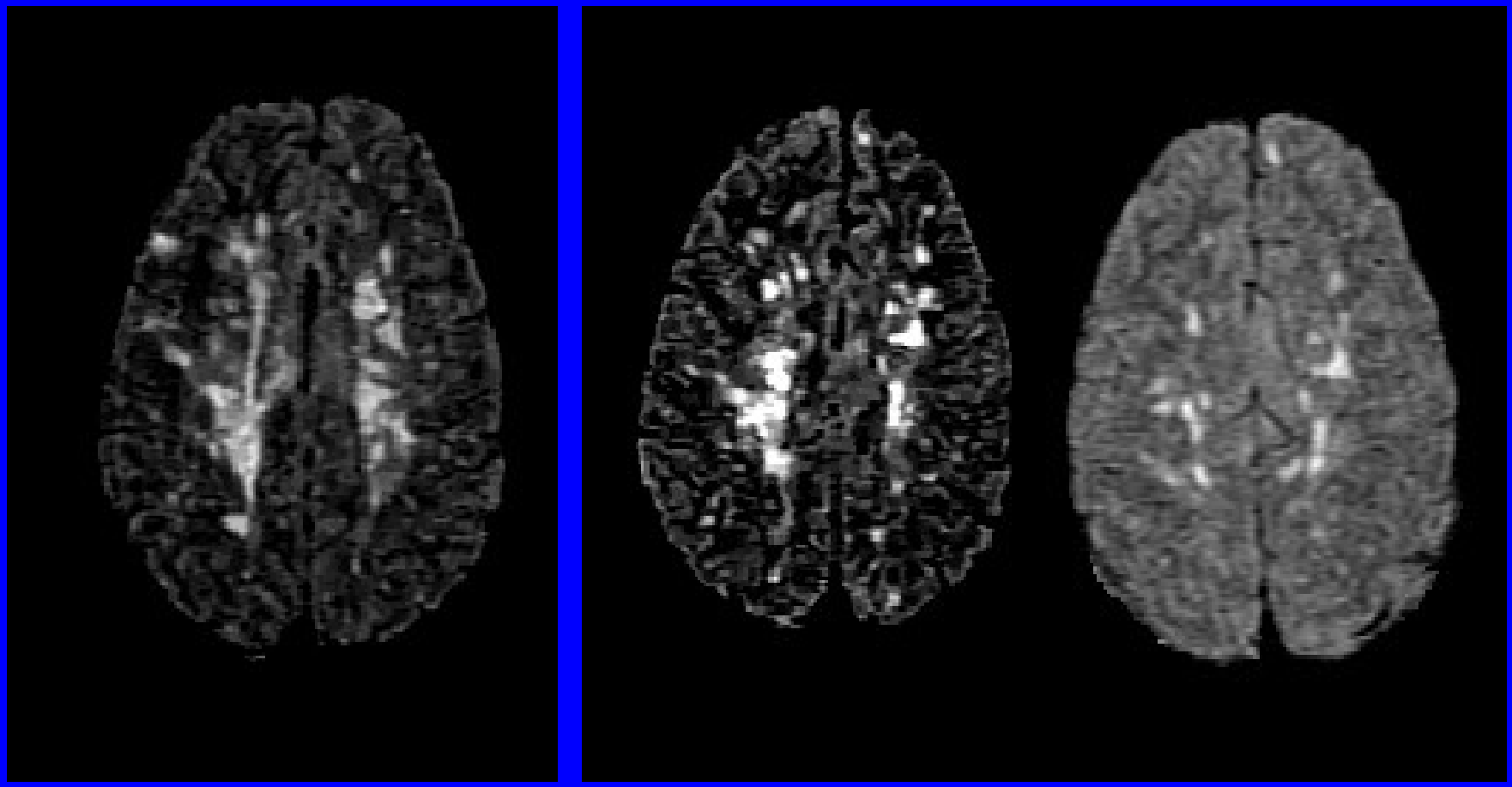
Methods

- 53 Relapsing remitting MS patients examined 1.5 T H-1 MRI and MRSI
- 3 mm thick axial interleaved contiguous images
- MS lesion visualization by AFFIRMATIVE and Quadruple Contrast pulse sequences
- MRSI data analysis by APSIP program

MS lesions showing abnormal appearance in GM and NAGM after Post-Gd Contrast



Localized Acute MS lesion in GM: Pre-Contrast and Post-Contrast images



New Generation of MRI Scanners

- High Magnetic Field Clinical Scanners at 4T, 7T, 11.7T and 17T Strengths

http://precedings.nature.com/documents/3485/versi

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Proton Magnetic Resonance Spectroscopic Imaging of Abnormal Brain in Multiple Sclerosis

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