uzh | eth | zürich

Magnetic Resonance Spectroscopy in Inflammation

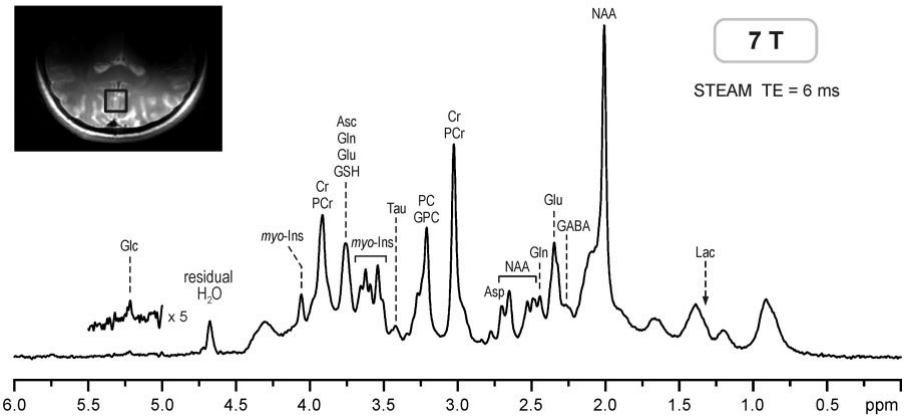
Anke Henning [1,2]

[1] Max Planck Institute for Biological Cybernetics, Tübingen, Germany

[2] Institute for Biomedical Engineering, University and ETH Zurich, Switzerland

MOTIVATION

1H-Single Voxel Spectrum of the Brain at 7T



concentrations of different metabolites

Tkac I, et al., MRM 62:868–879 (2009)

MOTIVATION

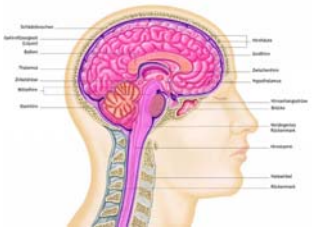
Tübingen:

9.4T human MRI
3T human MRI
3T human PET/MRI

7T rodent MRI
7T rodent PET/MRI
14.1 T rodent MRI

Central Nervous System

brain
spinal cord



Body

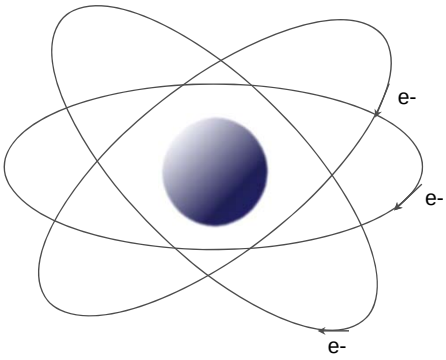
skeletal muscle
myocardium
liver
breast
prostate

http://www.jameda.de/gesundheits-lexikon/gehirn

http://www.jameda.de/gesundheits-lexikon/muskel

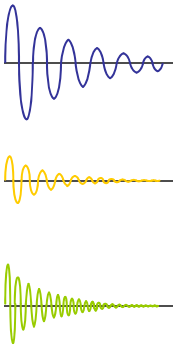
HOW DOES IT WORK ?

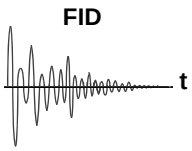
Chemical shift

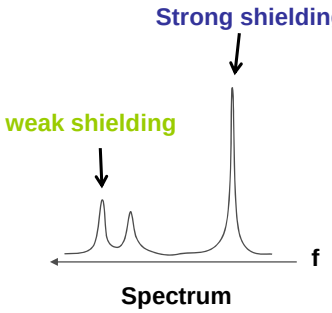


HOW DOES IT WORK ?

- strong shielding
- low res. frequency







Time domain — FT — Frequency domain

- weak shielding
- high res. frequency

Biologically Important NMR Visible Nuclei

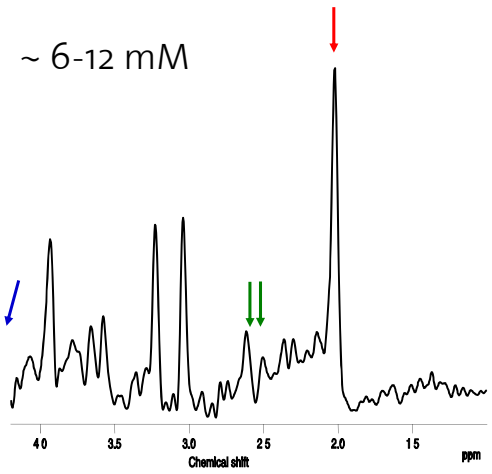
	Spin-quantum number	Gyro-magnetic ratio $\gamma^* = \gamma/2\pi$	Natural abundance [%]	Relative sensitivity for equal number of spins and constant magnetic field strength	Relative sensitivity corrected for natural abundance
^{1}H	1/2	42.58	99.98	1.00	1.00
^{13}C	1/2	10.71	1.11	$1.59\ 10^{-2}$	$1.8\ 10^{-4}$
^{14}N	1	3.08	99.64	$1.01\ 10^{-3}$	$1.0\ 10^{-3}$
^{17}O	5/2	5.77	0.04	$2.91\ 10^{-2}$	$1.1\ 10^{-5}$
^{19}F	1/2	40.06	100.00	$8.30\ 10^{-1}$	$8.3\ 10^{-1}$
^{23}Na	3/2	11.26	100.00	$9.27\ 10^{-2}$	$9.3\ 10^{-2}$
^{31}P	1/2	17.24	100.00	$6.64\ 10^{-2}$	$6.6\ 10^{-2}$
^{39}K	3/2	1.99	93.08	$5.08\ 10^{-4}$	$4.7\ 10^{-4}$
^{43}Ca	7/2	2.87	0.14	$6.40\ 10^{-3}$	$9.3\ 10^{-6}$

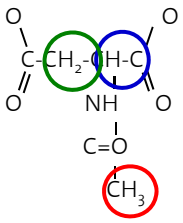
Nuclei of biological interest

^{1}H	> 20 metabolites:	neurotransmitter, energy metabolism, cell growth / death, inflammatory marker
	Advantages:	highest sensitivity: 1-11 mmol/l observable
	Problems:	water suppression (110 mol/l !!), fat suppression, heavily overlapping metabolite peaks
^{31}P	8 metabolites:	energy metabolism, membrane synthesis
	Advantages:	no solvent signal; specific insight into energy metabolism and related turnover rates and pH changes
	Problems:	low sensitivity (100* lower than ^{1}H MRS): > 10 mmol/l observable
^{13}C	> 20 metabolites:	basic atom in all organic molecules
	Advantages:	hardly any spectral overlap, tissue can be specifically enriched with desired ^{13}C isotopes → access to turnover rates
	Problems:	only 1% natural abundance of ^{13}C => *very* low sensitivity (10.000* lower than 1H MRS)

N-Acetyl Aspartate = NAA

~ 6-12 mM





CH_3 2.02 ppm

CH_2 2.69 & 2.49 ppm

CH 4.39 ppm

N-Acetyl Aspartate = NAA

Function: Neuronal marker, concentration correlates with

1. neuronal density
2. neuronal function

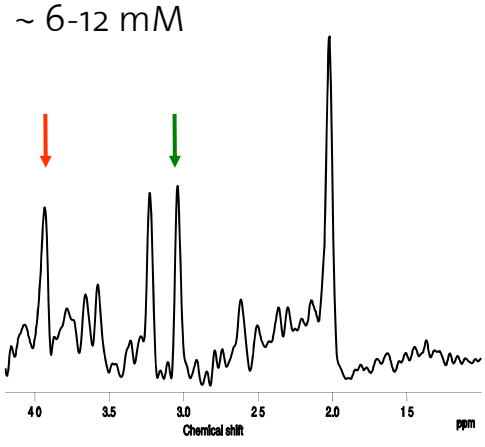
osmoregulation, breakdown product of NAAG, acetyl storage for fatty acid and myelin synthesis

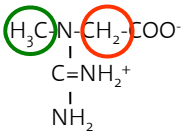
NAA Decrease: Tumor, Stroke, MS, Epilepsy, Hypoxia/Anoxia, Inflammation, Dementia, Trauma

NAA Increase: Brain Development and Maturation
Canavan's Disease (aspartoacylase deficiency)

Creatine / Phosphocreatine = Cre

~ 6-12 mM





CH_3 3.03 ppm

CH_2 3.93 ppm

Creatine / Phosphocreatine = Cre

Function: 1. Energy Buffer:

$H + PCr + ADP \Leftrightarrow ATP + Cr$

2. Energy shuttle: "Energy transport" from production (mitochondria) to energy utilizing sites

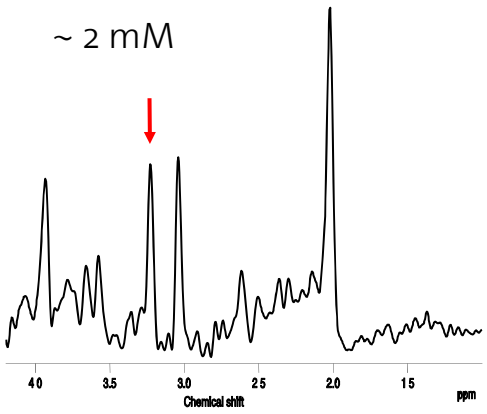
The CRE peak is stable during activation/exercise and therefore may serve as an internal reference

Exceptions:

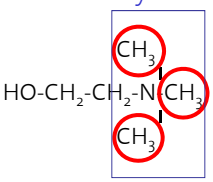
Cr/PCr Decrease: Acute and subacute stroke, Brain tumor, Brain metastasis, Abscesses, Inborn errors of Creatine synthesis, Inflammation

Choline-Containing Compounds = Cho

Cho = choline, phosphorylcholine and glycerophosphorylcholine, no contribution from acetylcholine



trimethylamine



CH_3 3.22 ppm

CH_2 3.54 & 4.05 ppm

Choline-Containing Compounds = Cho

Function: Involved in pathways of phospholipid synthesis and degradation.

=> reflecting membrane synthesis and degradation

Cho Increase: Brain Tumors, any cancer
MS-Plaques,
Stroke,
Inflammation,
White Matter Diseases

Cho Decrease: Hepatic Encephalopathy,
Necrosis

Physiological information from PME and PDE

PME:
PE - Phosphorylethalonamine
PC – Phosphorylcholine

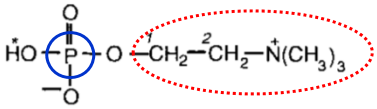
PDE:
GPC - Glycero-Phosphorylcholine
GPE - Glycero-Phosphorylethalonamine

Involved in pathways of phospholipid

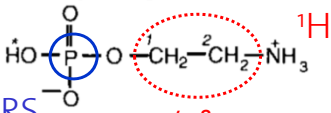
synthesis and degradation.

=> reflecting membrane synthesis and degradation

Phosphorylcholine



Phosphorylethanolamine

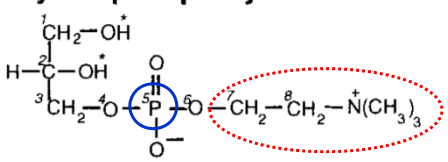


^{1}H MRS

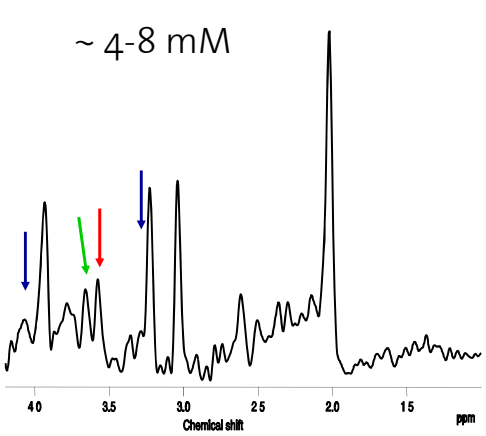
^{31}P MRS

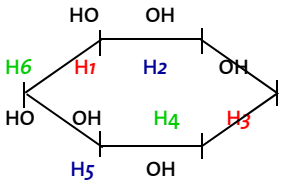
3.1-3.2 / 3.8-4.0 ppm

Glycerophosphorylcholine



Myo-Inositol = mI



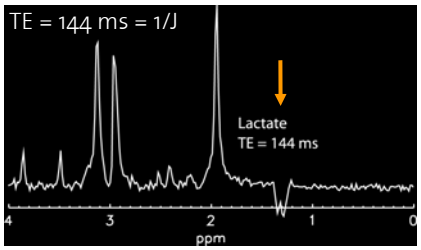


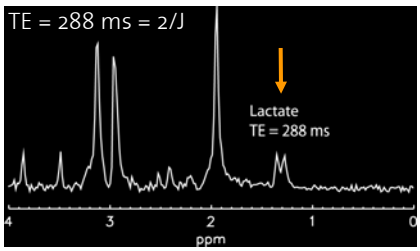
H6, H4	3.60 ppm
H1, H3	3.54 ppm
H5	3.28 ppm
H2	4.05 ppm

Myo-Inositol = mI

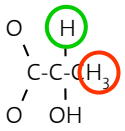
Function of Myo-Inositol:	astrocyte / glial marker second messenger osmoregulator
Increased mI:	Alzheimers' Disease Renal Failure Diabetes mellitus Hyperosmolar States
Decreased mI:	Abscesses Hepatic encephalopathy Tumors Stroke

Lactate = Lac





~ 1 mM



CH_3	doublet	1.33 ppm
CH	quartet	4.11 ppm

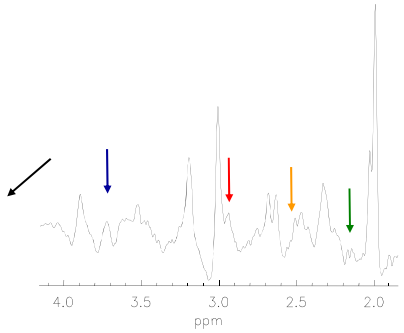
Lactate = Lac

Function: Sign of impaired energy metabolism, impaired oxygen delivery (anaerobic glycolysis)

Not or hardly detectable in normal brain tissue (~1 mM)

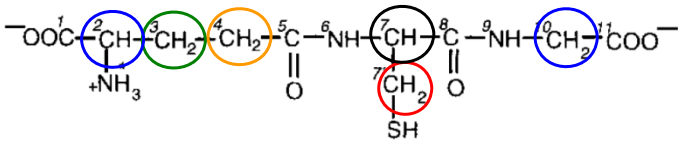
Lac Increase: Stroke, Anoxia/Hypoxia, Mitochondrial diseases, Tumors (Brain and Metastases), Epileptic discharges, Abscesses/Infection, Prolonged neuronal activation

Glutathion = GSH



Function: antioxidant
amino acid transport
cysteine storage
primarily in astrocytes

Alterations: Parkinson's disease
Schizophrenia
neurodegenerative disorders

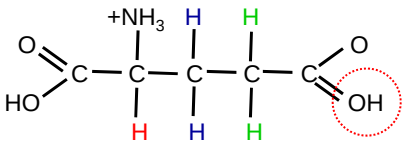


3.77 ppm
4.56 ppm
2.92/2.97 ppm
2.16/2.15 ppm
2.51/2.56 ppm

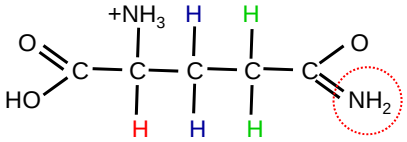
~ 1-3 mM

Govindaraju et al, NMR in Biomedicine 2000;13:129-153.

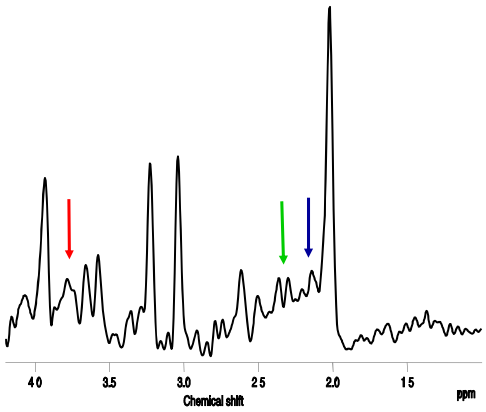
Glutamate & Glutamine = Glu & Gln (Glx)



Glu ~ 6 – 12 mM



Gln ~ 2 mM

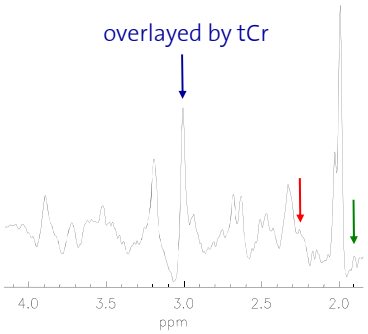


	Glu	Gln
Ha	3.75 ppm	3.76 ppm
Hb	2.05ppm	2.13 ppm
Hb'	2.12 ppm	2.11 ppm
Hg	2.34 ppm	2.44 ppm

Glutamate and Glutamine = Glx

Function of Glutamate:	excitatory neurotransmitter substrate for TCA-cycle protein Biosynthesis
Function of Glutamine:	substrate for neurotransmitter synthesis (precursor GABA, Glutamate) protein Biosynthesis
Increase of Glx peak:	Stroke, Hypoxia/Anoxia Epilepsy Neurodegenerative Diseases (ALS etc.) Hepatic Encephalopathy

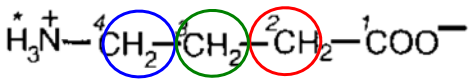
GABA



Function: inhibitory neurotransmitter

Alterations: psychiatric disorders
major depression
schizophrenia
neurological disorders
epilepsy
alcohol / drug abuse

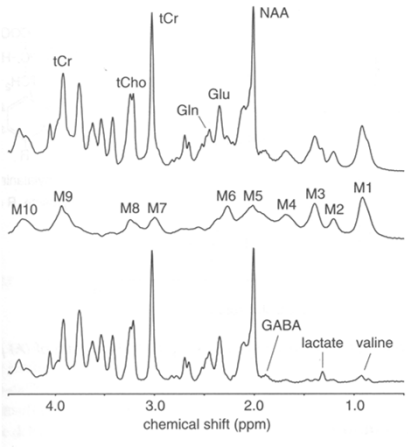
3.01 ppm
2.28 ppm
1.89 ppm



~ 1 mM

Govindaraju et al, NMR in Biomedicine 2000;13:129-153.

Macromolecules and Lipids

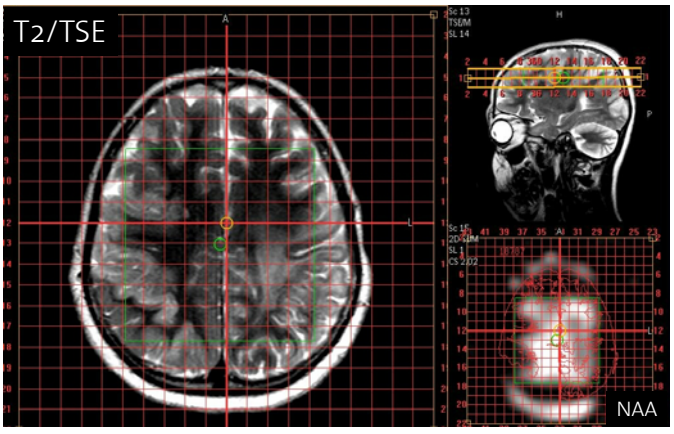


Increased Macromolecules:

Stroke
Tumors
Demyelinating Diseases
Inflammation

Robin A. de Graaf; in vivo NMR Spectroscopy; 2nd edition, WILEY 2007

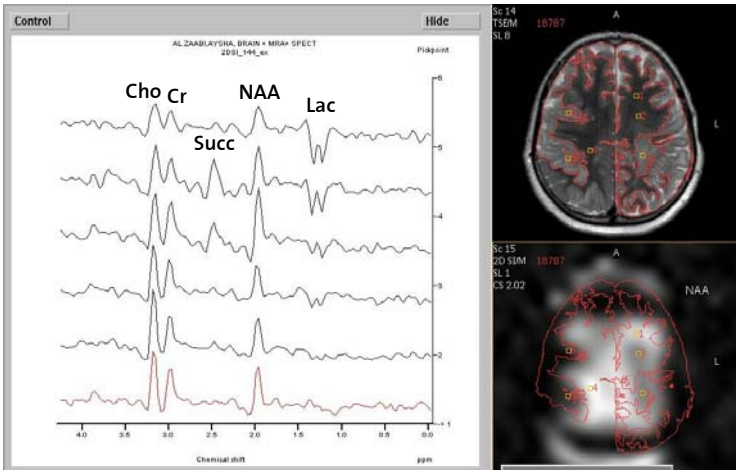
Case 9:



12 years; female
disturbed motion & speech, headache, dizziness

Case 9:

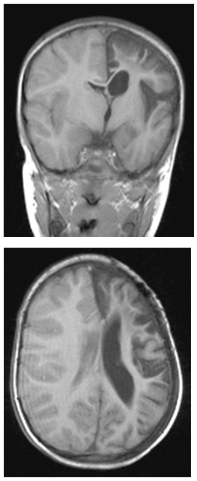
T_E = 144 ms

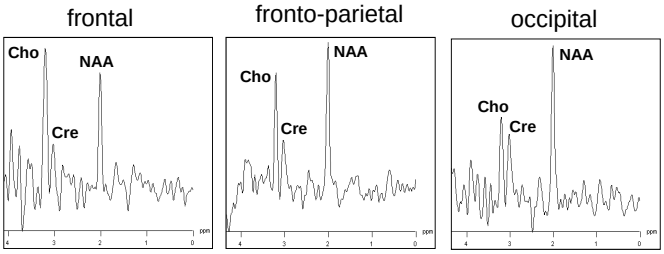


Diagnosis: Staphylo-cocci infection

Case 10:

Diagnosis: Rasmussen encephalitis





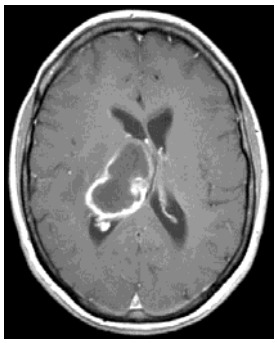
1.5T CSI SE TE 270

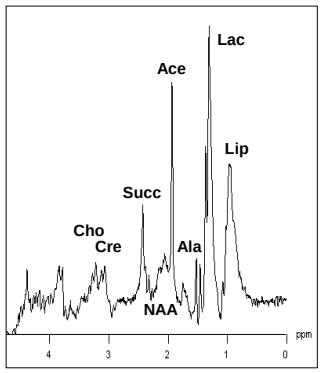
all contralateral

Isabella M. Björkman-Burtscher, MD, PhD, Lund University Hospital, Sweden

Case 6:

Diagnosis: Brain abscess





cystic part:

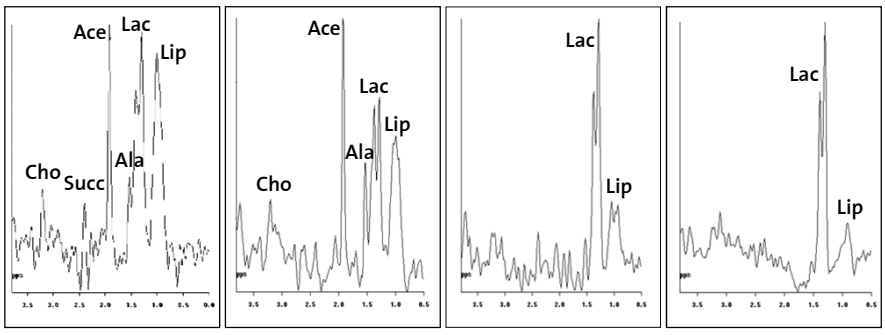
Lac	↑
Lip	↑
AA	↑
Ala	↑
Succ	↑
Ace	↑
NAA + Cho + Cr	↓↓↓

Isabella M. Björkman-Burtscher, MD, PhD, Lund University Hospital, Sweden

Remark VII: infections

Monitor treatment !!

1.5T CSI SE TE 270

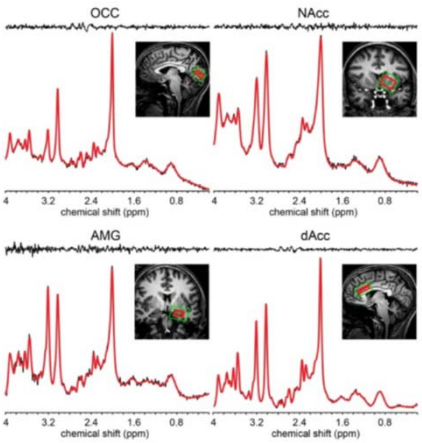


day 1 day 3 day 7 day 14

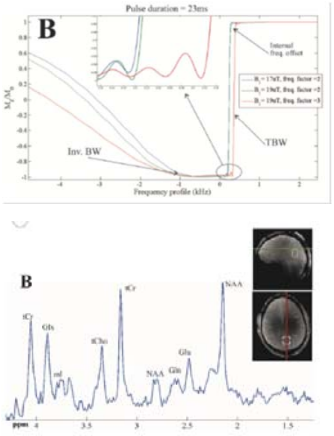
Isabella M. Björkman-Burtscher, MD, PhD, Lund University Hospital, Sweden

Brain ^{1}H MRS: Bo correction with MC

3T



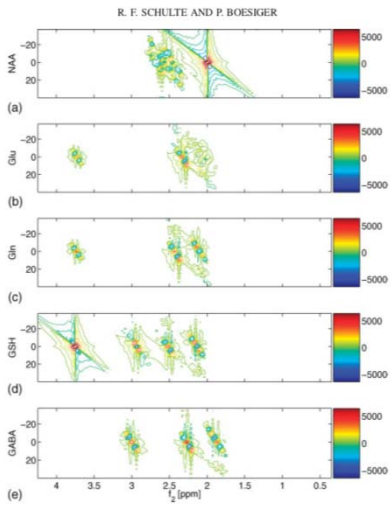
9.4T

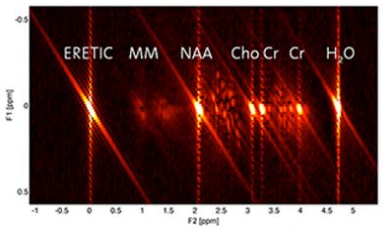


small specific voxels

functional ^{1}H MRS

2D JPRESS & ProFIT @ 3T





68 sites downloaded ProFit

http://www.biomed.ee.ethz.ch/research/bioimaging/mr-spectroscopy/Software/ProFit

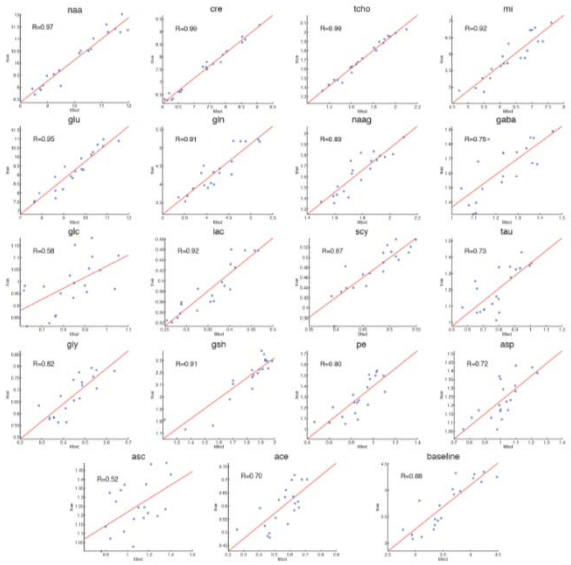
Schulte et al, NMR Biomed 19(2), 255-263 & 264-270, 2006.

Fuchs et al; ISMRM 2012

2D JPRESS & ProFIT 2.0 @ 3T

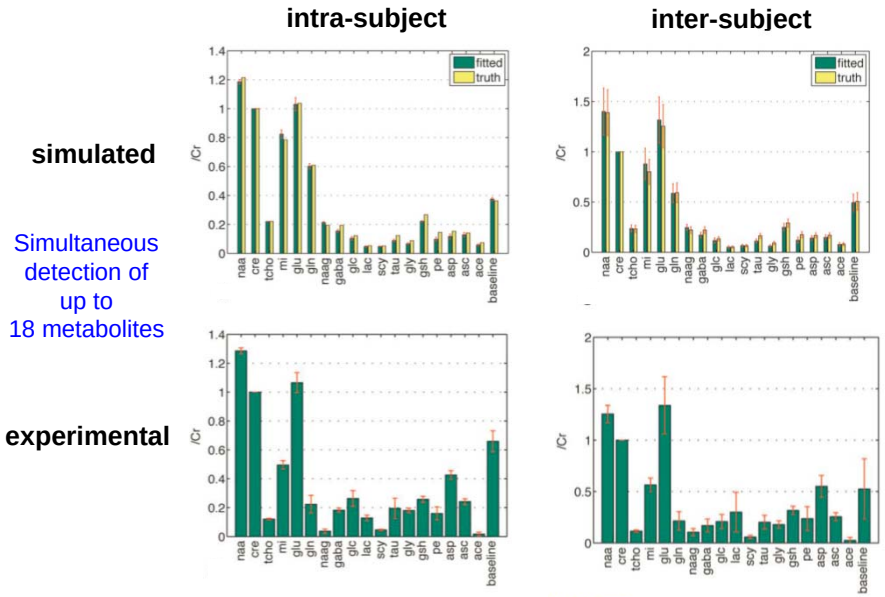
Validation against ground truth

Simultaneous detection of up to 18 metabolites



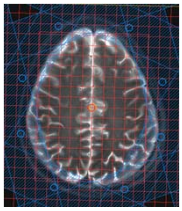
Fuchs A, Boesiger P, Schulte RF, Henning A. ProFit revisited. Magn Reson Med. 2013 Mar 8.

2D JPRESS & ProFIT 2.0 @ 3T



Fuchs A, Boesiger P, Schulte RF, Henning A. ProFit revisited. Magn Reson Med. 71(2) 458–468, 2014.

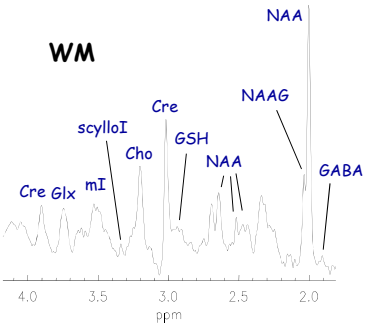
FIDLOVS ^{1}H MRSI @ 7T



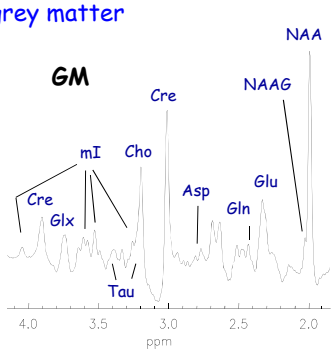
Non-apodized spectra from individual voxels

Voxel size: 1 ml; T_R = 4500 ms; Acquisition time: 26 min

white matter



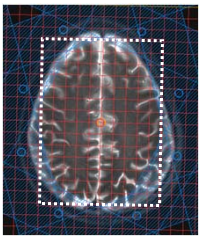
grey matter

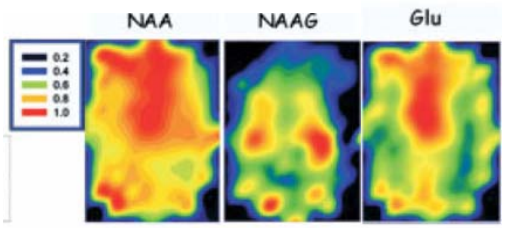


Henning et al, NMR in Biomedicine 22(7), 683-696, 2009.

FIDLOVS ^{1}H MRSI @ 7T

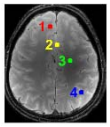
medium spatial resolution:
voxel size: 1 ml (1 cm^3)

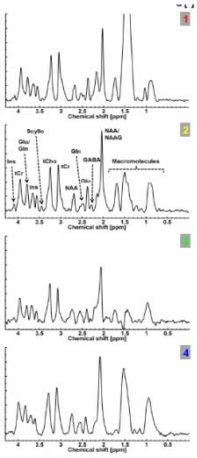


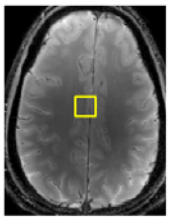


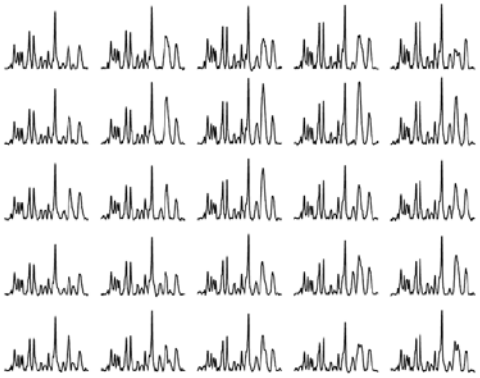
differences between grey matter and white matter

FID ^{1}H MRSI @ 9.4T









TR = 340 ms; Acq Delay = 2.6ms
64x64 voxel; 3.1 x 3.1 x 10 mm
no lipid suppression;
k-space weighting & Hamming

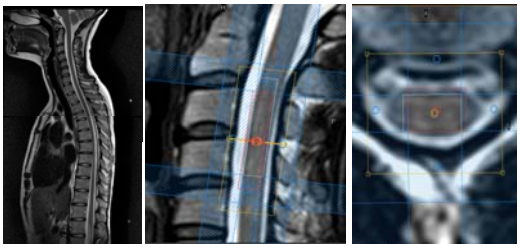
Courtesy of Grezgorz Chadzynski

Spinal cord 1H MRS: Challenges

lipid contamination
→inner volume saturation

pulsatile CSF flow
→ECG triggering
→flow compensation

susceptibility borders
→2nd order FASTERMAP B_0 shimming
→ voxel positioning



Low SNR: small size and deep location
→ultra-high field
→dedicated receive array

respiratory & patient motion
→non-water suppressed MRS for frequency alignment
→respiratory gating

Cook FJ et al MRM 2004, 51:1122-8; Marliani AF et al MRM 2007, 57: 160-3; Henning A et al MRM 2008, 59:1250-8;
Hock Andreas et al ISMRM 2011 # 406 & ISMRM 2010 # 5042;

GABA, GSH & Asp detection in the human spinal cord

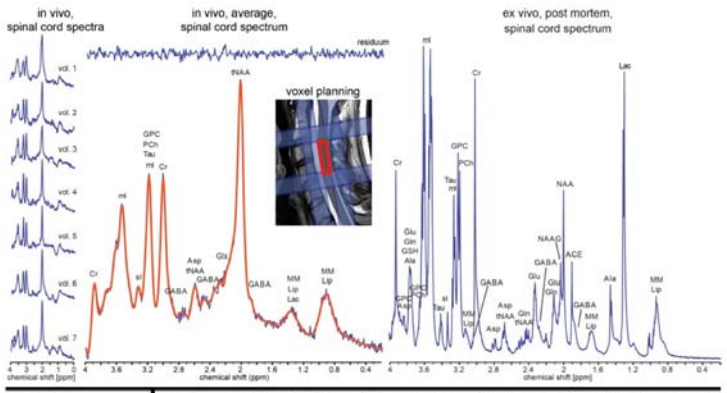
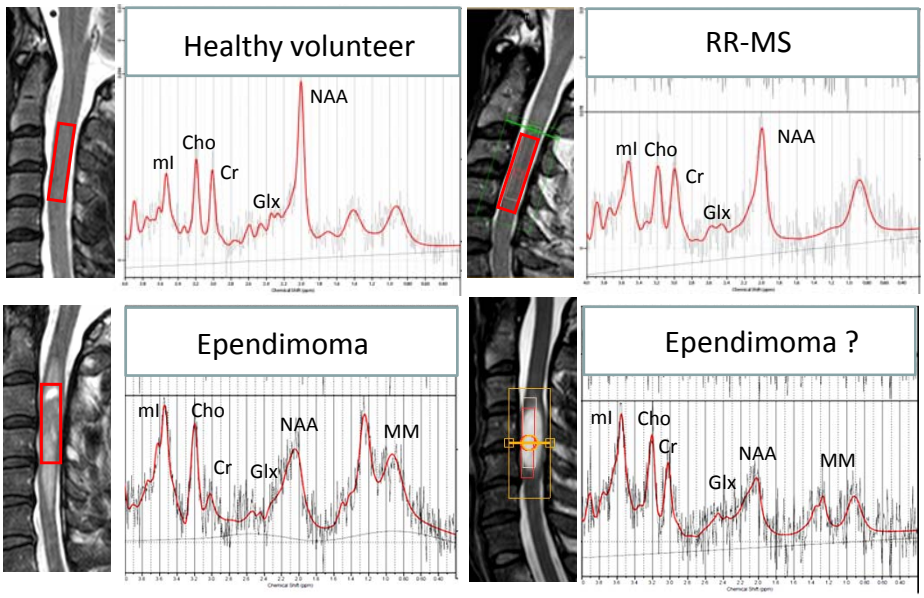


table 1		NAA/Cr	mI/Cr	Cho/Cr	sI/Cr	Glx/Cr	GSH/Cr	Asp/Cr	GABA/Cr	Lac/Cr
spinal cord (individual)	conc/Cr	1.2±0.1	3.2±0.6	0.4±0.1	0.2±0.1	2.4±0.5	0.3±0.2	0.5±0.2	0.4±0.1	0.3±0.1
	valid #	7	7	7	7	7	7	4	3	3
	CRLB [%]	6±2	6±1	7±1	13±4	15±4	30±9	31±12	39±9	24±4
spinal cord (group)	conc/Cr	1.0	2.8	0.4	0.2	2.1	0.1	0.6	0.4	
	valid #	1	1	1	1	1	1	1	1	-
	CRLB [%]	2	4	3	7	8	21	15	22	
brain Cr ratios, (min-max)		0.8-3.78	0.36-1.59	0.08-0.49	0.03-0.12	0.85-3.59	0.19-0.39	0.09-0.27	0.52-2.11	0.05-0.11

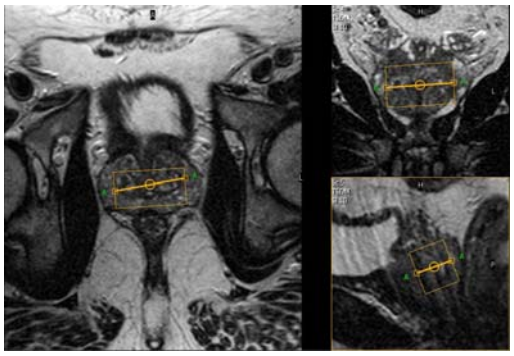
Andreas Hock; UZH & ETH Zurich

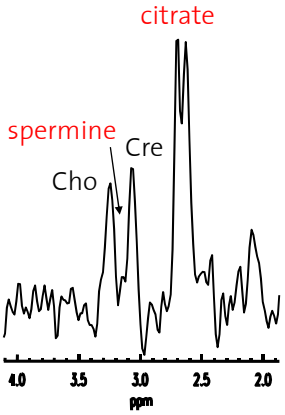
^{1}H MRS in the Human Spinal Cord: Patients @ 3T



Andreas Hock; UZH & ETH Zurich

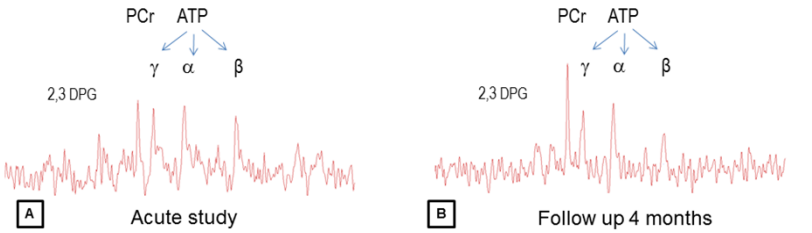
Prostate 1H MRS: Citrate

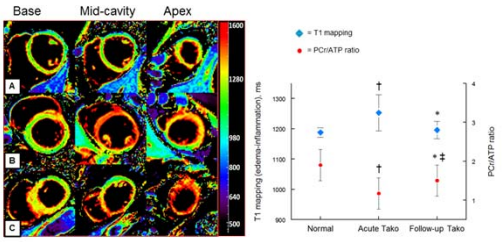




prostatitis versus prostate cancer

^{31}P MRS In the myocardium



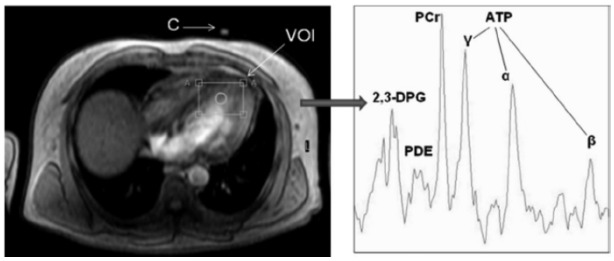


A: normal healthy control
B: a mid-cavity Tako-tsubo patient
C: an apical ballooning patient

normal myocardium: light blue - green
edematous myocardium: yellow - red.

Tako-tsubo Cardiomyopathy: A Heart Stressed out of Energy? Dana K. Dawson, Christopher J. Neil, Anke Henning, Donnie Cameron, Baljit Jagpal, Margaret Bruce, John Horowitz, Michael P. Frenneaux. JACC subm.

^{31}P MRS In the myocardium



PCr / γATP

Perhexiline corrects energy deficit in symptomatic hypertrophic cardiomyopathy:
Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, Maher AR, Kaur K, Taylor J, Henning A, Ashrafian H, Watkins H, Frenneaux M.. Circulation. 2010 Oct 19;122(16):1562-9.

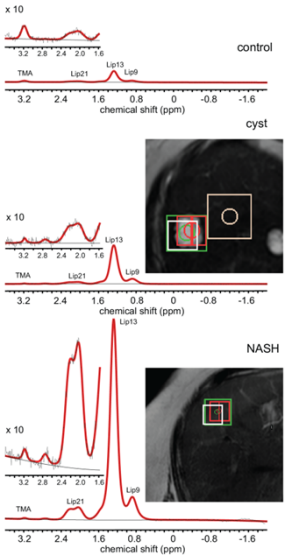
Type 1 diabetes mellitus:
Shivu GN, Phan TT, Abozguia K, Ahmed I, Wagenmakers A, Henning A, Narendran P, Stevens M, Frenneaux M. Circulation. 2010 Mar 16;121(10):1209-15.

Heart failure with preserved ejection fraction:
Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux M. J Am Coll Cardiol. 2009 Jul 28;54(5):402-9.

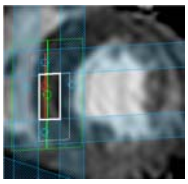
Hypertrophic cardiomyopathy: Shivu GN, Abozguia K, Phan TT, Ahmed I, Henning A, Frenneaux M.. Eur J Radiol. 2010 Feb;73(2):255-9.

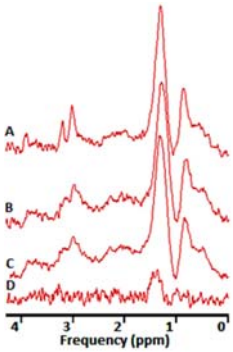
Body ^{1}H MRS: motion correction – MC & NAV

Liver



Heart

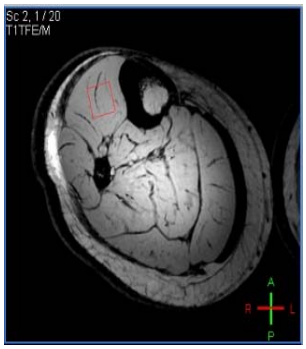


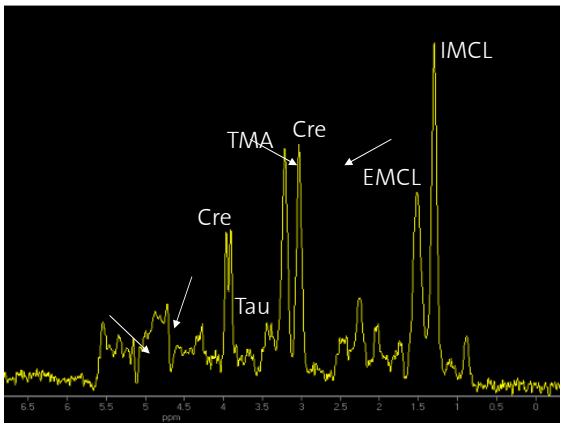


Non-Alcoholic Steatohepatitis

Andreas Hock, Ariane Fillmer, Donnie Cameron, Ladislav Valkovic & Anke Henning; IBT Zurich

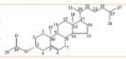
Skeletal Muscle: ^{1}H MRS @ 7.0T

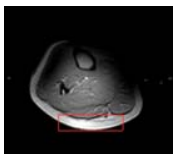




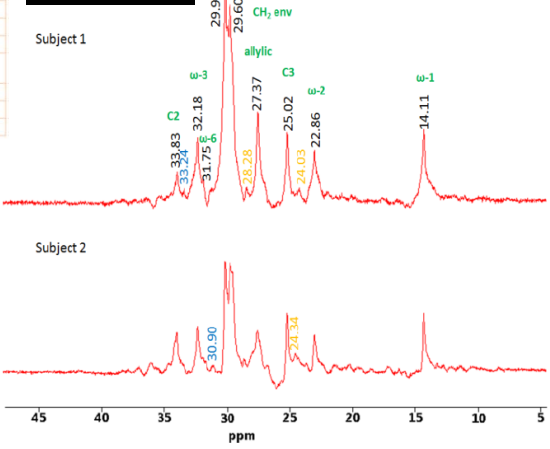
IMCL – intra myocellular lipids
EMCL – extra myocellular lipids
TMA – trimethyl ammonium containing compounds (e.g choline & betaine/trimethylglycine → methyl group donor)

J-refocused PRESS localized DEPT for ^{13}C MRS

Name *	Structure	Chemical shift
ω-1	$-CH_2-CH_3$	14.11
ω-2	$-CH_2-CH_2-CH_3$	22.86
ω-3 (β-CH_3)	$=CH-CH_2-CH_3$	32.18
C2	$COO-CH_2-CH_2-$	33.83
C3	$COO-CH_2-CH_2-$	25.02
allylic	$=CH-CH_2-$	27.37
CH_2 envR	$-CH_2-CH_2-CH_2-$	29.98
CH_2 envL	$-CH_2-CH_2-CH_2-$	29.60
C16 (ω-6)	$-CH_2-CH_2-CH_2-CH_3$	31.75
C13 trans [4, 5]	$=C-CH=CH-CH_2-CH_2-$	33.24
C18 [6]	$-CH_2-CH_2-CH_2-CH_3$ (20:4) $=CH-CH_2-CH=CH-CH_2-CH_3$ (22:6)	30.90
C16 cholesterol [7, 8]		28.28
C23 cholesterol [7, 8]		24.03
C15 cholesterol [7, 8]		24.34



7T



Detection of cholesterol and trans-fatty acids in adipose tissue ?

Xing Chen, Anke Henning, IBT

Spectroscopy & Ultra High Field Group

v.l.n.r.: ***Thomas Kirchner****, Michael Wyss,* ***Milan Scheidegger, Andreas Hock, Niklaus Zoelch****, (me), Alexander Fuchs, Erin L. MacMillan,* ***Ariane Fillmer****, Xing Chen,*
Susanne Heinzer; Ladislav Valkovic, Mariska Luttje, Sila Dokumaci, **Patrik Wyss**, Donnie Cameron, Lukas Eisenring, **Nicole Fichtner**, Peter Bösiger