Magnetic Resonance Spectroscopy

- A measure of brain chemistry
- $^1$H (proton), $^{23}$Na, $^{31}$P
- Serially monitor biochemical changes: tumors, stroke, epilepsy, metabolic disorders, inflammation/infection, neurodegenerative disease
- Correlate with anatomic MRI for diagnosis
- Recognized by AMA, Medicare, Medicaid
Electromagnetic Spectrum

Radio waves | Infrared | Visible light | Ultraviolet | X-rays | Gamma rays | Cosmic rays

10^2 10^6 10^{10} 10^{14} 10^{16} 10^{18} 10^{20} 10^{22}

Frequency (Hertz)

NMR

Shortwave AM Radio | UHF/VHF/FM | Radar | Microwave

10^2 10^4 10^6 10^8 10^{10} 10^{12}

Frequency (Hertz)
NMR Spectrum

Proton Resonance Frequencies at Different Field Strengths

<table>
<thead>
<tr>
<th>Frequency (MHz)</th>
<th>0.3T</th>
<th>1.0T</th>
<th>1.5T</th>
<th>3.0T</th>
<th>4.0T</th>
<th>7.0T</th>
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<td></td>
<td>10</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>300</td>
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Nuclear Resonance Frequencies at 1.5T

<table>
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<tr>
<th>Frequency (MHz)</th>
<th>K</th>
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<th>O</th>
<th>C</th>
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<th>Li</th>
<th>P</th>
<th>F</th>
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<tr>
<td></td>
<td>1</td>
<td>25</td>
<td>50</td>
<td>75</td>
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Basic Principles of MRS

- Imaging: Use all the signal from fat to water to make the image
- Fat suppression: Put voxel inside brain
- Water suppression: CHESS or IR
- STEAM or PRESS pulse sequence acquisition
- Fourier transform to separate signal into individual frequencies
- Chemical shift: Electron cloud affects the local magnetic field experienced by the protons
- Convert hertz to ppm, assign NAA as the reference at 2.0 ppm, & reverse the order
Proton MR Spectrum

Effect of Field Strength

1.5T

0.75T

Frequency (Hertz)

ppm

Hertz

ppm

64Hz
Normal MR Spectrum

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Status</th>
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<tr>
<td>Lipid</td>
<td>Lying</td>
</tr>
<tr>
<td>Lactate</td>
<td>Lazy</td>
</tr>
<tr>
<td>NAA</td>
<td>No</td>
</tr>
<tr>
<td>Glutamates</td>
<td>Good</td>
</tr>
<tr>
<td>Creatine</td>
<td>Crooks</td>
</tr>
<tr>
<td>Choline</td>
<td>Cheat</td>
</tr>
<tr>
<td>Myo-Inositol</td>
<td>My Insurance</td>
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</table>

Brian Ross, Huntington Medical Research Institute
Observable Proton Metabolites

<table>
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<tr>
<th>ppm</th>
<th>Metabolite</th>
<th>Properties</th>
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<tr>
<td>0.9-1.4</td>
<td>Lipids</td>
<td>Products of brain destruction</td>
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<tr>
<td>1.3</td>
<td>Lactate</td>
<td>Product of anaerobic glycolysis</td>
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<tr>
<td>2.0</td>
<td>NAA</td>
<td>Neuronal marker</td>
</tr>
<tr>
<td>2.0-2.4</td>
<td>Glutamine/Glx</td>
<td>Neurotransmitters</td>
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<tr>
<td>3.0</td>
<td>Creatine</td>
<td>Energy metabolism</td>
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<tr>
<td>3.2</td>
<td>Choline</td>
<td>Cell membrane marker</td>
</tr>
<tr>
<td>3.5</td>
<td>myo-inositol</td>
<td>Glial cell marker, osmolyte hormone receptor mechanisms</td>
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<tr>
<td>1.2</td>
<td>Ethanol</td>
<td>Triplet</td>
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<tr>
<td>1.48</td>
<td>Alanine</td>
<td>Present in meningiomas</td>
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<tr>
<td>3.4&amp;3.8</td>
<td>Glucose</td>
<td>Increased in diabetes</td>
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<tr>
<td>3.8</td>
<td>Mannitol</td>
<td>Rx for increased ICP</td>
</tr>
</tbody>
</table>
Basic Principles (MRS)

- **STEAM** (STimulated Echo Acquisition Mode)
  - 90° refocusing pulse (like GRE)
  - shorter echo times
  - decreased signal-to-noise

- **PRESS** (Point REsolved SpectroScopy)
  - 180° refocusing pulse (spin-echo)

- **CSI** (Chemical Shift Imaging)
  - multi-voxel MRS

- **SI** (Spectroscopic Imaging)
  - overlay of MR spectrum on MR image
MR Spectroscopy
Effect of Echo Time

- Similar to MRI in that different echo times change the information obtained
- Short TE (30 msec): metabolites with short and long T2 relaxation times observed
- Long TE (270 msec): only metabolites with long T2 relaxation times observed
  - lose peaks from lipid, Glx & mI
- TE 144 msec: inverts lactate @ 1.3 ppm
Effect of Echo Time

Grade 2 Fibrillary Astrocytoma

Lipids, glutamates & myo-inositol have short T2 and drop out at longer echoes
- **Single voxel, short TE**
  - Single large voxel
  - For initial diagnosis

- **Multi-voxel, long TE**
  - Multiple small voxels
  - Assess extent of gliomas
  - Followup of gliomas
Observable Metabolites
What’s missing?

- DNA, RNA, most proteins, enzymes, phospholipids
- Where are the Neurotransmitters?? Glutamate/GABA – Yes, but why not acetylcholine, dopamine, serotonin?
- Either concentration too low, or molecules immobile & invisible to MRS
Normal MR Spectrum

Hunter’s angle
## Metabolite Ratios

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<th>Normal</th>
<th>Abnormal</th>
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<td>TE 30 msec</td>
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<tr>
<td>NAA/Cr</td>
<td>2.0</td>
<td>&lt; 1.5</td>
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<tr>
<td>NAA/Cho</td>
<td>1.6</td>
<td>&lt; 1.2</td>
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<tr>
<td>Cho/Cr</td>
<td>1.2</td>
<td>&gt; 1.5</td>
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<tr>
<td>TE 144 msec</td>
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<tr>
<td>NAA/Cho</td>
<td>1.5</td>
<td>&lt; 1.0</td>
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</tbody>
</table>
MRS & Perfusion of Brain Tumors

- Tumor histology
- Degree of malignancy
- Delineate tumor beyond T2 and enhancing margins
- Guide biopsy
- Follow response to therapy
MRS of Brain Tumors

- NAA decreased in tumors that displace or destroy neurons
- Cr relatively constant, but decreased in malignant lesions
- Cho increased in tumors (hypercellularity)
- Lipids seen in necrotic tumors - indicative of high malignancy
- Lactate noted in highly cellular malignant tumors that outgrow blood supply
- Myo-inositol elevated in low-grade gliomas
History: 27 y/o male with a single seizure
History: 68 y/o man with episodes of severe parietal headaches

TE 35 msec
Dx: Grade 2 fibrillary astrocytoma

3 years later
History: 39 y/o woman with fluctuating visual deficits for several weeks
Dx: Highly anaplastic astrocytoma

TE 35 msec
MR Spectra Changes with Tumor Grade

- As malignancy increases:
  - NAA decreases
  - Cr decreases
  - Cho increases
  - Lactate increases
  - Lipids may increase
History: 34 y/o man with headache and mental status changes
Dx: GBM

TE 35 msec
History: 25 y/o woman with a well-controlled seizure disorder & 3-week history of nausea & headaches
Dx: Gliomatosis cerebri

5 months later
Effects of Radiation Therapy
MR Spectroscopy

- Low NAA
- Low Cr
- Low Cho
- High lipids
- High lactate

High-grade Astrocytoma

6 Years s/p Radiation

Pre-treatment

Neuroimaging Clinics, November, 1998
History: 53 y/o man 9 weeks s/p XRT & chemo for a GBM
4 months later
Dx: Recurrent GBM
Other Brain Tumors

- **Metastases**
  - ↑ choline, ↓ NAA, ↑ lipids

- **Lymphoma**
  - ↑↑ choline, ↓ NAA, ↑ lipids

- **Meningioma**
  - ↑ choline, no NAA, ↓↓ creatine
  - ↑ alanine (1.48 ppm)
  - ↑ glutamates (β and γ at 2.0-2.4 ppm; α at 3.8 ppm)

- **PNET**
  - Very high choline
History: 31 y/o woman with nausea, vomiting, and altered mental status
Dx: Metastatic Adeno CA Lung

TE 30 ms

TE 144 ms

Dx:
History: 41 y/o man with a right hemiparesis & speech difficulty
TE 35 msec
Dx: Primary CNS Lymphoma
Three volumes
3100 pages
4700 images

Full color

www.clinicalmri.com

Chapter 43 - Perfusion and MRS for Brain Tumor Diagnosis by Meng Law, NYU
History: 56 y/o man with new onset of seizures
Dx: Meningioma

- $\alpha$ Glx
- $\beta$ & $\gamma$ Glx
- Alanine
- Lactate

TE 35 msec
History: 42 y/o man with diabetes & a brain mass
Dx: Tumefactive MS

TE 35 msec
History: 53 y/o woman with 4 days of headache, fatigue, ataxia and poor memory
Pathophysiology

- \( \downarrow \text{O}_2 \downarrow \) oxidative phosphorylation \( \downarrow \) ATP
- \( \downarrow \) PCr \( \rightarrow \) anaerobic glycolysis \( \uparrow \) lactate

Ischemia - disrupt cell electrical activity
Infarction - compromise cell integrity
Cell death depends on vascular supply (collateral flow) & cell type (neurons > glia)
Cellular Energy Production

glucose → pyruvate → Acetyl CoA

PFK

lactate

H₂O, CO₂ → NADH → CoA

O₂ → ADP → MITOCHONDRIA

oxidative phosphorylation → ATP
History: 4 day old boy with low Apgars
Dx: HIE

TE 35 msec

TE 144 msec

Dx:
Newborn with low APGAR scores
T2W

TE 35 msec
Dx: Severe HIE
The Developing Brain
A Changing Spectrum

- Less NAA
- Increased choline and myo-inositol
- Progression to adult pattern follows myelination

Danielsen & Ross, MRS Diagnosis of Neurological Diseases, Marcel Dekker, Inc. 1999
History: Newborn with high pitched cry after difficult delivery
Dx:

TE 35 msec
History: 24 week fetus with intracranial fluid on ultrasound.

Dx: Normal fetal MRS – mega cisterna magna.
MRS of Trauma

- Diffuse axonal shear injury
- Outcome correlates with NAA/Cr ratio
- Any lactate or lipid = worse prognosis

Danielsen & Ross, MRS Diagnosis of Neurological Diseases, Marcel Dekker, Inc. 1999
History: 68 y/o woman with chronic MS
TE 35 msec
Dx: Gliosis - brain scar

TE 35 msec
Inflammatory/Infectious Brain Disorders (MRS)

- Pyogenic abscess/cysticercosis/hydatid cyst
  Resonances from lactate, amino acids\(_{(0.9\text{ppm})}\),
  alanine\(_{(1.5\text{ppm})}\), acetate\(_{(1.92\text{ppm})}\) & succinate\(_{(2.4\text{ppm})}\)
  No NAA peak
  

- Tuberculoma: resonance from lipid due to caseous material
  
Pyogenic Brain Abscess

AJNR 16:1593, 1995
Pyogenic Brain Abscess

Courtesy of ED Gotsis, PhD, Euromedica, Athens, Greece
History: 87 y/o woman on treatment for abdominal lymphoma
Dx: Abscess (Nocardia & Gram + rods)

{Page 2}
History: 38 y/o HIV$^+$ male with headache & weakness
Dx: Toxoplasmosis

TE 35 msec

[Image of an MRI scan with regions of interest labeled 1 and 2]
History: 67 y/o woman with progressively altered mental status over several days
Dx: Probable ADEM

Bronchitis 3 weeks earlier

TE 35 msec

TE 144 msec
Pediatric Metabolic Brain Disorders (MRS)

- **Canavan’s disease**
  - Markedly increased NAA

- **Leigh’s, MERRF, MELAS**
  - Mitochondrial disorders
  - Markedly increased lactate
  - Ketones at 2.2

- **Peroxisomal disorders**
  - Increased sI @ 3.35 (syllo-inositol)
Canavan’s Disease

TE = 30

TE = 270

Danielsen & Ross, MRS Diagnosis of Neurological Diseases, Marcel Dekker, Inc. 1999
History: 7 month old boy with marked developmental delay
Dx: Leigh's disease with metabolic acidosis

Ketones

Lactate

TE 35 msec
History: 41 y/o diabetic with headache, lethargy & inappropriate behavior
Dx: Streptococcal abscess & diabetic ketoacidosis (venous pH = 7.28)

Ketones (2.2 ppm)

TE 35 msec
Hepatic Encephalopathy

- Missing *myo*-inositol
- Reduced choline
- Increased glutamine

Danielsen & Ross, MRS Diagnosis of Neurological Diseases, Marcel Dekker, Inc. 1999
History: 62 y/o woman with hepatitis C, chronic alcoholism and increasing dementia following liver transplantation
Dx: Marchiafava Bignami disease

TE 35 msec
Human Dementia (MRS)

- Alzheimer's disease: reduced NAA, elevated myo-Inositol
- Disease theories:
  1. β-Amyloid theory
  2. Cholinergic hypothesis
  3. Apolipoprotein E theory
  4. Inositol hypothesis
MRS in Dementia

Normal patient

Alzheimer disease

Danielsen & Ross, MRS Diagnosis of Neurological Diseases, Marcel Dekker, Inc. 1999
## BRAIN PROTON MRS PATTERNS

<table>
<thead>
<tr>
<th>DISEASES</th>
<th>myo-inositol ml (3.56)</th>
<th>Choline Cho (3.2)</th>
<th>Creatine Cr (3.0)</th>
<th>Glutamate Glx (2-2.5,3.8)</th>
<th>NAA 2.0</th>
<th>Lipid 0.9 &amp; 1.6</th>
<th>Lactate 1.33</th>
<th>Comments</th>
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<td>Gliomas</td>
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<td>NC</td>
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<td>↓</td>
<td>↑</td>
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<td>↑ if low grade</td>
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<td>0</td>
<td>↑</td>
<td>↑</td>
<td>↑ Alanine @ 1.48</td>
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<td>Acetate (1.9), Alanine (1.48) Cytosolic acid (0.9), Succinate (1.4)</td>
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<td>DISEASES</td>
<td>myo-inositol ml (3.56)</td>
<td>Choline Cho (3.2)</td>
<td>Creatine Cr (3.0)</td>
<td>Glutamate Glx (2-2.5)</td>
<td>NAA 2.0</td>
<td>Lipid 0.9 &amp; 1.6</td>
<td>Lactate 1.33</td>
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↑ Glucose (3.4), Acetone (2.2)
Pseudo increases {↑} due to decreased creatine