

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 explained 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 T1, T2, and T2* 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 T1 and/or T2 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 T1- and T2*-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
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 (infers 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 1. The art of MRI. Contrast mechanisms provide a palette of colors that protocols can be drawn upon to paint the desired tissue scene.
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 T₂ value of the tissues, since the signal at time TE is attenuated by an exponential factor TE/T₂. 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:

\[ S \propto \rho \exp(-TE/T₂) \]  

(1)

The signal S, then, indeed reflects both proton density and local T₂ values, with the degree of sensitivity to T₂ (the "T₂-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/T₂, thus introducing sensitivity to T₂.

Given the above described sensitivity of spin-echo sequences to the parameter T₂, and the fact that T₂ 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 "T₂-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
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 structures, 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 $256 \times 256$ 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, 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 multi-shot (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...
same acquisition, in which parallel imaging was incorporated (acceleration factor ×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 (Mz) component of magnetization over time, t, is given by Eq. [2], where ρ again relates to the proton density.

\[ M_z \approx \rho (1 - \exp(-t/T_1)). \]  \( \text{(2)} \)

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 influences 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.

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]:

\[ S \approx \rho (1 - \exp(-TR/T_1)). \]  \( \text{(3)} \)

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 T1’s 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-
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 T1-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 Mz 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 (Mz) 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 T1, 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 Mz 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 T1 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 the diagnostic qualities of a T2-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 T2-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 T1 and T2 contrast mechanisms to improve diagnostic utility.

Gd-Based Contrast Agents for Enhancement of T1-Weighted Images

Despite the power and utility of endogenous contrast mechanisms exploiting tissue-specific differences in T1 and T2 values, there are situations in which the diag-
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 10.** $T_1$-weighted image showing hyperintensity post-Gd administration revealing blood brain barrier disruption in this patient with a high-grade glioma.
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,” \( \chi \). 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 \( T_2 \) 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 \( T_2 \) and \( T_1 \)-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 \( T_1 \)-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 Gd\(^{3+} \) moiety extends well beyond the physical location of the Gd\(^{3+} \) ion itself, spin dephasing and signal loss occurs not just in the immediate vicinity of the Gd\(^{3+} \) 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

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**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].

$$S(t) \propto \rho \exp(-TE/T_2^*)$$.

(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]:

$$1/T_2^* (t) = 1/T_2^*[0] + r_2^*[\text{Gd}]$$.

(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 $[\text{Gd}]$ through the surrogate, $\Delta R_2^*$, where $R_2^* = 1/T_2^*$. Thus,

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

(6)

So the signal intensity curve is transformed into a time-varying function, $\Delta R_2^*$, 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
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$^{3+}$/H$_{11001}$ 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 deoxy- 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
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 T₂* (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, 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

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**Table 3**

Summary of T₂*-Weighted Sequences

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Common acronyms</th>
<th>Feature</th>
<th>Key variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient recalled echo</td>
<td>SPGR, GRE, FLASH, FFE</td>
<td>Sensitive to T₂* shortening associated with iron (e.g., hemorrhage). Sensitive to magnetic susceptibility artifact at tissue interfaces.</td>
<td>TE</td>
</tr>
<tr>
<td>Echo planar imaging</td>
<td>EPI</td>
<td>Essentially a single-shot GRE. Highly sensitive to magnetic susceptibility differences. Tendency toward anatomic distortion and blur. Historically, low resolution. Demanding of hardware performance.</td>
<td>TE, ETL, overall acquisition time</td>
</tr>
<tr>
<td>Perfusion</td>
<td>EPI</td>
<td>Uses dynamic imaging with T₂*-sensitivity to track Gd-bolus passing through brain due to “negative enhancing” effect of paramagnetic Gd.</td>
<td>Temporal resolution. Choice of GRE (sensitivity) vs. spin-echo (increased capillary specificity)</td>
</tr>
<tr>
<td>BOLD</td>
<td>EPI</td>
<td>Uses T₂*-sensitivity to track endogenous changes in deoxy- and oxy-hemoglobin concentration (secondary to neuronal activity, or breathhold, or O₂ administration)</td>
<td>TE (for sensitivity), TR (for temporal resolution)</td>
</tr>
</tbody>
</table>

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**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 T₂, since there is no spin echo refocusing.

**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 ×2 shortening the ETL to 64 and reducing the TE to 60 msec; and (c) 256 × 256 matrix with a parallel imaging acceleration of ×2 (i.e., an ETL of 128), resulting in a TE of 65 msec.
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 T2 (since diffusion weighting was effectively created by augmenting a T2-weighted pulse sequence with diffusion encoding gradient pulses).

\[ S \propto \rho \exp(\text{TE}/T_2) \exp(-b\cdot\text{ADC}). \]  

(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 T2, 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/mm²). From such a pair of images with b-values of for example 0 and 1000 seconds/mm², it is possible to eliminate confounding weighting (from proton density, and indeed T2) 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”:

\[ \text{ADC} = \frac{-1}{b} \ln(S_b/S_0). \]  

(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/mm²) 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/mm² is widely used (note typical tissue ADC values are approximately the reciprocal of this, such that the product b.ADC ≈ 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/mm²).](image-url)
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 physico-chemical 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 $\sim$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) in contrast to the sharp resonance of the free water
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]

$$\text{MTR} = (M_s - M_o)/M_o,$$

where $M_o$ 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 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 ($T_1^*$ 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 hyperfine 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