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Imaging techniques

High field MRI in clinical practice

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Magnetic resonance imaging and spectroscopy can provide detailed morphologic, functional and metabolic information that may provide unique biomarkers to assist drug discovery and development. To overcome the inherent low signal to noise of *in vivo* magnetic resonance applications, stronger magnetic field strengths can be applied that not only boost signal strengths, but can also be used to improve contrast and specificity as well.

Introduction

One of the most important unmet needs in the development of new drugs as well as the delivery and monitoring of new medicinal entities is the development of new biomarkers that can be used as (surrogate) endpoints to assess the therapeutic effect. Imaging, combining high-resolution spatial information with specific functional and molecular information, is making important inroads in producing such new biomarkers. Nuclear medicine techniques such as positron emission tomography (PET) are of value for sensitive visualization and quantification of critical disease targets and targeting molecules. High field magnetic resonance imaging by contrast is capable of detecting subtle morphological, functional or even metabolic changes based on the detection of endogenous contrast. To overcome the inherent sensitivity limitation of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), increasingly stronger magnetic field strengths are being used to boost signal to noise. MRI systems based on magnetic field strengths of 7 T and higher have recently been introduced to further increase the sensitivity and specificity of clinical magnetic resonance applications. Currently, worldwide more than 50 such 'ultra high field' MRI systems have been installed in clinical research centers exploring new techniques that can be used for the *non-invasive, in vivo* tissue characterization.

Ultra high field MRI and complementary imaging technology

MRI is totally non-invasive and does not use any ionizing radiation. As a result, MRI is the modality of choice for structural, functional and molecular imaging of *soft tissue* for early detection of pathology or (long-term) follow-up of therapy response. Several clinical applications in translational neurology are under development for early diagnosis of neurodegenerative disease (Alzheimer [1], vascular dementia [2]), multiple sclerosis [3], epilepsy, brain neoplasm and stroke, as well as applications outside the brain addressing oncology (breast and prostate cancer), diabetes (liver metabolism), cardio-vascular diseases (carotid atherosclerosis, peripheral and coronary artery disease) and rheumatoid arthritis. High magnetic field strength contributes to more signal and concomitantly better spatial resolution and/or shorter scan times. Even more important is the substantially altered potential for very specific contrast generation based on intrinsic tissue characteristics and the increased capabilities to measure metabolic changes using proton (^{1}H) and non-proton (^{31}P, ^{13}C) magnetic resonance signals. Where PET provides high sensitivity to detect very low concentrations of tracer molecules and ultrasound technology may derive its strength from the capability to study dynamic processes, MRI excels in spatial resolution and detailed functional information directly derived from the (pathological)

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Table 1. The optimal spatial resolution and the detection limit (sensitivity) in terms of tracer/metabolite concentration for five *clinical* tomographic imaging techniques. (Optical: near infrared diffuse optical tomography for breast or extremities using either endogenous contract (absorption) or tracers (fluorescence)). The MRI sensitivity relates to high field MR spectroscopy and the ability to measure (small) metabolites up to approximately 1 mmol concentration in tissue

	MRI	PET	Optical	SPECT	CT
Spatial resolution (mm)	0.5	2.5	10	8	0.2
Sensitivity	mM	pM	nM	nM	n.a.

tissue itself. This creates an important opportunity to study *in vivo* biology in human subjects without the need for agents that may interfere with the biological processes under examination or that may be harmful to the patients. This will also drive future applications in *hybrid* imaging technology, combining optimal imaging techniques for spatial resolution and sensitivity to quantify certain tracers/molecules. PET equipment is hardly sold as a dedicated PET only machine anymore and most PET systems are offered as a PET-CT hybrid imaging platform. However, of the current clinical three-dimensional imaging techniques MRI provides the best spatial resolution and contrast for *soft tissue* and PET the highest sensitivity for tracer detection. This drives the current development of new, highly integrated PET-MRI equipment [4,5].

Other techniques that are frequently used have different limitations (Table 1). Computed tomography (CT) using X-rays delivers superb spatial resolution, but cannot be used to obtain molecular information and lacks tissue contrast in certain applications, whereas the spatial resolution and sensitivity of single photon emission computed tomography (SPECT) is outperformed by PET. 3D applications of ultrasound (US) are becoming more frequently used in clinical diagnosis as well, where the temporal resolution of this technique offers clear advantages over the other imaging modalities. It should be stated that both CT, SPECT and (3D) US play a very important and indispensable role in clinical diagnosis and the technology involved in these imaging modalities is still improving. Moreover, SPECT offers advantages in tracer production (no need for a cyclotron, long half life times and simplified chemistry) which makes it an accessible tool also for less advanced medical environments. Optical technology as a clinical diagnostic tool is still in its infancy. Diffuse optical tomography is being used in some breast cancer applications [6], but challenges for the reconstruction of optical data absorbed and scattered in tissue remain unresolved and the spatial resolution is too limited at this point in time for clinical applications. (An alternative may be obtained by using photo acoustics, combining optical excitation with ultrasonic detection technology [7]. This technique combines submillimeter spatial resolution of ultra sound technology with the sensitivity (nM) of optical detection of fluorescent probes.)

Increased spatial resolution

For neurological disorders (degeneration, depression, multiple sclerosis) there is a clear need for early assessment of the onset of abnormal phenotypes of the brain. Multiple sclerosis (MS) is one of the best examples of an important, frequently seen disease of which the pathogenesis is still not fully understood and early disease markers may provide important information on potential (new) drug candidates. In a recent review article [8] on the pathogenesis of MS it was stated that the paradox of the poor correlation between MRI observed white matter lesions and neurologic disability may be partly explained by demyelinating lesions and neuronal disease in the cerebral cortex and deep gray matter that with the use of standard imaging acquisition sequences cannot be detected by MRI in living patients. This paradox is an important impediment to use MRI as a surrogate endpoint in drug trials for MS. Recently it was shown that higher (7 T) field strengths aiming to detect demyelinating lesions in white matter can reveal cortical lesions due to substantially increased spatial resolution, thus overcoming the partial volume effects that obscured many of these lesions at lower field strengths [9]. This may open a new window of opportunity to combine drug efficacy studies with high field MRI to quantify small lesions in the cortex (Fig. 1).

Contrast

A second, important characteristic of high field MRI is its increased sensitivity for the detection of vascular pathology and micro-bleeds in the brain. Change in magnetic susceptibility of tissue resulting from altered oxidative metabolism or the breakdown of blood cells after an hemorrhagic event result in substantially more pronounced contrast at high field MRI. Imaging of brain activity using the blood oxygen level dependent (BOLD) functional MRI signal has pushed the field to higher field strengths. Although the BOLD response may not increase linearly with field strength, sub-cortical layer specific brain activity can be studied at higher field strengths [10]. From a clinical point of view, the pathogenesis of cerebro-vascular diseases has focused on the effects of hypertension on the brain, for instance altered arterial anatomy and function, thereby gaining insight into hypertension-based pathology. Figure 2 shows multiple micro-bleeds at 7.0 T MRI in a patient with a hypertensive cerebral

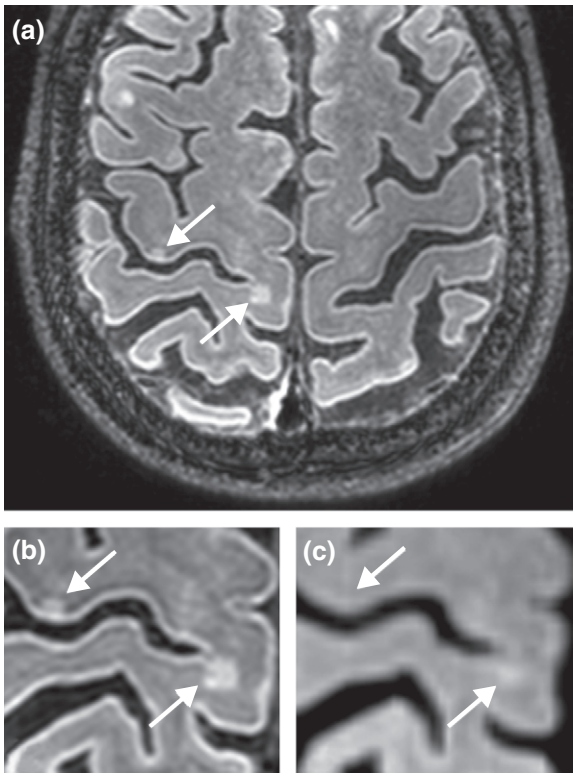

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Figure 1. Detection of cortical lesions in MS. Patient with primary progressive multiple sclerosis (MS, EDSS 6.0). A 7.0 T MRI scan was performed for detection of possible cortical lesions. **(a)** Axial overview and **(b)** zoomed-in image of a high parietal cortical MS lesion (right arrow) on axial 7.0 T 3D-FLAIR sequence. The 3 T **(c)** image in retrospect did show the lesion as well, but the increased conspicuity of the lesion at 7 T is clearly demonstrating the clinical potential of 7 T neuro-MRI.
Courtesy: de Graaf *et al.* [9].

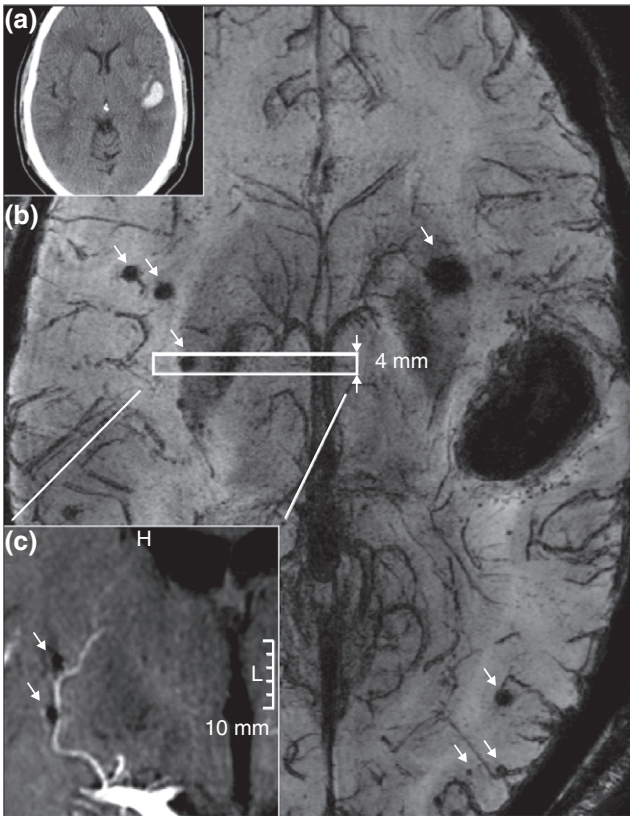

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Figure 2. Vascular imaging: *imaging the leak*. High resolution 7 T imaging of small vessels including visualization of leaking vessels (arrows in **(C)**).

hemorrhage, and visualizes a direct relationship between some of the micro-bleeds and a small 'leaking' penetrating artery [11]. The results of these studies show a variable pathophysiology of hypertension-based brain pathology, in which microvascularity and micro-bleeds play a prominent role [12,13]. In an era where hypertension is recognized as a very common risk factor, it is important to assess these underlying pathogenic effects of hypertension in brain pathology, not only for diagnostic imaging but also for treatment monitoring.

Ultra high field MRI: applications beyond the brain

The clinical use of MRI at ultra high field strengths (7 T and higher) has been mostly restricted to the brain. The main reason for this restriction is the shortened wavelength of the radiofrequency used for excitation and detection of the nuclear magnetic resonance signals in MRI and MRS. For 7 T the operating frequency is 300 MHz, which results in a 12 cm wavelength in tissue [14]. As this wavelength is shorter than the object to be imaged in whole body applications, interferences will result in a very inhomogeneous image. This effect is even seen at 3 T body imaging and has resulted in the introduction of multiple transmitter arrays to overcome the inhomogeneity in the radiofrequency excitation (B_1^+) field at 3 T and higher field strengths [15]. This technology will pave the way for new applications beyond the brain. The first reports on the feasibility of 7 T imaging applications in breast [16], prostate [17], liver [18] and the heart [19] have already appeared in the literature.

Metabolism

Magnetic resonance spectroscopy at higher magnetic field strengths will gain in sensitivity (increased signal to noise) as well as in specificity (increased chemical shift dispersion). Whereas almost all clinical MRI studies are based on chemical and physical changes of water (and to a lesser extent lipid) protons that are highly abundant in tissue (water proton concentration of approximately 80 M), MRS derives its signal from protons and other isotopes of *endogenous* biochemical compounds in the concentration range of approximately 1–40 mM. Proton MR spectroscopy at high field in the brain can be used for a quantitative assessment of a series of different metabolites (e.g. *N*-acetyl aspartate, choline, creatine,

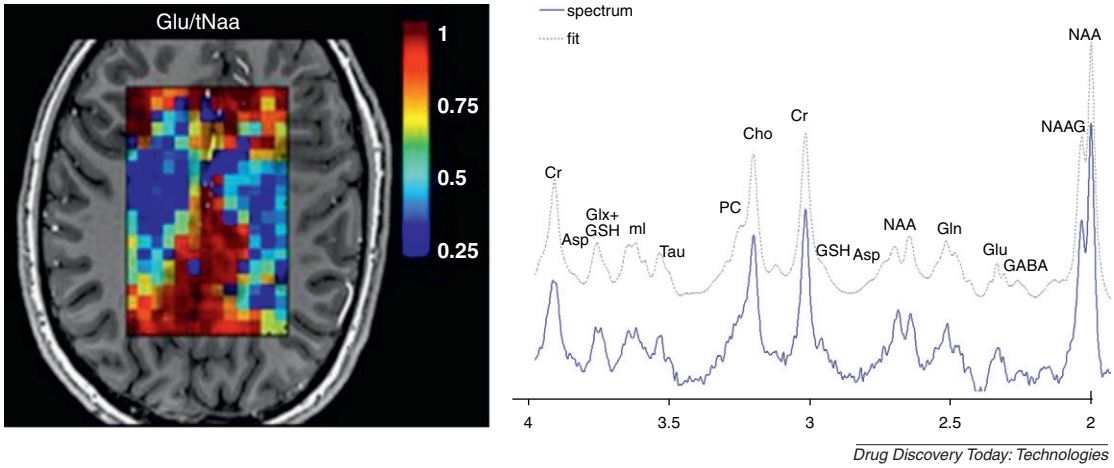

Figure 3. Proton spectroscopy and spectroscopic imaging of the human brain at 7 T. Spatially resolved magnetic resonance spectra (right) showing individual resonances from creatine, glutamate/glutamine, myo-inositol, (total)choline, creatine, *N*-acetyl aspartate. From these resonances metabolite maps and metabolite ratio maps (left) can be derived to display the spatial distribution of the individual chemical compounds in the brain. Courtesy: Boer *et al.* [20].

myo-inositol, glutamate, glutamine, lactate; Fig. 3). Several technical improvements have been proposed to optimally leverage the advantages of high field strength for proton MRS in the brain [20]. Outside the brain, proton MR spectroscopy can be used to characterize prostate cancer by measuring choline, citrate and polyamines concentrations [21]. Other nuclei that can be used to assess biomarkers for drug targets or therapy response are phosphorus (^{31}P), fluorine (^{19}F) and carbon (^{13}C).

An important biomarker for cancer viability and drug response is the choline metabolism. Phosphocholine (PC) and total choline containing metabolite levels [tCho; glycerophosphocholine (GPC) + PC + free choline (Cho)] are elevated in many different tumors in which the most aggressive tumors display the highest PC and tCho levels [22]. More than two decades ago combined PET and MRS studies in brain tumor patients described the correlation between high fluoro-deoxy glucose (FDG) metabolism and the related increased total choline (tCho) and lactate signal in high grade glioma's. The study showed co-localization of the increased FDG and tCho signal on PET and MRS images respectively, whereas increased lactate could be observed in the more necrotic area of the tumors [23,24]. For a more specific assessment of the spatial localization of different choline containing compounds to study the metabolic pathway from a more system biology point of view, different *ex vivo* methods have been proposed in animal models [25]. Ultra high field ^{31}P MRS has the unique capability to detect the different choline metabolites *in vivo* as shown in a recent feasibility study in human breast cancer [26] (Fig. 4).

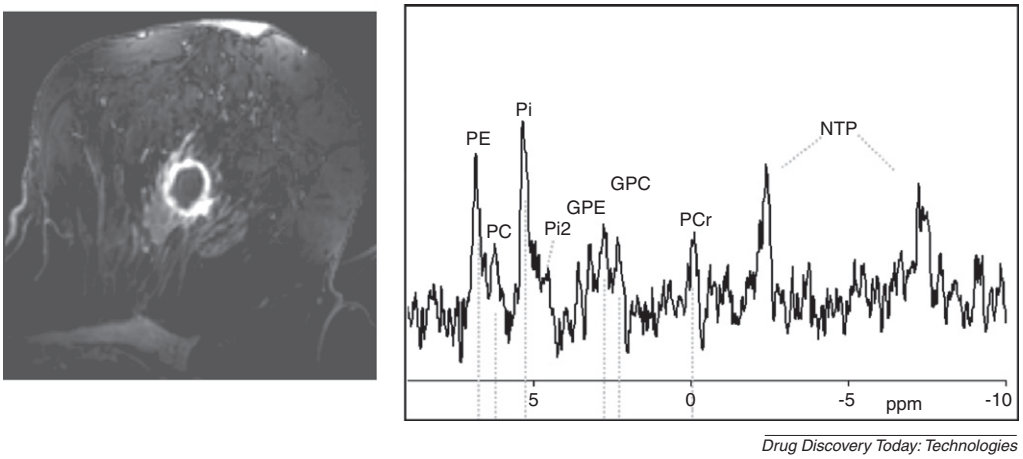

Figure 4. High field MRI and MRS in breast cancer. A 7.0 T breast tumor image (left) and ^{31}P spectrum (right [26]) showing different metabolites that can be used to determine therapy response rates for patients with neo-adjuvant breast cancer chemo therapy. (PE: phospho-ethanolamine, PC: phosphor-choline, Pi: inorganic phosphate, GPE: glycerol-phosphoethanolamine, GPC: glycerophosphocholine, PCr: phosphor-creatine, NTP: high energy phosphates (ATP).)

Challenges to overcome

In spite of extensive monitoring of potential side effects related to the use of strong static magnetic fields for ultra high MRI and human subjects, no serious adverse events have been reported to date [27,28]. The FDA has cleared the use of MRI up to 8 T as a non-significant risk device which will make 7 T research contingent local IRB approval. As stated, the use of higher frequencies (300 MHz for proton imaging at 7 T) poses more challenges. New insights using RF simulations at 7 T MRI have demonstrated the heterogeneity of the magnetic excitation (B_1^+) fields and RF power deposition due to the relatively short RF wavelengths compared to the human body. RF excitation using multiple RF coils to simultaneously transmit several RF waves in the human body with each of its own phase and amplitude settings can be used to create constructive interferences to optimize B_1^+ uniformity. By carefully adjusting the relative phase and amplitude of the RF wave of each antenna, the location of constructive interference can be positioned to the area of pathologic interest. Also, the concomitant higher RF frequencies of higher magnetic fields, lead to increased global and local specific absorption rate (SAR) deposition which may result in tissue heating. In the lower field regime (1.5–7 T), a quadratic rise with RF frequency can be observed. Research towards means to reduce SAR deposition at high field MRI systems will be important. Fortunately, research at 3 and 7 T has already indicated that with transmit arrays this is possible. For example, RF shimming can be used to reduce power deposition by optimizing destructive interferences of electric fields [29]. In parallel transmit RF pulse design there is even more flexibility to control SAR. These new challenges in the application of radio frequency waves in high field MRI.

Lastly, the costs for these ultra high field systems are considerably higher than that for MRI systems operating at 1.5 or 3 T. It may take a while before these systems will become available for more routine clinical scanning. This will depend on the development of new relevant biomarkers that rely on ultra high field MRI for their prognostic and/or predictive value for the diseases and related treatments as discussed.

Conclusion

By combining new contrast mechanisms and increased spatial resolution, detailed characterization of substructures of the hippocampus, cortical layer determination, abnormalities of subtle vascular structures, neuro-transmitter metabolism (glutamate [30], GABA [31]) and many other examples have proven to become feasible using ultra high field MRI.

These new insights will have a major impact on biomarker development for early diagnosis of many different pathologies, the development of surrogate endpoints of drug trials, drug response monitoring and *in vivo* monitoring of regenerative medicine applications. Several technical challenges will have to be resolved before these applications will reach their full potential at 7 T. But as the development of nuclear magnetic resonance technology over the past half century has shown, the field will progressively move forward and result in new, unexpected applications that will expedite the translation of new fundamental insights in the clinical setting.

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