Magnetic Resonance Spectroscopy of the Human Brain
Motivation

⭐ Role of the Central Nervous System
- results of the improper diagnosis
- precise measurement of the biopsy location
- intraoperative navigation in neurosurgery

⭐ Choice of the diagnostic method
- advantages of the MRI (has much higher detail in the soft tissues, noninvasive and there is no ionizing radiation)
- rapid development of the MRI technique

⭐ Magnetic Resonance Spectroscopy (MRS)
- noninvasive biochemical analysis of the brain
- growing role in diagnosis of the CNS disorder
Contents

1. The physical background of MRI
2. Fundamentals of MR Spectroscopy
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4. Clinical applications of MRS
1946 Felix Bloch and Edward Purcell independently discovered the magnetic resonance phenomenon (Nobel Prize for Physics 1952)

1971 Raymond Damadian showed that the nuclear magnetic relaxation times of tissues and tumors differed, thus motivating scientists to consider magnetic resonance for the detection of disease

1975 Richard Ernst proposed magnetic resonance imaging using phase and frequency encoding, and the Fourier Transform (Nobel Prize in Chemistry 1991)

1977 Raymond Damadian demonstrated MRI called field-focusing nuclear magnetic resonance. In this same year, Peter Mansfield developed the echo-planar imaging (EPI) technique
History in short

- 1980 Edelstein and coworkers demonstrated imaging of the body using Ernst’s technique
- 1987 echo-planar imaging was used to perform real-time movie imaging of a single cardiac cycle
- 1987 Charles Dumoulin was perfecting magnetic resonance angiography (MRA), which allowed imaging of flowing blood without the use of contrast agents
- 1992 functional MRI (fMRI) was developed. This technique allows the mapping of the function of the various regions of the human brain
- 2003 Paul C. Lauterbur Sir Peter Mansfield were awarded the Nobel Prize in Medicine for their discoveries concerning magnetic resonance imaging
The phenomenon of magnetic resonance results from the interaction of the magnetic moment $\mu$ of an atomic nucleus with an external magnetic field. The cause of this magnetic moment is the quantum mechanical angular momentum (spin angular momentum) of all nuclei that are not $(g,g)$ nuclei (even number of protons and neutrons).

spin quantization
(Stern-Gerlach experiment 1922, Stern - Nobel Prize 1943)

\[ J = \hbar \sqrt{I(I + 1)} \]

$J$ - spin angular momentum, $I$ - spin quantum number
$I$ can be 0, integral or half-integral:
- $I$ is zero for elements of even mass number (A) and even atomic number (Z)
- $I$ is integral (nonzero) when A is even and Z is odd
- $I$ is half-integral when A is odd
The physical background

- $I = 0$, NMR inactive; examples $^{12}C$ and $^{16}O$; unfortunately, these nuclei have no magnetic moment.
- $I > 1/2$, quadrupolar nuclei: examples $^{14}N$; these nuclei possess an electric quadrupole moment due to non-spherical nuclear charge distribution (short magnetic state life times, broad line widths, complex spectra).
- $I = 1/2$, spin $1/2$ nuclei: examples $^1H$, $^{13}C$, $^{15}N$, $^{31}P$, $^{19}F$; these are the mainstay nuclei for organic chemistry and biochemistry.

Magnetic moment

$$\mu = \gamma J = \gamma \hbar \sqrt{I(I+1)}$$

$\gamma$ - gyromagnetic ratio.

In the absence of a static, external magnetic field, the $2I + 1$ spin states of a nucleus are energetically equivalent or degenerate.
The external field leads to a splitting of the energy levels. For spin 1/2 nuclei (e.g. protons) two energy levels exist according to a parallel or antiparallel orientation of the magnetic moment with respect to the magnetic field.

\[
\frac{N_{up}}{N_{down}} \approx \exp \left( \frac{\gamma \hbar B_0}{kT} \right)
\]
Transitions between different energy levels occur if the frequency of radiation is equivalent to the energy difference between the two levels. The excited spins emit the absorbed radiation after the pulse. The emitted signal is a superposition of all excited frequencies. Its evolution in time is recorded. The Fourier transformation translates the time data into the frequency domain.

\[ \Delta E = \gamma \hbar B = h\nu \]

\( \nu \) - Larmor frequency:

\[ \nu = \frac{\gamma B}{2\pi} \]

For hydrogen:

\[ \gamma = 42.58 \frac{\text{MHz}}{\text{T}} \]

at \( B = 1.5\text{T} \) \( \nu = 63.87\text{MHz} \)
The physical background

\[ E = -\gamma \hbar m_z B = -\frac{\gamma \hbar B}{2} \]

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\[ \Delta E = \gamma \hbar B = h\nu \]

\[ E = E(m_I) = -\mu_z B = -(\gamma I_z)B = -\gamma \hbar m_z B \]
At equilibrium, the net magnetization vector lies along the direction $\hat{z}$ of the applied magnetic field $B$ and is called the equilibrium magnetization $M_0$.

There is no transverse $M_x$ or $M_y$ magnetization here. It is possible to change the net magnetization by exposing the nuclear spin system to energy of a frequency equal to the energy difference between the spin states. The time constant which describes how $M_z$ returns to its equilibrium value is called the spin lattice relaxation time.

$$M_z = M_0(1 - e^{-t/T_1})$$

$T_1$ corresponds to the time required for the system to return to 63% of its equilibrium value after it has been exposed to a 90° pulse.
The physical background of MRI
Fundamentals of MR Spectroscopy
The main brain metabolites
Clinical applications of MRS

\( T_2 \) weighted image

The time constant which describes the return to equilibrium of the transverse magnetization, \( M_{xy} \), is called the spin-spin relaxation time.

\[ M_{xy} = M_{xy0} e^{-t/T_2} \]

\( T_2 \) corresponds to the time required for the system to lose 63% of its equilibrium of the transverse magnetization.

Different scan sequences show up differences in these relaxation times generating what are referred to as \( T_1 \), \( T_2 \) or proton density \( \rho \) (the concentration of protons) weighted images.
MRI sequences

TR >> TE

- T1:
  short TR short TE

- T2:
  long TR long TE

- ρ:
  long TR short TE

\[ S = k \rho \left[ 1 - \exp\left(\frac{-TR}{T1}\right)\right] \exp\left(\frac{-TE}{T2}\right) \]
### T1 and T2 for different tissues

<table>
<thead>
<tr>
<th>T1 [s]</th>
<th>T2 [ms]</th>
<th>ρ [mM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>0.8-20</td>
<td>110-2000</td>
</tr>
<tr>
<td>WM</td>
<td>0.76-1.08</td>
<td>61-100</td>
</tr>
<tr>
<td>GM</td>
<td>1.09-2.15</td>
<td>61-109</td>
</tr>
<tr>
<td>Lip</td>
<td>0.2-0.75</td>
<td>53-94</td>
</tr>
<tr>
<td>Gadolin</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Different T1, T2, ρ give contrast in MRI.
T1 Weighted Imaging

Optimal TR = \frac{\ln \left( \frac{T_{1b}}{T_{1a}} \right) T_{1a} T_{1b}}{T_{1a} - T_{1b}}

Contrast

Optimal TR

white matter

grey matter

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**T1 Weighted Image**

<table>
<thead>
<tr>
<th></th>
<th>$T_1$</th>
<th>$R_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>white matter</td>
<td>0.7</td>
<td>1.43</td>
</tr>
<tr>
<td>grey matter</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CSF</td>
<td>4</td>
<td>0.25</td>
</tr>
</tbody>
</table>

SPGR, TR=14ms, TE=5ms, flip=20°
T1 weighted images

Without contrast medium (CM)

After CM injection
T2 Weighted Imaging

\[
\text{Optimum TE} = \frac{\ln\left(\frac{T_{2a}}{T_{2b}}\right) T_{2a} T_{2b}}{T_{2a} - T_{2b}}
\]
T2 Weighted Image

<table>
<thead>
<tr>
<th></th>
<th>T2/ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>500</td>
</tr>
<tr>
<td>grey matter</td>
<td>80–90</td>
</tr>
<tr>
<td>white matter</td>
<td>70–80</td>
</tr>
</tbody>
</table>

SE, TR=4000ms, TE=100ms
T2 weighted images

TIRM

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MRS of the Human Brain
When an atom is placed in a magnetic field, its electrons circulate about the direction of the applied magnetic field. This circulation causes a small magnetic field at the nucleus which opposes the externally applied field. The magnetic field at the nucleus (the effective field) is therefore generally less than the applied field by a fraction $\sigma$.

$$B_{\text{eff}} = B(1 - \sigma)$$

The electron density around each nucleus in a molecule varies according to the types of nuclei and bonds in the molecule. The opposing field and therefore the effective field at each nucleus will vary. This is called the chemical shift phenomenon.
Chemical shift

The chemical shift of a nucleus is the difference between the resonance frequency of the nucleus and a standard, relative to the standard. This quantity is reported in ppm:

$$\delta = \frac{\nu - \nu_{\text{ref}}}{\nu_{\text{ref}}} \times 10^6$$

In NMR spectroscopy, this standard is often tetramethylsilane (TMS). In the body there is no TMS, but there are two primary hydrogen containing substances, water and fat. The chemical shift difference between these two types of hydrogens is approximately 3.5 ppm.
Protons on adjacent carbons can influence the local magnetic field, leading to spin-spin splitting or j-j coupling. For example, in ethanol ($CH_3 - CH_2 - OH$), the two protons in the methylene can either both point up (25%), both point down (25%), or one up and one down (50%). This splits the adjacent methyl peak into three smaller peaks.
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Spectrum

A spectrum of the metabolites is plotted on a two dimensional graph. The horizontal axis represents the frequencies (chemical shifts) and the vertical axis represents the concentration of the metabolites. The area under a peak is contributed by the concentration of that metabolites.

$^1H$ spectrum of normal major brain metabolites. NAA: N-acetylaspartate, Glx: Glutamine and glutamate, Cr: Creatine, Cho: Choline, mI: Myo-Inositol
MRS Anatomy

- Head $^1$H, $^{31}$P
- Prostate $^1$H
- Liver $^1$H, $^{31}$P
- Breast $^1$H
- Heart $^{31}$P, $^1$H
- Muscles $^{31}$P

MRS Brain = $^1$H
MRI – enables anatomical and structural diagnosis

PATHOLOGY

MRS – provides metabolic information
• **MRI**
  - voxel volume: 1 – 5 mm\(^3\)
  - signal from water and fat
  - very large concentration

• **MRS**
  - voxel volume 1 – 8 cm\(^3\)
  - signal from metabolites
  - very small concentration
MRS TECHNIQUES

- **SVS** single voxel spectroscopy - a spectrum is obtained from a single sample selected volume. It has a better signal-to-noise ratio and is a more robust technique.

- **CSI** chemical shift imaging - in a localized slice of the brain tissue, allows the mapping of metabolic distribution. This can be helpful for differential diagnosis of tumors infiltrating surrounding tissue. Multivoxel spectroscopy is also used to assess response to therapy. A much larger area can be covered, eliminating the sampling error.

  - **spectroscopy 2D and 3D**
Main peaks for short and long TE

**TE 20-30ms**
- Alanine (Ala)
- Glutamate + Glutamine (Glx)
- Myo-inositol (Ins)
- Cho, Cr, NAA
- Lac, Lip

**TE 135-270ms**
- Choline (Cho)
- Creatine (Cr)
- N-acetylaspartate (NAA)
- Lactate (Lac)
- Lipids (Lip)
**NAA: N-acetylaspartate**

- **Amino acid**
- **2.0 ppm**
- **Singlet COCH$_3$**

**Specific marker of viable neurons, axons and dendrites**

- Decreased NAA – neuronal lost or dysfunction
- Tumors: gliomas, meningiomas, neurocytoma, lymphoma, metastasis
- Ischemia, inflammation, infection, stroke
- Gliomatosis
- Dementia
- Necrosis
- Trauma
Cr: Creatine

3.0 and 3.9 ppm
Singlets CH$_3$CH$_2$

Related to energy storage. Marker of energetic status of cells.
(Other metabolites are frequently expressed as ration to Cr: NAA/Cr, Cho/Cr)

Decreased Cr
Tumors, esp. Metastatic from lung, breast, prostate, kidney, lymphoma
Hypoxia, stroke
**Cho: Choline**

3.2 ppm
Singlet NCH$_3$

**Marker of cellular membrane turn-over**

**(Cell membrane component)**

- **Increased Cho**
  - Tumors (turn-over processes), marker of tumor infiltration
  - Inflammation, chronic hypoxia, demyelination, MS

- **Decreased Cho**
  - Stroke, HIV, liver disease
  - Necrosis

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**Ins: Myo-inositol**

- **Pentose-sugar**
  - 3.6 ppm
  - Dublet

- **Glial cell marker**
  - (astrocyte component, marker for intracellular osmotic integrity)

- **Increased Ins**
  - Neonates, Alzheimer's disease, Down syndrome, diabetes, LGG

- **Decreased Ins**
  - Chronic hepatic encephalopathy, stroke, HGG
Glx: Glutamate + Glutamine

Amino acids
2.1 - 2.4 ppm

Neurotransmitters
(products of Krebs cycle activity and mitochondrial redox systems)

- Increased Glx
  - Hepatic encephalopathy, severe hypoxia
  - acute MS
- Decreased Glx
  - Lymphoma
  - Alzheimer's disease

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Lac: Lactate

1.3 ppm
Dublet
inverted TE 135

End product of anaerobic metabolism – not seen in normal brain

Present Lac
Ischemia, hypoxia
Inborn errors of metabolism
Tumors (all grade)
Abscesses, inflammation
Cysts, MS
Lip: Lipids

0.9 and 1.3 ppm multiplets

Marker severe tissue damage with liberation of membrane lipids not seen in healthy brain

Present Lip
HGG Tumors
Abscesses, acute inflammation, acute stroke
Necrosis (also post-radiative)
Other metabolites
(amino acids)

Ala: Alanine
1.5 ppm
Inverted doublet
TE 135
Meningiomas
Abscesses

Ace
1.9 ppm
Suc
2.4 ppm
Abscesses
TE 30ms. Normal MRS from WM of the frontal lobe. More metabolites are visible at short TE.

TE 135ms. The normal relative values of the metabolite ratios: $\text{NAA}/\text{Cr} \approx 2.0$, $\text{Cho}/\text{Cr} \approx 1.0$, $\text{Cho}/\text{NAA} \approx 0.5$. 
Hunter’s angle - first insight into the spectrum result

A. Lin, B.D. Ross, K. Harris and W. Wong, NeuroRx. 2005 April; 2(2)
WCM Opole

$^1$H MRS

$\nu \approx 64\text{MHz}$

Methods: SVS, CSI

TE 30 ms, 135 ms

Metabolites:

NAA Cr Cho

Ins/Gly Glx Lip Lac

Ace Suc AA (Ala)
In comparison to the adults, newborns have much less NAA and increased choline and Ins. Prominent Lactate peak is visible. Progression to the adult pattern follows myelination.
MRS: localization dependence

Cerebellum

Frontal lobe

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MRS of the Human Brain
MRS: structure dependence

NAWM - more Cho

NAGM - more Cr
The resonance intensity of metabolites is quantified with respect to creatine (Cr).
MRS CSI results

metabolite map: NAA

metabolites ratio: NAA/Cr
MRS CSI results

spectral map

added spectrum
MR: artefacts

- artefacts from the metal fragment
- lipid contaminations

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MRS is useful in differential diagnosis via monitoring biochemical changes in tumors, stroke, epilepsy, metabolic disorders, infections and neurodegenerative diseases.

Different disease states have different MRS signature.

- **Low grade gliomas** have elevated choline and decreased creatine and NAA (due to displacement of normal brain).
- A similar spectrum is found in **demyelination**.
- **High grade tumors** typically have more elevation of choline and elevation of lipid and lactate as well.
- **Radiation necrosis** has elevated lipids but no elevation of choline.
- **Abscesses** also have elevated lipid as well as elevated amino acids - but no elevated choline.
In addition to being able to distinguish lesions that appear similar on MRI (like necrotic glioma, abscess, and radiation necrosis), MRS can also show abnormalities where nothing is seen on MRI. Infiltrating gliomas, for example, demonstrate elevated choline beyond the region of contrast enhancement. Using this sign, high grade glioma can be distinguished from metastases or abscesses, which have normal choline outside the region of enhancement.

The MR spectra require interpretation and always should be correlated with the MRI results before making a final reliable radiological diagnosis.
Differentiation

- low grade astrocytoma
- anaplastic astrocytoma
- glioblastoma
- metastasis
- meningioma

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MRS of the Human Brain
TE 136ms (C. Majósa et al., AJNR 2004 25: 1696)
GBM: the most common and aggressive brain tumor

CSI spectra from an area of malignant tumor, situated in the right brain hemisphere (l) and from the contralateral side as a control (r). Elevated peak Cho, decreased NAA and Cr and inverted peak of Lac are visible in tumor in comparison to healthy tissue.
GBM: a median survival time of approx. 14 months

Spectroscopic curve demonstrating necrosis in GBM tumor (l). Note dominating lipid peak, strongly reduced NAA and Cr and slightly increased Cho in comparison to healthy tissue.
Metastasis: dominated lipid (Lip) peak and lack of NAA
GBM. Infiltrating gliomas demonstrate elevated choline beyond the region of contrast enhancement: Cho/NAA > 1.
CSI in differentiation of tumors

Metastases have normal choline outside the region of enhancement
Distinguish between LGG and HGG

Dominating lipid peak in HGG in comparison to LGG.
Monitoring of tumor progression

MRS of the Human Brain

June 2011

MRI LGG
Monitoring of tumor progression

October 2011
No evident progression is seen in the follow-up MRS examinations.

NAA/Cr: 1.05 0.89 0.53
Cho/Cr: 1.98 2.56 1.41
Cho/NAA 1.88 2.90 2.65

May 2012
Helpful criterion is very high ratio Cho/NAA and not too significant Lip/Lac peaks.
MRS can be also helpful in diagnosis of atypical cases of meningioma. A pronounced rise in Cho level and absence or very strong reduction of NAA is observed. Presence of inverted alanine (Ala) peak at 1.5ppm can confirm the diagnosis.
In acute MS Cho is elevated, NAA reduced and Lac is present.
CSI demonstrates elevated Cho/Cr and Cho/NAA pattern of MS.
Hypoxic encephalopathy

MRS result shows elevated level Glx at 3.6-3.8 ppm. Most often, the underlying cause of HE remain unknown.
Physical background

• (Nuclear) Magnetic Resonance (N)MR discovered in 1946
  \[ \Delta E = h\nu = \hbar \gamma B \]

• Chemical shift
  – Screening (covalent electron structure surrounding the nucleus shields the magnetic field) causes shift in resonance frequency
  – J-J coupling causes splitting of the spectral lines

Each metabolite appears at a specific ppm value

The concentration of the metabolites is proportional to the area under the peak
Magnetic Resonance in medicine

- MRI in vivo 1980
- MRS in vivo 1990

Noninvasive method to detect the metabolic and biochemical profile of tissues

- MRS of brain = MRS $^1$H
- Techniques:
  - SVS (single voxel)
  - CSI (chemical shift imaging)

Metabolites (NAA, Cr, Cho, Ins, Glx,...)
MRS in brain examinations

- **Tumors**
  - Differentiating neoplasms from non-neoplasms
  - Differentiation of primary from secondary neoplasms
  - Intraoperative navigation in neurosurgery
  - Determination of the biopsy location
  - Monitoring responses to the treatment

- **Early diagnosis**
  - Inflammation, infection (Ala, Ace, Suc)
  - Ischemic lesions (Lac, NAA, Cho)
  - Alzheimer's disease (Ins), MS (Lac, NAA, Cho)
  - Hepatic encephalopathy (Glx, Ins, Cho)
Conclusions

MAGNETIC RESONANCE SPECTROSCOPY

A significant non-invasive diagnostic tool in the Central Nervous System diseases

MRI without MRS cannot be completely reliable

MRS without MRI cannot be uniquely interpreted
Thank you for your attention!