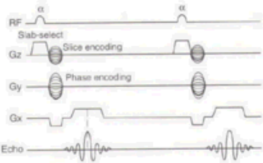
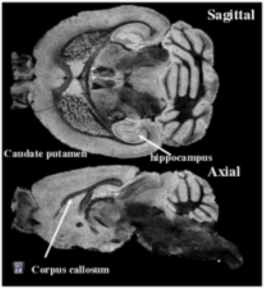
3D- Gradient Echo imaging

- Use phase encoding gradients along z and y.



- Replace slice selection gradient with a slab select (really thick slice – get you in the ballpark!)
- Higher resolution in z and y,
- Need to collect PE_z x PE_y phase encode steps

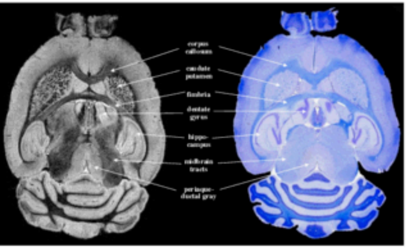
Ultra-High Resolution Ex-vivo mouse imaging (39 μm)



- **Perfused with Gd-DTPA (shortens T_1 and T_2)**
- **T_2*-weighted GE image:**
  - **TR=50 ms, TE=5 ms**
- **Isotropic resolution:**
  - **FOV= 2x1x1 cm**
  - **SI: 512x256x256, NE=2**
  - **1 h 50 min acquisition**
- **40 contiguous horizontal and sagittal slices.**
- **Delineation of WM tracts**
- **Clear delineation of hippocampal fissure**
- **Axonal projections in caudate-putamen from internal capsule**
- **Texture of WM tracts in midbrain/pons/medulla oblongata may reflect the orientations of the tracts.**

Kim *et al.*, NMR in Biomedicine 2009

Comparison with Histology



Gd-DTPA probably stains for myelin and dense nuclei;
Luxol fast blue for myelin, Cresyl violet (Nissl) for neurons.

Kim *et al.*, NMR in Biomedicine 2009

MRI Imaging Methods

Magnetic Resonance Angiography (MRA) It is possible to exploit the flow properties of the blood to produce images of the vasculature.

There are two major techniques for obtaining MRAs:

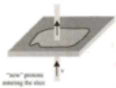
- Time-of-flight
- Phase-contrast

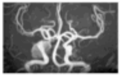
Time-of-flight: Time-of-flight (TOF) methods are based on saturating the signal in a slice with a series of RF pulses. During the imaging sequence, protons in blood that have not experienced the previous RF pulse enter the slice with full magnetization, creating high contrast

Usually slices are chosen perpendicular to blood flow to decrease the time flowing blood spends in the selected slice. The sequence is heavily T_1 weighted (short TR) so that signal intensity from tissue is very low and that from the blood is much higher.

T_1 of blood is ~1.2 seconds

T_1 of tissue is ~1 second





MRA of brain

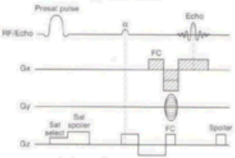
$T_{1(eff)}$ can be calculated using: $$\frac{1}{T_{1(eff)}} = \frac{1}{T_1} + \frac{v}{S_{th}}$$

v ← Blood velocity; S_{th} ← Slice Thickness

Time of Flight MRA

- Presaturation pulse with G_z gradient selects slice.
- Spoiler gradient destroys magnetization in that slice.
- The rest of the sequence is a fast gradient echo.

2D-TOF MRA



- FC: Flow compensation

MRI Imaging Methods

Magnetic Resonance Angiography (MRA)

Phase Contrast Angiography (PCA): During an MRI sequence, gradient magnetic fields are applied to spatially localize signal. This method assumes that everything remains stationary.

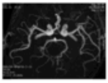
If signal producing tissue like blood moves significantly during the sequence the spatial encoding is incorrect and a ghost image of the object will be seen mis-mapped in the phase encoded direction.

The amount of phase error depends on the velocity of the movement and the strength and period of the applied gradient. In a motion compensated sequence these artifacts are avoided.

The PCA method acquires two sequences; one with and one without motion compensation.

By comparing the phase of the signals from each location in the two sequences the exact location of motion induced phase change can be determined.

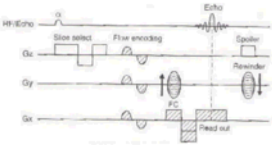
This give us a map where pixel brightness is proportional to spatial velocity. Regions that are stationary remain black while moving regions are represented as grey to white.

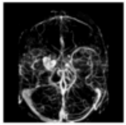


MRAs of brain

Phase Contrast MRA

- Fast gradient echo sequence.
- Flow encoding gradients induce additional phase.
- Magnetization in flowing spins additionally dephased by negative gradient.
- Stationary spins feel no effect.





MRI Imaging Methods – Functional MRI

Functional MRI Functional MRI (fMRI) is based on the increase in blood flow to the local vasculature that accompanies neural activity in the brain.

Hemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated.

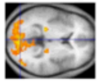
In deoxygentated blood (deoxyhemoglobin), four of the six outer electrons of the heme ion are unpaired placing the iron in a ferrous state (Fe^{2+}) that is paramagnetic.

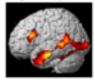
The MR signal of blood is therefore slightly different depending on the level of oxygenation, a phenomenon called Blood Oxygenation Level Dependent (BOLD) signal

In the absence of neuronal activity, the presence of deoxyghemoglobin in red blood cells causes a susceptibility gradient and has the effect of shortening T_2 and T_2^* in the surrounding media.

Neuronal activity causes a localized increase in blood flow, cerebral blood volume, and oxygen delivery. Oxygen extraction increases by a lesser amount.

The effect of this reduction in dephasing is a net increase in signal from tissue in the region of neuronal activation in T_2- and T_2^*-weighted images.

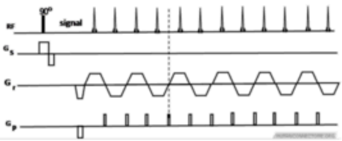




The regions of magnetic field inhomogeneity produce measurable effects over distances of two or more times the radius of the vessel.

fMRI pulse sequence

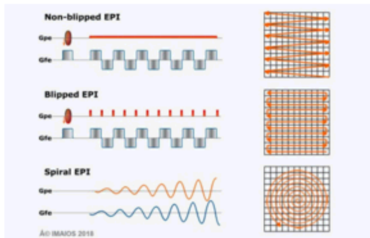
- Fast gradient (or spin) echo with EPI readout (echo planar imaging)



- Single RF-pulse followed by a strong switched frequency-encoding gradient with an intermittent (blipped) lower magnitude phase-encoding gradient.
- Gradient echoes collected with each oscillation of the readout gradient.

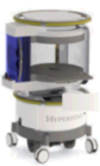
EPI k-space filling

- Examples of gradient waveforms needed to fill k-space



https://www.imaios.com/en/e-Courses/e-MRI/MRI-Sequences/echo-planar-imaging

Hyperfine: Portable Low Field MRI for Point-of-Care Imaging



Permanent magnet - 64 mT

Weighs 1200 lbs, plugs into a regular wall outlet,

Controlled via iPAD

Advantages:

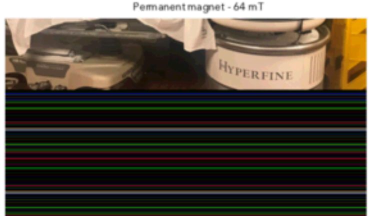
- Open design, smaller footprint. portable
- Safe, easy to use, low cost

Disadvantages:

- **Lower signal to noise ratio (SNR)**
- **Lower resolution and longer scan times**
- **Decreased gray-white contrast**
- **Weaker gradients**
- **More restricted imaging volume**

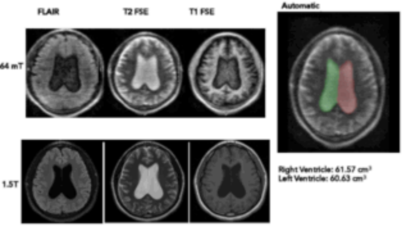
Hyperfine: Portable MRI for Point-of-Care Imaging

Permanent magnet - 64 mT



Penn Medicine Department of Radiology

Comparison of common pulse sequences at 0.64 and 1.5 T



"Persistent hydrocephalus following endoscopic third ventriculostomy for aqueductal stenosis" – courtesy Joel Stein, MD, Penn Radiology

MRI Imaging Methods – MR Spectroscopy

Magnetic Resonance Spectroscopy (MRS) MRS is the use of nuclear magnetic resonance for the determination of individual chemical compounds.

The underlying principle of MRS is that atomic nuclei are surrounded by electrons which slightly shield the nucleus from the external magnetic field.

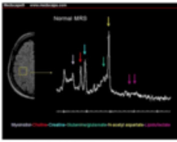
As the structure of the electron cloud is specific to an individual molecule or compound, then the magnitude of this screening effect is also characteristic of the chemical environment of individual nuclei.

Since resonance frequency is proportional to the magnetic field, it will be determined by the external applied field and the small shift generated by the electron cloud.

The shift in frequency is called the chemical shift.

The chemical shift is a very small effect, usually expressed in parts per million (ppm) of the main frequency.

Chemical shift is proportional to the magnetic field strength.



MRS can be used to monitor disease biochemistry by identifying altered chemical shifts or intensities.

MR Spectroscopy

- In its simplest form, the NMR spectrum is obtained from the Fourier transform of the free induction decay after a single pulse

- Recall that the FT converts the time domain signal (FID) to a frequency domain signal (spectrum).
- When observing biological samples, must use water suppression techniques
- Tissue water protons ~ 70 M, most observable metabolites: 1-20 mM.

Chemical Shift

Total field around the nucleus is the sum of the applied field and the local field

$$\omega_0 = \gamma B_{tot} = \gamma (B_{loc} + B_0)$$

Local field is modulated by interaction with surrounding electrons

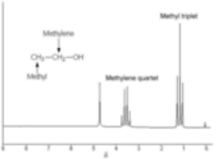
$$B_{tot} = B_0 (1 - B_{loc}) = B_0 (1 - \sigma)$$

σ is called the chemical shift, expressed in parts per million (ppm)

$$\sigma = (B_0 - B_{tot}) / B_0 = (\nu_0 - \nu_{tot}) / \nu_0$$

Chemical Shift

- ^1H NMR spectrum of ethanol



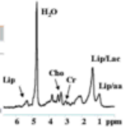
Shielding →

Fig http://www.eng.uc.edu/~gbeaucag/Classes/Analysis/Chapter6Pics/Chapter615.GIF

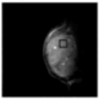
Commonly observed metabolites in ^1H MRS

Table 1. Observed resonances in one-dimensional proton MR spectra of cells and tissues

Chemical shift (ppm)	Molecule	Species (bold)
Lipids		
0.72	Cholesterol	$(CH_3)_2$-CH-
0.89	Fatty acyl chain	CH_3-CH_2-CH_2-
1.28	Fatty acyl chain	-CH_2-CH_2-CH_2-
1.58	Fatty acyl chain	-CH_2-CH_2-COO^-
2.03	Fatty acyl chain	-CH=CH-CH_2-
2.24	Fatty acyl chain	-CH_2-CH_2-COO^-
2.88	Fatty acyl chain	-CH=CH-CH_2-CH=CH-
4.30	Glycerol backbone	R1-O-CH_2-CH(O-R2)-CH_2(O-R3)
5.32	Fatty acyl chain	-CH=CH-
Amino acids		
0.9–1.0	Aliphatic branched chain (valine, leucine, isoleucine)	CH_3-
1.33	Threonine	CH_3-CH-
1.48	Alanine	CH_3-CH-
1.71	Lysine/polyamines	H_3N^+-CH_2-CH_2-CH_2-
2.03	N-Acetylaspartate	CH_3-COO-NH-
2.17	Glutamate/glutamine	CH-CH_2-CH_2-COO^-(-NH_2)
3.02	Lysine	H_3N^+-CH_2-CH_2-CH_2-
3.78	α-protons	OOC-CH(R)-NH-
Low-molecular-weight metabolites		
1.33	Lactate	CH_3-CH-
3.02	Creatine	CH_3-N-CH_2-COO^-
3.02	Phosphocreatine	CH_3-N-CH_2-COO^-
3.21	Choline	-$N^+(CH_3)_3$
3.23	Phosphocholine	-$N^+(CH_3)_3$
3.24	Glycerophosphocholine	-$N^+(CH_3)_3$
3.25	Myo-inositol	-CH-CH(OH)-
3.25	Taurine	H_3N^+-CH_2-CH_2-SO_3^-
3.43	Taurine	H_3N^+-CH_2-CH_2-SO_3^-
4.65	Water	H_2O, HOD



Single voxel STEAM spectrum



T_2 weighted image DU145 human tumor xenograft

Delikatny et al, NMR in Biomedicine, 24, 592-611, 2011

Localization in Single Voxel MRS: STEAM

- STimulated Echo Acquisition Mode
- Voxel selectivity based on application of orthogonal gradients during pulses
- Other gradients to crush unwanted magnetization

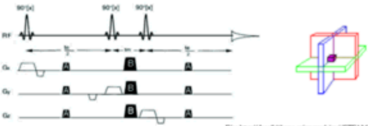


Fig: http://desolf03.usc.es/rmnweb/mri/STEAM.html

Localization in Single Voxel MRS: PRESS

- Point Resolved Spectroscopy
- Double spin echo, voxel selection performed by gradients applied during pulses:

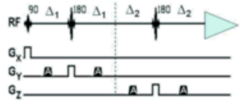
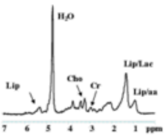
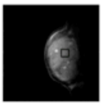


Fig: http://desolf03.usc.es/rmnweb/mri/press.html

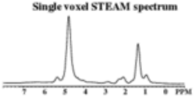
Examples: STEAM and PRESS spectra



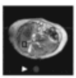
Single voxel STEAM spectrum



DU145 human tumor xenograft

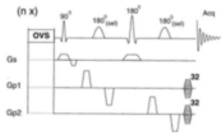


Single voxel PRESS spectrum



Mouse fatty liver

CSI - Chemical Shift Imaging

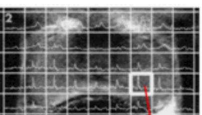


- Also called spectroscopic imaging
- Multivoxel spectroscopy
  - Can be 1D, 2D or 3D CSI
  - 2D – slice selection gradients during spin echo pulses
  - phase encode in x and y
  - solvent-suppression frequency-selective pulses ($180^\circ_{(sel)}$) with crusher gradients for water and fat suppression in the slice
- Selects $PE_X * PE_Y$ voxels in slice
- Allows metabolic mapping in a tumor or tissue

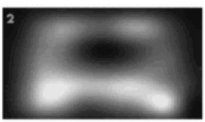
van der Graaf M et al. Radiology 1999;213:919-925

Chemical Shift Imaging of the Normal Human Prostate.

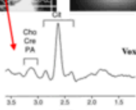
Sagittal T_1 weighted image with CSI spectra overlaid



Citrate metabolite map created from voxel intensities



CSI spectrum from a single voxel showing high levels of citrate

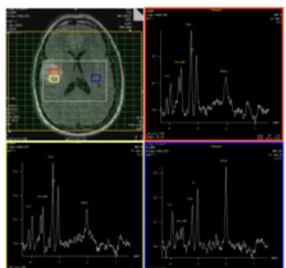


Voxel size: 10 mm x 240 mm x 240 mm

van der Graaf M et al. Radiology 1999;213:919-925

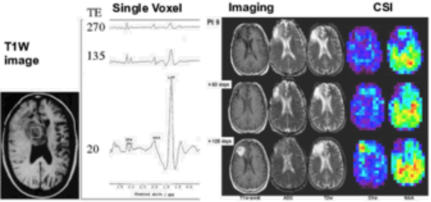
[1]H MRS – brain tumor

Tumor voxels (red and yellow) show increased choline (membrane synthesis precursor) and decreased NAA (neuronal marker) relative to normal voxel (blue).



Chawla *et al.*, AJNR 2007

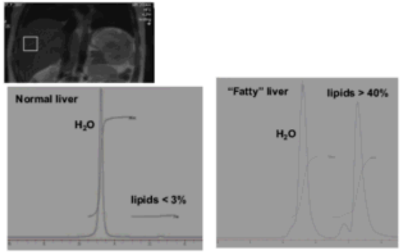
MRS- localization techniques –example of a clinical workup



Metabolites with shorter T2 (lipids) are enhanced at shorter TEs

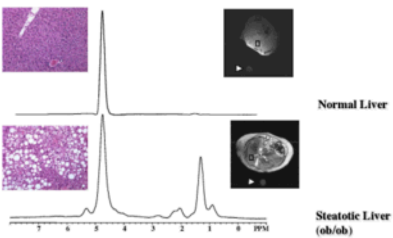
Elevated choline and decreased NAA at the tumor site.

^{1}H MRS – Human Liver



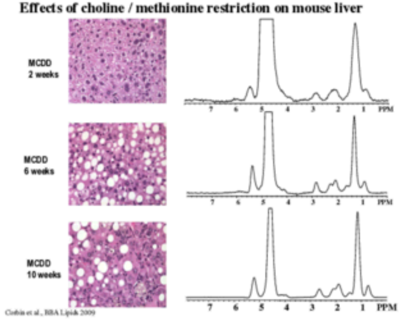
Rosen *et al.*, ISMRM 2009

In vivo ^{1}H MR Spectra from Mice with Normal and Fatty Liver



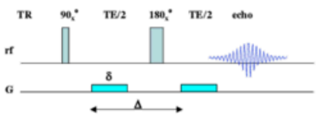
Corbin et al., BBA Lipids 2009

Effects of choline / methionine restriction on mouse liver



Corbin et al., BBA Lipids 2009

Diffusion weighted spectroscopy

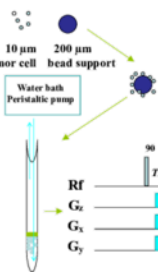


- Run multiple spectra incrementing gradient strength, G. The first gradient causes additional spin dephasing. Spins that diffuse out of the coil during TE are not refocused by the second diffusion gradient. Thus, echo intensity decreases with G and is further attenuated for molecules with high D.

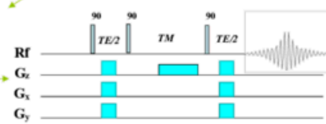
    - $\ln S/S_0 = [-(\gamma G \delta)^2 D (\Delta - \delta/3)]$

- where G = gradient strength, D = diffusion constant. D can be calculated from the slope of a linear plot of $\ln(S/S_0)$ vs G.

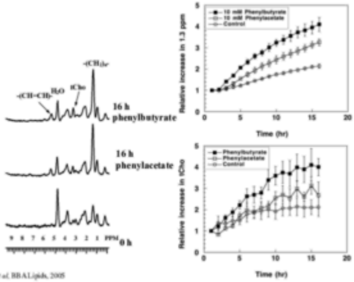
Diffusion weighted spectroscopy in live cells



- For examining cells in perfusion culture
- Diffusion weighting is used to eliminate signals from flowing water and culture media
- Leaves only intracellular metabolite resonances



Metabolic changes in prostate cancer cells treated with differentiating agents



Milkevitch *et al*, BBA Lipids, 2005

Basic Principles of MRI

Magnetic Nuclei Some nuclides that have a net magnetic moment are shown below.

Nuclides with a Net Magnetic Moment				
Nuclei	Unpaired Protons	Unpaired Neutrons	S	Magnetic Moment (MHz/T)
^{1}H	1	0	1/2	42.58
^{2}H	1	1	1	6.54
^{13}C	0	1	1/2	10.71
^{14}N	1	1	1	3.08
^{19}F	1	0	1/2	40.08
^{23}Na	1	2	3/2	11.27
^{31}P	1	0	1/2	17.25

Energy States Atomic nuclei have specific energy levels related to the property called "spin quantum number", S.

The number of energy states of a nucleus is determined by the formula:

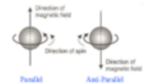
Number of energy states = 2S + 1

Example:

Hydrogen: S = 1/2

Number of energy states = 2(1/2) + 1 = 2

Hydrogen has 2 energy states +1/2 and -1/2



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^{23}Na	1	2	3/2	11.27
^{31}P	1	0	1/2	17.25

Energy States Atomic nuclei have specific energy levels related to the property called "spin quantum number", S.

The number of energy states of a nucleus is determined by the formula:

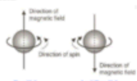
Number of energy states = 2S + 1

Example:

Hydrogen: S = 1/2

Number of energy states = 2(1/2) + 1 = 2

Hydrogen has 2 energy states +1/2 and -1/2

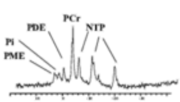


MR using other nuclei: ^{31}P

- Spin 1/2, Natural abundance = 100%
- Magnetic moment = 17.25 MHz/T.
- Resonance frequency = 25.9 MHz at 1.5 T
- Sensitivity relative to the proton: 6.7 %
- Voxel sizes:
  - ~ 27 cm^3 @ 1.5 T (3 x 3 x 3 cm)
  - ~ 8 cm^3 @ 3.0 T (2 x 2 x 2 cm)
- Useful for observing bioenergetics, pH, phospholipid metabolism

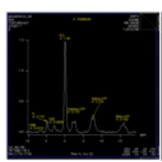
Commonly observed metabolites in ^{31}P spectra

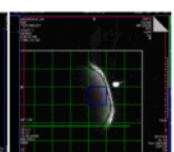
- Nucleoside triphosphates and diphosphates (NTP and NDP)
  - ~80% ATP/ADP – energy metabolism
- Inorganic phosphate (Pi)
  - pH dependent
- Phosphocreatine (PCr)
  - Energy storage
- Phosphomonoesters (PME)
  - Phosphocholine, phosphoethanolamine
  - Lipid synthesis
- Phosphodiesters (PDE)
  - Glycerophosphocholine, glycerophosphoethanolamine
  - Lipid catabolism



^{31}P MR spectrum of a DU145 prostate flank tumor

^{31}P MRS spectra from the soleus muscle (normal volunteer)

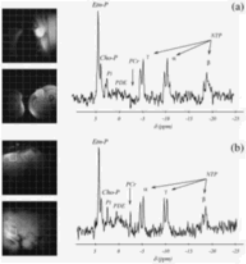




3D CSI | T_2w image

Spectra are taken from the voxel shown in blue

^{31}P MRS of non Hodgkin's Lymphoma



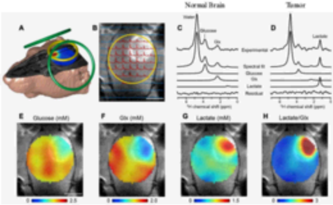
Elevated PME (PC and PE, membrane phospholipid precursors) relative to NTP, in more aggressive NHL tumors

Arias Mendoza *et al*, NMR in Biomedicine 19:504-512, 2006

MR using other nuclei: ^{2}H

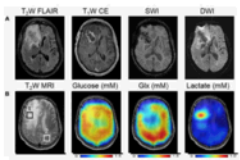
- Spin 1, natural abundance = 0.0156%.
- Magnetic moment = 6.54 MHz/T
- Resonance frequency at 1.5 T:
- Sensitivity relative to the proton: 0.0965%
- Chemical shirt dispersion identical to the proton
- Isotopic enrichment required in order to observe signal

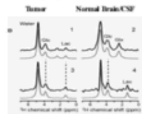
DMI in rat brain after [6,6′-$^{2}H_2$]glucose infusion

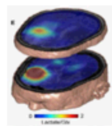


(A) MRI- rendering of a RG2 rat glioma tumor with radiofrequency (RF) coils show in green
(B) Contrast-enhanced T_1-weighted MR with overlaid ^{2}H NMR
(C - D) ^{2}H NMR spectra from normal brain and tumor (8-μl voxel size, 60-90 min post infusion).
(E - G) DMI maps of 2H-glucose, Glx/Gln and lactate, expressed in mM. (H) The ratio of lactate/Glx represents the Warburg effect characterized by high glycolysis and low oxidative metabolism

DMI in human brain after [6,6′-$^{2}H_2$]glucose infusion







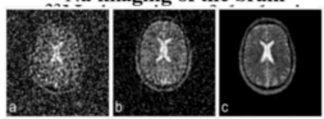
(A) Clinical MR images in a patient diagnosed with glioma in the right frontal lobe. SWI = susceptibility imaging
(B) T2W MRI image and DMI metabolite maps
(D) ^{2}H NMR spectra from tumor (1,3), normal (2), and CSF (4) voxels in the T2W MR image
(E) 3D overlaid MRI and DMI of the lactate/Glx ratio representing the spatial distribution of the Warburg effect.

De Feyter et al., Sci. Adv. 2018; 4 : eaat7314 22 August 2018

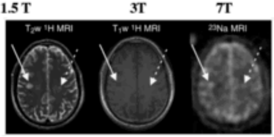
MR using other nuclei: ^{23}Na

- Spin 3/2, Natural abundance = 100%
- Magnetic moment = 11.27 MHz/T.
- Resonance frequency = 39.79 MHz at 1.5 T
- Sensitivity relative to the proton: 9.25%
- High levels of sodium in brain, cartilage, and spinal disks

^{23}Na imaging of the brain



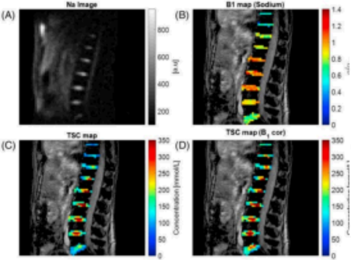
1.5 T **3T** **7T**

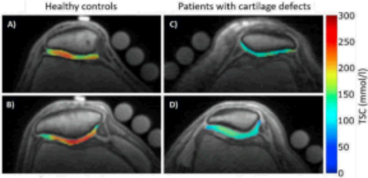


23Na MRI in a patient with multiple sclerosis

K. Huhn et al., Front Neurol 10:84 (2019).

23Na MRI of Spine and Knee Cartilage





Gast et al., *Prog NMR Spectrosc*, Vol 138-9, p1-51, 2023