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Studying brain microstructure with magnetic susceptibility contrast at high-field

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Abstract

A rapidly developing application of high field MRI is the study of brain anatomy and function with contrast based on the magnetic susceptibility of tissues. To study the subtle variations in susceptibility contrast between tissues and with changes in brain activity, dedicated scan techniques such as susceptibility-weighted MRI and blood-oxygen level dependent functional MRI have been developed. Particularly strong susceptibility contrast has been observed with systems that operate at 7 T and above, and their recent widespread use has led to an improved understanding of contributing sources and mechanisms. To interpret magnetic susceptibility contrast, analysis approaches have been developed with the goal of extracting measures that report on local tissue magnetic susceptibility, a physical quantity that, under certain conditions, allows estimation of blood oxygenation, local tissue iron content, and quantification of its changes with disease.

Interestingly, high field studies have also brought to light that not only the makeup of tissues affects MRI susceptibility contrast, but that also a tissue's sub-voxel structure at scales all the way down to the molecular level plays an important role as well. In this review, various ways will be discussed by which sub-voxel structure can affect the MRI signal in general, and magnetic susceptibility in particular, sometimes in a complex fashion. In the light of this complexity, it appears likely that accurate, brain-wide quantification of iron will require the combination of multiple contrasts that may include diffusion and magnetization transfer information with susceptibility-weighted contrast. On the other hand, this complexity also offers opportunities to use magnetic susceptibility contrast to inform about specific microstructural aspects of brain tissue. Details and several examples will be presented in this review.

Keywords

brain; magnetic susceptibility; MRI; microstructure; anatomy; myelin; iron

1. Introduction

One of the greatest strengths of MRI is its flexibility to generate a great variety of contrast. Depending on the type of application (i.e. the type of experiment or “pulse sequence” used) MRI contrasts can reveal various tissue properties based on the concentration and chemical and physical environment of water. Both tissue composition and structure can affect the MRI signal, most basically through longitudinal and transverse NMR relaxation processes (called T_1 and T_2 relaxation respectively); in general, this is reflected in changes in amplitude of the recorded signal. Precisely how composition and structure affect the MRI signal depends on the pulse sequence: various tissues properties can be emphasized to differing extent. Examples are techniques that sensitize to water concentration and diffusion, the presence of certain chemical groups, and the magnetic properties of tissues. Especially the latter, achieved with so-called “magnetic susceptibility-weighted (SW)”, or “ T_2^* -weighted” MRI, has seen a recent increase in use because of its exquisite sensitivity at high field and its potential in providing unique, cellular-level information about tissue microstructure. Here, after reviewing the basic mechanisms underlying SW contrast and their dependence on field strength, some promising applications that are uniquely suited for use at high field will be discussed. This is done in the context of several recent reviews that have been written on this topic, e.g. (Reichenbach, 2012, Haacke et al., 2015, Liu et al., 2015, Duyun and Schenck, 2016).

2. Susceptibility-weighted contrast: the basics

SW, or T_2^* contrast can be generated with so-called “free induction decay” (FID) or “gradient echo” (GRE) type pulse sequences which consist of a single radio-frequency (RF) signal excitation pulse followed by gradient encoding and signal acquisition over a range of “echo times” (TEs), i.e. delays after the RF excitation. The measured signal is generated by the fraction of water hydrogen proton (^1H) spins (below abbreviated as “spins”) that is polarized by static (main) magnetic field, also called B_0 . Since this fraction is proportional to B_0 , measurement sensitivity (indicated by signal-to-noise ratio or SNR) improves at high field. After image reconstruction there is both an amplitude (also called magnitude) and phase associated with each image element (or “voxel”). The phase is reflective of the voxel’s average ^1H Larmor frequency, whereas magnitude reflects the density of spins and the variation in Larmor frequencies in the voxel. Because Larmor frequencies represent local fields, and local fields result from a tissue’s magnetic structure, signal phase can together with signal amplitude, provide information about brain structure.

2.1. Various spatial scales of magnetic structure

Because of sub-voxel magnetic field variations, the SW MRI signal decays over a time frame of milliseconds to tens of milliseconds, depending on the strength of the variations. This is because the spins within an MRI-resolved volume element (voxel) experience a range of local fields, and as a result precess at different Larmor frequencies and, over time, lose coherence. This signal decay is generally modeled as a single-exponential process, indicated by time constant T_2^* , or decay rate R_2^* ($R_2^* = 1/T_2^*$). The actual, precise shape and decay rate depend on the local (within-voxel) field distribution. Local field variations

can result from magnetic sources from water and non-water molecules, including dipoles from electrons and nuclei, and molecular diamagnetism from the orbital motion of electrons. The distribution of these sources and their fields is generally non-uniform and has structure at a range of spatial scales (Fig. 1). At the smallest scale, there are individual magnetic dipole fields from e.g. ^1H nuclei from water and other molecules. These can affect the field at the sensing spin through dipolar coupling (Fig. 2). While these dipole fields only minimally contribute to magnetic susceptibility, the dipolar coupling mechanism can contribute substantially to R_2^* (and also to the rate of longitudinal relaxation R_1). Because of their fast dynamics, dipolar contributions are considered “non-refocusable” with RF refocusing pulses, and indicated by “ R_2 ” relaxation, whereas refocusable contributions are indicated by R_2' ($R_2^* = R_2 + R_2'$). The latter result from magnetic interactions with slower dynamics and operating at larger spatial scales. At scales larger than the sub-nanometer scale of dipolar interactions, there are the fields from the diamagnetic susceptibility of molecules resulting from electron orbital motion (Fig. 2). There may be isolated paramagnetic sources as well (e.g. unpaired electron spins in ferritin iron). At even larger scales, there is tissue magnetic structure associated with large molecular assemblies such as membranes, neurofilaments, dendrites and fibers, cells, and fiber bundles. Any of these larger scale sources may contribute to R_2^* , either through irrefocusable (R_2) or refocusable (R_2') contributions (or both).

2.2. Various time scales of magnetic dynamics

Although the fields associated with a tissue’s magnetic structure are reflected in the precession frequency of spins and thus their instantaneous phase, one should realize that a voxel’s phase and frequency represent averages over a great many protons: this average frequency (or phase) needs not be an accurate reflection of the voxel-averaged field. This has several reasons, one is the fact that water density (and its visibility by NMR) varies over biological tissues, even within a voxel, resulting in a biased, or weighted sampling of the magnetic field, and another is that the average of the spins’ phases is not generally identical to the phase of the average signal (see section on microstructural order). It furthermore should be noted that in general, neither the location of the sensors (the spins), nor that of the magnetic sources is static. Rather, there are dynamics that vary with spatial scale, with fastest dynamics occurring at the smallest spatial scale (Figure 1). The time constant (τ) of the dynamics has relevance for their effect on MRI contrast. For example, efficient dipolar coupling and T_1 relaxation occurs when τ approaches $1/\omega$, with ω the Larmor angular frequency (Bloembergen et al., 1947, 1948). For Larmor frequencies typical of clinical MRI, this may occur for rotational motions of intermediate-size molecules.

For larger scale magnetic structure associated with large (macro-) molecules and molecular structures such as membranes, it is the slower dynamics that are relevant. For example, diffusion over spatial scales R typical of the Larmor frequency variations (ω) associated with these structures may occur on the time scale of T_2^* relaxation (milliseconds), and therefore affect this relaxation rate. Generally, diffusion increases T_2^* (reduces R_2^*) due to averaging of field effects and reducing the loss in coherence due to phase spread (resulting from frequency variation). An important concept in this regard is the so-called “static-dephasing regime” (Weisskoff et al., 1994, Yablonskiy and Haacke, 1994, Kiselev and

Posse, 1999), which represents a condition in which diffusion is small and does not significantly affect R_2^* . In contrast, for diffusion constants D greater than ω^*R^2 , we enter a “motional narrowing” regime, in which diffusion will reduce R_2^* . For the smallest distribution scales of iron and myelin in the brain (e.g. isolated ferritin particles, and isolated fibers) this condition is generally met, resulting in a diffusion-mediated reduction in apparent R_2^* (Duyn and Schenck, 2016).

3. Tissue contributions to magnetic susceptibility

Most constituents of biological tissues have a volume magnetic susceptibility that is very close to that of water and therefore do not contribute to anatomical contrast in SW MRI (Schenck, 1996, Duyn and Schenck, 2016). In healthy brain, major contributors to magnetic susceptibility variations are storage iron (in ferritin and hemosiderin), iron in deoxyhemoglobin (found primarily in the venous vasculature), and myelin. Their concentrations vary substantially over the brain, leading to contrast in phase and amplitude of GRE MRI signal (Fig. 3).

Typically, iron content of brain tissues varies between 0–200 μg iron per gram tissue and at the highest level contributes about +0.2 ppm to tissue magnetic susceptibility. Higher levels (reaching 500 $\mu\text{g/g}$ or higher) are possible in diseases such as aceruloplasminemia, or neurodegeneration with brain iron accumulation (Schipper, 2012, Ward et al., 2014). Deoxyhemoglobin is at its highest concentration inside venous vessels and within the choroid plexus, where its contribution to the magnetic susceptibility may be as high as +0.5 ppm. Away from large vessels, the relative blood volume is generally only a few percent, and consequentially the contribution of deoxyhemoglobin to tissue magnetic susceptibility is much reduced.

Myelin concentration varies strongly over the brain and is highest in major white matter fiber bundles in the brain and spinal cord where myelin solids take up a 15–20 % fraction of the tissue weight. In these tissues, it may contribute -0.04 ppm to the magnetic susceptibility. In addition, in areas with highly aligned fiber orientation, the magnetic susceptibility itself varies by about 0.02 ppm with orientation in the magnetic field (see below) (Lee et al., 2010, Li et al., 2012, van Gelderen et al., 2013).

4. Field dependence of T_2^* contrast

Because of the fact that nuclear dipole strength is field independent, the field dependence of the contribution of dipolar coupling to R_1 and R_2^* (i.e. R_2) is generally limited (Bloembergen et al., 1948). For most brain tissues R_2 increases slowly with field strength, ranging from about 10–15 s^{-1} for grey and white matter at clinical field strengths. In contrast to direct dipolar effects, molecular diamagnetism and paramagnetic inclusions such as ferritin can extend over a long range and increase with B_0 field strength. Thus, at high field, R_2^* contrast between tissue types increases and furthermore becomes dominated by magnetic susceptibility effects. Combined with SNR gains with field strength, this makes SW MRI a promising application for high field studies of the brain. In fact, R_2^* -based fMRI, with contrast based on the susceptibility effects of deoxyhemoglobin in the vasculature, was

one of the main applications driving the push to higher field (Duong et al., 2002, Ugurbil, 2012). It was soon realized, that T_2^* contrast at high field also provided unique sensitivity for study the venous vasculature (for review see (Haacke et al., 2009)) and structural details not only between but also within grey and white matter (Li et al., 2006, Duyn et al., 2007a). Much of the latter contrast can be attributed to variations in the concentration in iron and myelin (Fukunaga et al., 2010a) whose effect on R_2^* increase with field strength (Figure 4). For example, R_2^* has been found to increase close to linearly with iron concentration, and the proportionality constant increases linearly with field strength. $R_2^* = (f^* B_0^* 10^{-3}) [Fe] + g^* B_0 + h$, with $f = 48$, $g = 1.6$, and $h = 8.5$, with B_0 in Tesla, $[Fe]$ the iron concentration in microgram iron per gram tissue (ppm weight fraction), and R_2^* in s^{-1} (Yao et al., 2009), consistent with dependence of R_2^* on iron found at 3 T (Gelman et al., 1999, Zheng et al., 2013), 4.7 T (Sun et al., 2015) and 7 T (Langkammer et al., 2012, Deistung et al., 2013, Stuber et al., 2014, Ropele and Langkammer, 2016).

5. Effects of microstructural order

By its nature, the dipolar field pattern around a magnetic point source is not isotropic (i.e. the field looks different along lines that go through the source at different directions). Because of this, even isotropic magnetic structures (e.g. uniformly magnetized spheres) will have a non-isotropic field distribution around them. For non-spherical structures, internal and external fields become dependent on the structure's orientation in the main magnetic field. For example, in long cylinder oriented with angle θ relative to the magnetic field B_0 , both the internal field as well as the strength of the external field distribution show a sine-squared dependence on θ . As a result, both MRI phase and R_2^* generally depend on θ . Nevertheless, microscopic magnetic structures within a tissue will often exist at many orientations within a voxel, and therefore the effect of tissue orientation on a voxel's R_2^* and frequency will be small. However, this is not true in general, and there are a number of examples of human tissues that have shown orientation dependence of both R_2^* and local frequency, including muscle, tendon, bone, kidney, and white matter fibers (Hwang and Wehrli, 1995, Boesch et al., 1997, Wiggins et al., 2008b, He and Yablonskiy, 2009, Sati et al., 2013, Dibb et al., 2016). In many of these cases, substantial magnetic order exists on both the cellular and molecular scale.

To understand the effect of microstructural order on susceptibility contrast, we have to consider both the distribution of field sources (magnetic moments of nuclei and their orbiting electrons) as well as the distribution of field sensing spins (the fraction of spins that is polarized by the B_0 magnetic field and responsible for the MRI signal). In addition, as mentioned above, their dynamics are relevant. Distribution of sensors and sources are generally correlated, e.g. areas with increased density of sources have decreased density of sensors. Thus, microstructure can affect both the field distribution and the way it is sensed by spins through their Larmor frequency. In the case of net orientational order within a voxel, both R_2^* and phase become dependent on orientation of the tissue in the magnetic field (Fig. 5; see also Fig. 8).

All in all, the complex field distributions associated with tissue magnetic microstructure leads to complex relaxation behavior, which only in approximation can be considered

exponential with an apparent R_2^* that depends on the part (TE range) of the signal decay curve that is analyzed. Only with substantial simplifications and assumptions can we estimate the effect of tissue microstructure on susceptibility contrast.

In a first simplification, we can consider that the phase of the voxel-averaged signal is equal to the average of phases of individual spins (this according to the classical view of nuclear magnetization, while ignoring quantum mechanical aspects). This is approximately true when the phase difference between spins is less than π , which turns out to generally be the case for typical TEs and field strengths used in MRI of biological tissue, even in cases of focal (small) paramagnetic sources such as ferritin. An exception may be in the vicinity of vasculature with a high concentration of deoxyhemoglobin in red blood cells (see below). The reason that this approximation is valid is that because of effects such as motion, exchange and diffusion of the sensing spins (and possibly the motion of the sources), spins rapidly traverse the inhomogeneous field around magnetic sources and this diminishes their phase differences. Second, we can assume that the average field sensed by a spin from many magnetic sources equals the field associated with an averaged source (Durrant et al., 2003). As a result, we can consider the average magnetic environment (AME) for the purpose of calculating a spin's phase and frequency shift. Third, we can assume the AME to be a smooth function, owing to the extensive amount of averaging occurring when considering the effects of all sources and all sensors. In fact:

- There are about $3 \cdot 10^{19}$ water molecules within a 1 mm^3 voxel, all of which are magnetic field sources. The number of effective sensors is smaller (only a tiny fraction of water protons is polarized with the B_0 field) but their numbers remain very high ($\sim 10^{15}$).
- Even within a 1 mm section of a typical axon, there are more than 10^{13} water molecules.
- Most of these water molecules reorient on a timescale of $< 10^{-10}$ s, and diffuse over $> 10^3$ molecular diameters within 1 ms.
- Thus, on the millisecond time scale of typical TE values, seen from the sensing spins frame of reference, there is rapid redistribution of field sources.

Based on this, we can consider the AME of a water proton surrounded by water molecules to be smooth and spherical (Fig. 6). Addition of a random distribution of spherical sources (e.g. ferritin particles), can be modeled as a secondary (smooth and spherical) AME, whereas for uniformly oriented ellipsoidal particles this AME is smooth and ellipsoidal (Fig. 7). In these simple cases, the effect of a smooth AME on the voxel-averaged phase can be taken into account with demagnetization factors (Durrant et al., 2003). For long, elongated cylinders, this would result in a sine-squared dependence of phase/frequency on the orientation θ relative to B_0 (He and Yablonskiy, 2009, Duyun and Schenck, 2016).

6. Microstructural order of contributors to magnetic susceptibility in brain tissue

6.1. Blood vessels

In healthy tissue, paramagnetic deoxyhemoglobin is constrained to the cerebral vasculature, whose architecture has orientational order at various scales. For example, in human neocortex, there is a relatively high density of veins that run parallel to the pial surface; these veins typically have diameters of one to several millimeters and their susceptibility effects generally involve multiple MRI voxels. At the sub-voxel scale, there are principal intracortical venules (diameter $\sim 100 \mu\text{m}$) that branch off of the pial veins at right angles and traverse the cortical depth in a direction that is approximately perpendicular to the surface (Reina-De La Torre et al., 1998). At the next smaller scale is the cortical capillary network (capillary diameter $5\text{--}10 \mu\text{m}$). While capillary density varies with cortical depth, capillary network architecture is extremely tortuous, generally with limited orientational order (Reina-De La Torre et al., 1998).

When modeled as a long cylinder, a single vessel (containing deoxyhemoglobin) generates a field pattern in its surround with a strength that depends as $\sin^2\theta$ on the angle θ with B_0 . As shown previously, the effect of this field around a cylinder (or a group of parallel cylinders) on R_2^* and phase is dependent on diffusion (Yablonskiy and Haacke, 1994), but nevertheless maintains a $\sin^2\theta$ dependence. Thus, because of the orientational order of venules (and possibly a limited order of capillaries) one would expect to see an orientation dependent effect on SW MRI. While a clear orientation dependence of SW-fMRI has been reported for pial (and larger) veins (see e.g. (Menon et al., 1993)), this is not the case for smaller vessels such as venules and capillaries. In part, this may be due to the relatively small fractional blood volume (a few %) within grey matter, a lower deoxyhemoglobin concentration compared to pial veins, and a limited orientational order of these vessels. In contrast, studies of heart muscle (blood volume $> 10\%$) with and without intravascular contrast agents have observed an orientation dependence of R_2 (Vignaud et al., 2006) and R_2^* (Kohler et al., 2003) respectively.

6.2. Myelinated nerve fibers

A number of studies have shown a correlation between white matter fiber orientation on one hand and R_2^* and phase/frequency on the other (Wiggins et al., 2008a, He and Yablonskiy, 2009, Bender and Klose, 2010, Denk et al., 2011, Lee et al., 2011, Sati et al., 2013), and this dependence becomes particularly strong at high field (Figure 8). This phenomenon has been attributed to the myelin sheath (Lee et al., 2012, Li et al., 2012), a cylindrical structure surrounding axons that is more diamagnetic than water. The effect is most prominent in voxels within major fiber bundles, where the strong alignment of axons (and their myelin sheath) leads to a high orientation order. As is the case with blood vessels, this can cause a sine-squared dependence of R_2^* on orientation θ relative to B_0 . Consideration of AME and demagnetization factors predicts the Larmor frequency of water both within axons and within the interstitial space between them to show this $\sin^2\theta$ dependence as well (Duyun and Schenck, 2016); however, experimental data suggest a more complex signal behavior.

Experimental SW MRI data has shown that in major white matter fiber bundles, gradient-echo signal exhibits a complex amplitude decay with apparent multi-exponential characteristics (Hwang et al., 2010, van Gelderen et al., 2012). Theoretical modeling, simulations, and experimental data (Wharton and Bowtell, 2012, Sati et al., 2013) has indicated that this may be caused by a susceptibility that itself is anisotropic: the susceptibility of myelin may be more diamagnetic when fiber is perpendicular to the magnetic field compared to when it is parallel with the field. This phenomenon, well known in highly ordered materials such as crystals, can be attributed to the molecular order of the lipid membranes that make up the myelin sheath (Boroske and Helfrich, 1978, Scholz et al., 1984, Lounila et al., 1994). Dedicated experiments at 7 T have shown that this phenomenon is relevant for white matter as well (Figure 9). This anisotropy has been shown to render the field inside axon different than outside or within the myelin sheath (Wharton and Bowtell, 2012, Sati et al., 2013, Sukstanskii and Yablonskiy, 2014). Because of limited mixing of water between these compartments, owing to the restricted permeability of the myelin sheath, these field differences can lead to the presence of distinct frequency components in the SW MRI signal. Again, these frequencies can be estimated by considering the AME (Duyun and Schenck, 2016). The prediction of the R_2^* of these components is more complicated because of their dependence on diffusion as well as the precise geometry and distribution of myelinated axons.

One interesting consequence of the unique magnetic architecture of white matter is the possibility to estimate relative size of the myelin, interstitial, and axonal water compartments from multi-exponential fitting, with the important target being the size of the myelin water compartment (Li et al., 2015b, Nam et al., 2015). A thus obtained estimate of myelin water fraction may be used as proxy for tissue myelin content, with relevance to demyelinating diseases (Laule et al., 2008, Li et al., 2015b). Additionally the sensitivity of SW MRI to the structural arrangement of myelin may be exploited to detect pathological changes of myelin integrity (Yablonskiy et al., 2012).

6.3. Iron

Iron is one of the main contributors to the susceptibility of brain tissue, and in healthy tissue it is primarily found in the storage protein ferritin (Schenck and Zimmerman, 2004). In contrast to the myelin sheath, ferritin particles have an isotropic structure; they are spherical with a diameter of about 10 nm. Therefore, their effect on SW contrast is independent on their orientation in the magnetic field. Their distribution in the brain however may be structured and anisotropic: for example they may be arranged in non-spherical clusters or align with structures such as fibers or blood vessels (LeVine, 1991, Connor et al., 1992) and this may render their effect on SW MRI anisotropic. This anisotropy may originate directly from the effects of particle distribution on the sensed fields, but also from restricted, anisotropic diffusion around fibers. While this may result in some orientation dependence of the contribution of iron to susceptibility contrast no clear experimental demonstration of this putative phenomenon has been reported so far.

7. Effects of microstructure on the quantification of magnetic susceptibility contrast

A major, rapidly developing application of SW MRI is the quantification of tissue magnetic susceptibility, also called quantitative susceptibility mapping or QSM (for recent review, see (Deistung et al., 2016)). In this approach, tissue susceptibility values are calculated from the magnetic field distribution in the brain, which is inferred from the phase of the SW image. In principle, QSM values may be more reproducible and comparable (within and between different brains, across field strengths) than R_2^* and frequency, as they are less dependent on head orientation in the field and non-local effects associated with susceptibility-induced field distributions. For this reason, they may be scientifically and clinically more useful. In brain regions where a single contributing source to tissue susceptibility dominates, QSM may allow estimation of the local concentration of that source. For example, in the iron-rich regions of the basal ganglia, QSM was found to be quite reproducible, and may rival the sensitivity of R_2^* in determining local iron content (Santin et al., 2016). QSM furthermore may not be as sensitive as R_2^* (and R_2) to tissue water content, which may be quite variable in pathology. In addition, in areas where the contribution of deoxyhemoglobin is small, comparison of susceptibility values and R_2^* , possibly with incorporation of an estimate of myelin content from magnetization transfer (MT) contrast, may allow distinguishing between and quantification of iron and myelin (Schweser et al., 2011). Recently, rapid MT methods have been proposed that can be used at high field (Dortch et al., 2013, van Gelderen et al., 2016b), and allow estimation of myelin content with minimal contamination of confounding effects from iron (Jiang et al., 2017). Combined with QSM, these methods would aid quantification of both iron and myelin.

Nevertheless, QSM has its own drawbacks, some of which may be resolved with further development. Importantly, QSM methods have, until recently, ignored the contribution of microstructure to MRI phase and frequency and this may be a problem in tissue with substantial microstructural order such as white matter. The non-spherical shape of water compartments in white matter (He and Yablonskiy, 2009) together with the generally unaccounted for anisotropic nature of susceptibility in white matter, can significantly affect the accuracy of QSM (Wharton and Bowtell, 2015). Proper accounting for these effects may require additional measurements, such as estimation of fiber orientation from diffusion weighted MRI, acquisition of phase maps at multiple head orientations, or multi-component analysis of the T_2^* decay curve (see above). Another issue with QSM is its dependence of susceptibility values on the particular type of reconstruction used. Future development should aim at standardizing across the large variety of reconstruction methods currently in use (Santin et al., 2016).

8. Microstructural effects on other MRI contrasts

MRI, and the phenomenon of NMR on which it is based, are inherently sensitive to structure over a range of spatial scales, including the molecular scale. In fact, NMR spectroscopic techniques have long been and remain widely used for structural investigation of small and large molecules (e.g. proteins (Bax, 1989)), as well as tissue structures at the larger scales of

membranes (Zimmerberg and Gawrisch, 2006), and nerve fibers (Eliav and Navon, 2016). Generally these techniques have been based on non-water nuclei (generally nuclei other than ^1H) and often applied under particular conditions (e.g. small, purified samples, highly uniform field, spinning of the sample etc.), and are not or not generally applicable to in-vivo MRI and spectroscopy. The NMR spectroscopic techniques that can be applied in-vivo generally have poor ($\sim\text{cm}^3$) spatial resolution, resulting in extensive averaging that obscures all but the most general structural information.

In contrast, the spins that generate the signal in MRI are sensitive to tissue structural aspects in a more indirect manner, for example through diffusion and exchange processes that may affect signal properties such as amplitude, resonance frequency, and apparent T_1 , T_2 , T_2^* . This sensitivity is to some extent present in all MRI techniques, and needs to be accounted for accurate interpretation. With dedicated pulse sequences, sensitivity to certain biophysical processes may be enhanced.

Sensitization to diffusion with pulsed field gradients in diffusion-weighted MRI has long been used to study structural tissue aspects at the cellular scale and has become clinically important to detect inflammatory processes through their effect on cell swelling. Owing to anisotropic diffusion in white matter fibers, it also allows the study of white matter fiber orientation and geometry, and in this regard, when combined with SW MRI may be helpful in improving accuracy of QSM and the distinction between cellular compartments. Most recently, a number of new diffusion methods have been developed that allow estimation of axonal density and mean axonal diameter in brain and spinal cord (Assaf et al., 2008, Alexander et al., 2010, Duval et al., 2015, Huang et al., 2015, Benjamini et al., 2016, Xu et al., 2016). Combined with information about the density of myelin in the brain from proton density or magnetization transfer (MT) studies (see below), information about the myelin g-ratio (thickness of the myelin sheath relative to axonal diameter) may be obtainable (Stikov et al., 2015, Duval et al., 2016).

Axonal fiber geometry at sub-voxel scales (including aspects such as orientation, size and distribution) is not only reflected in diffusion and T_2^* contrast (above), but may also affect MT, T_2 , and even T_1 . For example in white matter, not only T_2^* decay, but also T_1 and T_2 have shown multi-exponentiality, with the fastest relaxing component attributed to myelin water (Laule et al., 2007, Labadie et al., 2014). In the case of T_1 , a more general interpretation is that bi-exponential decay is inherent to a system of exchanging spin pools that evolves from a condition with non-equilibrium longitudinal magnetizations (Gochberg et al., 1997, Prantner et al., 2008). In white matter, the relevant pools are those of non-water ^1H protons (e.g. protons on lipid and protein in myelin) and of water ^1H protons. Observation of the signal evolution characteristics after a saturation or inversion pulse offers an opportunity to measure exchange kinetics, which in turn may report on tissue structural aspects such as thickness of the myelin sheath size (Harkins et al., 2016). In this regard, MT and T_1 experiments geared at investigating myelin microstructure may uniquely benefit from high field due to the increased T_1 of myelin protons (van Gelderen et al., 2016a, b).

In tissues with high orientational order, T_2 may become orientation dependent due to a prevalent direction of dipolar coupling (Henkelman et al., 1994). This has been observed for

water protons in tendons, peripheral nerve, and cartilage (Henkelman et al., 1994, Xia, 2000, Chappell et al., 2004, Momot et al., 2010), as well as for lipid methylene protons in myelin (Pampel et al., 2015). The latter may introduce some orientation dependence in MT and T_1 relaxation experiments as well.

9. Opportunities at high field

The increased SNR and altered contrast at high field offer unique advantages for the study of brain tissue composition and (micro-)structure. Increased SNR and contrast allow reduction of the voxel volume, thereby lowering the spatial scale of structures that can be directly visualized. The achievable resolutions are somewhat dependent on type of contrast weighting, and the available motion-free scan time. Typically, for SW MRI at 7 T, resolutions of about 300 μm are feasible, allowing visualization of e.g. cortical laminar structure (Duyun et al., 2007b) and small structures in mid-brain and brainstem (Abosch et al., 2010, Cho et al., 2010, Keuken et al., 2013, Bianciardi et al., 2015, Chandran et al., 2016). One potential disadvantage of the increased susceptibility contrast and R_2^* relaxivity at high field is excessive signal loss in tissues with high iron levels, such as the basal ganglia.

Clinically, improved visualization of cortical dysplasia, MS lesions (Figure 10), and small hemorrhages are among the attractive advantages of SW MRI at 7 T (Madan and Grant, 2009, Bian et al., 2014, Absinta et al., 2015, Mainero et al., 2015, Absinta et al., 2016). Advantages of SW-MRI at high field for many other diseases have been reported or are currently being explored, and this area of research is expected to grow substantially with the increased availability of clinical high field systems (for review see e.g. (van der Kolk et al., 2013, Trattnig et al., 2016)). Outside SW MRI applications, T_1 -weighted studies of MS lesions (Figure 11) and cortical myelination patterns in normal brain (Lutti et al., 2014) benefit substantially from the increased resolution available at 7 T (Dinse et al., 2015) and lower T_1 values in these applications can be interpreted as a sign of reduced myelin content. High field MRI also allows resolution increases for vascular imaging (Koopmans et al., 2008). At high field, resolutions at the scale of cortical laminae (several 100's of μm) may also be possible for fMRI, although the vascular point-spread function may be a limiting factor in resolving lamina-specific activation patterns (Polimeni et al., 2010). Another application benefitting substantially from high field is vascular MRI, where SNR and contrast increases allow improved visualization the fine-grained architecture of intracranial arteries and veins (Koopmans et al., 2008, De Cocker et al., 2016).

As mentioned above, at high field strength, changes in contrast occur that may be particularly useful for the study of microstructure that escapes direct visualization. For example, the field variations associated with tissue magnetic microstructure increase linearly with field, rendering SW MRI more sensitive to it. This facilitates the investigation of fiber orientation and myelin fraction with methods such as frequency difference mapping (Wharton and Bowtell, 2013) and multi-exponential fitting to the signal decay curve (Li et al., 2015a). Combined with the increased spatial resolution, this improved microstructural sensitivity should aid in the detection of subtle tissue changes, such as small brain tissue lesions that may occur in pathologies such as MS and traumatic brain injury.

High field also offers the potential to jointly quantify iron and myelin in brain tissue. The ability to independently estimate tissue myelin content with MT contrast, which can be efficiently generated at high field (van Gelderen et al., 2016b), potentially combined with a fiber orientation estimate from diffusion-weighted MRI, offers opportunity to distinguish between the contributions of iron and myelin to T_2^* contrast.

10. Conclusion

High field MRI has led to improved visualization of brain anatomy with a spatial resolution of about 300 μm , facilitating the detection of focal pathology. In very specific cases, and specific tissues, structural aspects within this resolution, ranging from the molecular to the sub- and supra cellular scales, may be probed. A prominent example is the study of cellular-level white matter structure with magnetic susceptibility contrast.

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Highlights

High field MRI is particularly sensitive to tissue magnetic susceptibility variations

Both tissue composition and structure below the MRI resolution affect contrast

The provides the opportunity to extract cellular-scale structural information

Quantification of tissue constituents needs to take structural effects into account

Figure 1. Illustration of range of temporal and spatial scales relevant for the MRI study of brain structure. Below the smallest MRI-resolved scale of about 100 μm , there are many smaller scales of structural features that can affect the signal. These features are dynamic over a large range of time constants, with nanoscale molecular features reaching motional time constants on the sub-nanosecond scale. The effects of exchange are omitted from this overview.

Figure 2.

Various scales of magnetic fields can MRI contrast: at the smallest scales, ^1H dipoles on various molecules, whose magnetic field falls off rapidly with distance, interact with nearby water ^1H dipoles that generate the MRI signal. Larger scale fields from electron spins and orbits associated with molecules can affect the MRI signal some distance away.

Figure 3.

Example of brain structure directly visualized with SW MRI. The magnitude and phase of the SW MRI signal show distinctly different contrast, and primarily affect the field variation versus the average field within a voxel. Striking phase contrast is seen in the major fiber bundles, attributed to a combination of myelin density and fiber orientation. Iron and myelin stains (reproduced from (Drayer et al., 1986) and the Human Brain Atlas from Michigan State University respectively) are shown for comparison. The iron rich regions of Putamen (P), Globus Pallidus (G), and Caudate (C), are associated with SW MRI signal loss, as is apparent from the low intensity in the MR magnitude image.

Figure 4.

R_2^* contrast in ex-vivo brain sample from human occipital lobe. In cortical grey matter and subcortical white matter, R_2^* contrast results from variations in the concentration of iron, and to a lesser extent myelin. Reproduced from (Fukunaga et al., 2010b). The (Perls') iron stain reflects primarily ferric iron in the storage protein ferritin, whereas the Luxol Fast Blue myelin stain reflects myelin's lipoproteins.

Figure 5.

Dependence of magnetic field on distribution of magnetic field sources, comparing spherical particles aligned in rows aligned with the field (left) or perpendicular to the field (right). Field distribution (and R_2^*) is dependent on particle (source) distribution. While average magnetic field in voxel is insensitive to particle distribution, this is not true for the average field sensed by spins outside the particles.

Figure 6.

In pure water, the AME is spherical. Due to the rapid isotropic reorientation and motion of the water molecule, each proton sees a smooth, isotropic distribution of field sources (i.e. magnetization) with a relative sparsity in the exclusionary zone within the van der Waals radius. For purpose of calculating the average field sensed by the proton, its AME can be modeled as uniform outside a spherical cavity. Strictly speaking, the AME contains a secondary region contained in a spherical shell representing the (host) water molecule's van der Waals volume, which does not affect the average sensed field. Note that this model ignores effect of electron orbits (which is taken into account into water's chemical shift), and effects such as hydrogen bonds and the self-ionization of water.

Figure 7.

2D Simulation of AME in water containing randomly distributed magnetic particles. AME is sensitive to particle shape: it is spherical for spherical particles, and ellipsoidal for uniformly oriented ellipsoidal particles. Lines in right column reflect horizontal and vertical intensity profiles. Left column images are shown at larger spatial scale.

Figure 8.

Demonstration of contrast dependence on microscopic (sub-voxel) white matter fiber orientation. SW MRI was performed in-vivo at 7 T in marmoset brain at two head orientations relative to B_0 . Both R_2^* (top row) and frequency (bottom row) strongly depend on fiber orientation. For reference, fiber orientation is indicated with color coded diffusion tensor image (DTI) on the right. Figure reproduced from (Sati et al., 2013).

Figure 9.

Demonstration of dependence of magnetic susceptibility on white matter fiber orientation at 7 T. Spinal cord samples were cut in cubes, after which orientation dependence of contrast was demonstrated by rotating selected cubes. Color coded DTI images indicate microstructural orientation (top row). Frequency images (bottom row) show an effect on microstructural orientation inside and outside the rotated cubes, with the outside effects (black arrows) indicating a change in susceptibility. Figure reproduced from (Lee et al., 2010)

Figure 10.

The increased resolution of SW MRI at 7T allows improved visualization of MS lesions. Both magnitude and phase show detail within highlighted lesion indicating the presence of deoxyhemoglobin in a vein that traverses the lesion, myelin loss, and an increase in iron at the outer edges of the lesion. Microstructural tissue aspects (e.g. compromised integrity of the myelin sheath) may be reflected in the contrast as well. Image resolution 0.25x0.25x1 mm, scan time 9 minutes; Image courtesy of Pascal Sati and Daniel Reich, NINDS, NIH.

Figure 11. High resolution T_1 -weighted MP2RAGE at 7T, allowing detailed visualization of MS pathology. Areas of low intensity (circles) indicate myelin loss, a hallmark of MS lesions. Image resolution 0.35 mm isotropic, scan time 56 minutes; Image courtesy of Pascal Sati and Daniel Reich, NINDS, NIH.