1) **Diffusion weighted imaging**

DWI is a term used to describe moving molecules due to random thermal motion. This motion is restricted by boundaries such as ligaments, membranes and macro molecules. Diffusion is measurement of water mobility, when cells swell and absorb water from the extra-cellular space so water mobility is abnormal then the diffusion is restricted (Cytotoxic edema). This allows early detection of stroke & other diseases.

**Mechanism of DWI:**

- DWI is acquired by combining EPI or fast gradient echo sequences with two large gradient pulses applied after excitation.
- The gradient pulses are designed to cancel each other out if spins do not move, whilst moving spins experience phase shift.
- Signal attenuation therefore occurs in normal tissues with random motion and high signal appears in tissues with restricted diffusion.
- Diffusion gradients must be strong to achieve enough diffusion weighting.
- Gradient pulses can be applied along the X, Y and Z axes to determine the axis of restricted diffusion.

**N.B:** The term **Isotropic Diffusion** is used to describe diffusion gradients applied in all three axes. In this type the possibility of a water protons moving in any one particular direction is equal to the probability that it will move in any other direction.

While the term **Anisotropic Diffusion** water diffusion has preferred direction. Water protons move more easily in some direction.

**Values:** Diffusion sensitivity is controlled by a parameter ‘b’ that determines the diffusion attenuation by modification of the time duration and amplitude of the diffusion gradient. (b) is expressed in units of s/mm². Typical (b) values range from 500 s/mm² to 1000 s/mm².

**Clinical applications of DWI**

Is mainly useful in the brain to differentiate salvageable and non-salvageable tissue after stroke where areas of decreased diffusion represent infarction & will appear as high signal intensity. Diffusion imaging promising to further understand brain disorders and abnormalities such as tumors, multiple sclerosis, and schizophrenia. It is also useful in the liver, prostate, spine and bone marrow.
**Apparent Diffusion Coefficient**

This term is to represent the measurement of diffusion constant within biological tissue. ADC Map is created by combining at least two DWI with different “b” values.
2) Diffusion Tensor Imaging (DTI)

When the diffusion of water along the three orthogonal directions of the magnet (X, Y and Z) is measured and the average obtained, only isotropic diffusion information is acquired; that is diffusion that is random in direction. In the brain this is seen in gray matter. In white matter the structure of the tissue 'orders' the diffusion. In white matter diffusion is ordered along the white matter tracts. This type of ordered diffusion is referred to as anisotropy (anisotropic diffusion). In order to image anisotropic diffusion, diffusion in more than three axes is measured. In physics, a tensor is basically motion as a function of direction. DTI is essentially imaging diffusion that is ordered in direction (anisotropic rather than isotropic). At a minimum, DTI must measure the diffusion along at least six axes. In clinical practice twelve or more directions are measured. Due to a loss in SNR as the number of directions measured increases, DTI is particularly useful at high field strengths such as 3 T. DTI is currently used for mapping white matter tracts as fractional anisotropy (FA) maps, or as tractography images.

Clinical applications
Diffusion tensor measures the magnitude of the ADC in the preferred direction of water diffusion and also perpendicular to the direction. The resultant image shows white matter tracts very well. Hence this technique also called as "Tractography". It is useful for relationship of tracts with tumor, tumor invasion of tracts and preoperative planning.

DWI image (fractional analysis image) in one direction (anterior to posterior) shows bright genu and optic radiations because these fibers are perpendicular in this direction. Such images in 12 or 24 directions are taken to get the tractography.
3) Perfusion Imaging

Perfusion refers to the passage of blood from an arterial supply to venous drainage through the microcirculation. Perfusion is necessary for the nutritive supply to tissues and for clearance of products of metabolism. Perfusion gets changed by various pathologies affecting the particular tissue. Hence measuring changes in perfusion can be helpful in diagnosis of diseases, monitoring and assessing treatment response.

Mechanism

Perfusion imaging is the measure of the quality of vascular supply to a tissue. Since vascular supply and metabolism are usually related, perfusion can also be used to measure tissue activity. The MR sequence is sensitized to the very transient changes in T2* as bolus of contrast first passes through the capillary bed of the area under investigation. Therefore GRE sequences are always used and typically SS-GE-EPI (single shot gradient echo-echo planar imaging) is common. Images are acquired very rapidly before, during and after an injection of a small bolus of gadolinium administered intravenously in the ante-cubital fossa. Images are then post-processed and perfusion graph and haemodynamic images are produced. CBV (cerebral blood volume) map, areas of low perfusion appear dark (stroke) whereas areas of higher perfusion appear bright (malignancies).

N.B: Paramagnetic agents like Gd cause shortening of both T1 and T2 of the tissue or region in which they go. Decrease in T1 relaxation time on T1 weighted images results into increased signals or brightening. Reduction in T2 relaxation time on T2 or T2* weighted images results into signals drop or blackening {Table}. In perfusion as Gd passes through the microvasculature there is decrease in signal from magnetic susceptibility induced shortening of T2* relaxation times. So more the signal drop more will be the perfusion.

**Routine contrast enhancement versus perfusion imaging**

<table>
<thead>
<tr>
<th></th>
<th>Routine contrast enhancement</th>
<th>Perfusion imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1- Sequence</strong></td>
<td>T1-weighted imaging</td>
<td>T2*-weighted EPI sequence</td>
</tr>
<tr>
<td><strong>2- Mechanism</strong></td>
<td>Gd caused reduction in T1 relaxation time</td>
<td>Gd caused reduction in T2 or T2* relaxation time and magnetic susceptibility</td>
</tr>
<tr>
<td><strong>3- Signal change</strong></td>
<td>Increase in signal intensity</td>
<td>Drop in signal intensity</td>
</tr>
<tr>
<td><strong>4- Detects</strong></td>
<td>Break in blood-brain barrier leading to leakage of Gd</td>
<td>Gd in microvasculature (capillaries). Thus gives information about amount of small vessels (vascularity) and perfusion of the tissue.</td>
</tr>
</tbody>
</table>

Clinical applications

Evaluation of ischemic disease like stroke, metabolic disorders, brain tumors, dementia, psychiatric illness, migraine headaches, trauma, epilepsy and multiple sclerosis.
A. Post-contrast T1-w axial image of the brain shows non-enhancing tumor in the right cerebral hemisphere.

B. CCBV map shows the tumor to be hypervascular (red) suggestive of high grade tumor.

C. Post-contrast T1-w axial image of the brain shows cystic solid lesion in the Pons.

D. On perfusion the lesion is hypovascular suggestive of low grade tumor.
4) MR Spectroscopy

The basic principles of MRS are same as magnetic resonance imaging (MRI). However, few differences exist.
- MR images are reconstructed from the entire proton signal from the tissue dominated by water and fat proton signals. Protons from other metabolites do not contribute to imaging because of their negligible concentration.
- As against MRI, the aim in MRS itself is to detect these small metabolites. Most metabolite signals of clinical interest resonate between resonant frequencies of water and fat. To be able to detect these small metabolites large signal from water protons need to be suppressed.

MR spectroscopy is used to measure the levels of different metabolites in body tissues. The most common nuclei that are used are $^1$H (proton), $^{23}$Na (sodium), $^{31}$P (phosphorus). Proton spectroscopy is easier to perform and provides much higher signal-to-noise than either sodium or phosphorus. The MR signal produces a spectrum of resonances that correspond to different molecular arrangements of the isotope being "excited". This signature is used to diagnose certain metabolic disorders. Magnetic resonance spectroscopic imaging (MRSI) combines both spectroscopic and imaging methods to produce spatially localized spectra from within the sample or patient. The spatial resolution is much lower (limited by the available SNR), but the spectra in each voxel contains information about many metabolites. Because the available signal is used to encode spatial and spectral information, MRSI requires high SNR achievable only at higher field strengths (1.5T and above).

Proton MRS can be performed within 10-15 minutes and can be added on to conventional MR imaging protocols. It can be used to serially monitor biochemical changes in tumors, stroke, epilepsy, metabolic disorders, infections, and neurodegenerative diseases. The MR spectra do not come labeled with diagnoses. They require interpretation and should always be correlated with the MR images before making a final diagnosis.
4) MR Spectroscopy

MR spectroscopy provides a measure of brain chemistry. The most common nuclei that are used are $^1$H (proton), $^{23}$Na (sodium), $^{31}$P (phosphorus). Proton spectroscopy is easier to perform and provides much higher signal-to-noise than either sodium or phosphorus. Proton MRS can be performed within 10-15 minutes and can be added on to conventional MR imaging protocols. It can be used to serially monitor biochemical changes in tumors, stroke, epilepsy, metabolic disorders, infections, and neurodegenerative diseases. The MR spectra do not come labeled with diagnoses. They require interpretation and should always be correlated with the MR images before making a final diagnosis.

Basic Physical Principles

The resonant frequencies of nuclei are at the lower end of the electromagnetic spectrum between FM radio and radar. The resonant frequencies of protons range between about 10 MHz at 0.3 T to about 300 MHz on a 7 T magnet. The advantages of higher field strength are higher signal-to-noise and better separation of the metabolite peaks. In a proton spectrum at 1.5 T, the metabolites are spread out between 63,000,000 and 64,000,000 Hertz. Rather than use these large numbers, some very smart person decided to express the resonant frequencies in parts per million (ppm), and he/she positioned NAA at 2.0 ppm and let the other metabolites fall into their proper positions on the spectral line. Then, for unknown reasons, he/she reversed the ppm scale so that it reads from right to left.

Observable Proton Metabolites

<table>
<thead>
<tr>
<th>ppm</th>
<th>Metabolite</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9-1.4</td>
<td>Lipids</td>
<td>Products of brain destruction</td>
</tr>
<tr>
<td>1.3</td>
<td>Lactate</td>
<td>Product of anaerobic glycolysis</td>
</tr>
<tr>
<td>2.0</td>
<td>NAA</td>
<td>Neuronal marker</td>
</tr>
<tr>
<td>2.2-2.4</td>
<td>Glutamine/GABA</td>
<td>Neurotransmitters</td>
</tr>
<tr>
<td>3.0</td>
<td>Creatine</td>
<td>Energy metabolism</td>
</tr>
<tr>
<td>3.2</td>
<td>Choline</td>
<td>Cell membrane marker</td>
</tr>
<tr>
<td>3.5</td>
<td>myo-inositol</td>
<td>Glial cell marker, osmolyte, hormone receptor mechanisms</td>
</tr>
<tr>
<td>1.2</td>
<td>Ethanol</td>
<td>Triplet</td>
</tr>
<tr>
<td>1.48</td>
<td>Alanine</td>
<td>Present in meningiomas</td>
</tr>
<tr>
<td>3.4&amp;3.8</td>
<td>Glucose</td>
<td>Increased in diabetes</td>
</tr>
<tr>
<td>3.8</td>
<td>Mannitol</td>
<td>Rx for increased ICP</td>
</tr>
</tbody>
</table>

For MR imaging, the total signal from all the protons in each voxel is used to make the image. If all the signals were used for MRS, the fat and water peaks would be huge and scaling would make the other metabolite peaks invisible. Since we aren't interested in fat and water anyway, the fat and water are eliminated. Fat is avoided by placing the voxel for MRS within the brain, away from the fat in bone marrow and scalp. Water suppression is accomplished with either a CHESS (CHEmical-Shift Selective) or IR (Inversion Recovery) technique. These suppression techniques are used with a STEAM or PRESS
pulse sequence acquisition. A Fourier transform is then applied to the data to separate the signal into individual frequencies. Protons in different molecules resonate at slightly different frequencies because the local electron cloud affects the magnetic field experienced by the proton.

The STEAM (STimulated Echo Acquisition Mode) pulse sequence uses a 90° refocusing pulse to collect the signal like a gradient echo. STEAM can achieve shorter echo times but at the expense of less signal-to-noise. The PRESS (Point RESolved SpectroScopy) sequence refocuses the spins with a 180° RF pulse like a spin echo. Two other acronyms require definition. CSI (Chemical Shift Imaging) refers to multi-voxel MRS. SI (Spectroscopic Imaging) displays the data as an image with the signal intensity representing the concentration of a particular metabolite.

As in MR imaging, the echo time affects the information obtained with MRS. With a short TE of 30 msec, metabolites with both short and long T2 relaxation times are observed. With a long TE of 270 msec, only metabolites with a long T2 are seen, producing a spectrum with primarily NAA, creatine, and choline. One other helpful TE is 144 msec because it inverts lactate at 1.3 ppm.

As a general rule, the single voxel, short TE technique is used to make the initial diagnosis, because the signal-to-noise is high and all metabolites are represented. Multi-voxel, long TE techniques are used to further characterize different regions of a mass and to assess brain parenchyma around or adjacent to the mass. Multi-voxel, long TE techniques are also used to assess response to therapy and to search for tumor recurrence.

![Normal MR Spectrum](image)

Normal MR Spectra obtained from gray matter and white matter

Each metabolite appears at a specific ppm, and each one reflects specific cellular and biochemical processes. NAA is a neuronal marker and decreases with any disease that adversely affects neuronal integrity. Creatine provides a measure of energy stores. Choline is a measure of increased cellular turnover and is elevated in tumors and inflammatory processes. The observable MR metabolites provide powerful information, but unfortunately, many notable metabolites are not represented in brain MR spectra. DNA, RNA, most proteins, enzymes, and phospholipids are missing. Some key
neurotransmitters, such as acetylcholine, dopamine, and serotonin, are absent. Either their concentrations are too low, or the molecules are invisible to MRS. The predominant metabolites, displayed from right to left, are NAA, creatine, choline, and myo-inositol. The primary difference between the two spectra is that gray matter has more creatine. Hunter's angle is the line formed by the metabolites on the white matter spectrum. The common way to analyze clinical spectra is to look at metabolite ratios, namely NAA/Cr, NAA/Cho, and Cho/Cr. Normal and abnormal values are shown in the chart to the right. By including a known reference solution when acquiring the MR spectral data, absolute concentrations of metabolites can be calculated.

### Metabolite Ratios

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td>2.0</td>
<td>&lt; 1.6</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>1.6</td>
<td>&lt; 1.2</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>1.2</td>
<td>&gt; 1.5</td>
</tr>
</tbody>
</table>

### Clinical Applications

#### Brain Tumors

MRS can be used to determine the degree of malignancy. As a general rule, as malignancy increases, NAA and creatine decrease, and choline, lactate, and lipids increase. NAA decreases as tumor growth displaces or destroys neurons. Very malignant tumors have high metabolic activity and deplete the energy stores, resulting in reduced creatine. Very hypercellular tumors with rapid growth elevate the choline levels. Lipids are found in necrotic portions of tumors, and lactate appears when tumors outgrow their blood supply and start utilizing anaerobic glycolysis. To get an accurate assessment of the tumor chemistry, the spectroscopic voxel should be placed over an enhancing region of the tumor, avoiding areas of necrosis, hemorrhage, calcification, or cysts. Multi-voxel spectroscopy is best to detect infiltration of malignant cells beyond the enhancing margins of tumors. Particularly in the case of cerebral glioma, elevated choline levels are frequently detected in edematous regions of the brain outside the enhancing mass. Finally, MRS can direct the surgeon to the most metabolically active part of the tumor for biopsy to obtain accurate grading of the malignancy.

A common clinical problem is distinguishing tumor recurrence from radiation effects several months following surgery and radiation therapy. Elevated choline is a marker for recurrent tumor. Radiation change generally exhibits low NAA, creatine, and choline on spectroscopy. If radiation necrosis is present, the spectrum may reveal elevated lipids and lactate.
MRS cannot always distinguish primary and secondary tumors of the brain from one another. As mentioned above, one key feature of gliomas is elevated choline beyond the margin of enhancement due to infiltration of tumor into the adjacent brain tissue. Most non-glial tumors have little or no NAA. Elevated alanine at 1.48 ppm is a signature of meningiomas. They also have no NAA, very low creatine, and elevated glutamates.

References:
4. John R. Hesselink, MD, FACR
http://spinwarp.ucsd.edu/NeuroWeb/Text/mrs-TXT.htm

Afnan A. Malaih