Advanced MRI in the Clinic: MR Spectroscopy

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Information Encoding

Larmor equation

$$\omega = \gamma B$$

Magnetic information encoded in frequency

fixed for a specific nucleus (^{1}H, ^{13}C, etc.)

Extrinsic factors

- B_0
- Magnetic field gradients
- Magnetic field inhomogeneity

Intrinsic factors

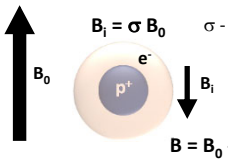
- Electron shielding
- J-coupling

Information Encoding

Larmor frequency $\omega = \gamma B$

Electron shielding

$B_i = \sigma B_0$ σ - shielding constant



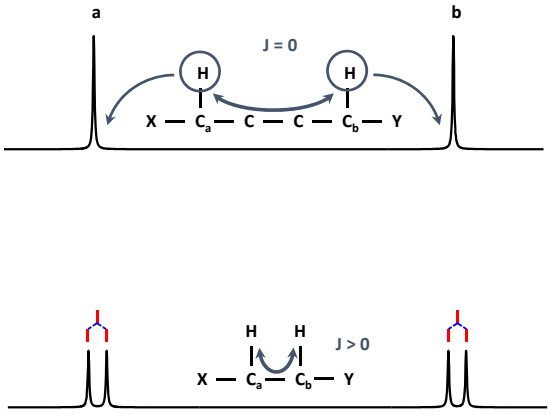
$B = B_0 - B_i$

$B = B_0 (1 - \sigma)$

$\omega = \gamma B_0 (1 - \sigma)$

Scalar spin-spin interaction (J-coupling)

Interaction between spins mediated through chemical bonds



Slide courtesy of Ivan Tkáč.

Chemical Shift

$\omega_i = \gamma B_0 (1 - \sigma_i)$

$\nu_i = \gamma B_0 (1 - \sigma_i)/2\pi$

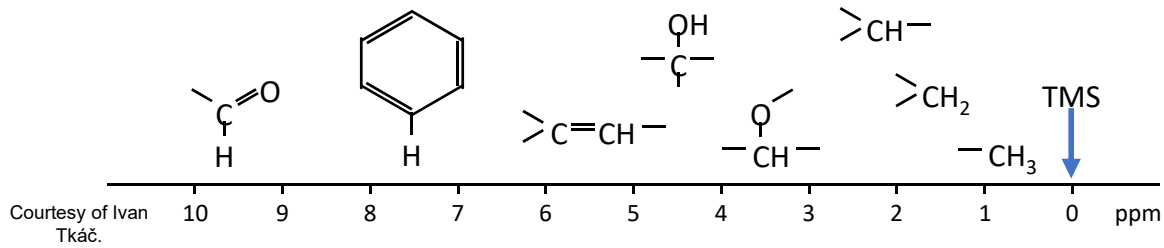
$\delta_i = (\nu_i - \nu_{ref})/\nu_0$

Chemical shift reference

Tetramethylsilane (TMS)

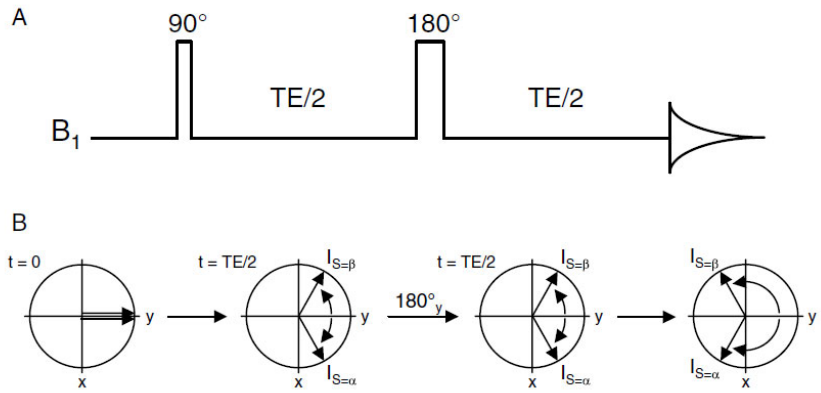
- **independent of B_0**
- **units: ppm**

increased proton shielding



Courtesy of Ivan Tkáč.

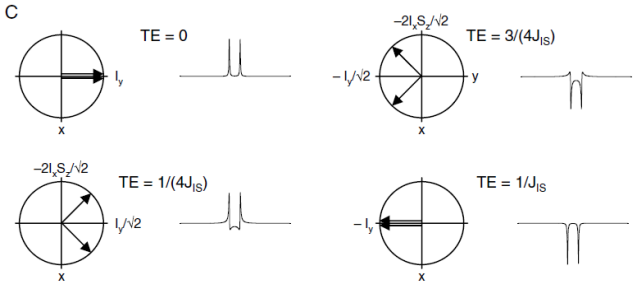
J-coupling evolution



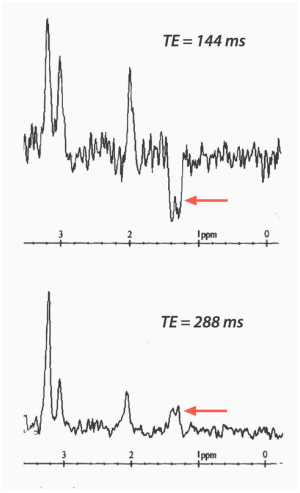
De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.

180° RF pulse does NOT re-phase evolution due to J-coupling.

J-coupling evolution



De Graaf, Robin A. *In vivo NMR spectroscopy: principles and techniques*. John Wiley & Sons, 2007.



Courtesy of Allen D. Elster, MRIquestions.com.

Choice of TE affects spectral peak appearance of coupled nuclei.

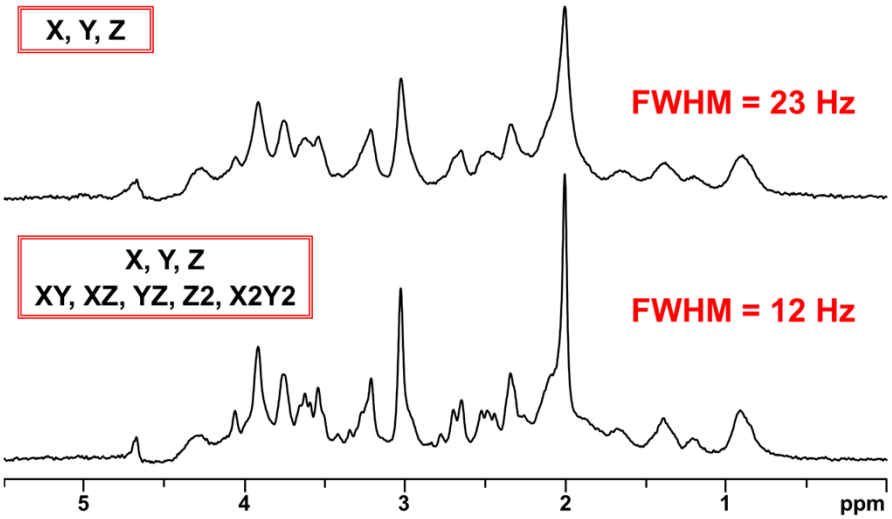
4 Requirements for Successful MRS

1. Incredibly homogeneous magnetic field
2. Effective water/fat suppression
3. High-quality localization
4. Robust analysis

Magnetic Field Homogeneity

- MRI requires a homogeneous magnetic field. MRS requires an incredibly homogeneous field.
- FWHM $\propto 1/T_2^*$ so better homogeneity $\rightarrow$ narrower peaks (i.e. better spectral resolution).
- Narrow peaks are also required for good water suppression.
- Good shimming is critical
  - Figure out which technique works best on your scanner.
  - Repeat the shim and/or re-position the patient if necessary.
  - Use a system with at least 2nd-order shims.

Magnetic Field Homogeneity



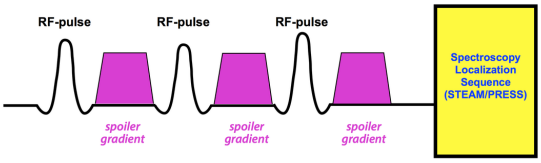
Courtesy of Ivan Tkáč.

Water suppression

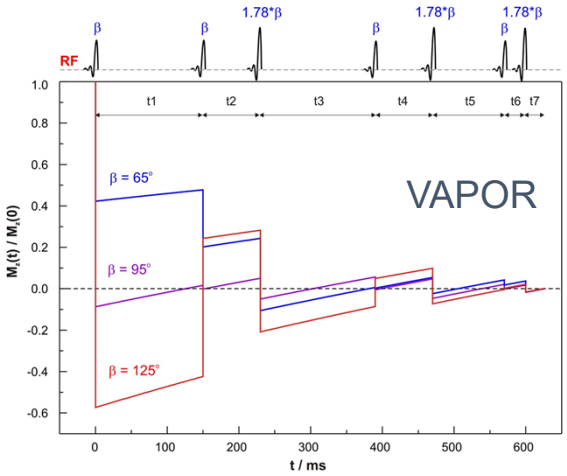
- Water signal (55M) must be suppressed to accurately visualize metabolite signals (0.5-10mM), even with high-quality digital ADCs.
- Our goal is to suppress the water signal by >98%.
- Relaxation-based methods (e.g. IR prep) are problematic so most clinical techniques use chemically-selective saturation (i.e. FatSat tuned to water).
- CHESS is the most common in the clinic.
- As a general rule, the longer and stronger (i.e. more time and/or SAR), the better the water suppression.

Water suppression

3x CHESS

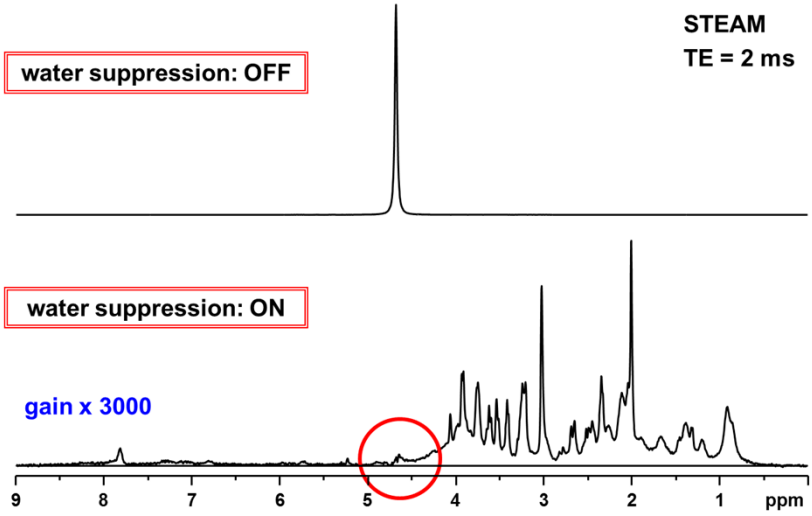


Courtesy of Allen D. Elster, MRIquestions.com



Tkáč, Ivan, et al. "In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time." *Magnetic Resonance in Medicine* 41.4 (1999): 649-656.

Water suppression



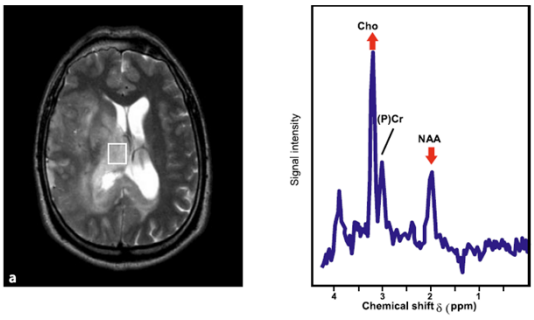
Courtesy of Ivan Tkáč

Localization

- For a spectrum to aid clinical diagnosis, the location from which it was obtained must be known accurately.
- Surface coil localization was originally used for superficial lesions and cardiac studies, but is no longer common.
- Single voxel spectroscopy (SVS) and multi-voxel spectroscopy (MVS, a.k.a. spectroscopic imaging [SI]) are currently used in the clinic.

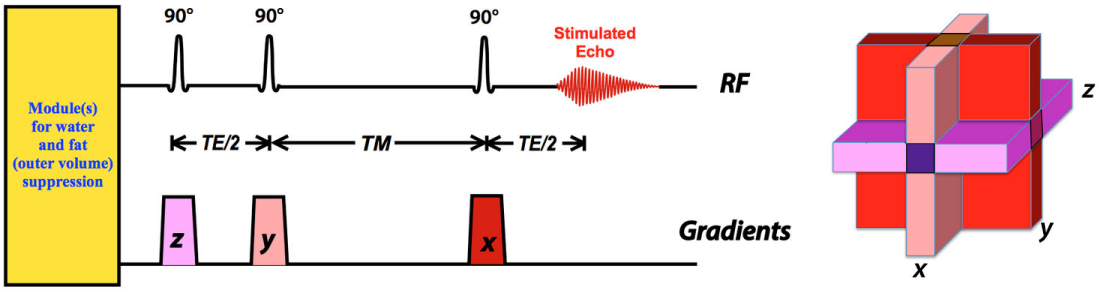
Single voxel spectroscopy (SVS)

- Most common technique.
- Simple to acquire and interpret.
- Excellent SNR efficiency.
- Single, localized voxel allows for excellent shimming and, therefore, high-quality spectra.
- Many sequences clinically available.



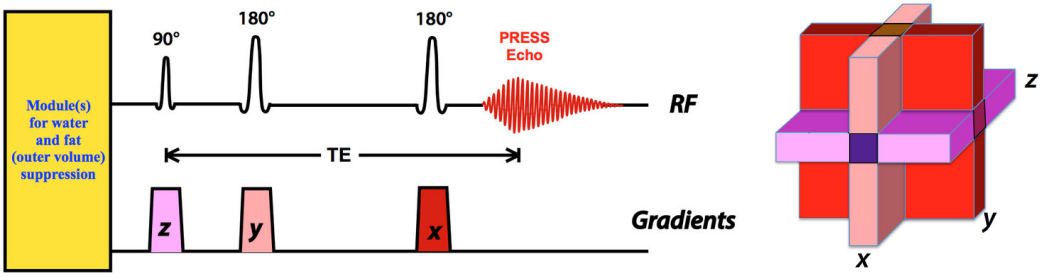
Courtesy of R. Jason Stafford

Stimulated Echo Acquisition Mode (STEAM)



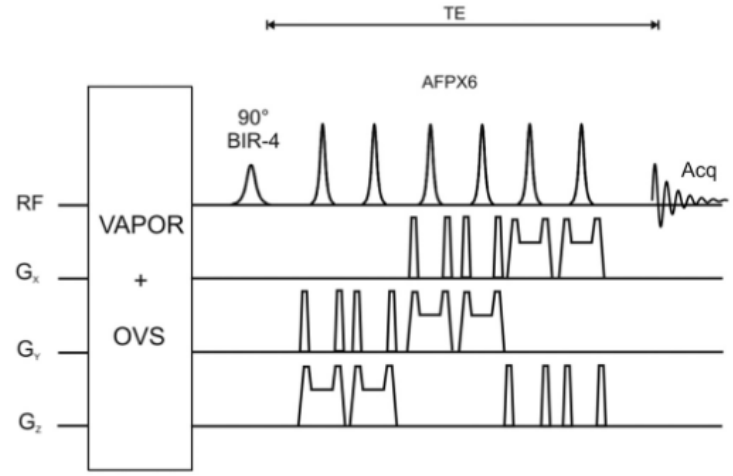
Courtesy of Allen D. Elster, MRIquestions.com

Point Resolved Spectroscopy (PRESS)



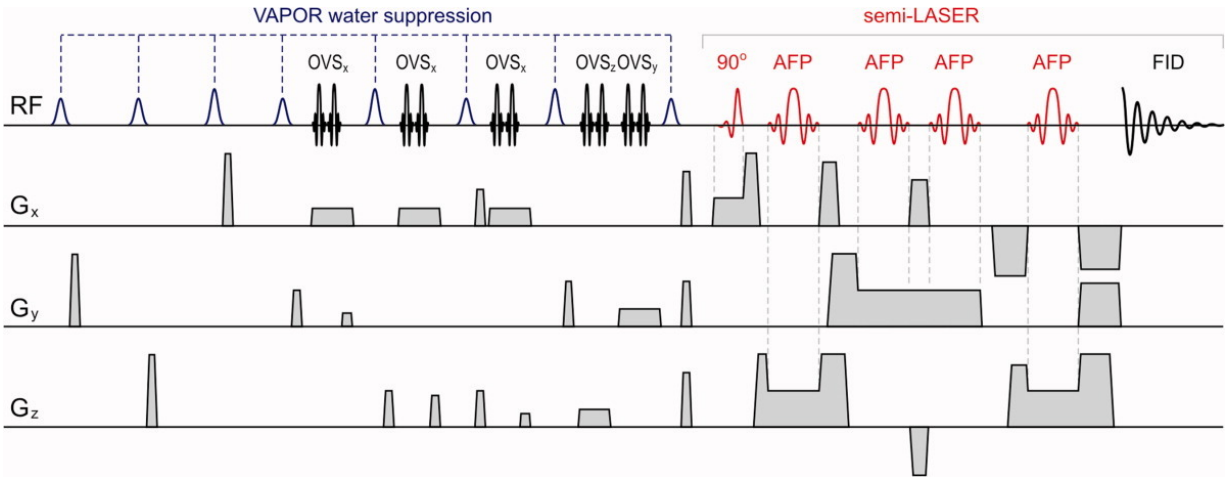
Courtesy of Allen D. Elster, MRIquestions.com

Localization by Adiabatic Selective Refocusing (LASER)



Stagg, Charlotte, and Douglas L. Rothman, eds. *Magnetic resonance spectroscopy: tools for neuroscience research and emerging clinical applications*. Academic Press, 2013.

semi-LASER



Öz, Gülin, and Ivan Tkáč. "Short-echo, single-shot, full-intensity proton magnetic resonance spectroscopy for neurochemical profiling at 4 T: validation in the cerebellum and brainstem." Magnetic resonance in medicine 65.4 (2011): 901-910.

semi-LASER

Mitigates most of the problems with LASER, while keeping most of the benefits of using adiabatic pulses.

Sequence Recommendation

For routine clinical use:

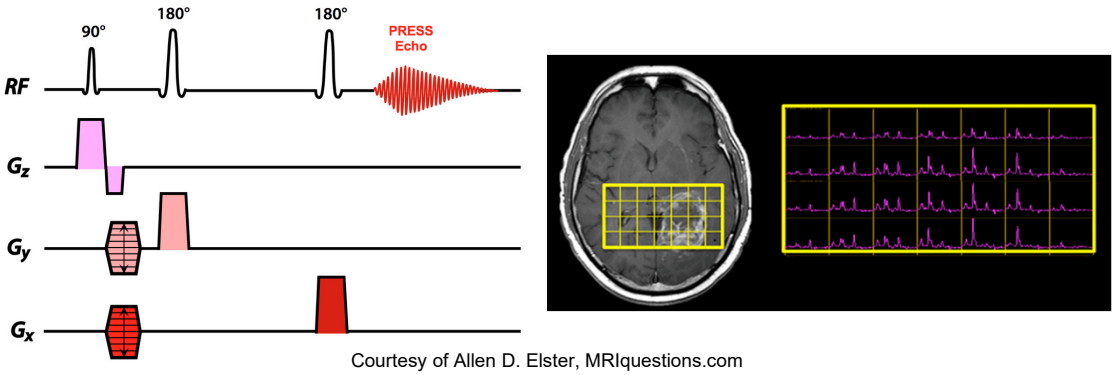
1. Try semi-LASER if you have it.
2. If not available, try PRESS (3 T and lower) or STEAM (7 T).

Wilson, Martin, et al. "Methodological consensus on clinical proton MRS of the brain: Review and recommendations." Magnetic resonance in medicine 82.2 (2019): 527-550.

Multi-Voxel Spectroscopy (MVS)

- A larger total coverage area takes the guesswork out of SVS voxel placement and permits “mapping” of metabolite distribution.
- Smaller individual voxels are possible, which leads to higher spatial resolution, but lower SNR and potential spectral contamination from adjacent voxels.
- Acquisition times are usually long, though acceleration techniques are clinically available.
- Difficulties obtaining a good shim/water suppression over the entire region often results in reduced quality.
- MVS sequences are usually just SVS sequences with phase encoding.

Multi-Voxel Spectroscopy (MVS)



Courtesy of Allen D. Elster, MRIquestions.com

MRS Analysis

- Goal is to quantify different metabolites and several software packages are available.
- Spectra are processed (baseline correction, phase correction, apodization, Fourier transform, etc.) and then quantified.
- Some software programs are significantly more advanced than others.

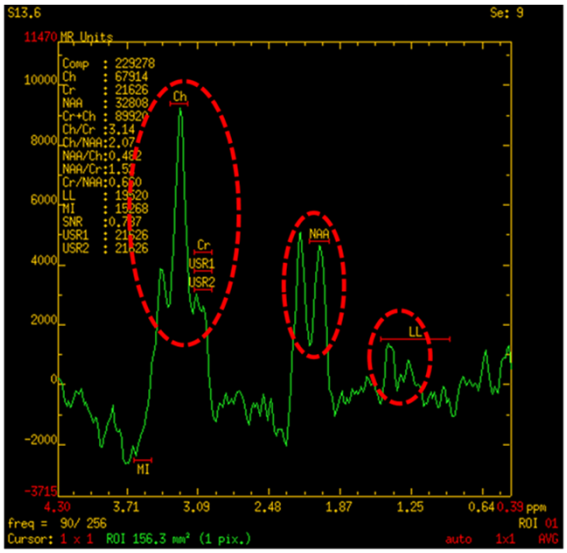
MRS Analysis Software

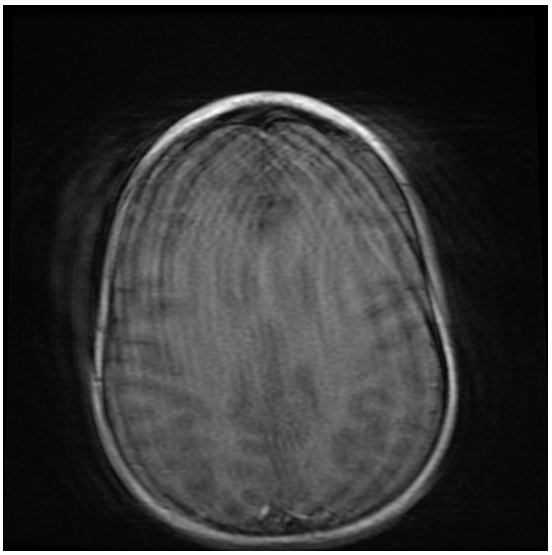
Vendor Basic	Vendor Agnostic	Vendor Advanced
Comes with the vendor MRS package.	e.g. LCModel, Tarquin	e.g. Syngo, IntelliSpace, READYView
Often automatic.	Very advanced software with sophisticated fitting algorithms.	Best of both worlds.
Very simple peak height or integral quantification.	Fully customizable (basis sets, metabolites, processing, etc.).	Rapidly approaching vendor agnostic software in terms advanced features.
Only a few metabolites can be quantified.	Provide estimates of quantification errors and metrics of spectral quality.	Allows for sophisticated processing, custom metabolites, error estimation, etc.
	Not FDA approved.	

MRS Artifacts

- Artifacts in MRS appear very different from artifacts in MRI and are often less conspicuous.
- Kreis, Roland. "Issues of spectral quality in clinical 1H-magnetic resonance spectroscopy and a gallery of artifacts." NMR in Biomedicine 17.6 (2004): 361-381.

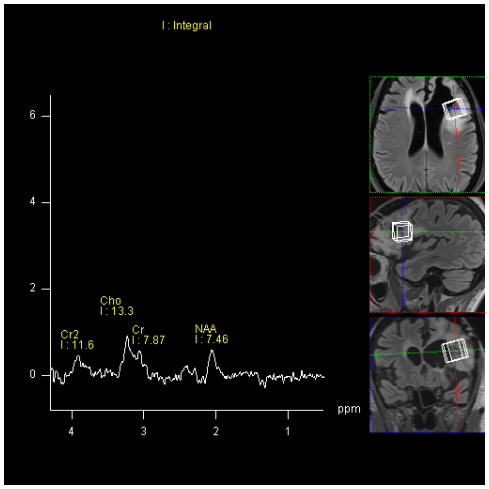
Motion artifact





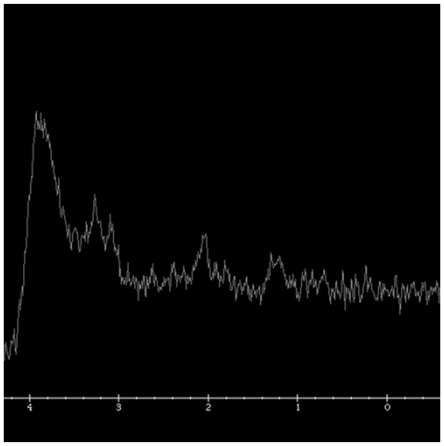
Susceptibility Artifact

- Poor shimming results in wide, short (low SNR), and poorly-separated peaks.
- Strong susceptibility artifacts may arise from air-tissue interfaces, blood products, etc.
- The presence of strong susceptibility gradients may prevent a good shim and, therefore, the acquisition of high-quality spectra.



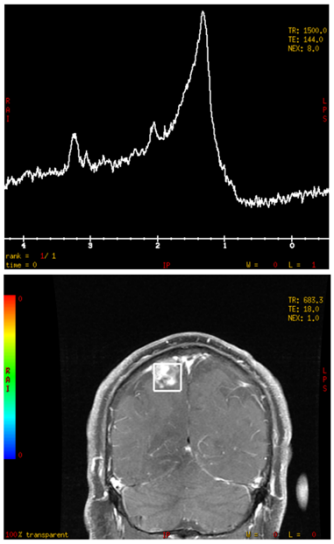
Poor Water Suppression

- Poor water suppression is usually evidenced by non-linear baselines and low peak SNR, especially above 3.5 ppm.
- Often due to poor shim and more common in MVS (where getting a good shim over the entire volume is challenging).



Signal Bleed

- Typically evidenced by the phase difference and broadness of the peak.
- This particular voxel was located very near the skull and sequence/pulse imperfections (and, possibly, patient motion) acquired some signal from the scalp.
- OVS is important.



CNS

- MRS is indicated for a variety of neurological conditions
- The most common uses include:
  - Primary diagnosis of brain lesions.
  - Distinguishing recurrent brain tumor from radiation necrosis.
  - Diagnosis of inborn errors of metabolism affecting the CNS.

ACR–ASNR–SPR Practice Parameter for the Performance and Interpretation of Magnetic Resonance Spectroscopy of the Central Nervous System (2019).

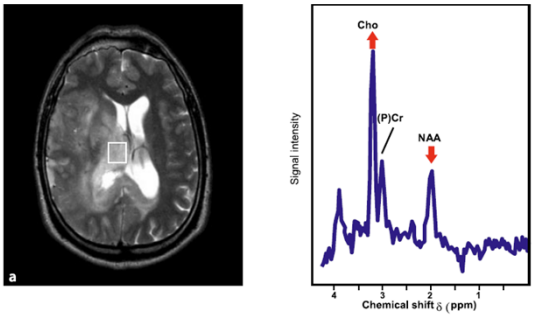
II. INDICATIONS

When conventional imaging by magnetic resonance imaging (MRI) or computed tomography (CT) provides limited information regarding specific clinical questions, indications for MRS in adults and children include, but are not limited to, the following:

1. Evidence or suspicion of primary or secondary neoplasm (pretreatment and posttreatment)
2. Grading of primary glial neoplasm, particularly high-grade versus low-grade glioma [5,6]
3. Evidence or suspicion of brain infection, especially cerebral abscess (pretreatment and posttreatment) and HIV-related infections
4. Seizures, especially temporal lobe epilepsy
5. Evidence or suspicion of neurodegenerative disease, especially Alzheimer's disease, Parkinson's disease, and Huntington's disease [7-9]
6. Evidence or suspicion of subclinical or clinical hepatic encephalopathy
7. Evidence or suspicion of an inherited metabolic disorder, such as Canavan disease, mitochondrial encephalopathies, and other leukodystrophies [10,11]
8. Suspicion of acute brain ischemia or infarction, including birth asphyxia [12]
9. Evidence or suspicion of a demyelination or dysmyelination disorder [13-16]
10. Evidence or suspicion of traumatic brain injury
11. Evidence or suspicion of brain developmental abnormality and cerebral palsy
12. Evidence or suspicion of other neurodegenerative diseases, such as amyotrophic lateral sclerosis
13. Evidence or suspicion of chronic pain syndromes
14. Evidence or suspicion of chromosomal and inherited neurocutaneous disorders, such as neurofibromatosis and tuberous sclerosis
15. Evidence or suspicion of neurotoxicity, such as misuse of medications, and exposure to environmental hazards, such as carbon monoxide and inhalants
16. Evidence or suspicion of hypoxic ischemic encephalopathy
17. Evidence or suspicion of spinal cord disorders, such as tumors, demyelination, infection, and trauma
18. Evidence of neuropsychiatric disorders, such as depression, posttraumatic stress syndrome, and schizophrenia [17-26]
19. Differentiation between recurrent tumor and treatment-related changes or radiation injury
20. Differentiation of cystic lesions (eg, abscess versus cystic metastasis or cystic primary neoplasm)
21. Evidence or suspicion of cerebral vasculitis, systemic lupus erythematosus (SLE), and neuropsychiatric systemic lupus erythematosus (NPSLE)
22. Evaluation of response to treatment of neurological disorders (eg, tumor evaluation)
23. Detection of 2-hydroxyglutarate (2-HG) in suspected IDH1 mutant gliomas
24. Developmental delay
25. Evaluation of response to treatment of metabolic disorders

CNS

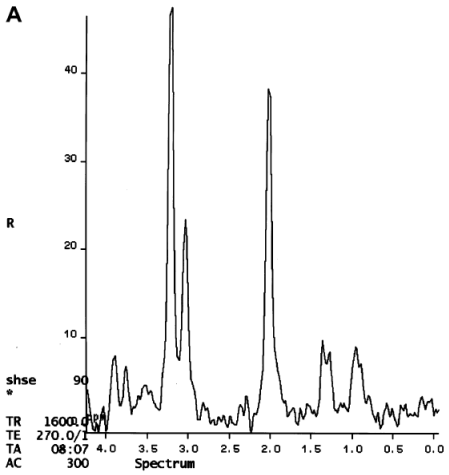
- Primary peaks:
  - Total NAA (2.0 ppm)
    - N-acetylaspartate and N-acetylaspartylglutamate
    - Neuronal marker
  - Total Cr (3.0 ppm)
    - Creatine and phosphocreatine
    - Energy buffer
  - Total Ch (3.2 ppm)
    - Choline, glycerophosphorylcholine and phosphorylcholine
    - Membrane turnover



Courtesy of R. Jason Stafford

CNS

- Other peaks:
  - Glx (glutamine, glutamate)
  - γ-Aminobutyric acid
  - Lactate
  - Lipids
  - Myo- and scyllo-inositol
  - Citrate
  - (D)-2-hydroxyglutarate (2HG)
  - Taurine
  - Glucose
  - Ethanol
  - Mannitol
  - Acetate and succinate
  - Branched-chain amino acids



Jan, Wajanat, et al. "MR diffusion imaging and MR spectroscopy of maple syrup urine disease during acute metabolic decompensation." Neuroradiology 45.6 (2003): 393-399.

MRS QA

- AAPM Report 78 (2002) details recommended MRS QA based on a simple phantom.
- AAPM Report 100 (2010) details recommended MRS acceptance testing using a phantom.
- I personally argue that phantom-based MRS QA alone is insufficient since the phantom poorly emulates both the biochemical milieu and electromagnetic environment found in vivo.
- I would argue that every spectrum from every scan from every patient be verified for quality before being sent to a radiologist.

Reimbursement

- CPT code 76390

Thank you!