MRS

From bench to bedside

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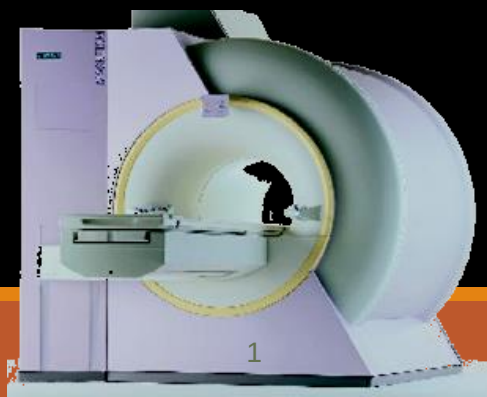
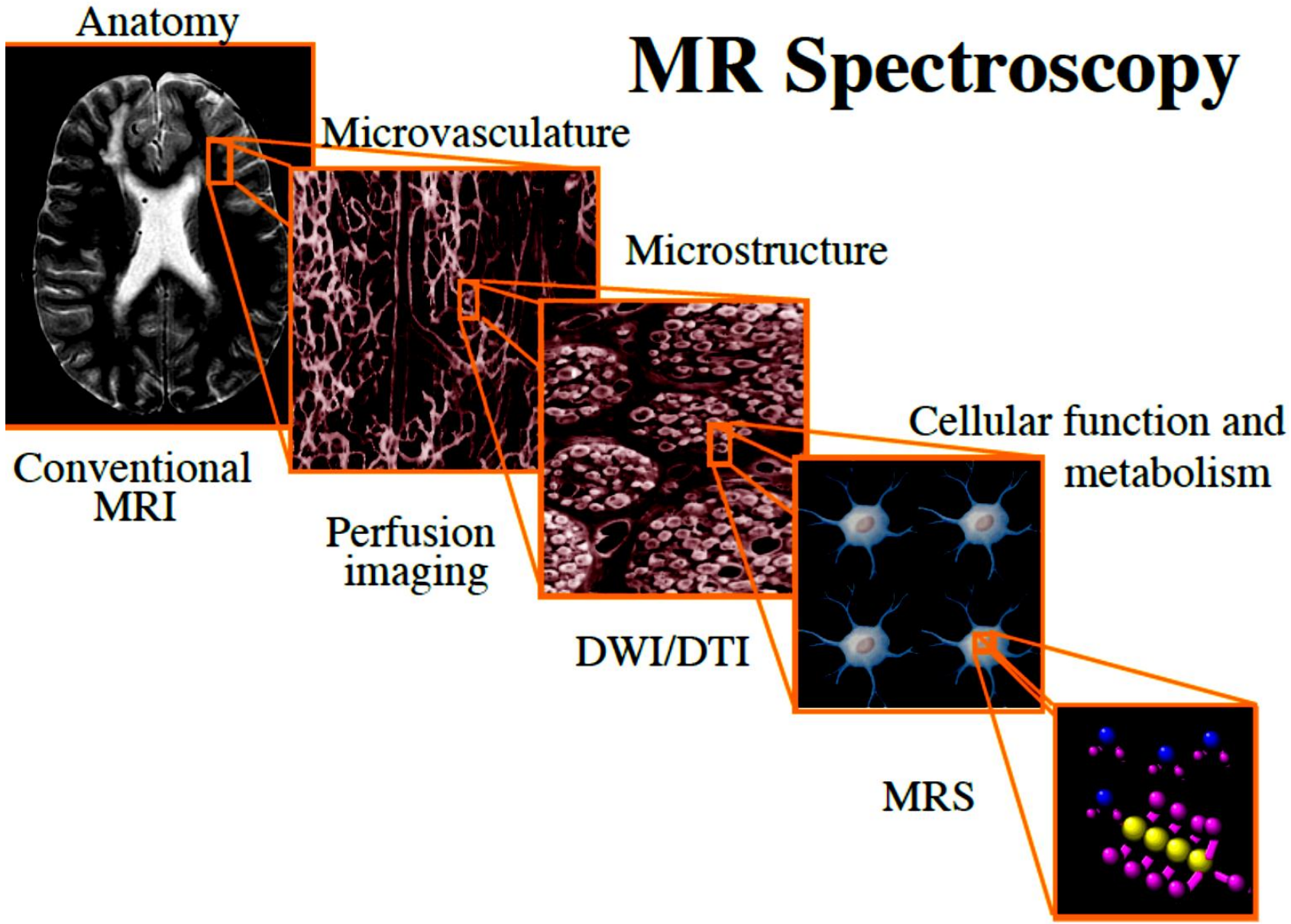


MR Spectroscopy



MRS was first described in 1946 simultaneously by the Nobel Prize winner Edward Purcell.

Nobel 1944

Columbia University

His discovery of NMR led to his receipt in 1944 of the Nobel Prize in Physics "for his resonance method for recording the magnetic properties of atomic nuclei"

Figure 5. Isidor Isaac Rabi (1898–1988). Courtesy, Nobel Foundation.

Nobel 1989

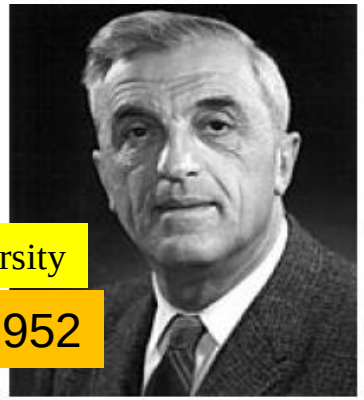
Figure 6. Norman Foster Ramsey, Jr. (1915–2011). Courtesy, Nobel Foundation.

In 1949 he developed the first successful chemical shift theory

Nobel 2003

University of Illinois

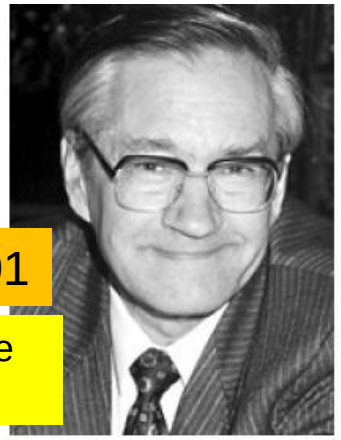
Figure 1. Paul Christian Lauterbur (1929–2007). Courtesy, Nobel



Stanford University

Nobel 1952

Figure 7. Felix Bloch (1905–1983). Courtesy, Nobel Foundation.



Nobel 1991

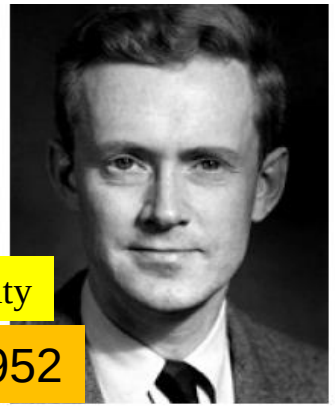
Zürich Institute of Technology

Figure 11. Richard R. Ernst (b. 1933). Courtesy, Nobel Foundation.

University of Nottingham

Nobel 2003

Figure 2. Sir Peter Mansfield (b. 1933). Courtesy, Nobel Foundation.



Stanford University

Nobel 1952

Figure 8. Edward Mills Purcell (1912–1997). Courtesy, Nobel Foundation.

University of Arizona

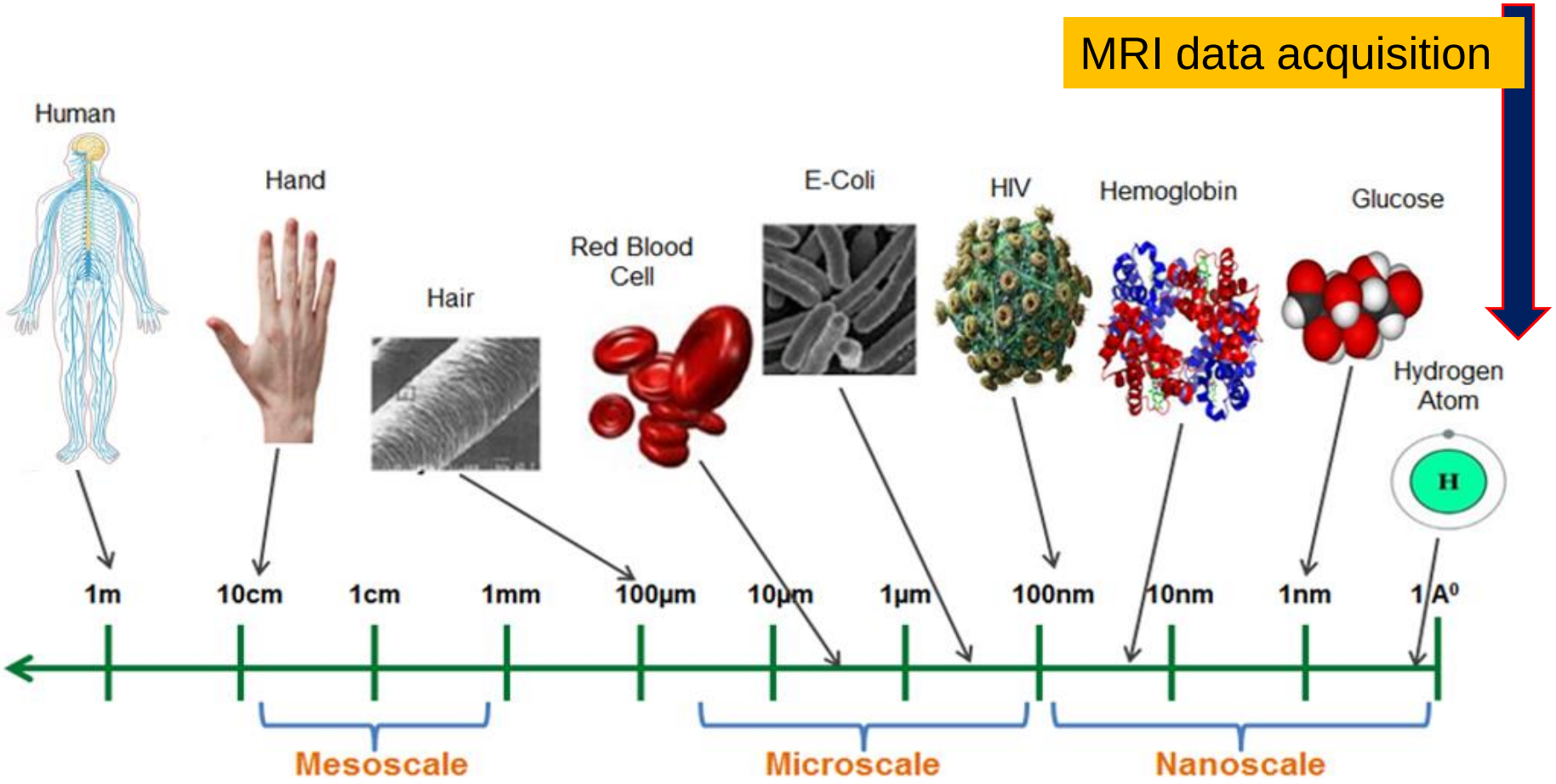
Nobel 1981

As Purcell's first graduate student. In 1981 he shared the Nobel Prize in Physics with Arthur L. Schalow

Figure 9. Nicolaas Bloembergen (b. 1920).

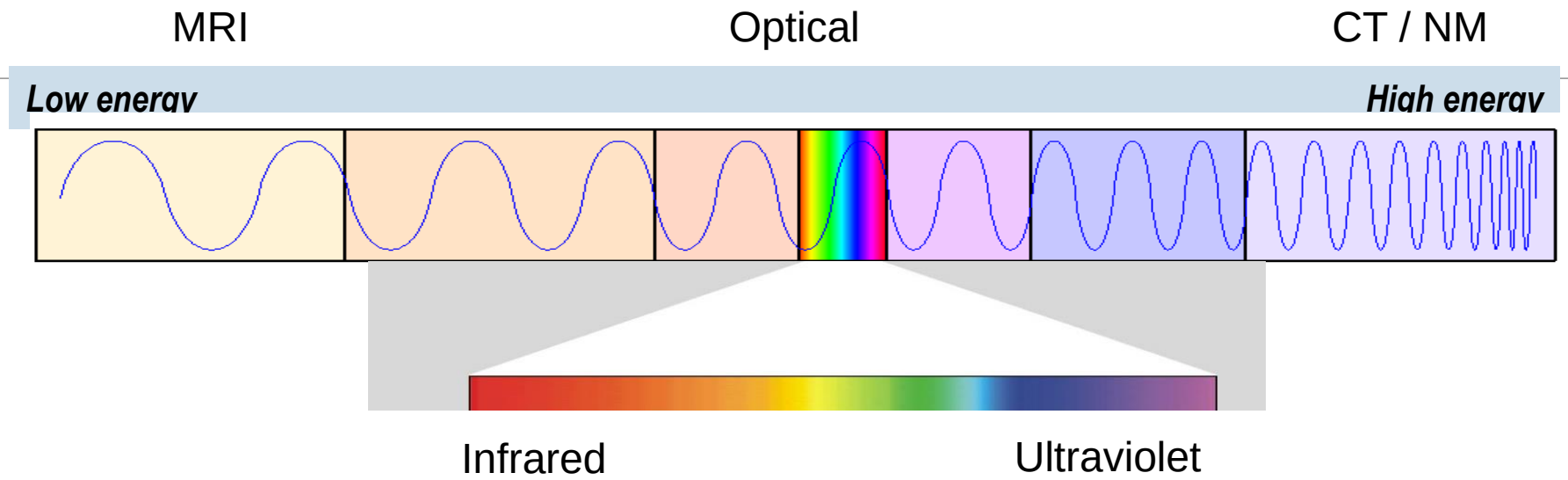
Virtual Biopsy

Magnetic resonance spectroscopy (MRS) allows the non-invasive measurement of selected biological compounds in vivo.


MRI data acquisition
Human
Hand
Hair
Red Blood Cell
E-Coli
HIV
Hemoglobin
Glucose
Hydrogen Atom
H
1m
10cm
1cm
1mm
100µm
10µm
1µm
100nm
10nm
1nm
1 A⁰
Mesoscale
Microscale
Nanoscale

Spectrum of wavelenghts

Eletromagnetic radiation



"Reporter" molecules:

1)Fluorescence,

2)Radiation,

3)Magnetic

4)Radiopharmaceuticals

Positron emitters

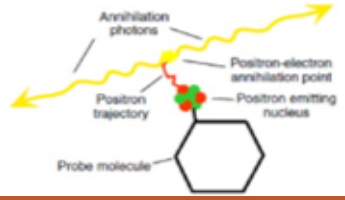
Nuclides	half life
F-18	**110 min**
C-11	**20 min**
N-13	10 min
O-15 1	2 min
Ga-68	68 min
Rb-82	1.3 min

Positron:

-Same mass as electron

-opposite electrical charge

-annihilation generates a pair of gamma-ray photons – 180°



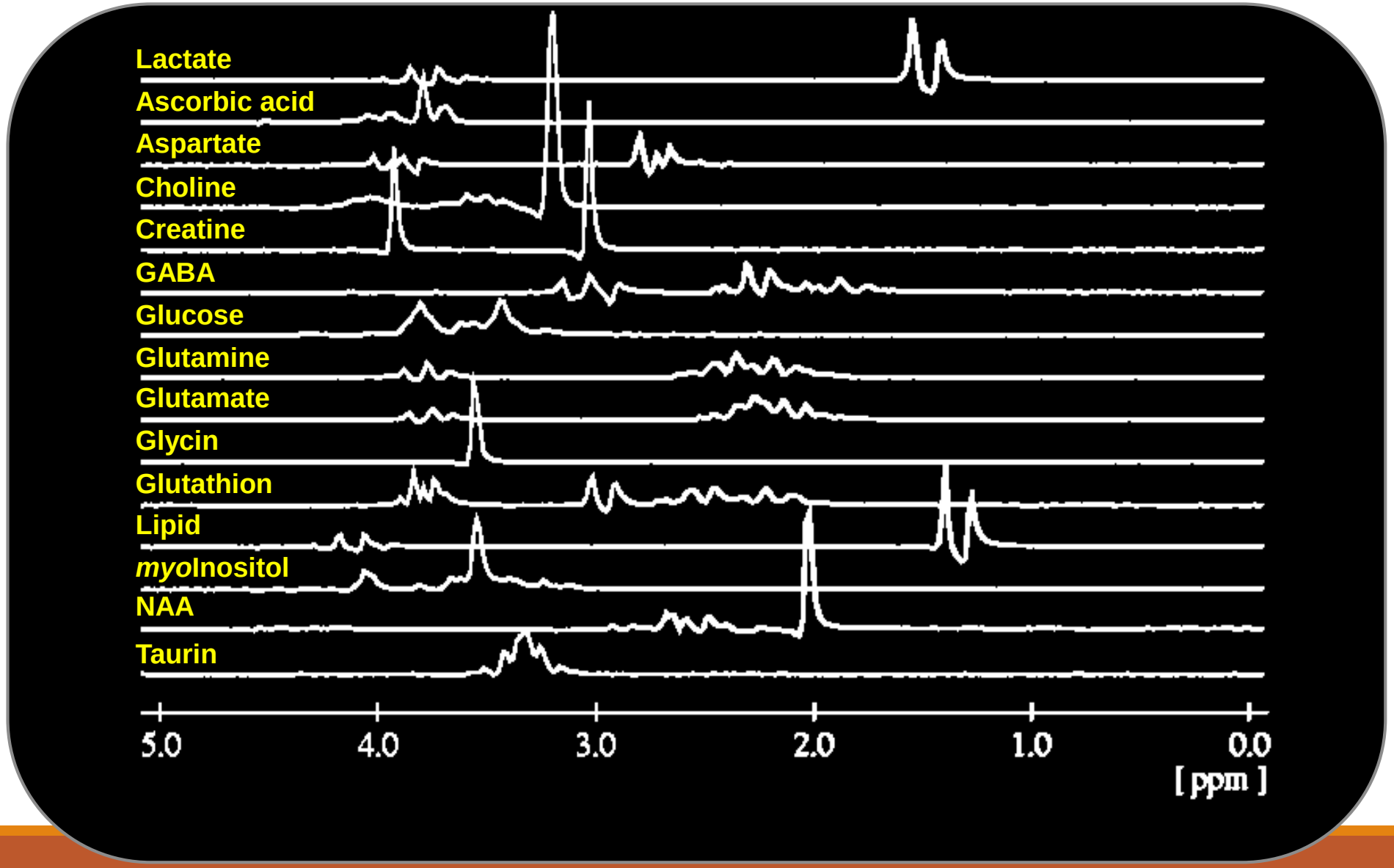
MRI: Signal versus time

(anatomic changes)

MRS: signal versus frequency

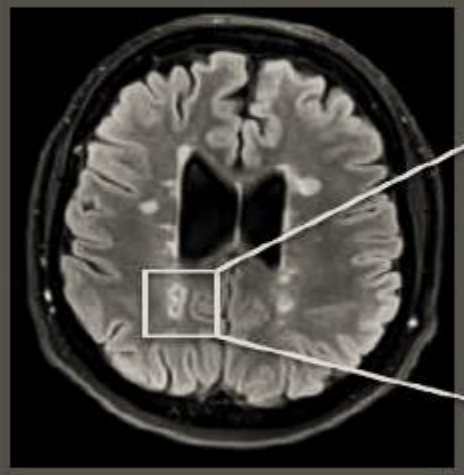
(biochemical and metabolic changes)

Signal intensity of metabolites based on Basis Set

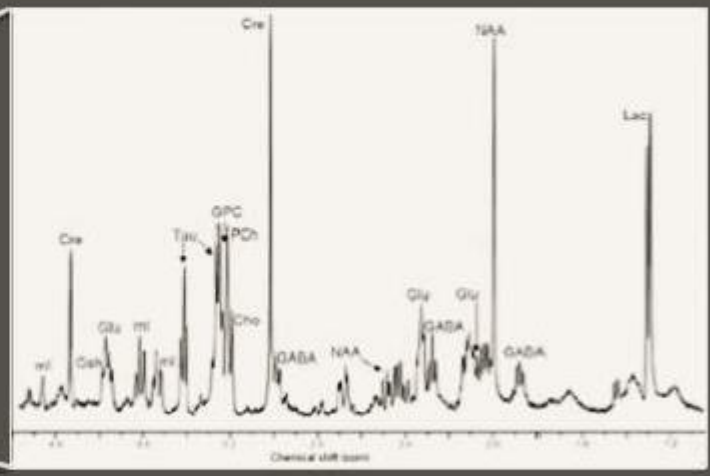


MRI vs. MRS

T2w FLAIR MRI in Multiple Sclerosis Patient



Spectroscopy



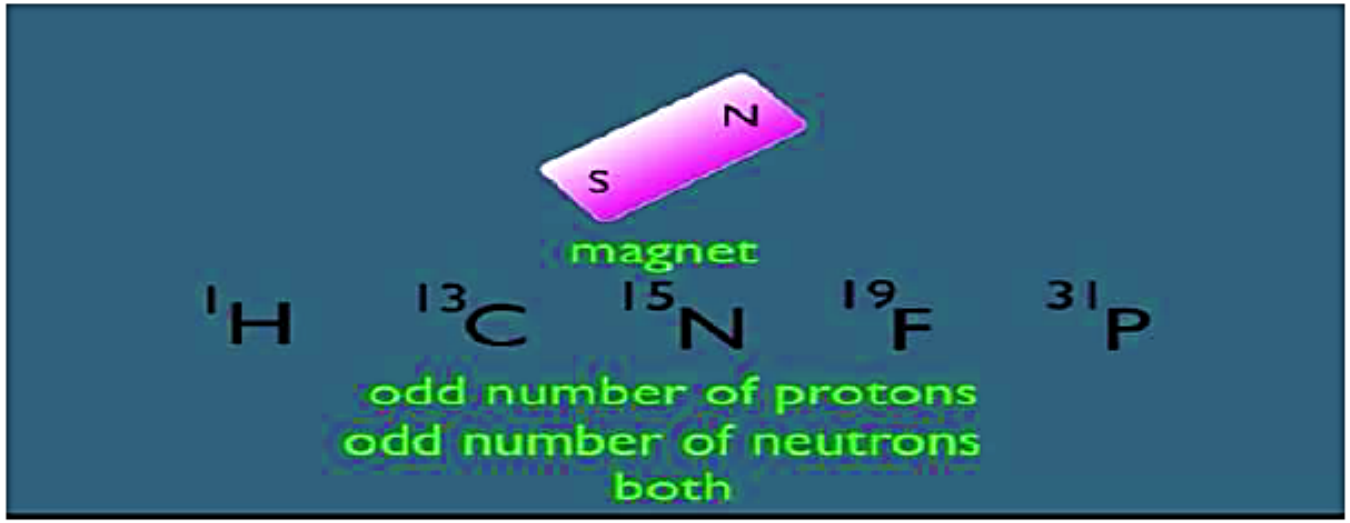
Imaging signal comes from water protons

Spectroscopy signal comes from protons in other environments

MRS: Basic Physics

Basic physics of MRS

- Theoretically MRS can be performed with spins or nuclei of 1H,13C,19F,23Na and 31P.
- But In present, MRS clinical uses are mainly 1H(Hydrogen) & 31P(Phosphorus) spectroscopy.



LOCALIZATION TECHNIQUES IN MRS

Four methods commonly used for localisation in clinical practice:

- **STEAM (Stimulated echo acquisition method)-** three 90 degree excited pulse applied along three planes. Short TE (20ms) is used.
- **PRESS (point resolved spectroscopy)-** one 90 degree and two 180 degree pulse are applied along three planes. longer TE (270ms) is used.
- **ISIS(Image Selective In vivo Spectroscopy):**Used in 31P spectroscopy.
- **CSI(chemical shift** Imaging):Used for multi voxel spectrosopy.

SINGLE VOXEL SPECTROSCOPY (SVS)

•In SVS, the signal is received of a volume limited to a single voxel. This acquisition is fairly fast (1 to 3 minutes) and a spectrum is easily obtained. It is performed in three steps:

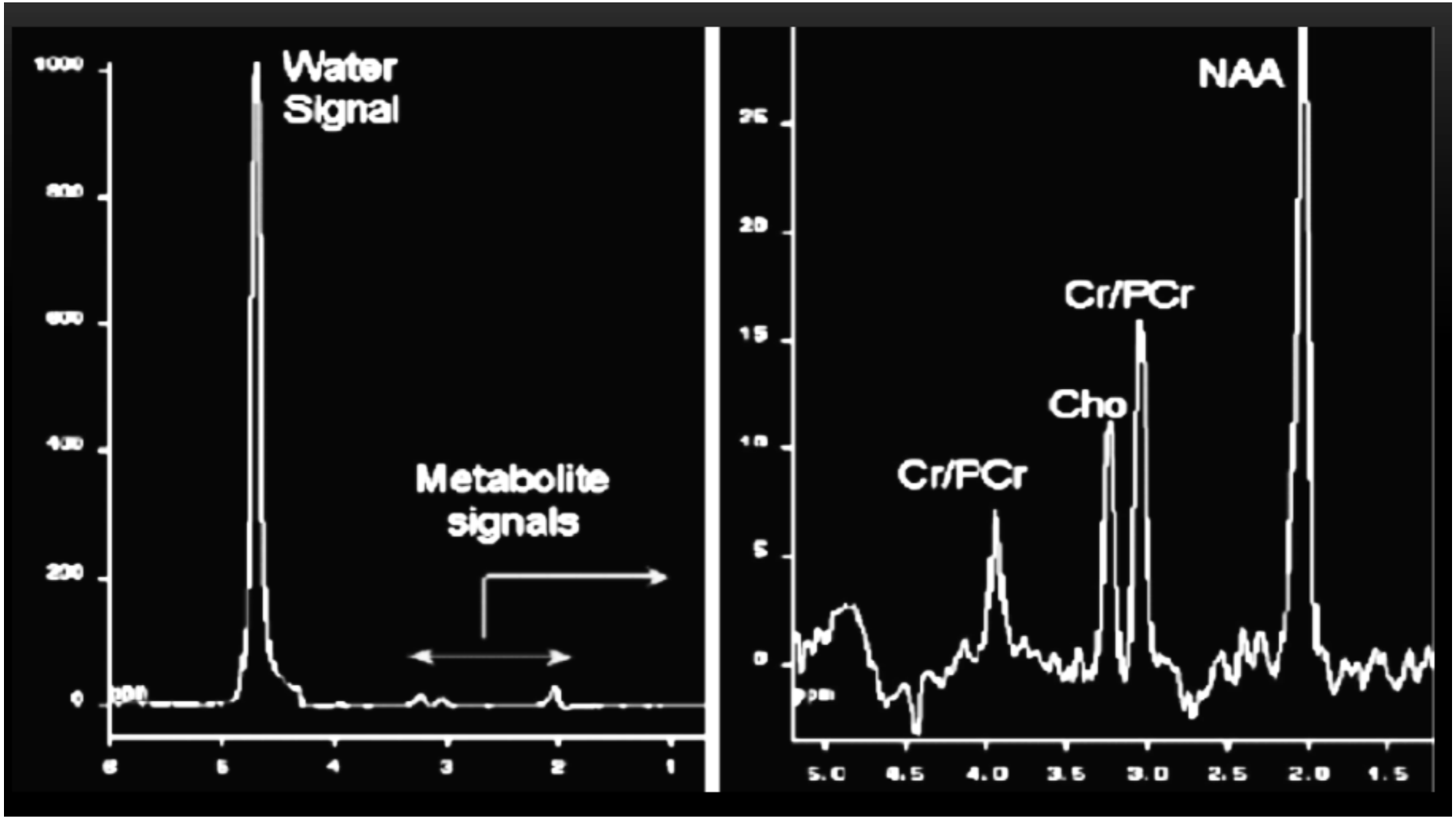
•**Suppression of the water signal**: the quantity of hydrogen nuclei in the water molecules in the human body is such that the water peak at 4.7 ppm “drowns” and masks the spectroscopic signal from the other metabolites.

•It is therefore vital to suppress the water peak to observe the metabolites of interest.

•**Selection of the voxel of interest**

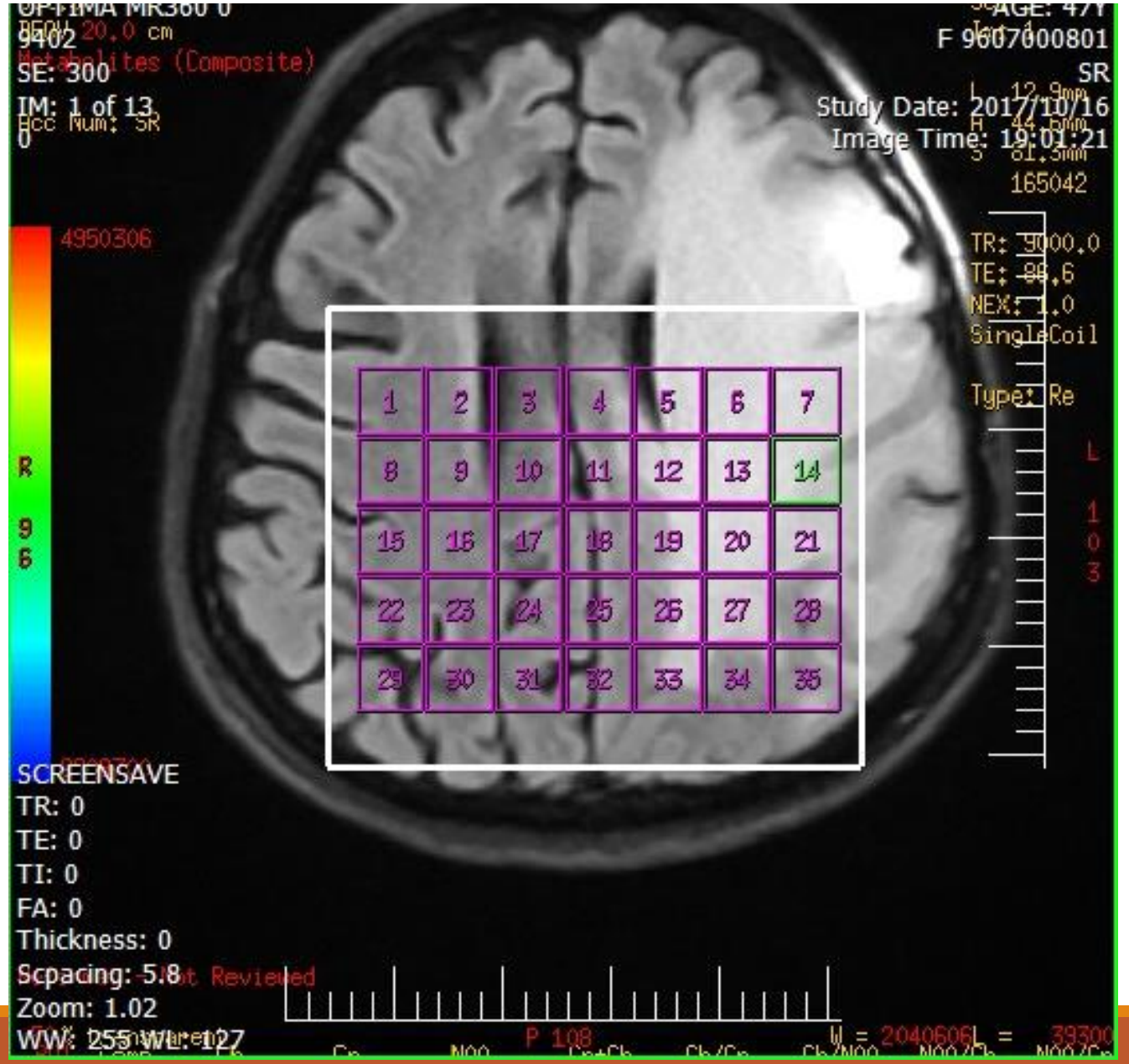
•**Acquisition of the spectrum**, for which two types of sequence are available:

1) PRESS: Point-RESolved Spectroscopy,
2) STEAM: STimulated Echo Acquisition Mode

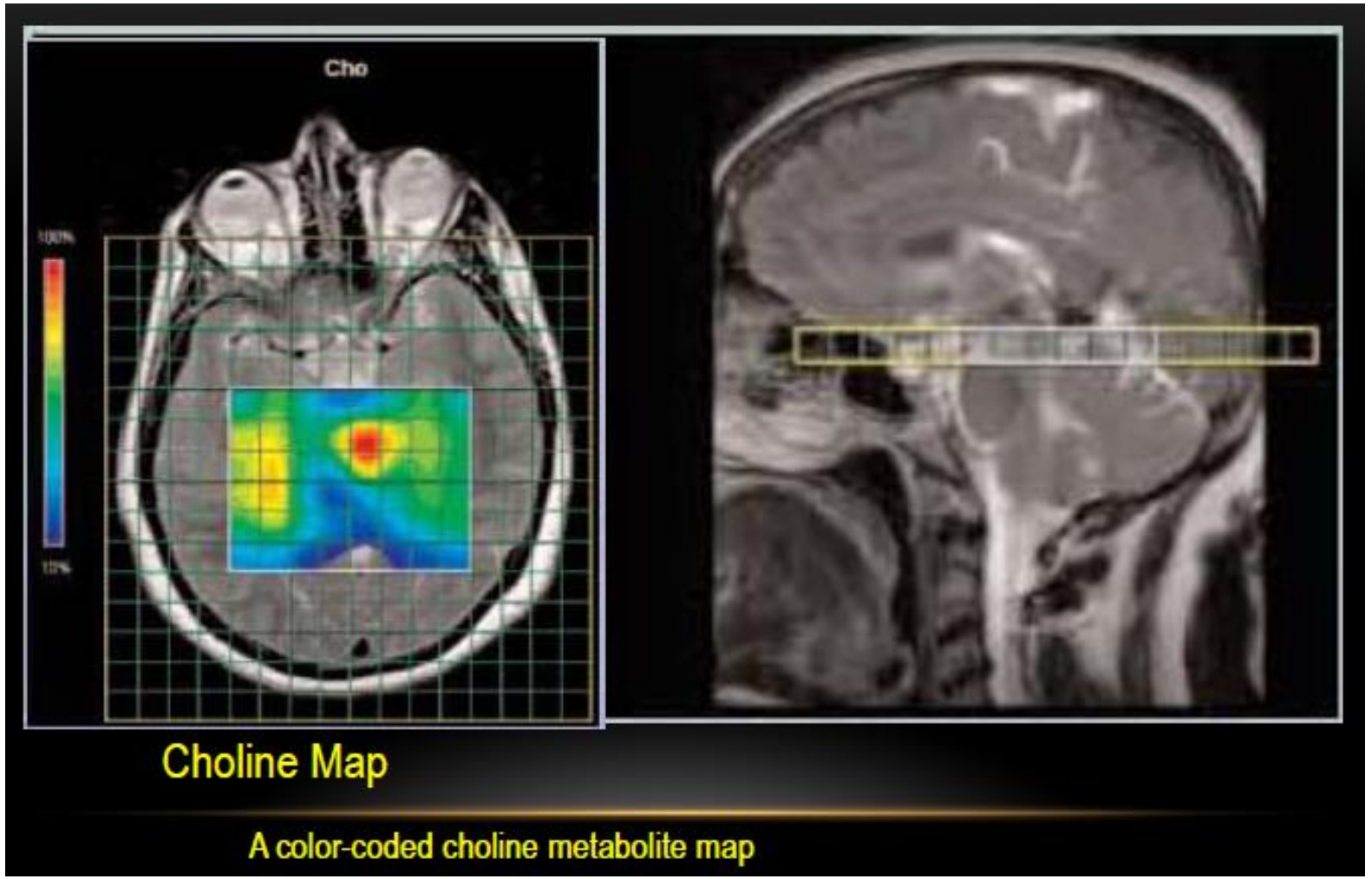


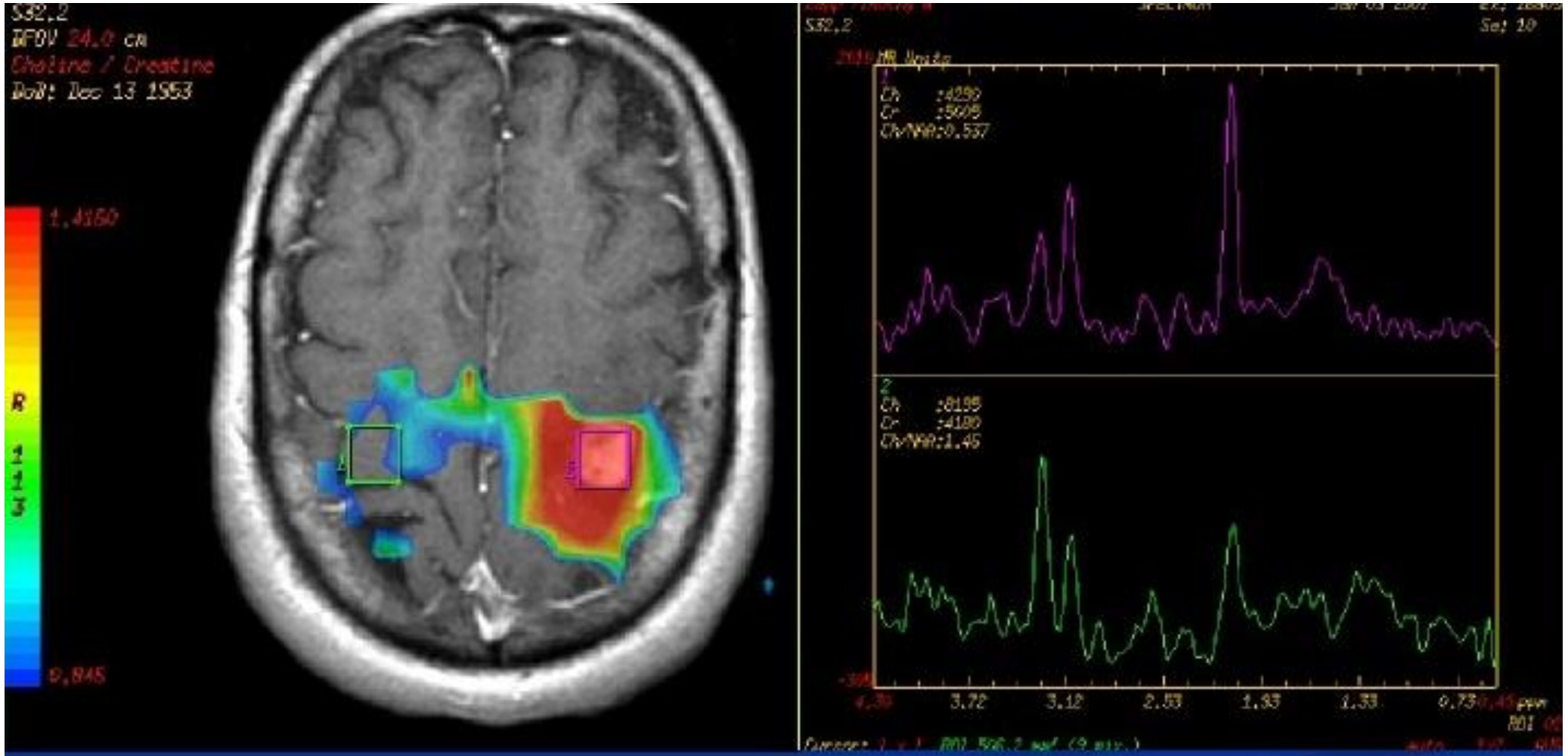
This figure demonstrates the importance of suppressing the water signal.
The metabolites of interest have a signal one hundred times smaller than that of the water peak, and without water suppression would be poorly resolved

Multivoxel Spectroscopy (MVS)



Multivoxel Spectroscopy (MVS)





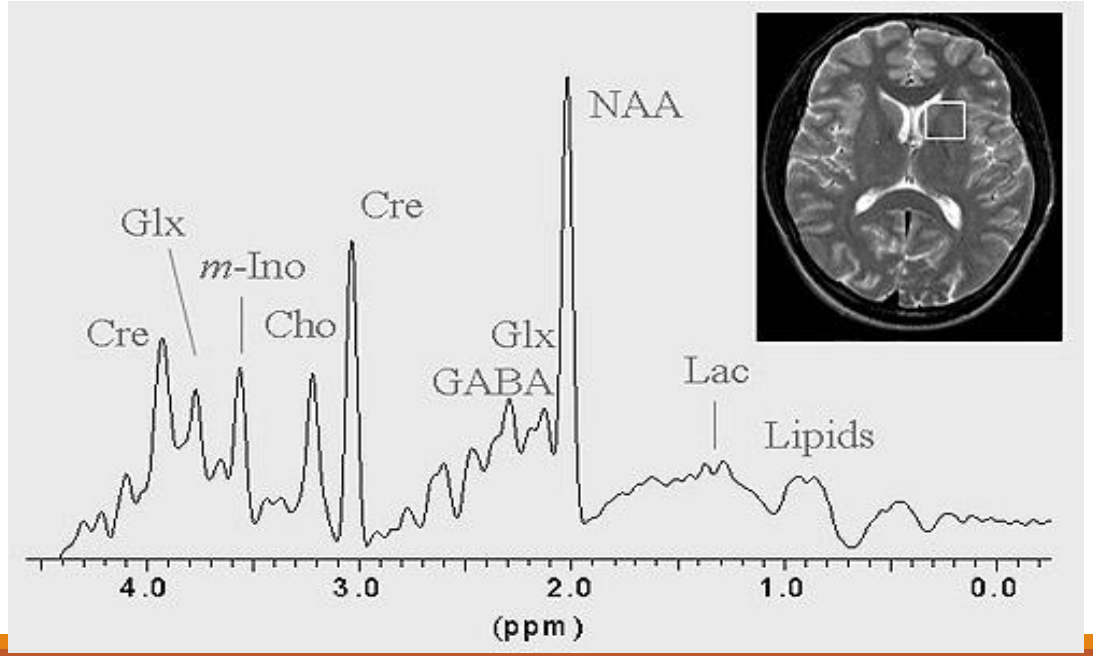
MAPS HAVE IMPLICATIONS FOR PROGNOSIS AND RT PLANNING

Normal Brain Spectrum

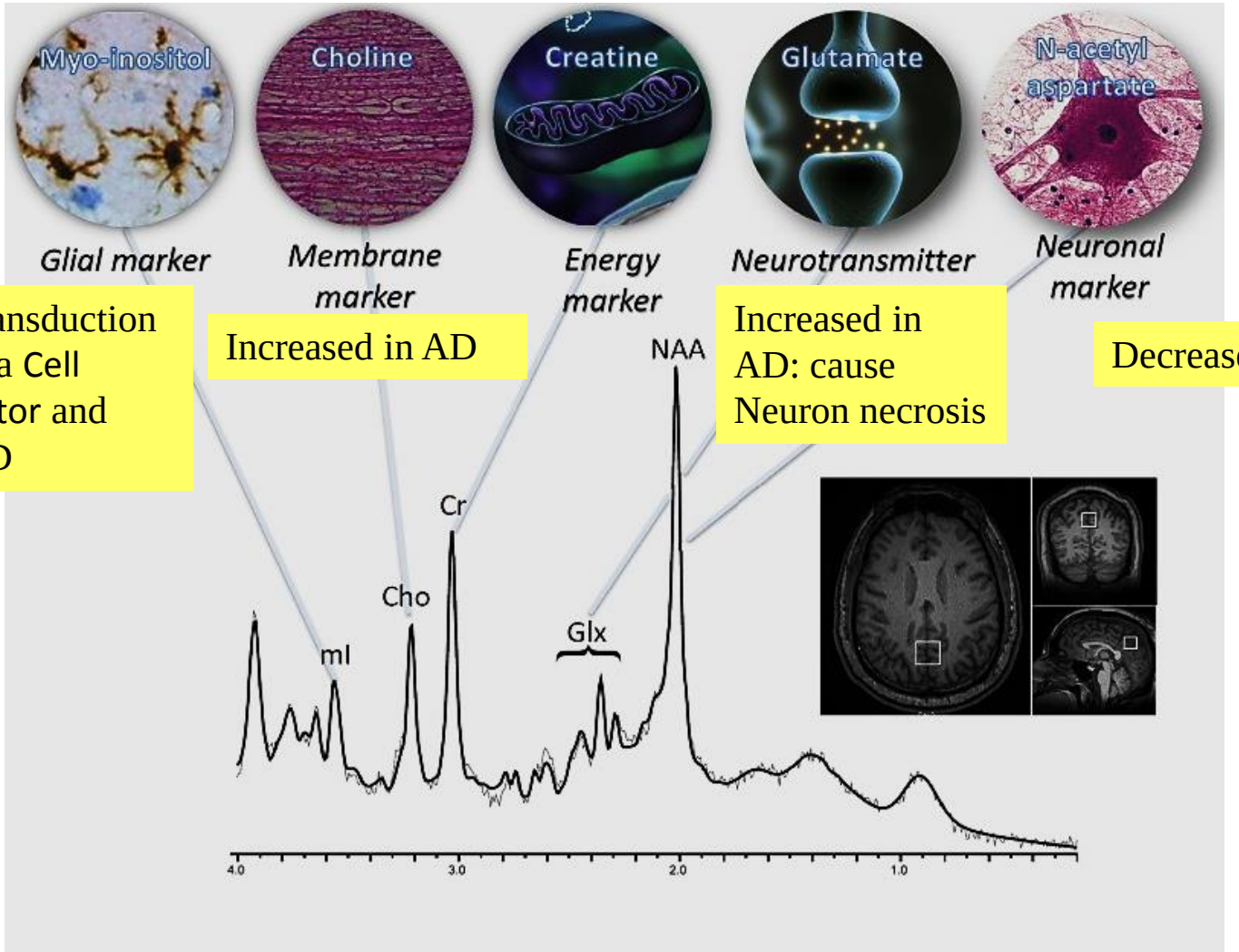
A spectrum of the metabolites is plotted on a two dimensional graph.

The horizontal axis = frequencies (chemical shifts)

The vertical axis = concentration of the metabolites.



Some common MRS metabolites that are assessed as biomarkers



mediates the transduction of cell signals, a Cell Volume Regulator and Increased in AD

Increased in AD

Increased in AD: cause Neuron necrosis

Decreased in AD

Gray matter has more creatine

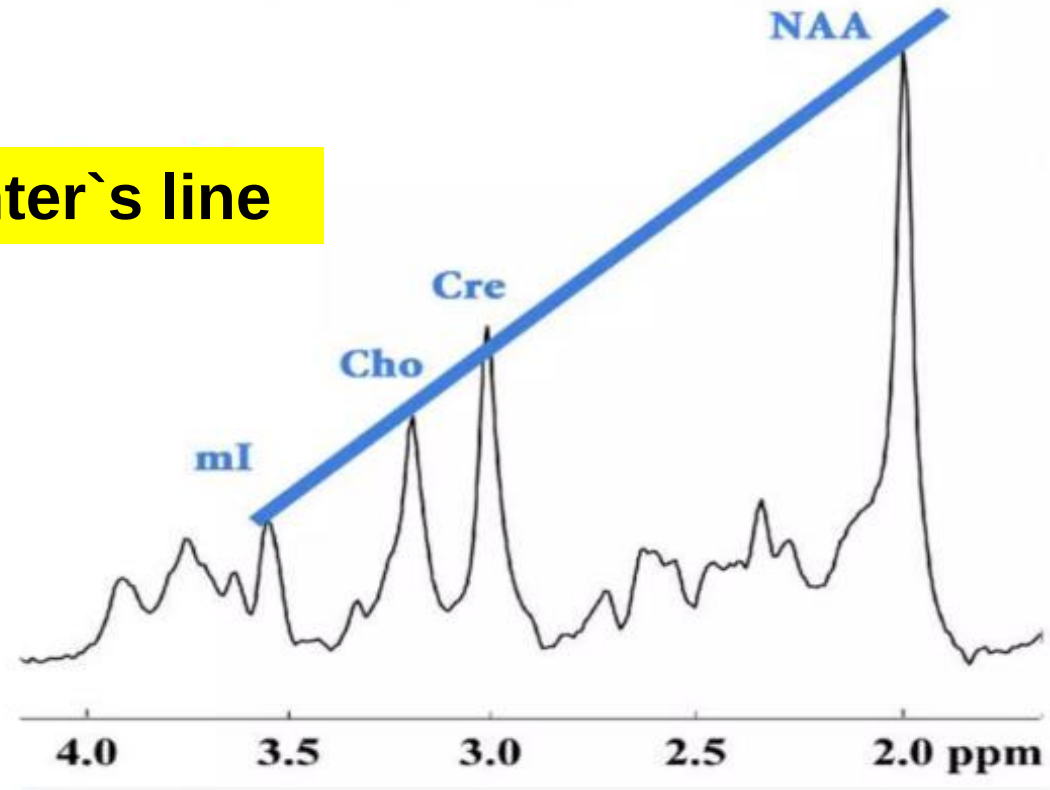
Standard range of MRS metabolites

ppm	Metabolite	Properties
0.9-1.4	Lipids	Products of brain destruction
1.3	Lactate	Product of anaerobic glycolysis
2.0	NAA	Neuronal marker
2.2-2.4	Glutamine/GABA	Neurotransmitters
3.0	Creatine	Energy metabolism
3.2	Choline	Cell membrane marker
3.5	*myo*-inositol	Glial cell marker, osmolyte hormone receptor mechanisms

- **NAA** is considered as a **good** metabolite (as it represents neuronal health)
- **Choline** is considered as a **bad** metabolite (as it is seen in tumors) and
- **Lipid lactate** doublet as an **ugly** metabolite (as it is seen in necrotic tumors).

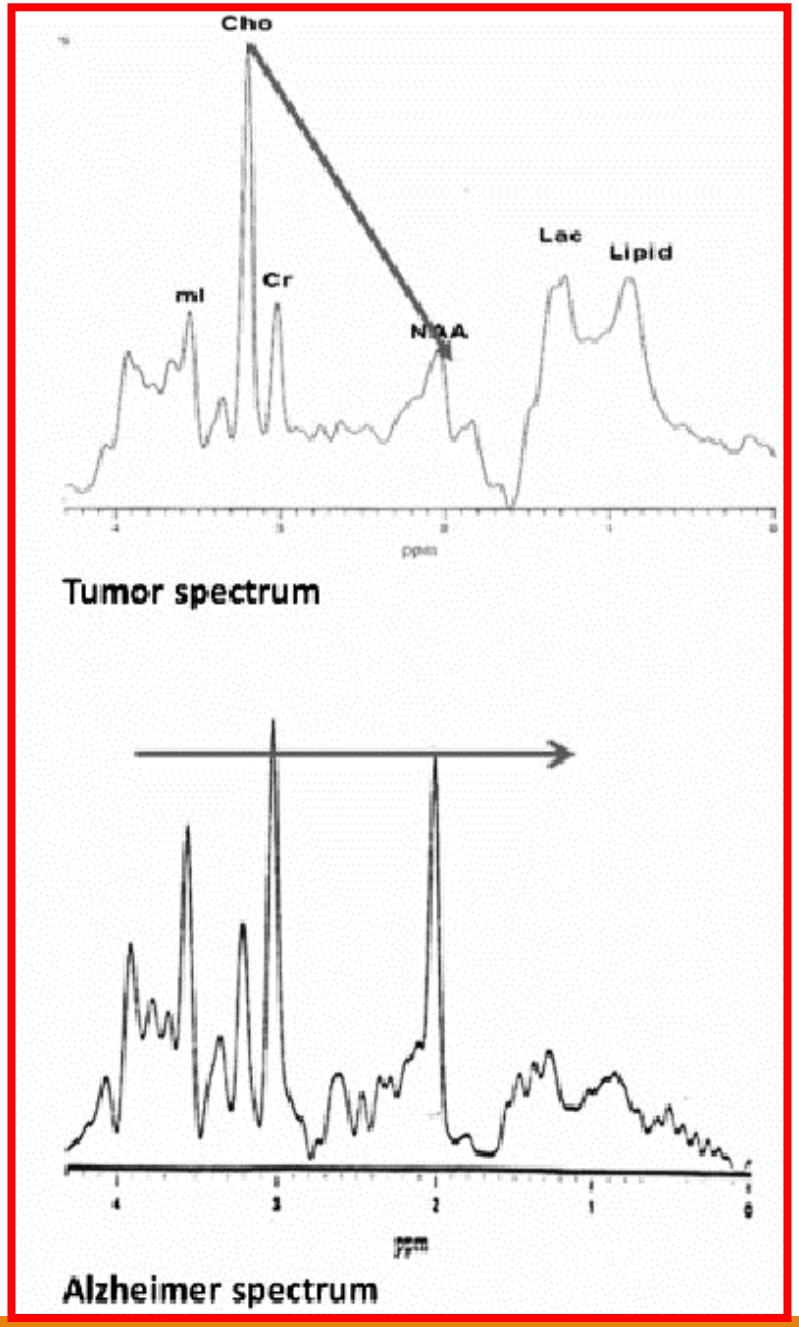
MRS of normal white matter

Hunter`s line



Hunter's line at a 45° angle connecting the 3 major peaks of a normal MR spectrum

➢A good quality spectrum should present a flat horizontal baseline with distinct narrow peaks



Clinical and cellular application of MRS

MRS metabolites

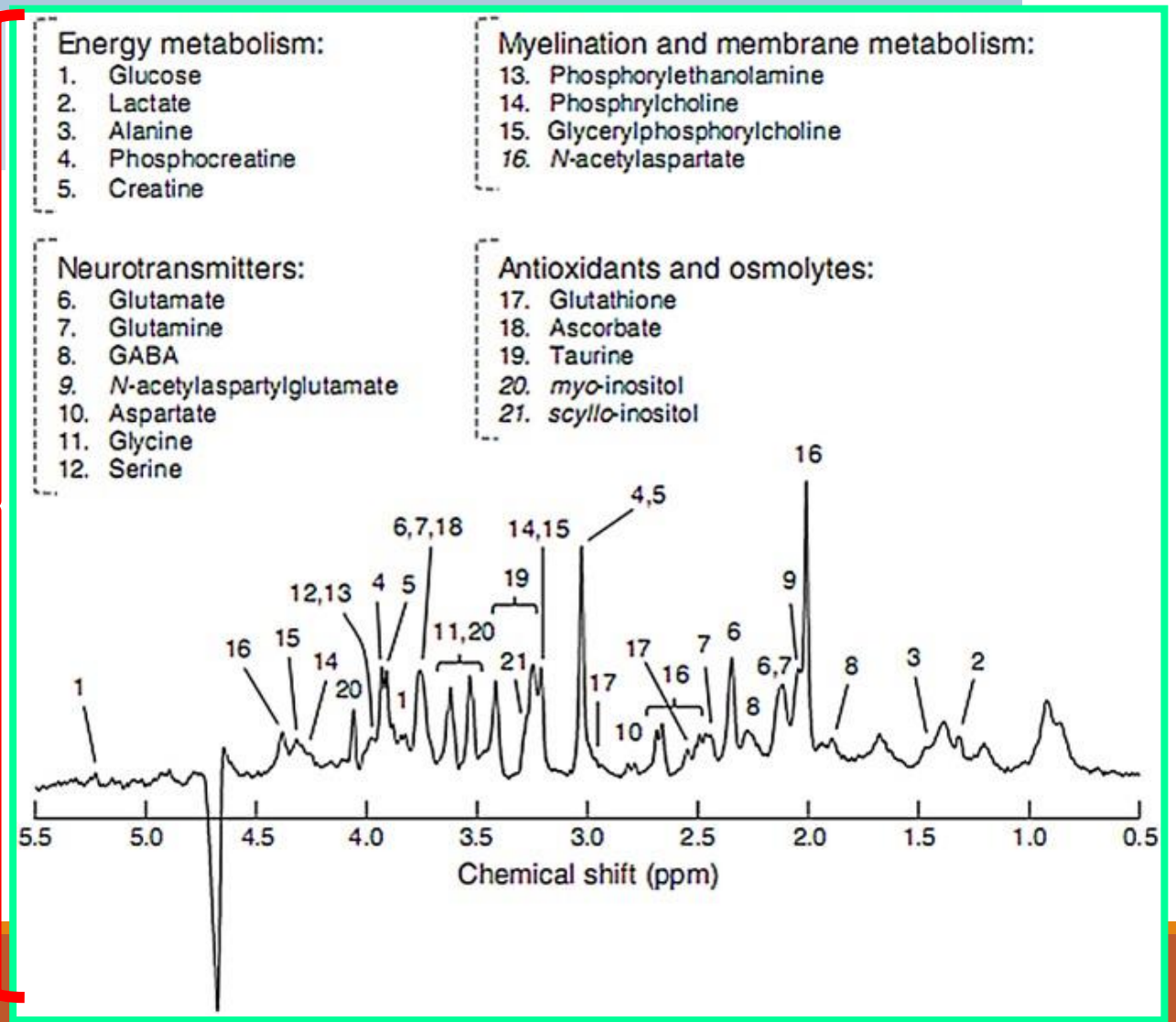
The neurochemical profile detected by ^{1}H MRS in the brain

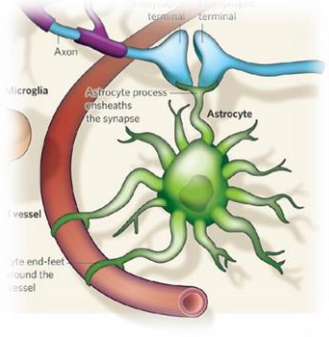
At high magnetic field [7 T and above], a neurochemical profile of more than 20 metabolites can be determined under normal physiological conditions

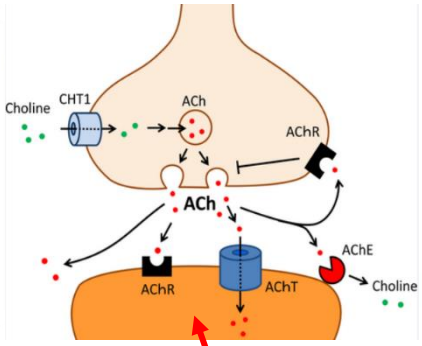
^{1}H MRS can detect all compounds existing in a concentration above 0.5 µmol/g (Ref: Duarte)

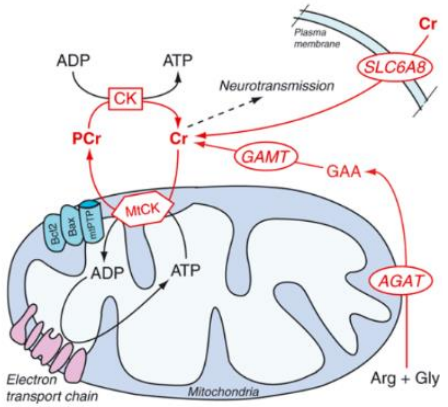
Duarte JM, Lei H, Mlynárik V, Gruetter R. The neurochemical profile quantified by in vivo 1H NMR spectroscopy. Neuroimage. 2012 Jun 1;61(2):342-62.

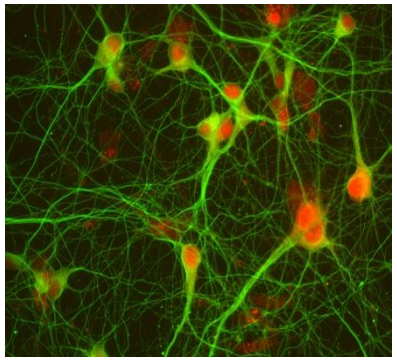
1) **These metabolites categorized into four types:**
2) **neurotransmitters,**
3) **energy metabolism,**
4) **myelination and membrane metabolism,**
5) **antioxidants and osmolytes**

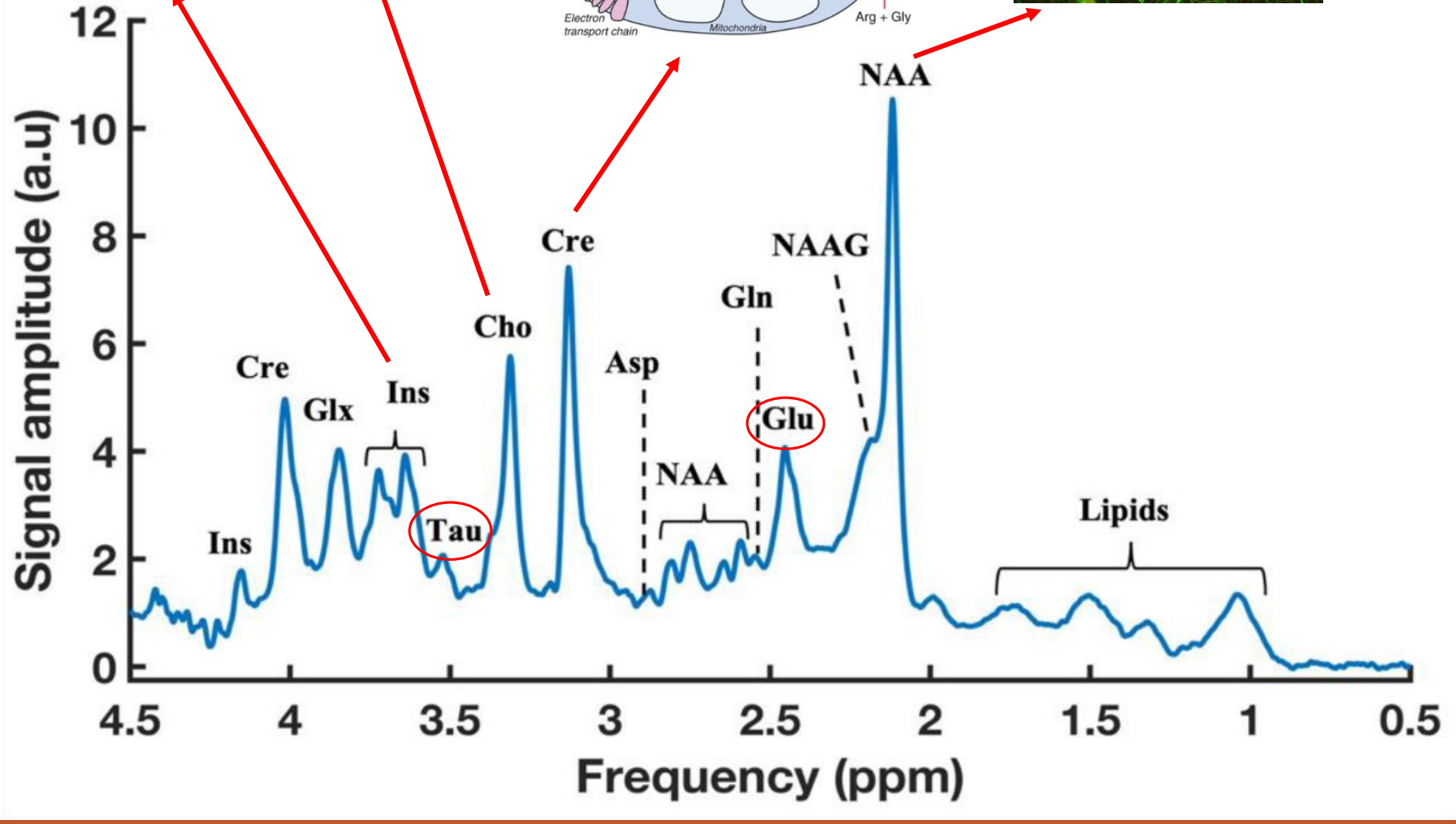



Axon
Astrocyte process ensheaths the synapse
Astrocyte


Choline
CHT1
ACh
AChR
ACh
AChE
Choline
AChR
AChT


ADP
ATP
CK
Neurotransmission
Plasma membrane
Cr
SLC6A8
PCr
Cr
GAMT
GAA
MtCK
ADP
ATP
AGAT
Electron transport chain
Mitochondria
Arg + Gly




Signal amplitude (a.u)
12
10
8
6
4
2
0
4.5
4
3.5
3
2.5
2
1.5
1
0.5
Frequency (ppm)
Ins
Cre
Glx
Ins
Tau
Cho
Cre
Asp
NAA
Gln
Glu
NAAG
NAA
Lipids

Detailed of Brain Metabolites

N-acetylaspartate (NAA)

- The peak of NAA is the highest peak in normal brain, assigned at 2.02 ppm.
- NAA is synthesized in the mitochondria of neurons, then transported into neuronal cytoplasm and along axons.
- NAA is exclusively found in the nervous system (peripheral and central), and is detected in both gray and white matter.
- It is a marker of neuronal and axonal viability and density.
- NAA can additionally be found in immature oligodendrocytes and astrocyte progenitor cells.
- NAA also plays a role as a cerebral osmolyte.
- Absence or decreased concentration of NAA is a sign of neuronal loss or degradation.
- Neuronal destruction from malignant neoplasms and many white-matter diseases results in decreased concentration of NAA. By contrast, increased NAA indicates Canavan disease, although it may also be demonstrated in Salla disease and Pelizaeus- Merzbacher disease.
- NAA is not demonstrated in extra-axial lesions such as meningiomas or intra-axial ones originating from outside of the brain such as metastases, unless there is a partial volume effect with normal parenchyma.

Detailed of Brain Metabolites

Creatine

- The peak of the Cr spectrum is assigned at 3.02 ppm.
- This peak represents a combination of molecules containing creatine and phosphocreatine.
- Cr is a marker of energetic systems and intracellular metabolism.
- The concentration of Cr is relatively constant, and it is considered a stable metabolite.
- It is therefore usedas an internal reference for calculating metabolite ratios. However, there is regional and individual variability in Cr concentrations.
- In brain tumors, the Cr signal is relatively variable. Gliosis may cause minimally increased Cr, owing to increased density of glial cells (glial proliferation).
- Creatine and phosphocreatine are metabolized to creatinine, then the creatinine is excreted via the kidneys. Systemic disease (eg, renal disease) may also affect Cr levels in the brain.

Detailed of Brain Metabolites

Choline

- Cho is a marker of cellular membrane turnover (phospholipids synthesis and degradation) reflecting cellular proliferation.
- Because the brain cannot synthesis choline de novo, **uptake of choline** from extracellular fluids is essential.
- The main fate of choline is the **synthesis of PC**, the principal component of **cell membranes.**
- **a precursor for the formation of acetylcholine.**
- In tumors, Cho levels correlate with degree of malignancy reflecting cellularity.
- Increased Cho may be seen in infarction (from gliosis or ischemic damage to myelin) or inflammation (glial proliferation). For this reason, Cho is considered to be nonspecific.

Detailed of Brain Metabolites

Lactate

- The Lac peak is difficult to visualize in the normal brain.
- The peak of Lac is a doublet at 1.33 ppm, which projects above the baseline on short/long TE acquisition and inverts below the baseline at TE of 135 to 144 milliseconds.
- A small peak of Lac is visible in some physiologic states such as newborn brains during the first hours of life.
- Lac is a product of anaerobic glycolysis, so its concentration increases under an-aerobic metabolism such as cerebral hypoxia, ischemia, seizures, and metabolic disorders (especially mitochondrial ones).
- Increased Lac signals also occur with macrophage accumulation (eg, acute inflammation).
- Lac also accumulates in tissues with poor washout such as cysts, normal-pressure hydrocephalus, and necrotic and cystic tumors

Detailed of Brain Metabolites

Lipids

- Lipids are components of cell membranes not visualized with long TE because of their very short relaxation time.
- There are 2 peaks of lipids: methylene protons at 1.3 ppm and methyl protons at 0.9ppm.
- These peaks are absent in the normal brain, but presence of lipids may result from improper voxel selection, causing voxel contamination from adjacent fatty tissues (eg, fat in subcutaneous tissue, scalp, and diploic space).
- Lipid peaks can be seen when there is cellular membrane breakdown or necrosis, such as in metastases or primary malignant tumors.

Detailed of Brain Metabolites

Myoinositol

- ✓ Myo is a simple sugar assigned at 3.56 ppm.
- ✓ Myo is considered a glial marker because it is primarily synthesized in glial cells, almost only in astrocytes.
- ✓ It is also the most important osmolyte in astrocytes.
- ✓ Myo may represent a product of myelin degradation.
- ✓ Elevated Myo occurs with proliferation of glial cells or with increased glial cell size, as found in inflammation.
- ✓ Myo is elevated in gliosis, astrocytosis, and Alzheimer disease (AD).

Detailed of Brain Metabolites

Alanine

- Ala is an amino acid that has a doublet centered at 1.48 ppm.
- This peak is located above the baseline in spectra obtained with short/long TE and inverts below the baseline on acquisition using TE of 135 to 144 milliseconds.
- Its peak may be obscured by Lac (at 1.33 ppm).
- The function of Ala is uncertain, but it plays a role in the citric acid cycle.
- Increased concentration of Ala may occur in defects of oxidative metabolism.
- In tumors, an elevated level of Ala is specific for meningiomas

Detailed of Brain Metabolites

Glutamate-glutamine

- Glx has complex peaks from glutamate, glutamine, and g-aminobutyric acid assigned at 2.05 to 2.50 ppm.
- These metabolite peaks are difficult to separate at 1.5 T.
- Glutamate is an important excitatory neurotransmitter and also plays a role in the redox cycle.
- Elevated concentration of glutamine are found in a few diseases such as hepatic encephalopathy

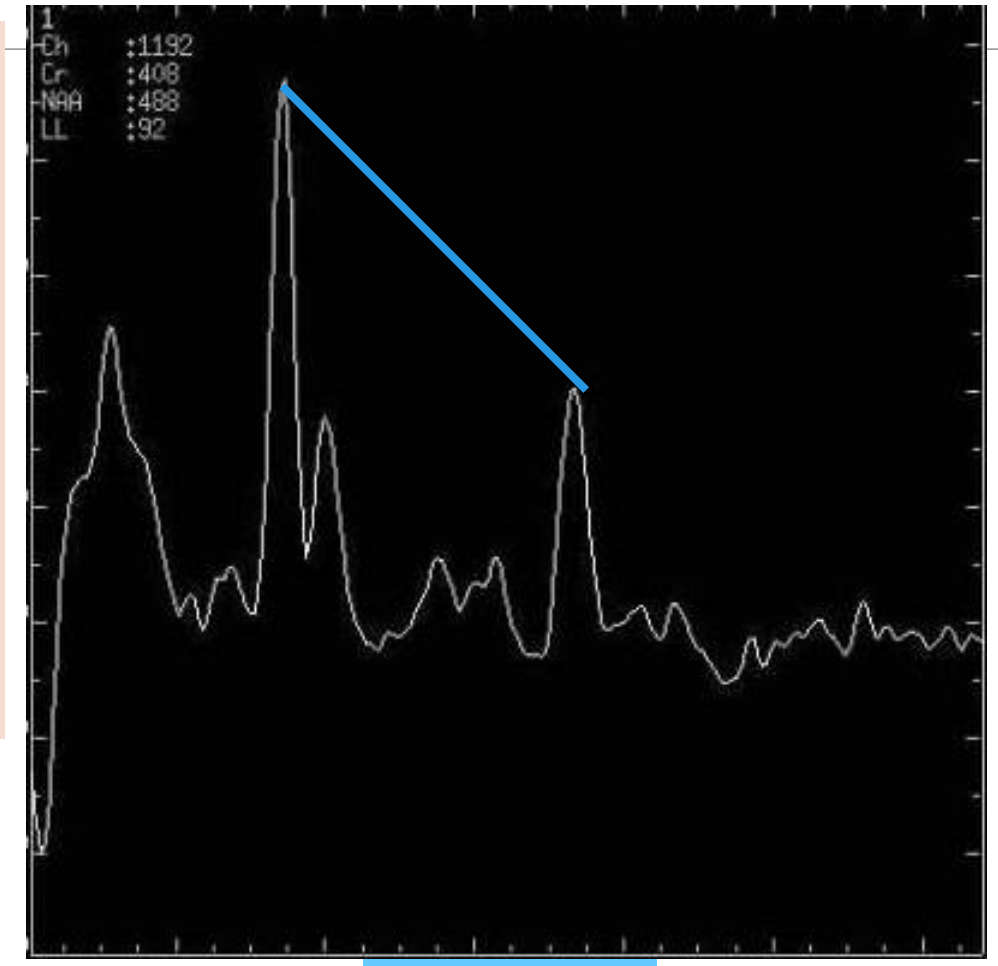
Age Considerations in Brain MRS

synaptogenesis and neuroplasticity

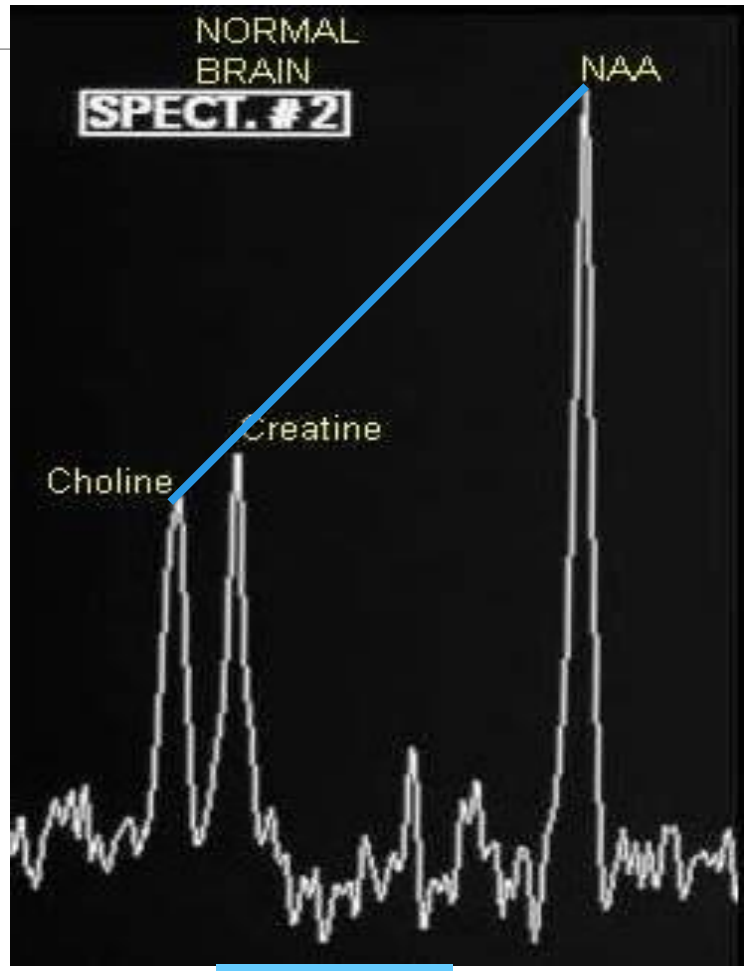
There are two main types of neuroplasticity:

1) **Functional plasticity**: The brain's ability to move functions from a damaged area of the brain to other undamaged areas

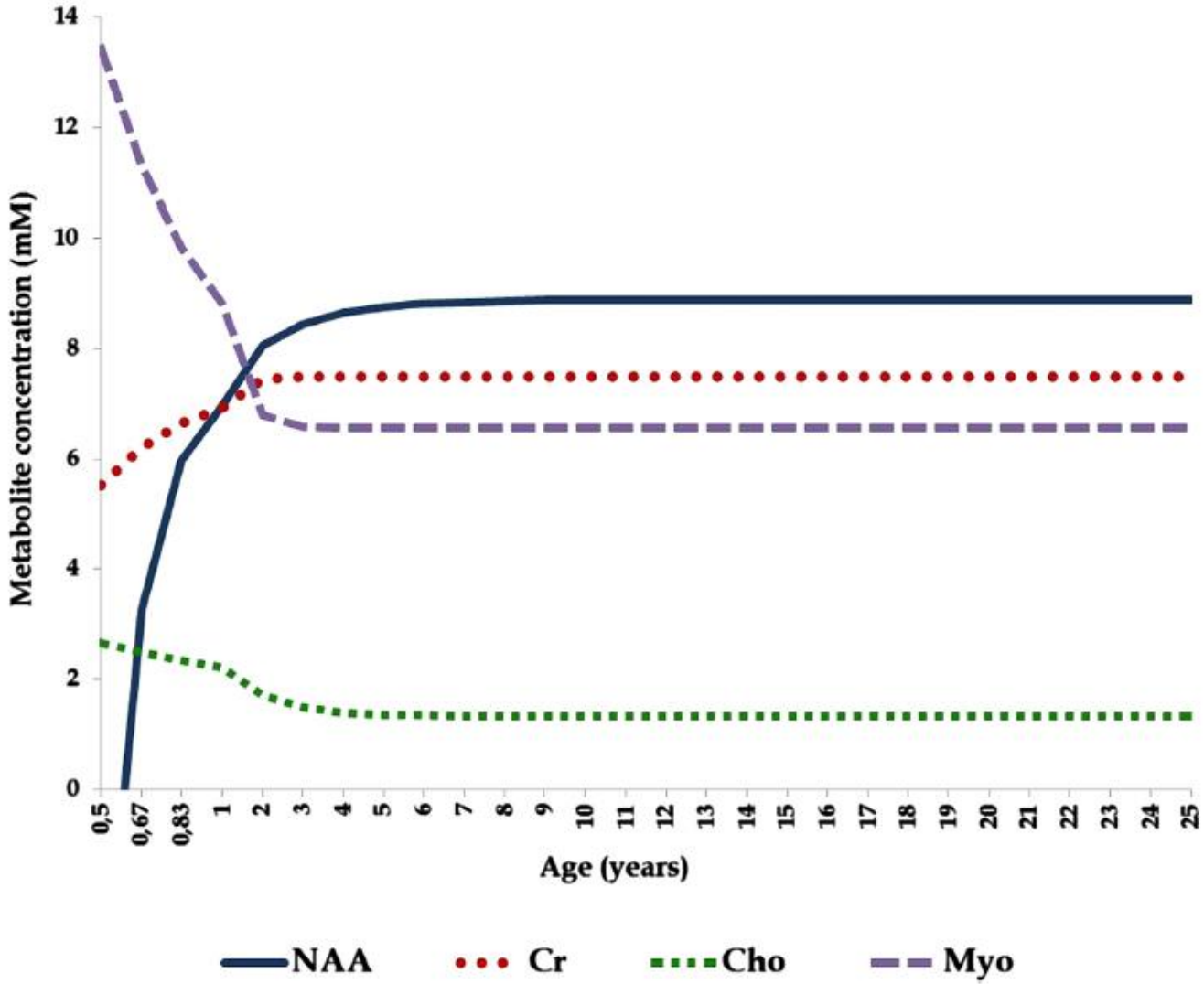
2) **Structural plasticity**: The brain's ability to actually change its physical structure as a result of learning



Infant



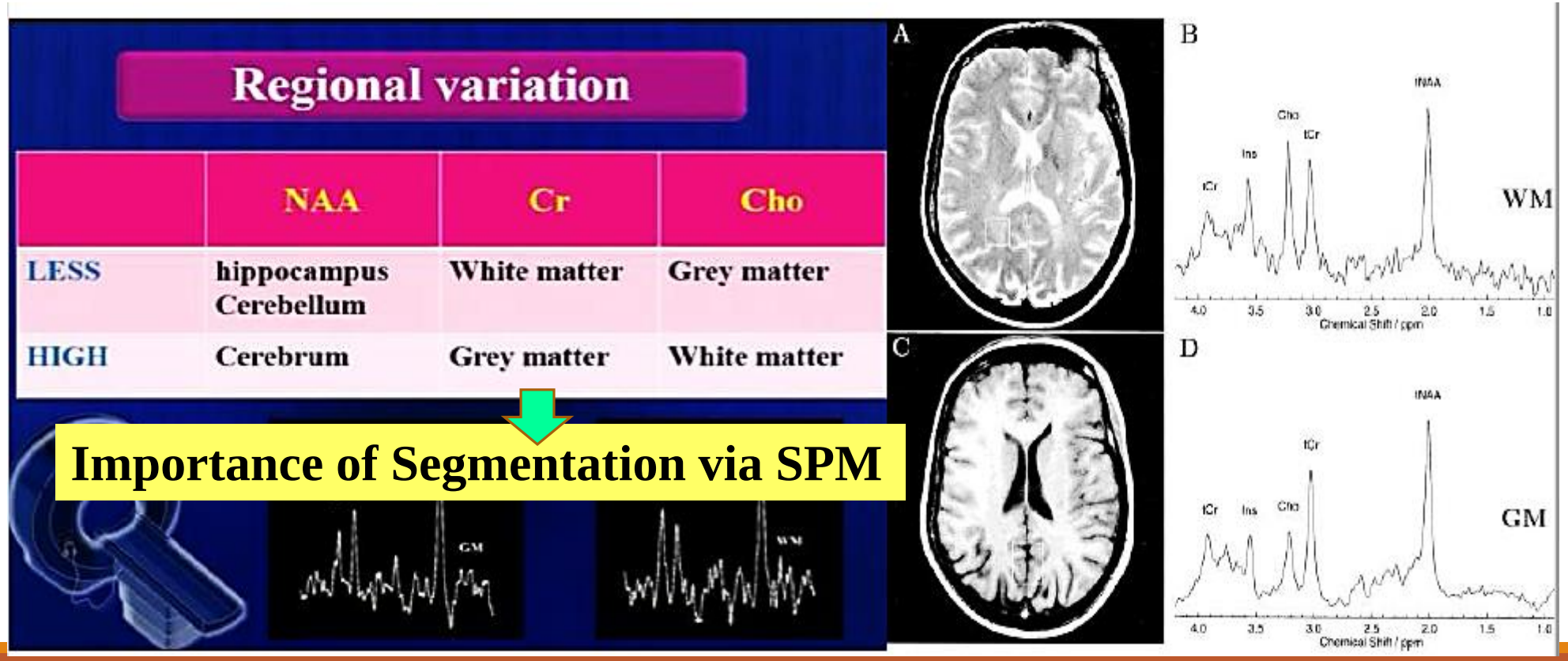
Adult



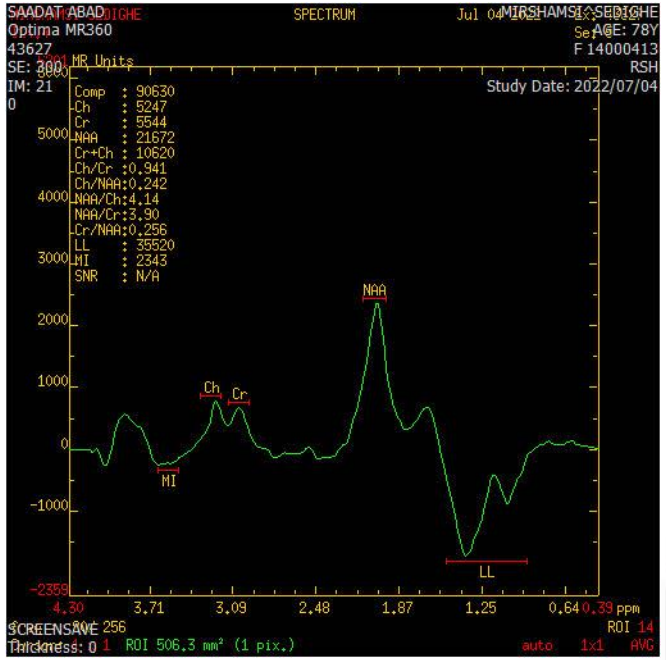
Kries graph in developmental MRS

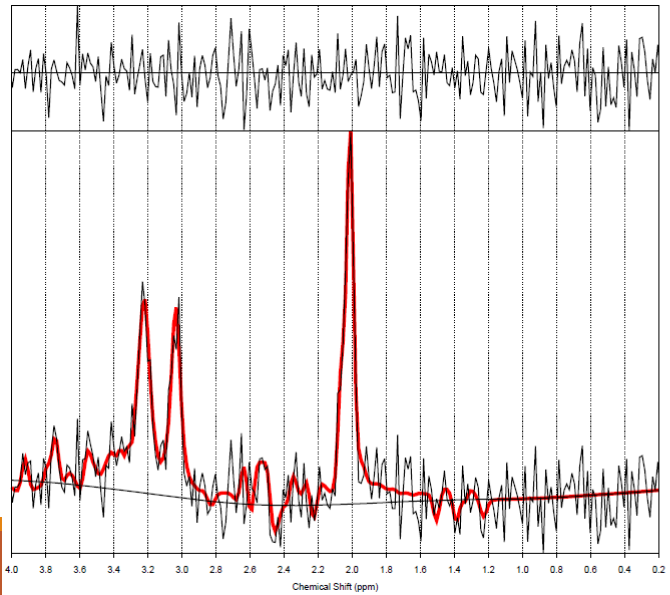
Key points

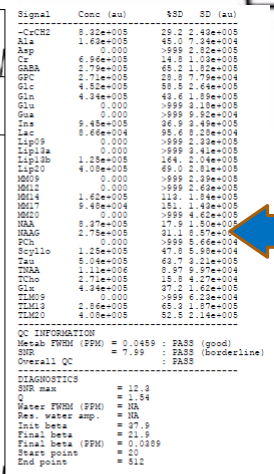
1) High Cho - High tumor cell density & high vascular proliferation.
2) Low Cho and elevation of lipids - Necrosis.
3) Cho higher enhancing rim -may be the faster growing side of the tumor.
4) Vasogenic edema -Normal Cho and slightly decreased NAA.

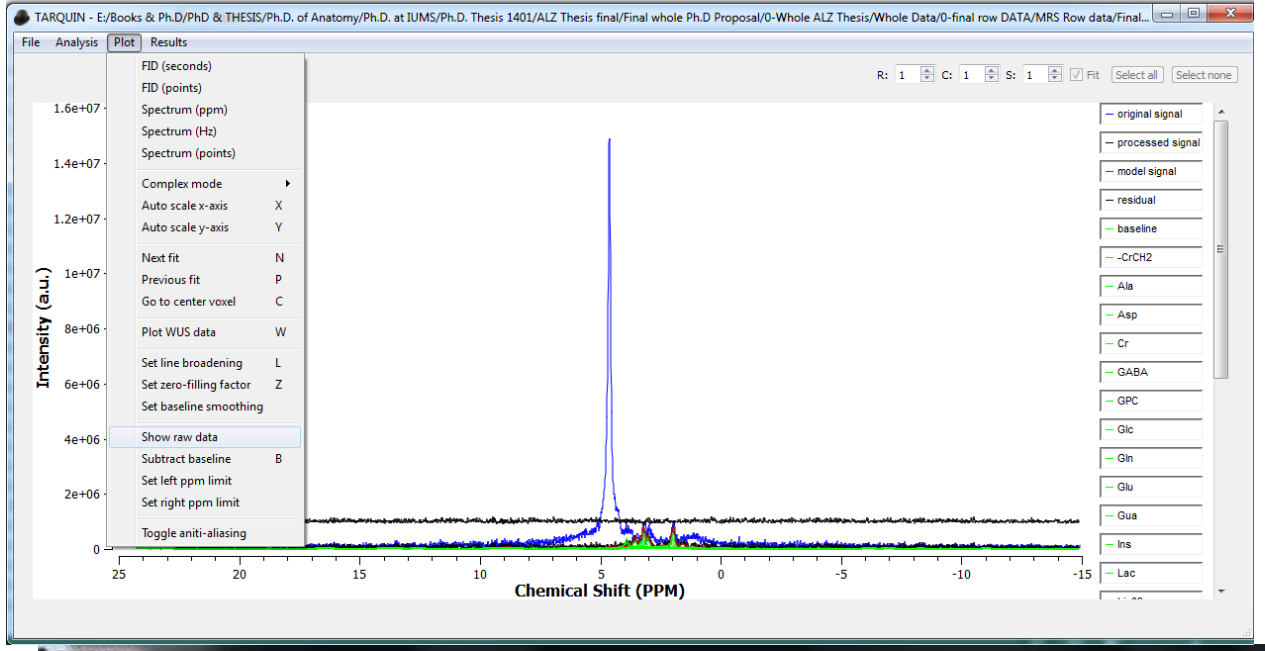


Complete MRS quantification and data analysis





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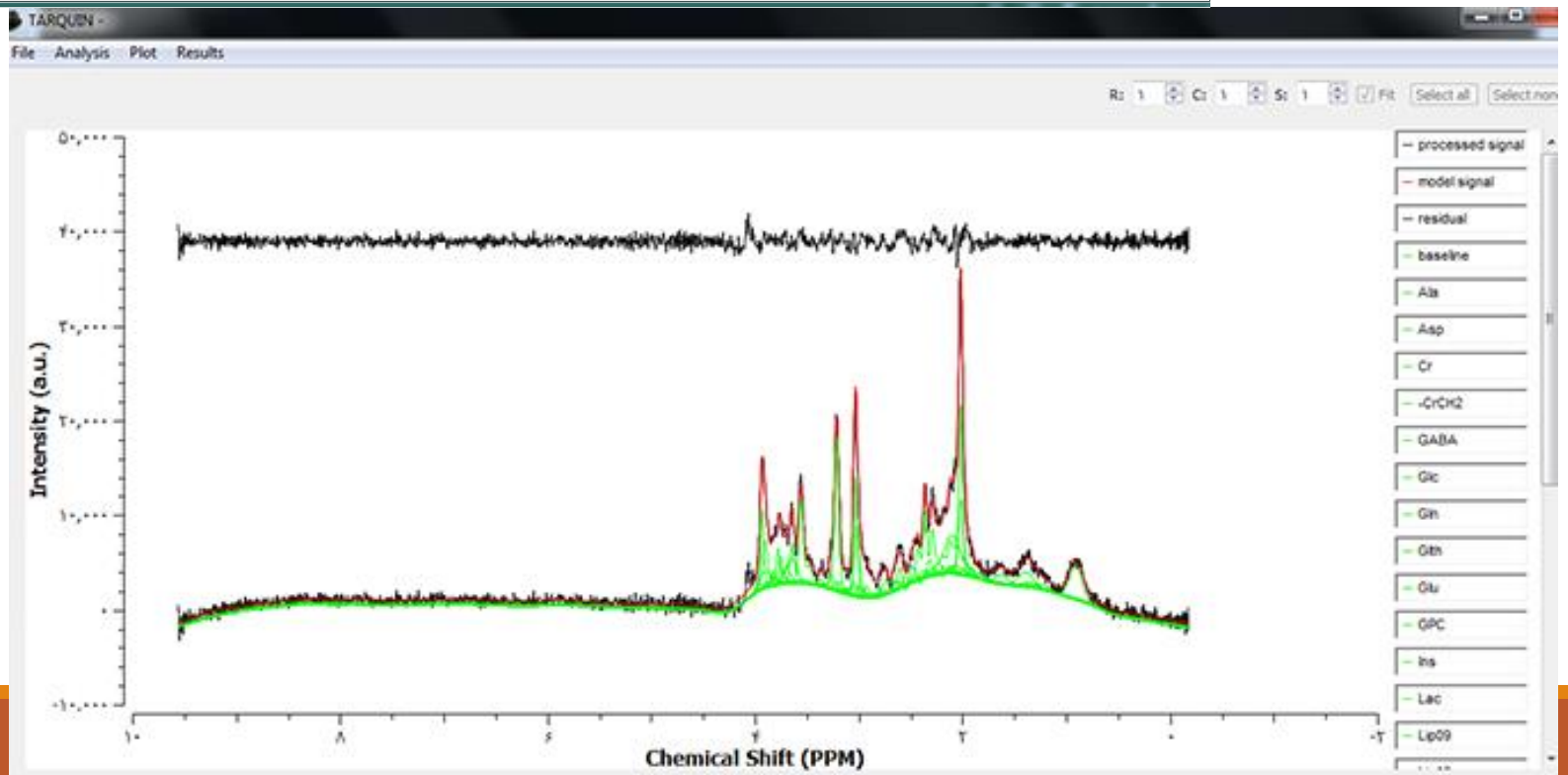
File
Analysis
Plot
Results
FID (seconds)
FID (points)
Spectrum (ppm)
Spectrum (Hz)
Spectrum (points)
Complex mode
Auto scale x-axis X
Auto scale y-axis Y
Next fit N
Previous fit P
Go to center voxel C
Plot WUS data W
Set line broadening L
Set zero-filling factor Z
Set baseline smoothing
Show raw data
Subtract baseline B
Set left ppm limit
Set right ppm limit
Toggle aniti-aliasing
R: 1 C: 1 S: 1 Fit Select all Select none
original signal
processed signal
model signal
residual
baseline
-CrCH2
Ala
Asp
Cr
GABA
GPC
Glc
Gln
Glu
Gua
Ins
Lac
Intensity (a.u.)
Chemical Shift (PPM)


TARQUIN -
File
Analysis
Plot
Results
processed signal
model signal
residual
baseline
Ala
Asp
Cr
-CrCH2
GABA
Glc
Gln
Gth
Glu
GPC
Ins
Lac
Lip09
Intensity (a.u.)
Chemical Shift (PPM)