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MRI for Technologists

4712-103 Advanced MRI Neurological Applications

This material will be reviewed for continued accuracy and relevance.
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> ***MRI for Technologists*** is a training program designed to meet the needs of radiologic technologists entering and/or working in the field of magnetic resonance imaging (MRI). These units are designed to augment classroom instruction and on-site training for radiologic technology students and professionals planning to take the review board examinations, as well as to provide a review for those looking to refresh their knowledge base in MR imaging.

Note: Terms in **bold** throughout this material can be found in the glossary.

OVERVIEW

The skill of the technologist is the single most important factor in obtaining good quality diagnostic images. A successful MRI examination is the culmination of many factors under the direct control of the technologist.

MRI for Technologists: Advanced MRI Neurological Applications introduces the learner to the multiple approaches used to assess brain function, including diffusion-weighted imaging, perfusion-weighted imaging, BOLD imaging, and MR spectroscopy. Each of these techniques provides unique information about the brain's function in the presence of pathology.

After completing this educational material, the reader will be able to:

- Explain the fundamental principles of echo planar imaging
- Describe the mechanisms of diffusion- and perfusion-weighted imaging
- Identify clinical uses of diffusion- and perfusion-weighted imaging
- Describe the principles and applications of BOLD imaging
- Explain the basis of magnetic resonance spectroscopy
- Identify the various techniques used with MR spectroscopy
- Evaluate the factors that can affect the quality of MR spectroscopy

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FACULTY BIOGRAPHY

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Currently serving as Manager of MR Education and Technical Development at Fairfax Radiological Consultants in Fairfax, VA, Thomas Schrack served as Adjunct Faculty Instructor for Northern Virginia Community College from more than 10 years, teaching MR physics and clinical procedures. He serves on the Board of Examiners of the American Registry of Magnetic Resonance Imaging Technologists (ARMRIT) and in 2013 was elected to the Board of Directors. Mr. Schrack is also the Co-Founder and Program Director of the Tesla Institute of MRI Technology, a school offering certification in MRI for radiologic technologists and others interested in entering the field of MRI.

Mr. Schrack is the author of *Echo Planar Imaging: An Applications Guide,* GE Healthcare, 1996, and contributing author, *Magnetic Resonance Imaging in Orthopaedics & Sports Medicine* with David Stroller, MD, 1997. Working with International Center for Postgraduate Medical Education, Mr. Schrack has authored or co-authored several units of the *MRI for Technologists* series, including *MRI Systems and Coil Technology, MR Image Postprocessing and Artifacts, Patient and Facility Safety in MRI, MRI Contrast Agent Safety, Advanced MRI Neurological Applications, MRI of the Brain and Spine, Musculoskeletal MRI, Clinical Magnetic Resonance Angiography, MRI of the Body, and Cardiac MRI.*

Mr. Schrack is a graduate of The Pittsburgh NMR Institute, James Madison University, and Northern Virginia Community College.

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FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings

https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm Accessed June 14, 2018.

05-16-2018 Update

In addition to approving the updated prescribing information concerning the gadolinium retention safety issues described in the Drug Safety Communication below, FDA has also approved new patient Medication Guides for all GBCAs.

Health care professionals and patients can access the patient Medication Guides according to the GBCA drug name* on the Medication Guides webpage, or the latest prescribing information by searching in Drugs@FDA.

All MRI centers should provide a Medication Guide the first time an outpatient receives a GBCA injection or when the information is substantially changed. In general, hospital inpatients are not required to receive a Medication Guide unless the patient or caregiver requests it. A health care professional who determines that it is not in a patient's best interest to receive a Medication Guide because of significant concerns about its effects may direct that it not be provided to that patient; however, the Medication Guide should be provided to any patient who requests the information.†

*The brand names of the GBCAs can be found in Table 1 below.
†For more information on distribution of Medication Guides, see the Guidance Document, the Drug Info Rounds Video, or the Code of Federal Regulations at 21 CFR 208.26.

This is an update to the FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue issued on May 22, 2017.

12-19-2017 Safety Announcement

The U.S. Food and Drug Administration (FDA) is requiring a new class warning and other safety measures for all gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs. Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and we have concluded that the benefit of all approved GBCAs continues to outweigh any potential risks.

However, after additional review and consultation with the Medical Imaging Drugs Advisory Committee, we are requiring several actions to alert health care professionals and patients about gadolinium retention after an MRI using a GBCA, and actions that can help minimize problems. These include requiring a new patient Medication Guide*, providing educational information that every patient will be asked to read before receiving a GBCA. We are also requiring manufacturers of GBCAs to conduct human and animal studies to further assess the safety of these contrast agents.

GBCAs are used with medical imaging devices called MRI scanners to examine the body for problems such as cancer, infections, or bleeding. GBCAs contain gadolinium, a heavy metal. These contrast agents are injected into a vein to improve visualization of internal organs, blood vessels, and tissues during an MRI, which helps health care professionals diagnose medical conditions. After being administered, GBCAs are mostly eliminated from the body through the kidneys. However, trace amounts of gadolinium may stay in the body long-term. Many GBCAs have been on the market for more than a decade.

Health care professionals should consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention (see Table 1 listing GBCAs). These patients include those requiring multiple lifetime doses, pregnant women, children, and patients with

inflammatory conditions. Minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies. However, do not avoid or defer necessary GBCA MRI scans.

Patients, parents, and caregivers should carefully read the new patient Medication Guide* that will be given to you before receiving a GBCA. The Medication Guide explains the risks associated with GBCAs. Also tell your health care professional about all your medical conditions, including:

- If you are pregnant or think you might be pregnant
- The date of your last MRI with gadolinium and if you have had repeat scans with gadolinium
- If you have kidney problems

There are two types of GBCAs based on their chemical structures: linear and macrocyclic (see Table 1 below). Linear GBCAs result in more retention and retention for a longer time than macrocyclic GBCAs. Gadolinium levels remaining in the body are higher after administration of Omniscan (gadodiamide) or OptiMARK (gadoversetamide) than after Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), or MultiHance (gadobenate dimeglumine). Gadolinium levels in the body are lowest after administration of Dotarem (gadoterate meglumine), Gadavist (gadobutrol), and ProHance (gadoteridol); the gadolinium levels are also similar across these agents.

*The Medication Guide will be posted once it is approved.

Table 1. FDA-Approved GBCAs*

Brand name	Generic name	Chemical Structure
Dotarem†	gadoterate meglumine	Macrocyclic
Eovist	gadoxetate disodium	Linear
Gadavist†	gadobutrol	Macrocyclic
Magnevist	gadopentetate dimeglumine	Linear
MultiHance	gadobenate dimeglumine	Linear
Omniscan‡	gadodiamide	Linear
OptiMARK‡	gadoversetamide	Linear
ProHance†	gadoteridol	Macrocyclic

*Linear GBCAs result in more gadolinium retention in the body than macrocyclic GBCAs.
†Gadolinium levels remaining in the body are LOWEST and similar after use of these agents.
‡Gadolinium levels remaining in the body are HIGHEST after use of these agents.

To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. We have also received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and gadolinium retention could not be established.

We are continuing to assess the health effects of gadolinium retention in the body and will update the public when new information becomes available. We are requiring the following specific changes to the labeling of all GBCAs:

- A *Warning and Precaution*
- Changes related to gadolinium retention in the *Adverse Reactions, Pregnancy, Clinical Pharmacology*, and *Patient Instructions* sections

We urge patients and health care professionals to report side effects involving GBCAs or other medicines to the FDA MedWatch program.

4712-103 Advanced MRI Neurological Applications

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INTRODUCTION and OVERVIEW

The development and implementation of advanced MRI neurological applications goes beyond anatomical structural imaging of the brain and into evaluation of brain function. Brain function can be assessed through multiple approaches, including diffusion-weighted imaging, perfusion-weighted imaging, BOLD imaging, and MR spectroscopy. Each of these techniques provides unique information about brain function in the clinical setting of pathology:

Diffusion-weighted Imaging	Describes movement of water within brain tissue and reveals the presence of acute ischemia
Perfusion-weighted Imaging	Identifies brain tissue at risk of ischemia
BOLD Imaging	Depicts oxygen utilization localized to specific anatomic regions during brain activation, demonstrating task performance
MR Spectroscopy	Visualizes chemical components of brain tissue and alterations in the setting of pathology. Changes in brain function may be detected before structural changes are apparent

Diffusion, perfusion, and BOLD imaging were all made possible through the development of echo planar imaging (EPI). Virtually every imaging facility in the world regularly uses at least one of the many applications enabled by EPI. Diffusion-weighted imaging has become standard to most brain imaging protocols, and perfusion-weighted imaging is widely implemented in both hospital-based and outpatient imaging facilities. To better understand the mechanics of diffusion-weighted, perfusion-weighted imaging, and BOLD imaging, one must have a basic understanding of the originating pulse sequence, echo planar imaging, which is fundamental to all of them.

DEVELOPMENT AND FUNDAMENTAL PRINCIPLES OF ECHO PLANAR IMAGING

Echo planar imaging was first described by Sir Peter Mansfield (1933-1996) in the article *Multi-planar Imaging Formation using NMR Spin Echoes*, published in 1977.[1] In 2003, Dr. Mansfield shared the Nobel Prize in Medicine with Dr. Paul Lauterbur for their accomplishments in the development of MRI in medicine. It was also in 1977 that Dr. Raymond Damadian used **nuclear magnetic resonance** to create the first ***in vivo*** human image, bringing magnetic resonance imaging (MRI) into the vernacular.

It would be almost two decades before EPI could be clinically implemented for practical use in medicine. Many advances in computer processing, radiofrequency (RF) development, and high-powered gradient subsystems would be required before Dr. Mansfield's theories would have practical application.

The mid-1990s was a time of significant development in MRI hardware, particularly in gradient hardware. The first very-high amplitude (milliTesla/meter) and high slew rate gradients (Tesla/meter/sec) were developed and made available for the mass MRI market. Concurrent with the development of high-speed gradients was the implementation of the first clinically feasible EPI sequences.

For the sake of simplicity, EPI can be thought of as a hybrid of a gradient-recalled echo-based pulse sequence (GRE) and a fast/turbo spin echo (FSE or TSE) pulse sequence.

Principles of Gradient-recalled Echo-based Sequence

In a GRE sequence, the frequency-encoding gradient reversal is applied to "rewind" dephasing spins in the transverse plane; in a standard spin echo (SE) sequence, an 180^{o} RF pulse is used.

Compared to an 180° RF echo, the advantages of a gradient-induced echo are:

1. Gradient echoes can be obtained in extremely fast intervals, significantly faster than RF-induced echoes (**Figure 1**).
2. Gradient-induced echoes do not impart greater **specific absorption rate** (SAR), the amount of RF energy absorbed by the patient, whereas RF-induced echoes do impart greater SAR.
3. Gradient-induced echoes do not correct for dephasing caused by **T2´ (prime)**.

T2´ is the dephasing of spins in the transverse plane due to local field **susceptibility effects**. These effects include small field **inhomogeneities** that cause areas of high susceptibility, such as water, and those with little or no susceptibility, such as air, compact bone, or even iron deposits like hemosiderin. Even the metabolism of oxyhemoglobin to deoxyhemoglobin within cells causes a slight variation in local spin-spin susceptibility. This sensitivity to susceptibility effects with GRE-induced echoes poses both a "curse and a blessing" in the EPI sequence.

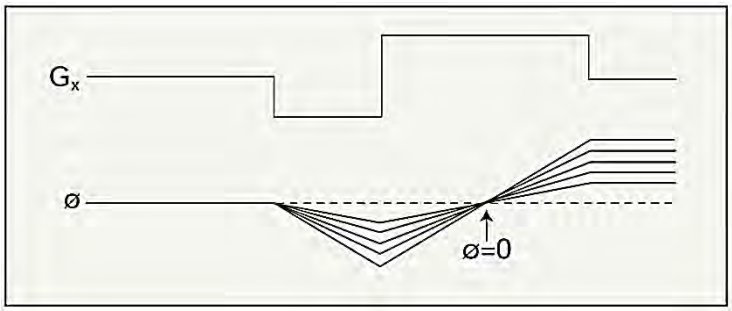


Figure 1. Pulse sequence illustration of the gradient-recalled echo sequence demonstrating how the frequency-encoding gradient de-phases and re-phases spins to be phase coherent under the readout portion of the gradient.

Principles of Basic Fast/Turbo Spin Echo

In the FSE/TSE pulse sequence, a train of 180° RF-induced echoes are played out within a single TR (repetition time) (**Figure 2**). This permits multiple lines of ***k*-space** filling per TR, greatly increasing data acquisition compared to standard spin echo (SE) sequences. For example, in a standard SE pulse echo, if 256 phase-encoding steps are required to create the desired MR image, the TR period must be repeated 256 times (one line of *k*-space/TR). However, if one applies a train of eight RF-induced echoes, eight lines of *k*-space are filled within each TR period. Hence, only 32 TR intervals are required to gather the desired 256 lines of *k*-space. All other factors remaining the same, the FSE/TSE sequence is 8x faster. Taken to the extreme, one could theoretically apply a train of 256 RF echoes and collect all 256 lines of *k*-space within a *single* TR period. When all the required lines of *k*-space are acquired within a single TR, this is referred to as a "snapshot" or a "single-shot" technique.

However, FSE/TSE has some disadvantages. First, since each phase-encoding step acquired in the same TR has a varying amount of T2 decay, that is, each echo in the train has a different echo time (TE), significant blurring of the image can occur. This makes snapshot FSE/TSE impractical for high resolution imaging. Secondly, 180º RF-induced echoes correct for dephasing caused by T2´ effects. Just like GRE imaging, T2´ effects are both a "curse and a blessing." FSE/TSE sequences are not sensitive to susceptibility effects, making detection of minute differences in local susceptibility difficult (**Figure 3**).

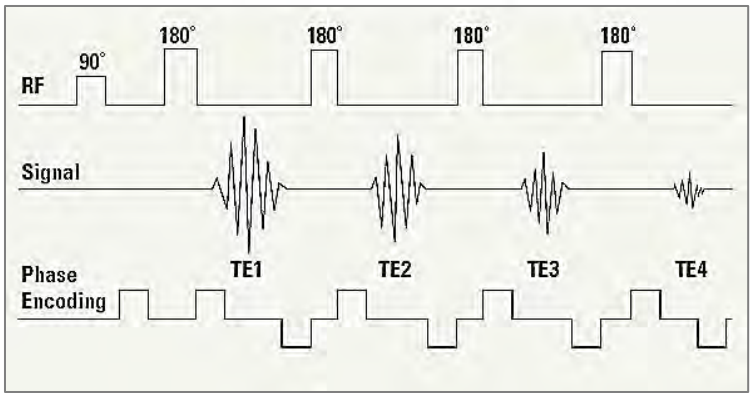


Figure 2.Fast/turbo spin echo pulse sequence illustrating an echo train of four 180º RF-induced echoes with corresponding TEs and phase-encoding steps within a single TR period.

The EPI sequence, which was described long before GRE and FSE sequences were conceived, uses principles of both GRE and FSE. EPI uses a train of GRE-induced echoes instead of 180º RF-induced echoes. EPI is typically either an SE or GRE. In the SE-EPI sequence, a 90º slice selective pulse is applied followed by an 180º RF pulse, as in standard SE (**Figure 4**). After the 180º RF pulse, a train of gradient-induced echoes are applied in rapid unison (**Figure 5**). Because gradient echoes can be obtained extremely quickly as compared to FSE/TSE, snapshot EPI is very practical.

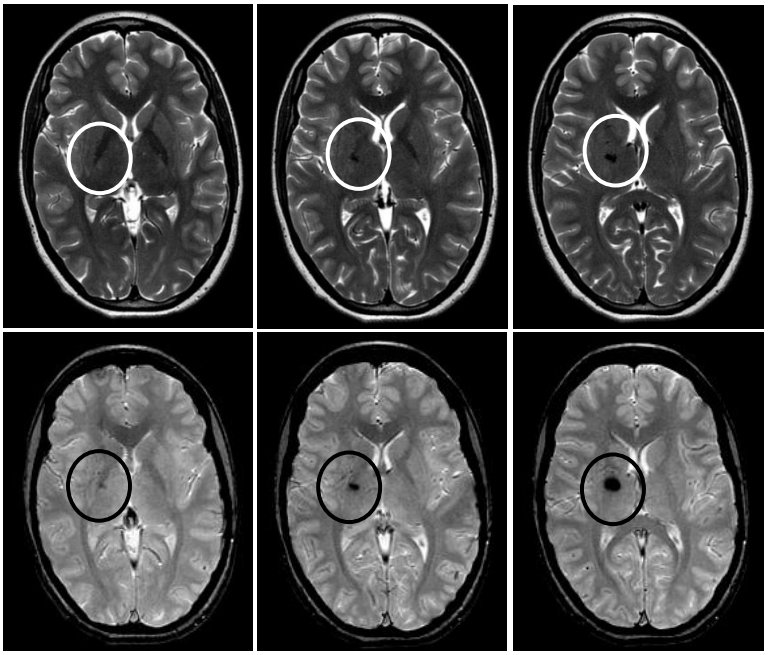


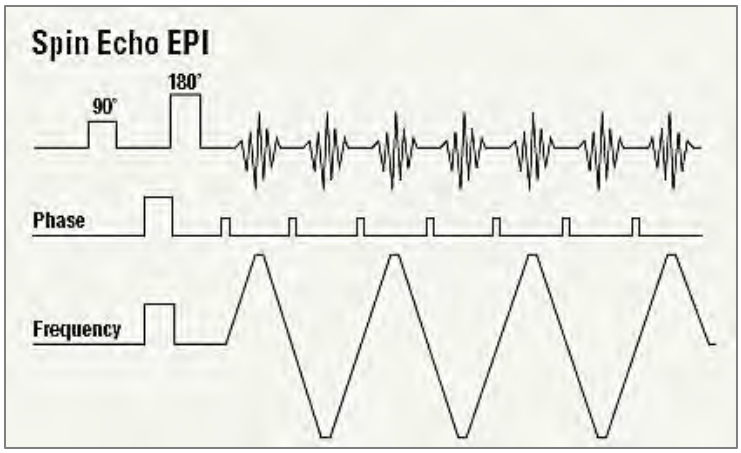
Figure 3. (Top row) T2W FSE of the brain. (Bottom row) Corresponding GRE images.

Note the area of hypointense signal on the right side (circles). The GRE images demonstrate superior detection of the hemorrhagic component of the old stroke; this susceptibility effect is known as "blooming." FSE images, while perhaps not useful for demonstrating hemorrhage, provide superior and useful T2 information.

In a GRE-EPI, the root of the sequence is exactly like a standard GRE sequence in that it begins with a slice selective pulse, followed by a standard gradient-recalled echo. At this point, a train of gradient-induced echoes are applied in rapid sequence. As with SE-EPI, GRE-EPI can also be done in a snapshot, although the GRE-EPI sequence is more sensitive to susceptibility effects than the SE-EPI sequence.

EPI was first used clinically as a "speed" technique in brain imaging due to its ability to quickly acquire data. As a practical application, snapshot SE-EPI (SS SE-EPI) was used for patients who were unable to hold still for brain imaging. Images could be obtained through the entire head in as little as two seconds.

Today EPI is available in numerous forms, including inversion-recovery EPI, short TI inversion-recovery EPI, diffusion EPI, diffusion tensor EPI, perfusion EPI, and BOLD imaging. EPI can also be performed in both 2D and 3D imaging modes.



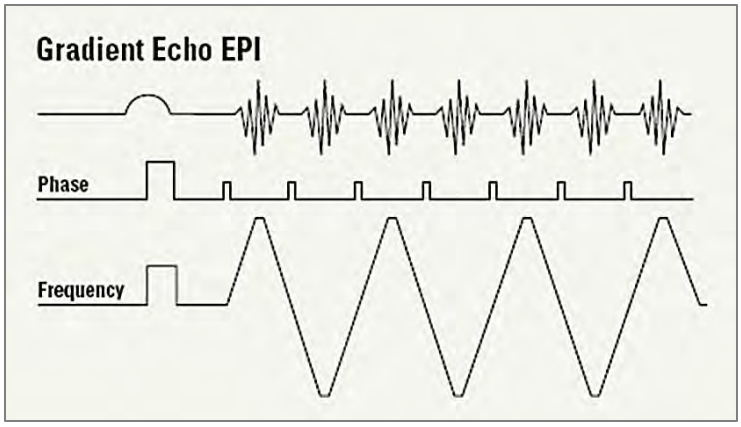


Figure 4. (Top) SE-EPI sequence. The spacing between echoes is not to scale but expanded outward for presentation purposes.

Figure 5. (Bottom) GRE sequence.

DIFFUSION–WEIGHTED IMAGING

Diffusion-weighted imaging (DWI) has changed the way MRI facilities manage acute stroke protocols. Because of its very short acquisition time and versatility, DWI is performed on every MR brain exam regardless of clinical indications. However, it was in the visualization of acute stroke that the utility of DWI was first demonstrated.

Isotropy and Anisotropy

DWI measures the mobility of freely moving water molecules in extracellular brain tissue. Water may diffuse freely into cells but is often restricted to some degree due to cell membrane and intracellular structures (**organelles**). In *gray* matter, water diffuses via numerous pathways depending on the cell structure. This diffusion of water is referred to as **isotropic**, meaning "the same in all directions" (**Figure 6**).

In *white* matter, the neuronal axons or nerve tracts restrict the mobility of water, which prefers to diffuse along a linear path of the white matter tracts. This type of diffusion is called ***anisotropic***, meaning the water follows a non-random, preferred pathway (**Figure 7**).

When placed in two equal but opposing gradient fields called **diffusion gradients**, free-moving, unrestricted molecular water creates a signal void much like that of flowing blood but on a molecular scale. Free-moving water appears dark, or hypointense. Conversely, diffusion gradients do not cancel out spins from restricted water motion, and therefore restricted water motion appears bright or hyperintense.

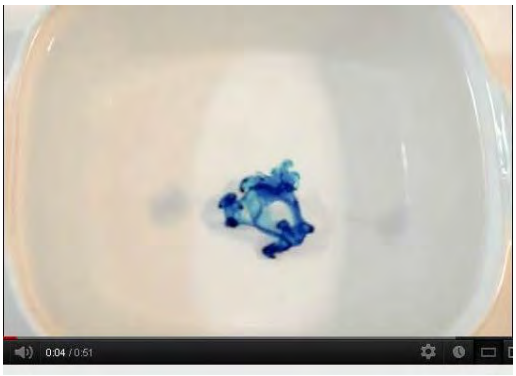


Figure 6. (Top) Demonstration of the principle of anisotropy.
Click here to view movie. Anisotropic movement.

Figure 7. (Bottom) Demonstration of the principle of isotropy.
Click here to view movie. Isotropic movement.

In the event of a vascular accident due to acute stroke or infarction, blood supply to the cells is cut off. As cellular metabolism stops, the cells begin to release massive amounts of water, swell, and die. The cellular swelling greatly impedes the pathway of extracellular water movement. At this point, all molecular water motion stops, and acute stroke will appear hyperintense on diffusion-weighted imaging, reflecting restricted diffusion. DWI has been shown to demonstrate this mechanism within minutes of acute ischemic event, allowing timely diagnosis and intervention. Older infarctions appear hypointense on DWI, which easily distinguishes old stroke from acute stroke.

The strength of the diffusion gradient determines the amount of diffusion contrast inherent in the image; the greater the strength of the gradient, the greater the contrast between the moving and restricted water. The diffusion gradient strength is given as a ***b*-value.** The higher the *b*-value, the greater the diffusion contrast. Note that with a higher *b*-value, the overall SNR is also lower; this is rarely an impediment as long as the *b*-values are not extremely high (**Figure 8**).

The movement of extracellular water in and out of cells is random since water moves more freely in some directions and less freely in others. Therefore, DWI is done in at least three directions. Typically these directions are **orthogonally** oriented in the x, y, and z planes.
We will discuss diffusion tensor imaging, acquiring data in multiple additional directions, later in this material.

Applying a diffusion gradient in only one plane will yield images indicating restricted diffusion that mimic stroke; in actuality, this may represent the normal water movement in those particular cells.

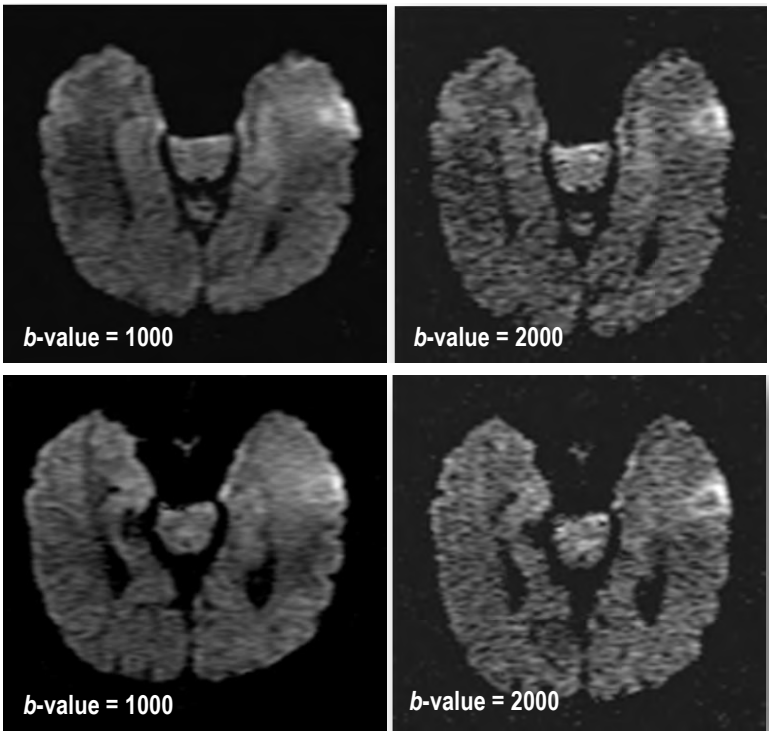


Figure 8. (Top) 1.5T DWI images using a *b*-value of 1000 and 2000. (Bottom) 1.5T DWI images of the same location. Note the increased diffusion contrast but decreased SNR in the *b*-value = 2000 images. A *b*-value of 1000 is considered the standard for most 1.5T DWI imaging, although some facilities increase the *b*-value to 1500–2000 in the brain.

To avoid this phenomenon, each anatomic location is acquired three times with the diffusion gradient applied once in each orthogonal plane. Each location is constructed separately, and the images are combined and displayed as a T2-weighted "trace" or composite image that displays the *average* of all three images (**Figure 9**). While this capability is possible with other pulse sequences such as FSE/TSE, the time required makes these sequences impractical for common use. The speed of SS-EPI permits large amounts of data to be acquired quickly and greatly reduces the chances of patient movement from one acquisition to the next. A typical DWI acquisition through the entire brain is typically done in less than one minute.

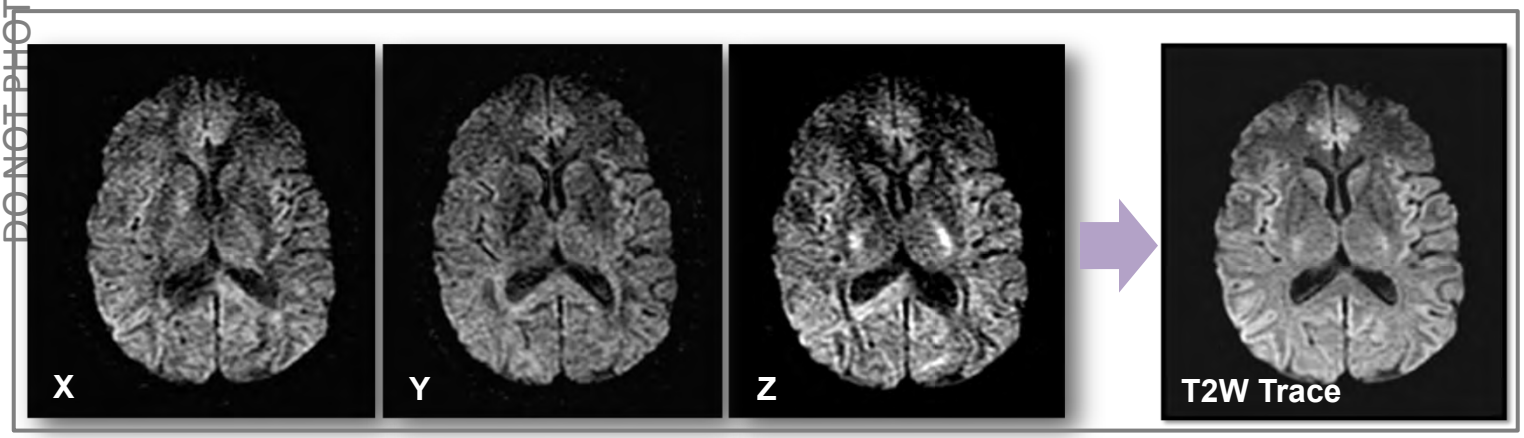


Figure 9. Images X, Y, and Z above are the individually acquired DWI images at the same anatomical location in three orthogonal directions. The T2-weighted trace image is the composite of those three images. Note the lack of restricted yet normal diffusion in the z-direction image.

Apparent Diffusion Coefficient Mapping

In some instances, there are areas within the brain that yield hyperintense signal on DWI yet do not represent restricted diffusion. This occurs because the tissue has a very long T2 due to edema. This phenomenon is called **T2 shine-through**, or simply **T2 shine**. In most instances, the radiologist can easily discern whether bright signal on DWI represents T2 shine-through or restricted diffusion. However, that distinction is not always clear. To circumvent this issue, DWI images are acquired using at least two different *b*-values, the lowest *b*-value always being 0. This creates yet another set of images and is typically referred to as T2* (star) images because the *b*-value is 0 (no diffusion gradient), and EPI images exhibit both true T2 as well as T2´ information. Each voxel for each set of *b*-value images is compared for the *apparent* change in T2 signal from one *b*-value to the next. Voxels with hyperintense signal due to T2 will lose signal intensity from the lower to the higher *b*-value. Areas of hyperintensity due to restricted diffusion will lose signal intensity as well but not nearly to the same extent. The coefficient of those changes is calculated and displayed in another set of images called the **apparent diffusion coefficient (ADC) map.**

The ADC map is typically displayed as a “subtraction” image where the areas of bright T2 (T2 shine-through) are hyperintense and areas of restricted diffusion are hypointense. The ADC map can be returned to the “look” of the DWI images, where the restricted diffusion is bright again through a further computation that yields an “exponential” or eADC map. Today most MRI systems calculate the ADC map automatically and require no additional post-processing by the technologist or radiologist (**Figure 10**).

The most common use of diffusion imaging is in the early detection of acute ischemia and infarction. With conventional MR imaging, changes due to brain infarction may not be visible on T2-weighted images for several hours. With diffusion imaging, however, these changes are often visible within minutes, with greater than 90% sensitivity. Consequently, diffusion imaging has become critical in patients in whom stroke is suspected.

In cases of *suspected* acute infarction, diffusion imaging can confirm the diagnosis. In these cases, an area of hyperintensity is noted, corresponding to an arterial territory. These hyperintense foci may be visible on DWI even when other sequences show no signal abnormality.

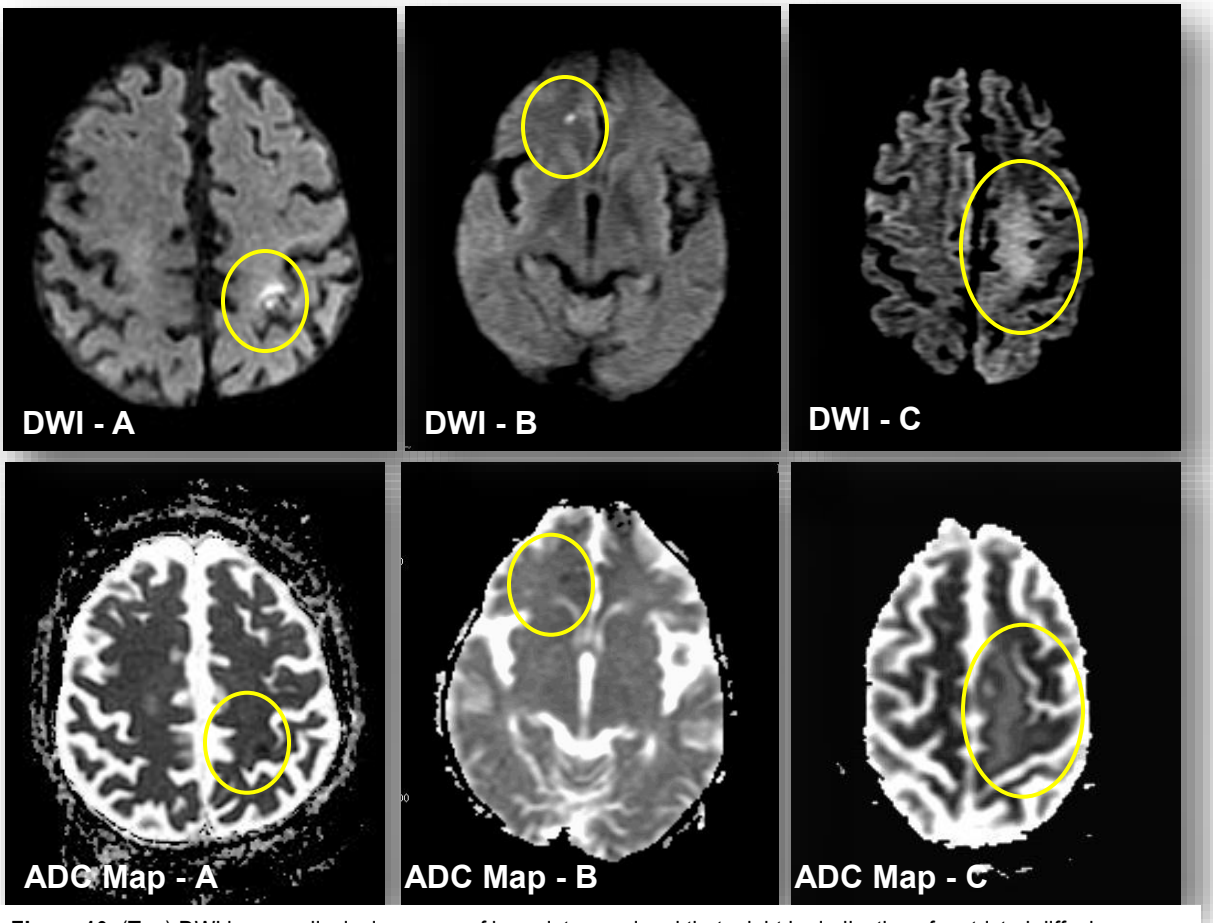


Figure 10. (Top) DWI images displaying areas of hyperintense signal that might be indicative of restricted diffusion. (Bottom) ADC maps of the corresponding DWI images. Note the areas of hypointensity on DWI images A and B become hyperintense on the ADC map, demonstrating restricted diffusion. The area on image C retains its hyperintensity, demonstrating T2 shine-through.

Diffusion imaging is also useful in patients with chronic ischemic changes due to small vessel disease and who then suffer additional acute deficits. Diffusion imaging can differentiate acute infarct from chronic ischemic changes or old infarcts.

Finally, in patients with equivocal histories, diffusion imaging can be used to detect ischemia. Hyperacute infarcts generally appear hyperintense within a few minutes, and the signal hyperintensity persists for several weeks. As the cells die, however, they eventually become atrophic. At this point, the contrast mechanism reverses and in the chronic phase of an infarction, the amount of intracellular water is markedly decreased compared to the amount of extracellular water. Thus, in chronic infarction, signal changes approaching those of CSF occur, resulting in facilitated diffusion rather than restricted diffusion. Consequently, after several months, an infarction tends to appear hypointense rather than hyperintense on diffusion images.

Diffusion imaging is also useful in some cases of infection. In early infection, changes may be visible on diffusion imaging, while conventional MR images remain relatively nonspecific. In some types of infection, increased intracellular water leads to restricted diffusion. Abscesses in the brain demonstrate significant restricted diffusion, helping to differentiate them from tumors.

DIFFUSION TENSOR IMAGING

As stated earlier, the motion of molecular water is complex. In DWI, three-directional diffusion gradients are applied to describe the *average* of restricted versus freely-moving extracellular water molecules. However, the complexity of the direction and magnitude of the moving water cannot be fully described by mapping the three orthogonal planes. For example, in the white matter tracts of the brain, water tends to move along the linear structure of the tracts. Water diffusing in the linear direction of the tract diffuses more quickly than water attempting to diffuse in a more perpendicular direction. The direction and magnitude of the motion of water can be described as a **vector.** Most simply, a vector can be displayed as a simple line or arrow with a particular angle and length that corresponds to the direction and magnitude of a force or object in motion. When that motion is multi-directional, the vectors can then be described as a diffusion tensor (**Figure 11**). To calculate the diffusion tensor of water motion in the brain, at least six multi-directional diffusion gradients must be applied. As with DWI, diffusion tensor imaging (DTI) creates a set of images for each direction of the diffusion gradients (including at least two *b*-values). These images are likewise combined and mapped to provide T2-weighted diffusion trace images as well as ADC maps. While this increases the overall scan time, DTI displays greater SNR and superior diffusion contrast than DWI.

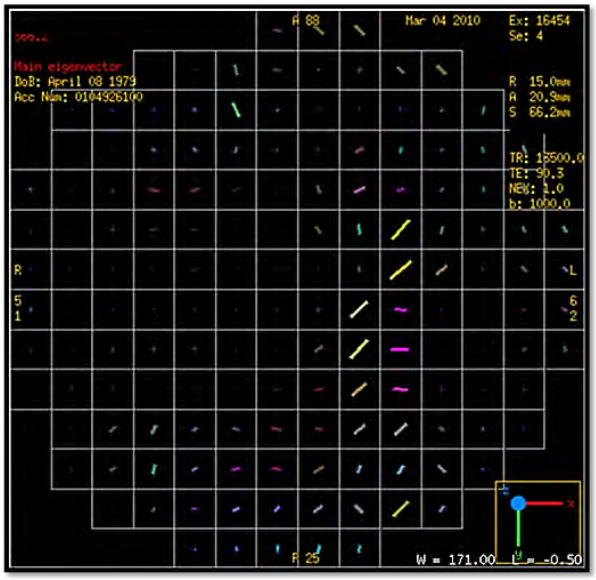


Figure 11. A visual display of individual voxel tensors is known as an ***eginvector.*** Each box represents a voxel within a prescribed region of interest. The color, angle, length of each vector in a voxel are indicative of the direction and magnitude of the movement of water.

In addition to higher quality diffusion information, DTI permits further analysis based on the mathematical information provided by diffusion tensors on a voxel-by-voxel basis. Each voxel in a DTI series contains information regarding the direction and magnitude of water motion. This is

particularly useful with regard to water movement along the white matter tracts since the preferred motion is along the linear, but curved, path of the tracts. Since each voxel can be analyzed, it is possible to construct a map of the anisotropy of water diffusion along the white matter tracts. In this image, known as a **fractional anisotropy map,** flow information is displayed on a molecular scale, rather than anatomical information. This information can be colorized to indicate the direction of water diffusion along white matter tracts (**Figure 12**).

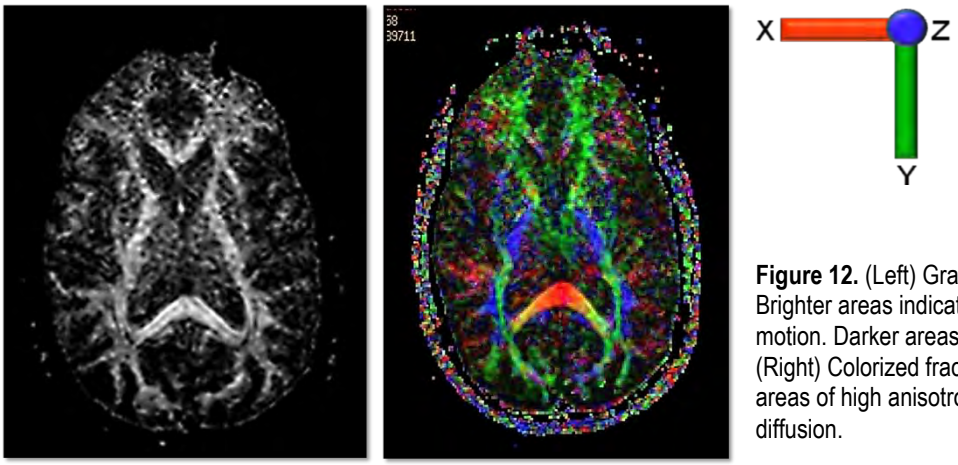


Figure 12. (Left) Gray scale fractional anisotropy map. Brighter areas indicate areas of high anisotropic motion. Darker areas indicate lower anisotropic motion. (Right) Colorized fractional anisotropy map showing areas of high anisotropic motion and direction of water diffusion.

Another useful tool provided by DTI is the postprocessing of 3D representations of white matter tracts throughout the brain. This is helpful in a number of clinical settings, such as surgical planning, by showing the relationship of certain white matter tracts to pathology. Postprocessing of 3D representations, or **tractography**, is also useful for visualizing disruption of white matter tracts caused by multiple sclerosis. Tractography is possible because the direction and magnitude of anisotropic motion in each voxel is known. However, instead of projecting voxel information in a 2D projection, voxels are displayed in a 3D projection. In this process, the operator selects a range of voxels within a region of interest. A 3D projection of those voxels is displayed and manipulated in any plane, much like 3D MRA projections are manipulated (**Figures 13 and 14**).

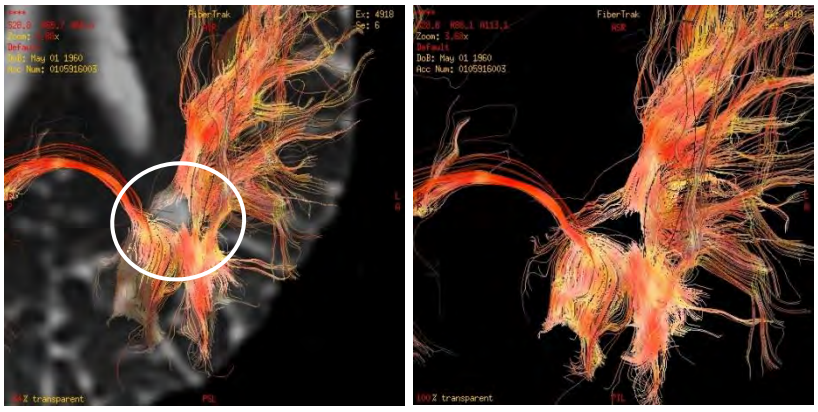


Figure 13. Tractography projection from a DTI series of a patient with known multiple sclerosis. A large MS plaque is seen near the posterior horn of the left lateral ventricle. (Left) Axial 2D projection of the fiber tracts overlaid on *b*-value = 0 image. (Right) Image of the fiber tracts alone. Note the area that corresponds to the large plaque shows near-total disruption of the white matter tracts.

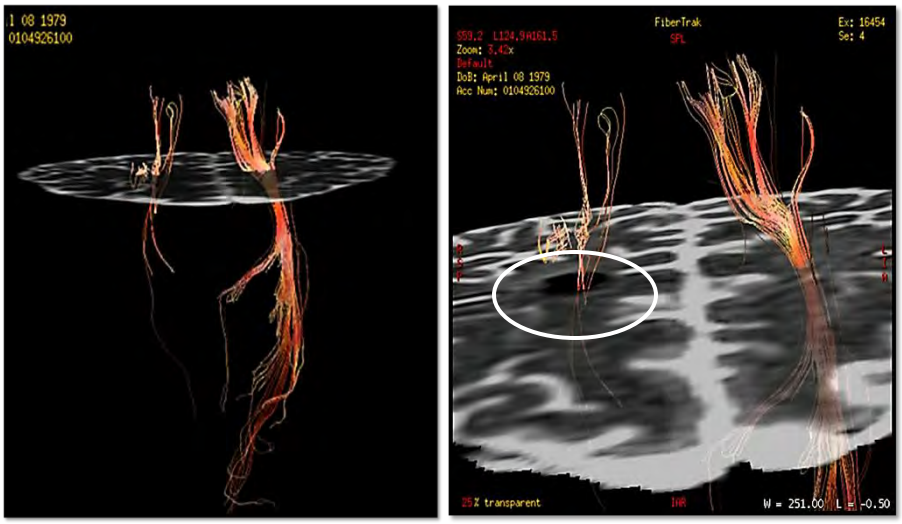


Figure 14. Tractography projection from a DTI series of a patient with an old infarct (circle). Two regions of interest were selected to compare z-direction fiber tracts on the left and right sides. Note the lack of fiber tracts in the area of infarct on the right side of the brain.

PERFUSION-WEIGHTED IMAGING

Perfusion-weighted imaging of the brain has become another extremely useful tool for evaluating brain pathology. Originally thought of as an adjunct to DWI in the diagnosis and characterization of acute stroke, perfusion imaging has proven to be helpful in the characterization of numerous other pathologies.

Perfusion imaging measures and displays information about the *perfusion* (permeation or penetration) of blood in the brain on a microscopic level. This is different from the imaging of blood *flow* within vessels. The perfusion acquisition permits measurement of relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and mean transmit time (MTT). This information is useful not only in the evaluation of acute stroke but also for tumor characterization, response to therapy, and recurrence.

Perfusion imaging takes advantage of the extreme sensitivity of GRE-EPI to local field susceptibility effects. During data acquisition, gadolinium-based contrast is injected in a rapid bolus, typically 5.0ml/sec. The GRE-EPI series is acquired in extremely rapid succession over many passes or phases, typically 30-35 phases per anatomic location. This captures the "**wash-in**" and "**wash-out**" effects of the contrast agent. Gadolinium is paramagnetic; therefore at the moment it enters into the capillary beds, the signal response is hypointense. This is the "wash-in" phase. Absent pathology that breaks down the blood-brain barrier, the contrast does not enter the cells and begins to move out of the capillary beds. At this point the contrast effect is a return to equilibrium, known as the "wash-out" phase. The speed of data acquisition is critical. The transit time from wash-in to wash-out in the brain is very fast; from the beginning of the injection and data acquisition (typically at the same time) until the return to tissue equilibrium can be as short as 90–100 seconds. The speed of

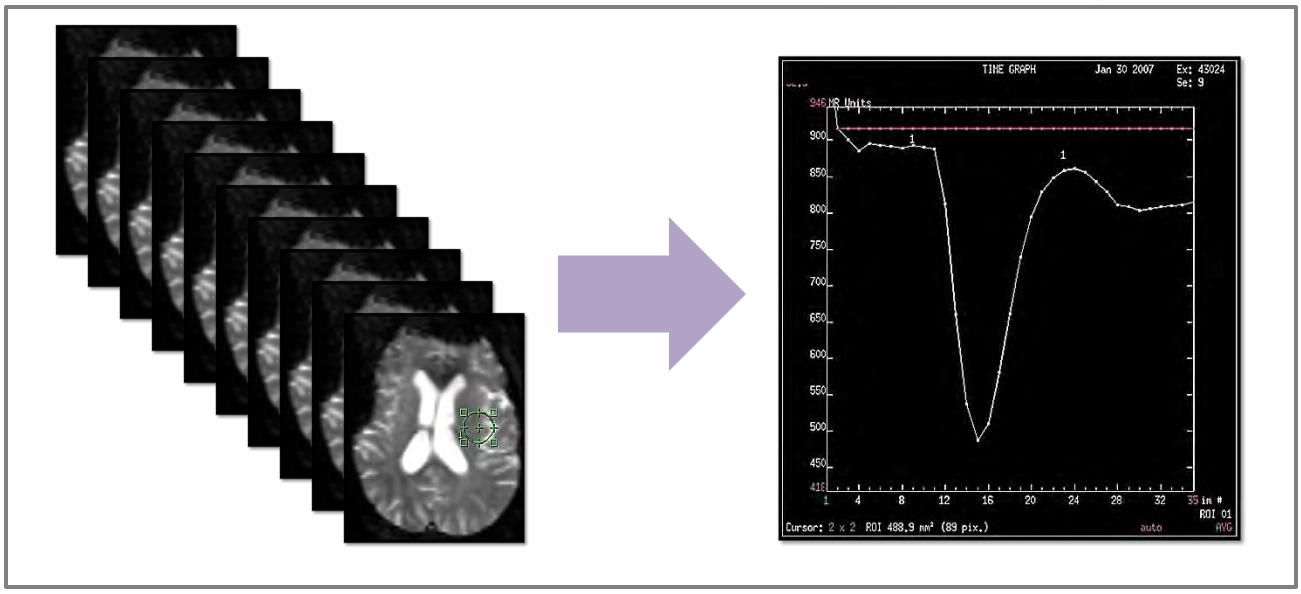


Figure 15. With normal brain tissue, gadolinium contrast does not cross the blood-brain barrier. Contrast flows into the surrounding intercellular tissue, then flows out, displaying a quick "wash-in, wash-out" effect.

EPI, along with a very high performance gradient subsystem, allows for rapid data acquisition of 10–15 slice locations in 30–35 phases in 90–100 seconds. It is conceivable that running a perfusion series using GRE-EPI could produce as many as 350–525 images in as little as 60 seconds (**Figure 15**).

Once acquired, the entire data set is analyzed and a graph displaying relative pixel value (brightness) against time-point is produced. The graph provides useful information regarding the function of the blood flow in the brain. The area under the curve is a measure of **relative cerebral blood volume** (rCBV). The time from the steady state of the contrast bolus to the peak negative enhancement interval represents **relative cerebral blood flow** (rCBF)**.** The time interval from the beginning of the wash-in phase to the return of equilibrium (wash-out) is the **mean transit time** (MTT) (**Figure 16**).

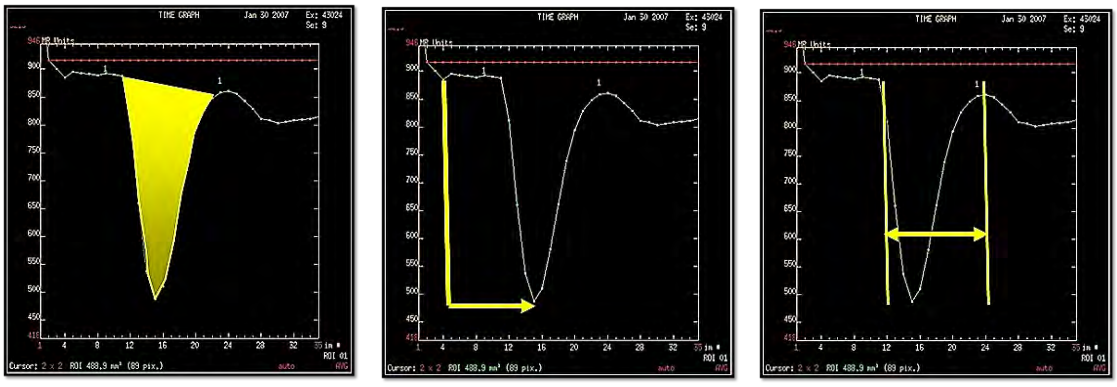


Figure 16. (Left) Perfusion wash-in-/wash-out graph; area in yellow indicates rCBV. (Center) Perfusion wash-in/wash-out; arrow indicates rCBF. (Right) Mean transit time (arrow).

This type of analysis is extremely useful in the diagnosis of acute stroke to differentiate brain tissue death from brain tissue *at risk* of death. Where there is dead brain tissue, perfusion maps display the area as "cold" with blue or dark colors and with a graph that is relatively flat, indicating reduced perfusion. Areas where perfusion is active but very low might surround the dead tissue area. This is often referred to as the perfusion "penumbra." The **perfusion penumbra** defines tissue-at-risk and guides emergency clinical treatment to prevent further brain tissue death (**Figures 17 and 18**).

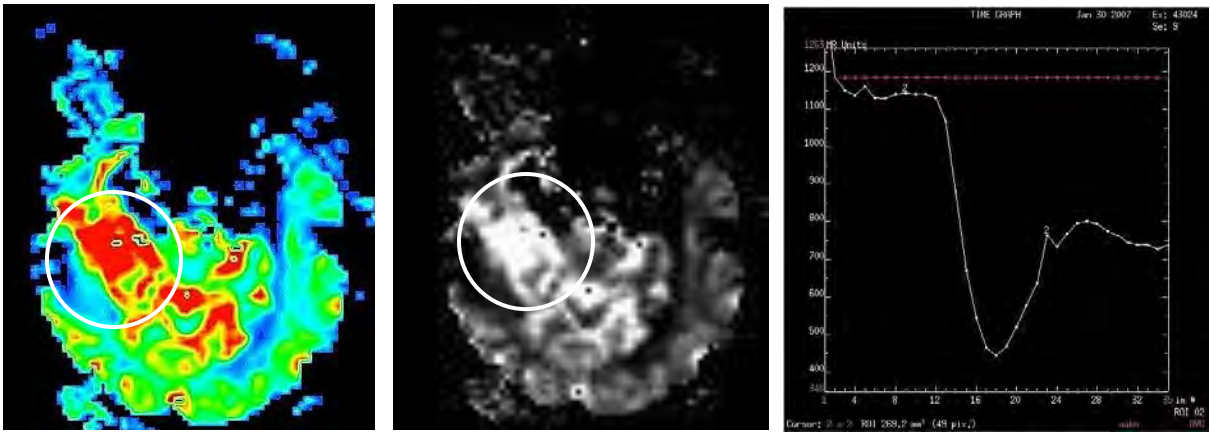


Figure 17. Recurrent brain tumor. (Left) Colorized rCBV map. The red color (hot) indicates areas of very high rCBV. (Center)Gray scale representation of the same map; the bright areas indicate high rCBV. (Right) Graph corresponding to the circled areas indicates high vascularity, characteristic of recurrent tumor.

Perfusion imaging is used for tumor evaluation. High-grade tumors have been shown to have increased cerebral blood volume compared to low-grade lesions. These changes do not necessarily correspond to areas of contrast enhancement. Tumors with uniformly low rCBV are not likely to represent high-grade lesions regardless of the extent of enhancement on conventional MR imaging. Therefore, increased blood volume or increased signal on perfusion-weighted images may aid in the planning of surgical biopsy and excision. Perfusion imaging also can be used for assessing treatment response.

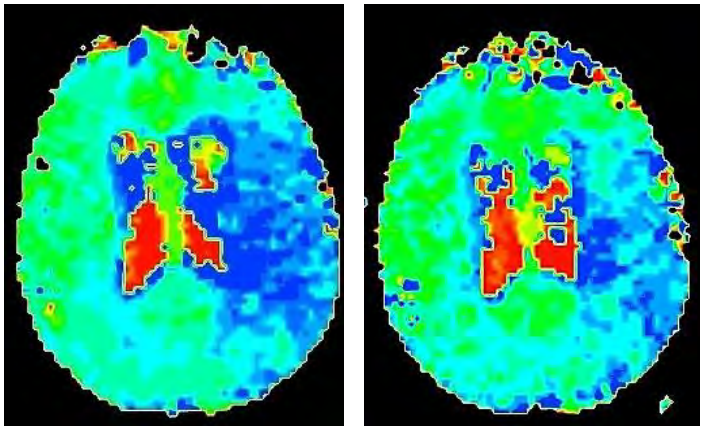


Figure 18. 56-year-old male with limited blood flow in the left middle cerebral artery.

(Left) rCBV map indicating lower blood volume to the left hemisphere.

(Right) Same slice after injecting the vasodilator Diamox® (acetazolamide). Note the slight increase in rCBV in the left hemisphere. An increase in the rCBV is noted in the right hemisphere as well.

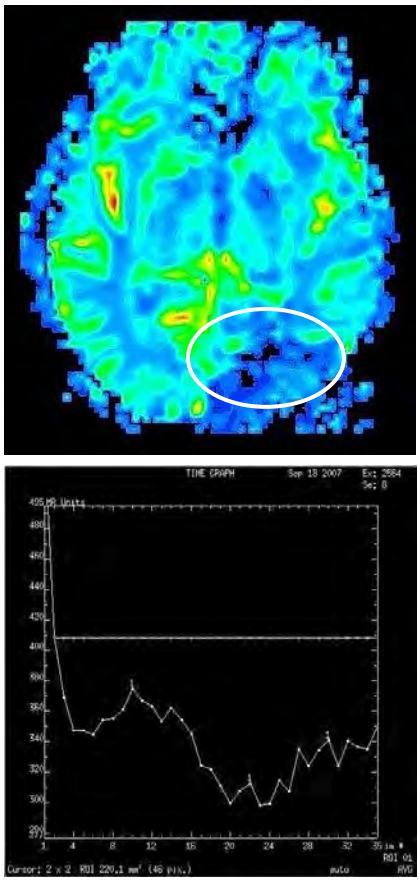


Figure 19. Perfusion imaging showing area of perfusion deficit (circle) following radiation treatment for glioma. Corresponding graph indicates near total lack of perfusion, indicating radiation necrosis of tissue.

Perfusion imaging is also useful in the evaluation of the brain following radiation treatments for intraaxial tumors such as gliomas (**Figure 19**). Radiation often causes cellular edema, which can obscure evidence of new tumor on some sequences. Perfusion can also be effective in determining radiation necrosis versus new tumor. Necrosis appears "cold" on perfusion images with a flat line graph, while new or residual tumor is highly vascularized and will display "warm" with a strong wash-in/wash-out curve, indicating high rCBF and rCBV.

Arterial Spin Labeling

Arterial spin labeling (ASL) is a recently developed alternative to EPI-based perfusion imaging (**Figures 20 – 23**). ASL is a non-invasive technique requiring no IV contrast. An inversion pulse is applied to inflowing arterial blood proximal to the tissue of interest. For brain perfusion, the inversion pulse is applied at the skull base. Several assumptions are made with ASL, particularly the rate of blood flow into the brain. When tagged or labeled with an inversion pulse, the longitudinal magnetization of blood relaxes via normal T1 relaxation processes. Once the blood reaches the capillary beds, a certain degree of T1 relaxation and consequent net magnetization can be assumed. After comparing the ASL images to images of the same area obtained pre-labeling, a map of the relative cerebral blood flow can be calculated and displayed. Again, assumptions required for ASL are that there is an average rate of blood flow from the neck to the brain and also equal rates of blood flow within the left and right internal carotid arteries and basilar artery.

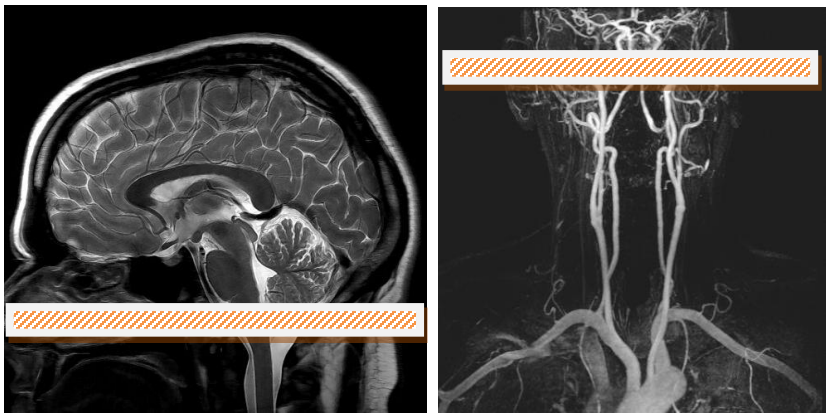


Figure 20. Typical anatomic levels of tagging of the arterial blood flow into the brain for arterial spin labeling.

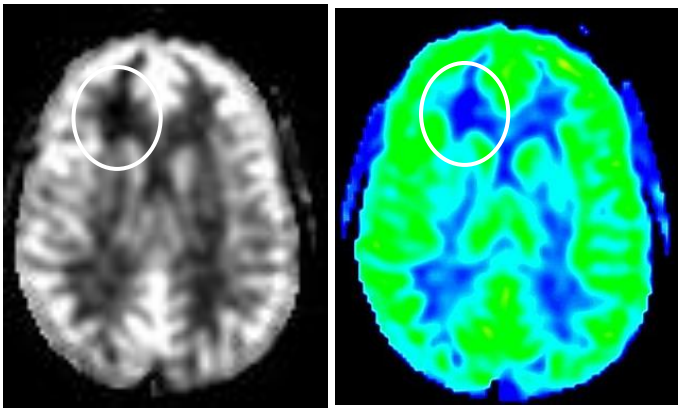


Figure 21. 28-year-old female with an ill-defined lesion in the right frontal lobe. (Left) ASL perfusion gray scale. (Right) Colorized ASL, same location. Note the area of lower rCBF compared to the left side of the brain (circles).

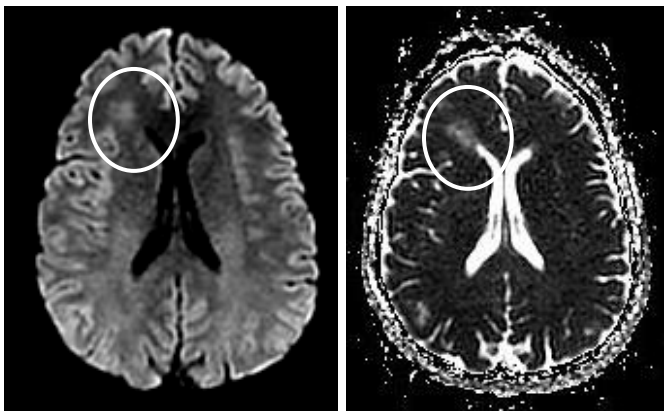


Figure 22. (Left) DWI trace. (Right) Corresponding ADC map. The lesion remains bright on both images, indicating T2 shine-through rather than acute ischemia or infarction (circles).

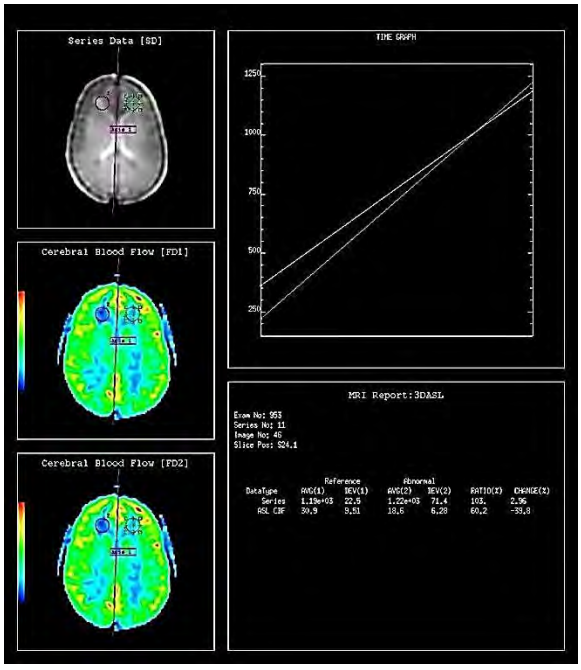


Figure 23. Analysis of an ASL series quantifying rCBF. This patient was contraindicated for IV contrast. The lower rCBF gives strong evidence that the lesion may not have enhanced. Multivoxel spectroscopy displayed normal metabolite ratio and distribution. Differential diagnosis was a possible low-grade neoplasm or infection.

While results can be reliably reproduced, ASL does have pitfalls. Particularly when compared to GRE-EPI perfusion, ASL scan times are relatively long at five minutes or more, increasing the chance of motion artifact and consequent unreliable rCBF. It is important that the patient's head be secured and positioned at precise orthogonal angles so that tagging occurs equally from one side of the neck to the other. For example, if the head and neck are aligned slightly to the left, the tagging on the right-sided vessels will appear to be more proximal to the brain than on the left, in essence giving the righted-sided blood a "head-start." This can result in skewed images as one side will appear to have a differing amount of T1 relaxation as compared to the other. Still, arterial spin labeling offers a valuable alternative to EPI-based perfusion for patients who cannot receive gadolinium-based contrast agents due to kidney disease or potential allergic reactions. ASL is also useful for pediatric patients or patients with limited IV access where high bolus injection rates are not possible.

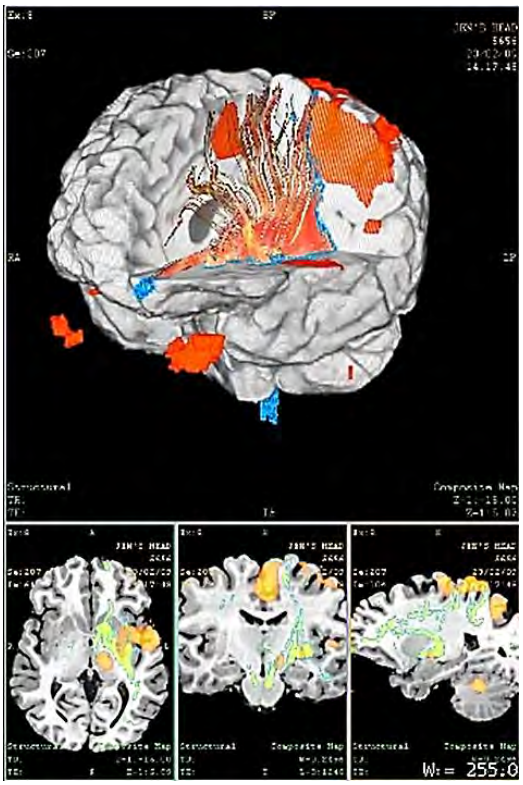


Figure 24. BOLD map of a normal volunteer undergoing motor cortex stimulation by touching the thumb of the right hand to the fingers (stimulus "on") and then remaining motionless (stimulus "off") at 30-second intervals. The stimulated area is mapped in orange on the 3D image data set and in yellow in the 2D images.

BLOOD OXYGEN-LEVEL DEPENDENT IMAGING

The popular media often use the term *functional* MR imaging (*f*MRI) when referring to the technique technically known as blood oxygen-level dependent or BOLD imaging. BOLD imaging is just one method of *functional* MR imaging; other examples of *f*MRI include perfusion imaging and MR spectroscopy (MRS). Functional MRI is most often applied to the central nervous system; *f*MRI can also be applied to non-neurological areas, such as cardiac imaging.

BOLD imaging visually captures activated areas of the brain. In other words, BOLD imaging allows real-time monitoring of brain activation and function during a mental task. These tasks, referred to as **paradigms**, range from simple to complex. Mapping the cerebral motor cortex, for example, is a well-known and robust BOLD paradigm. Other paradigms include visual tasks, hearing, reading, word recognition, and smell.

In the non-research clinical setting, BOLD imaging is useful for presurgical planning. Mapping functional areas of the brain prior to surgery in cases of tumor resection may alter the surgical approach, avoiding damage to eloquent areas of the brain. Today the vast majority of BOLD imaging is done in the research-academic arena, particularly in evaluation of normal versus autistic brain function, permanent effects of drug

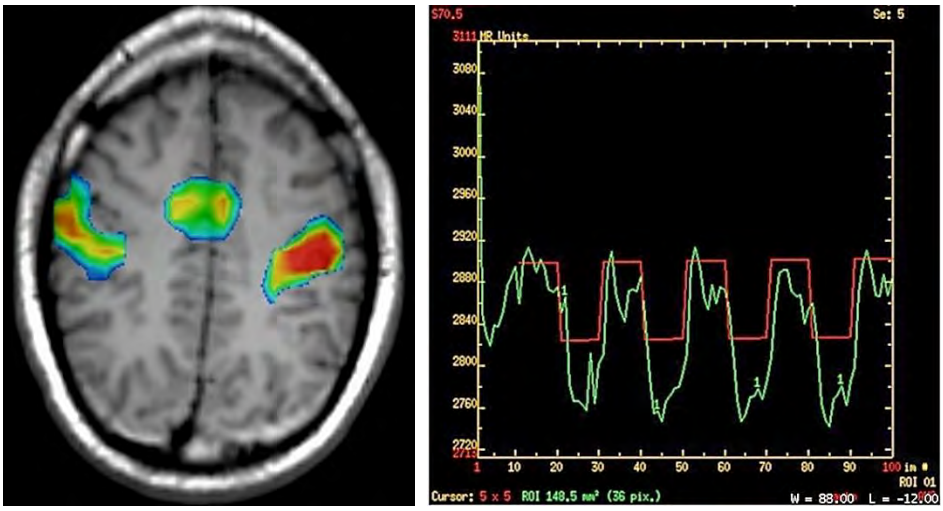


Figure 25. (Left) BOLD map of bilateral finger tapping to stimulate the motor cortex area for hand motion. (Right) Graph indicating the stimulus "on/off" interval (red graph) correlates extremely well with the changes in voxel intensity based on susceptibility changes. During task "on," oxyhemoglobin slightly increases voxel intensity. Task "off" indicates deoxyhemoglobin slightly decreases voxel intensity. Voxels that show increase/decrease at the same timing interval as the task iteration are shown in red.

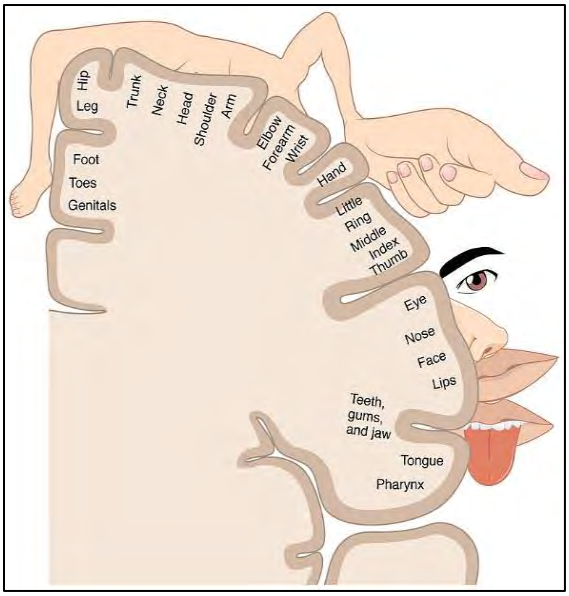


Figure 26. The cortical **homunculus** is a visual illustration of the areas of the motor cortex that control certain functions. For more information, refer to: Wikimedia

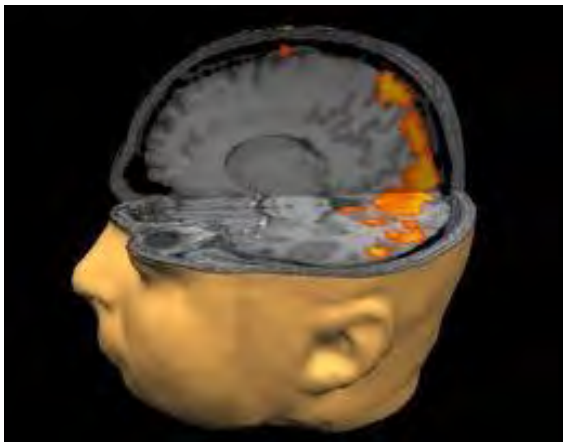


Figure 27. BOLD map of the visual cortex of the occipital lobe.

For more information, refer to: Mail Online.

abuse, Alzheimer's versus age-related memory loss, and even how the male brain differs functionally from the female brain. The equipment used in BOLD imaging of patients or subjects may include the wearing of goggles or headphones and use of microphones and finger touch pads.

BOLD imaging employs the concept of **magnetic susceptibility**, requiring careful application of a functional or clinical paradigm or stimulus to capture minute increases and decreases in susceptibility during imaging. BOLD imaging techniques provide a tremendous amount of qualitative information about the functional integrity of the area of interest in the brain, enabling physicians to carefully map an appropriate course of action, such as for surgical planning.

Performing BOLD imaging requires the use of a stimulus or task that is stopped and started at regular intervals like finger tapping. During scanning the area of the brain controlling or processing that task will show increases as well as decreases in blood flow in the targeted area. In the brain, as with many organs, when an area is "working," blood flow increases to that area. When the stimulus is removed, the blood flow returns to normal, and equilibrium is restored.

To provide energy for cell metabolism, oxyhemoglobin is converted into deoxyhemoglobin. Increased levels of deoxyhemoglobin to any area of the brain cause a change in local magnetic susceptibility due to the slight differences in paramagnetic properties between oxyhemoglobin and deoxyhemoglobin. This change in susceptibility results in minute changes in signal intensity, which increase or decrease. While the human eye cannot discern these minute changes, a computer can, if provided with enough information for statistical analysis. Typical BOLD sequences yield 500 to more than 7000 images.

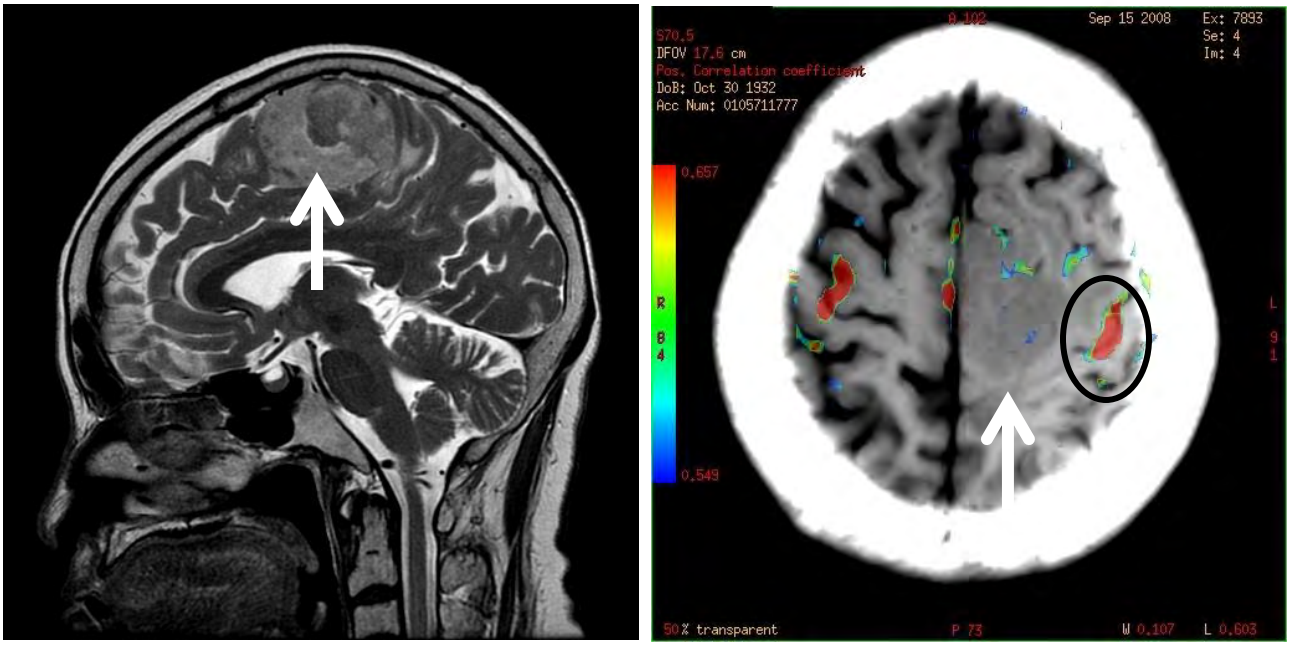


Figure 28. Presurgical patient with a large meningioma (arrows). (Left) Sagittal T2W demonstrating mass effect, displacing the motor cortex away from its normal location. (Right) Axial BOLD map obtained using bilateral thumb-to-finger stimulus showing positive correlation with the superior motor cortex (circle) in relation to the meningioma. Positive correlation can be seen in the right hemisphere as well. This information aided the surgeon in how best to approach the tumor resection.

In performing a BOLD exam, the patient or subject is given a mental stimulus or paradigm that results in increased blood flow to the pertinent area of the brain. The paradigm, such as touching the thumb to each finger to localize the motor cortex is turned "on" with activation (fingers tapping) and turned "off" during rest (no hand motion). The process is repeated several times during a single-shot gradient echo-based EPI sequence (SS-GRE-EPI) acquisition. Over time, a computer analysis program will recognize very small changes in image contrast based on small changes in susceptibility as oxyhemoglobin is converted into deoxyhemoglobin. If the timing of those small changes correspond to the timing of the stimulus "on/off" sequence, it is highly probable that that part of the brain represents the functioning anatomy identified. The voxels of the functional area are colorized and mapped over a 2D or 3D MRI of the brain, typically a T1-weighted image. The timing and intensity of stimulation during active vs rest periods allows functional localization that the clinician or researcher can map spatially (**Figures 24 -28**).

MR SPECTROSCOPY

Long before MR *imaging* existed, there was *nuclear* magnetic resonance (NMR). The phenomenon of bombarding a chemical compound with a range of radiofrequencies and observing the absorption and re-emission of radiofrequencies from that compound is known as nuclear magnetic resonance. NMR has been well understood since the early 20th century.

When emitted radiofrequencies from a chemical compound are measured and analyzed, a spectrum is produced that demonstrates peaks that identify individual chemicals and molecular concentrations in the compound. This is the basis for MR Spectroscopy (MRS).

MRI provides high *spatial* information of human tissue. MRS provides *chemical* information, which in turn may imply *functional* information. As such, MRS was the first functional application of magnetic resonance imaging.

Since the early 1970s, MRS has been used extensively for obtaining biochemical information *in vivo* in animals.[2] As improvements in MR hardware and software have become available, spectroscopic information for human tissue is more reliable.

As mentioned previously, MRS uses the process of NMR in its simplest and purest form. Chemical compounds can absorb radiofrequencies transmitted to them that match the **gyromagnetic ratio** of a particular molecule in a given field strength. In MRI, the human body's abundance of hydrogen atoms (^{1}H), bound mostly to water and fat, serves as the major source of re-emitted MR signal. Most MR operators perform a simple form of MRS each time they perform a manual prescan to observe and manipulate the MR spectrum wherein the resonant frequency must be altered to precisely match the frequency of water or fat. Hydrogen bound to water absorbs energy at a slightly different frequency than hydrogen bound to fat. At 1.5 Tesla, the chemical shift between fat and water is 220 Hz. **Figure 29** is an example of a spectrum routinely observed by MR technologists. The height of the peak indicates the degree of concentration of a chemical or molecule. The distance between different peaks indicates the **chemical shift** between two compounds, which varies with field strength. The higher the magnetic field strength, the greater the chemical shift between peaks. It is for this reason that MRS is impractical at lower field strengths as the chemical shift is so narrow as to superimpose the peak of one molecule onto another peak, rendering almost no diagnostic value.

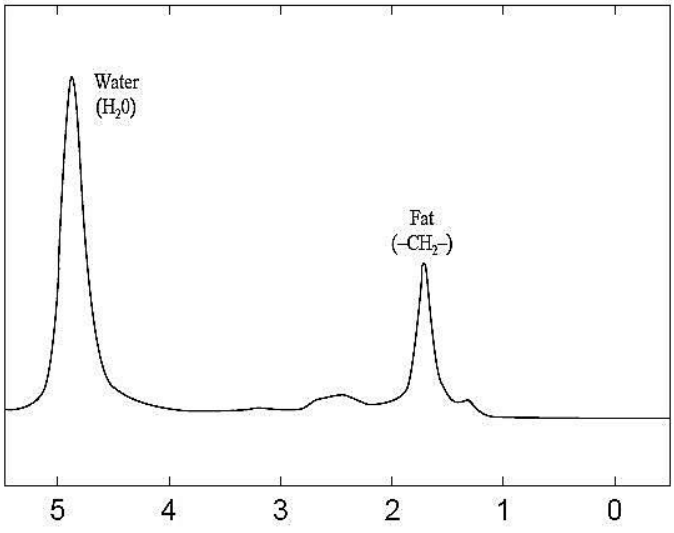


Figure 29. Basic spectroscopy. The spectrum of water and fat peaks. Note the height of the peaks indicating the relative concentrations of both water and fat. The frequency difference between each is the "chemical shift."

Courtesy of GE Healthcare

Hydrogen Spectroscopy of the Brain

Hydrogen spectroscopy of the brain is the most common clinically performed MRS exam. Technically, brain MRS can be performed using standard MR imaging hardware without the addition of a special coil, and the required software is available on most commercial systems. Thus, MRS evaluation can be performed as part of a standard MRI exam. Compared to other body regions, the brain is easier to study with hydrogen spectroscopy — ^{1}HMRS — for several reasons: physiologic motion is minor, **shimming** is easy to perform, and signal from lipids in the brain is minimal, allowing for detection of other metabolites.

MRS and MRI are significantly different from a technical perspective. As previously mentioned, the goal of ^{1}HMRS is to detect small concentrations of metabolites in the presence of a large concentration of water. Therefore, the technical requirements with respect to field homogeneity and effective water suppression are greater for MRS than for MRI. With loss of field homogeneity, the widths of the metabolite peaks widen until they eventually merge to form one very broad peak, losing any significant metabolite information. Since scalp lipids (fats) may contaminate brain spectra, effective methods for excluding or suppressing fat are essential. In addition, localization techniques differ between MRS and MRI.

Phosphorous Spectroscopy

Phosphorus-containing molecules are involved in cellular energy metabolism, and most clinical applications pertain to the brain, muscle, and heart. Phosphorous spectroscopy – ^{31}PMRS - has a much lower sensitivity than ^{1}HMRS because the concentration of phosphorus in tissues is much lower than that of hydrogen. Phosphorous spectroscopy requires larger voxel sizes, resulting in lower spatial resolution and increased exam times to achieve adequate signal-to-noise ratio, typically 27cm^{3} voxel sizes with multivoxel imaging. Spectroscopy with phosphorus (or nuclei other than hydrogen) requires special hardware consisting of specially designed transmit-and-receive coils. The coils are composed of two antennae – one tuned to the hydrogen frequency and the other to the phosphorus frequency. The antenna at the hydrogen frequency is used for imaging and shimming of the water signal. The other antenna is tuned to the ^{31}P frequency and used as both a transmitter and receiver for actual MRS data acquisition. Phosphorus localization software is commercially available on some scanners. Non-^{1}H spectroscopy is also referred to as **multi-nuclear spectroscopy.** Because of its increased complexity and heavy user-dependent parameter input, phosphorus MRS is performed almost exclusively in the academic setting.

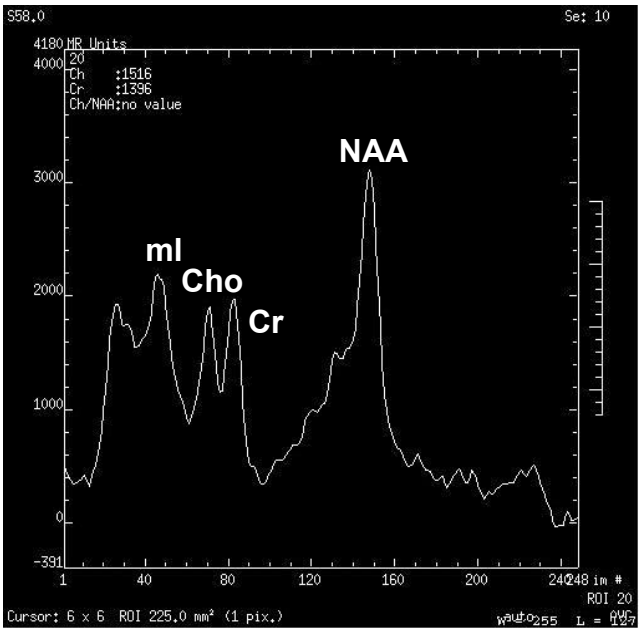


Figure 30. Normal brain spectra displaying the normal height, chemical shifts, and peak-to-peak ratios.

Brain Metabolites

Useful information can be obtained in the brain by specific ^{1}H-bound metabolites emitting radiofrequencies that obtain resonance with transmitted radiofrequencies.

These metabolites include:

- N-acetylaspartate
- Creatine
- Choline
- Myo-inositol
- Lactate

Each of these metabolites has its own particular signature. When observed in a spectral display, each metabolite has a particular place on the scale in parts per million (ppm). This scale is normalized for standardization, independent of field strength. For example, NAA is always placed at a chemical shift of 2.0ppm. The remaining chemical shift locations are listed in **Table 1**. The height of each peak and the ratio between peaks characterize numerous pathological processes. Here, the great benefit of MRS becomes apparent: before an *anatomical* change can be seen in an MR image, a *chemical* change may occur first and in some cases be detected by MR spectroscopy. **Figure 30** displays normal brain spectra.

- *N-acetylaspartate* (NAA) produces the largest peak in the normal adult. NAA represents a neuronal and axonal marker and is decreased in patients with epilepsy, dementia, stroke, hypoxia, multiple sclerosis, tumors, and leukoencephalopathies. The only instance of increased NAA is in in children with Canavan's Disease.
- *Creatine* (Cr) is involved in energy metabolism and is typically used as an internal reference for reporting relative concentrations of other brain metabolites.
- *Choline* (Cho) is thought of as a product of cell membrane breakdown. The choline peak is increased in patients with brain tumors, Alzheimer's disease, chronic hypoxia, post-liver transplant, and epilepsy and is decreased in hepatic encephalopathy.
- *Myo-inositol* (ml) is the dominant peak in spectroscopy of normal newborns. Myo-inositol is increased in patients with Alzheimer's disease and diabetes and decreased in patients with stoke, tumor, hypoxia, and chronic hepatic encephalopathy.

- *Lactate* (Lac) is not visualized on normal brain spectra but rather reflects anaerobic glycosis and thus may be seen in patients with stroke, hypoxia, brain tumors, and mitochondrial disorders. Lactate presents as a doublet, or double peak, at 1.3 ppm and is inverted with a TE of 135ms.

- *Lipid* appears as sharp peaks occurring between 0.9 and 1.3 ppm and may be superimposed on the lactate peak. Lipid signals are associated with acute destruction of myelin and are elevated in patients with tumor, stroke, and acute MS lesions.

METABOLITE	CHEMICAL SHIFT (ppm)
Lactate (Lac)	**1.3**
N-acetylaspartate (NAA)	**2.0**
Creatine (Cr)	**3.0**
Choline (Cho)	**3.2**
Myo-inositol (ml)	**3.6**
Water	**4.7**

Table 1. Metabolites and standardized chemical shift

It is important to understand that metabolites detected by brain MRS occur in concentrations that are significantly less than water and fat — by orders of magnitude! Therefore, one of greatest challenges of MRS is to obtain the necessary required signal-to-noise ratio to produce useful metabolite spectra. The challenge is two-fold. First, since water and fat concentrations far exceed the metabolites, their spectra can "overrun" the desired metabolite information. Second, the SNR ratios are so low in the metabolites that effort must be taken to boost the signal in order to produce useful spectra.

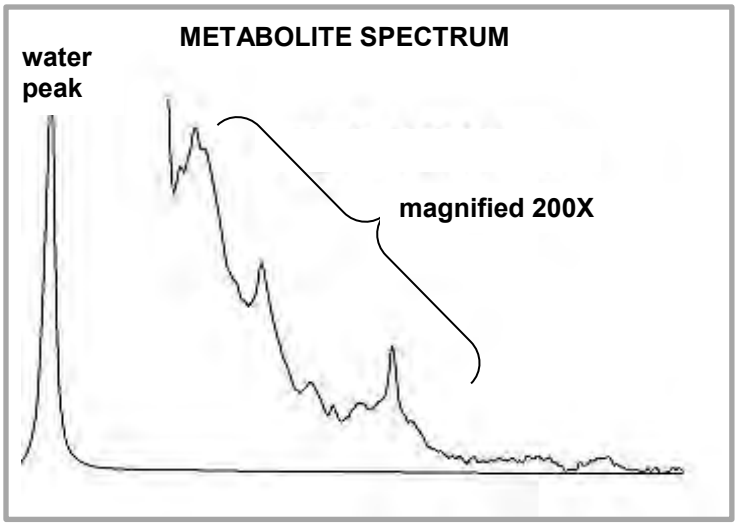


Figure 31. Brain spectrum without water suppression. The metabolite spectrum is magnified 200 times to show the distortion of the metabolite spectra and demonstrate the concentration ratios between ^{1}H in water and ^{1}H-bound metabolites.

Courtesy of GE Healthcare

Water Suppression

One of the most crucial and challenging tasks in MRS is the suppression of water. If water is not suppressed, the water peak will overwhelm the rest of the metabolite spectra, corrupting any useful information. As mentioned previously, MRS is a display of chemical concentration. The concentration of water-bound hydrogen is more than 10,000 times greater than the concentration of the metabolites detected by brain MRS. **Figure 31** shows an example of brain spectra without water suppression.

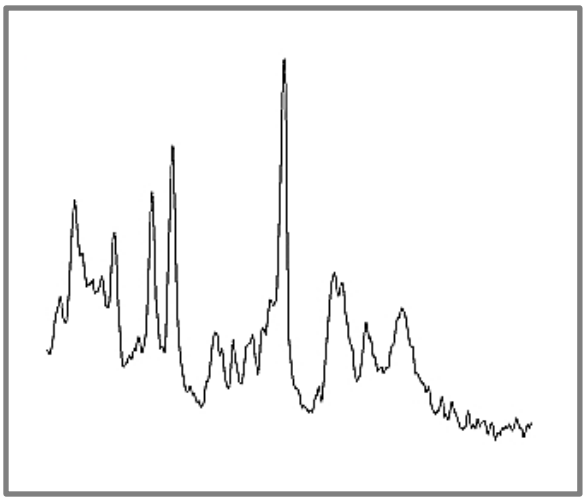


Figure 32. Brain spectra with successful water suppression.

Courtesy of GE Healthcare

Signal detection of metabolites is nearly impossible without first suppressing the predominant water signal **(Figure 32**). After initially using the water peak to perform local shimming, the water peak is suppressed, and the excitation and collection of the metabolite signals can take place.

Water signal suppression is accomplished by performing a saturation pulse known as **spectrally selective saturation** that is only 50Hz in bandwidth. This pulse excites only the water, placing the water spins into the transverse (x, y) plane. The excitation is followed by a dephasing or "crusher" gradient pulse, thus eliminating water signal. However, some T1 relaxation of water will occur between the saturation pulse and the application of the crusher gradient pulse. To compensate for this T1 relaxation, the saturation pulse tips the water spins slightly more than 90^0.[3] The efficiency of the water suppression using this technique is dependent on extremely homogeneous magnetic field strength (B_0) and radiofrequency pulses and multiple repetitions of the spectral saturation pulses.

In clinical MR systems today, this process is completely automated.

Brain Spectroscopy: Types of Data Acquisition

Brain spectroscopy is typically available as two primary types: single voxel MRS and multivoxel MRS. Single voxel MRS (S/V MRS) can be further broken down into two sub-types: PRESS and STEAM.

Single voxel MRS: PRESS vs STEAM

Two different techniques are typically used to obtain single voxel spectroscopy, often referred to as point resolved spectroscopy (PRESS) and stimulated echo acquisition mode (STEAM). Both define a small volume of tissue by exciting three orthogonal planes with frequency selective radiofrequency pulses and often require three to six minutes to perform.

- PRESS: Slice selective pulses excite the three intersecting orthogonal planes with 90º, 180º, 180º pulses (**Figure 33**).
- STEAM: Uses a volume selection similar to PRESS except that all three slice selective pulses are 90º pulses. This generates an echo known as a stimulated echo (**Figure 34**).

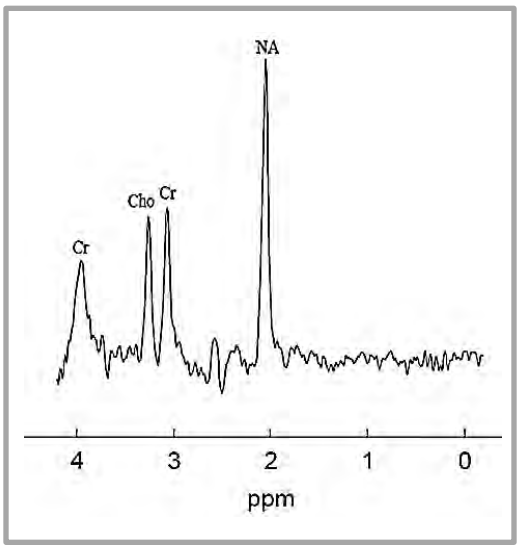


Figure 33. PRESS with a 135 TE of a 2x2x2 cm single voxel MRS.

Courtesy of GE Healthcare

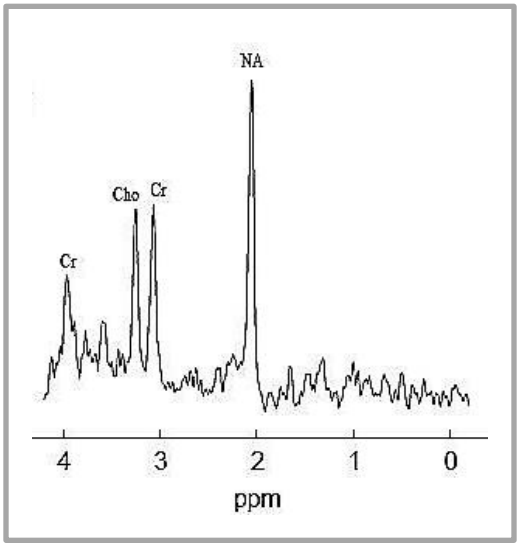


Figure 34. STEAM with a 135 TE of a 2x2x2 cm single voxel MRS. Note the SNR of the long TE PRESS is higher than the long TE STEAM.

The characteristic ways these echoes are formed are responsible for a number of differences between the two techniques. The signal-to-noise ratio using PRESS is two times that of STEAM. However, STEAM allows for shorter TE sequences and thus detection of molecules with short T2 values as short TE sequences decrease signal loss from T2 relaxation. Since both techniques require the same amount of time (~4:00mins), most clinical applications favor PRESS S/V MRS. **J-coupling**, the process responsible for splitting of a single peak into multiple peaks (doublets, triplets, etc.) and also known as **spin-spin coupling**, is decreased with STEAM compared to PRESS (**Figure 35**).

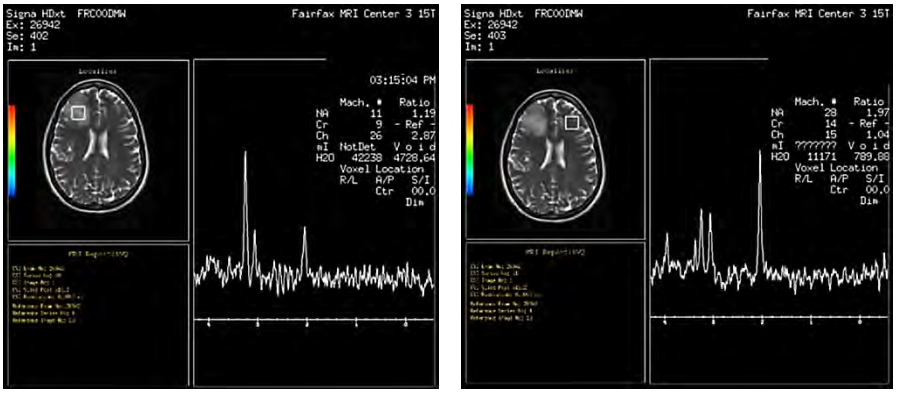


Figure 35. S/V PRESS MRS of a 43-year-old female with a non-enhancing lesion in the right frontal lobe. A 2x2x2cm voxel was localized in the lesion and corresponding side with a 135 TE.

(Left) Spectra in the right frontal lobe demonstrate marked decreases in NAA and a marked increase in choline. (Right) Spectra in the left frontal lobe demonstrate normal metabolite concentration and ratios. Diagnosis favors a low-grade glioma.

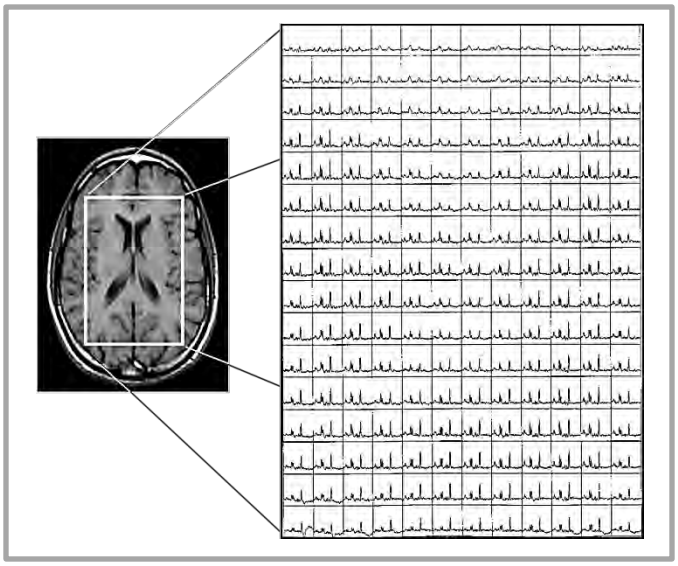


Figure 36. Multivoxel CSI MRS demonstrates a single large region of interest that is constructed into a grid of individual spectra.

Courtesy of GE Healthcare

Multivoxel spectroscopy

Multivoxel spectroscopy uses a technique known as **chemical shift imaging** (CSI). Analogous to 3D MR imaging where a large volume of tissue is excited and then reconstructed into many thin slices, chemical shift imaging collects spectroscopic data from a single large volume of interest during a single measurement and then constructs multiple adjacent voxels in a grid containing spatially relevant spectra (**Figure 36**). This is performed by phase encoding the **free induction decay** (FID). The spectral data can be presented in multiple ways: as single spectra related to individual voxels, as spectral maps, or as a metabolite map displaying one metabolite or ratios of metabolites. The spectral maps and metabolite images are usually overlaid on an MR image (**Figures 37** and **38**). Typical proton spectra may produce up to 12 x 12cm cubic voxels in approximately six to twelve minutes.

How does multivoxel MRS compare to single voxel MRS?

Multivoxel MRS is an efficient method for comparing spectra from voxels of different tissue types, such as a region of diseased brain to normal brain tissue. Using single voxel techniques, repeat measurements are necessary for comparison. Multivoxel MRS allows adjustment in the voxel positioning after a measurement is finished, known as **gray shifting** or **voxel shifting**, which may be important for evaluating focal diseases. Multivoxel MRS also allows the combination of adjacent voxels to duplicate the shape of the lesion and then add the corresponding spectra. However, compared

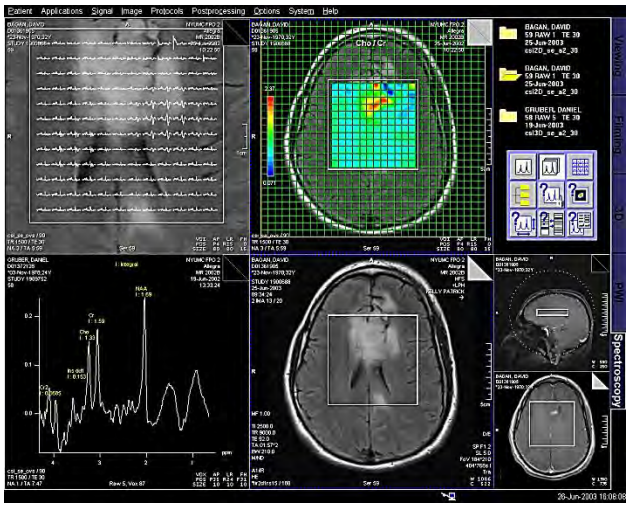


Figure 37. Multivoxel CSI MRS demonstrating spectral grid with a single magnified spectrum (bottom left) as well as metabolite map (upper right).

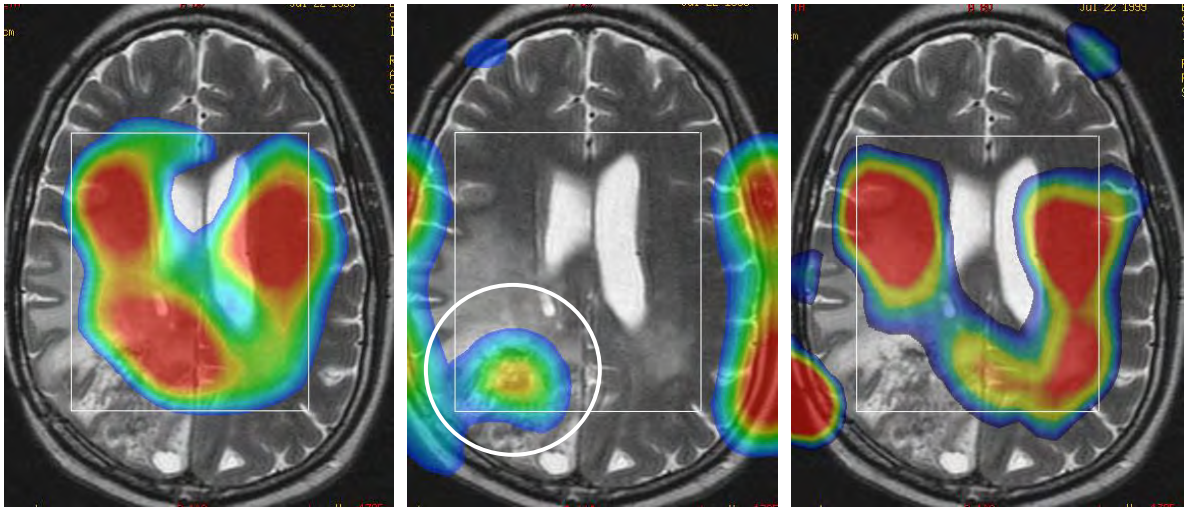


Figure 38. (Left) Multivoxel CSI choline metabolite map shows areas of high concentrations of choline (red). (Center) Multivoxel CSI lactate metabolite map shows high concentrations of lactate (circle). (Right) Multivoxel CSI NAA metabolite map shows high concentrations of NAA (red).

Courtesy of GE Healthcare

to single voxel techniques, it is more difficult using multivoxel MRS to achieve good shim and uniform water suppression over a large area that includes magnetic susceptibility changes. Another challenge of multivoxel MRS is accuracy of regional spectra. Spectrum from any given voxel contains information from neighboring voxels, as defined by the concept known as the **point spread function**. Compared to multivoxel MRS, single voxel techniques may be easier to use from an operational perspective.

Pathological MRS Signatures

Through careful experimentation and thorough analysis, MRS has been shown to be a powerful diagnostic tool in brain imaging, particularly when a definitive diagnosis cannot be made on MR structural or anatomical imaging.

MRS has been shown to be particularly useful for visualizing various pathologies that typically lack structural or anatomical change, including:

- tumor infiltration
- diffuse axonal injury
- hepatic encephalopathy
- herpes encephalitis
- ischemia

MRS is also useful in differentiating abnormalities with the same anatomical appearance such as:

- tumor vs radiation necrosis
- toxoplasmosis vs lymphoma
- metastatic disease vs primary tumor

Typical metabolite abnormalities

Table 2 lists typical abnormalities seen in imaging of the brain and their metabolic markers.

Metabolic Marker	Abnormality
Choline is **INCREASED** in:	▲ brain tumor ▲ multiple sclerosis ▲ adenoma
Creatine is **INCREASED** in:	▲ anoxia
NAA is **DECREASED** in	▼ destruction of neurons and neural pathways ▼ tumor
Myo-inositol is **INCREASED** in:	▲ Alzheimer's disease
Lactate is **PRESENT** in:	anoxia anaerobic glycolysis necrosis

Table 2. Metabolic markers and typical abnormalities.

MRS after Contrast Administration

Theoretically, gadolinium-based contrast media may shorten T1 relaxation times of metabolites, increasing their signal for short TR scans, or gadolinium may reduce T2*. However, high-quality spectra can be obtained using postcontrast MRS measurements. Reports are mixed regarding whether quantitative differences between pre- and postcontrast spectra are constant. Therefore, it is prudent to perform spectroscopy before administration of contrast when possible.

SUMMARY

Clinical MRI has benefited greatly from the rapid and continued development of advanced neuro-based applications. MRI in general has benefited from advances in computing power and speed, magnet development, and user interface design. Where MRI was first seen as an advanced structural and anatomical imaging technique, it is now a *functional* technique as well. Today, advanced neuro applications allow clinicians to peer deeply into the brain on a molecular level to predict at-risk tissue, observe the presence or absence of cellular diffusion and disruption along essential neuronal pathways, as well as pathologies that have yet to cause structural or anatomical change. With the recent and numerous advances in neuro-based MRI applications, it is both clear and fortunate that MRI is an imaging modality still undergoing development.

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2. Kohler S. GE Single-Voxel Proton Brain Exam Applications Guide. 1993 (1st ed.).

3. Kohler S.

GLOSSARY

anisotropic/anisotropy
in diffusion-weighted imaging, the diffusion of water in a non-random, preferred pathway

apparent diffusion coefficient map
the coefficient of signal loss that is calculated and displayed as another set of images. Used with diffusion and diffusion tensor imaging to characterize T2 shine-through

arterial spin labeling (ASL)
an alternative to echo-planar imaging that is noninvasive; involves labeling or tagging flowing blood with an inversion pulse to map the relative cerebral blood flow of the brain

***b*-value**
diffusion gradient strength. As the *b*-value rises, so does the diffusion contrast at the cost of the signal-to-noise ratio

Canavan's disease
a rare, fatal, inherited disease that leads to the progressive deterioration of the brain and nervous system; one of a group of disorders call leukodystrophies

chemical shift
a change in the Larmor frequency due to chemical shielding. This is the same frequency at which the nucleus resonates and occurs when the chemical properties of a substance cause a shift in frequency at which it resonates as compared to other substances. The placement of varying chemical compounds on a frequency spectrum is a visual display of the chemical shifts between compounds.

chemical shift imaging (CSI)
collection of spectroscopic data from a single large volume of interest during a single measurement and then constructing multiple adjacent voxels in a grid, each containing spatially relevant spectra

diffusion gradients
two equal but opposing gradient fields used in diffusion and diffusion tensor imaging to differentiate between mobile and restricted water motion on a molecular scale

eginvector
visual display of individual voxels tensors

fractional anisotropy map
display of anisotropic water diffusion on a molecular scale

free induction decay (FID)
decay of the transient RF signal induced by a 90° RF pulse, although the frequency remains the same; more often, refers to the signal itself

functional MRI (*f*MRI)
any MR imaging that visualizes organ function over anatomy. Also, a specific neuroimaging technique used to study activity in the brain by showing which structures are active during particular mental operations

gray shifting
in multivoxel MR spectroscopy, the adjustment of voxel positioning after a measurement is finished; also known as *voxel shifting*

gyromagnetic ratio (ɣ)
the ratio of the magnetic moment to the angular momentum of a particle, which is a constant for a given nucleus; also called *magnetogyric ratio*

homunculus
scale model of the human body that in some way illustrates physiological, psychological, or other abstract human characteristics or functions
See: Wikipedia

inhomogeneity
absence of homogeneity or uniformity; inhomogeneity in a magnetic field may occur as one area of the field deviates from the average magnetic field strength

isotropic/isotropy
in diffusion-weighted imaging, the diffusion of water via numerous pathways; moving the same in all directions

j-coupling
the process responsible for splitting of a single peak into multiple peaks (doublets, triplets, etc.); also known as *spin-spin coupling*

***k*-space**
the domain in which the information from each phase-encoding step is placed during a pulse sequence. Each "filled in" line of *k*-space corresponds to each phase-encoding step; once the required amount of *k*-space is filled in, image reconstruction with a Fourier transform can begin

magnetic susceptibility
the ability of a tissue to become magnetized

magnetic susceptibility artifact
distortions or signal loss in an image due to extreme differences in magnetic susceptibility between two adjacent tissues, one with very high susceptibility and one with little or no susceptibility, eg, metal implants or air pockets like the paranasal sinuses

mean transit time (MTT)
in perfusion-weighted imaging, the time interval from the beginning of the wash-in phase to the return of equilibrium or wash-out phase

multi-nuclear spectroscopy
non-^{1}H spectroscopy

nuclear magnetic resonance (NMR)
bombarding a chemical compound with a range of radiofrequencies and observing the absorption and re-emission of radiofrequencies of that compound

organelle
specialized structure within a cell that has its own function

orthogonal
angles that are perpendicular, as in x, y, and z-axes or sagittal, coronal, and axial planes

paradigm
simple to complicated tasks performed while the patient is being scanned in the MRI

perfusion penumbra
in perfusion imaging, areas where perfusion is active but very low and surround dead tissue

point spread function
in multivoxel MRS, voxels that contain information from neighboring voxels, perhaps decreasing accuracy of regional spectra

shimming
the task of making the magnetic field more homogeneous by adding to, or subtracting from, the B_0 field by adding or removing slight amounts of electrical current at various points on the magnet

specific absorption rate (SAR)
strictly defined by the FDA, the amount of RF energy absorbed by the patient

spectrally selective saturation
a saturation pulse that excites a very limited spectrum of frequencies and thereby suppresses signal outside the excited spectrum, that is, by exciting only water frequencies, fat frequencies are suppressed

spin-spin coupling
see *j-coupling*

T2 shine-through
in diffusion imaging, areas within the brain that yield hyperintense signal due to very long T2 times yet do not represent acute stroke; also known as *T2 shine*

T2´ (prime)
the dephasing of spins in the transverse plan due to local field susceptibility effects. When in combination with “true” T2 dephasing, anatomy will display T2* (star) contrast.

tractography
visualization of white matter tracts using anisotropic motion

vector
in diffusion tensor imaging, the direction and magnitude or strength of the motion of water

voxel shifting
see gray shifting

wash-in phase
the point at which gadolinium contrast begins to enter the capillary beds

wash-out phase
the point at which gadolinium contrast moves out of the capillary beds and the contrast effect returns to equilibrium

ACRONYMS

ADC	apparent diffusion coefficient
ASL	arterial spin labeling
BOLD	blood oxygen level-dependent imaging
Cho	choline
Cr	creatine
CSI	chemical shift imaging
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
eADC	exponential apparent diffusion coefficient
EPI	echo planar imaging
FID	free induction decay
***f*MRI**	functional MRI
FSE	fast spin echo
GRE	gradient-recalled echo-based pulse sequence
IR	inversion recovery
mI	myo-inositol
mT/m	milliTesla per meter
MRS	magnetic resonance spectroscopy
MTT	mean transit time
NMR	nuclear magnetic resonance
ppm	parts per million
PRESS	point resolved spectroscopy
rCBF	relative cerebral blood flow
rCBV	relative cerebral blood volume
RF	radiofrequency
SAR	specific absorption rate
SE	spin echo
SE-EPI	spin echo planar imaging
SS-GRE-EPI	single-shot or snapshot gradient echo-based EPI sequence
STEAM	stimulated echo acquisition mode
S/V MRS	single voxel magnetic resonance spectroscopy
TE	echo time
TR	repetition time
TSE	turbo spin echo
T2'	T2 prime
T2*	T2 star