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Life at the edge – exploring the limits of our "fields"

The most wonderful thing about magnetic resonance imaging is its remarkable ability to reinvent itself. What we can do to explore and exploit the natural laws of physics, learn about the biology of tissues, and apply that knowledge to help better understand disease in our patients has been constantly shifting and expanding over the last 50 years of MRI's existence. At nearly every conference we hear of new forms of image contrast to map, new quantitative measurements to make, new biology or clinical disorders we can now see that we couldn't before. Anatomy invisible before becomes visible, measure of tissue function expand from one organ to the next, and on its own and fused in real time with PET, imaging of molecular pathways moves from bench to bedside. This is why we love MR – it's always new.

Today of course is no exception. In just a few short years the use of artificial intelligence has provided an amazing boost in image clarity and resolution, and technologies like dense array coils combine now with novel image acquisition schemes to shorten our imaging times from tens of minutes to sometimes just seconds, with comprehensive multicontrast examinations in a few short minutes (watch out CT!). And interestingly, these advances are now not only pushing the envelope on workflow, but they are also allowing us to revisit some of the means we once performed MRI in new and compelling ways – image quality that rivals "standard" 1.5T examinations are no longer limited to the complexity and footprint (and cost) of these larger magnets – this is expanding greatly our ability to provide access to patients in more and more settings, and setting new goals as we push for value-based care.

But with all of that said, there is another facet of MRI that has remained constant. The fundamentals of the physics of MRI tell us there is more signal to be seen as magnetic field strengths increase, and more ability to encode spatial properties both at the macroscopic scale of our images and at the microscopic scale of cells and tissues when our other "magnet", the magnet field gradients, increase their power and speed. These "constants" in MR physics have in turn pushed MR engineers to keep a steady focus on increasing our fields, both static B_0 magnet and gradients G_{xyz}, to exploit the power that these higher and faster fields have, to map the underlying pathophysiology of our patients in both research and clinical settings.

Looked at over the five decades of MRI, the progress might appear slow but steady. Looked at more closely though and we can see that progress in these domains has been made in a more "stepwise" fashion – some of us are old enough to remember when the step to imaging at 1.5 Tesla was a remarkable engineering feat, and quickly brought MRI from its infancy into something that would look familiar to radiologists today. Gradient technology advances have followed a similar path – the first human diffusion images in stroke were acquired with 5 mT/m gradients and slew rates well below what was needed for single shot imaging (at 0.6T to boot!), it was the major advance in gradient systems now capable of echo planar imaging that brought diffusion imaging quickly into our routine clinical practices.

Today, we are lucky to be facing another of these important steps. Imaging magnets at 7 Telsa more than doubled the field strength of what was once "high field" MRI – though explored in research laboratories for several years, ultra-high field (UHF) 7 Tesla MR systems are now entering mainstream clinical practice. At the same time, through investments targeting how our human brains are wired, including the NIH Human Connectome Project and other major research initiatives, "Connectom" class gradient performance seen in laboratories is now poised to also move into the clinic. As with past leaps forward, we can predict that these new engineering capabilities will lead to wholly new ways to understand how our bodies work, and to detect and characterize what goes wrong in disease. But what can we anticipate these remarkable new machines will provide to our research community, and to clinical practice? Read on!

Our B_0 magnet – sometimes bigger really is better

High signal-to-noise-ratio (SNR) and increased spectral resolution at ultra-high field promise submillimeter anatomical resolution and new insights into human tissue function and metabolism. This information could be of key importance for diagnosis, prognosis, and treatment response monitoring in a wide spectrum of diseases.

As conventional neuroimaging techniques at typical clinical field strengths (≤ 3 Tesla) don't always provide sufficient metabolic and functional information, or adequate SNR to robustly measure these in individual patients, the advent of UHF MRI paves the way for many different imaging technologies that can provide additional insights into brain physiology and pathophysiological processes.

Generally, there is a fast-growing body of evidence that UHF MRI has the potential to improve depiction of anatomical substructures and therefore diagnostic confidence. Conventional high-resolution proton imaging is still the mainstay of clinical imaging at 7T. As one important example, multiple studies have provided evidence for an added clinical value of 7T MRI in the diagnostic work-up of patients with epilepsy. High-resolution anatomical imaging at 7 Tesla aids the identification of potential epileptogenic lesions, such as focal cortical dysplasias. A recent consensus report from the "7T Epilepsy Task Force" reported experience from 21 7T MRI centers including scans of over 2,000 patients together with recommendations for appropriate clinical indications, patient selection and preparation, acquisition protocols and setup, and technical challenges [1].

In many diseases, such as cancer, neurodegeneration, and neuroinflammation, morphologic changes often occur only at an advanced stage of illness. For instance in patients with brain tumors, current diagnostic approaches mainly detect changes associated with disease progression, such as blood brain barrier (BBB) disruption, necrosis, and edema in the case of aggressively growing tumors. However, tumor cells have distinct properties different from healthy tissue, such as altered metabolic pathways (e.g. Warburg effect) and increased proliferation rates.

Until today, PET imaging techniques have successfully targeted these characteristics mainly using (deoxy-2-[^{18}F] fluoro-D-glucose) FDG-PET with great implications for patient care, particularly in body imaging. In the human brain, however, high ground level metabolic activity limits the potential of FDG-PET for the detection of cancer tissue. In this context, the increased SNR and the higher spectral resolution at 7 Tesla have enabled not only ultra-high

Nucleus	Relative sensitivity [%]	SNR relative to ^{1}H [%]	I [$\hbar$]	γ [MHz/T]	c [mol/L] of the isotope in-vivo
^{1}H	100	100	1/2	42.6	79
^{23}Na	9.25	35.0	3/2	11.3	0.041
^{31}P	6.63	16.4	1/2	17.2	0.003*
^{35}Cl	0.356	3.64	3/2	4.2	0.027
^{17}O	0.0011	0.00815	5/2	-5.8	0.015

Table 1: Overview of the most commonly used X-nuclei for MRI and their physical properties.
I: spin, γ: gyromagnetic ratio, c: typical concentration of the isotope in vivo, $\hbar$: Planck's constant. *Reproduced from [2]*.

resolution anatomical imaging and improved MR spectroscopy, but also the introduction of new metabolic MR imaging technologies, in particular employing X-nuclei technology.

The term X-nuclei refers to all non-proton nuclei with a magnetic moment, such as sodium (^{23}Na), phosphorus (^{31}P), phosphorous (^{31}P), deuterium (^{2}H), potassium (^{39}K), and the oxygen-17 isotope (^{17}O). These nuclei are directly involved in many biological processes. However, the relatively low sensitivity and in vivo concentration pose challenges (Table 1).

Sodium ^{23}Na MRI is the currently best explored X-nuclei due to its high natural abundance in the human body and its relatively high gyromagnetic ratio compared to other X-nuclei. Sodium plays an important role in many physiological processes. Transmembrane sodium gradients control the transmission of action potentials, the maintenance of cell homeostasis and the regulation of physical properties such as pH, blood volume, and blood pressure. Therefore, sodium MRI has a variety of potential applications in order to study physiological and pathophysiological processes [3].

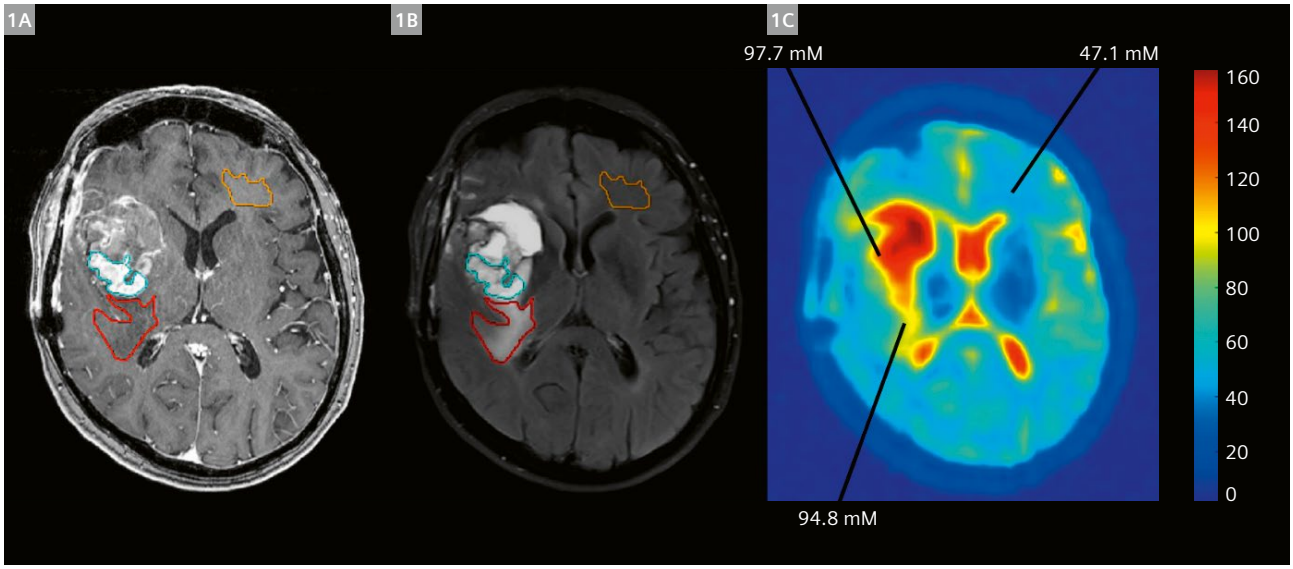
The tissue sodium concentration (TSC) has been shown to be increased in brain tumor tissue compared to normal-appearing white and gray matter regions (Fig. 1), and to be associated with different histologic and genetic subtypes, such as the isocitrate dehydrogenase (IDH) mutation status [4].

Abnormal TSC in brain tissue has also been demonstrated as a potential marker for neuroinflammatory processes, such as multiple sclerosis, and in neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington disease [3]. Overall, ^{23}Na MRI is emerging as a promising tool in the field of neuroimaging with broad applicability.

Another nucleus that has recently gained considerable attention is the oxygen-17 isotope (^{17}O). Oxygen-17 has a magnetic moment (spin 5/2), is non-toxic, and the only stable oxygen isotope that can be detected via MRI. The natural abundance of ^{17}O is very low (0.038%) [5]. However, the in vivo concentration of the isotope can be enhanced through inhalation of enriched $^{17}O_2$ gas during an MRI scan. The oxygen isotope is detectable only when it is bound to water ($H_2{}^{17}O$), which makes the approach a specific modality to measure the rate of oxidative phosphorylation at the mitochondrial membrane. Thus, ^{17}O MRI provides a direct window into oxygen-dependent tissue metabolism.

Clinical applications of ^{17}O MRI have so far been performed in study participants with brain tumors. Decreased cerebral metabolic rates of oxygen consumption ($CMRO_2$) have been reported in tumors of patients with gliomas (Fig. 2) [6]. This observation is in agreement with the theorem of Otto Warburg, who described a metabolic shift in cancer cells towards glucose fermentation, even in the presence of abundant oxygen. In addition to metabolic characterization of brain tumors, ^{17}O MRI offers great potential for studying oxygen metabolism in patients with stroke, and neurodegenerative diseases such as Alzheimer's or Parkinson's disease.

To date, X-nuclei methods have predominantly been investigated in experimental studies. However, with



1 **Sodium MRI at 7 Tesla in a patient with right-sided fronto-temporal glioblastoma.**
The images include a **(1A)** contrast-enhanced T1w MRI, **(1B)** T2 fluid-attenuated inversion recovery (FLAIR), **(1C)** sodium MRI. Three regions of interest have been selected on (1A, 1B) in the contrast-enhancing tumor region, the peritumoral edema, and contralateral normal appearing white matter. Corresponding sodium concentrations are additionally shown.

increasing magnetic field strengths and new technical developments, X-nuclei imaging may play an important role in routine clinical practice. Also in the context of artificial intelligence (AI) enhanced diagnostics, metabolic MRI methods have the potential to boost the performance of AI approaches by adding independent information compared to existing MR sequences.

The large majority of 7T MRI clinical studies have been performed in brain imaging, which is primarily due to the additional challenges, such as respiratory motion, B_0/B_1 inhomogeneities, and wave effects in body imaging (at 7T, the wavelength in tissue is shorter than the diameter of a human torso). In the near future, the increasing availability and technical advancements of parallel transmit (pTx) technology will permit the exploitation of further applications in human UHF imaging throughout the body and MSK systems [5].

UHF MRI already plays a key role in neuroscience and preclinical neural research, and its role in clinical diagnostics is certain to increase as more systems with clinical approval as medical devices are installed. In the future, even further increases in field strength may enhance our capabilities in clinical research and will certainly lead to significant advances in these imaging modalities.

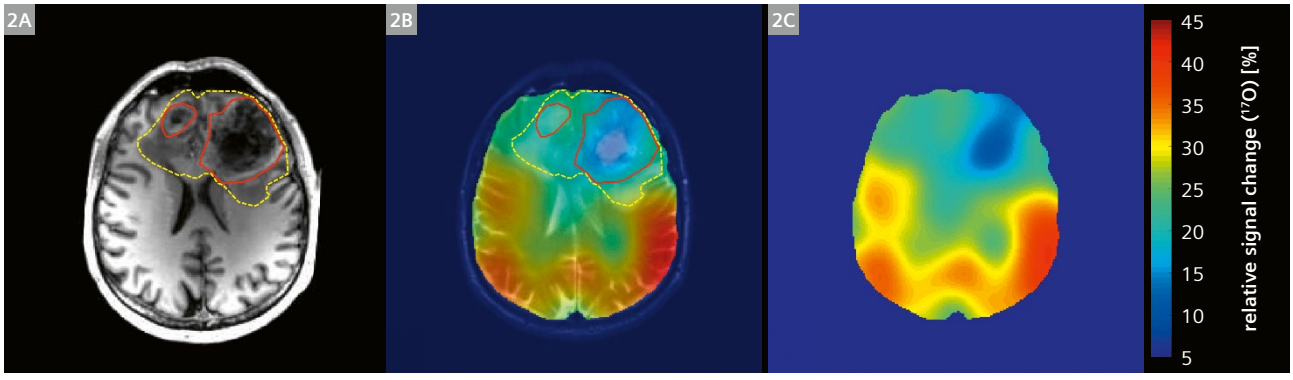
Gradients – not just for making pictures anymore

The gradient system is a key component of the MRI machine, being responsible for the spatial encoding in image generation and integral to controlling a range of physiological imaging contrasts, most notably diffusion-weighted MRI. The design and performance of the gradient system has substantial influence on the overall quality of the acquired images and has been the focus of intense engineering efforts over the last three decades in the quest for better image quality and ever-faster imaging speed.

Gradient performance is parameterized by the maximum gradient amplitude, which is measured in mT/m, and the slew rate, which describes how fast a gradient can attain a desired amplitude within a given amount of time and is measured in T/m/s. Since the inception of MRI, gradient amplitudes and slew rates have increased by orders of magnitude, roughly doubling every 10 years since the 1990's. In parallel, the push for stronger and faster gradients has been spurred by research applications, particularly in the brain. Early efforts to boost gradient performance for diffusion spectrum imaging led to the development of the AC88 head gradient by Siemens with a maximum gradient strength of 80 mT/m at a slew rate of 400 T/m/s. A seminal breakthrough in whole-body gradient design was achieved for the Human Connectome Project (HCP), culminating in the installation of the first Connectom[1] MRI scanner at the MGH Martinos Center in 2011, which featured a whole-body gradient with a peak gradient performance of 300 mT/m at a slew rate of 200 T/m/s. More recently, we have embarked on developing the next-generation Connectom scanner (Connectom 2.0)[1] in partnership with Siemens Healthineers, funded in part by the NIH BRAIN Initiative with the goal of comprehensive multi-scale mapping of structure and connectivity across the entire living human brain.

While advances in gradient technology have improved our understanding of the human brain through large-scale research efforts like the HCP and NIH BRAIN Initiative, the engineering advances required to achieve such strong gradient amplitudes and fast slew rates have directly informed and benefitted the radiological sciences and clinical imaging by encouraging the incorporation of stronger and

[1] *MAGNETOM Connectom is ongoing research. All data shown are acquired using a non-commercial system under institutional review board permission. Siemens Healthcare GmbH does not intend to commercialize the system.*



2 **Oxygen-17 MRI at 7 Tesla in a 63-year-old man with World Health Organization (WHO) grade IV glioblastoma.** **(2A)** Axial slice on T2-weighted fast spin-echo image (0.4 × 0.4 × 0.5 mm^3), **(2B)** T1-weighted magnetization-prepared rapid-acquisition gradient-echo image fused with a color-coded map of relative oxygen 17 (^{17}O) signal change, and **(2C)** without fusion of anatomical imaging. Regions of tumor tissue show a clearly reduced metabolic activity.

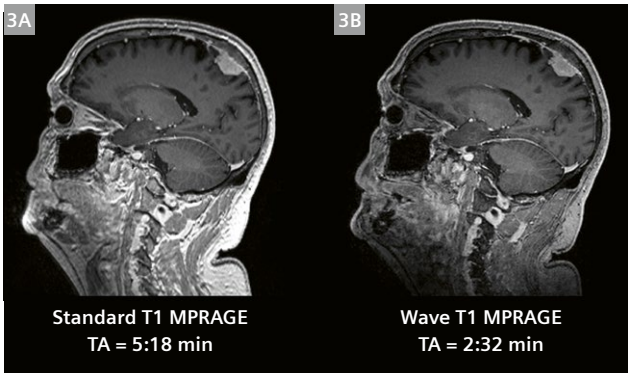
faster gradients into widely available products. The latest commercial scanners now feature integrated whole-body gradient systems with a maximum gradient amplitude of at least 80 mT/m, with maximum slew rates of at least 200 T/m/s; and with the Gemini gradient system[2] even 200 mT/m[3] with a slew rate of 200 T/m/s.

Where does the future lie with such powerful technology, and how can we best leverage such advances to make a difference for our patients? Below, we highlight a few of the key clinical and research applications that will benefit most from such powerful gradients, listed in order of those that are closest to our current clinical practice to those that will advance our limits of detecting, understanding, and managing disease in patients across a range of pathologies.

Anatomical MRI: The need for speed

Stronger and faster gradients stand to benefit the workhorse of clinical MRI – multi-contrast anatomical MRI – by substantially reducing image acquisition times across the full range of 2D and 3D imaging sequences that are routinely used in clinical imaging protocols. In the last decade, fast MRI has become mainstream in clinical practice, no longer limited to echo planar imaging, or relegated to specialized protocols designated for motion-prone or acutely ill patients. The benefits of stronger gradients for image encoding are straightforward. As a case in point, for a 3D T1-weighted MPRAGE sequence on the MGH Connectome[1] whole-body gradient system with G_{max} of 300 mT/m and slew rate of 200 T/m/s compared to a standard whole-body gradient system with G_{max} of 60 mT/m and slew rate of 200 T/m/s, the stronger gradients enable a reduction of repetition time by ~25% and reduction in echo time by ~50% through achieving shorter echo spacing, which translates into roughly ~25% reduction in acquisition time. Faster and stronger gradients act synergistically with AI-based tools, enabling higher acceleration factors that result in noisier images, which can then be cleaned up afterward with dedicated networks trained to reduce noise and sharpen images.

The push for shorter scan times has also led to the development of more efficient *k*-space sampling schemes for 2D and 3D imaging, which also benefit from better gradient performance, enabling such strategies to make it into the mainstream and introducing a range of novel fast imaging techniques to the clinic. Spiral *k*-space encoding makes efficient use of the gradient system hardware and has been used to achieve ultrashort echo times for real-time and rapid imaging applications. As another example, wave-controlled aliasing in parallel imaging (CAIPI) is a



3 Comparison of post-contrast three-dimensional T1-weighted magnetization prepared rapid acquisition gradient recalled echo (MPRAGE) images acquired with conventional parallel imaging and Wave-Controlled Aliasing in Parallel Imaging (CAIPI) encoding demonstrating a meningioma. Standard **(3A)** and Wave-CAIPI **(3B)** T1-weighted MPRAGE images show equivalent visualization of the dural-based enhancing mass along the parietal convexity. Both images were acquired on a 3T Siemens Healthineers MAGNETOM Prisma MRI scanner equipped with 80 mT/m maximum gradient strength and 200 T/m/s maximum slew rate. The Wave-CAIPI sequence was more than twice as fast as the standard sequence (acquisition time = 2:32 min for Wave-CAIPI compared to 5:18 min for the standard sequence). *Reproduced from [7]*.

3D parallel imaging technique that is using sinusoidal gradients to create corkscrew-shaped *k*-space sampling trajectories in all three dimensions. Wave-CAIPI takes full advantage of the 3D coil sensitivity information when using the high-channel count receiver coils to provide high acceleration factors with negligible artifacts and noise penalty across a variety of contrasts. In general, higher gradient amplitudes and lower bandwidth generate more voxel spreading, which is beneficial for reconstructing cleaner images, while faster slew rates make it possible to fit more sinusoidal cycles per encoding period, diminishing the amount of artifact in the resulting images. The diagnostic performance of Wave-CAIPI has been shown to be equivalent to that of standard 3D anatomical sequences acquired with conventional parallel imaging across a variety of contrasts with reduced scan time and motion artifacts (Fig. 3) [8–11].

In short, fast MRI techniques take advantage of strong gradients and fast slew rates to enable more efficient, higher resolution anatomical images for diagnosis across a variety of contrasts with reduced scan time and concomitant motion artifacts.

Diffusion MRI: From connectional anatomy to the microstructure revolution

The advent of stronger gradients has been a boon to diffusion-weighted MRI by boosting the efficiency of diffusion encoding. Stronger gradients enable a given b-value to be achieved in less time, resulting in shorter echo times and less signal loss from T2 relaxation. Beyond the straight-

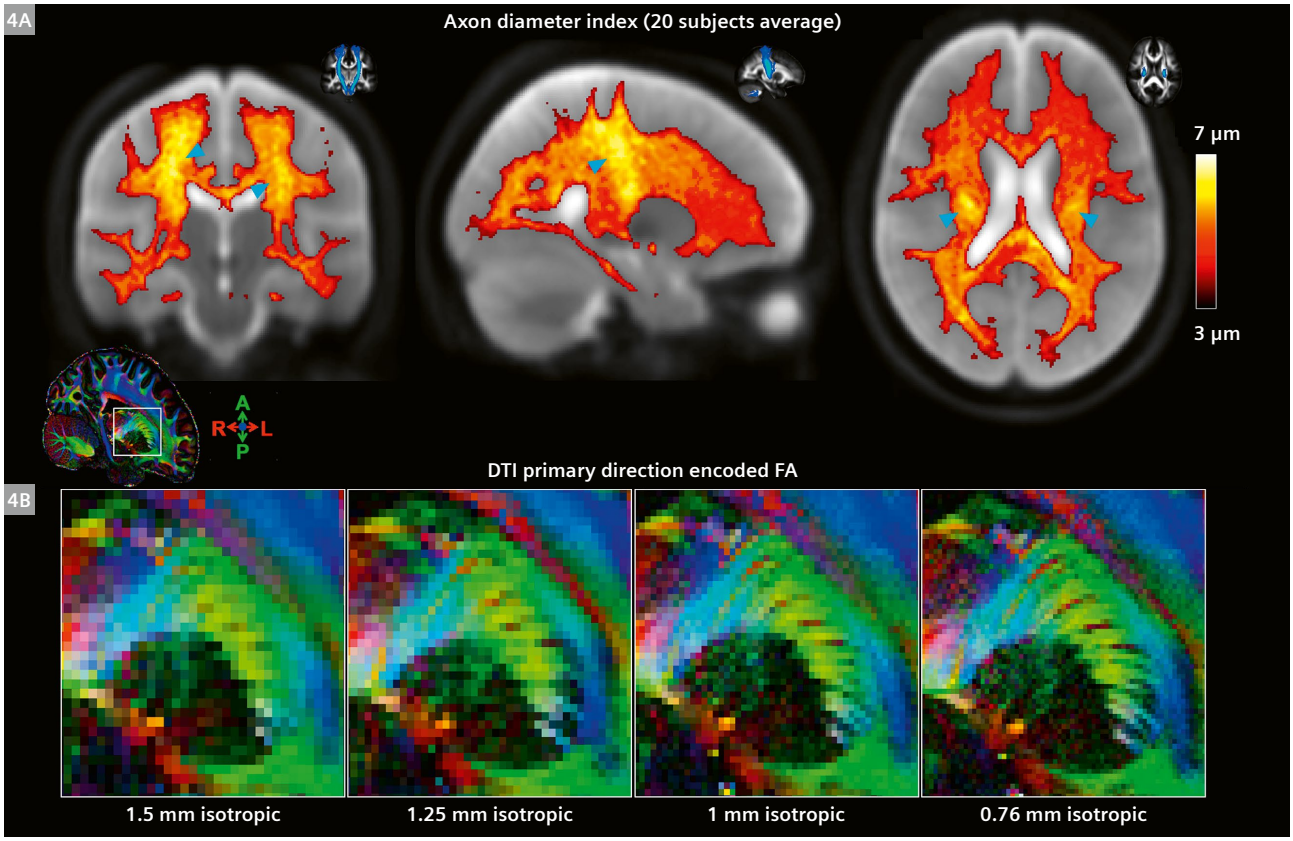
[2] *Work in progress. The system is currently under development and is not for sale in the U.S. and in other countries. Its future availability cannot be ensured.*
[3] *≥ 200 (±3% for design tolerances)*

forward SNR argument, stronger gradients enable higher b-values to be achieved for better resolution of microscopic tissue structure and exquisite delineation of crossing fibers (Fig. 4). The increased signal-to-noise ratio can be deployed to increase the spatial resolution of diffusion MRI, enabling sub-millimeter voxel size, which benefits applications such as diffusion tractography in the deep brain, where white matter tracts coursing through the deep gray nuclei and brainstem are packed together tightly, making it very difficult to resolve such structures for important therapeutic applications such as deep brain stimulation and focused ultrasound targeting.

The availability of dedicated high-performance gradient coils with large maximum gradient amplitudes also enables new classes of diffusion MRI measurements to be performed and provides a more sensitive probe of gray and white matter microstructure in various neurological diseases. High gradient amplitudes benefit the estimation of tissue microstructural properties such as cellular size and density, axon diameter mapping, and the dimensions of the extracellular space, which opens the door to improving pathological specificity with the level of detail typically relegated to the realm of invasive tissue biopsies and histological analysis, without the constraints of sampling bias or the risks associated with invasive procedures.

The advent of strong gradients for diffusion microstructural imaging may enable MRI to realize its true promise as a noninvasive imaging modality – monitoring disease activity and pathologic tissue change at the microscopic level in real-time, without the risk of radiation or the inherent risks of invasive sampling. The possibility of mapping tissue-level changes with a high degree of specificity might offer indicators of disease progression in a wide range of pathologic processes, such as increased cellular density within the tumor treatment bed, axonal loss and disability progression in multiple sclerosis, or impaired CSF clearance in neurodegenerative disorders such as Alzheimer's disease. Strong gradients will broaden our access as radiologists to a range of tissue-level parameters that are histologically and pathophysiologically relevant, offering new information to prompt a change in treatment course or management at an earlier disease stage, when such changes stand to make the biggest difference.

The greater availability of strong gradients for diffusion MRI will also enable the translation of novel diffusion-encoding paradigms to probe brain tissue microstructure



4 Benefits of strong gradients for diffusion MRI. **(4A)** In vivo axon diameter index maps enabled by high b-values using G_{max}~200-300 mT/m. Average axon diameter across 20 healthy subjects [12]. Blue arrowheads point to the corticospinal tracts, which show larger axonal diameter than the surrounding white matter. **(4B)** Fractional anisotropy (FA) maps of internal capsule at different spatial resolutions down to sub-millimeter 0.76 mm^3 spatial resolution [13]. *Reproduced from [14].*

in patients, including oscillating-gradient waveforms, double-diffusion encoding, and q-space trajectory imaging. As a case in point, a recent study combined isotropic diffusion encoding with strong diffusion gradients to achieve high diffusion-weighting in highly restricted, spherical compartments in the cerebellar gray matter while suppressing signal arising from anisotropic water within axons. By gaining greater specificity to cellular signatures in the cerebellum, such spherical tensor encoding performed with high gradient strengths may enable the earlier identification of cerebellar gray matter loss in patients with hereditary ataxias such as spinocerebellar ataxia type 2, which selectively affects the granule and Purkinje cells. The ability to probe microscopic diffusion anisotropy in brain tumors using q-space trajectory imaging may enable the differentiation of relatively indolent tumors such as meningiomas from high-grade glial tumors based on their cellular morphology and composition.

The results of these and many other clinical research studies demonstrate the potential of high-gradient diffusion MRI to uncover changes in axonal and cellular microstructure and motivate the continued development, application, and dissemination of high-gradient technology for use in commercially available human MRI scanners. Just as advances in fiber technology, starting from undersea cables to fiber optics and then the wireless revolution dramatically increased the accessibility and ease of communication, we believe that advances in gradient technology will increase the speed, availability, and clarity of imaging, while enabling the closer marriage between scientific discovery and clinical science to the benefit of patient care. Moving Connectome-like gradient strengths out of a few dedicated research facilities into the hands of radiologists and imaging scientists around the world promises to open up a whole new generation of clinical applications and discovery.

Conclusion

It is clear that in addition to the remarkable applications of the computational tools of AI and machine learning which we hear so much about today, the fundamentals of MR physics will continue to drive the benefits of, indeed the necessity for, further advances in the foundational components of our MRI systems: the primary magnetic fields which control and manipulate our MR signals, B_0, and gradients. We are fortunate to be witnessing yet another key step forward in these technologies with the arrival of 7T systems for clinical and broad translational research use, and "Connectom" class gradients for widespread applications outside select laboratories. As it has for four decades now, MRI continues to excite our imaginations for a boundless future.

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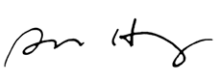

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