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Study of Brain Anatomy with High Field MRI: Recent Progress

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Abstract

Recent developments in high field MRI technology have led to improved contrast and resolution and are opening up new possibilities for the study of human brain anatomy. In particular, techniques sensitized to magnetic susceptibility contrast provide particular advantages at high field that have allowed visualization of brain structures that have been difficult to detect with conventional technology. In this review, some of these developments and techniques will be discussed, and an attempt will be made to interpret magnetic susceptibility contrast based on recent studies.

Keywords

high field MRI; magnetic susceptibility; brain; contrast; iron

INTRODUCTION

Ever since its introduction into clinical practice three decades ago, MRI has continuously developed. Major improvements have occurred in a number of areas, and together they have increased the ability to detect subtle variations in brain anatomy in health and disease.

One area of improvement has been MRI magnet technology, which has allowed stronger, more compact and less costly magnets to be built. Whereas early MRI magnets had field strengths at or below 1 T, state of the art commercial systems now reach 7 T, and experimental systems with field strengths as high as 11.7 T are currently being developed. These stronger magnets have led to improvements in intrinsic sensitivity (expressed as signal-to-noise ratio or SNR) and, in specific cases, in image contrast.

Significant improvements have also been made in the area of detector technology. Multichannel detectors, with as many as 128 detector elements, have led to further SNR increases. In addition, these novel detectors allow acceleration of the image acquisition process, reducing the study time as well as the detrimental effects of motion on image quality.

A third area of improvement has been the use of novel contrasts through manipulation of the MRI signal. Where initial MRI studies primarily used proton density, T_1 and T_2 contrast, today's MRI exam may exploit a number of other contrast mechanisms including flow, diffusion, and T_2^* .

The increases in resolution and contrast provided with these novel technologies are making it possible to reveal structural features in human brain that were difficult or impossible to detect

previously. In addition, early clinical applications show that high field MRI holds significant promise for the study of a range of diseases (1–6). In the following we will review some of the latest technology in detail and highlight recent progress in visualizing detailed structures in human brain.

DETECTOR ARRAYS AT HIGH FIELD

Loop coils placed on the object's surface have been long known to locally improve SNR as compared to volume coils (7). The underlying principle can be understood when considering that MRI localizes the NMR resonance signal, but not the thermal noise, and that noise pickup of surface coils is limited to a relatively small region of the object. Placement of an array of surface coils around the object, combined with appropriate, location specific signal combination during image reconstruction, would extend the SNR improvements to larger areas (8). However, it was not realized until more recently that with appropriate detector design, surface coils arrays can improve SNR in any area in the object (9,10). Practical realization of this concept was enabled with the development of ultra-low impedance pre-amplifiers that minimize coil-to-coil inductive coupling. Optimized arrays have many small loop coils placed in close proximity to the brain (see example in Fig. 1), and can provide 2–6 fold increases in SNR (11,12). At 3.0 T, 32 channel arrays allow an SNR of about $25 \text{ s}^{-0.5} \mu\text{l}^{-1}$ in most cortical areas (assuming gradient echo acquisition and $T_2^* = 50 \text{ ms}$, $T_1 = 1.5 \text{ s}$)

Because the intrinsic SNR increases close to linearly with field strength, experimental high-field scanners, operating at fields from 7.0 T to 9.4 T (13–15), allow a two- to three-fold improvement in image SNR over 3.0 T systems. This advantage is somewhat tempered by the reduced T_2^* and increased T_1 at high field. A small additional gain comes from a synergistic effect from high field and array-type detectors, since at high field, coils can be made smaller before coil noise limits the achievable SNR gains. The combined advantages of these techniques allow an order of magnitude increase in average SNR over birdcage coils at 3.0 T and reduction of the voxel volume to below $0.1 \mu\text{l}$ (16) (see Figure 2).

A further advantage of array detectors is the fact that they enable image acceleration through parallel imaging techniques (17,18). This is a particularly useful feature to achieve high resolution at high field, which requires more data to be acquired and therefore longer scan times.

MRI CONTRAST AT HIGH FIELD

A major challenge of high-field MRI is the generation of strong tissue contrast that is spatially uniform. For example, MRI pulse sequences that work well at low field, often do not work as well at high field, primarily because of spatial variation in magnetic and electromagnetic fields (B_0 and B_1 amplitude) and restrictions on RF power deposition. As a result, image intensity and contrast at high field may be spatially highly non-uniform. These issues limit the use of efficient T_2 -weighted imaging techniques such as RARE (19). T_1 -weighted techniques such as Magnetization-Prepared Rapid Gradient-Echo (MP-RAGE) (20) can provide excellent contrast between GM and WM across much of the brain but are also hampered by B_1 power deposition issues, have relatively low SNR, and, at high resolution, require long scan times. Another drawback of traditional T_1 -weighted and T_2 -weighted MRI techniques is the relatively low sensitivity to structural variation within each brain tissue type, i.e. within grey and white matter.

Several recent studies suggest that T_2^* -weighting with gradient echo (GRE) techniques allows for strong tissue contrast at high field, allowing excellent delineation of deoxyhemoglobin and iron rich structures (21,22), as well as myelinated fiber bundles (16). At high field, much of the T_2^* signal decay is caused by local variations in tissue magnetic susceptibility, which may affect the NMR resonance frequency and lead to intra-voxel dephasing (coherence loss). The

associated relaxation rate (R_2^*) increases roughly linearly with field strength and may be calculated from a multi-echo acquisition.

In addition, large scale variations in magnetic susceptibility may lead to net NMR resonance frequency shifts that are reflected in the phase of the GRE image (23–27). In conventional GRE, signal phase represents the local resonance frequency offset or B_0 shift that is, at least in part, caused by the magnetic susceptibility differences between tissues (23,24). Therefore, both R_2^* images and frequency shift images derived from GRE acquisition may provide information about tissue composition that is more quantitative and easier to obtain at high field than T_1 and T_2 contrast.

A striking feature of the GRE phase and their derived frequency shift images is the strong contrast between grey and white matter (Figs. 3,4). In addition, substantial frequency shifts have been observed in iron-rich regions and deep white matter regions (24), and most recently, between cortical layers (28,29) (Fig. 4). The latter contrast opens up the exciting possibility of mapping variations in cyto-architecture across functional areas, disease processes, and populations.

INTERPRETATION OF CONTRAST

MRI contrasts such as T_1 , T_2 , T_2^* and resonance frequency shifts depend on a number of factors, including the bio-chemical and bio-physical properties of the tissue. However, this dependency is generally not straightforward and not well understood. This complicates interpretation of the observations and may ultimately limit the clinical value of MRI findings. A number of studies is currently underway to identify the contributors to the recent observations with T_2^* and frequency contrasts at high field. We will briefly review some of the potential contributors.

Magnetic susceptibility effects

Brain tissues contain a number of compounds that have a magnetic susceptibility different than that of water. For example, tissue iron and iron-containing compounds such as deoxyhemoglobin and ferritin are paramagnetic and alter the MRI scanner's magnetic field. This magnetic field change is generally not constrained to the area of altered susceptibility but occurs in a spatial pattern that depends on the shape and orientation of this area. As a result, a range of NMR resonance frequencies may occur in a voxel, leading to apparent shortening of the T_2^* relaxation time. In addition an average resonance frequency shift may occur.

A number of compounds may significantly affect tissue magnetic susceptibility, including tissue iron, iron in deoxyhemoglobin, myelin, and proteins. Their relative contribution to T_2^* effects and frequency shifts is likely dependent on brain region and may vary with pathology. For example, the contrast found in the basal ganglia, neo-cortex, between white matter fibers, and between grey and white matter each may be dominated by a different compound.

In the basal ganglia, iron content is relatively high and constitutes the dominant source of T_2^* effects and frequency shifts. Evidence from this comes from a number of studies that have compared MRI findings with histological measures of iron in these brain regions (30–33). In this case, calculated R_2^* values and frequency shifts may allow quantitative estimation of tissue iron content *in-vivo*.

Within neo-cortex, iron content is much lower (around 40–50 $\mu\text{g/ml}$, (34)), and therefore may have competing contrast mechanisms. The laminar variation in resonance frequency observed in a number of studies may be at least partly caused by compounds such as myelin, deoxyhemoglobin, and other macromolecules, some of which are known to vary substantially across cortical laminae. However, recent studies suggest that the contribution of

deoxyhemoglobin and myelin is rather small (35,36), and that, at least in primary visual cortex, much of the contrast can be explained by laminar variation of ferritin-bound iron (37).

The strong R_2^* and frequency contrast between some of the major fiber bundles is still poorly understood. For example, the optic radiations generally show a down-field frequency shift and an increased R_2^* (16,38), which may be caused by their increased myelin and content and/or a decreased iron content. Potential confounds are tissue orientation and geometry effects, which can affect susceptibility-weighted MRI in general, but may be particularly severe for the highly ordered structures found in white matter. These effects can arise from ordering at both the sub- and supra-voxel scale. For example, the macroscopic (supra-voxel) geometry of a structure and its orientation relative to B_0 affect the spatial extent and size of susceptibility-induced frequency shift. Proper interpretation of the MRI findings therefore will require the conversion of phase data into magnetic susceptibility maps, which would be insensitive to effects from geometry and orientation. This is currently an area of active research (39–43).

Similarly, frequency contrast between white matter and grey matter in GRE MRI is not well understood. In general, grey matter frequency is shifted down-field relative to white matter, suggesting a higher content of paramagnetic substance such as iron and deoxyhemoglobin. However, average white matter iron content is at least similar to that in grey matter (34), excluding iron as the dominant source for this contrast. In addition, differences in deoxyhemoglobin content may be too small to cause this observation, as suggested by a recent animal study that employed intravascular injection of a paramagnetic contrast agent (35). It is possible that the grey-white matter frequency differences are dominated by difference in myelin content, which may be slightly diamagnetic. This would explain the generally small frequency differences seen between white matter and CSF as the proposed diamagnetic shift from myelin may offset the paramagnetic shift from iron.

While the precise mechanism for contrast in GRE MRI at high field has not yet been established, it is becoming increasingly clear that a number of compounds could be responsible for the contrast variations observed in GRE MRI at high field, and that their relative importance may vary across brain regions. In addition to the mechanisms described above, additional contributions could come from sources that may not relate to bulk susceptibility of the tissue. Two of these mechanisms will be discussed in the following.

Exchange effects

A recent study on protein solution suggests that exchange effects may affect the NMR resonance frequency and that exchange differences in grey and white matter may be large enough to explain the GM-WM frequency shift observed in GRE MRI at high field (44). The authors proposed that exchange between protons on NH or OH groups on macromolecules and those of the water molecule could alter their respective resonance frequencies. This could lead to a frequency shift in the observed signal, which is dominated by water protons. Similarly, this effect would lead to coherence loss, resulting in R_2 (and R_2^*) increase (45). However, it is not clear what the size of the frequency shift would be in realistic conditions in-vivo. Preliminary data obtained from postmortem tissue suggests that the direction of the frequency shift induced by exchange may be inconsistent with that seen between grey and white matter (46).

Effects of tissue compartmentalization and orientation relative to B_0

A couple of studies have suggested that R_2^* and frequency shifts in human brain are dependent on the microscopic tissue structure and its orientation relative to B_0 (47,48). When compounds with a magnetic susceptibility different than water are non-uniformly distributed throughout the tissue, they could lead to local field variations. The latter could result in incoherent dephasing, and R_2^* increase, which forms the basis of fMRI and studies based on intravascular

contrast agents. In addition, frequency shifts may occur due to selective sampling of field distributions generated by inclusions of altered susceptibility. For example in white matter fibers, myelinated axons may generate field distributions in their surround that are selectively sampled by water protons. The selective sampling in this case arises from the fact that water is excluded from the myelin sheets. While the evidence is still sparse, this mechanism may contribute significantly to the contrast in GRE at high field.

CONCLUSIONS AND FUTURE IMPROVEMENTS

State of the art multi-channel detectors, combined with high field MRI, have led to dramatic improvements in resolution. Combined with phase contrast in T_2^* -weighting gradient echo MRI, this has enabled the unprecedented visualization of brain fine structure, including intra-cortical detail. Further improvements are possible with increased temporal averaging, however this will require improved methods for signal stabilization. For example, subtle head motion will reduce resolution through motion blurring. This could be ameliorated with the use of sophisticated navigators, or motion tracking devices (49,50). Brain pulsations are another issue that will require attention when one aims at further improving resolution. A third important factor affecting signal stability is respiration, which can cause fluctuations in signal magnitude and phase. This can to a large effect be suppressed with recently developed real-time shimming methods (51). Widespread clinical application of high field technology will require robust integration of these methods into commercial MRI systems.

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Figure 1. Example of 32 channel detector array for brain imaging. Shown (left) is a design with gaps in the transverse direction and overlap in the axial direction. Excellent brain coverage can be achieved with this design (right).

Figure 2. Resolution improvement achieved in T1-weighted MRI with high field and a 24-channel array detector.

Figure 3.

Comparison of contrast and resolution available with T_1 -weighted and T_2^* -weighted MRI. The GRE images have 40 nl voxel volume, compared to 160 nl for T_1 -weighted MP-RAGE. Note the strong grey-white matter contrast in the GRE phase data.

Figure 4. Examples of phase contrast in axial slice through the motor cortex (left) in primary visual cortex (right). In most areas, substantial grey-white matter contrast exists. In addition, an apparent laminar variation is seen in several cortical areas (arrow), most prominently in the primary visual cortex. Resolution: 40 μ m, acquisition time: 10 min.