Declaration of Financial Interests or Relationships

Speaker Name: Lucio Frydman

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

In vivo metabolic profiling of brain rodent models by relaxation-enhanced MRS of the downfield 1H region at 21.1T

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מכון ויצמן למדע
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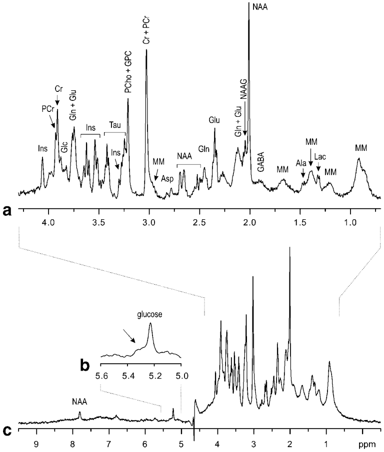
MRS: A most versatile tool for studying metabolites. But...



In vivo ^1H NMR spectrum of the rat brain measured with TE=1.0 ms. I Tkac et al. Magn Reson Med. 41:649-656 (1999)

- Low metabolite concentrations
- Short T_2s and J-coupling multiplicities
- Spectral overlapping among peaks of chemically similar metabolites (GABA/Glu/Gln)
- Problems with water suppression ($C_{H_2O} = 40\,\mathrm{M}$)
- Long recycle delays leading to slow experiments

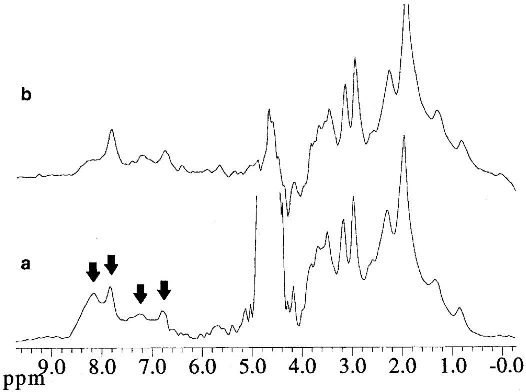
Peaks resonating downfield from water?

Few studies report downfield resonances

- SNR is low
- Peaks are broad
- Strong macromolecular baseline

Exchangeable protons

Water saturation can dramatically reduce the intensity of downfield resonances!



Spectra of MCF-7 cells recorded by water flip-back WATERGATE without (a) and with (b) CHESS water presaturation. S Mori, SM Eleff, U Pilatus, N Mori & PC van Zijl. Magn Reson Med. 40:36-42 (1998)

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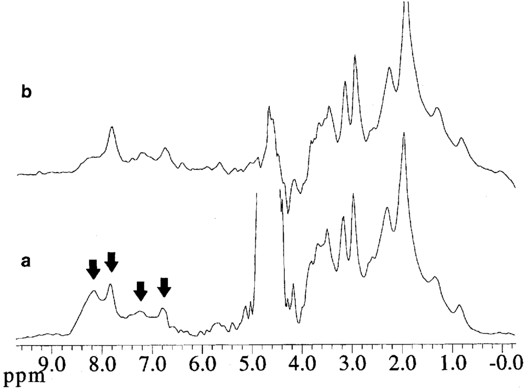

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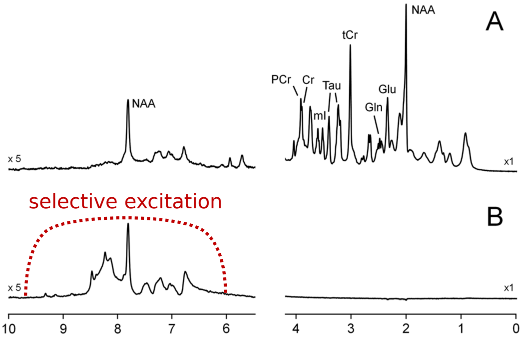
Existing *in vivo* MRS techniques

Water-suppressing MRS techniques

- WATERGATE
- CHESS
- VAPOR

Spectrally selective excitation

- Shaped RF pulses[1]
- Relaxation Enhancement[2]



Localized NMR spectra obtained from rat cerebral cortex in vivo employing (A) variable pulse power and optimized relaxation delays (VAPOR) and (B) no water suppression. RA de Graaf & KL Behar. NMR Biomed. 27:802-809 (2014)

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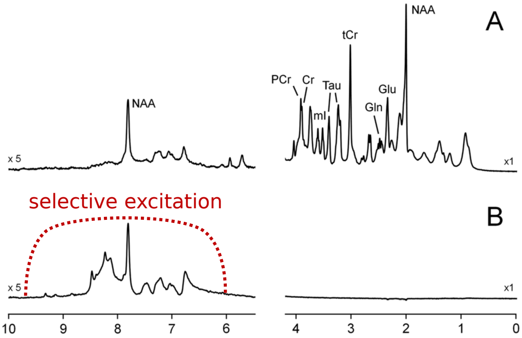

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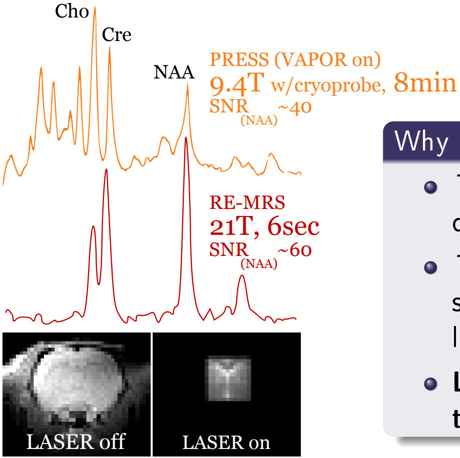
Relaxation Enhanced (RE) MRS at ultrahigh fields



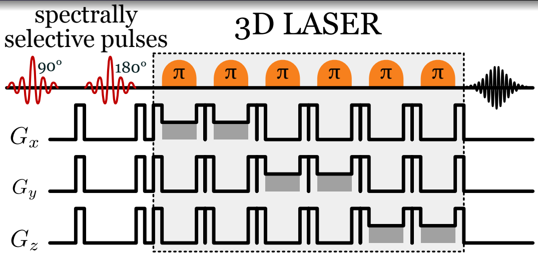
Why is UHF RE-MRS perform so good?

- T_1 of water increases with B_0 field while T_2 decreases
- T_1 and T_2 of metabolites are, respectively, shorter and longer than water counterparts. And less dependent on B_0 field
- **Less chemical exchange and saturation transfer effects**

Downfield MRS: sequence implementation at 21.1 T

21.1 T UWB vertical magnet (NHMFL)

- Bruker Avance III and Paravison 5.1
- Homebuilt ^1H surface quadrature coil
- 64-mm 0.6 T/m, triple axis gradients



Spectrally selective excitation

- Excite & refocus the 5.5-9.5ppm range
- 5.55-ms 10-lobe-sinc shaped pulse
- 4-ms 180° SLR[3] pulse

Spatial localization

- 3D LASER[4] scheme
- Six 5-ms adiabatic 180° pulses
- 0.3-ms gradient crushers

[3] Shinnar LeRoux algorithm
[4] Localization by Adiabatic Spin-Echo Refocusing

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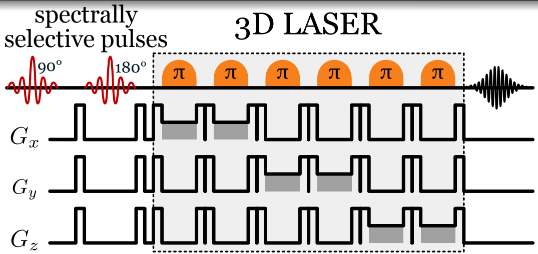

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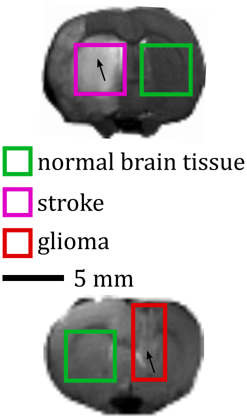
Animal preparation



Middle cerebral artery occlusion[5]

- N=7 juvenile male Sprague-Dawley rats
- MCAO mimicking ischemic stroke
- 1.5 hr occlusion, re-perfusion, and MRI/S experiments 24 h later

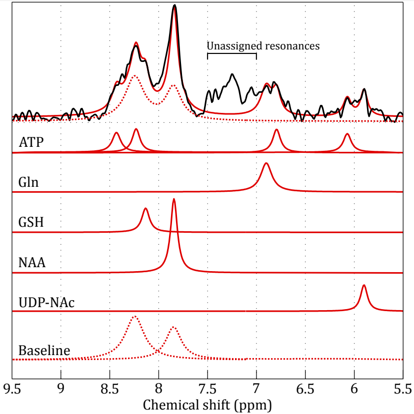
Glioblastoma animal model

- 9L Glioma rat cells cultured using standard cell growth methods
- 100,000 cells injected 3.5 mm deep in N=5 male Sprague-Dawley rats
- Animals were scanned 7 and 11 days after injection

All animal experiments were approved by the FSU ACUC.

[5] EZ Longa et al. Stroke 20 (1989); K Uluç et al. J Vis Exp 48 (2011)

Data Quantification

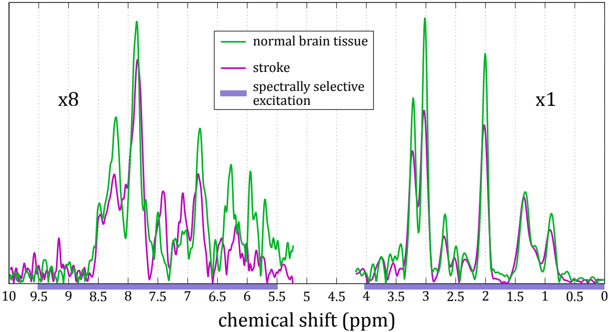


Quantification algorithm

- Home-made software in Matlab[6]
- Based on the GAMMA library[7]
- Prior-knowledge: spectral signatures of ATP, Gln, GSH, NAA, ...
- Baseline modeled using Gaussians
- Absolute concentrations assuming a 5 mmol/L creatine in normal tissue[8]

[6] T Roussel, S Cavassila & H Ratiney. ISMRM-ESMRMB (2010)
[7] SA Smith et al. JMR(A) 106 (1994)
[8] RA de Graaf. In Vivo NMR Spectroscopy: Principles and Techniques (2007)

Ischemic brain tissue metabolic profile



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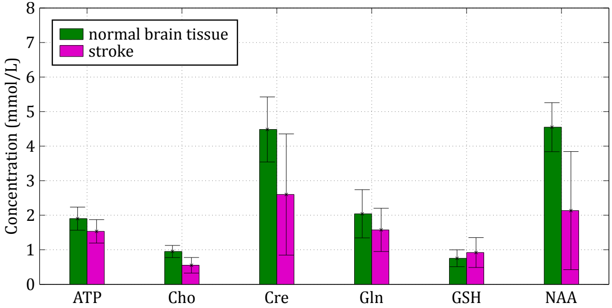

- 50 % average decrease for Cho, Cre, NAA and 20 % decrease for ATP, Gln
  - Cell death and increased edema
- 25 % increase for GSH in ischemic tissue
  - Neuroprotective measure against oxidative stress

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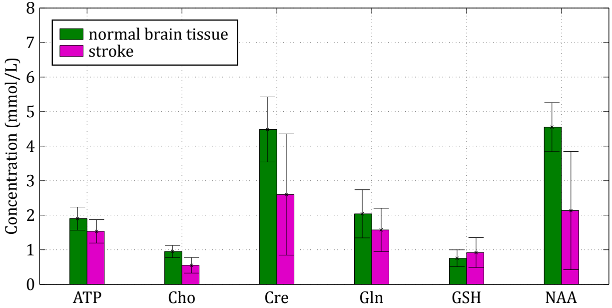

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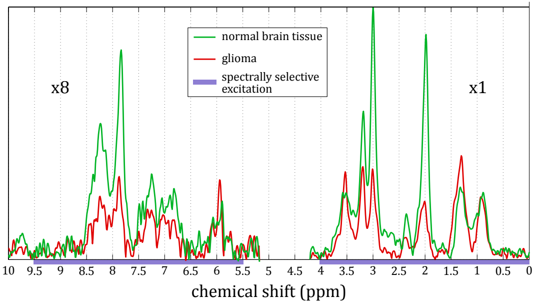

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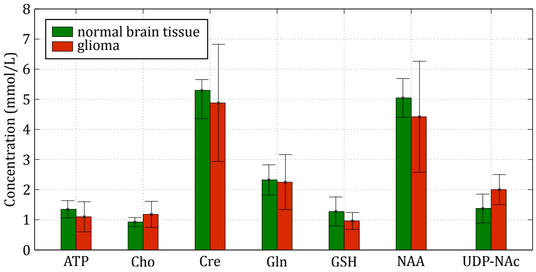
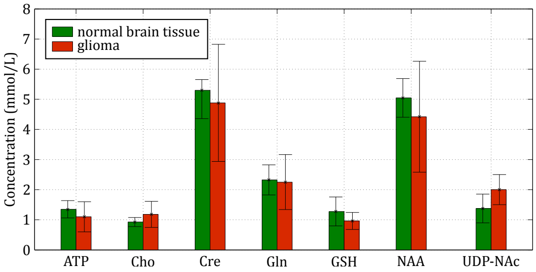


- 20 % average decrease for ATP, Cho, GSH
  - 10 % average decrease for Cre, NAA and 3 % decrease for Gln
- 30 % increase for Cho: glioma tumor growth
  - Glioma tumor growth

Glioma brain tissue metabolic profile



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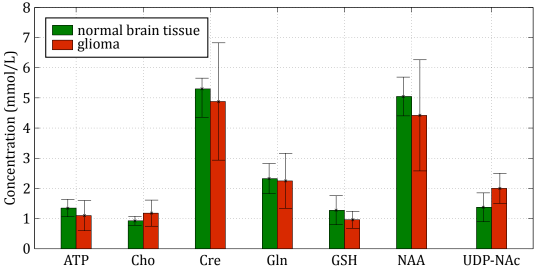

- *45 % increase for a 5.9 ppm resonance tentatively assigned to UDP-NAc*
  - UDP-NAcGal and UDP-NAcGlc were previously detected in rat glioblastoma cells extract[9] and intact human brain tumor cells[10]

[9] X Pan et al. J Proteome Res 10 (2011)
[10] S Grande et al. NMR Biomed 24 (2011)

Conclusion

- 21.1 T
  - High sensitivity and large frequency dispersion allowing efficient spectral selection
- Relaxation Enhanced MRS
  - Increased SNR, especially for resonances originating from exchangeable protons
- First ultrahigh-field quantitative study of the downfield spectral region
  - *In vivo* quantification of UDP-NAc, a potential biomarker for gliomas
- Additional information to identify and quantify *in vivo* metabolic signatures
- Potential to provide a unique fingerprint of metabolism in pathology

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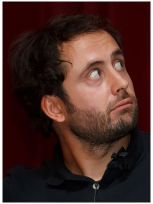
Acknowledgment

Jens Rosenberg



Tangi Roussel

Sam Grant

National MAGLAB

User time available at www.nationalmaglab.org

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