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Insights from Ultra-High Field Imaging in Multiple Sclerosis

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Abstract

Ultrahigh-field (7 tesla) magnetic resonance imaging (MRI) is increasingly being utilized at many leading academic medical centers to study neurological disorders. The improved spatial resolution and anatomical detail are due to the increase in signal-to-noise and contrast-to-noise ratio at higher magnetic field strengths. Ultrahigh-field MRI improves multiple sclerosis (MS) lesion detection, with particular sensitivity to detect cortical lesions. The increase in magnetic susceptibility effects inherent to ultrahigh field can be used to detect pathological features of MS lesions including a central vein, potentially useful for diagnostic considerations, and heterogeneity amongst MS lesions, potentially useful in determining lesion outcomes. Limitations of ultrahigh-field MRI include exquisite sensitivity to patient motion, unique artifacts, unknown safety of implantable objects, and patient tolerability.

Introduction

The application of magnetic resonance imaging (MRI) to multiple sclerosis (MS) occurred soon after human scanners were developed. Today, MRI is paramount for the MS clinician and researcher and is used for diagnosis, disease monitoring, clinical trial outcomes, and studying disease pathophysiology. As MRI technologies have advanced from the first imaging in MS patients at 0.25-tesla (T) [1], the term “ultra-high field” (UHF) imaging itself has evolved as ever more powerful magnets have been adopted into routine clinical practice.

Currently, 1.5T magnets are available in most clinical centers, and 3T magnets are found in many major academic centers. UHF imaging now applies to 7T and higher MRI, and imaging at these magnetic field strengths has become increasingly common in the last 5 years. Although these advances have generally started in academic medical centers, many have ultimately made their way into routine clinical care.

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The two main advantages that come with increasing magnetic field strength are: (1) the increase in the signal-to-noise ratio (SNR) that approximately scales with the field; and (2) the increased contrast-to-noise ratio (CNR) caused by substantial changes in T1, T2, and T2* relaxation times. These advantages can be used to improve spatial resolution and detection of anatomical features; for an in-depth review of the technical improvements inherent with 7T MRI see [2]. At 7T, resolutions can be pushed below 0.5 mm with isotropic voxels yielding volumes of 125 nL or less, thus providing exquisite levels of details [3]. As a result, MS pathology that could previously only be appreciated under the microscopic can now be seen with MRI. This review will describe the advances and applications of UHF strength imaging (7T and greater) as it applies to MS. We will focus on the advances in our understanding of the biology of MS, current limitations, and future directions of UHF imaging.

Lesion detection and characterization

White matter

Pathology studies of MS brains show a panoply of inflammatory demyelinating lesions of various sizes, including very small white matter (WM) and cortical gray matter (GM) lesions. The ability of MRI to detect these lesions is constrained by the physical properties of limits on spatial resolution. Clinically, this may be most important at the time of first presentation, as missing existing lesions and new lesions could delay diagnosis due to reduced ability to meet current MRI diagnostic criteria, resulting in delayed initiation of disease-modifying therapy. Additionally, detecting new lesions, especially early in their development, could in principle allow clinicians to intervene to limit the extent of damage. The finer spatial resolution of UHF MRI has improved our ability to detect ever smaller lesions, in both white and gray matter, and to improve their localization of such lesions. It is important to note that the limits on improved spatial resolution from UHF are not known [2]. Additionally, finer spatial resolution does not necessarily mean improved imaging, as artifacts related to B0 and B1 field inhomogeneities, exquisite sensitivity to patient motion, and safety concerns from implants and objects not tested at 7T can limit both the target population and the interpretability of the acquired images. Even with these limitations, imaging at 7T has proven safe, and advances in pulse sequences continue to improve upon these limitations.

The first in vivo studies at 7T in MS showed ~25% improvement in the number of white matter lesions detected at 7T compared to 1.5T [4]. The fact that this improvement was only modest indicates how well sequences have been tuned on conventional scanners to detect focal white matter lesions. Additionally, early studies used T2-weighted sequences, which are the preferred imaging sequence for white matter lesion detection at 3T, but have proven difficult to implement at 7T due to the high specific absorption rate (SAR) of radio-frequency (RF) energy caused by the refocusing pulses. On the other hand, T1-weighted sequences, which typically have lower SAR, show more sensitivity to detecting MS lesions at 7T. Indeed, T1-weighted imaging at 7T showed nearly 50% more MS lesions than T1-weighted imaging at 1.5T [5]. In a direct comparison of 7T T1-weighted imaging to 3T T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging – the gold standard in WM

lesion detection – in 14 people with MS, 1075 lesions were detected on 7T MPRAGE (magnetization-prepared rapid gradient echo) compared to 812 lesions on 3T FLAIR [6]. Importantly, many of the lesions only detected on 7T were within what would have been interpreted as normal appearing white matter at 3T. This improved lesion detection was tempered by the presence of 3T FLAIR lesions not seen on 7T, mostly in the infratentorium, where signal drop out was noticed at 7T. However, this issue might be resolved through the use of the advanced T1-weighted MP2RAGE (two inversion-contrast magnetization-prepared rapid gradient echo) technique, which corrects for large spatial inhomogeneity in transmit B1 field and thus can provide homogeneous T1 contrast across the entire brain at 7T [7]. Figure 1 shows representative images from a person with MS imaged both at 1.5T, with a conventional T1-weighted sequence, and at 7T, using MP2RAGE. The improvement in contrast between gray and white matter structures, and in the conspicuity of MS lesions, is easily appreciable.

Gray matter

In addition to detecting WM lesions, the increased spatial resolution and improved tissue contrast of UHF imaging have been instrumental for detecting gray matter (GM) lesions, both in the cortex and in the deep gray matter nuclei. Demyelination in deep GM structures have been described in MS pathology and these lesions share characteristics with WM inflammatory demyelinating lesions [8]. But, few radiological studies have assessed for focal lesions in these structures. Instead, studies have primarily focused on iron deposition (see below) and changes in metabolites. Harrison, et. al. [9], evaluated 34 MS cases at 7T and found ~ 70% of cases had thalamic lesions, including focal lesions and diffuse confluent signal at the thalamus - ventricular border. Interestingly, focal thalamic lesion burden was associated with progressive clinical disease and correlated with cortical lesion burden, suggesting that gray matter lesions, regardless of location, may be related by common pathology.

Cortical lesions have been described in pathological studies for decades. Early work by Brownell and Hughes [10] noted the widespread presence of cortical pathology in MS, and later characterization of lesion subtypes [11] focused on characterizing patterns of lesion distribution, but imaging correlates of these pathological findings have proven difficult to come by. This difficulty was attributed to many factors, including lower amounts of inflammation in cortical lesions and small size of the lesions, both of which contribute to low contrast of lesions relative to normal cortical gray matter.

UHF imaging has enabled both ex vivo and in vivo observation of cortical lesions. Initial studies show improved detection of cortical lesions at 7T compared to 3T, as well as the ability to differentiate their pathologically defined subtypes [4, 5, 12–20]. Figure 2 shows cortical lesions seen on T1-weighted MP2RAGE and T2*-weighted gradient echo. A leukocortical lesion can be seen in the primary motor cortex of the left hemisphere.

Most 7T cortical lesion studies utilize a single imaging modality for cortical lesion detection, or simply make comparisons across sequences in order to identify the optimal approach, but each sequence has its own limitations and advantages. Sequences are constantly and iteratively being optimized. In one study, which used three different pulse

sequences, only 25% of lesions were detectable on all sequences, with particularly low concordance for intracortical lesions [21]. Additionally, histopathological-radiological correlation studies still show that UHF MRI, even using the most sensitive imaging techniques, still misses cortical lesions seen on pathology [16, 19, 22, 23].

The subpial type of cortical lesions remains the most challenging to image by MRI, but with improvements in acquisition and post-processing quantitative analysis, even these lesions are starting to be visualized. Mainero's group [24] recently showed that quantitative mapping of the T2* relaxation time within the cortical layers can provide evidence of pathological changes that are most prominent in the outer layers of the cortex. The extent, depth, and distribution of the laminar changes in T2* relaxation were different depending on the clinical stage of MS, suggesting a radiological correlate to what had been described previously only by pathology studies. However, it is important to appreciate that signal changes seen on T2*-weighted images, and indeed on all MRI sequences at all field strengths, represent an average of multiple, sometimes competing, processes. Iron deposition and loss of myelin, both of which occur pathologically in MS, cause opposite effects on T2*-weighted sequences, highlighting the disconnection between imaging physics and biology and making in vivo interpretation sometimes difficult. Moreover, many advanced techniques require complicated post-processing and hence are difficult to translate to the clinic.

The addition of summary measures of cortical lesion burden to WM lesion burden has also improved the modest correlation of MRI lesion number and volume with disability measures [24, 25]. However, volumetric and numeric measures of MS lesions still do not capture the heterogeneity of disability seen in clinical practice. Even with perfect resolution of all MS lesions, it is evident that the full extent and range of clinical disability will not be completely captured by lesion number and/or volume. As pulse sequences and spatial resolution continue to improve, the limitations of UHF imaging on MS lesion detection remain unknown. However, detecting more MS lesions may be a futile measure, as improvements in sensitivity ignore the import in differences between MS lesions, which may ultimately be more important than lesion number or volume. Additionally, MRI scans are snapshots in time, limiting our ability to fully appreciate the dynamic and complex biological processes that occur in MS.

Central veins

Beyond improvements in detection of MS lesion, UHF imaging has been instrumental in improving the detection of pathologic features of MS lesions, such as the presence of a central vein. The perivenular configuration of MS lesions was described in autopsy specimens by JD Dawson in 1916. These veins are very small in caliber and are thus rarely detectable on conventional MRIs. Magnetic susceptibility effects increase with field-strength, allowing improved visualization of small anatomical structures based on susceptibility differences between blood, iron, and myelin. In particular, T2*-weighted gradient-echo (GRE) imaging is exquisitely sensitive to deoxyhemoglobin within veins. UHF studies have shown that detecting a central vein within MS lesions is greatly improved at 7T compared to 3T [4, 26–29], and visualization of small veins is difficult at 1.5T. Figure

3 shows images from a T2*-weighted GRE and demonstrates multiple MS lesions that surround a central vein. The vein is easily visualized due to the prominent loss of signal from deoxyhemoglobin found in greater amounts in veins.

The usefulness of central vein identification goes well beyond recapitulating a pathological phenomenon, as the presence (or absence) of a central vein is a particularly important feature that can help differentiate MS from other diseases with overlapping imaging features. Studies have shown that >90% of lesions in people with MS have a central vein, whereas other disorders with prominent neuroinflammation but different therapeutic approaches, including Susac syndrome [30] and neuromyelitis optica [31], do not. Additionally, common radiologic mimics such as migraine [32] and small vessel ischemic disease [29] are less commonly characterized by white matter lesions with a central vein. Differentiating nonperivenular small vessel ischemic lesions or other nonspecific white matter lesions from new MS lesions is important to limit unnecessarily changing disease modifying therapy and exposing patients to more potent, and riskier, drugs. The “central vessel sign” has been proposed to be part of the diagnostic criteria for MS [33, 34], but recent evidence-based guidelines by the MAGNIMS group recommends further inquiry into its use [35].

Acute lesion evolution

Opening of the blood-brain-barrier (BBB), as seen on MRI by contrast leakage on T1-weighted sequences, is accepted as an early event in lesion formation and radiologically defines active inflammatory demyelination [36, 37]. These early studies found nodular and ring-enhancing morphologies in MS lesions, and for years the two types were thought to be entirely distinct. Imaging techniques including dynamic contrast enhanced (DCE) imaging, in which images are collected before, during, and after intravenous injection of a contrast agent, have disclosed the spatial-temporal dynamics of lesion enhancement. As first observed at 3T MRI, contrast-enhancing MS lesions can display a centrifugal pattern of enhancement that starts at the central vein and fills outward, or a centripetal pattern that starts at the lesion periphery and fills inward [38]. The enhancement pattern can change from centrifugal to centripetal, indicating that enhancement is a dynamic process that may represent different pathophysiological processes depending on the age of the lesion.

DCE imaging at UHF confirmed the findings seen at 3T and demonstrated that small lesions typically show a centrifugal enhancement pattern originating from around the central vein, whereas larger lesions and leukocortical lesions display the centripetal enhancement pattern [39]. A study in a larger cohort of patients, followed up to 1 year (or more) after the detection of a new enhancing lesion, showed that the enhancement pattern on DCE corresponds to concurrent and subsequent changes seen in images made from the phase of the T2*-weighted GRE signal [40]. Indeed, phase imaging is sensitive to changes both during lesion formation, corresponding to the location of the centripetal enhancement, and following resolution of enhancement, such that in some lesions, phase contrast remains abnormal at the periphery of chronic lesions (see below). This finding may have important ramifications in characterizing lesion outcomes.

Lesion outcomes

Qualitative imaging

Many techniques have been applied to image MS lesions and brain regions at UHF, particularly pulse sequences tuned to changes in iron content (including susceptibility weighted imaging (SWI) and its parent sequence, T2*-weighted GRE). Iron-sensitive techniques have proved extremely useful for visualization of the central vein, as described above. Also, as myelin has a large component of iron, demyelination within MS lesions can be visualized and quantified as changes in signal intensity on iron-sensitive sequences.

An early observation was the heterogeneity of MS lesions on GRE images. The GRE technique obtains magnitude and phase images (Figure 4). Susceptibility shifts, whether paramagnetic or diamagnetic, cause signal loss on magnitude images, and the direction of the shift can be determined from the phase image. Interestingly, MS lesions showed heterogeneous characteristics on phase and magnitude images [41]. In this first published analysis of changes in GRE at 7T in 18 MS patients, 403 lesions were detected on GRE, with 52% seen both on phase and magnitude images, 22% on phase images only, and 26% on magnitude images only. In this study, 8% of lesions had a rim on the phase images, suggesting a population of MS lesions that is potentially pathologically distinct from other lesions. In a longitudinal study, both nodular and rim lesions were stable in appearance over the 2.5 years of follow-up imaging [42].

Radiological-histopathological correlation studies have verified the presence of iron in phase-rim lesions, and suggesting that iron within phagocytic macrophages and/or microglia is the histological basis for this radiological finding [16, 43–45]. Importantly, chronic phase-rim lesions also display characteristics suggesting greater tissue destruction (longer T1 relaxation values and larger size) compared to non-phase-rim lesions, supporting the notion that these lesions are important in the clinical pathophysiology of MS [45].

The factors that influence if, when, and in whom these lesions develop are not yet fully understood, but these lesion characteristics could well provide an important radiological biomarker to identify a unique subset of MS lesions, i.e. those with chronic inflammatory activity. Pathologically, chronic active lesions show active, often mild demyelination, with myelin breakdown products evident within microglia and/or macrophages. Autopsy studies have described this finding in a small percentage of MS lesions, and from these studies, chronic immunological activity within lesions is hypothesized to engender lesion expansion. The extent to which this process is associated with clinical progression is a subject of current research. Importantly, inflammation in chronic active lesions is probably distinct in character from inflammation within new or newly contrast-enhancing lesions, and as such is likely to require different treatment approaches. In principle, identifying chronic active lesions could identify patients at risk for more aggressive disease or progression and usher in new treatments focused on stopping this type of inflammation.

It is important to reiterate that iron-sensitive sequences are also sensitive to changes in tissue density, water, fiber orientation, and other types of pathology. Additionally, recent studies utilizing quantitative susceptibility mapping (QSM) may assist in detecting changes at the

periphery of MS lesions, as QSM removes part of the non-local contributions (such as the dipolar patterns), which can complicate interpretation of phase images [46], sometimes at the expense of image quality. This highlights the inherent problems associated with reliance on a single sequence or quantitative post-processing technique. Combining information gained from the different iron-sensitive imaging techniques may improve upon the interpretation of a given lesion or region of interest [47].

Quantitative imaging

As described above, there has been advances in the understanding of MS lesion formation and evolution marshalled by UHF MRI by careful observation and using histopathological findings to drive radiologic techniques that recapitulate those findings. Radiologic techniques have also driven the field of MS research, particularly at UHF. One particular technique in MRI that has garnered much attention is quantitative iron imaging. UHF imaging with sequences sensitive to iron particularly T2* weighted-sequences goes beyond characterizing lesion subtypes, but have been utilized to study changes in iron within lesions, within the NAWM, and within the deep gray nuclei. This technique can also be used to derive quantitative values related to iron concentration, including the R2* relaxation rate and quantitative susceptibility mapping (QSM).

As iron is a major component of myelin, there have been attempts to provide a quantitative value of the extent of tissue injury in MS using UHF pulse sequences that can quantify iron content in MS lesions. Additionally, some studies have reported abnormally high levels of iron within structures, such as the deep gray nuclei, in both MS and CIS [48]. In one study of people with MS compared to age-matched healthy controls, increased iron concentration in the deep gray matter correlated with a functional measure associated with the affected nuclei [49]. These findings were tempered by fact that the specific nuclei affected were not consistent across sequences, complicating the interpretation.

Other studies have used quantitative iron imaging as a way of probing changes in the extraleSIONal WM. Using a multi-echo GRE sequence and fitting the T2* decay curve to a 3-component model, subtle changes in extraleSIONal WM were reported in MS, potentially indicating widespread loss of myelin [50]. Extending this model to MS lesions, Li, et. al, [51]. report reduced myelin water fraction in both enhancing and nonenhancing MS lesion, indicating this technique can be sensitive to detecting demyelination.

Though intriguing, these studies, and others like them, also highlight the limitations of quantitative techniques, as the derived iron concentrations are often affected by extraneous features such as concentration of deoxyhemoglobin in blood vessels, orientation of the brain during the imaging session, and the presence or absence of lesions. Interpreting radiological findings in the context of MS is often extremely difficult and have led to disparate ideas about whether iron drives, plays a minor role, or is simply a bystander in MS pathophysiology.

Spinal cord

UHF imaging is also being optimized for spinal cord imaging, albeit slowly. In principle, the increased SNR and higher spatial resolution of UHF imaging could be marshaled to improve identification of spinal cord inflammatory demyelination. Imaging the spinal cord at any field strength is difficult given its small size and propensity to artifacts related to respiratory and cardiac-induced motion, which together severely limit lesion identification. However, recent studies have used UHF sequences to produce high resolution images of MS spinal cord lesions. In a small pilot study, both resolution of the normal spinal cord anatomy and lesion detection were improved at 7T compared to 3T [52]. Additionally, myelin water imaging was applied to an MS spinal cord postmortem, albeit on a preclinical scanner [53], showing reductions of the myelin water fraction in regions with histologically proven MS lesions. Of course, application in vivo presents difficulties beyond image sequence, but at least in proof-of-principle, this sequence, and others, may be feasible at UHF.

Limitations and challenges

Even with important advances in the understanding of MS pathophysiology, 7T MRI has proven difficult to apply in all contexts. Limitations from artifacts, patient motion, additional safety concerns, and patient comfort have all made application of 7 T imaging less universal. New techniques, such as integrated navigator for motion correction, are needed before large scale 7T clinical application [3]. Nonetheless, many of these problems existed at 1.5T and 3T and were subsequently overcome, leading to widespread clinical adoption of higher magnetic field-strength systems. While 7T magnets are regarded as investigational tools at this time, one manufacturer (Siemens) recently stated its intent to produce 7T magnets for clinical use. This marks the next advance in clinical MR imaging and will lead to much larger cohort studies of neuroinflammatory disorders, and hopefully to new insights into MS pathophysiology.

Future directions

UHF is a relative term, as advances in technology continue to press the boundaries of MRI field strength, shrinking the voxel size toward microscopic resolution. Advances in pulse sequences and new technology to overcome motion artifacts will allow MS researchers ever more detailed glimpses at the biology of MS lesion formation and evolution. Technological advances will also allow for better in vivo spinal cord imaging.

What new information will the next generation of UHF scanners be able to resolve that we are missing today? In the newly forming MS lesion, BBB leakage is detected by gadolinium leakage, which is a nonspecific marker of BBB disruption. Biochemical and cellular changes presumably precede this event, but these changes are not yet detectable. Microglial nodules are described in pathological specimens as clumps of inflammatory cells surrounding a vessel, and one hypothesis is that this is an early sign of impending lesion formation. These nodules are too small to image currently, but once detectable they may become an important biomarker of lesion development or treatment effectiveness. Additionally, in place of gadolinium contrast, new, more specific, contrast agents capable of attaching to specific

receptors or cells are on the horizon. High field-strength scanners can be useful for detecting the changes caused by these agents, particularly if the changes are spatially restricted. In addition to acute MS lesions, there is much we do not know about what underlies the profound heterogeneity in disability and pathological expression of MS. Imaging degrees of tissue destruction and repair – and in particular where and when those features are liable to be detected – will provide insights into how MS is different across patients and will potentially revolutionize clinical decision-making.

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Key Points

1. Ultrahigh-field (UHF) MRI enables superior detection of MS pathology in the white matter and gray matter
2. The detection of the “central vein sign” within MS lesions is improved with UHF MRI
3. UHF MRI provides new insights about the mechanisms of lesion development
4. Susceptibility-based MRI at UHF may provide new information about the outcome of MS lesions

Figure 1.

Representative slices of T1-weighted scan of a 62 year-old woman with relapsing-remitting multiple sclerosis. A and B were obtained using the spin-echo sequence on a 1.5T magnet (TR 600, TE 16ms, $1 \times 1 \times 3$ mm resolution). C and D were obtained using the MP2RAGE (two inversion-contrast magnetization-prepared rapid gradient echo) at 7T (0.7 mm isotropic resolution). Improved contrast between white matter and gray matter (blue arrows) is evident. Lesion detection is also improved at 7T.

Figure 2.

Representative T1-weighted MP2RAGE (two inversion-contrast magnetization-prepared rapid gradient echo) (500 mm isotropic voxel resolution) and T2*-weighted gradient-echo image (210 mm $\times$ 210 mm in-plane resolution) from a person with relapsing-remitting multiple sclerosis. A leukocortical lesion involving both cortex and subjacent juxtacortical white matter is located in the central sulcus.

Figure 3.

Representative T2*-weighted gradient-echo image (210 mm × 210 mm in-plane resolution) from a person with relapsing-remitting multiple sclerosis. Magnified boxes highlight different types of MS plaques: deep white matter lesions with a central vein (red chevrons in red and green boxes), a periventricular lesion with branching veins (yellow chevron in green box), a subcortical lesion near a cortical vein (green arrow in blue box), and an intracortical lesion with a possible central vein (orange chevron in yellow box). Note also the elongated perivascular spaces around some vessels (light blue chevron in yellow box).

Figure 4.

Representative T2*-weighted magnitude and phase contrast gradient-echo images (210 mm $\times$ 210 mm in-plane resolution) from a person with multiple sclerosis. On the magnitude image (left), lesions are hyperintense, and susceptibility shifts lead to signal loss. Lesions can display heterogeneous patterns on phase contrast (right), such as hypointense rims with isointense core (red chevrons) and uniform hypointensity (green chevrons). Some lesions are poorly detected on phase contrast (yellow chevrons).