

Review Article

Neuro MR: Principles

Timothy P.L. Roberts, PhD^{1*} and David Mikulis, MD²

The principles of contrast mechanisms and fast pulse sequences underlying neurological and neuroradiological application of MRI are introduced in this part of a two-part review. In particular, the relaxation time constants T_1 , T_2 , and T_2^* are introduced, along with pulse sequences harnessing their contrast, spin-echo, fast spin echo (FSE), inversion recovery (IR), gradient recalled echo (GRE), and echo planar imaging (EPI). The use of gadolinium (Gd)-based contrast is discussed in both T_1 - and T_2^* -weighted sequences. Tradeoffs between speed and image quality are discussed, particularly in the context of long echo train sequences (FSE imaging and EPI). The influence of parallel imaging strategies is also discussed. T_2^* sensitivity is discussed as both a source of artifact as well as a contrast mechanism (perfusion imaging with contrast agents, susceptibility weighted imaging [SWI], and blood oxygenation level dependent [BOLD] imaging). Finally, the contrast mechanism of diffusion is introduced, as well as the concept of anisotropy. From these principles, the other part of this two-part review draws upon the pulse sequences and contrast mechanisms to design disease and indication-specific protocols for state-of-the-art clinical use.

Key Words: pulse sequences; contrast mechanisms; neuroimaging; physics; techniques

J. Magn. Reson. Imaging 2007;26:823–837.

© 2007 Wiley-Liss, Inc.

THIS REVIEW along with its partner review, “Neuro MR: Protocols,” form a combined platform serving to illustrate the physical bases of image acquisition and contrast manipulation for MRI of the central nervous system (CNS) and the harnessing of these physical principles to form clinical imaging protocols, tailored to suit a range of clinical presentations. As such, the manuscripts seek to address a broad readership, with a strong clinical focus, but recognizing the need for thorough physical grounding. In writing such reviews, it is inevitable that some facets cannot be completely ex-

plained and the interested reader is pointed to an array of texts that describe both physical and clinical aspects of this domain in more detail (e.g., Refs. 1 and 2).

The various contrasts of MRI form an artist's palette of colors that can be drawn upon to compose the clinical neuroradiology protocol (Fig. 1). In this part of the review, we introduce the component contrasts, examine their interpretation, and explore the properties and limits of their implementation. The completed “palette” of contrast possibilities will then be passed on to the clinical neuroradiologist to create disease-specific protocols drawing on the available contrast mechanisms (see Neuro MR: Protocols).

In particular, we revisit T_1 , T_2 , and T_2^* and focus on specific neuroradiological issues associated with each relaxation time constant. We then proceed to examine the contrast mechanism of diffusion-weighting. Other articles in this issue of *JMRI* address flow-related enhancement and the basis and applications of magnetic resonance angiography. Intravenous administration of gadolinium (Gd)-based contrast media (“magnetic dye”) is introduced as a means of gaining additional physiologically relevant image contrast. The associated applied use of T_1 and/or T_2^* mechanisms additionally allow us to develop approaches to “perfusion-sensitive” imaging, imaging of microvascular permeability, and imaging sensitive to the oxygenation level of blood (blood oxygenation level dependent [BOLD] imaging). Some introductory applications of these approaches are introduced to yield maps of white matter fiber paths (based on diffusion-weighted imaging [DWI]), functional brain mapping (based on BOLD), and microvascular permeability (based on kinetic analysis of dynamic contrast-enhanced MRI). An introduction to magnetization transfer contrast (as it relates to T_1 - and T_2 -based relaxation) is offered, as well as a suggestion regarding its utility (particularly in the study of multiple sclerosis and in general for background tissue suppression in MR angiography). In general, an emphasis on the quantitation of physiologically-relevant parameters (such as cerebral blood flow [CBF] and apparent diffusion coefficient [ADC]) derived from multiple image acquisitions is stressed, since quantitation of tissue-specific parameters provides a basis for intersite comparison as well as for longitudinal studies of disease progression and response. Finally, recent advances in parallel imaging (with multiple receiver coils) are introduced, as the technology pertains to implementation issues of imaging with the above contrast mechanisms (3,4). Magnetic

¹Department of Radiology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.

²Department of Medical Imaging, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada.

*Address reprint requests to: T.R., Department of Radiology, Children's Hospital of Philadelphia, Wood Bldg., Suite 2115, 34th St. and Civic Center Blvd., Philadelphia, PA 19104.

E-mail: robertstim@email.chop.edu

Received February 11, 2006; Accepted May 3, 2007.

DOI 10.1002/jmri.21029

Published online in Wiley InterScience (www.interscience.wiley.com).

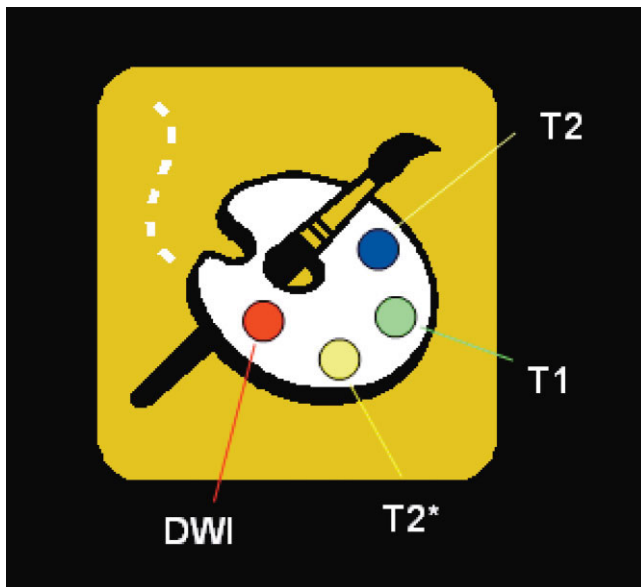


Figure 1. The art of MRI. Contrast mechanisms provide a palette of colors that protocols can be drawn upon to paint the desired tissue scene.

resonance spectroscopy and spectroscopic imaging are beyond the scope of this neuroimaging review. Furthermore, attention is drawn to the increasing availability of 3T MRI systems, and to the impact that higher field strength has on the underlying physical principles discussed (5).

RELAXATION TIME-BASED IMAGE CONTRAST

One of the main distinctive features of MRI compared to other cross-sectional imaging modalities (e.g., computed tomography [CT] and nuclear medicine techniques, single-photon emission computed tomography [SPECT], and positron emission tomography [PET]) is the dependence of the MR signal on properties of the tissue, collectively known as spin relaxation. Characterized by three relaxation time constants, T_1 , T_2 , and T_2^* , tissue spin relaxation describes the process and rate at which the nuclear spin population (from which the nuclear magnetic resonance [NMR] signal originates) evolves in different tissues. While the details of nuclear spin relaxation are discussed in multiple NMR and MRI texts, the key feature to be retained in this discussion is that T_1 and T_2 , in particular, are *properties of tissue*, distinct, for example, between gray matter and white matter, and, perhaps more importantly, often altered in the context of pathological changes to tissue. Of great interest, also, is T_2^* . This relaxation time constant, which is related to T_2 , also reflects the tissue microenvironment (particularly the inhomogeneity of the local magnetic field). This may not only be a property of tissue, per se, but may be influenced by external factors (such as poor magnet construction and shimming), by the nearby presence of tissues of different magnetic character, and, as is discussed below, by the presence of endogenous or exogenous materials that transiently

disrupt magnetic field homogeneity by virtue of their compartmentalized nature.

T_2 Contrast and T_2 -Weighted Imaging

Considering first of all the so-called transverse, or spin-spin, relaxation time-constant, T_2 , we encounter a property of tremendous impact to the field. Not only do T_2 values allow distinction between gray matter, white matter, cerebrospinal fluid (CSF), scalp fat, and other tissues of the neuroimage, but T_2 values of tissues are notably altered in a number of pathophysiological situations. Consider, simply, that transverse relaxation describes the process by which the coherence of a population of excited mobile nuclear spins (the proton nuclei of the hydrogen atoms of water molecules) is lost due to the transient experience by one spin of a magnetic field perturbation associated with proximity to another mobile excited spin. The rate at which this coherence is lost characterizes the rate at which potential signal is lost after initial excitation. Importantly, among other factors, the rate of coherence loss depends on the *duration* of such fleeting spin-spin interactions. That is, in highly mobile situations, spin-spin interactions are so fleeting that magnetic field perturbations are less pronounced. Combined with a unifying “averaging” effect associated with high mobility leading to more uniform distribution of such perturbations across the spin population, highly mobile fluid environments are characterized by relatively slower loss of transverse coherence and are characterized by longer transverse relaxation time constants, T_2 . More structured or constrained environments (e.g., ordered cell assemblies and microstructures) may be associated with more sustained spin-spin interactions, more effective magnetic field perturbation, and more rapid loss of coherence across the spin population (and thus shorter time constants, T_2). Of clinical significance, many of the pathophysiological processes that occur in disease of the CNS are associated physiologically with disruption of such structure in the microenvironment (and may be associated, for example, with cell lysis, mass fluid shift and pooling, or matrix breakdown). Consequently, such processes are associated with prolongation of tissue T_2 values compared with nonpathological states. As such, T_2 changes can be seen to reflect pathological changes at a submicroscopic tissue level (inferences about changes to the tissue microenvironment are made at dimension scales well below those of the “actual” images acquired). This ability to make submicroscopic inferences about the integrity of the tissue microenvironment is an inherent characteristic of MRI and a major advantage of the technology. Since the parameter T_2 reflects such important differences between tissue types and in pathophysiologic circumstances, a major advance is to “weight” MRI signal intensity, according to the local T_2 value—creating a “ T_2 -weighted” image, sensitive not only to proton density, but also reflective of local tissue T_2 properties. It should be borne in mind that a “ T_2 -weighted” image is not a pixel-by-pixel map of T_2 -values, but rather is a proton density image in which pixel intensities are additionally made sensitive to the local T_2 value, with the degree of such sensitivity being

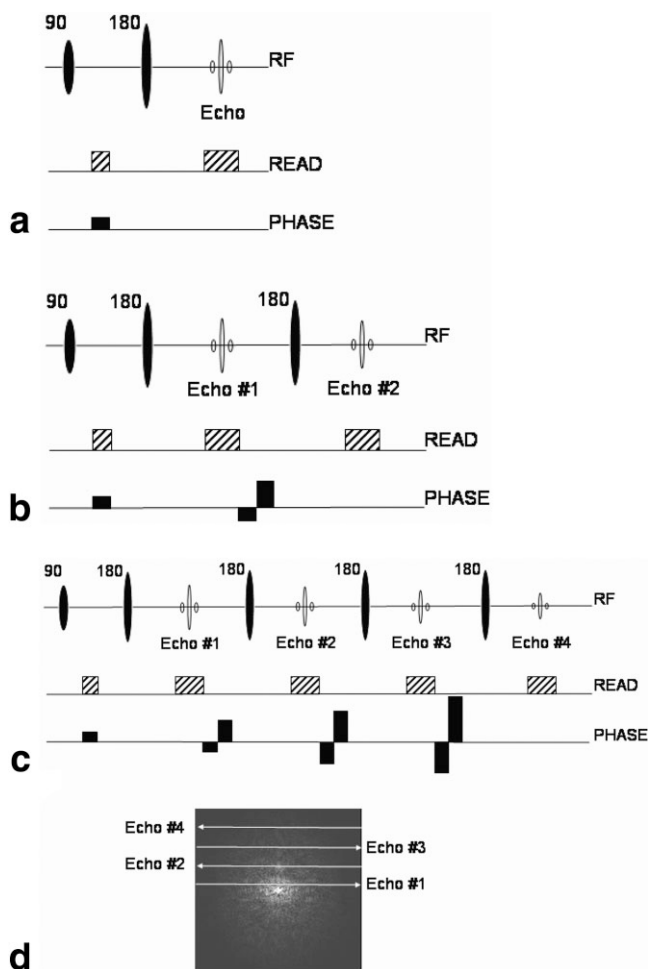


Figure 2. Pulse sequence timing diagrams for (a) spin-echo and FSE variants with ETLs of (b) 2 and (c) 4. (d) The schematic filling of k-space in the four echo pulse sequence shown in (c).

under the control of the MR operator, via the MRI pulse sequence parameters.

In the formation of the MR image, spin populations are excited by application of a radio frequency (RF) pulse that is considered to rotate the magnetic moments of the spins from an equilibrium (canonically z-axis) alignment into a transverse plane (in which plane, the above-discussed loss of coherence, or relaxation, occurs). A widely used MR pulse sequence manipulates this transverse spin population through application of a 180° refocusing pulse to form the “spin-echo,” at a time, TE, after initial excitation. TE is known as the “echo-time” and is a characteristic control parameter of the MRI sequence. The signal recovered at the echo time TE depends not only on the theoretically available signal (relating to the amount of water in the tissue being imaged), but also on the T_2 value of the tissues, since the signal at time TE is attenuated by an exponential factor, TE/T_2 . That is to say, for a given “proton density,” ρ , the signal collected at the time of the spin echo (TE) is given by equation 1:

$$S \propto \rho \exp(-TE/T_2) \quad (1)$$

The signal S, then, indeed reflects both proton density and local T_2 values, with the degree of sensitivity to T_2 (the “ T_2 -weighting”) controlled by the parameter TE (imagine if $TE = 0$, S is proportional only to ρ ; on the other hand, for high TE values, S is strongly determined by the ratio of TE/T_2 , thus introducing sensitivity to T_2 . Given the above described sensitivity of spin-echo sequences to the parameter T_2 , and the fact that T_2 is characteristically altered in a number of CNS pathologies, it is not surprising that spin-echo imaging has become the mainstay of clinical neuro-MRI.

However, conventional spin-echo imaging is also associated with relatively long scan acquisition times (typically several minutes). Ultimately, this limits spatial resolution, due to the inability of patients to avoid involuntary motion over the required long acquisition periods. Furthermore, in the case of noncompliant patients, image quality with conventional spin-echo acquisition strategies may be limited, due to motion over the acquisition time. This has led to the development of alternative “ T_2 -weighted” imaging sequences, which reduce acquisition times by, for example, the collection of multiple echoes from a single excitation. Since many echoes are required to form an image, the collection of more than one echo per excitation RF pulse has a clear effect on reducing scan time (for a given spatial resolution). These multiple spin-echo sequences are achieved by application of multiple 180° refocusing RF pulses and are collectively known by a variety of acronyms, such as RARE (rapid acquisition with relaxation enhancement), FSE (fast spin-echo) and TSE (turbo spin-echo). Figure 2 shows a schematic single-echo pulse sequence and corresponding schematic “multiple” spin-echo acquisition sequences, with echo train lengths (ETLs) = 2 and 4. The ETL directly relates to the acceleration of the multiple spin-echo sequence over its conventional alternative.

From Fig. 2d it can be seen that each of the echoes formed in the multiecho train (e.g., Fig. 2c) fills a different line of k-space, with the vertical position of the line determined by the amount of phase encoding gradient applied during formation of that particular echo.

Figure 3 compares a conventional spin-echo and FSE image of the same patient, using an ETL of 16 for the

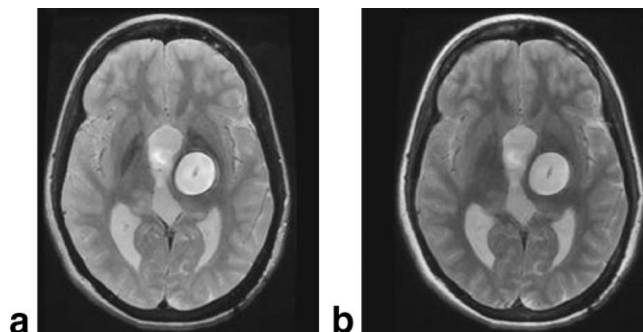


Figure 3. A patient with a large cystic lesion acquired using (a) a spin-echo sequence with an acquisition time of seven minutes and 17 seconds and (b) an FSE sequence with an ETL of 16 and an acquisition time of 34 seconds. Note that image contrast and SNR appear comparable.

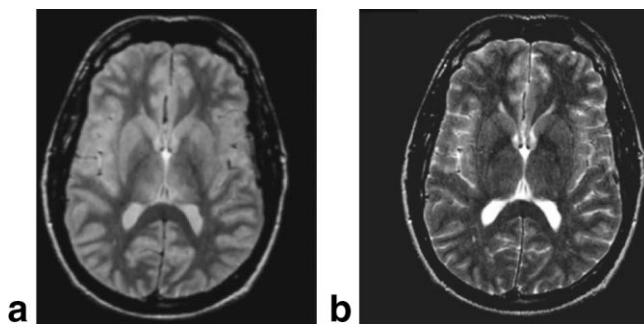


Figure 4. FSE images of a healthy volunteer with (a) proton density weighting ($TE_{eff} = 30$ msec) and (b) T_2 -weighting ($TE_{eff} = 105$ msec). Contrast is manipulated by altering the position in the echo train at which the central portion of k-space is acquired. There is a slight tendency toward blurring, especially in the proton density-weighted image.

FSE approach. Correspondingly, image acquisition time was reduced from seven minutes and 17 seconds in the conventional sequence to a mere 34 seconds in the FSE variant. In general, both image (tissue) contrast and signal-to-noise ratio (SNR) are largely conserved.

While T_2 -weighting appears an advantageous utilization of FSE imaging, it should be remembered that the separate phase-encoding of individual echoes in the echo train may influence image characteristics. Namely, the central portions of k-space (low phase encode values) typically confer most of the image's gross form, signal to noise and shape. Peripheral regions of k-space carry information relating to sharp spatial transitions in the image (small structures, details, edges, etc.). Thus, by applying different TEs to different portions of k-space, we are not only influencing signal contrast but also the relative weighting of gross vs. fine structures. Particularly considering a finite ETL, it is clear that if "early, short TE" (high SNR) echoes are applied to the central regions of k-space, then outer regions of k-space will be represented by lower SNR (longer TE) echoes. Upon Fourier transformation, this may be manifest as an underemphasis of image fine structure or detail, with resultant "blurry" appearance (see Fig. 4). Conversely, if later echoes (with longer TEs) are assigned to the central portions of k-space (in order to achieve the desired T_2 -weighted contrast), residual (shorter TE) echoes must be utilized for the periphery of k-space, leading to apparent overemphasis of the peripheral portions of k-space (with the transformed appearance of "edginess").

With improvements in MR scanner hardware, particularly gradient strength and receiver bandwidth, it has become feasible to consider single-shot FSE imaging. Particularly in conjunction with partial k-space reconstruction algorithms (which rely on the Hermitian symmetry, or conjugacy, of k-space), a high spatial resolution image may be achieved from a single-shot acquisition (e.g., consider that a 256×256 matrix might require only slightly more than 128 echoes to be formed; with an interecho spacing of 2–3 msec, this results in an overall acquisition time of somewhat less than 500 msec, within the limit imposed by tissue T_2 values). The resultant image, obtained in a single shot,

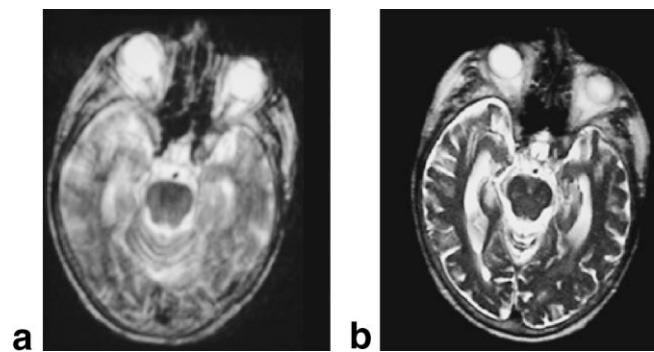


Figure 5. FSE of a moving patient. a: Multishot FSE (ETL = 16) is degraded by considerable patient movement, obscuring a brainstem lesion. b: Single-shot FSE (using partial k-space acquisition) allows an "instant" image to be acquired, freezing motion.

must be considered in terms of intrinsic blur (as described above) vs. the possible (motion-related) artifacts incurred by selecting a similar contrast with a multishot (e.g., conventional FSE) approach. This may be of particular significance in imaging the noncooperative patient, where conventional (multishot) sequences would be seriously degraded by patient motion (see Fig. 5).

FSE imaging has been a particular beneficiary of the recent advent of parallel imaging. Whether referred to as sensitivity encoding (SENSE), iPAT, or ASSET, the principles of multiple RF coil signal reception with sensitivity encoding allow fewer lines of k-space (fewer phase encoding steps) to be acquired, while still reconstructing an image with the desired spatial resolution. Although the details of parallel imaging are beyond the scope of this article (3,4) its implications for neuroradiology are presented in the context of influenced sequences.

Figure 6a shows an axial slice through the brain of a healthy volunteer acquired at 3T. Importantly for the scan protocol prescribed (TR = 3500, TE = 102 msec) with an ETL of 32, a maximum number of slices of 13 was incurred (seriously limiting anatomic coverage). Furthermore, the incurred specific absorption rate (SAR) was 1.34 W/kg (close to the maximum tolerable levels). Overall acquisition time was one minute and three seconds. Figure 6b shows a similar slice from the

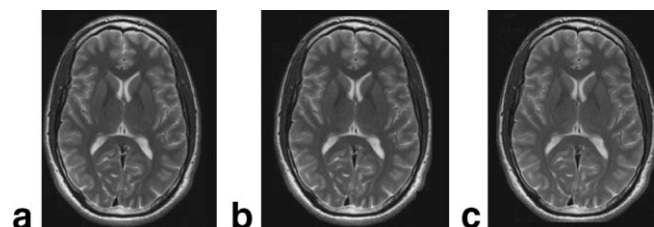


Figure 6. Parallel imaging in FSE. a: An FSE image (ETL = 32) acquired at 3T. b: Using parallel imaging acceleration can reduce the scan time by a factor of two. c: Parallel imaging can also be used to reduce ETL to 16, thus reducing the SAR, or accommodating more slices per TR, but not reducing overall acquisition time.

Table 1
Summary of T₂-Weighted Sequences

Sequence	Common acronyms	Feature	Key variables
Conventional spin-echo	SE, CSE	Proton density to T ₂ -weighted contrast. Long acquisition times	TE
Fast spin-echo	FSE, TSE, RARE	Typically 8-16 times faster than CSE. Can lead to blur	ETL
Single-shot fast spin-echo	ssFSE, HASTE	Uses long ETL and partial k-space to obtain all k-space data in a single shot. Can be blurry. High SAR.	Overall acquisition time (relates to interecho spacing and ETL)
Fluid-attenuated spin-echo	FLAIR	Uses IR prepulse and long TI to "null" signal from CSF	TI (to exactly null CSF)
Parallel imaging	SENSE, ASSET, iPAT	Can accelerate all above sequences by factors of typically 2-4, or reduce ETL by similar factor in multiecho sequences	Acceleration factor

IR = inversion-recovery.

same acquisition, in which parallel imaging was incorporated (acceleration factor $\times 2$) to reduce the number of RF excitation needed to acquire sufficient data for image reconstruction. Consequently (with the ETL retained at 32), the overall scan time was reduced by a factor of two (overall acquisition time 35 seconds), with no impact on SAR (per unit time) or the maximum number of tolerated slices. Conversely, Fig. 6c shows the same axial slice in which the parallel imaging benefit has been applied to reduce the ETL from each RF excitation. Consequently, the overall acquisition time remains one minute and three seconds, but (with an ETL of 16), the SAR is reduced to 0.71 W/kg. Alternatively, the maximum number of slices could be increased from 13 to 26. In common with all parallel imaging approaches, a penalty in SNR is inevitably incurred. However, this strategy for reducing SAR is highly important, particularly in the context of multiple spin-echo sequences and particularly in the climate of increasing B₀ magnetic field strength from 1.5T to 3T and above (since SAR values tend to increase as the square of magnetic field strength). Additionally, reducing the ETL has an important image quality benefit: by reducing the signal intensity modulation across echoes (e.g., 16 different TE values rather than 32), images are less susceptible to blurring degradation.

A summary of T₂-related pulse sequences and their features is offered in Table 1.

T₁ Contrast and T₁-Weighted Imaging

A second key contrast mechanism relates to the tissue property of longitudinal (or spin-lattice) relaxation. In brief, this process describes the recovery of magnetization after RF excitation back toward its equilibrium state (longitudinal). This exponential recovery process is described by an exponential time constant, T₁, and after a 90° excitation, recovery of the longitudinal (M_z) component of magnetization over time, *t*, is given by Eq. [2], where ρ again relates to the proton density.

$$M_z \propto \rho \{1 - \exp(-t/T_1)\}. \quad (2)$$

Analogous to T₂, tissues differ in their T₁ values. Since longitudinal relaxation describes the process of magnetization recovery to equilibrium after excitation, it is apparent that the microenvironment greatly influ-

ences this process. Relaxation is facilitated by the presence of relatively large moieties (such as macromolecules and membranes), which can effectively interact with the excited nuclear spins on passing water molecules. In the absence of such microstructural entities (e.g., in free fluids) longitudinal relaxation is slower. Thus, as with T₂, T₁ processes shed light on the microstructural environment of water molecules on a dimensional scale that is not directly resolvable.

In an imaging sequence, if 90° RF excitation pulses are applied at intervals, TR (repetition time), then the signal, S, obtained is given by Eq. [3]:

$$S \propto \rho \{1 - \exp(-TR/T_1)\}. \quad (3)$$

To the extent that S is less than its theoretical maximum (due to attenuation by the term $\exp(-TR/T_1)$), such images are described as "T₁-weighted." In general, the shorter the choice of TR value, the greater the degree of T₁-weighting. Figure 7 shows a schematic T₁-recovery curve for various tissues and indicates regimes that can be considered "T₁-weighted" vs. "proton density-weighted" (i.e., where T₁ differences between tissues do not exert much influence on signal characteristics—generally where TR is considerably greater than all T₁s present).

It can be seen that choosing a TR value on the order of 500 msec (Fig. 7; arrow) allows clear separation of the three illustrated tissue types, with CSF showing only ~20% of its theoretical maximum (fully relaxed) signal and therefore appearing relatively hypointense, with tissue exhibiting approximately 50% of its fully relaxed possibility (mid-intensity) and with fat having undergone considerable longitudinal relaxation (since fat is associated with a short T₁ time) and contributing more than 90% of its fully relaxed maximum (and thus appearing hyperintense). It is worth noting that increasing the TR will tend to increase signal from all moieties but that the benefit will be small for the fat tissue for example, in which there is only 10% more signal "available." Another key point is that tissue contrast as described in this example is achieved by selectively discarding SNR. That is, we achieve contrast between fat, brain tissue, and CSF by only allowing tissues to contribute a percentage of their theoretical maximum. Thus, we have traded signal for contrast. Hence, it is common in quan-

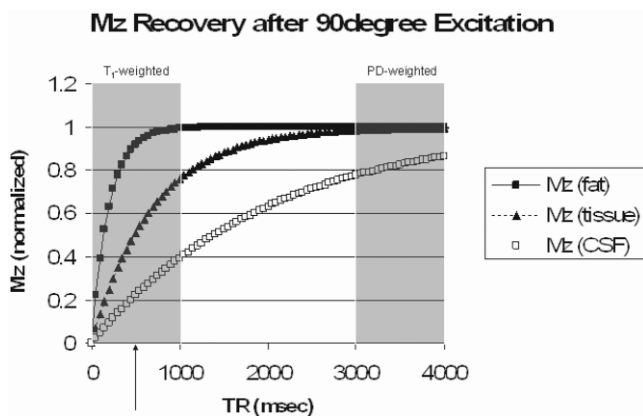


Figure 7. Schematic T_1 recovery curves for fat, tissue, and CSF as a function of increasing TR (approximate T_1 values of 200 msec, 700 msec, and 2000 msec, respectively, are simulated). The lightly shaded area between 0 and 1000 msec can be considered to provide T_1 -weighting (with marked differences in M_z values between tissue types); a typical TR choice of 500 msec is marked with a vertical arrow; the longer TR regime (illustrated as TR = 3000–4000 msec) can be seen to be little influenced by T_1 and thus images acquired with such TRs will exhibit contrast that is largely dependent on proton density. (Note that even at TR = 4000 msec, some species such as CSF are still not fully relaxed and thus will be partially suppressed in intensity).

tifying MRI not only to describe an SNR, but also to describe a contrast to noise ratio (CNR) between two tissue types. It is the soft tissue *contrast* achievable with MRI that is largely responsible for the wide adoption of this imaging modality.

To increase the dynamic range of T_1 -weighting even further, it is possible to apply not a 90° RF pulse but rather a 180° RF pulse, to “fully invert” the longitudinal magnetization. The M_z component then proceeds to recovery by longitudinal relaxation, as described above, but now starts from a value of -1 , rather than 0 as before. A schematic inversion recovery curve is shown in Fig. 8.

Since longitudinal magnetization (M_z) is initially negative and recovers to its eventual positive equilibrium value, it must at some point pass through an instantaneous value of zero. This is known as the “null point” and occurs at a time, $t = 0.69 T_1$, for each species. If an imaging sequence (initiated by a 90° RF excitation) is commenced a time t after a 180° inversion pulse, the signal intensity of tissues in the image will be scaled by the instantaneous value of M_z at time t . If t is chosen to be the null point for a given tissue, then this tissue’s signal intensity will be scaled by zero in the subsequent image and it will be “suppressed.” This powerful technique has several indications, but two variants are widely encountered: short tau inversion recovery (STIR), in which fat signal is suppressed by choice of a short inversion recovery time t ; and fluid attenuated inversion recovery (FLAIR), in which the inversion recovery time t is chosen to “null” the signal of the long T_1 species from the CSF (see arrow in Fig. 8) (6). FLAIR images (by virtue of allowing most species to fully recover) offer a great deal of clinical utility as they retain

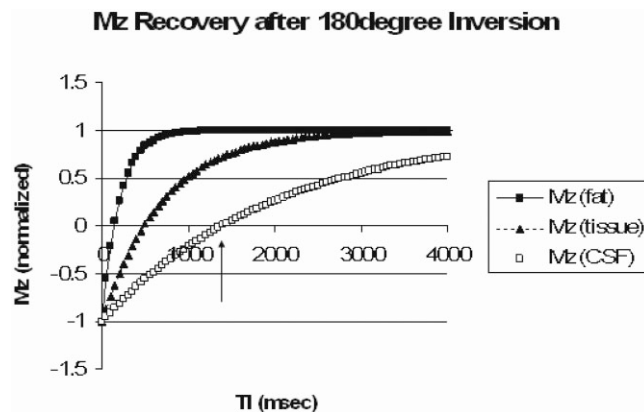


Figure 8. Schematic T_1 inversion recovery curves for fat, tissue, and CSF as a function of increasing TR. Note that M_z is initially negative, but recovers over time to its positive equilibrium value. At a characteristic time (marked by arrow for CSF curve), M_z must pass through zero. This is termed the “null point”.

the diagnostic qualities of a T_2 -weighted spin echo image (sensitive to edema, inflammation, etc.), as described above, but with the signal from the CSF eliminated, improving the delineation of a lesion that might otherwise be approximately isointense with CSF on a conventional T_2 -weighted image and for which it would thus be difficult to determine the margins (see Fig. 9). As can be seen, the FLAIR sequence draws on both T_1 and T_2 contrast mechanisms to improve diagnostic utility.

Gd-Based Contrast Agents for Enhancement of T_1 -Weighted Images

Despite the power and utility of endogenous contrast mechanisms exploiting tissue-specific differences in T_1 and T_2 values, there are situations in which the diag-

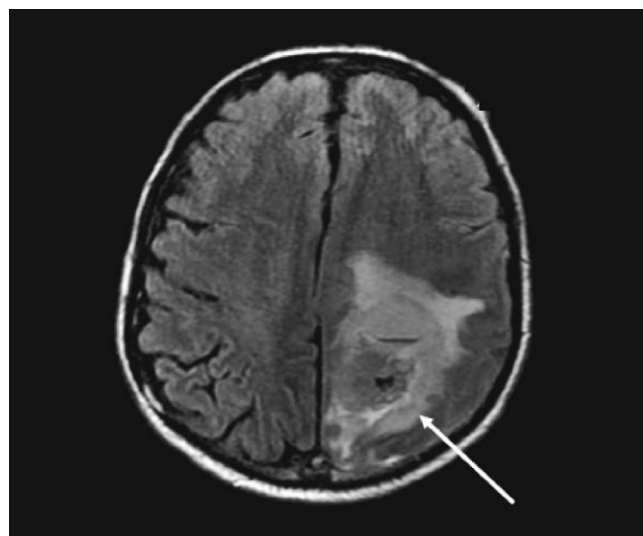


Figure 9. FLAIR. By suppressing otherwise hyperintense signal from CSF, this T_2 -weighted image allows delineation of pathologies such as brain tumor (arrow).

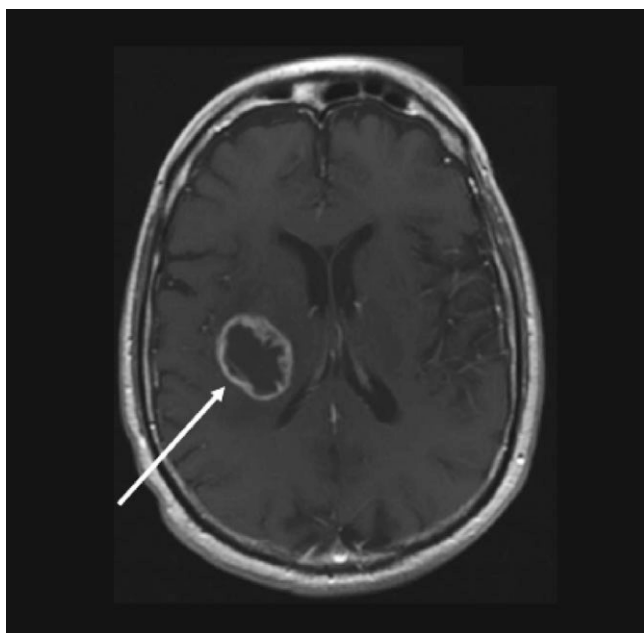


Figure 10. T_1 -weighted image showing hyperintensity post-Gd administration revealing blood brain barrier disruption in this patient with a high-grade glioma.

nostic utility of MRI can be further improved by the administration of an exogenous contrast medium. A contrast medium can be considered as a “magnetic dye” that is administered by intravenous injection and can be visualized as it distributes. All presently available (U.S. Food and Drug Administration [FDA]-approved) contrast agents are based on low molecular weight (~ 500 Da) organic molecules that chelate or encase an ion of the rare earth metal, Gd. The Gd^{3+} ion, by virtue of its electron configuration, is a highly potent “enhancer” of longitudinal relaxation. That is to say, wherever the nuclear spins of water molecules encounter and interact with the Gd^{3+} ion, their T_1 value is substantially shortened. Such T_1 -shortening can be revealed on T_1 -weighted images, as described above, and is commonly observed as a relative hyperintensity. All approved contrast agents can also be considered as nonspecific markers of the extracellular fluid (ECF). Sometimes they are referred to as “ECF agents.” They freely distribute in the extravascular, extracellular space of the body, but do not enter healthy cells. Importantly for neuroradiology, they do not cross an intact blood brain barrier. Thus administered intravascularly, they remain intravascular on passage through the healthy brain. Given the low fractional blood volume of brain tissue, it is relatively difficult to discern the presence of the contrast agent in tissue parenchyma (signal in larger vessels, however, may well be enhanced). If, however, the blood brain barrier integrity has been compromised (as is the case in a large number of brain pathologies), contrast agent will extravasate out of the intravascular compartment and into the tissue space. The contrast agent concentration may thus accumulate locally and have a substantial T_1 -shortening effect within that region, leading to conspicuous hyperintensity on T_1 -weighted images (see Fig. 10).

In fact, not only the presence, but also the degree of blood brain disruption can be interrogated with MRI. Use of sequential T_1 -weighted images allows the progression of tissue enhancement to be characterized. Upon appropriate kinetic modeling of the dynamic enhancement data, it is possible to estimate both the vascularity (fractional blood volume) and the microvascular permeability of tissues (7), revealing subtle but physiologically significant hyperpermeability of the blood brain barrier (Fig. 11).

In fact, some studies suggest that the microvascular permeability of tumors may reflect the degree of angiogenic activity within the tumor (Fig. 11b). In principle, therefore, monitoring tumor microvascular permeability might offer a useful strategy in the assessment of antiangiogenic therapies. Recent data also suggests that evidence of hyperpermeability of brain microvessels in regions of acute cerebral ischemia may be predictive of subsequent hemorrhagic transformation. Table 2 summarizes considerations for T_1 -weighted sequences.

T_2^* -Weighted Image Contrast

While the use of Gd-based contrast agents in conjunction with T_1 -weighted imaging as described above tends to lead to local hyperintensity, or “positive enhancement,” Gd-based contrast agents are also widely used in another guise as “negative enhancing agents.” This exploits the strong paramagnetic nature of the Gd^{3+} ion and a final relaxation mechanism, described by the time constant T_2^* . Related to T_2 , as it describes the rate at which transverse coherence is lost after initial RF excitation, T_2^* embodies all mechanisms that lead to such dephasing, not only the interactions between excited nuclei, but also spatially-dependent variations in magnetic field that lead to different spin precession rates, and thus to dephasing and signal loss. Such

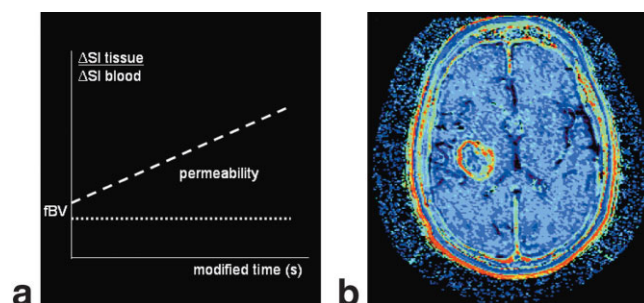


Figure 11. a: Schematic of microvascular permeability derivation as the slope of progressive enhancement in tissue. By plotting the ratio of tissue enhancement to reference vascular enhancement, progressive extravasation of contrast agent into tissue can be resolved, even in the presence of ongoing plasma clearance. In practice, the time axis is often “stretched” to reflect the decreasing plasma concentration of tracer (and a pseudotime, or “Patlak” time axis is generated to maintain the linearity of progressive enhancement implied by the schematic. **b:** Permeability (K_{ps}) map of patient in Fig. 10. This permeability map was generated by pixel-wise kinetic modeling of the dynamic enhancement data as described in Ref. 7 and shown schematically in (a).

Table 2
Summary of T₁-Weighted Sequences

Sequence	Common acronyms	Feature	Key variables
Conventional spin-echo	SE, CSE	Proton density to T ₁ -weighted contrast. Weak contrast at 3T and above.	TR
IR-prepped 3D gradient-recalled echo	MP-RAGE, FSPGR, FFE	3D sequence with IR-prep to achieve desired T ₁ contrast	TI
TOF-MRA	2D or 3D gradient recalled echo	Uses inflow enhancement of blood (and suppression of stationary tissue) to yield angiographic images. Multislice 2D or 3D. Usually 3D postprocessed (MIP)	Flip angle, slab thickness (to ameliorate tapering saturation of inflow)
+ Gd	SE, 3D GRE	Uses T ₁ -shortening effect of i.v.-administered GdDTPA to probe BBB disruption	TR (to ensure T ₁ -weighting)
Permeability imaging	Gd-enhanced dynamic 3D GRE	Can image progressive enhancement of tissue and model this to estimate microvascular permeability	Flip angle, temporal resolution

IR = inversion-recovery, TOF-MRA = time-of-flight MR angiography, BBB, blood brain barrier.

variations may arise from limits to the quality of magnet construction or to inherent differences in the magnetic character of tissues—different tissues exhibit differing degrees of dia-/paramagnetism (i.e., their magnetic response to being placed in an external magnetic field). The degree to which a tissue (or indeed any entity) responds magnetically to being placed in a magnetic field is described by its “magnetic susceptibility,” χ . Differences in magnetic susceptibility between soft tissues and bone, or air, thus lead to strong local variation in magnetic field at the interface between them. This field variation leads to rapid spin dephasing, described by a short T₂* value, and signal loss. Resultant signal voiding is often termed “magnetic susceptibility artifact” (see Fig. 12).

While some magnetic field inhomogeneity can be improved by the process of shimming (application of external magnetic field gradients to attempt to compensate for observed field variation), magnetic susceptibility effects are largely corrected by the formation of the spin echo (as in T₂- and T₁-weighted images). They remain, however, potentially significant in gradient recalled echo sequences and echo planar imaging (EPI) (see below). Gradient recalled echo techniques (with short TE values) are nonetheless typically preferred over spin echo sequences for

the rapid acquisition of volumetric data (three-dimensional [3D] sequences) as well as MR angiography and MR venography. EPI, due to its tremendous speed of acquisition is widely used to study dynamic (or functional) changes, or to “freeze” involuntary patient motion. Since magnetic susceptibility-related “dephasing” necessarily evolves over the time between excitation and echo formation (the echo time, TE), it is clear that effects can be minimized by selection of short TE values. Practically, TE can generally be shortened by: 1) use of higher receive bandwidths (increasing the rate of data acquisition and thus decreasing the overall duration of each echo); or 2) using partial k-space techniques to only partially sample the echo.

However, rather than seeking to ameliorate or reduce the sensitivity of an MR sequence to magnetic field inhomogeneity, there are notable circumstances in which such sensitivity can be positively exploited. Indeed, this contrast mechanism forms the basis of three exciting emerging MRI applications: perfusion imaging, susceptibility-weighted imaging, and functional brain mapping.

Gd-Based Contrast Agents as Negative Enhancing Agents

As discussed above clinically-available contrast media (e.g., Gd-diethylenetriamine pentaacetic acid [DTPA]), injected intravenously, remain intravascular during passage through the brain, with extravasation (leak) prohibited by the intact blood brain barrier. With T₁-weighted imaging, the low blood volume fraction of brain tissue makes enhancement subtle and generally not resolvable. However, since the magnetic field-disturbing effect of the paramagnetic Gd³⁺ moiety extends well beyond the physical location of the Gd³⁺ ion itself, spin dephasing and signal loss occurs not just in the immediate vicinity of the Gd³⁺ ion (i.e., intravascularly) but also within the extravascular space of parenchymal tissue. As such “negative enhancement” can be considered to be occurring in both intra- and extravascular compartments, considerably amplifying sensitivity of

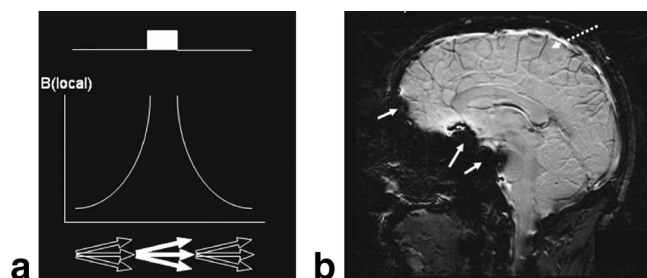


Figure 12. **a:** Magnetic susceptibility schematic and **(b)** artifact (solid arrows) at tissue:air interface. Note hypointensity in cortical veins (dotted arrows) resulting from endogenous, paramagnetic deoxyhemoglobin.

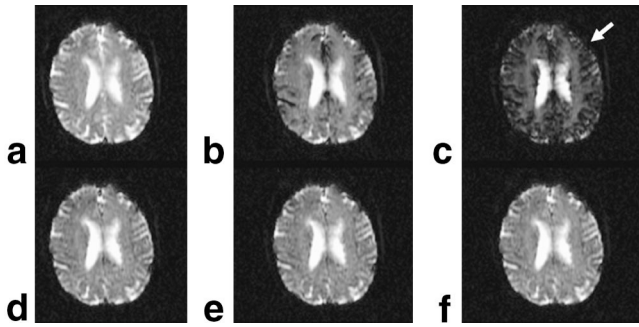


Figure 13. A series of six T_2^* -weighted echo planar images acquired during passage of a bolus of 0.1 mmol/kg Gd-DTPA. Temporal resolution of the sequential images is two seconds. The negative enhancing property of the Gd-DTPA may be most clearly visualized in (c) at the moment the local concentration of Gd-DTPA peaks. Absence of contrast media in the ventricles is seen as preserved signal.

detection. In fact, dynamic T_2^* -weighted imaging (gradient-recalled echo [GRE] or, more typically, EPI) is widely used to serially image brain tissue, before during and after injection of a short bolus of Gd-containing contrast medium, and effectively to “track” its passage into, through, and out of the brain (Fig. 13) (8,9). The time-varying signal intensity, $S(t)$, of a given pixel can be described by Eq. [4].

$$S(t) \propto \rho \exp(-TE/T_2^*), \quad (4)$$

where TE controls the sensitivity of the sequence to the parameter T_2^* . Since T_2^* is shortened by the presence of the paramagnetic contrast medium, according to Eq. [5]:

$$1/T_2^*(t) = 1/T_2^*(0) + r_2^*[Gd], \quad (5)$$

(where r_2^* is a constant of proportionality, known as the effective transverse relaxivity), the time-varying signal intensity $S(t)$ can be related to $[Gd]$ through the surrogate, ΔR_2^* , where $R_2^* = 1/T_2^*$. Thus,

$$[Gd](t) \propto \Delta R_2^*(t) = (1/TE) \ln(S(t)/S(0)). \quad (6)$$

So the signal intensity curve is transformed into a time-varying function, ΔR_2^* , which is taken proportional to the instantaneous tracer concentration (Fig. 14). From this time-varying estimate of tracer concentration, standard tracer kinetic modeling approaches can be employed to derive physiologically-specific parameters of the vascular system (10,11).

Analysis of such “bolus-tracking” experiments can yield relative, and increasingly quantitative, absolute measures of cerebral hemodynamics, such as cerebral blood volume (CBV), mean transit time (MTT), and CBF. So-called “MR perfusion” imaging is widely used in the study of acute cerebral ischemia, and is also encountered in brain tumor imaging (however, the disruption of the blood brain barrier in brain tumors leads to contrast agent extravasation and considerable complication in the kinetic analysis and interpretation of such

data). In fact, there are alternative approaches to MR assessment of CBF and perfusion that are emerging as advantageous in some circumstances. Particularly, the methodology of arterial spin labeling (ASL), originally introduced by Detre et al (12) offers a quantitative approach to CBF measurement entirely without the use of exogenous contrast agents. A full discussion of this approach is beyond the scope of this article, especially since this technique is not yet widely adopted in clinical protocols. Nonetheless, a brief description is warranted. Rather than dynamically imaging (or “tracking”) a bolus of contrast agent as it passes through the brain, inflowing arterial blood is “magnetically labeled,” typically by applying a spatially-selective 180° inversion RF pulse, for example at the level of the carotid artery. Such labeled blood then travels toward the more superior slice or slices of interest in the brain, carrying with it a population of spins with inverted magnetization (i.e., a z -component of magnetization, M_z , with a value of -1). Since stationary (unlabeled) tissue spins have an M_z of $+1$, the signal intensity in a subsequent image will be weighted by the fraction of inflowing labeled spins (effectively decreasing the net or ensemble M_z value). A comparison image is acquired without such labeling (in which the net magnetization M_z remains 1). The difference between the two images (obtained by pixel-wise subtraction) is then entirely attributable to the fractional content of inflowing/perfusing water molecules. Thus the magnetically-labeled water can be considered as a freely diffusible tracer, allowing subsequent quantitative modeling of perfusion parameters. A substantial limitation of ASL is the requirement to wait between “labeling” and “imaging” for the blood to arrive and for the labeled water to exchange into tissue. The impact of this waiting period arises from the T_1 -based recovery of the inverted “labeled” spin population, effectively causing the “label” to fade over time (according to the T_1 value of blood). This effect appears to motivate the continuing development of ASL in the context of higher field

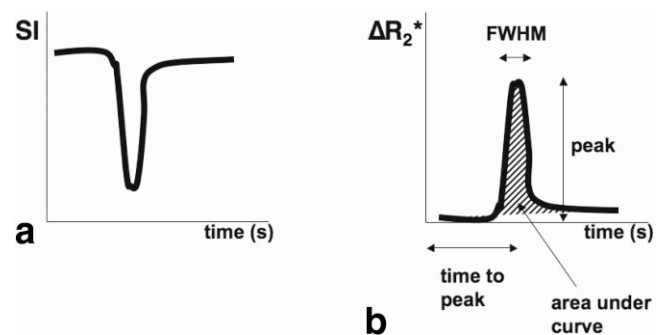


Figure 14. **a:** Dynamic signal intensity time course from rapidly acquired sequential T_2^* -weighted images reveals a transient signal loss associated with the presence of the contrast medium bolus. This rapidly recovers toward the baseline. **b:** Transforming the signal intensity time course into the time-varying measure of ΔR_2^* , which is taken as proportional to $[Gd]$, we obtain a concentration–time curve for the tracer. This is amenable to simple parametric description (e.g., time to peak, magnitude of peak, area under the curve, peak full width at half maximum [FWHM]) as well as more sophisticated kinetic analysis, to yield parameters such as MTT and CBF.

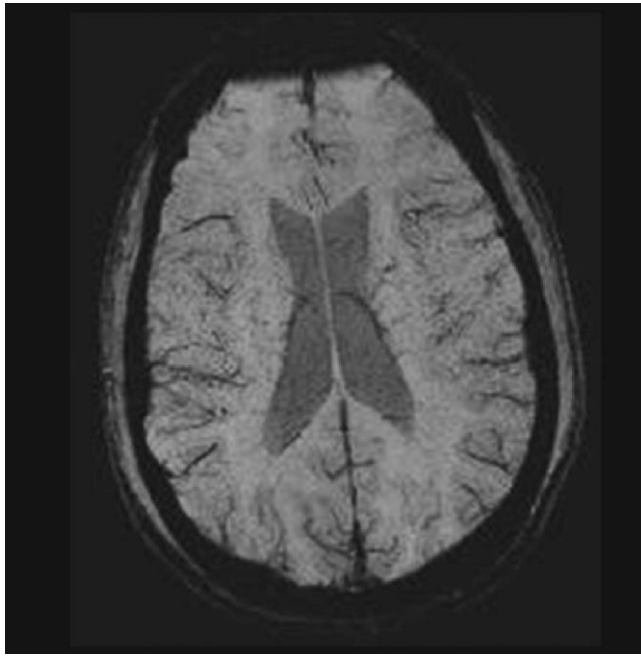


Figure 15. Susceptibility-weighted image. Minimum intensity projection through a set of axial T_2^* -weighted images of a healthy adult volunteer. Images were acquired at 3T and post-processed to weight the resulting image not only by the signal magnitude, but also according to its phase.

MRI systems (3T and above, see below), since a phenomenon of higher field strength is the prolongation of T_1 values, which in this setting will lead to stronger and longer persistence of the magnetic label.

In fact, the signal loss associated with the transient presence of paramagnetic Gd^{3+} would in principle occur with any paramagnetic species. At high magnetic field strength, this was originally reported by Ogawa et al (13) as causing the marked hypointensity in cerebral veins (see Fig. 12b). It was hypothesized that the increased deoxyhemoglobin content of veins compared to arteries would lead to increased magnetic field disruption and signal loss, due to the paramagnetic nature of deoxyhemoglobin (while oxyhemoglobin is diamagnetic and has little negative impact on magnetic field homogeneity). For visualizing cerebral veins, this phenomenon has been enhanced in the work of Reichenbach et al (14) and Haacke et al (15), whereby the magnitude of signal is masked by the phase image (since phase is also disturbed by the deoxyhemoglobin). The resultant postprocessed images are typically “MinIP’d,” using an algorithm similarly to maximum intensity projection (common in MR angiography to identify the brightest structures in a 3D data set), where the MinIP algorithm identifies and forms a projection image of the darkest voxels within a 3D dataset. Figure 15 illustrates the resultant, so-called “susceptibility weighted image” (SWI) from a healthy volunteer, acquired at 3T.

BOLD Contrast—Functional MRI

However, the major application resulting from the differing influences on local image signal intensity of de-

oxy- vs. oxyhemoglobin is the field of functional magnetic resonance imaging (fMRI), which exploits the “BOLD contrast” and a remarkable physiological phenomenon. Secondary to neural activity associated with peripheral stimulation, task performance or cognitive activity, there is a transient increase in regional CBF (in response to the increased demands of the active neurons). This increased CBF is not, however, balanced with a commensurately increased demand for tissue oxygen, O_2 . Consequently, there is a net increase of oxyhemoglobin in the capillary bed, compared to the period prior to the neuronal activity (Fig. 16). An increase in oxy-hemoglobin is associated with a relative decrease in deoxyhemoglobin. Since deoxyhemoglobin, being paramagnetic, is associated with signal loss on T_2^* -weighted images, its transient decrease in concentration is visualizable as a transient increase in local signal. That is, in the capillary bed of tissue closely coupled to the neurons that were active, there will be an increase in signal intensity. Thus the field of human brain mapping with fMRI was initiated (16).

Table 3 summarizes considerations and applications of T_2^* -weighted MRI.

EPI

To achieve the above-desired magnetic susceptibility-weighted contrast, and at the same time to have adequate temporal resolution to monitor the transient dynamic changes in oxy-/deoxyhemoglobin concentration with whole brain coverage requires a high performance imaging sequence. Most widely used is the GRE

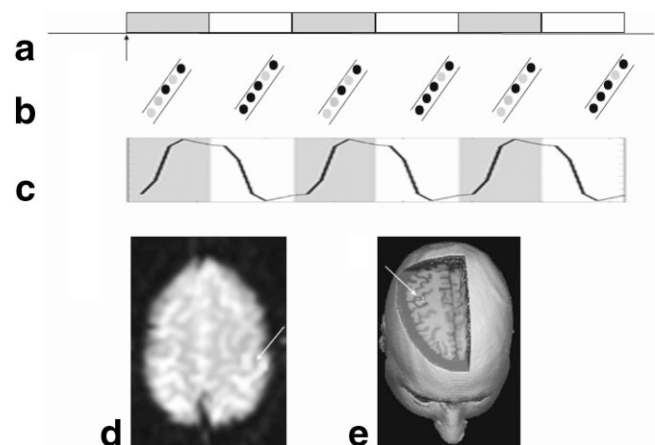


Figure 16. fMRI. **a:** Schematic of typical “block design” paradigm in which periods of task performance (black) and rest (open) are alternated. **b:** The theoretical basis of BOLD fMRI is the replacement of paramagnetic deoxyhemoglobin (filled circles) with diamagnetic oxyhemoglobin (open circles) during regional neuronal activation associated with the task. **c:** Consequent fluctuations in signal intensity on T_2^* -weighted images (signal increasing locally during task performance) also reflect the “hemodynamic lag” or delay in the BOLD response with respect to neuronal electrical activity. **d:** Identification of pixels with signal intensity time courses significantly correlated with the model in (c) allows construction of statistical parameter maps effectively identifying functional centers. **e:** Such maps can be reconstructed in 3D, for example for use in surgical planning.

Table 3
Summary of T_2^* -Weighted Sequences

Sequence	Common acronyms	Feature	Key variables
Gradient recalled echo	SPGR, GRE, FLASH, FFE	Sensitive to T_2^* shortening associated with iron (e.g., hemorrhage). Sensitive to magnetic susceptibility artifact at tissue interfaces.	TE
Echo planar imaging	EPI	Essentially a single-shot GRE. Highly sensitive to magnetic susceptibility differences. Tendency toward anatomic distortion and blur. Historically, low resolution. Demanding of hardware performance.	TE, ETL, overall acquisition time
Perfusion	EPI	Uses dynamic imaging with T_2^* -sensitivity to track Gd-bolus passing through brain due to "negative enhancing" effect of paramagnetic Gd.	Temporal resolution. Choice of GRE (sensitivity) vs. spin-echo (increased capillary specificity)
BOLD	EPI	Uses T_2^* -sensitivity to track endogenous changes in deoxy- and oxyhemoglobin concentration (secondary to neuronal activity, or breathhold, or O_2 administration)	TE (for sensitivity), TR (for temporal resolution)

EPI sequence (17). In much the same way as the FSE and TSE variants of spin-echo imaging collect multiple spin echoes (i.e., lines of k-space/phase encoding steps) per RF excitation, EPI collects multiple gradient recalled echoes. Unlike the FSE approach, which applies multiple 180° RF refocusing pulses, the EPI approach applies multiple reversals of the readout gradient polarity (see Fig. 17).

Most implementations of EPI are as (relatively) low-resolution single-shot acquisitions (with a matrix size of 64×64 or 128×128). Indeed, if one considers that the limitation to an EPI echo train is ultimately governed by the tissue T_2^* (as in Fig. 17), increasing receiver bandwidth is also a major factor in reducing the amount of time required to collect each echo, ultimately shortening the total acquisition time. Importantly, in addition,

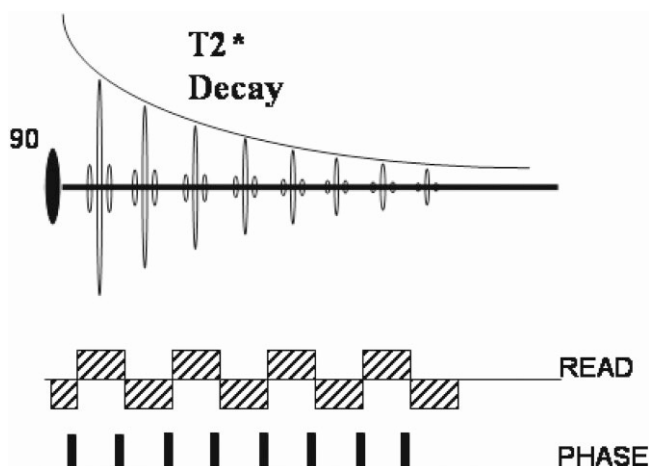


Figure 17. EPI. Successive echoes (and thus lines of k-space) are acquired by reversal of polarity of the readout gradient. Each echo is associated with a different history integral of phase encoding (effectively shifting the vertical coordinate in k-space). Echo amplitude decreases according to T_2^* , since there is no spin echo refocusing.

the recent advent of parallel imaging makes it indeed feasible to reconstruct single-shot EPI images with a matrix size of 256×256 or more. The use of high-bandwidth receivers allows the acquisition of 128 echoes faster (and therefore with less signal loss and blur); the use of parallel imaging allows such echoes to be reconstructed into a 256×256 matrix. Thus in combination (see Fig. 18), it is now possible to acquire higher spatial resolution single-shot EPI images with lower signal degradation (compare images Fig. 18a and c).

DWI

Exploiting the rapid image acquisition of single-shot EPI, visualization of an additional tissue contrast mechanism is offered. Images can be made sensitive to, or weighted by, the process of water molecule diffusion. By addition of a pair of magnetic field gradient pulses prior to the image readout module of the EPI sequence it is possible to probe the movement of water molecules, by "labeling" the proton position during the first gradient pulse and "unlabeling" it during the second pulse. If the proton position does not change between gradient pulses (typically ~ 40 msec apart), then signal will be retained in the subsequent echo. To the extent that the

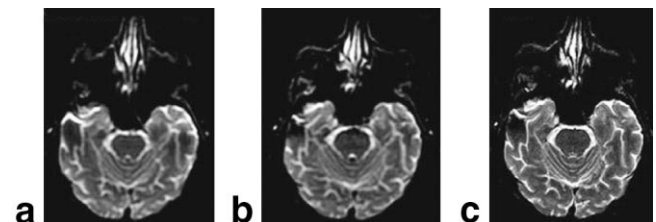


Figure 18. EPI images acquired with: (a) 128×128 matrix and no parallel imaging, TE = 69 msec; (b) 128×128 matrix with a parallel imaging acceleration of $\times 2$ shortening the ETL to 64 and reducing the TE to 60 msec; and (c) 256×256 matrix with a parallel imaging acceleration of $\times 2$ (i.e., an ETL of 128), resulting in a TE of 65 msec.

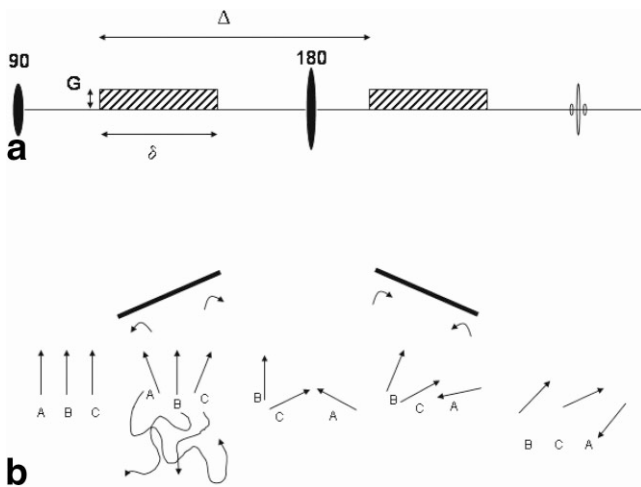


Figure 19. Schematic of DWI imaging. **a:** Diffusion sensitization is achieved by applying a pair of magnetic field gradient pulses to a spine echo (or spin echo EPI) sequence. The degree of sensitization (called the b-value) depends on choice of gradient amplitude (G), duration (δ), and separation (Δ). **b:** Schematic of spin dephasing and incomplete rephasing secondary to diffusion (or displacement).

proton's position has altered over this time, the “unlabeling” step will be incomplete and overall signal will drop. The greater the displacement, the greater the signal attenuation (Fig. 19). Again, this contrast mechanism, exposed over a spatial resolution of the order of 1 mm, allows inference about water molecule movement on a spatial scale of 5–10 μm (since the mean free path of diffusion over ~ 40 msec has a magnitude measured in μm).

The most widespread application of DWI is in the identification of acute ischemic stroke (wherein water diffusion in the ischemic region is restricted, perhaps secondary to cytotoxic edema or reduced cytosolic streaming) (18,19). This early manifestation of cell membrane pumping failure (most of these mechanisms require energy consumption and adenosine triphosphate [ATP] dephosphorylation) becomes apparent early after the ischemic event (minutes in animal models and within approximately one hour in clinical settings). Figure 20 shows an example of a DWI image acquired in an acute stroke patient.

It is clear from Eq. [7] that the signal intensity on such a DWI image in fact depends additionally on proton density and also on T_2 (since diffusion weighting was effectively created by augmenting a T_2 -weighted pulse sequence with diffusion encoding gradient pulses).

$$S \propto \rho \exp(\text{TE}/T_2) \cdot \exp(-b \cdot \text{ADC}). \quad (7)$$

These additional weightings may confound interpretation of a DWI image in isolation—it may be difficult to distinguish between hyperintensity on a DWI image that arises from reduced ADC vs. prolonged T_2 , for example (20). Fortunately, the ability to quantify parameters such as the ADC can resolve this ambiguity. Instead of obtaining a single DWI image with a certain

b-value, one is required to acquire two images with different b-values (typically, one image has a b-value close to 0 seconds/ mm^2). From such a pair of images with b-values of for example 0 and 1000 seconds/ mm^2 , it is possible to eliminate confounding weighting (from proton density, and indeed T_2) and derive on a pixel-by-pixel basis the value of the ADC (Eq. [8]), which can be represented in grayscale as the ADC “map”:

$$\text{ADC} = (-1/b) \ln(S_b/S_0), \quad (8)$$

where S_b is the signal intensity in a given pixel for the image acquired with the high b-value (e.g., 1000 seconds/ mm^2) and S_0 is the signal intensity in the corresponding pixel of the image acquired without diffusion weighting ($b = 0$) (Fig. 21), where b is the sensitivity of the diffusion weighted sequence to the process of diffusion.

The b-value is dependent on several imaging sequence choices, namely the duration, separation, and amplitude of the diffusion encoding gradient pulses. For maximum sensitivity to changes in diffusion coefficient, while retaining adequate SNR, a choice of $b = 1000$ seconds/ mm^2 is widely used (note typical tissue ADC values are approximately the reciprocal of this, such that the product $b \cdot \text{ADC} \approx 1$).

Anisotropy and Diffusion Tensor Imaging (DTI)

Since diffusion encoding gradient pulse pairs can be applied on any (or all) of the gradient axes, the resultant image can be made sensitive to diffusion processes in different directions. This is of particular utility in the characterization of anisotropic diffusion (i.e. diffusion in which one direction is preferred, e.g., within white matter tracts; Fig. 22a) (21). Acquiring DWI images with diffusion-sensitization in different directions allows both the magnitude and orientation of anisotropy to be determined. To fully describe the degree and direction of anisotropy, diffusion is often considered as a tensor quantity (a 3×3 matrix) rather than as a single scalar (22). DTI is thus the term applied to successive DWI acquisitions, with encoding in different directions to allow determination of the diffusion tensor. Note at least six different directions of diffusion encoding are required in order to solve the diffusion tensor. Figure 22b illustrates a typical representation of the degree of

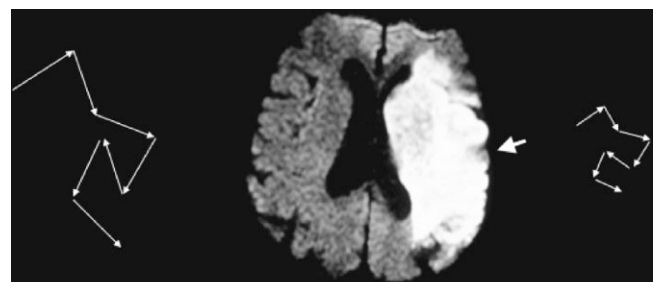


Figure 20. DWI image in acute stroke. Reduced diffusion in the region of ischemia (arrow) is visualized as hyperintensity on the DWI image (b-value = 1000 seconds/ mm^2).

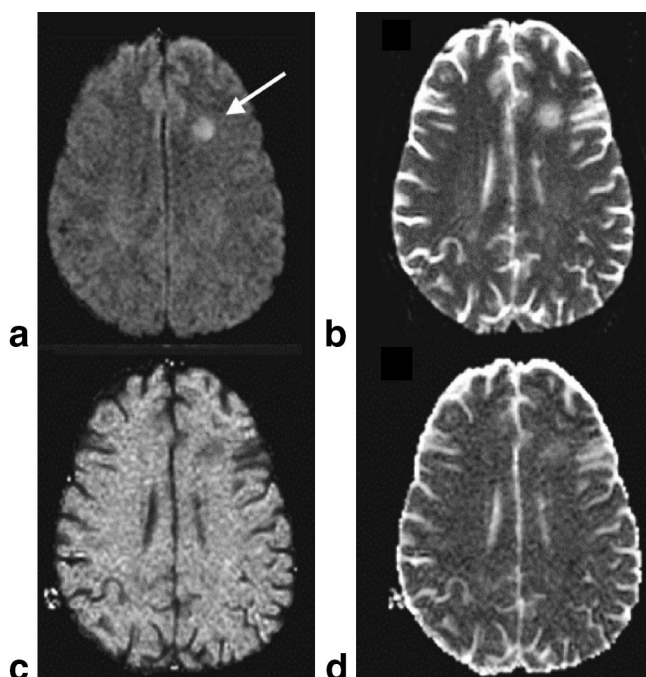


Figure 21. **a:** A DWI image reveals focal signal hyperintensity, in this case of active multiple sclerosis. However, inspection of the baseline ($b = 0$), T_2 -weighted image reveals hyperintensity attributable to T_2 prolongation. It is not clear whether the hyperintensity on the DWI image reflects reduced diffusion or prolonged T_2 . By constructing a ratio image (**c**), formed by dividing the DWI image by the T_2 -weighted image, we are left with an image, weighted by $\exp(-b \cdot \text{ADC})$, which reveals hypointensity (consistent with elevated diffusion). Synthesizing a pixel-by-pixel map of the ADC itself from the natural logarithm of (**c**) confirms the slightly elevated ADC value in this zone. This phenomenon (termed T_2 -shinethrough), leading to ambiguous interpretation of the DWI image in isolation, is resolved by the subsequent image analysis (ratio formation and/or ADC mapping).

diffusion anisotropy using one metric, the fractional anisotropy (FA).

Taking such pixel-by-pixel information on diffusion anisotropy, it is possible to track the pathway of white matter tracts through the brain. One algorithm, fiber assignment by continuous tracking (FACT) considers

the direction of anisotropy (the principal eigenvector of the diffusion tensor) and proceeds from an initial seed point in the direction of the principal eigenvector from pixel to pixel (updating the direction at each new pixel) (23). This continues until a predetermined lower threshold of FA is encountered, at which point the fiber path is terminated (as the pixel no longer is considered to be dominated by white matter). Figure 22c shows examples of white matter fiber tracts, with different colors representing different initial seed points. It can be seen that this method offers a powerful approach to the study of brain connectivity and is expected to provide synergistic insights when used in combination with functional center identification using fMRI.

Magnetization Transfer Contrast

T_1 , T_2 , and indeed ADCs provide MR-accessible parameters of tissue that in various ways reflect the physicochemical nature of the microenvironment. The insights that can be drawn from resultant image contrast can be seen as reflecting the power and scope of MRI and accounting for its exquisite soft tissue contrast. An additional level of insight into the tissue microenvironment can be obtained using a mechanism known as magnetization transfer contrast. In this approach, the microscopic composition of tissue is probed, specifically the content and accessibility of macromolecular and microstructural components such as myelin. In brief, the physical phenomenon exploited is the ongoing exchange between protons of appropriate macromolecular entities and protons of free water. Effectively, two “pools” of protons can be considered—the free pool and those protons “bound” by a chemical bond to the macromolecular entities (typically as part of a hydroxyl $\sim\text{OH}$) group. If considered separately, the T_2 values of the two pools would be found to be very different (with the relatively immobile bound protons having a very short T_2 value). Consequently, imaging of a pixel containing both pools reveals only the free pool content (since signal is lost very rapidly from the short T_2 species). Essentially, the bound pool protons are invisible. Another feature of the short T_2 species is that a chemical spectrum of this population would reveal a very broad resonance (extending over several kHz) is contrast distinction to the sharp resonance of the free water

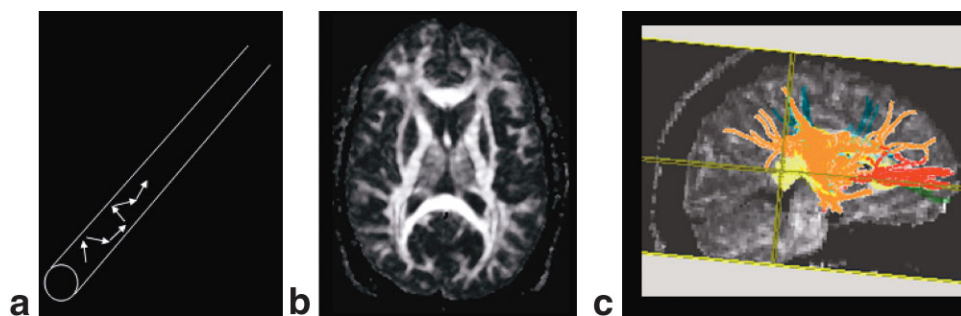


Figure 22. **a:** Anisotropy of diffusion schematic. **b:** The degree of anisotropy is calculated on a pixel-by-pixel basis and can be represented as a map of metrics such as FA. **c:** Pixel-wise computation of the direction (as well as degree) of anisotropy allows stepwise reconstruction of fiber tract paths (typically by advancing from a seed point in single pixel steps), the direction of which is determined by the principal diffusion direction of each pixel.

protons. The peak of both resonances might be coincident, but the linewidths differ considerably. If a strong pulse of RF radiation is applied at a frequency shifted from the spectral peak of the two pools in such a way that it impacts the broad line of the bound pool but is shifted beyond the narrow line of the free pool (so-called “off-resonance” excitation), one might expect to excite and ultimately saturate the magnetization of the bound pool protons, with minimal impact on the protons of the free pool. Initially, one might expect this process to have no effect on subsequent image signal intensity (since the bound pool protons were “invisible” anyway, because of their short T_2 values). However, under appropriate chemical and microstructural circumstances, as suggested above, protons in the two pools exchange. For the purpose of signal intensity this means that some protons of the bound pool carry their saturated magnetization with them as they join the free pool, while corresponding protons of the free pool join the invisible group of bound protons (as they experience the short T_2 environment). The availability of unsaturated magnetization in the free pool is therefore decreased and, consequently, signal intensity decreases (Fig. 23). The degree of reduction depends on the amount and availability of protons in the bound pool and the effectiveness of the proton exchange. It can be quantified by acquiring two images, one with and one without the extra (off-resonance) RF irradiation. The loss of signal associated with magnetization transfer is described mathematically in the magnetization transfer ratio (MTR) given by Eq. [9]

$$\text{MTR} = (M_0 - M_s) / M_0, \quad (9)$$

where M_0 is the signal intensity without off-resonance irradiation and M_s is the signal intensity in the image acquired after off-resonance irradiation. MTR values tend to be highest in white matter (since myelin appears to provide the necessary chemical and physical environment to promote effective magnetization transfer). Quantitation of MTR appears very promising in the characterization of white matter disorders such as multiple sclerosis (24). Nonetheless, most tissues exhibit some degree of MTR. More fluid moieties (e.g., blood), however, tend not to exhibit magnetization transfer effects and retain similar signal intensity after such off-resonance irradiation. This difference between blood and tissue is commonly exploited in MR angiography (the subject of another article), in which extra contrast between (bright) blood and (dark) background tissue is achieved by applying the off-resonance irradiation and exploiting the magnetization transfer effect to further reduce the signal intensity of background tissue structures.

High-Field MRI

Recent advances in MRI hardware have seen the increasing clinical adoption of MRI systems at field strengths higher than 1.5T. The vast majority of these systems operate at a field strength of 3T (although systems at 7T and higher are emerging). While it is beyond the scope of this review to deal thoroughly with issues of

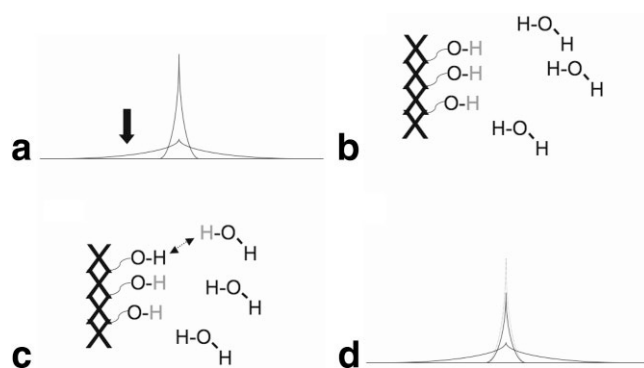


Figure 23. Schematic of the magnetization transfer effect. **a:** Free water protons are characterized by a sharp resonance, whereas the pool of “bound” protons has a much broader resonance, which is still impacted by off-resonance RF excitation (arrow). **b:** After irradiation, the “bound pool” protons are saturated (represented by gray lettering), while the free water protons are unaffected. **c:** Chemical exchange between the proton pools transfers saturated magnetization (gray “H”s) to the free water pool, which is reflected in **(d)** in a diminished spectral peak amplitude (solid sharp resonance), compared to a similar acquisition without the off-resonance irradiation (dotted sharp resonance).

high field MRI, a brief summary of the influences of higher field strengths on the above image contrasts and acquisition mechanisms is warranted. A number of recent texts and collections address these issues in significant detail (e.g., Ref. 5). The driving motivation toward high-field MRI lies in the Boltzmann statistics underlying MR signal intensity. While noise scales approximately linearly with magnetic field strength, “signal” increases approximately quadratically; as such, the SNR of an image might be expected to increase approximately linearly with magnetic field strength. As is generally true in MRI, this increase in SNR can be exploited in several ways: either to simply increase image quality directly, or to permit smaller image pixels (with reduced water content)—i.e., to increase spatial resolution, or to image faster (increase temporal resolution), which might otherwise come at a prohibitive cost in terms of SNR reduction.

However, in practice, there are several other pertinent considerations associated with higher field MRI that may compromise the apparent gain predicted above. First, it is generally true that T_1 relaxation times of tissue become prolonged at higher magnetic field strength; thus for conventional spin echo pulse sequences, as discussed earlier, longer TR values would be required to elicit a similar degree of T_1 -weighting, thus increasing image acquisition times. Worse still, not only do tissue T_1 values become prolonged, but they tend to converge, rendering good T_1 -based soft-tissue contrast hard to achieve using such conventional spin echo approaches. The generally-adopted solution to this problem is to learn from the STIR and FLAIR sequences and to apply an inversion pulse with a recovery period optimal for distinguishing between gray and white matter (700–900 msec), prior to a fast 3D gradient recalled echo volumetric acquisition. Such an ap-

proach is often referred to as a rapid gradient echo with “magnetization preparation” or MP-RAGE.

Similarly, sensitivity to magnetic susceptibility differences increases with magnetic field strength (T_2^* values are shortened). This can be considered as an advantage or a disadvantage. Sensitivity to tissue interface “susceptibility artifacts” is generally exacerbated, requiring shorter TE choices in the pulse sequence. On the other hand, sensitivity to BOLD contrast mechanisms and/or paramagnetic contrast media in perfusion studies is also enhanced, improving the quality of fMRI examinations and potentially reducing the injected volume of contrast agent.

Other considerations include the increased spectral separation between metabolite peaks in MR spectra, which is offset somewhat by the broader spectral lines (since linewidth relates to local T_2^*). Furthermore, in some settings (e.g., imaging of the orbits), this increased spectral separation can be manifest by increasing profound chemical shift artifact (fat–water misregistration). However, this is generally a minor concern in CNS imaging, and may be ameliorated, whether through fat suppression techniques or through pulse sequence changes (increasing the acquisition bandwidth) that reduce the impact of the chemical shift misregistration.

Finally, the RF system becomes less efficient at higher field strengths (higher RF frequencies), such that stronger RF pulses are required. Increasing the amplitude of an RF pulse linearly increases the power deposited in the subject quadratically. Thus there is increased potential for subject heating. The power deposition is generally described in terms of the SAR and since safety limits prohibit exceeding defined SAR thresholds this can lead to compromised scan performance (e.g., the need to decrease TR or reduce flip angle). A variety of solutions exist to address this issue, including modulating the RF flip angle (e.g., VERSE and hyperecho techniques), or invoking parallel imaging to reduce the number of RF pulses applied in the echo train (typically in FSE pulse sequences).

Despite the potential confounds at higher field strengths, it is becoming clear that many, if not all, neuroradiologic applications are considerably enhanced by the migration from 1.5 to 3T and that higher field strengths will become increasingly prevalent in this domain.

In summary, MRI of the CNS offers a broad range of contrast mechanisms reflecting different aspects of the physicochemical microenvironment and probing the functional viability of the tissue at the cellular and microvascular level, as well as emerging interpretation in terms of functional organization and connectivity on a larger-scale systems level. By analogy, when considering these contrast mechanisms, especially T_1 , T_2 , T_2^* , and diffusion, as colors in an artist’s palette, this review has described the principles of neuro-MR in such a way that the tailoring of neuroradiological protocols can be considered as the selection and weighting of these contrasts in the composition of the ultimate image.

REFERENCES

1. Kucharczyk J, Moseley M, Barkovich AJ. Magnetic resonance neuroimaging. Boca Raton, FL: CRC Press; 1994.
2. Stark DD, Bradley WG. Magnetic resonance imaging, 3rd edition. St. Louis: Mosby; 1999.
3. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med* 1999;42:952–962.
4. Sodickson DK, Manning WJ. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. *Magn Reson Med* 1997;38:591–603.
5. Special Issue: 3.0 versus 1.5T imaging. Roberts TPL, editor. *Neuroimaging Clin N Am* 2006;16(2):217–370.
6. Hajnal JV, Bryant DJ, Kasuboski L, et al. Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain. *J Comput Assist Tomogr* 1992;16:841–844.
7. Roberts HC, Roberts TPL, Brasch RC, Dillon WP. Quantitative measurement of microvascular permeability in human brain tumors achieved using dynamic contrast-enhanced MR imaging: correlation with histologic grade. *AJNR Am J Neuroradiol* 2000;21:891–899.
8. Villringer A, Rosen BR, Belliveau JW, et al. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. *Magn Reson Med* 1988;6:164–174.
9. Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. *Magn Reson Med* 1990;14:249–265.
10. Ostergaard L. Cerebral perfusion imaging by bolus tracking. *Top Magn Reson Imaging* 2004;15:3–9.
11. Calamante F, Gadian DG, Connelly A. Quantification of perfusion using bolus tracking magnetic resonance imaging in stroke: assumptions, limitations, and potential implications for clinical use. *Stroke* 2002;33:1146–1151.
12. Detre JA, Leigh JS, Williams DS, Kortesky AP. Perfusion imaging. *Magn Reson Med* 1992;23:37–45.
13. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 1990;87:9868–9872.
14. Reichenbach JR, Venkatesan R, Yablonskiy DA, Thompson MR, Lai S, Haacke EM. Theory and application of static field inhomogeneity effects in gradient-echo imaging. *J Magn Reson Imaging* 1997;7:266–279.
15. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). *Magn Reson Med* 2004;52:612–618.
16. Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 1992;89:5675–5679.
17. Mansfield P. Multiplanar image formation using NMR spin echoes. *J Phys C* 1977;10:L55–L58.
18. LeBihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986;161:401–407.
19. Moseley ME, Cohen Y, Mintonovitch J, et al. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. *Magn Reson Med* 1990;14:330–346.
20. Rowley HA, Grant PE, Roberts TPL. Diffusion MR imaging: theory and applications. *Neuroimaging Clin N Am* 1999;9:343–361.
21. Moseley ME, Kucharczyk J, Asgari HS, Normal D. Anisotropy in diffusion-weighted MRI. *Magn Reson Med* 1991;19:321–326.
22. Basser PJ, Mattiello J, Le Bihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B* 1994;103:247–254.
23. Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol* 1999;45:265–269.
24. Grossman RI, Gomori JM, Ramer KN, Lexa FJ, Schnall MD. Magnetization transfer: theory and clinical applications in neuroradiology. *Radiographics* 1994;14:279–290.