Quantitative MRI and MR spectroscopy of Multiple Sclerosis, Alzheimer’s Disease, Epilepsy and Cancer Microimaging Techniques

Rakesh Sharma, Ph.D
Center of Interdisciplinary Magnetic Applied Research (CIMAR),
National High Magnetic Field Laboratory,
Florida State University,
Tallahassee, FL 32310
Imaging Combines Molecular Information with Anatomy

Visualization of Biological Processes In Vivo: Imaging Signal

- CT: Dynamic, Perfusion
- US: Dynamic, Flow, Perfusion
- MRI, MRS: Dynamic, Flow, Perfusion, Diffusion, Molecules
- NM/PET/SPECT: Perfusion, Molecules
- Fluorescence-Optical: Molecules
- MR-PET: Morphology, Physiology, Metabolism, Molecules

- $10^6 - 10^8$ molecules/cell
- $10^5 - 10^8$ molecules/cell
- 1 molecule/cell
- Several molecules/cell
MRI Imaging: Concepts

- Proton spins resonate with RF pulse in high magnetic field gradients: Slice imaging
- High magnetic field α high MRI signal
  (900 MHz is highest field 21 T MRI magnet at NHMFL)
  (171 MHz is highest field 4 T MRI approved by FDA)
  (64 - 128 MHz is routine 1.5 - 3 T MRI in hospitals)
- T1, T2, proton density weighting by scan parameters of TE, TR, TI etc.
- Quantitative Analysis: Interactive co-analysis by MRI and MR Spectroscopic Imaging measure localized morphometry and metabolism
Quantitative MRI

Optimized Scan parameters: TR, TE, FOV, NEX, ETL,
- 2D Slice imaging: MSME, DWI, EPI,
- 3D Volume imaging: FLASH, RARE; Factors: ST, SNR
- Dynamic imaging: SENSE, GRAPPA

Registration: Edge-detection, Morphometry-matching

Segmentation: Classification of tissues
  Boundary-based; Region-based: Thresholding, Feature plot
- Masking to highlight subtle points
- Manipulation and Analysis: Interactive
- Surface rendering: Surface Formation Contours, Patches, Surface Tracking;
  Rendering: Hidden-part removal, Shading
- Volume Rendering: Preprocessing Binary volumes, Gray Volumes
- Preprocessing: VOI selection
- Filtering
- Interpolation

Multidimensional display and multiparametric data
Quantitative MRS + MRI predict hippocampal volumes and measure the neurometabolites.

PRESS: H-1 MRS of Hippocampus
Quantitative MRSI: Slice Selection, Metabolite Maps and CSI imaging

- Selective Single Voxel Spectroscopy
- Single Plane Chemical Shift Imaging

Proton MRI  NAA, Cho, Cr

MRSI

MRS metabolite peaks in Normal Volunteer

NAA, Cr and Cho peaks visible
Quantitative Proton Magnetic Resonance Spectroscopic Imaging (MRSI) Technique

Data Acquisition:
- In-house developed MRSI sequence (AFFIRMATIVE)
- Prelocalization with stimulated sequence
- Volume-of-interest 90 x 90 x 15 mm³ with centrum semiovale
- Field-of-view 240 mm²
- 32 x 32 phase encoding steps; TE/TR/NEX = 30/1000/1
- Bandwidth 1000 Hz; data points 256; voxel size 0.8 cc

Image Postprocessing
- Outer volume suppression for minimizing extrameningial lipids
- Variable TR for reducing scan time
- Automatic analysis software (APSIP)
  - Spectral analysis
  - Metabolic map generation, Segmentation, Co-registration
- Interfacing MRS with MRI by software (MRIAP)
Outcome of Quantitative MRI-SI

- Transfer and storage of MRI scans from various MRI acquisition centers
  - Preprocessing per scan, including:
    - Image sorting
    - Inhomogeneity correction
    - Noise reduction
    - Conversion of image format
    - Coregistration
    - Database creation and export to SPSS or Excel file

- Calculation of number and volume of Gd-enhancing lesions
- Calculation of number and volume of T2 lesions
- Calculation of number and volume of T1 hypointense lesions
- Calculation of brain atrophy, gray and white matter atrophy
- Calculation of regional brain atrophy (26 regions)
- Calculation of third ventricular width and bicaudate ratio
- Calculation of lateral ventricular volume
- Calculation of magnetization transfer ratio (MTR) (including WB-MTR, NABT-MTR, NAGM-MTR and NAWM-MTR)
- Calculation of regional MTR (26 regions)
- Calculation of diffusion tensor imaging (DTI) measures (ADC, FA, entropy) and tractography
- MRI Spectroscopy analysis
- MRI Iron measures analysis
- FMRI analysis
- PET-MRI combined analysis
- Optic nerve analysis (including determination of lesions, calculation of optic nerve atrophy, MTR, and DTI measures)
- Spinal cord analysis (including determination of lesions, calculation of spinal cord atrophy, MTR, and DTI measures)
- Development of MRI pulse and software programs, web-based programs and slide animations
MS: Non-Inflammatory GM Lipid Disorder

- Multiple Sclerosis (MS) shows lesions due to demyelinating White Matter disorder
- Occasional presence of GM lesions on MRI
- Multiple Sclerosis is non-inflammatory with lipid-rich Normal Appearing White Matter or Gray Matter (NAWM or NAGM)
Can we measure MS load by MRI/MRS?

Hypothesis

Lipids accumulate and NAA lost initially followed by amino acid release at lesion sites.

Lesion load: lesion volume and neurochemicals
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
Feature maps of different regions in MS brain: Minimization of false lesion
PROMISCOL Trial: MS Lesions Showing Abnormal Tissue and Metabolites in WM/GM and NAWM/GM

Sharma et al. (2000) IEEE CBMS Proc. 12,87
PROMISCOL® Trial: Time dependent metabolite changes in MS brain

- Brain volume
- Lesion volume
- NAA, Choline, Cr/PCr concentrations

Promiscol:
Reduces lesion burden
Quantitative MRI + MRSI of Alzheimer’s Disease

AD: Amyloid plaques, hippocampal atrophy change due to dementia

Hypothesis

MRI combined with MRSI characterize & measures the disease better
Tissue MRI segmentation (supervised K-NN cluster method)

AD: Gray matter loss and viscous CSF

**MRSSI: Metabolite* distribution and tissue content in AD**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>AD</th>
<th>Control</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA(mM)</td>
<td>Right</td>
<td>7.55 ± 0.5</td>
<td>10.01±0.6</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>7.61 ± 0.4</td>
<td>9.82 ±0.9</td>
</tr>
<tr>
<td>Cho(mM)</td>
<td>Right</td>
<td>2.02 ± 0.7</td>
<td>2.08 ±0.2</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>2.04 ± 0.4</td>
<td>1.89 ±0.5</td>
</tr>
<tr>
<td>Cr(mM)</td>
<td>Right</td>
<td>7.02 ± 0.6</td>
<td>7.75 ±0.5</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>7.96 ± 0.6</td>
<td>7.49 ±0.8</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>AD</th>
<th>Control</th>
<th>% Diff</th>
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</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td>Right</td>
<td>1.08 ±0.06</td>
<td>1.39±0.03</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>0.96 ±0.04</td>
<td>1.31±0.02</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>Right</td>
<td>3.74 ±0.07</td>
<td>4.81±0.09</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>3.73 ±0.03</td>
<td>5.1±0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue content ρ (%)</th>
<th>AD</th>
<th>Control</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>84 ± 3</td>
<td>98± 2</td>
<td>14.3</td>
</tr>
<tr>
<td>Left</td>
<td>87 ± 3</td>
<td>96 ± 3</td>
<td>0.93</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Gray matter index (f)</th>
<th>AD</th>
<th>Control</th>
<th>% Diff</th>
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</thead>
<tbody>
<tr>
<td>Right</td>
<td>0.45 ±0.03</td>
<td>0.55 ±0.05</td>
<td>18.2</td>
</tr>
<tr>
<td>Left</td>
<td>0.62 ±0.02</td>
<td>0.62 ±0.04</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*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.

AD: Where are sites of poor glycolysis?

Poor Glucose metabolism in both Temporal sites due to amyloid plaques
Anisotropy for Fiber Tracking: Precursor of Alzheimer’s disease?
MRI+MRSI Predicts Better Tissue Composition and Volume in AD

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>Control</th>
<th>% diff.</th>
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</thead>
<tbody>
<tr>
<td>HP-volume $(\text{mm}^3)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1982 ± 134</td>
<td>2884 ± 102</td>
<td>31.1</td>
</tr>
<tr>
<td>Left</td>
<td>1868 ± 88</td>
<td>2943 ± 86</td>
<td>36.5</td>
</tr>
<tr>
<td>Ventricular CSF (%)</td>
<td>4.2 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>33.3</td>
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<tr>
<td>Sulcus CSF (%)</td>
<td>23.4 ± 2</td>
<td>18.2 ± 0.5</td>
<td>22.2</td>
</tr>
<tr>
<td>White Matter (%)</td>
<td>35.2 ± 0.9</td>
<td>38.1 ± 0.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Cortical GM (%)</td>
<td>38.8 ± 1.1</td>
<td>42.2 ± 0.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Subcortical GM (%)</td>
<td>1.2 ± 0.08</td>
<td>1.4 ± 0.03</td>
<td>n.s</td>
</tr>
<tr>
<td>TIV$(\text{cm}^3)$</td>
<td>1342 ± 5</td>
<td>1402 ± 52</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>FDG-PET+MRI</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Asymmetry Index $&gt; 3$</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NAA/(Cho+Cr)</td>
<td>1.2</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>AI $&gt; 12$ %</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Sharma et al. (2003) Medica Inform. 3(4) 386
MRI + MRSI: Epilepsy

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

3rd Example
Combined (multislice MRI+ PRESS MRSI) in mLE

- Unilateral mTLE (ipsilateral side)
- PRESS volume pre-selection on hippocampus (TR/TE=1800/140 ms; voxel $9 \times 9 \times 15 \text{ mm}^3$); circular K-space encoding of 24 points
- Multislice (TR/TE=1800/140 ms; voxel $8 \times 8 \times 15 \text{ mm}^3$); circular K-space encoding of 36 points
Hippocampus Volume Reduction and PRESS-MRS Lipids and Choline

(A) Control
(B) Mesial lobe Epilepsy
MRSI: Metabolites in Pre-op vs post-op Epilepsy

Sharma et al (2005) Slovenia Medical Informatica, 3(4) 686

Neurochemicals by MRS lateralize Hippocampus in Mesial Lobe Epilepsy
NAA/(Cr+Cho) in Control vs Epilepsy ipsi- and contra-lateral sides at different brain regions

CONCLUSION 1

• Gray Matter and Normal Appearing Gray Matter and White Matter regions in MS are abnormal and measurable.

• Neurochemicals in AD, Epilepsy suggest the utility of MRI and MRS to confirm hippocampus volume heterogeneity and regional (tissue composition and neurochemical) differences due to neuronal dysfunction in brain.
Outcome of MRI +MRSI

- Metabolites measure optimum lateralization
- Decreased NAA to 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)
- Multi-slice MRI approach for better Asymmetry Index
Macaque Monkey Brain images by 5 Tesla Clinical Imager
Detection of GABA, an inhibitory neurotransmitter

4th Example
The GABA molecule

γ-Amino butyric acid: C₄H₉NO₂
methylene groups form A₂M₂X₂ system
γ and β protons are weakly coupled, A₂X₂
J = 7.3 Hz
The challenge of GABA detection

- GABA conc. in the healthy right occipital cortex: 1.0 mM
- Signal 40,000 times smaller than water proton signal
GABA detection = suppressing overlapping other signals

- singlet signals (Cr, NAA)
- coupled signals (Glu, Gln)
- macromolecules
GABA editing: experience at 3T

Voxel size = 27 cc, TA = 6’24 min

TE = 69 ms

TE = 136 ms
In vivo spectral editing (MEGA, 2-shot)

- TE 68 ms
- voxelsize = 27 cc
- TA = 6'24min
- 8-Channel Array Coil and offline signal combination
- fitting with MRUI program
CONCLUSION 2

- GABA is inhibitory neurotransmitter
- GABA is predictive of seizure outcome
- GABA is MRS visible
MICROIMAGING
In
Mouse Brain
21 T MRI of Mice Brain

Aim: MRI imaging of mice brain anatomy

Outcome: Frontal (F), Parietal (P), Temporal (T), Occipital (O) lobes and Hippocampus (H) visible
First time 21 Tesla MRI processed images of Mice Brain Reveal Details

Morphology

Hippocampus DG and other regions
21 T MRI: Colchicine Injection in Mice Reduced the Brain Hippocampus Volume
CONCLUSION 3

- Mouse brain hippocampus is MRI visible in different regions
- Drug effect on hippocampus is MRI measurable
21 Tesla MRI Microimaging

Possibility of imaging cells and measurement up to 20 micron resolution with high MRI signal

Some examples
Micro-scale resolution by MRI

**Aim:** MRI of 50 μm, 90 μm, 500 μm polymer beads in tube with FeO-Gadolinium

**Outcome:** MRI visualizes 50 μm beads (left) and ½ mm beads (rightmost)

**Experiment:** Polymer 50 μm beads (left) and 500 μm beads (right) were pushed in device at physiologic conditions & imaged by SE using T1 and proton density weight

**Spatial resolution = 1mm /128 x 128, in-plane resolution = 0.1 mm**
Nanotechnology:
First time Carbon Nanotube Transport Across The Skin by 21 Tesla MRI

• Carbon Nanotubes (CNT) as future drug delivery system
• CNT are 1.8 million times lighter than iron.
• CNT can penetrate anywhere across the membrane channels (200 nm) in body tissues
Conclusion 4

• Microimaging provide high sensitivity and resolution upto micron level
• Microimaging can be useful in micro-Anatomy, subcellular transport physiology

• Final Take-home Message:
  Quantitative MRI/MRS with PET is future molecular imaging choice, while Quantitative Microimaging is future dynamic monitoring/imaging choice.
MRI-PET in Brain Assessment
Sodium $[\text{Na}]_{\text{ex}}$ and $[\text{Na}]_{\text{i}}$ are MRI visible by IR pulse sequence at different null points

- Null points of $[\text{Na}]_{\text{ex}}$ and $[\text{Na}]_{\text{i}}$ are different
- Null point is inversion Time (TI) specific
- Distinct null points are tools for contrast

Sharma et al. (2001) ISMRM workshop 11,126
4.25 T Sodium-MRI in human

Raw Sodium images

Simultaneous Imaging of a [F-18]-FDG Mouse Head with Two Coincident APD Based LSO Block-Detectors and a 7 Tesla Small Animal MRT System

- Step and shoot PET acquisition (12 angles, each 6 min) while MRT images were taken.
- Filtered Back Projection (2.5 mm Gaussian image filtering post reconstruction)

70/30 Bruker Biospec system. B-GA20 gradient set. Micro Imaging Coil. FLASH MRT sequence. 1mm slice thickness.
MR-PET Applications

- **Neurology**
  - **Surgery and RT:** delineation of functionally significant brain sections and tumor mass
  - **Movement disorders:** Delineation of gray matter with receptor density
  - **Dementia:** Structure volumetry and metabolism (FDG) or even Plaque Imaging (FDDNP)
  - **Stroke:** improve MR perfusion by functional PET
  - **Epileptic foci:** accurate localization
## Compatibility Challenges

What does it mean to really combine: MR-PET?

<table>
<thead>
<tr>
<th>MR</th>
<th>MR-PET Challenge</th>
<th>PET</th>
</tr>
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<tbody>
<tr>
<td><strong>Cost</strong></td>
<td><strong>Space</strong></td>
<td><strong>Resolution</strong></td>
</tr>
<tr>
<td><strong>Homogeneity</strong></td>
<td><strong>Magnetic Field</strong></td>
<td><strong>Material restriction</strong></td>
</tr>
<tr>
<td>No eddy currents</td>
<td><strong>Gradient Field</strong></td>
<td><strong>Design restrictions, Heating, Signal interference</strong></td>
</tr>
<tr>
<td>??</td>
<td><strong>RF Field TX</strong></td>
<td><strong>Signal interference</strong></td>
</tr>
<tr>
<td>Signal interference</td>
<td><strong>RF Field RX</strong></td>
<td><strong>Shielding</strong></td>
</tr>
<tr>
<td>Design restrictions</td>
<td><strong>Attenuation</strong></td>
<td><strong>Signal loss</strong></td>
</tr>
</tbody>
</table>
CONCLUSION 5

- MRI-PET predicts both morphology and oxygen metabolism
Functional MRI Measures the Blood Oxygen Stimulated Neuroactivation

Right and left finger tipping involves different brain regions & shows specific brain BOLD fMRI signal.

Sharma et al. 2004 Biomed Engg 1(2) 29.
Acknowledgements

NHMFL, Tallahassee:
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Columbia University, New York
Richard Kline

University of Texas Medical School, Houston
Ponnada A. Narayana
Jerry Wolinsky

Thank You
• Breast Spectroscopy
• Liver Spectroscopy
• IMAPS: An International Multi-Center Assessment of Prostate Spectroscopy
• Prostate Spectroscopy using Array Coils
• Spectroscopy of the Spinal Cord
• Detection of GABA
• Fast CSI I: EPSI
• Fast CSI II: SSFP
• 31P Spectroscopy of the Heart: Improvements
• DEPT 1H → 13C
• Metabolite Report
Breast Spectroscopy
Breast Cancer - Clinical $^1$H MRS Studies

- (ce)MRI provides high sensitivity for differential diagnosis
- Will Cho-detection by $^1$H MRS improve specificity?
  - overall cancer types true positive detection rate: 74%
  - sensitivity low for non-infiltrating & high for infiltrating carcinoma
  - axillary node metastasis: sens. = 82%, spec. = 100%, acc. = 90%
  - all results with respect to FNAB as gold standard
  - benign vs. malignant breast lesions: sens. = 82%, spec. = 85%
Lipid-Water Suppressed SE Sequence

\[ \text{svs}_\text{se}_\text{bB1} = \text{svs}_\text{se} + \text{Spectral Suppression} \]

- optimized spectrally selective pulses
- applied twice during TE; TE\(_{\text{min}}\) = 100 ms
- lipid and water suppression
- Acquisition using the Siemens Breast Coil
Breast Cancer

the effect of lipid suppression
Breast Cancer

no artefactual signal at 3.2 ppm

residual lipid signal
(suppr. factor 220)
Breast Cancer

Voxel size = 3.4 cc, TA = 3 mins. 12 s
Breast Cancer

- voxelsize = 6 cc, TA = 6 mins. 24 s
- patient undergoing CT-MRI
Breast Cancer: Coherent Accumulation

uncoherent accumulation

coherent accumulation
Pre-Clinical Results: Breast Cancer

Voxel size = 2.3 cc, TA = 9 mins. 36 s
Breast cancer: MRSI monitoring

Before Chemo-therapy

1st cycle

2nd cycle

3rd cycle
MRS monitoring of CT

4th cycle

5th cycle

6th cycle
Lactating Breast

Voxel size = 8 cc, TA = 3 mins. 12 s  TR/TE = 1500/135 ms
MAGNETOM Trio: Lactating Breast

- Residual Water
- Lactose
- Residual lipids
- Chol

MAGNETOM Tim Trio: Breast MRS

- svs_se body WIP
- spectral lipid suppression
- multi-array signal combination
- frequ. correction before accumulation

Detection of choline by MRS in pathologically proven adenocarcinoma
Liver Spectroscopy
Magnetom Trio: $^1$H spectrum of liver

- free breathing SVS data acquisition
- frequency/phase lock for each acquisition
- combining spectra of 8 coil elements

$\text{TE} = 30 \text{ ms}$
$\text{TR} = 2000 \text{ ms}$
$\text{TA} = 4:16 \text{ min}$
$\text{Voxel} = 8 \text{ cm}^3$
Magnetom Avanto: \(^1\text{H}\) spectrum of liver

universal body WIP svs_se
free breathing
freq. / phase lock
coil element combination
TR / TE = 650 / 30 ms
Voxel size = 8 cc
TA = 0:54 min

→ feasibility
→ the 3 major lipid signals and choline compounds detected
Single Voxel Spectroscopy in liver tumor

- free breathing SVS data acquisition
- frequency/phase lock for each acquisition
- combining spectra of 8 coil elements

Magnetom Sonata:
Spectrum shows lipid signals and increased Choline signal

TE = 135 ms
TR = 1500 ms
TA = 0:48 min
Voxel = 8 cm³
SVS in liver tumor

- free breathing SVS data acquisition
- frequency/phase lock for each acquisition
- combining spectra of 8 coil elements
- Spectral lipid supression

Magnetom Sonata:
Spectrum shows highly increased Choline signal

- TE = 135 ms
- TR = 1500 ms
- TA = 0:48 min
- Voxel = 8 cm$^3$
SVS in liver tumor

Reference spectrum:

Choline peak
SVS in liver tumor

Comparison:

reference spectrum       tumor spectrum
Prostate MR Spectroscopy
Prostate Cancer Trial

- MR spectroscopy of the prostate
- Outline of the trial
- Data
- PRISMA: Automatic post-processing
- status report
- Participating clinical institutions & partners
MRS of the Prostate

3D MRSI in prostate cancer

- Functional prostate tissue shows a marked citrate signal.
- In tumors the choline signal is elevated while the citrate signal is decreased.
Objectives of the trial

- Primary objectives
  - 3D $^1$H CSI detects prostate carcinoma
  - 3D $^1$H CSI localizes prostate carcinoma

- Secondary objectives
  - documenting inter-patient reproducibility of method
  - documenting intra-patient reproducibility of method
  - documenting variation due to patient age
  - documenting the robustness of the method

- Hypothesis
  - Cho/Citrate or (Cho+Cr)/Citrate is significantly higher in tumor compared to healthy prostate tissue.
Trial
Patient’s Prostate Cancer MRI-Histology

- The axial T2-weighted image is used for matching voxel locations to histopathological specimens.
- One of the spectral maps, partially expanded, shows the quality of the MRSI data throughout the slice.
- Deviations in the \((\text{Cho} + \text{Cr}) / \text{Ci}\) metabolite ratio map largely correspond to the tumor location indicated with the blue line.
Automatic Post-Processing with PRISMA*

- Complex time domain fit

- Metabolite model
  - Prior knowledge based model signals using complete spectral shapes

- Baseline model
  - Finite time model

- Automatic processing of 3D CSI data

* prior knowledge based modeling of spectroscopic magnetic resonance applications
PRISMA: Quantification of Prostate Cancer Metabolites

* This information about this product is preliminary. The product is under development and not commercially available in the U.S., and its future availability cannot be ensured.
Methodology

- Patients with prostate cancer who underwent a radical prostatectomy without prior treatment
  - Anatomical imaging
  - 3D MRSI
  - Histopathology
  - Case report forms
- Young (<40 years) and age-matched (>55 years) healthy volunteers
  - Current work
  - Matching and classification of the data by experienced radiologists and physicists
  - Data processing at two independent evaluation sites with PRISMA
Surface Coils
Surface coils consisting of many small elements
- Utilization of 24 imaging elements

2D HASTE with PAT 2
1.3x1.7x6 mm³, 20 slices, TA 9 sec

50 cm
Signal Combination

\[ \lambda \sum_i W_i^* S_i \]

Matrix Spectroscopy
Pulse sequence

Pulse spacing in sequence defines spectral shape of citrate, while choline and creatine as singlet signals remain unaffected by pulse timing.

![Diagram of pulse sequence](image)
Spectral shape of citrate at 3T

Simulations

*In vitro* measurements

$\tau_1 = 10 \text{ ms}$
Spectral shape of citrate at 3T

$$\tau_1 = 25 \text{ ms}$$
Selected spectral shapes for quantification

Sensitivity $A_{(TE)}$

<table>
<thead>
<tr>
<th></th>
<th>0.90</th>
<th>0.86</th>
<th>0.83</th>
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<tbody>
<tr>
<td>$\tau_1$ 25 ms TE 75 ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\tau_1$ 10 ms TE 100 ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\tau_1$ 25 ms TE 145 ms</td>
<td></td>
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</tbody>
</table>
No need of guided wires
$^1$H-Prostate Spectroscopy at 3T
MAGNETOM Trio a Tim System

- 3D-CSI-SE scan for complete coverage of the prostate
- Measurement without an Endorectal Coil by using only Array Coils
- Optimized sequence timing for 3T
  - TE 145 ms
  - TR 750 ms
- 7x7x7 mm$^3$ voxel
- Spectral and spatial saturation pulses
- Scan time: 10 min
TIM Trio: Matrix Spectroscopy of the Prostate

- 3D Spin-Echo CSI
- sequence timing optimization →
  TE = 145 ms; TR = 700 ms
- TA = 5:19 min !!
- scan matrix 14 x 14 x 8
- nominal voxel size
  \[7 \times 7 \times 7 \text{ mm}^3 = 0.33 \text{ cc}\]

- combined Spine and Body Matrix coil reception,
  no usage of ER coil
- truly non-invasive determination of the metabolic state of the entire prostate
Spinal Cord Spectroscopy
Magnetom Avanto:
Single Voxel Spectroscopy in the Spinal Cord

- svse in the spinal cord, benefits from
  - Combined signal of body matrix
  - ECG triggering
  - Small voxel size: 7 x 9 x 25 mm³
Magnetom Trio:
Single Voxel Spectroscopy in the Spinal Cord

svs_se in the spinal cord, benefits from

- Combined signal of body matrix
- ECG triggering
- Small voxel size: 5 x 11 x 25 mm³
Avanto

Not triggered

Triggered:
Same voxel

Lines are narrower than on non triggered scan
The GABA molecule

γ-Amino butyric acid: $\text{C}_4\text{H}_9\text{NO}_2$
methylene groups form $A_2M_2X_2$ system
γ and β protons are weakly coupled, $A_2X_2$
$J = 7.3$ Hz
The challenge of GABA detection

- GABA conc. in the healthy occipital cortex: 1.0 mM
- Signal 40,000 times smaller than water
GABA detection = suppressing overlapping signals

- singlet signals (Cr, NAA)
- coupled signals (Glu, Gln)
- macromolecules
1. γ-Amino butyric acid: $\text{C}_4\text{H}_9\text{NO}_2$

2. Methylene groups form A$_2$M$_2$X$_2$ system

3. γ and β protons are weakly coupled, A$_2$X$_2$

$J = 7.3 \text{ Hz}$
GABA editing: first experience at 3T

- GABA?
- Glx?

voxelsize = 27 cc, TA = 6’24 min

TE = 69 ms

TE = 136 ms
MAGNETOM Trio: GABA Editing

svs_se_edit
by Mescher, Merkle, Kirsch, Garwood, Gruetter

*In vivo spectral editing (MEGA, 2-shot)*

TE 68 ms
voxelsize = 27 cc
TA = 6’24min
8-Channel Array Coil and offline signal combination
fitting with MRUI

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The GABA user group
Works in Progress:

Echo-Planar Spectroscopic Imaging
3D EPSI with interleaved water reference

RF
Gz
Gy
Gx

Water Suppr.
Inversion Recovery

90° 180° 20°

metabolite acq.
water reference acq.

TRwr

TE/2

TD

Slice selection Rephasing Spoiling Readout Phase encoding
Volumetric High Resolution (64 x 64) EPSI on the MAGNETOM Trio
Volumetric High Resolution (64 x 64) EPSI on the MAGNETOM Trio
Works in Progress:
Steady State Free Precession Techniques
SSFP-based Pulse Sequences I

- SSFP = steady state free precession
- fast sequence of RF-pulses, TR < T₂, T₁
- constant gradient net effect

→ formation of 2 echo types
  - fid-type of signal S₁
  - echo-type signal S₂
SSFP-based Pulse Sequences II

4 sequence types

True-FISP = coherent combination of S1 and S2
- FAST = detection of only S1
- CE-FAST = detection of only S2
- FADE = separate detection of S1 and S2

Usage in MRI
- suggested already in the 80s
- since end of the 90s: broad usage due to short $T_{A_{\text{min}}}$ and high efficiency

Usage for MRS to be explored
- is spectral resolution sufficient?
- can water suppression be integrated?
- what sequence type to be preferred?
- how do $J$-coupled spins behave?
SSFP-based Pulse Sequences III

sequence efficiency

  • utilizing high sequence efficiency
  • avoiding interferences between S1 and S2
    – FAST = detection of only S1
    – CE-FAST = detection of only S2
    – FADE = separate detection of S1 and S2
  • acquiring complete spectra

CE-FAST using spatial-spectral selective RF-pulses

• 2D RF-pulses, selecting
  – a spectral dimension
  – a spatial dimension [1,2]
• composite pulse of
  – hard-pulses
  – slice-selective pulses [3]
  – timing 1-2τ-5.4-τ-5.4-2τ-1

Spatial-spectral selective RF-pulse profile

- straightforward implementation
- 8 ms duration
CE-FAST using spatial-spectral selective RF-pulses

- SSFP sequence
- TR = 83 ms, acqu. window = 64 ms, $\alpha = 40^\circ$
- voxelsize = 1 cc, matrix 32 x 32, FoV 200
- TA = 1:29 min
  - short acquisition time
  - high sequence efficiency
Works in Progress:

$^{31}P$ Spectroscopy of the Heart:

Improvements
PCr map of the control subject shows the influence of the chest muscle.
Work in Progress: csi_fid with regional saturation

RSat package:
- Up to 8 RSat pulses
- 1 repetition of each RSat pulse
- Pulse duration: 6400us
- (also available for 1H)
Volunteer PCr map with csi-fid RSat WIP

spectrum of saturated chest muscle
volunteer PCr map

without and with RSats
31P spectrum of the myocardium without and with RSats

chest muscle spectrum
31P metabolite map of myocardial infarction

High correlation to late enhancement

Late enhancement shows the infarct region in the anterior septal wall

The metabolite map shows low PCr in the anterior septal region in good correlation with the late enhancement results
Works in Progress:

$^1\text{H} \rightarrow ^{13}\text{C}$ Polarisation Transfer by DEPT
NMR sensitivity of $^{13}$C vs. $^1$H

- identical $B_0$, identical conc. of nuclei
  sensitivity of $^1$H detection: 1
  sensitivity of $^{13}$C detection in vitro: $\propto (\gamma_{^{13}C} / \gamma_{^1H})^3 = 0.016$
  sensitivity of $^{13}$C detection in vivo: $\propto (\gamma_{^{13}C} / \gamma_{^1H})^2 = 0.06$

$^1$H, 3T, TA = 7 min.

$^{13}$C, 3T, TA = 7 min.
Chemical dispersion $^{13}$C vs. $^1$H

- dispersion $^{13}$C = 20 x dispersion $^1$H
  - shimming less important for $^{13}$C applications
  - easier quantification
- $^{13}$C spectra show wealth of biochemical information
- $^{13}$C MRS can be used with labeled compounds
  - enables dynamic studies of biochemical fluxes
$^{13}\text{C}$ spectroscopy: the quest for sensitivity

Coil design

- Increased sensitivity
- Homogeneous SAR
- Homogeneous decoupling

Surface coil vs. $^1\text{H}$ volume & $^{13}\text{C}$ quad.

$^1\text{H}$ (CP birdcage)
$^{13}$C spectroscopy: the quest for sensitivity

DEPT Polarisation Transfer

classical simultaneous-

Tx DEPT

without localization

localized DEPT Using Pulses Sequentially (DEPTUPS)
$^{13}$C spectroscopy: Sequential DEPT (DEPTUPS) 

*In vivo* results  MAGNETOM Trio

*In vivo* enhancement by DEPT Using Pulses Sequentially (DEPTUPS) reaches the theoretical upper limit!
Works in Progress:
Metabolite Report
Metabolite Report: New Spectroscopic Post-Processing

- **Algorithm:**
  - Automated
  - Prior knowledge based
  - Complex time-domain fitting
  - With qualification of results

- **Report generation:**
  - Fully automated mode
  - No interaction for voxel/data selection or post-processing
  - Based on predefined settings

- **Report format:**
  - Structured Report
  - DICOM compatible
  - HTML compatible
Algorithm: PRISMA

- Complex fit in time-domain

\[ s(t, t_0, \varphi_0, A_i, \omega_i, T_{2,i}, T_{G,i}) = \sum_{i} A_i M_i \exp[-t / T_{2,i} - (t / T_{G,i})^2] \cdot \exp[-I(\omega_i (t - t_0) + \varphi_0)] \]

- Using model signals, based on analytical or simulated (GAMMA) models

- Gaussian, Lorentzian and Voigt lineshapes

- Result qualification based on Cramer-Rao-Bounds, SNR, …

Fit of short TE in vivo data (SVS, SE, TE 30 ms)
Metabolite report includes

- patient info
- localization info
- metabolic info
- diagnostic info