^{1}H MR Spectroscopy of the Human Brain at 7T

Li An

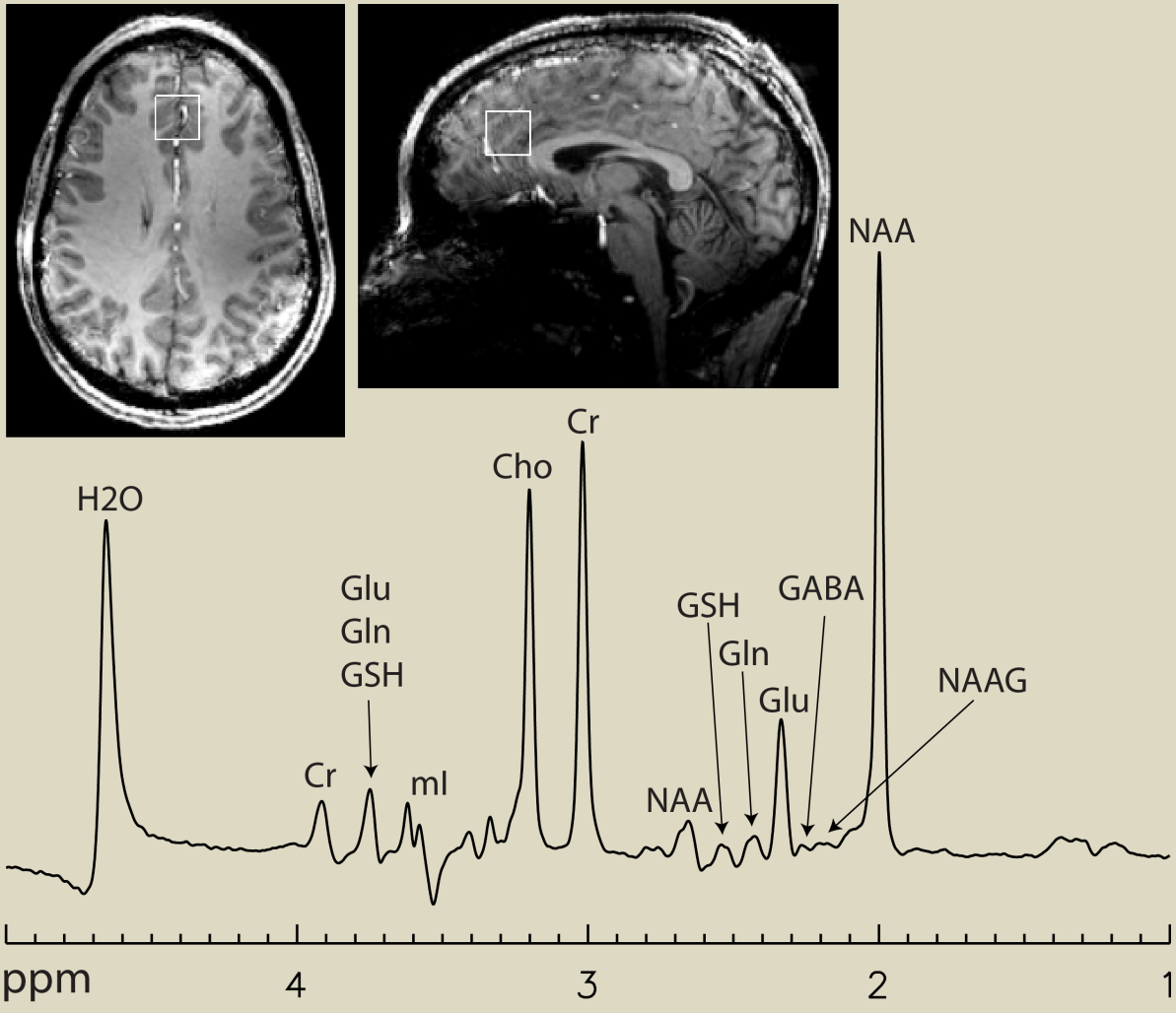
June 30, 2017

Section on Magnetic Resonance Spectroscopy, Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD

NIMH
National Institute of Mental Health

Overview

- Introduction to ^{1}H MR Spectroscopy (MRS) of the human brain
- Detection of glutamate, glutamine, and glutathione at 7T
- Dynamic ^{13}C labeling of glutamate and glutamine using ^{1}H MRS at 7T
- Simultaneous measurement of metabolite T1 and T2 relaxation times at 7T



Spectrum of a 2 x 2 x 2 cm^3 voxel in the prefrontal cortex of a healthy volunteer acquired using the 7T Siemens scanner at the NIH NMR center. TR = 2.5 s, TE = 106 ms.

NAA: N-acetyl-aspartate

NAAG:N-acetyl-aspartyl-glutamate

GABA: γ-aminobutyric acid

Glu: glutamate

Gln: glutamine

GSH: glutathione

Cr: creatine

Cho: choline

mI: myoInositol

Concentrations of Metabolites in Brain Tissue

NAA: ~ 10 mmol/L

Creatine: 6-12 mmol/L

Choline: ~ 2 mmol/L

Tissue water

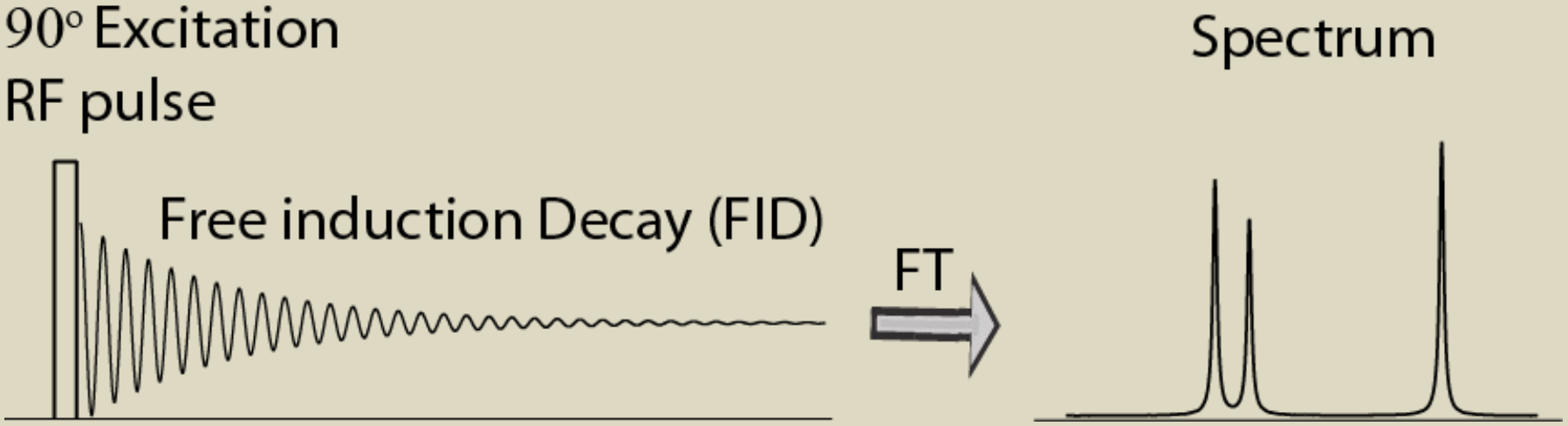
35-52 mol/L

- Metabolite concentrations are several thousand times smaller than that of tissue water.
- Low sensitivity is the main limitation of MR Spectroscopy (MRS).
- Voxel size > 1 cm^3 is necessary to achieve reasonable SNR.

MR Spectroscopy (MRS)

- MR spectroscopy provides a measure of chemical composition of the tissue.
- MR spectroscopy and imaging share the same physical principles.

A Non-Localized MRS Experiment



No magnetic field gradients are applied during data acquisition.
A spectrum of different resonance frequencies of metabolites.

Chemical Shift:

- When an atom is place in a magnetic field, the effective field at the nucleus is reduced from the external B0 field due to the shielding effect of the surrounding electrons.
- The electron density around each nucleus in a molecule varies depending on the types of nuclei and bonds in the molecule. The effective field at each nucleus and subsequently the resonance frequency of each nucleus will vary. This is called the chemical shift phenomenon.

Chemical Shift and Resonance Frequency

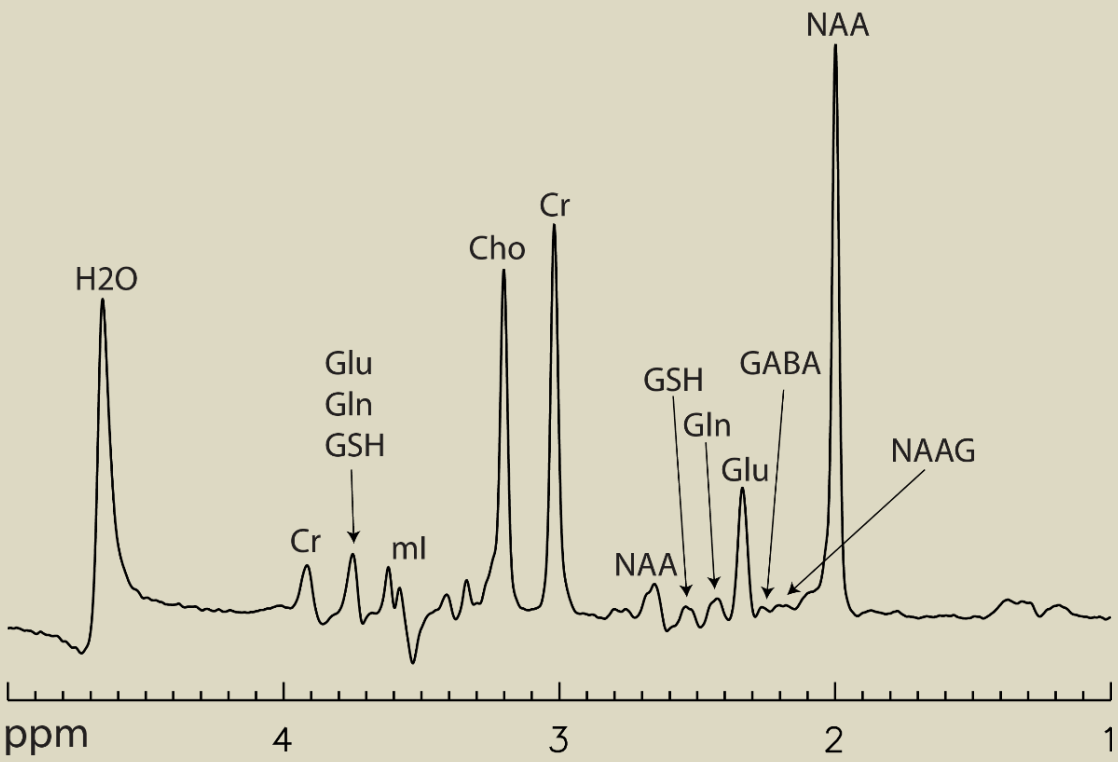
- $\nu = \gamma^*_H B_0$ $\quad (\gamma^*_H = \gamma_H / 2\pi = 42.577$ MHz/T)
- $\nu \approx 300$ MHz when $B_0 = 7$ T
- The ^{1}H nuclei in different molecules or different sites of the same molecule have different chemical environments, resulting in different effective field strengths at the nuclei and thus different resonance frequencies.
- At 7 T, the resonance frequencies of different metabolites can differ hundreds of Hz, which are a few parts per million (PPM) of 300 MHz.

Chemical Shift in PPM:

- $\delta = (\nu - \nu_{ref}) / \nu_{ref} \cdot 10^6$ Unit: ppm – parts per million
- The standard is often tetramethylsilane, $Si(CH_3)_4$, abbreviated TMS.
- Chemical shift in ppm is independent of B0
- At a higher magnetic field, metabolite peaks have larger separations in Hz, which makes higher fields desirable for MRS.

Scalar Coupling (J-Coupling)

- J-coupling is a through-bond interaction between the spins of neighboring nuclei.
- The spin of one nucleus polarizes the spins of the intervening electrons, and the neighboring nuclei are in turn perturbed by the polarized electrons.
- The J-coupling effect is observable if the distance between the non-equivalent nuclei is ≤ three bond lengths.
- J-coupling determines the fine structures of peaks and also modulates the peak amplitudes.



Singlet peaks (NAA, Cr, and Cho):

- No J-coupling
- Chemical shift determines peak positions
- Metabolite concentration and T2 determine peak area

Multiplet peaks (NAA aspartyl moiety, GABA, Glu, Gln, GSH, and mI):

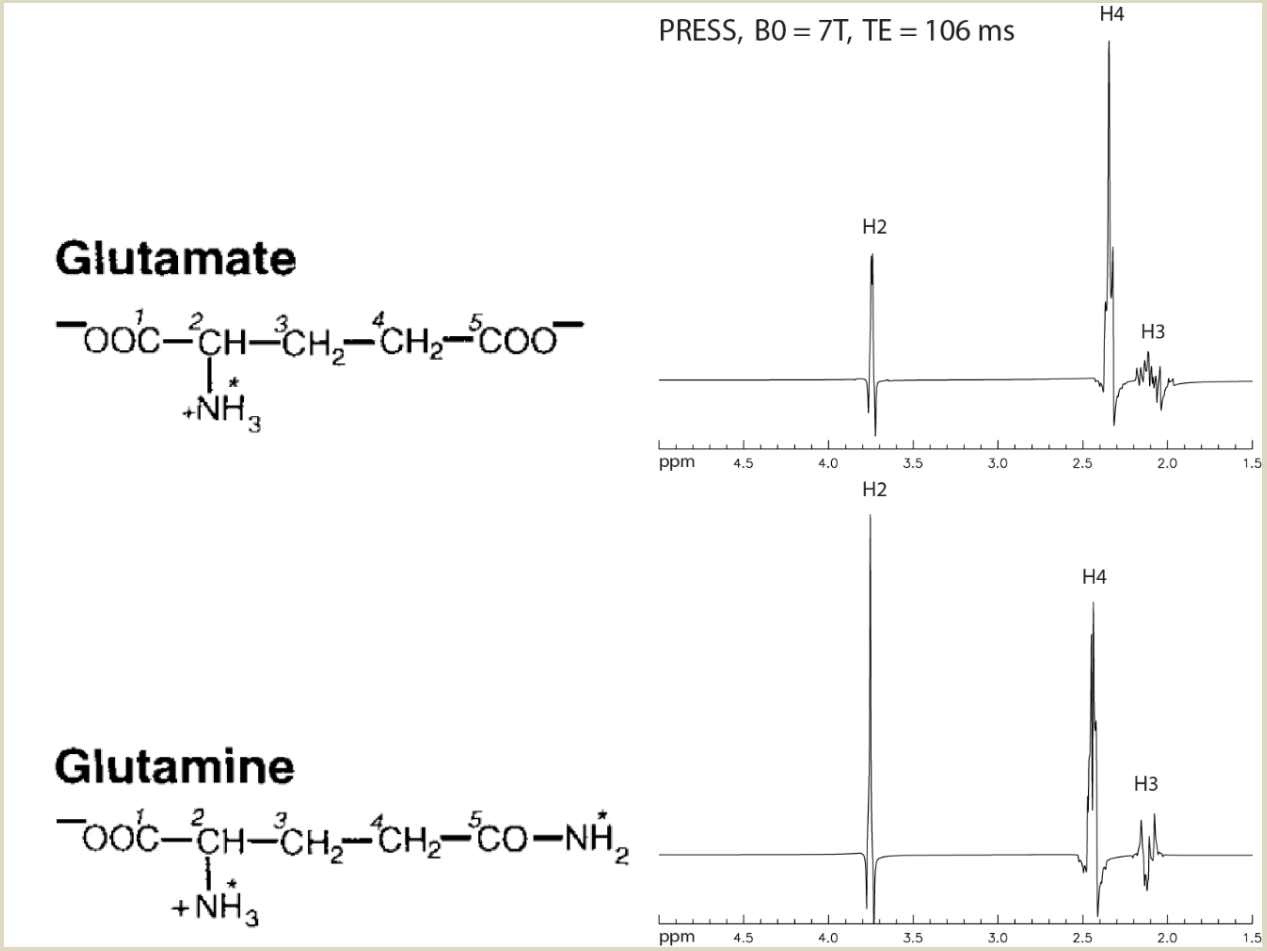
- J-coupling
- Chemical shift determines peak positions
- Metabolite concentration, T2, and J-modulation determine peak area

Density Matrix Simulation

- MRI and MRS are fundamentally governed by quantum mechanics
- MR imaging acquires signals from water, which does not have J-coupling. Bloch equation is enough.
- MR spectroscopy acquires signals from metabolites, which often experience strong J-coupling. Density matrix is needed to describe the quantum system in a mixed state.

Density Matrix Simulated Glu and Gln Spectra

- Homonucleus ^{1}H-^{1}H J-coupling
- No ^{1}H- ^{12}C J-coupling because ^{12}C nucleus has no magnetic moment.
- There is ^{1}H- ^{13}C J-coupling but the natural abundance of ^{13}C is 1%.



Govindaraju V, Young K, Maudsley AA. Proton NMR chemical shifts and coupling constants for brain metabolites. Nmr in Biomedicine 2000;13(3):129-153

Metabolite Quantification

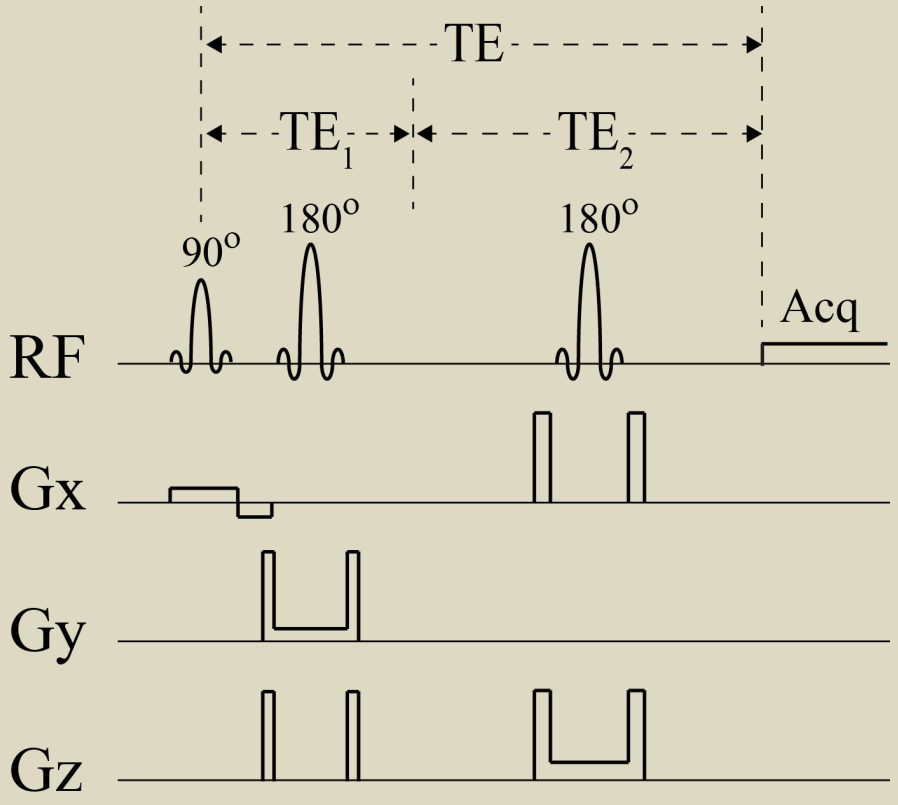
- B0 field inhomogeneity changes peak linewidths.
- Peak amplitudes are affected by peak linewidths.
- Peak areas are not affected by peak linewidths and are proportional to metabolite concentrations.
- Peak area is good for quantifying metabolite concentration.
- Absolute quantification is difficult. Ratio to [Cr] is often used.
- When peaks overlap, fitting is needed.

Linear Combination Modeling

- FID or Spectrum of each metabolite is obtained from phantom experiments or computed using density matrix simulations.
- Individual FIDs or spectra of metabolites are called basis sets
- An experimental spectrum is fitted as a linear combination of the scaled, line-broadened, and frequency-shifted basis sets.
- Line-broadening and frequency-shifting do not change peak areas
- The scaling factor for each basis set is proportional to the peak area and thus the concentration of the corresponding metabolite.
- A commercial software LCModel is widely used.

Point Resolved Spectroscopy (PRESS)

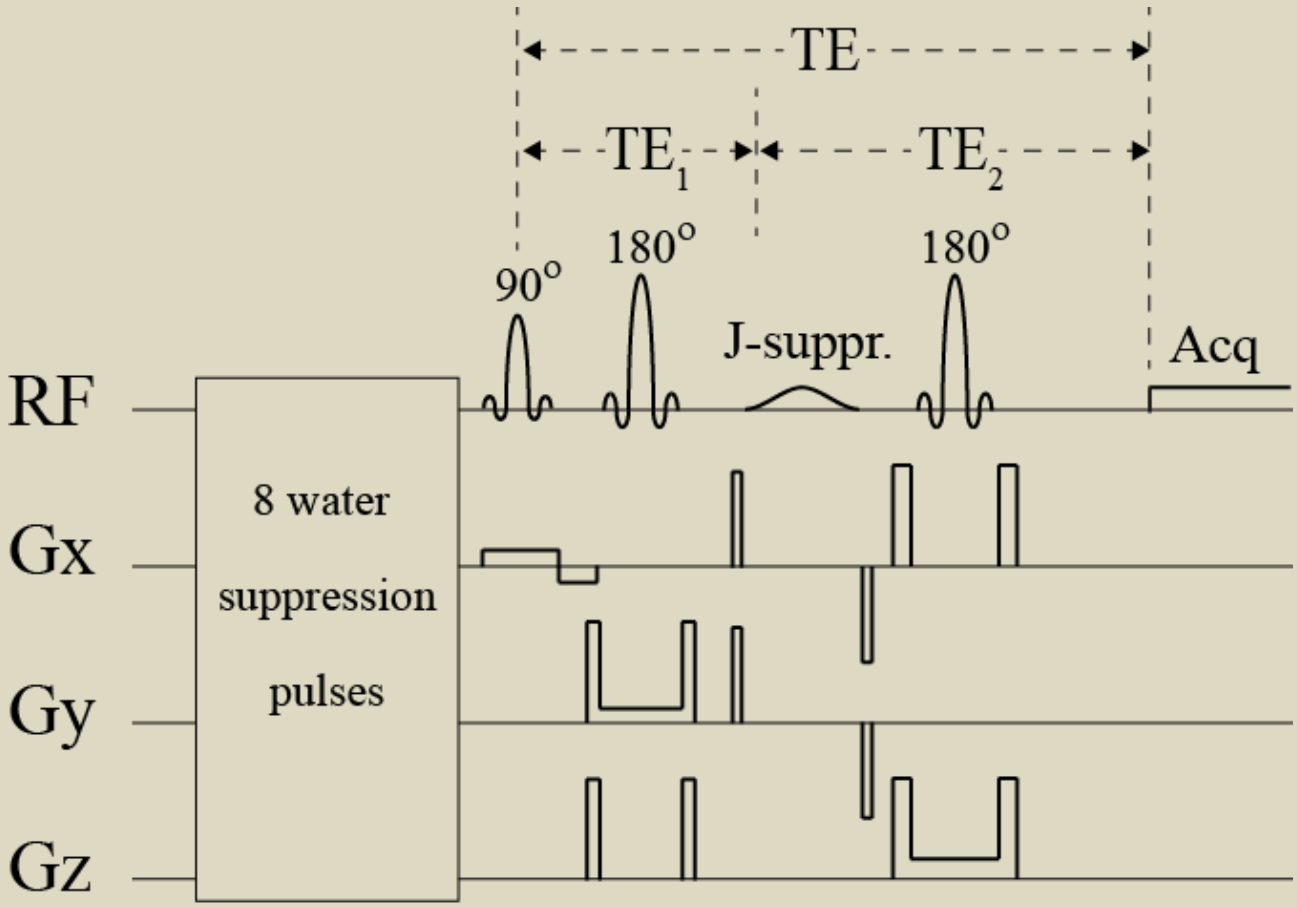
- Spatial localization is necessary for *in vivo* MRS.
- The intersection of the three selected planes forms the MRS voxel in the shape of rectangular prism.



Detection of Glu, Gln, and GSH at 7T

Improve the detection of Glu, Gln, and GSH by minimizing the NAA multiplet signals at 2.5 ppm using a TE-optimized PRESS pulse sequence and a novel J-suppression RF pulse.

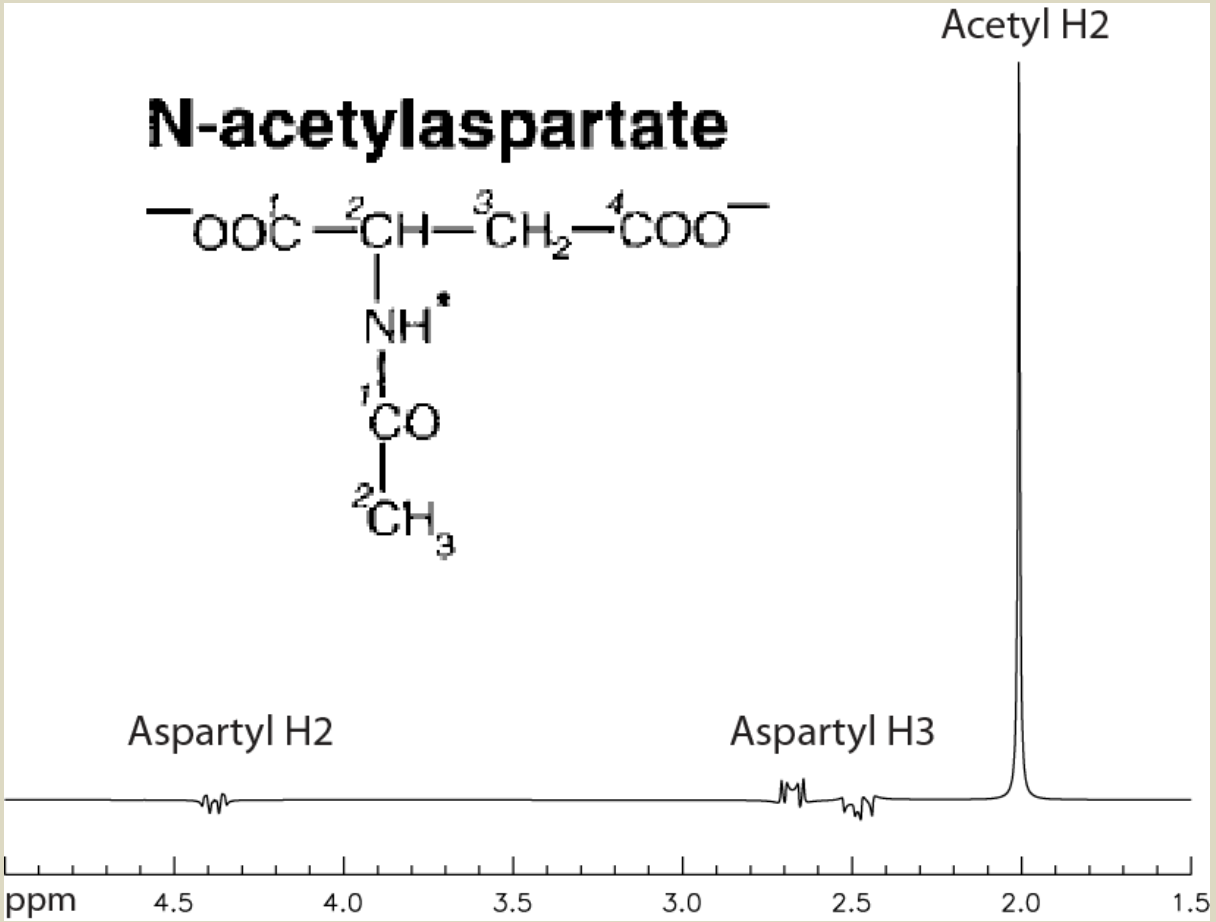
An L, Li S, Murdoch JB, Araneta MF, Johnson C, Shen J. Detection of glutamate, glutamine, and glutathione by radiofrequency suppression and echo time optimization at 7 tesla. Magnetic Resonance in Medicine 2015;73:451-458.



Modified pulse sequence with the J-suppression pulse

J-Suppression RF pulse

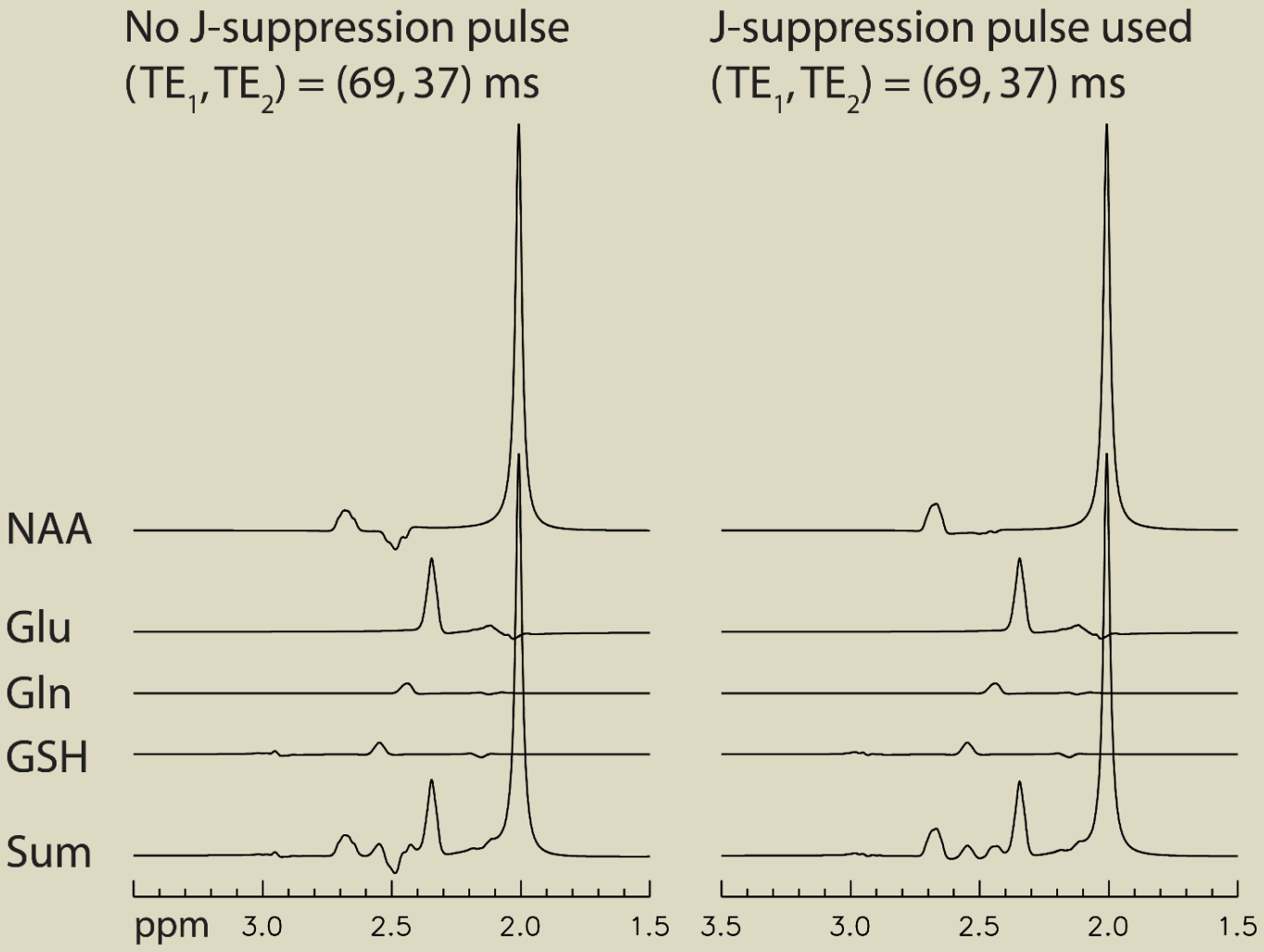
A frequency selective RF pulse placed at the resonance frequency of the aspartyl CH proton of N-acetyl-aspartate (NAA) at 4.38 ppm, which alters the J-evolution of the NAA aspartyl CH_2 multiplet at 2.5 ppm.



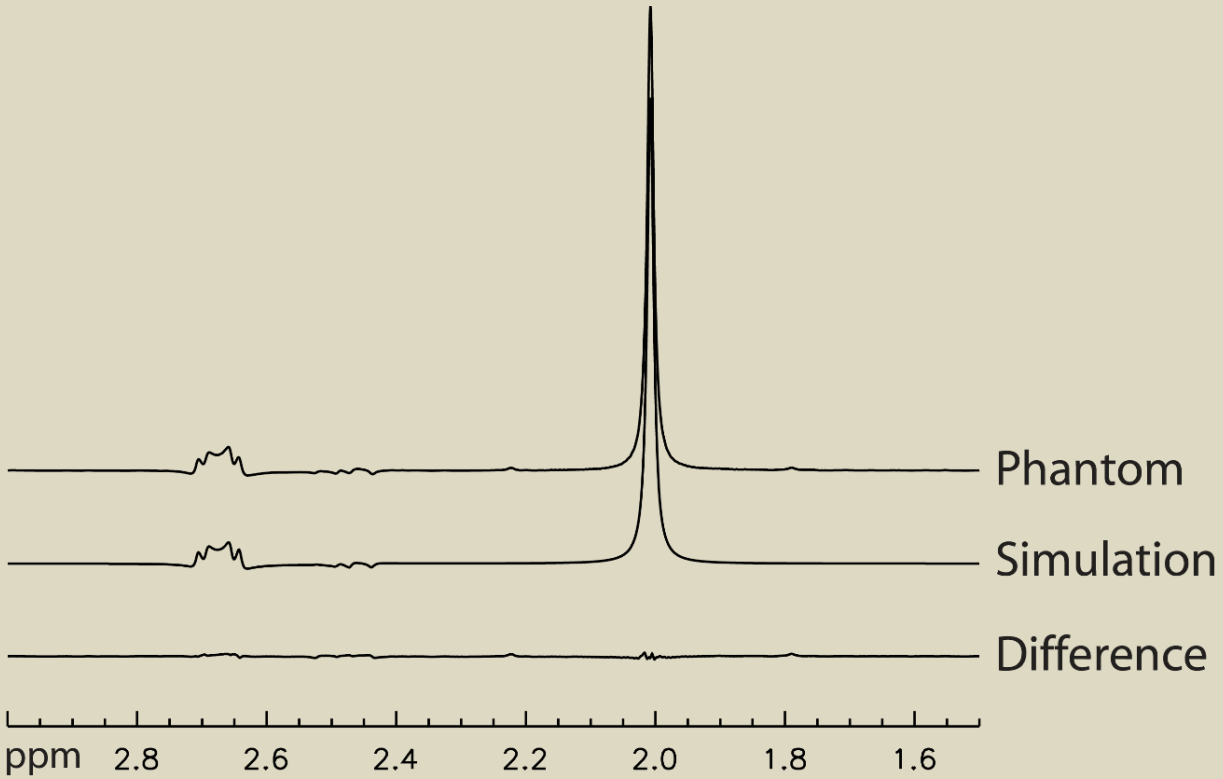
Optimization of the J-suppression pulse

- Density matrix simulations using experimental RF pulse shapes with 3D localization were performed to find optimal values for TE_1, TE_2, flip angle and time delay of the J-suppression pulse to minimize the NAA multiplet at 2.5 ppm.
- An in-house developed density matrix simulation program was used, which was thousands of times faster than existing programs. Instead of directly computing the evolution of density operators over 3D spatial points, we decoupled the three spatial dimensions and computed propagator operators in 1D.

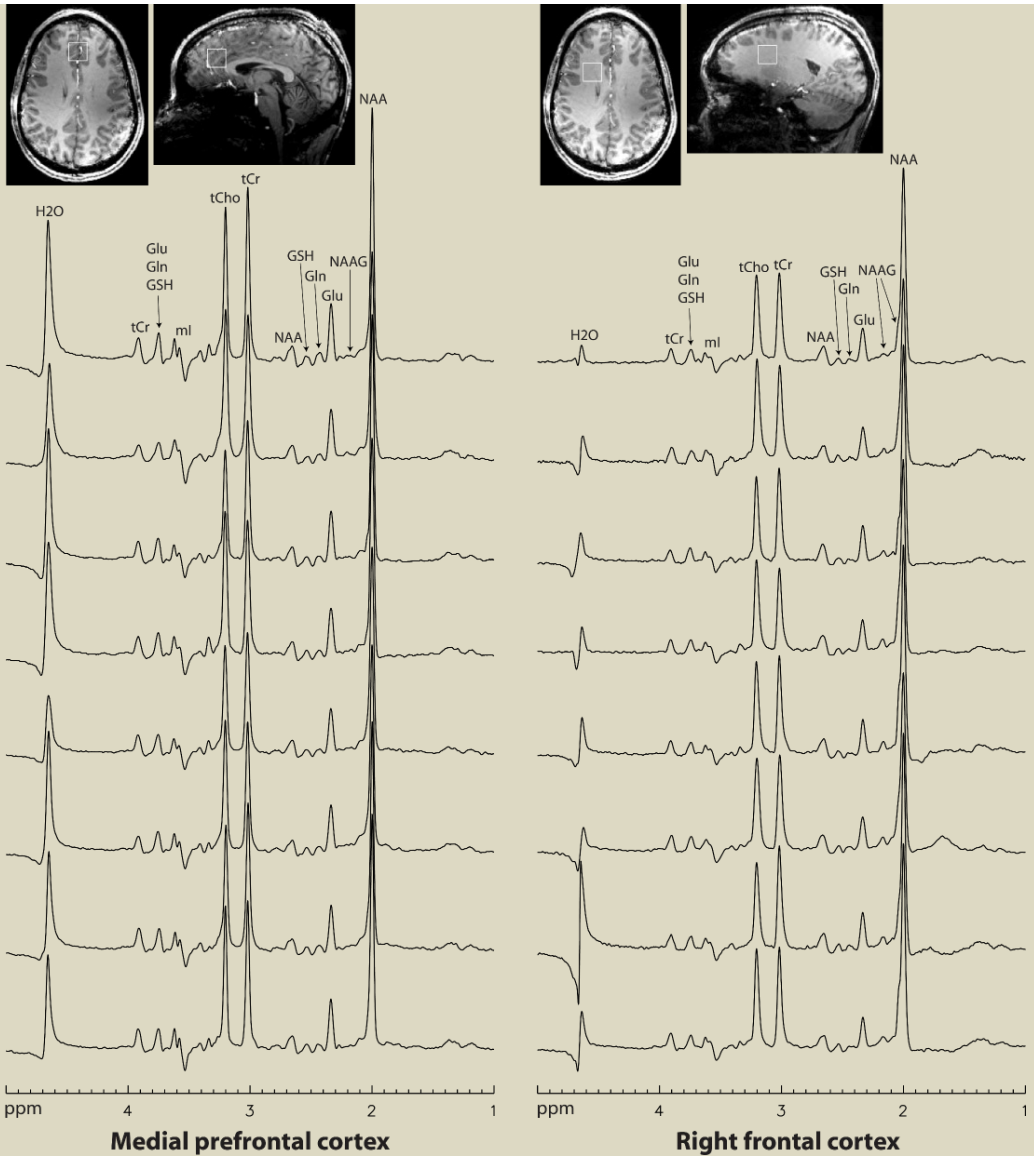
An L, Li SZ, Wood ET, Reich DS, Shen J. N-Acetyl-Aspartyl-Glutamate Detection in the Human Brain at 7 Tesla by Echo Time Optimization and Improved Wiener Filtering. Magnetic Resonance in Medicine 2014;72(4):903-912.



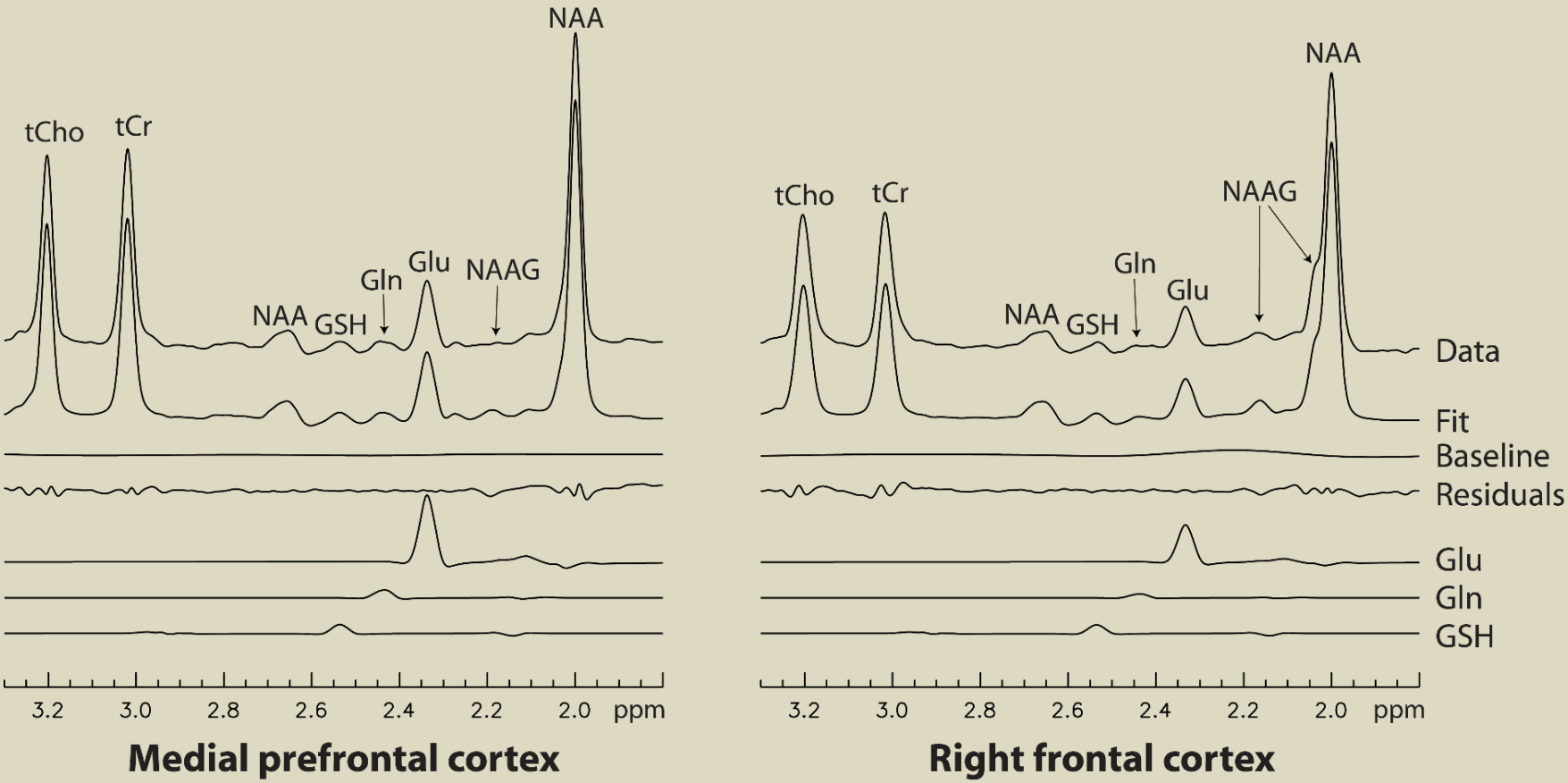
Density matrix simulated spectra of NAA, Glu, Gln, and GSH with a concentration ratio of 1 : 0.7 : 0.15 : 0.15 using the PRESS sequence without and with the J-suppression pulse.



Comparison of experimental and density matrix simulated NAA spectra. The experimental spectrum was obtained by measuring a NAA phantom at 37 deg Celsius using the modified PRESS sequence with the J-suppression pulse (TR = 2.5 s, TE_1 = 69 ms, TE_2 = 37 ms, suppression pulse flip angle = 90º). The simulated spectrum was obtained by density matrix simulation and fitted to the phantom spectrum by phase correction, frequency shift, and line broadening.



Stack plots of spectra from the prefrontal cortex and right frontal cortex of eight healthy volunteers acquired using the modified PRESS sequence with the J-suppression pulse (TR = 2.5 s, TE_1 = 69 ms, TE_2 = 37 ms, suppression pulse flip angle = 90º). Metabolite peaks downfield from 3.7 ppm were partially suppressed by the water suppression pulses that had a bandwidth of ~350 Hz. Gaussian line broadening of 3 Hz was applied to all spectra.



Linear combination fitting plots for one healthy volunteer. Spectral data between 1.8 - 3.3 ppm were used in the data fitting.

	Medial prefrontal cortex	Right frontal cortex
Glu	1.17±0.07	1.06±0.09
Gln	0.25±0.03	0.20±0.04
GSH	0.21±0.02	0.27±0.03
NAA	1.52±0.14	1.90±0.18
NAAG	0.12±0.04	0.35±0.09
tCr	1	1
tCho	0.30±0.03	0.35±0.03

Metabolite ratios (/[tCr]) in the grey matter (GM) dominant medial prefrontal cortex and white matter (WM) dominant right frontal cortex of eight healthy volunteers.

Dynamic ^{13}C Labeling of Glu and Gln Using ^{1}H MRS

- *In vivo* measurement of Glu and Gln turnover from intravenously infused ^{13}C labeled substrates is a powerful tool for investigations of energy metabolism and neurotransmission in the human brain.
- Demonstrate the feasibility of quantifying the time-courses of [4-^{13}C]Glu and [4-^{13}C]Gln concentrations during intravenous infusion of [U-$^{13}C_6$]glucose using ^{1}H MRS at 7 Tesla

1. An L, Li S, Murdoch JB, Araneta MF, Johnson C, Shen J. Detection of glutamate, glutamine, and glutathione by radiofrequency suppression and echo time optimization at 7 tesla. Magnetic Resonance in Medicine 2015;73:451-458
2. An L, Li S, Araneta MF, Johnson C, Murdoch JB, and Shen J. "*In Vivo* Detection of ^{13}C Labeling of Glutamate and Glutamine Using Proton MRS at 7T", ISMRM 2015:0207, Toronto, Canada.

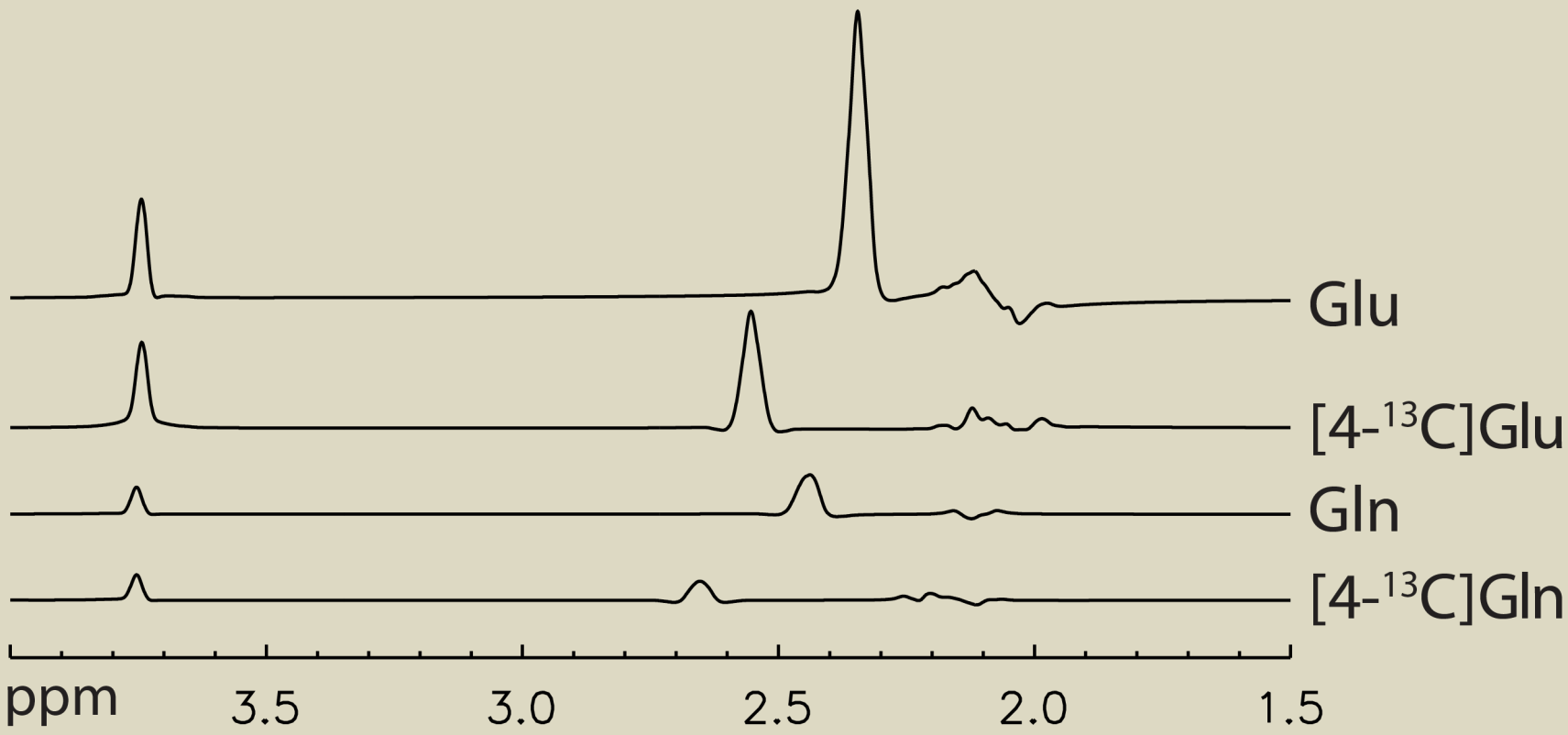
Strategy:

To observe and quantify signal changes of the C4 protons of Glu and Gln because:

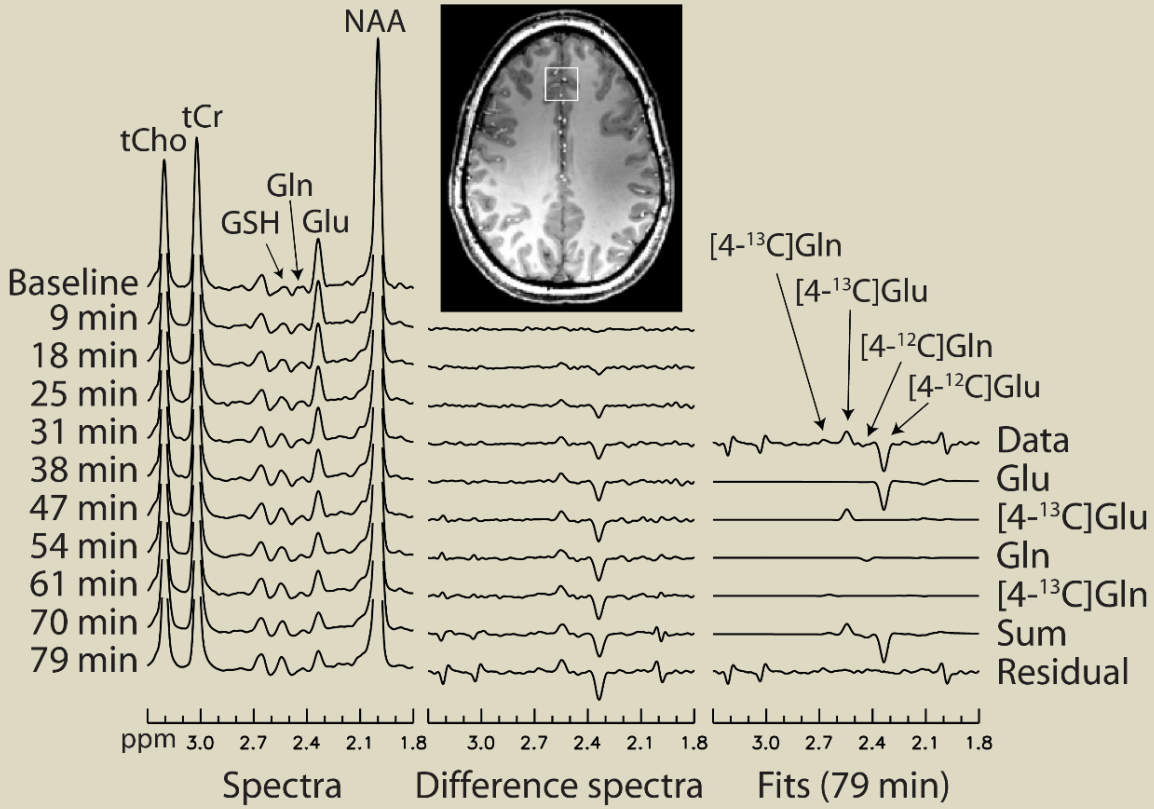
1) In the ^{1}H spectra of Glu and Gln, the largest peaks come from the H4 protons
2) During infusion of [U-$^{13}C_6$]glucose, ^{13}C is incorporated into the C4 sites of Glu and Gln in the first turn of the tricarboxylic acid cycle.

***In Vivo* Study:**

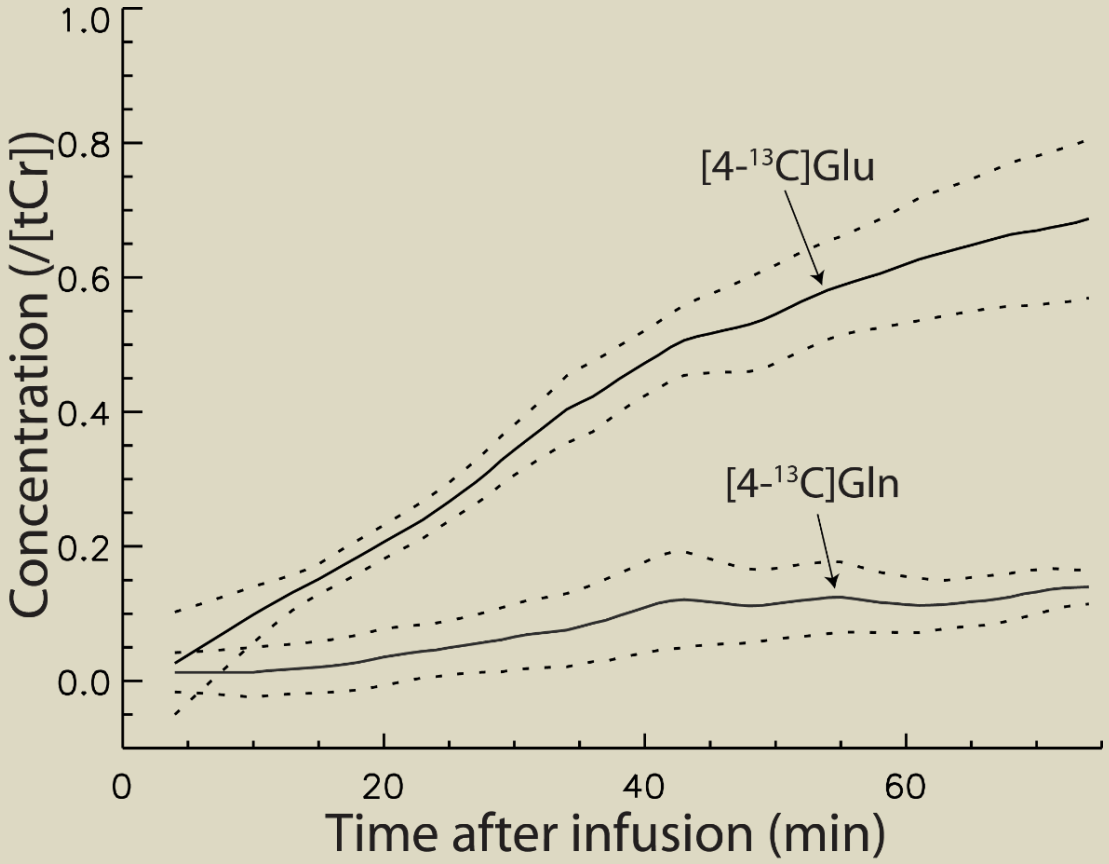
- Eight healthy volunteers
- Two antecubital veins cannulated
- Baseline MRS scan
- Repeated MRS scans during infusion
- Each MRS scan lasted 5’45”



Density matrix simulation of Glu and Gln with ^{13}C infusion



Spectra of one healthy volunteer during infusion. Time-course spectra (left), time-course difference spectra (middle), and fitting results for the last time point (right) from a 2×2×2 cm^3 voxel in the medial prefrontal cortex of a healthy volunteer during [U-$^{13}C_6$]glucose infusion.

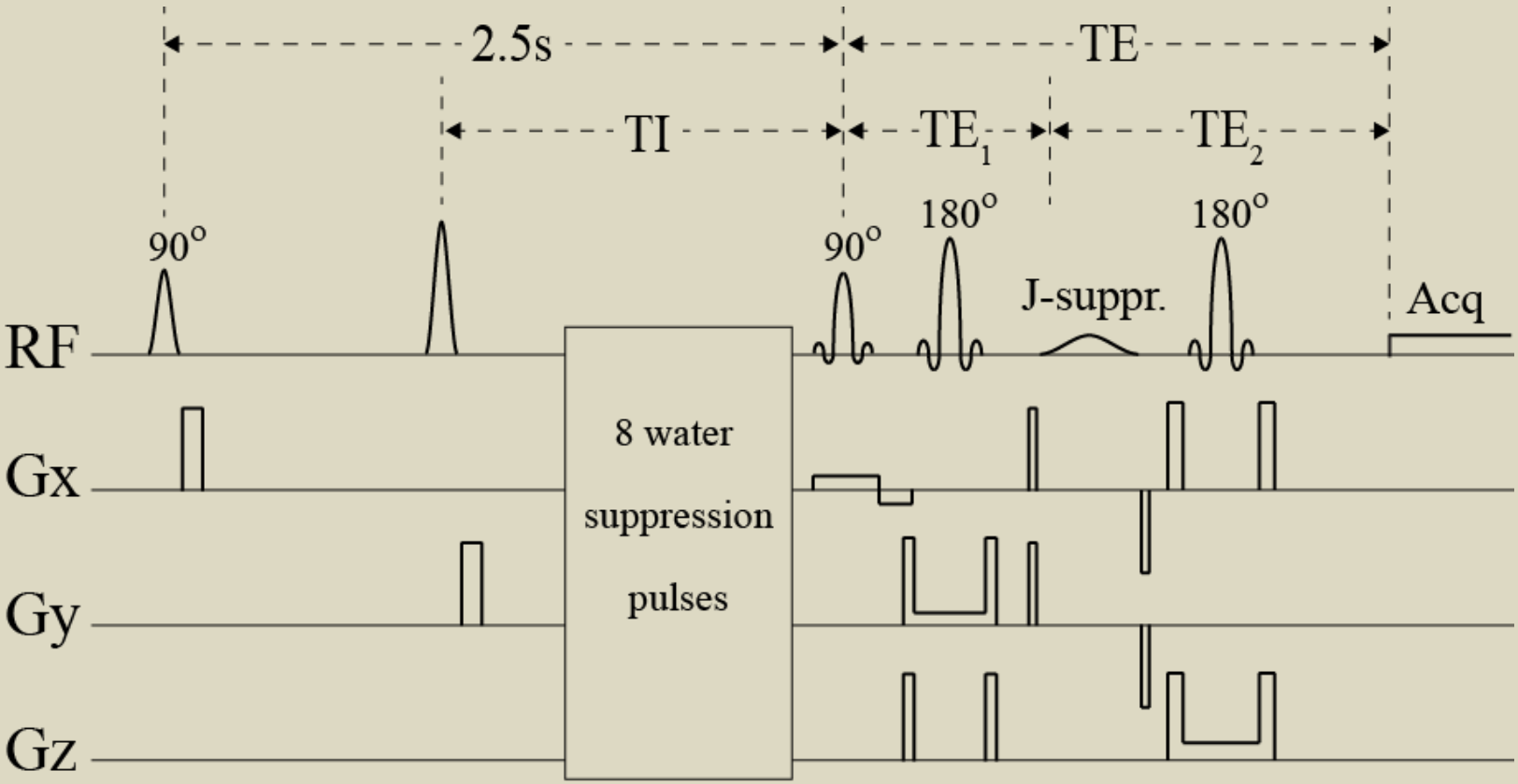


Time courses of [4-^{13}C]Glu and[4-^{13}C]Gln concentrations averaged over eight healthy volunteers. The dotted lines represent 95% confidence intervals.

Simultaneous Measurement of Metabolite T1 and T2 Relaxation Times

- Conventional approach: Measure metabolite T1 and T2 separately
- Proposed approach: Measure metabolite T1 and T2 simultaneously

An L, Li S, and Shen J. (2017), Simultaneous determination of metabolite concentrations, T_1 and T_2 relaxation times. Magn. Reson. Med. doi:10.1002/mrm.26612

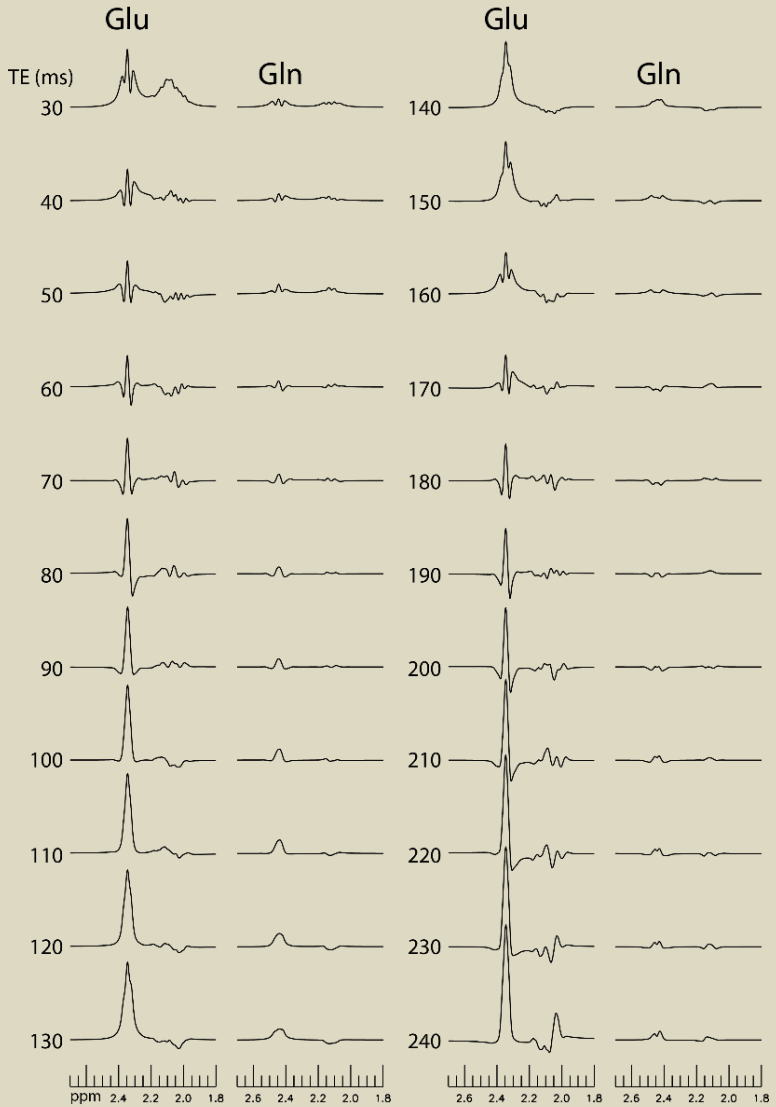


Pulse sequence for measuring T1 and T2 simultaneously

Set #	TE (ms)	TE1 (ms)	TI (ms)	J-Sup angle (deg)	Ave
1	60	30	None	0	4
2	60	37	None	0	4
3	70	30	None	0	4
4	70	30	1600	0	4
5	70	30	1150	0	4
6	70	30	800	0	4
7	70	30	471	0	4
8	70	30	244	0	4
9	70	40	None	0	4
10	70	40	1600	0	4
11	70	40	1150	0	4
12	70	40	800	0	4
13	70	40	471	0	4
14	70	40	244	0	4
15	80	38	None	0	4

Set #	TE (ms)	TE1 (ms)	TI (ms)	J-Sup angle (deg)	Ave
16	80	50	None	0	4
17	90	45	None	60	4
18	90	72	None	60	4
19	100	70	None	90	8
20	100	70	1600	90	8
21	100	70	1150	90	8
22	100	70	800	90	8
23	100	70	471	90	8
24	100	70	244	90	8
25	110	70	None	90	8
26	120	80	None	90	8
27	130	90	None	90	8
28	170	16	None	90	16
29	220	18	None	90	16
30	230	26	None	90	16

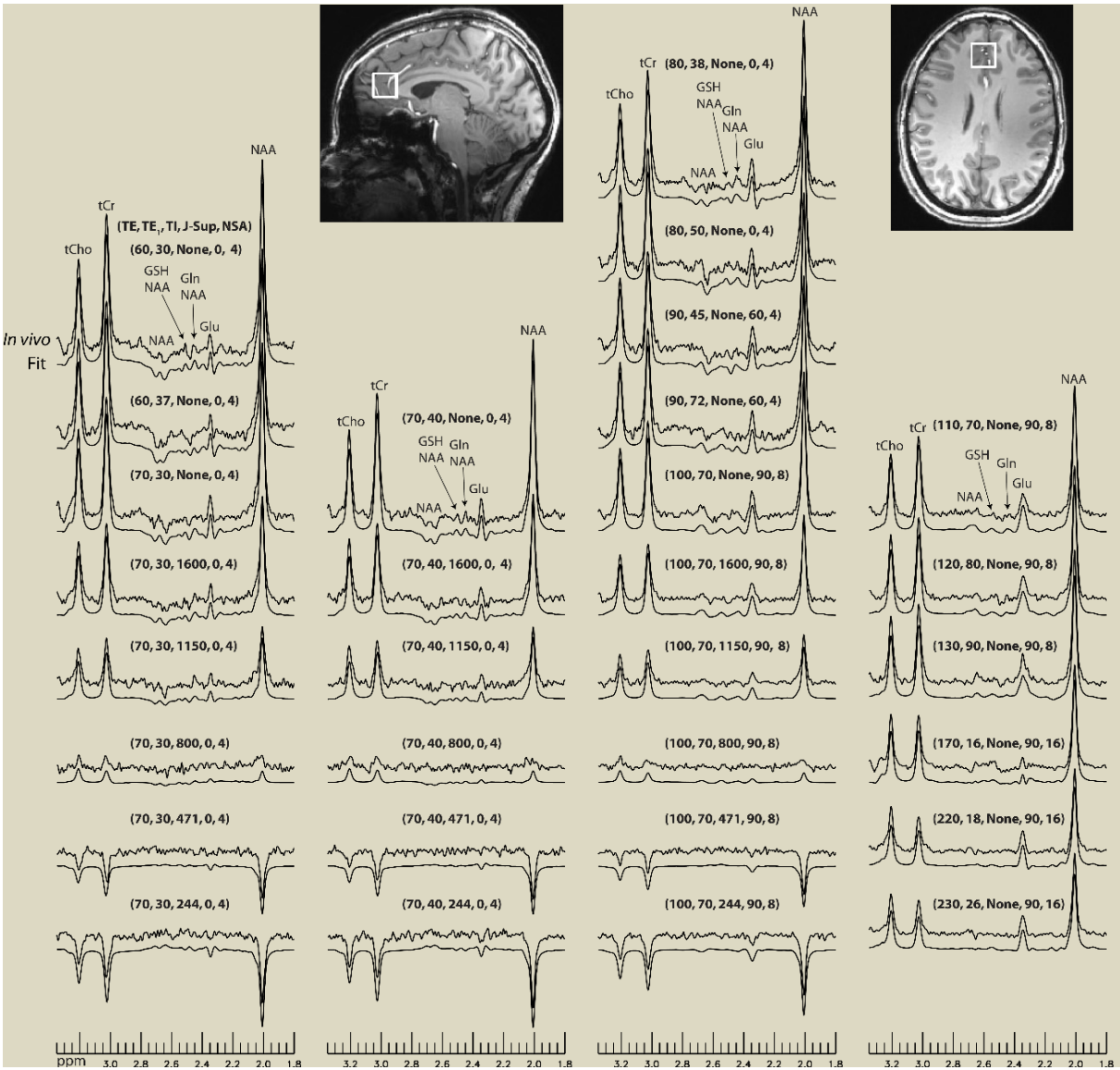
Values for the 30 sets of acquisition parameters . TR = 3 s, total scan time = 9 min and 48 s



Density matrix simulated spectra of Glu and Gln for TE = 30 – 240 ms with a 10 ms increment. The concentration ratio was [Glu] : [Gln] = 4 : 1. T_2 relaxation was ignored here.

In Vivo Experiments

- Nine healthy volunteers
- Two 2x2x2 cm^3 voxels in each volunteer:
    1. prefrontal cortex
    2. right frontal cortex
- Basis sets were computed for 12 metabolites and all 30 sets of parameters.
- A novel two passage fitting approach. In the second passage, all 30 sets of spectra were fitted together.



Reconstructed spectra and corresponding Fits

	Metabolite ratio (/[tCr])		T_1 (s)		T_2 (ms)	
	GM	WM	GM	WM	GM	WM
NAA (CH_3)	1.16 ± 0.10	1.32 ± 0.11	1.43 ± 0.02	1.54 ± 0.05	203 ± 17	169 ± 16
NAA (CH_2)	1.16 ± 0.10	1.32 ± 0.11	0.94 ± 0.11	0.99 ± 0.12	141 ±17	122 ± 14
Glu	0.94 ± 0.14	0.94 ± 0.11	1.27 ± 0.12	1.55 ± 0.14	184 ± 18	139 ± 8
Gln	0.40 ± 0.15	-	1.04 ± 0.27	-	84 ± 25	-
GSH	-	-	0.49 ± 0.11	-	-	-
tCr	1	1	1.31 ± 0.03	1.53 ± 0.04	127 ± 6	109 ± 7
tCho	0.25 ± 0.04	0.30 ± 0.08	1.17 ± 0.03	1.19 ± 0.03	197 ± 11	130 ± 14

Metabolite concentration (/[tCr]), T_1, and T_2 values in the frontal GM and WM dominant regions of nine healthy volunteers.

Compared to conventional methods where T_1 and T_2 are determined separately, the proposed method had smaller variations in computed T_1 and T_2 values because information from all collected data was utilized in computing both T_1 and T_2.