Journal of Magnetic Resonance 306 (2019) 55–65

Contents lists available at ScienceDirect

Journal of Magnetic Resonance

journal homepage: www.elsevier.com/locate/jmr

In vivo magnetic resonance imaging and spectroscopy. Technological advances and opportunities for applications continue to abound

Peter van Zijl [a,*], Linda Knutsson [b]

[a] Department of Radiology, Johns Hopkins University, F.M. Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA
[b] Department of Medical Radiation Physics, Lund University, Lund, Sweden

ARTICLE INFO

Article history:
Received 17 June 2019
Revised 19 June 2019
Accepted 8 July 2019
Available online 9 July 2019

Keywords:
MRI
Future
Perspective
Fast imaging
fMRI
Diffusion
Perfusion
Metabolism
Quantitative MRI
Standardization
Deep learning
Big data
Metabolic imaging
CEST
Molecular binding
Finger printing

ABSTRACT

Over the past decades, the field of in vivo magnetic resonance (MR) has built up an impressive repertoire of data acquisition and analysis technologies for anatomical, functional, physiological, and molecular imaging, the description of which requires many book volumes. As such it is impossible for a few authors to have an authoritative overview of the field and for a brief article to be inclusive. We will therefore focus mainly on data acquisition and attempt to give some insight into the principles underlying current advanced methods in the field and the potential for further innovation. In our view, the foreseeable future is expected to show continued rapid progress, for instance in imaging of microscopic tissue properties in vivo, assessment of functional and anatomical connectivity, higher resolution physiologic and metabolic imaging, and even imaging of receptor binding. In addition, acquisition speed and information content will continue to increase due to the continuous development of approaches for parallel imaging (including simultaneous multi-slice imaging), compressed sensing, and MRI fingerprinting. Finally, artificial intelligence approaches are becoming more realistic and will have a tremendous effect on both acquisition and analysis strategies. Together, these developments will continue to provide opportunity for scientific discovery and, in combination with large data sets from other fields such as genomics, allow the ultimate realization of precision medicine in the clinic.

1. Introduction

About 30 years ago, the field of in vivo magnetic resonance (MR) could approximately be separated into anatomical imaging for the clinic and research focused predominantly on multinuclear spectroscopy, large vessel flow technologies, relaxation mechanisms, hardware (RF and gradient coils) and faster scanning. Imaging approaches assessing tissue water diffusion, perfusion, and magnetization transfer processes were in their infancy and brain functional MRI (fMRI) approaches nonexistent. This is clear from reading a state-of-the-art review article from 1990 entitled "Functional Magnetic Resonance Imaging in Medicine and Physiology" [1], where the word "function" does not apply to brain activity, but to tissue macroscopic kinematics (cardiac, joint motion), tissue perfusion (macrovascular and microvascular), and water diffusion. The state of the field at that time was well represented by two societies, one more clinical (the Society for Magnetic Resonance Imaging, SMRI), and one more research oriented (the Society for Magnetic Resonance in Medicine, SMRM). The past 30 years has shown tremendous growth in a field now represented by a single International Society for Magnetic Resonance in Medicine (ISMRM) with close to 6000 members. The ISMRM currently has an annual meeting with more than ten parallel sessions containing new developments in anatomical, functional, physiological and molecular imaging approaches, both from a data acquisition and analysis point of view. This wide breadth of investigation is possible because of the inherent capability of MR to use radiofrequency (RF) pulses for "magnetic labeling" of nuclear spins and magnetic field gradients for "spatial encoding" of nuclear spins. Pulse sequences employing series of such RF and gradient pulses can be used for discerning magnetic relaxation (T_1, T_2, $T_{1\rho}$), physiological, functional, and molecular properties of the tissues under investigation. While these capabilities are spurring new discover-

* Corresponding author.
E-mail address: pvanzijl@mri.jhu.edu (P. van Zijl).

https://doi.org/10.1016/j.jmr.2019.07.034
1090-7807/

ies for basic science, this tremendous progress has mostly not been translated to the clinic, where only a small fraction of the many advanced methods (e.g. some dynamic contrast-based approaches, a few diffusion methods, and sometimes susceptibility weighted imaging or presurgical fMRI mapping) are being used routinely. This is not so surprising in view of the basic clinical model of need for reimbursement and validation for patient management, for which the versatility of MR is often counterproductive because of a lack of standardization, difficulty of interpretation of many advanced methods, and cost. However, recent progress in both data acquisition and analysis approaches and applicable artificial intelligence approaches makes clinical translation more likely in the near future. In this brief glance into the future of MRI, we will go over some of the subspecialty methodologies of MR and discuss potential for future innovation. Due to limited space and expertise (our work is mainly in brain imaging research) we are definitely not fully inclusive, but we hope that the general principles outlined will provide some insight into the possibilities for improvement of the technologies and their potential for influencing medicine and basic science.

2. Fast imaging

While early fast MRI approaches generally focused on adding more encoding gradients during the readout period, trends in the past two decades have exploited the redundancy of points in k-space in order to reduce their number. One approach is parallel imaging (PI) [2–4], in which the reduced sampling is compensated by an increase in the number of detection coils and spatial encoding is performed using simultaneous acquisition with multiple coils in different locations (so-called "sensitivity encoding"). However, the signal-to-noise ratio (SNR) reduces by the square root of the data reduction factor and by a geometric factor (g-factor). The latter depends on coil loading and the number of coil elements and their position and thus coil designs should be optimized for the organ size and shape in order to minimize SNR losses. More efficient PI alternatives are the simultaneous acquisition of slices [5,6], called simultaneous multi-slice (SMS) or multi-band (MB) MRI, and related 3D approaches [6], which allow acceleration by close to an order of magnitude. These do not suffer from SNR loss with the acceleration factor and can achieve a reduced g-factor due to the use of controlled aliasing [7]. A different approach that is gaining popularity is compressed sensing (CS) [8,9]. CS uses random-like under-sampling in k-space that leads to incoherent rather than coherent aliasing, which appears as noise in the data. This is followed by a non-linear analysis method that exploits the data sparsity and can remove incoherent aliasing because it is not compressible while image data are. Other approaches for fast MRI involve non-cartesian sampling, such as spiral [10,11] or radial acquisitions [12–14]. Especially radial acquisition is undergoing a revival and being combined with CS and SMS approaches [14–17]. This approach oversamples the center of k-space leading to higher SNR and also has the advantage that motion artifacts are spread out more over the image and can even be corrected for using the phase of the center point as reference. All of these methods are in the future likely to be combined with deep and machine learning approaches that can enhance SNR [18].

The use of faster imaging with preserved image quality has inherent advantages for the clinic. PI approaches like SENSE [3] and GRAPPA [2] are now available on commercial scanners and some manufacturers already have CS as a product. SMS/MB is also becoming available, but often still as a research package. In the future all of these approaches are expected to be further optimized (e.g. in terms of RF pulse power reduction and use of multi-transmit approaches [6]) and validated and to become generally available. They can be expected to greatly affect clinical efficiency by reducing scan time typically at least by a factor of two, but sometimes close to an order of magnitude (depending on the type of MR contrast), while retaining diagnostic quality [19]. Ultimately these advances, together with active motion tracking (MRI-based or optical [20,21]) and real-time correction of the field of view, may even reduce the need for anesthesia in the pediatric setting [22]. For research, these approaches will allow us to keep increasing the information content of studies by retaining the same total scan time, while increasing spatial or temporal resolution, adding contrast information (e.g. more orientations or weighting strengths for diffusion MRI), or adding additional contrast types [23–25].

3. Imaging of microvascular perfusion and macrovascular flow

MR angiography (MRA) and contrast-enhanced (CE) MRI using gadolinium (Gd) based contrast agents (GBCAs) have been essential mainstays in the clinic since the mid-eighties. Some clinics now also include dynamic susceptibility contrast (DSC) imaging to assess perfusion and perfusion-related parameters such as cerebral blood flow (CBF) and volume (CBV), time to peak (TTP), and mean transit time (MTT = CBV/CBF). CBV is quantified from the ratio of the first-pass dynamic tissue concentration time curve and the arterial input function (AIF) on T_2/T_2^*-weighted images, while CBF is estimated by deconvolving this tissue curve with the AIF [26–28]. DSC technology has been improved substantially over the past decades, now including for instance a pre-bolus injection to minimize T_1 effects [29] and use of venous output functions (VOFs) to correct the AIF for partial volume effects [30,31]. Dynamic contrast enhanced (DCE) MRI uses T_1-weighted contrast to assess microvascular hemodynamics, especially for the study of blood brain barrier (BBB) disruption, for instance in tumors and dementia [32–36]. A semi-quantitative approach is to determine the area under the curve (AUC) for the tissue input function, but a more quantitative assessment of tissue microvascular properties is possible using curve fitting based on the Kety approach for inert tracers [37], such as for instance the Tofts and "extended Tofts" models [38–40]. When using a dual injection, both DCE and DSC parameters can be assessed, with the first Gd injection correcting for T_1 effects in the DSC acquisition [41]. Simultaneous measurement of DCE and DSC has also been proposed using a multi-echo approach [42,43]. DSC and (to a lesser extent) DCE are already in the clinic and standardization efforts are ongoing [36,44]. For the future, a main issue is patient concern about being injected with a metallic contrast agent now that GBCAs are being issued with regulatory warnings. While the risk for Gd-based macrocyclics is minimal, the abundant press releases about tissue uptake of GBCAs upon repeated use (e.g. in multiple sclerosis patients) are instilling fear in patients. In addition, these compounds are expensive. An important future effort will therefore be in contrast agent design, for instance metallic agents that are more kinetically and thermodynamically stable, but especially non-metallic alternatives. In this respect, the recent development of the field of Chemical Exchange Saturation Transfer (CEST) MRI [45,46] is very timely. In this contrast type, millimolar concentrations of both paramagnetic (paraCEST [47–50]) and diamagnetic agents (diaCEST [46]) can be detected with the water signal due to the fact that the saturation (a type of magnetic labeling) of exchangeable protons (diaCEST) or water molecules (paraCEST) on the solutes is repeatedly transferred to the water and the presence of these solutes can be detected with greatly enhanced sensitivity (two-three orders of magnitude). Some of the diamagnetic agents are already being tested in humans, including the use of clinically improved CT agents such as iopamidol and iopromide [49,51] and sugars [52–56]. Other compounds being developed are aspirin

derivatives [57] that have a large chemical shift difference with water. In addition to detecting these agents with CEST methods, they also affect spin-lock and transverse relaxation times [58–60], expanding opportunities to detect them. This is a field with great potential because any compound that contains exchangeable protons can in principle be used as a contrast agent. However, due to a small effect size, motion artifacts will be more problematic and have to be resolved [61].

CBF can be assessed noninvasively with arterial spin labeling (ASL). Conventionally, this approach is based on the difference signal of two scans, with and without labeling of blood water protons flowing into the brain, and contains a post-labeling delay period for delivery of label to tissue. As a consequence, this method suffers from low SNR (about 0.5–2% of the water signal) and because multiple scans need to be averaged, from motion effects. Many approaches for labeling blood water protons have been proposed, but a recent consensus paper [62] suggesting the use of pseudo-continuous ASL (PCASL) has stimulated the manufacturers to implement this approach as a product, which may ultimately lead to clinical reimbursement as applications look promising, e.g. for the assessment of cerebrovascular disease, cancer, and dementia [63]. As is typical for MR, new and promising approaches are around the corner, especially velocity-selective ASL (VSASL [64]), in which water spins are labeled in the vessels in the brain either by dephasing or inversion [65]. This approach has a sensitivity comparable to PCASL, but the advantage of not needing a long delay, providing better sensitivity in regions like white matter and the occipital lobe. The latter is especially important when using ASL for functional MRI [66]. This approach can also be used to quantitatively assess CBV [67], and can be combined with SMS/MB approaches for higher sensitivity per time unit and faster acquisition.

Another non-invasive method proposed for measuring perfusion and its related parameters is intravoxel incoherent motion (IVIM) MRI [68,69]. It was originally based on the assumption that, within a voxel, the capillary microvasculature is oriented randomly, causing a diffusion-like phenomenon with a much higher pseudo-diffusion coefficient D^*. This IVIM principle interprets the typically multi-exponential signal decay in a diffusion experiment in terms of two compartments, microvascular (fraction *f*, constant D^*) and tissue (fraction *1-f*, constant *D*). While experiencing some enthusiasm early on, this approach was never very practical due to the need for very high SNR (~400) of the IVIM signal component to reliably determine *f* and D^* [70,71]. Improvements in equipment and extension of IVIM to other "incoherent" motions in a voxel have spurred a recent revival, leading to some optimism about potential applications for perfusion parameter assessment, especially in tissues with higher microvascular fraction (kidney, pancreas, liver, placenta, malignant tumors) [72–75]. However, this method needs careful assessment and additional validation. Much of the data appears to show that, even in the body, large vessel arterial signal (long T_2^*) dominates the effect. Similarly, in the brain, where CBV is only about 5% and the capillary fraction 3%, voxel components such as CSF and arterial blood will also dominate the signal at longer TE and higher field. Recent data show that flow compensation can remove most of the multi-exponential decay in the brain [76]. This indicates that much of the motion for this fast-decaying water contribution in the voxel really is coherent, and the decay in large part due to velocity encoding or pass-through-voxel suppression. In addition, it is clear that transverse relaxation needs to be corrected for to avoid: (i) an apparent TE-dependent increase in *f* [70], and (ii) an apparent field dependence of *f*. Recent work in the field has shown some intriguing possible IVIM applications, e.g. for retrieving CBV and CBF related effects [72,74] and for assessing malignancy [75]. More applications may exist, which have to be tested in terms of reproducibility, specificity and sensitivity for individual organs and applications. However, while changes in IVIM-theory-based parameters may prove to be valuable for assessing tissue changes in disease, this is not a validation of the presence of an IVIM (incoherent motion) effect, and care has to be taken not to make erroneous interpretations in terms of the physiological contributions underlying such effects.

With respect to advances in large-vessel imaging, it is of importance to realize that velocity-selective encoding can also be used for MR angiography or venography with several advantages over time of flight (TOF) approaches. These include a much larger field of view, superior slow-flow depiction, and high time efficiency (no subtraction needed) [77]. When combined with compressed sensing, VS-MRA and VS-MRV can be performed in less than two minutes each, making this clinically attractive.

4. Imaging of tissue water diffusion

Imaging of water diffusion is a large field of study with thousands of papers each year. The main topics are anatomical imaging of anisotropic tissue structures, e.g. white matter fibers in the brain [78–80], and the assessment of microstructural tissue properties [81,82]. From an acquisition point of view, the principles employed for diffusion encoding are very similar to those laid out before the turn of the millennium, but these are now being extended for new types of data acquisition that are leading to new applications. All of this innovation is possible due to a major increase in fast imaging technology (see above) and in the gradient strength available on human scanners spurred by the interest in white matter connection atlases [83], especially as part of the human connectome project [84].

The random microscopic motion of diffusion can be assessed using dephasing-rephasing pairs of gradients with only a few variable acquisition parameters, i.e. the strength (G) and orientation ($\widehat{\boldsymbol{G}}$) of the gradient vector ($\bar{\boldsymbol{G}} = G \cdot \widehat{\boldsymbol{G}}$), its pulse duration ($\delta$), and the diffusion time, t_{dif}, combined in the b-value, defined as $b = \gamma^2 \bar{\boldsymbol{G}}^2 \delta^2 t_{dif}$ (diffusion weighting factor). These can be varied to assess the apparent diffusion coefficient (ADC) in a voxel and the apparent diffusion displacement $\bar{\boldsymbol{r}}_{\boldsymbol{A}}$. This sounds simple, but tissue voxels consist of multiple microenvironments (e.g. cells, microvessels, extravascular extracellular space (EES)) at multiple orientations, separated by barriers of variable permeability. This causes $\bar{\boldsymbol{r}}_{\boldsymbol{A}}$ to become susceptible to restrictions that vary with the diffusion direction and microstructure dimensions, causing the measured ADC to be dependent on both gradient-vector orientation and diffusion time. The water signal reduction is described by:

$$\frac{S}{S_0} = e^{-\gamma^2 G^2 \delta^2 t_{dif}\, \widehat{\boldsymbol{G}} \cdot \bar{\bar{\boldsymbol{D}}} \cdot \widehat{\boldsymbol{G}}} \quad \text{or} \quad S/S_0 = e^{-\bar{\bar{\boldsymbol{B}}} : \bar{\bar{\boldsymbol{D}}}} \tag{1}$$

in which S and S_0 are signals with and without diffusion weighting, respectively, $\bar{\bar{\boldsymbol{D}}}$ the apparent diffusion tensor, and $\bar{\bar{\boldsymbol{B}}}$ the so-called "b-tensor" [85] or b-matrix [86], a matrix proportional to b and the outer product of the gradient orientation with itself ($\bar{\bar{\boldsymbol{B}}} = b\widehat{\boldsymbol{G}} \otimes \widehat{\boldsymbol{G}}$). The tensor order is indicated by a superscript line (scalar is order zero, vector order 1, etc) and each dot product represents a tensor contraction, leading to a reduction of two in the order of the tensor product. The b-tensor formalism is convenient when applying gradients of different directions simultaneously before data acquisition, which induces detection of combinations of diagonal and off-diagonal diffusion tensor elements [87–89]. The b-tensor can be crafted to assume different shapes such as linear, spherical and planar [85,90,91] and, by using a variety of b-tensor shapes, anisotropic and isotropic (orientation-invariant) properties of the diffusion tensor (or, better, of the distribution of tissue diffusion tensors in a voxel) can be studied [81,85,87,91–98]. This can for

instance be used to distinguish tissue average orientation (voxel-level anisotropy) from microscopic anisotropy and isotropic tissue heterogeneity [81,91]. Anisotropy can be quantified in many ways, either in terms of different ratios of diffusion tensor element combinations [99,100] or by assessing elements of the fourth-order diffusion tensor covariance tensor [85,101].

Because tissue consists of many compartments, the above equation should in principle contain a sum of exponentials over all of these if compartments could be separated. However, since most membranes are permeable, compartments mix and, depending on the diffusion time, the system can be seen to be in the slow, intermediate, or fast exchange regime. If the system can be simplified as consisting of two compartments of sufficiently differing ADC, variation of the diffusion time can in principle be used to assess permeability and transport [102–104]. However, when varying the diffusion time in an experiment with a single pair of pulsed gradients, the effects of restriction and exchange will be mixed. This can be avoided by using a set of two equivalent diffusion blocks in which the diffusion time is fixed and the time between (mixing time t_m) varied [105]. The first functions as a diffusion filter to separate the more restricted compartment (slower ADC) from the free compartment (fast ADC) by substantially reducing signal from the latter. The second measures the diffusion constant of the system prior to imaging, which will change as a function of t_m. In tissue, correcting for the filter efficiency and assuming comparable T_1 and T_2, one can use the t_m dependence to determine an apparent exchange rate (AXR), a reflection of cell membrane permeability and compartment fractional water population [106,107].

Due to the improved hardware in terms of gradient strength and the advances in diffusion encoding, there is a renaissance in the field of diffusion-based microstructural assessment on the human scanners [81,91]. Recent exciting developments include the optimization of b-tensor encoding patterns [108–110] and parameters for assessment of tissue anisotropy versus heterogeneity and density [81,91] or of permeability [111]. This is a necessary effort to facilitate practical application to clinical problems (i.e. minimize acquisition time with maximum and reproducible information content). We foresee continued progress in this field in the coming decade, especially for tumor imaging [112,113]. In addition to the development of these practical tissue assessment approaches, there also will be a continued push toward higher resolution acquisition and many efforts in the advanced diffusion-based modeling of tissue microstructure, [81,82,114–117] exploiting diffusion data based on linear, planar and spherical tensor encoding and probes of the time dependence of diffusion and relaxation properties.

5. Functional magnetic resonance imaging (fMRI)

Data acquisition for fMRI has benefitted tremendously from many technological advances in the past decades, especially the move to higher fields (3T, now standard, and 7T or higher [118,119]). This provides the combined advantages of higher BOLD contrast to noise ratio (CNR) and higher SNR (both approximately linear with field), allowing improved spatial resolution and, concomitantly, better localization of the neuronal activation foci. The simultaneous development of high-density phased-array coils [120,121] has improved SNR even further (especially in the cortex), allowing rapid advances in parallel imaging approaches [6], which at high field benefit from a strongly reduced g-factor. Using the SMS/MB approaches (see above) developed as part of the human connectome project (HCP, [122]), fMRI temporal resolution can be reduced to below 700–800 ms. This and further reductions will enable investigators to separate out aliasing effects of body physiological effects such as cardiac and breathing motion, allowing more specific detection of brain networks [123,124], and even the tracking of dynamic changes among networks [125,126]. We foresee that all of these developments will in the future be commercially available products. This will likely lead to new neuroscience discoveries at high-end research sites (3T, 7T or higher field), while providing more standardized fMRI acquisitions that can fit in a timeframe sufficiently short for the clinic (3T and even 1.5T), where some fMRI applications may be useful, e.g. for neurosurgical and psychiatric disease [127] assessment. This is already happening to some extent in the research setting, allowing the acquisition of large datasets that are widely available for the neuroscience community, such as for the HCP and other multisite projects in the USA (see below).

With respect to advances in fMRI contrast, work by Kim et al. [128,129] has shown better localization of spin echo signal changes for the BOLD effect in tissue. It is now possible to perform whole-brain T_2 fMRI studies at 7 Tesla [130], which benefit from reduced dropout in regions like the frontal (near nasal cavities) and temporal lobes. In addition, the vascular space occupancy (VASO) functional MRI method based on blood volume changes, which also is much better localized to the microvasculature [131,132], improves strongly at high field [133]. CBF based fMRI is often harder at high field due to the excitation limit of the transmit coil and B_1 inhomogeneity, but this can be addressed either with local coils or multi-transmit coils or, better, by using alternative ASL approaches such as VS-ASL (see above). BOLD, VASO and ASL methods can be acquired simultaneously and combined for actual quantification of changes in oxygen metabolism [134–136]. In the future it should be possible to speed up such single-shot ASL/CBV/BOLD methods with fast acquisition and allow whole-brain determination of $CMRO_2$ for scientific or clinical purposes. Overall, we expect the bulk of whole-brain fMRI studies for neuroscience to remain at 3 Tesla, while high field scanners using high-resolution scanning for the approaches above will push the limits of scientific discovery, e.g. by allowing the study of cortical layers [119,137–140].

6. Quantitative MRI (T_2, T_2^*, T_1, magnetic susceptibility, MT) for assessing tissue properties

The intensity and frequency of the water signal in an MRI voxel depend on the fields its protons experience, which are determined not only by the static magnetic field and the magnetic susceptibility effect of the voxel tissue and its surroundings (tissue, air, etc), but in addition by the local microscopic fields and field differences imposed by tissue compartments and molecules [141]. To complicate matters, these fields are affected by the shape of tissue structures, the effect of which is modulated by the orientation of the organ in the static magnetic field, as well as by local microscopic motion (e.g. diffusion or molecular rotation) and molecular or proton exchange processes (e.g. between structures of different mobility or different susceptibility). While the frequency measured for the water reflects the field average, the line shape reflects the field differences (frequency spread). The signal amplitude and frequency also depend strongly on the pulse sequence timing, which affects the visibility of the different water components. For instance, a longer echo time (TE) will reduce signals with short T_2 (T_2^*), while signal of protons encoded by pairs of dephase-rephase gradients will be lost depending on the length of t_{dif} and the gradient strength and length (see above). Increases in TE, t_{dif} or inversion delay time (TI) will cause averaging between compartments, mix diffusion and relaxation effects (see diffusion section), and increase the influence of magnetization transfer (MT) contributions. Basically, such timing variation transitions the MRI measurement into different exchange or diffusion regimes that

can be fast, slow or intermediate [102,142,143]. The pulse sequence character itself is obviously important, e.g. a spin echo will refocus static field inhomogeneities, while a gradient echo sequence does not. More RF pulses will increase saturation of solid-like tissues and signal will be lost due to MT. Overall, MRI signal interpretation is complicated and even though tissue modeling can be done, this is generally only based on simplified models and thus incomplete.

Importantly, however, the parameters determining the water signal, i.e. Proton Density, T_2, T_2^*, T_1, the magnetic susceptibility (χ), MT (exchange rates, tissue populations) and diffusion constants (exchange rates, restrictions) reflect the tissue composition and may have value for clinical diagnosis of tissue disorders. For example, χ, T_2, and T_2^* are affected by the tissue concentrations of iron (ferritin in tissue and hemoglobin in blood), calcium, myelin, etc. [141,144]. These properties are the subject of investigation in the fields of susceptibility-weighted imaging (SWI) [145] and quantitative susceptibility mapping (QSM) [146,147], which continue to progress rapidly, with their status summarized in a recent special issue of NMR in Biomedicine [148]. QSM has great potential for the use of quantitative iron imaging for assessing neurodegenerative diseases [149–152], such as Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), as well as for determining blood vessel oxygenation [153]. Its use for myelin and calcium assessment is being investigated [147,154–156]. Several other fields of quantitative myelin mapping are also progressing steadily, e.g. fitting of multiple T_2 pools [157] from multi-TE data or determination of MT parameters [158–160], such as exchange rate of bound water to free water and tissue fraction, from data acquired as a function of saturation parameters (length, strength). The use of transverse relaxation rates to determine blood vessel oxygenation is also becoming more popular [161]. These are just some examples out of many possibilities for tissue property assessment.

This development of qualitative or quantitative techniques to assess these properties is important, because any of these parameters, or their combination, is a potential biomarker that can affect diagnosis or prognosis of disease. With respect to the future, the development of such quantification methods and their validation with respect to providing a biomarker are fields of continuing active research in MRI. Quantification involves variation of the timing of the pulse sequences and the strength and length of RF and gradient pulses. As this is time consuming and not very practical for a clinical exam, there is an ongoing effort to speed up such approaches. The fast imaging approaches discussed above are a good start, but more is needed. Recently, a strategy called "MR fingerprinting (MRF)" was introduced [24,162], in which the most time-efficient and optimal variation of multiple pulse sequence parameters is used to acquire an under-sampled data set. Tissue parameters are then quantified by comparing this minimal dataset with a simulated library of signal variation patterns based on the sequence used. While under-sampling leads to image artifacts, these are not destructive for determining quantitative parameters when such artifacts are spatially or temporally incoherent, which thus becomes a factor in sampling design [24,162]. The analysis portion of MRF is expected to be readily combined with or replaced by deep learning technologies and many MRF approaches are expected to become available in the near future both for existing MRI sequences and new combinations of sequences [162]. There is a great expectation that multiple biomarkers useful for the clinic will come out of this, which can then be combined with markers from other imaging or clinical markers for precision medicine. In addition, the availability of these parameters can be used to synthetically generate other image contrasts with which the radiologists are familiar and that are now being acquired separately, a field called synthetic MRI [163,164]. This trend of time savings combined with availability of more information will likely continue for many years to come. Ultimately, all of this information will be available in age-dependent brain or other tissue atlases in a manner that can be referenced for clinical and research analysis [165,166].

Finally, as mentioned above, the field in a voxel depends on the tissue microstructure and the magnitude of some of the above MRI parameters, especially T_2^*, depends on the orientation of the tissue with respect to the magnetic field. This can be described by the average magnetic susceptibility tensor for such a voxel [167]. Similar to diffusion tensor MRI, where the gradient direction is varied, tissue susceptibility tensor information can be obtained by varying the orientation of the magnetic field with respect to the subject, which has already been used to successfully assess white matter fiber orientation in animals [168]. Efforts are ongoing to also do this in humans, but these are hampered by the impracticality of rotating the subject in the narrow coil in the scanner and the fact that even more than six orientations are in principle needed, because the tensor has to be determined while at the same time solving the inverse problem for determining voxel tissue susceptibility [167,168]. However, since susceptibility images can be acquired at much higher spatial resolution than DTI images, there is the potential to perform fiber tracking of smaller structures, which is currently being pursued.

7. Metabolic spectroscopy and imaging

Magnetic resonance spectroscopy (MRS) and imaging (MRSI) for the assessment of metabolites has been around for decades and remains an exciting topic for research and discovery [169]. For instance, the field of spectral editing [170,171] has made a strong come-back and the proton MRS field is benefitting from SNR improvements due to the availability of higher field and phased-array coils. However, despite a brief period of clinical reimbursement for single-voxel proton MRS, this method is generally considered too complicated for standard clinical use, which is a pity due to the great potential of metabolic information to provide important biomarkers for many diseases and disorders, especially for the brain [172,173]. A recent technical consensus paper [174] on what is required to progress proton MRS and MRSI as clinical tools still lists problems that have been around for decades. Two main reasons prohibiting such implementation are the duration of comprehensive organ studies and the need for MRS expertise to assess the presence or absence of artifacts, e.g. due to chemical shift displacements, lipid contamination and motion. Improved speed is becoming available through technologies for reduced sampling and SMS acquisition (see fast imaging section). However, until automation for both acquisition and data analysis is achieved together with manufacturer standardization, the need for high-level specialized expertise will probably remain the conclusive barrier. One potentially bright aspect for the future of automation is the rise of deep learning approaches, especially if these methods can account for the influence of artifacts [18,175]. For metabolite assessment, one could envision these to exploit large training datasets of spectra and libraries of simulated spectra for the coupled nuclei, which is a quite realistic prospect.

MRS and MRSI predominantly focus on equilibrium metabolite levels. While these may change as a consequence to disease, such assessments may be misleading. For instance, high lactate in tumors could be showing necrosis as well as ongoing anaerobic glucose turnover. Assessment of active metabolism is more informative, which is also possible with MRS(I) using substrates labeled with heteronuclei, especially ^{13}C, which, contrary to PET can provide information not only on glucose uptake, transport and phosphorylation, but also downstream cellular products [176–178].

Unfortunately, such nuclei are less sensitive than ^{1}H and require hardware not available on standard MRI scanners, reducing clinical potential even more. However, despite these obstacles, there has been great progress in this field through the use of hyperpolarized ^{13}C substrates [179]. This has led to the development of dedicated hyperpolarizers that can provide sterile and pyrogen free tracers close to the scanner, a necessity due to the short T_1 of such substrates and the availability of a single large Z-magnetization and thus a single acquisition when a 90° pulse is used or more with lower flip angle. There is clear clinical potential, especially for ^{13}C-pyruvate based assessment of active tumor metabolism [180–183], but the short T_1, the large expense per experiment, and need for dedicated polarization equipment and scanner hardware remain formidable issues. However, there is a continuing strong basic science interest in the field, which has led to new approaches for hyperpolarization, such as using signal amplification by reversible exchange (SABRE) [184], and for lengthening ^{13}C T_1, e.g. using singlet states [185]. An interesting approach to avoid the need for specialized equipment is the indirect detection of ^{13}C substrates and metabolites through the water signal [186] using magnetization transfer through the nuclear Overhauser enhancement (NOE). Recently, an alternative and promising method for studying active brain metabolism has been suggested [187], using deuterated instead of ^{13}C labeled tracers, also allowing the detection of metabolic products from cellular metabolic pathways. This approach has great potential for human research, but will need to be further explored for feasibility in the clinic, where it suffers from the disadvantage of needing non-standard hardware.

A main issue for spectroscopy has always been that the concentrations of the metabolites are in the millimolar range, requiring a voxel size on the order of about 1 mL to achieve sufficient signal for ^{1}H spectroscopy and even larger for other nuclei (^{31}P, ^{13}C). This issue is now being addressed using the CEST MRI approach (see above) which allows mM concentration compounds to be detected with molar water sensitivity [45,46,188,189]. MRS and CEST are intrinsically related [190], with MRS providing better specificity in the spectrum due to narrower signals, but with the saturation spectrum (Z-spectrum [191]) having one to two orders of magnitude more SNR. Despite reduced specificity due to the presence of multiple overlapping exchange- and saturation-broadened spectral components, early CEST work shows potential for imaging tissue components such as glycosaminoglycans [192] and mobile cellular proteins [193], as well as metabolites such as glutamate [194] and creatine derivatives [195–197]. Some of these are already showing great potential [188], especial for tumor assessment [198–202], muscle exercise [196,197], neurodegeneration [203,204] and lateralization of epilepsy focus [205]. The CEST field has grown fast (the most recent CEST workshop had about 200 attendees) and extensive growth is expected to continue. However, many technical issues remain to be addressed. For instance, since CEST is a magnetization transfer effect, there are many potential contributions to the signal and the specific detection of particular compounds is far from trivial. Contrary to MRS, where spectral composition changes with TE, the relative contributions of Z-spectral components (metabolite-based CEST, direct water saturation, semi-solid based MT contrast) change as a function of RF parameters such as saturation power (B_1) and length, the number of RF pulses, and the inter-pulse spacing [191]. Even when components can be separated out with fitting, their signal may not reflect the true concentration at each B_1 because the different saturation components compete for intensity. In addition, the proton exchange rates and thus the signal contributions of these components depend on the pH of the system with sometimes opposite effects. For instance, very fast exchanging protons become better visible at lower pH as they can be better saturated, while the signal of slow exchanging protons will reduce. In order to move the field forward, theoretical developments to improve spectral interpretation and new approaches to improve specificity are being developed at a high rate. Some examples of the latter include including fingerprint like approaches [206–208] to separate exchange rates and signal intensities, and spectral editing approaches to remove interfering signals. The latter ones, instead of continuous saturation, use repeated series of so-called label-transfer modules to combine the principle of editing with signal enhancement [190,209–211]. These developments will be important to avoid misinterpretation of the CEST data. However, the potential of this field for investigating tissue components with the resolution of water imaging and for the development of contrast agents (see Perfusion section) seems unlimited, with many technologies still to be developed and many applications still to be explored. One recent promising aspect is the use of CEST MRI to assess both strong [212] and low-affinity [213] molecular binding.

8. Data standardization, big data, radiomics, deep and machine learning

We live in an age of interconnectivity, allowing scientists to more easily share and combine data for more in depth scientific query with larger numbers of subjects. However, the versatility of MR technologies comes with the disadvantage that, even for presumably the same pulse sequence, data between different sites are often incompatible due to small parameter mismatches. Even minor differences, such as in RF pulse shape and strength, gradient pulse shape and strength, and inter-pulse delay times, will cause changes in the magnitude or specificity of contrast, especially when competing contrasts use very similar pulse sequences, such as for instance CEST, ASL and MT acquisitions [214]. In addition, depending on the intellectual property arrangements, manufacturers often have slightly different parameter implementations for the same acquisition methods and even use different nomenclature, e.g. for spoiled gradient echo: T_1-FFE (Philips), FLASH (Siemens), SPGR (GE), RSSG (Hitachi). To make matters worse, any scanner upgrade may again come with small changes and even at the same physical sites such upgrades have led to data differences that are hard to account for without proper insight into the technical adjustments. A good example of this is for brain segmentation, where spatially varying improvements in SNR may lead to changes in the tissue boundary clarity and result in different tissue volumes. Similar things happen when improving spatial resolution with better scanners and changing contrast with increasing field strength. A promising approach to account for such changes in a longitudinal study at a single site, or even for multi-site studies, is the recent availability of deep-learning approaches that can be trained by acquiring datasets on the same volunteers before and after an upgrade or at different sites and then applied to harmonize the other data [215].

In this era of "Big Data", the call for data standardization is increasing, more consensus papers are appearing, and several countries have organizations pursuing more coherent quantification efforts for MRI measurements, for example the Quantitative Imaging Biomarkers Alliance (QIBA) in the USA [216] and the European Imaging Biomarker Alliance (EIBALL) in Europe [217]. Data harmonization approaches will certainly be important to help with this. Currently, several large longitudinal studies are ongoing that depend on proper data standardization (e.g. Alzheimer's disease neuroimaging initiative [218,219], human connectome project [220], Adolescent Brain Cognitive Development [221], UK biobank [222], baby connectome project [223]) and the expectation is that more and more of such studies will be initiated by the large fund-

ing agencies. While there is a danger that the requirement for similar acquisitions may stifle the continuing improvement of acquisitions and even lead to the undesirable and unscientific tendency for manufacturer-preferred decisions at grant review, it has the advantage of the generation of common data sets that may accelerate discovery of disease mechanisms. In addition, such datasets can be used as training sets for deep and machine learning approaches that can ultimately be applied to more automatically and sometimes better recognize patterns that will allow clinicians to diagnose otherwise hard to find lesions, disease progression, or treatment responses [224–226]. Deep and Machine learning methods will continue to grow and lead a paradigm shift in MRI in the field of medicine. Coupling with quantitative measures of image texture, called radiomics [225,227,228], is expected to give clinicians a better understanding of the patients health, more accurate diagnosis, and improved understanding of the disease. These MRI data will ultimately be combined with data from other imaging modalities and from genetic, histologic, neurologic, and other clinical assessments, thus leading to the realization of precision medicine and increasing the potential for new discoveries in basic science.

9. Conclusions

It remains truly amazing how the availability of two tools, radiofrequency application for "magnetic labeling" and gradient pulse application for "spatial encoding" continues to spur the development of innovative tools for anatomical, functional, physiological, metabolic and molecular imaging using magnetic resonance. At the same time, advances in coil hardware (another paper in this issue) continue to tremendously increase signal to noise and the versatility of acquisition approaches, while the development of computer hardware is allowing faster and often real-time on-scanner reconstruction as well as the use of advanced library-based data interpretation technologies using compressed sensing and deep learning. More information for multiple contrasts will be acquired per time unit, benefitting both research and the clinic. As such, at an age of a little over 40 years, the field of in vivo magnetic resonance continues to innovate and expand beyond what was envisioned.

We expect a drive towards the generation of large data sets, which in turn requires a standardization of methodology. While this will be useful for the development and use of deep learning approaches and will no doubt lead to new and important discoveries, we should not forget that MR technology is characterized by versatility and we will continue to see the development of more powerful methods and new contrasts that can and should be included in future studies. For the clinic, standardization of methods is crucial and the increase in speed provided by parallel imaging, reduced sampling, and machine learning will quickly become commercially available. This will allow new types of contrast to be included in clinical exams, that is as soon as they have proven to be relatively straightforward to interpret or can be automatically assessed, e.g. with machine learning. Approval for reimbursement for such exams will of course facilitate implementation. We foresee the availability of automated quantitative multiparameter multi-contrast methods on most MRI scanners, which will no doubt stimulate new basic discoveries in research and contribute to precision medicine becoming a reality in clinical diagnosis.

Acknowledgements

We are grateful to Drs. Markus Nilsson (Lund University) and Drs. Peter B. Barker, Michael A. Jacobs, Hanzhang Lu, James J. Pekar, and Jinyuan Zhou (All from Johns Hopkins University School of Medicine and Kennedy Krieger Institute) for carefully reading the manuscript. This work was supported by funds from the National Institutes of Health (NIH), National Institute of Biomedical Imaging and Bioengineering (EB015909, EB019934, EB015032, EB024495), National Institute of Child Health and Human Development (HD079123), the Swedish Research Council (grant 2015-04170), the Swedish Cancer Society (CAN 2015/251, CAN 2018/550) and the Swedish Brain Foundation (FO2017-0236).

References

[1] C.T. Moonen, P.C. van Zijl, J.A. Frank, D. Le Bihan, E.D. Becker, Functional magnetic resonance imaging in medicine and physiology, Science 250 (1990) 53–61.
[2] M.A. Griswold, P.M. Jakob, R.M. Heidemann, M. Nittka, V. Jellus, J. Wang, B. Kiefer, A. Haase, Generalized autocalibrating partially parallel acquisitions (GRAPPA), Magn. Reson. Med. 47 (2002) 1202–1210.
[3] K.P. Pruessmann, M. Weiger, M.B. Scheidegger, P. Boesiger, SENSE: sensitivity encoding for fast MRI, Magn. Reson. Med. 42 (1999) 952–962.
[4] D.K. Sodickson, W.J. Manning, Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays, Magn. Reson. Med. 38 (1997) 591–603.
[5] D.J. Larkman, J.V. Hajnal, A.H. Herlihy, G.A. Coutts, I.R. Young, G. Ehnholm, Use of multicoil arrays for separation of signal from multiple slices simultaneously excited, J. Magn. Reson. Imaging 13 (2001) 313–317.
[6] K. Setsompop, D.A. Feinberg, J.R. Polimeni, Rapid brain MRI acquisition techniques at ultra-high fields, NMR Biomed. 29 (2016) 1198–1221.
[7] K. Setsompop, B.A. Gagoski, J.R. Polimeni, T. Witzel, V.J. Wedeen, L.L. Wald, Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty, Magn. Reson. Med. 67 (2012) 1210–1224.
[8] U. Gamper, P. Boesiger, S. Kozerke, Compressed sensing in dynamic MRI, Magn. Reson. Med. 59 (2008) 365–373.
[9] M. Lustig, D. Donoho, J.M. Pauly, Sparse MRI: the application of compressed sensing for rapid MR imaging, Magn. Reson. Med. 58 (2007) 1182–1195.
[10] G.H. Glover, Spiral imaging in fMRI, Neuroimage 62 (2012) 706–712.
[11] G.H. Glover, A.T. Lee, Motion artifacts in fMRI: comparison of 2DFT with PR and spiral scan methods, Magn. Reson. Med. 33 (1995) 624–635.
[12] P.C. Lauterbur, Image formation by induced local interactions: examples employing nuclear magnetic resonance, Nature 242 (1973) 190–191.
[13] J.G. Pipe, Motion correction with PROPELLER MRI: application to head motion and free-breathing cardiac imaging, Magn. Reson. Med. 42 (1999) 963–969.
[14] M. Uecker, S. Zhang, D. Voit, A. Karaus, K.D. Merboldt, J. Frahm, Real-time MRI at a resolution of 20 ms, NMR Biomed. 23 (2010) 986–994.
[15] L. Feng, R. Grimm, K.T. Block, H. Chandarana, S. Kim, J. Xu, L. Axel, D.K. Sodickson, R. Otazo, Golden-angle radial sparse parallel MRI: combination of compressed sensing, parallel imaging, and golden-angle radial sampling for fast and flexible dynamic volumetric MRI, Magn. Reson. Med. 72 (2014) 707–717.
[16] S. Rosenzweig, H.C.M. Holme, R.N. Wilke, D. Voit, J. Frahm, M. Uecker, Simultaneous multi-slice MRI using cartesian and radial FLASH and regularized nonlinear inversion: SMS-NLINV, Magn. Reson. Med. 79 (2018) 2057–2066.
[17] J. Zhang, L. Feng, R. Otazo, S.G. Kim, Rapid dynamic contrast-enhanced MRI for small animals at 7T using 3D ultra-short echo time and golden-angle radial sparse parallel MRI, Magn. Reson. Med. 81 (2019) 140–152.
[18] B. Zhu, J.Z. Liu, S.F. Cauley, B.R. Rosen, M.S. Rosen, Image reconstruction by domain-transform manifold learning, Nature 555 (2018) 487–492.
[19] O.N. Jaspan, R. Fleysher, M.L. Lipton, Compressed sensing MRI: a review of the clinical literature, Br. J. Radiol. 88 (2015) 20150487.
[20] K. Gumus, B. Keating, N. White, B. Andrews-Shigaki, B. Armstrong, J. Maclaren, M. Zaitsev, A. Dale, T. Ernst, Comparison of optical and MR-based tracking, Magn. Reson. Med. 74 (2015) 894–902.
[21] N. White, C. Roddey, A. Shankaranarayanan, E. Han, D. Rettmann, J. Santos, J. Kuperman, A. Dale, PROMO: real-time prospective motion correction in MRI using image-based tracking, Magn. Reson. Med. 63 (2010) 91–105.
[22] S.S. Vasanawala, M.T. Alley, B.A. Hargreaves, R.A. Barth, J.M. Pauly, M. Lustig, Improved pediatric MR imaging with compressed sensing, Radiology 256 (2010) 607–616.
[23] A.F. Delgado, A. Kits, J. Bystam, M. Kaijser, M. Skorpil, T. Sprenger, S. Skare, Diagnostic performance of a new multicontrast one-minute full brain exam (EPIMix) in neuroradiology: a prospective study, J. Magn. Reson. Imaging (2019).
[24] D. Ma, V. Gulani, N. Seiberlich, K. Liu, J.L. Sunshine, J.L. Duerk, M.A. Griswold, Magnetic resonance fingerprinting, Nature 495 (2013) 187–192.
[25] S. Skare, T. Sprenger, O. Norbeck, H. Ryden, L. Blomberg, E. Avventi, M. Engstrom, A 1-minute full brain MR exam using a multicontrast EPI sequence, Magn. Reson. Med. 79 (2018) 3045–3054.
[26] L. Knutsson, F. Stahlberg, R. Wirestam, Absolute quantification of perfusion using dynamic susceptibility contrast MRI: pitfalls and possibilities, MAGMA 23 (2010) 1–21.
[27] L. Ostergaard, R.M. Weisskoff, D.A. Chesler, C. Gyldensted, B.R. Rosen, High resolution measurement of cerebral blood flow using intravascular tracer

bolus passages. Part I: Mathematical approach and statistical analysis, Magn. Reson. Med. 36 (1996) 715–725.
[28] K.A. Rempp, G. Brix, F. Wenz, C.R. Becker, F. Guckel, W.J. Lorenz, Quantification of regional cerebral blood flow and volume with dynamic susceptibility contrast-enhanced MR imaging, Radiology 193 (1994) 637–641.
[29] L. Knutsson, E. Lindgren, A. Ahlgren, M.J. van Osch, K.M. Bloch, Y. Surova, F. Stahlberg, D. van Westen, R. Wirestam, Dynamic susceptibility contrast MRI with a prebolus contrast agent administration design for improved absolute quantification of perfusion, Magn. Reson. Med. 72 (2014) 996–1006.
[30] L. Knutsson, E. Lindgren, A. Ahlgren, M.J. van Osch, K. Markenroth Bloch, Y. Surova, F. Stahlberg, D. van Westen, R. Wirestam, Reduction of arterial partial volume effects for improved absolute quantification of DSC-MRI perfusion estimates: comparison between tail scaling and prebolus administration, J. Magn. Reson. Imaging 41 (2015) 903–908.
[31] R. Wirestam, E. Lind, A. Ahlgren, F. Stahlberg, L. Knutsson, Dynamic susceptibility contrast perfusion MRI using phase-based venous output functions: comparison with pseudo-continuous arterial spin labelling and assessment of contrast agent concentration in large veins, MAGMA 29 (2016) 823–831.
[32] M. Bergamino, L. Bonzano, F. Levrero, G.L. Mancardi, L. Roccatagliata, A review of technical aspects of T1-weighted dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in human brain tumors, Phys. Med. 30 (2014) 635–643.
[33] A.K. Heye, R.D. Culling, C. Valdes Hernandez Mdel, M.J. Thrippleton, J.M. Wardlaw, Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review, Neuroimage Clin 6 (2014) 262–274.
[34] R. Raja, G.A. Rosenberg, A. Caprihan, MRI measurements of Blood-Brain Barrier function in dementia: a review of recent studies, Neuropharmacology 134 (2018) 259–271.
[35] P. Sujlana, J. Skrok, L.M. Fayad, Review of dynamic contrast-enhanced MRI: technical aspects and applications in the musculoskeletal system, J. Magn. Reson. Imaging 47 (2018) 875–890.
[36] M.J. Thrippleton, W.H. Backes, S. Sourbron, M. Ingrisch, M.J.P. van Osch, M. Dichgans, F. Fazekas, S. Ropele, R. Frayne, R.J. van Oostenbrugge, E.E. Smith, J. M. Wardlaw, Quantifying blood-brain barrier leakage in small vessel disease: review and consensus recommendations, Alzheimers Dement (2019).
[37] S.S. Kety, The theory and applications of the exchange of inert gas at the lungs and tissues, Pharmacol. Rev. 3 (1951) 1–41.
[38] H.B. Larsson, M. Stubgaard, L. Sondergaard, O. Henriksen, In vivo quantification of the unidirectional influx constant for Gd-DTPA diffusion across the myocardial capillaries with MR imaging, J. Magn. Reson. Imaging 4 (1994) 433–440.
[39] S.P. Sourbron, D.L. Buckley, On the scope and interpretation of the Tofts models for DCE-MRI, Magn. Reson. Med. 66 (2011) 735–745.
[40] P.S. Tofts, G. Brix, D.L. Buckley, J.L. Evelhoch, E. Henderson, M.V. Knopp, H.B. Larsson, T.Y. Lee, N.A. Mayr, G.J. Parker, R.E. Port, J. Taylor, R.M. Weisskoff, Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols, J. Magn. Reson. Imaging 10 (1999) 223–232.
[41] M. Essig, T.B. Nguyen, M.S. Shiroishi, M. Saake, J.M. Provenzale, D.S. Enterline, N. Anzalone, A. Dorfler, A. Rovira, M. Wintermark, M. Law, Perfusion MRI: the five most frequently asked clinical questions, AJR Am. J. Roentgenol. 201 (2013) W495–510.
[42] E.S. Paulson, D.E. Prah, K.M. Schmainda, Spiral perfusion imaging with consecutive echoes (SPICE) for the simultaneous mapping of DSC- and DCE-MRI parameters in brain tumor patients: theory and initial feasibility, Tomography 2 (2016) 295–307.
[43] C.C. Quarles, J.C. Gore, L. Xu, T.E. Yankeelov, Comparison of dual-echo DSC-MRI- and DCE-MRI-derived contrast agent kinetic parameters, Magn. Reson. Imaging 30 (2012) 944–953.
[44] A. Shukla-Dave, N.A. Obuchowski, T.L. Chenevert, S. Jambawalikar, L.H. Schwartz, D. Malyarenko, W. Huang, S.M. Noworolski, R.J. Young, M.S. Shiroishi, H. Kim, C. Coolens, H. Laue, C. Chung, M. Rosen, M. Boss, E.F. Jackson, Quantitative imaging biomarkers alliance (QIBA) recommendations for improved precision of DWI and DCE-MRI derived biomarkers in multicenter oncology trials, J. Magn. Reson. Imaging (2018).
[45] P.C. van Zijl, N.N. Yadav, Chemical exchange saturation transfer (CEST): what is in a name and what isn't?, Magn Reson. Med. 65 (2011) 927–948.
[46] K.M. Ward, A.H. Aletras, R.S. Balaban, A new class of contrast agents for MRI based on proton chemical exchange dependent saturation transfer (CEST), J. Magn. Reson. 143 (2000) 79–87.
[47] L.M. De Leon-Rodriguez, A.F. Martins, M.C. Pinho, N.M. Rofsky, A.D. Sherry, Basic MR relaxation mechanisms and contrast agent design, J. Magn. Reson. Imaging 42 (2015) 545–565.
[48] I. Hancu, W.T. Dixon, M. Woods, E. Vinogradov, A.D. Sherry, R.E. Lenkinski, CEST and PARACEST MR contrast agents, Acta Radiol. 51 (2010) 910–923.
[49] S. Sinharay, M.D. Pagel, Advances in magnetic resonance imaging contrast agents for biomarker detection, Annu. Rev. Anal. Chem. (Palo Alto Calif.) 9 (2016) 95–115.
[50] E. Terreno, D.D. Castelli, S. Aime, Encoding the frequency dependence in MRI contrast media: the emerging class of CEST agents, Contrast Media Mol. Imaging 5 (2010) 78–98.
[51] Y. Wu, I.Y. Zhou, T. Igarashi, D.L. Longo, S. Aime, P.Z. Sun, A generalized ratiometric chemical exchange saturation transfer (CEST) MRI approach for mapping renal pH using iopamidol, Magn. Reson. Med. 79 (2018) 1553–1558.
[52] K.W. Chan, M.T. McMahon, Y. Kato, G. Liu, J.W. Bulte, Z.M. Bhujwalla, D. Artemov, P.C. van Zijl, Natural D-glucose as a biodegradable MRI contrast agent for detecting cancer, Magn. Reson. Med. 68 (2012) 1764–1773.
[53] Z. Han, G. Liu, Sugar-based biopolymers as novel imaging agents for molecular magnetic resonance imaging, Wiley Interdiscip Rev. Nanomed. Nanobiotechnol. (2019) e1551.
[54] S. Walker-Samuel, R. Ramasawmy, F. Torrealdea, M. Rega, V. Rajkumar, S.P. Johnson, S. Richardson, M. Goncalves, H.G. Parkes, E. Arstad, D.L. Thomas, R.B. Pedley, M.F. Lythgoe, X. Golay, In vivo imaging of glucose uptake and metabolism in tumors, Nat. Med. 19 (2013) 1067–1072.
[55] X. Xu, K.W. Chan, L. Knutsson, D. Artemov, J. Xu, G. Liu, Y. Kato, B. Lal, J. Laterra, M.T. McMahon, P.C. van Zijl, Dynamic glucose enhanced (DGE) MRI for combined imaging of blood-brain barrier break down and increased blood volume in brain cancer, Magn. Reson. Med. 74 (2015) 1556–1563.
[56] X. Xu, N.N. Yadav, L. Knutsson, J. Hua, R. Kalyani, E. Hall, J. Laterra, J. Blakeley, R. Strowd, M. Pomper, P. Barker, K. Chan, G. Liu, M.T. McMahon, R.D. Stevens, P.C. van Zijl, Dynamic glucose-enhanced (DGE) MRI: translation to human scanning and first results in glioma patients, Tomography 1 (2015) 105–114.
[57] S.R. Banerjee, X. Song, X. Yang, I. Minn, A. Lisok, Y. Chen, A. Bui, S. Chatterjee, J. Chen, P.C.M. van Zijl, M.T. McMahon, M.G. Pomper, Salicylic acid-based polymeric contrast agents for molecular magnetic resonance imaging of prostate cancer, Chemistry 24 (2018) 7235–7242.
[58] J.C. Gore, M.S. Brown, C.T. Mizumoto, I.M. Armitage, Influence of glycogen on water proton relaxation times, Magn. Reson. Med. 3 (1986) 463–466.
[59] T. Jin, B. Iordanova, T.K. Hitchens, M. Modo, P. Wang, H. Mehrens, S.G. Kim, Chemical exchange-sensitive spin-lock (CESL) MRI of glucose and analogs in brain tumors, Magn. Reson. Med. 80 (2018) 488–495.
[60] N.N. Yadav, J. Xu, A. Bar-Shir, Q. Qin, K.W. Chan, K. Grgac, W. Li, M.T. McMahon, P.C. van Zijl, Natural D-glucose as a biodegradable MRI relaxation agent, Magn. Reson. Med. 72 (2014) 823–828.
[61] M. Zaiss, K. Herz, A. Deshmane, M. Kim, X. Golay, T. Lindig, B. Bender, U. Ernemann, K. Scheffler, Possible artifacts in dynamic CEST MRI due to motion and field alterations, J. Magn. Reson. 298 (2019) 16–22.
[62] D.C. Alsop, J.A. Detre, X. Golay, M. Gunther, J. Hendrikse, L. Hernandez-Garcia, H. Lu, B.J. MacIntosh, L.M. Parkes, M. Smits, M.J. van Osch, D.J. Wang, E.C. Wong, G. Zaharchuk, Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia, Magn. Reson. Med. 73 (2015) 102–116.
[63] M. Grade, J.A. Hernandez Tamames, F.B. Pizzini, E. Achten, X. Golay, M. Smits, A neuroradiologist's guide to arterial spin labeling MRI in clinical practice, Neuroradiology 57 (2015) 1181–1202.
[64] E.C. Wong, M. Cronin, W.C. Wu, B. Inglis, L.R. Frank, T.T. Liu, Velocity-selective arterial spin labeling, Magn. Reson. Med. 55 (2006) 1334–1341.
[65] Q. Qin, P.C. van Zijl, Velocity-selective-inversion prepared arterial spin labeling, Magn. Reson. Med. 76 (2016) 1136–1148.
[66] L. Hernandez-Garcia, J.F. Nielsen, D.C. Noll, Improved sensitivity and temporal resolution in perfusion FMRI using velocity selective inversion ASL, Magn. Reson. Med. 81 (2019) 1004–1015.
[67] Q. Qin, Y. Qu, W. Li, D. Liu, T. Shin, Y. Zhao, D.D. Lin, P.C.M. van Zijl, Z. Wen, Cerebral blood volume mapping using Fourier-transform-based velocity-selective saturation pulse trains, Magn. Reson. Med. 81 (2019) 3544–3554.
[68] D. Le Bihan, E. Breton, D. Lallemand, P. Grenier, E. Cabanis, M. Laval-Jeantet, MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders, Radiology 161 (1986) 401–407.
[69] D. Le Bihan, R. Turner, C.T. Moonen, J. Pekar, Imaging of diffusion and microcirculation with gradient sensitization: design, strategy, and significance, J. Magn. Reson. Imaging 1 (1991) 7–28.
[70] A. Lemke, F.B. Laun, D. Simon, B. Stieltjes, L.R. Schad, An in vivo verification of the intravoxel incoherent motion effect in diffusion-weighted imaging of the abdomen, Magn. Reson. Med. 64 (2010) 1580–1585.
[71] J. Pekar, C.T. Moonen, P.C. van Zijl, On the precision of diffusion/perfusion imaging by gradient sensitization, Magn. Reson. Med. 23 (1992) 122–129.
[72] C. Federau, Intravoxel incoherent motion MRI as a means to measure in vivo perfusion: a review of the evidence, NMR Biomed. 30 (2017).
[73] D. Le Bihan, What can we see with IVIM MRI?, Neuroimage 187 (2019) 56–67
[74] A.M. Paschoal, R.F. Leoni, A.C. Dos Santos, F.F. Paiva, Intravoxel incoherent motion MRI in neurological and cerebrovascular diseases, Neuroimage Clin. 20 (2018) 705–714.
[75] H. Wu, S. Zhang, C. Liang, H. Liu, Y. Liu, Y. Mei, H. Liu, Z. Liu, F. Xu, Intravoxel incoherent motion MRI for the differentiation of benign, intermediate, and malignant solid soft-tissue tumors, J. Magn. Reson. Imaging 46 (2017) 1611–1618.
[76] A. Ahlgren, L. Knutsson, R. Wirestam, M. Nilsson, F. Stahlberg, D. Topgaard, S. Lasic, Quantification of microcirculatory parameters by joint analysis of flow-compensated and non-flow-compensated intravoxel incoherent motion (IVIM) data, NMR Biomed. 29 (2016) 640–649.
[77] W. Li, F. Xu, M. Schar, J. Liu, T. Shin, Y. Zhao, P.C.M. van Zijl, B.A. Wasserman, Y. Qiao, Q. Qin, Whole-brain arteriography and venography: Using improved velocity-selective saturation pulse trains, Magn. Reson. Med. 79 (2018) 2014–2023.
[78] Y. Assaf, H. Johansen-Berg, M. Thiebaut de Schotten, The role of diffusion MRI in neuroscience, NMR Biomed. 32 (2019) e3762.
[79] B. Jeurissen, M. Descoteaux, S. Mori, A. Leemans, Diffusion MRI fiber tractography of the brain, NMR Biomed. 32 (2019) e3785.

[80] S. Mori, P.C. van Zijl, Fiber tracking: principles and strategies - a technical review, NMR Biomed. 15 (2002) 468–480.
[81] D.C. Alexander, T.B. Dyrby, M. Nilsson, H. Zhang, Imaging brain microstructure with diffusion MRI: practicality and applications, NMR Biomed. 32 (2019) e3841.
[82] D.S. Novikov, E. Fieremans, S.N. Jespersen, V.G. Kiselev, Quantifying brain microstructure with diffusion MRI: theory and parameter estimation, NMR Biomed. 32 (2019) e3998.
[83] S. Wakana, H. Jiang, L.M. Nagae-Poetscher, P.C. van Zijl, S. Mori, Fiber tract-based atlas of human white matter anatomy, Radiology 230 (2004) 77–87.
[84] K. Setsompop, R. Kimmlingen, E. Eberlein, T. Witzel, J. Cohen-Adad, J.A. McNab, B. Keil, M.D. Tisdall, P. Hoecht, P. Dietz, S.F. Cauley, V. Tountcheva, V. Matschl, V.H. Lenz, K. Heberlein, A. Potthast, H. Thein, J. Van Horn, A. Toga, F. Schmitt, D. Lehne, B.R. Rosen, V. Wedeen, L.L. Wald, Pushing the limits of in vivo diffusion MRI for the Human Connectome Project, Neuroimage 80 (2013) 220–233.
[85] C.F. Westin, H. Knutsson, O. Pasternak, F. Szczepankiewicz, E. Ozarslan, D. van Westen, C. Mattisson, M. Bogren, L.J. O'Donnell, M. Kubicki, D. Topgaard, M. Nilsson, Q-space trajectory imaging for multidimensional diffusion MRI of the human brain, Neuroimage 135 (2016) 345–362.
[86] J. Mattiello, P.J. Basser, D. Le Bihan, The b matrix in diffusion tensor echo-planar imaging, Magn. Reson. Med. 37 (1997) 292–300.
[87] P.P. Mitra, Multiple wave-vector extensions of the NMR pulsed-field-gradient spin-echo diffusion measurement, Phys. Rev. B: Condens. Matter 51 (1995) 15074–15078.
[88] S. Mori, P.C. van Zijl, Diffusion weighting by the trace of the diffusion tensor within a single scan, Magn. Reson. Med. 33 (1995) 41–52.
[89] E.C. Wong, R.W. Cox, A.W. Song, Optimized isotropic diffusion weighting, Magn. Reson. Med. 34 (1995) 139–143.
[90] S. Eriksson, S. Lasic, M. Nilsson, C.F. Westin, D. Topgaard, NMR diffusion-encoding with axial symmetry and variable anisotropy: Distinguishing between prolate and oblate microscopic diffusion tensors with unknown orientation distribution, J. Chem. Phys. 142 (2015) 104201.
[91] F. Szczepankiewicz, J. Sjolund, F. Stahlberg, J. Latt, M. Nilsson, Tensor-valued diffusion encoding for diffusional variance decomposition (DIVIDE): technical feasibility in clinical MRI systems, PLoS ONE 14 (2019) e0214238.
[92] A.V. Avram, E. Ozarslan, J.E. Sarlls, P.J. Basser, In vivo detection of microscopic anisotropy using quadruple pulsed-field gradient (qPFG) diffusion MRI on a clinical scanner, Neuroimage 64 (2013) 229–239.
[93] J.P. de Almeida Martins, D. Topgaard, Two-dimensional correlation of isotropic and directional diffusion using NMR, Phys. Rev. Lett. 116 (2016) 087601.
[94] S.N. Jespersen, H. Lundell, C.K. Sonderby, T.B. Dyrby, Orientationally invariant metrics of apparent compartment eccentricity from double pulsed field gradient diffusion experiments, NMR Biomed. 26 (2013) 1647–1662.
[95] M. Lawrenz, J. Finsterbusch, Detection of microscopic diffusion anisotropy on a whole-body MR system with double wave vector imaging, Magn. Reson. Med. 66 (2011) 1405–1415.
[96] E. Ozarsian, P.J. Basser, Microscopic anisotropy revealed by NMR double pulsed field gradient experiments with arbitrary timing parameters, J. Chem. Phys. 128 (2008) 154511.
[97] N. Shemesh, E. Ozarslan, T. Adiri, P.J. Basser, Y. Cohen, Noninvasive bipolar double-pulsed-field-gradient NMR reveals signatures for pore size and shape in polydisperse, randomly oriented, inhomogeneous porous media, J. Chem. Phys. 133 (2010) 044705.
[98] C.F. Westin, F. Szczepankiewicz, O. Pasternak, E. Ozarslan, D. Topgaard, H. Knutsson, M. Nilsson, Measurement tensors in diffusion MRI: generalizing the concept of diffusion encoding, Med. Image Comput. Comput. Assist. Interv. 17 (2014) 209–216.
[99] C. Pierpaoli, P.J. Basser, Toward a quantitative assessment of diffusion anisotropy, Magn. Reson. Med. 36 (1996) 893–906.
[100] A.M. Ulug, P.C. van Zijl, Orientation-independent diffusion imaging without tensor diagonalization: anisotropy definitions based on physical attributes of the diffusion ellipsoid, J. Magn. Reson. Imaging 9 (1999) 804–813.
[101] J.H. Jensen, J.A. Helpern, A. Ramani, H. Lu, K. Kaczynski, Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging, Magn. Reson. Med. 53 (2005) 1432–1440.
[102] J. Andrasko, Water diffusion permeability of human erythrocytes studied by a pulsed gradient NMR technique, BBA 428 (1976) 304–311.
[103] S. Hwang, J. Karger, NMR diffusometry with guest molecules in nanoporous materials, Magn. Reson. Imaging 56 (2019) 3–13.
[104] P.C. Van Zijl, C.T. Moonen, P. Faustino, J. Pekar, O. Kaplan, J.S. Cohen, Complete separation of intracellular and extracellular information in NMR spectra of perfused cells by diffusion-weighted spectroscopy, Proc. Natl. Acad. Sci. USA 88 (1991) 3228–3232.
[105] P.T. Callaghan, I. Furo, Diffusion-diffusion correlation and exchange as a signature for local order and dynamics, J. Chem. Phys. 120 (2004) 4032–4038.
[106] S. Lasic, M. Nilsson, J. Latt, F. Stahlberg, D. Topgaard, Apparent exchange rate mapping with diffusion MRI, Magn. Reson. Med. 66 (2011) 356–365.
[107] M. Nilsson, J. Latt, D. van Westen, S. Brockstedt, S. Lasic, F. Stahlberg, D. Topgaard, Noninvasive mapping of water diffusional exchange in the human brain using filter-exchange imaging, Magn. Reson. Med. 69 (2013) 1573–1581.
[108] J. Sjolund, F. Szczepankiewicz, M. Nilsson, D. Topgaard, C.F. Westin, H. Knutsson, Constrained optimization of gradient waveforms for generalized diffusion encoding, J. Magn. Reson. 261 (2015) 157–168.
[109] F. Szczepankiewicz, C.F. Westin, M. Nilsson, Maxwell-compensated design of asymmetric gradient waveforms for tensor-valued diffusion encoding, Magn. Reson. Med. (2019).
[110] G. Yang, J.A. McNab, Eddy current nulled constrained optimization of isotropic diffusion encoding gradient waveforms, Magn. Reson. Med. 81 (2019) 1818–1832.
[111] B. Lampinen, F. Szczepankiewicz, D. van Westen, E. Englund, C.S. P, J. Latt, F. Stahlberg, M. Nilsson, Optimal experimental design for filter exchange imaging: apparent exchange rate measurements in the healthy brain and in intracranial tumors, Magn. Reson. Med. 77 (2017) 1104–1114.
[112] M. Nilsson, E. Englund, F. Szczepankiewicz, D. van Westen, P.C. Sundgren, Imaging brain tumour microstructure, Neuroimage 182 (2018) 232–250.
[113] O. Reynaud, Time-dependent diffusion MRI in cancer: tissue modeling and applications, Front. Phys. 5 (2017) 58.
[114] S.N. Jespersen, J.L. Olesen, B. Hansen, N. Shemesh, Diffusion time dependence of microstructural parameters in fixed spinal cord, Neuroimage 182 (2018) 329–342.
[115] B. Lampinen, F. Szczepankiewicz, M. Noven, D. van Westen, O. Hansson, E. Englund, J. Martensson, C.F. Westin, M. Nilsson, Searching for the neurite density with diffusion MRI: challenges for biophysical modeling, Hum. Brain Mapp. 40 (2019) 2529–2545.
[116] G. Lemberskiy, E. Fieremans, J. Veraart, F.M. Deng, A.B. Rosenkrantz, D.S. Novikov, Characterization of prostate microstructure using water diffusion and NMR relaxation, Front. Phys. 6 (2018).
[117] J. Veraart, D.S. Novikov, E. Fieremans, TE dependent Diffusion Imaging (TEdDI) distinguishes between compartmental T2 relaxation times, Neuroimage 182 (2018) 360–369.
[118] T.F. Budinger, M.D. Bird, L. Frydman, J.R. Long, T.H. Mareci, W.D. Rooney, B. Rosen, J.F. Schenck, V.D. Schepkin, A.D. Sherry, D.K. Sodickson, C.S. Springer, K.R. Thulborn, K. Ugurbil, L.L. Wald, Toward 20 T magnetic resonance for human brain studies: opportunities for discovery and neuroscience rationale, MAGMA 29 (2016) 617–639.
[119] F. De Martino, E. Yacoub, V. Kemper, M. Moerel, K. Uludag, P. De Weerd, K. Ugurbil, R. Goebel, E. Formisano, The impact of ultra-high field MRI on cognitive and computational neuroimaging, Neuroimage 168 (2018) 366–382.
[120] G. Adriany, P.F. Van de Moortele, F. Wiesinger, S. Moeller, J.P. Strupp, P. Andersen, C. Snyder, X. Zhang, W. Chen, K.P. Pruessmann, P. Boesiger, T. Vaughan, K. Ugurbil, Transmit and receive transmission line arrays for 7 Tesla parallel imaging, Magn. Reson. Med. 53 (2005) 434–445.
[121] B. Keil, L.L. Wald, Massively parallel MRI detector arrays, J. Magn. Reson. 229 (2013) 75–89.
[122] M.F. Glasser, S.M. Smith, D.S. Marcus, J.L. Andersson, E.J. Auerbach, T.E. Behrens, T.S. Coalson, M.P. Harms, M. Jenkinson, S. Moeller, E.C. Robinson, S. N. Sotiropoulos, J. Xu, E. Yacoub, K. Ugurbil, D.C. Van Essen, The Human Connectome Project's neuroimaging approach, Nat. Neurosci. 19 (2016) 1175–1187.
[123] S.M. Smith, K.L. Miller, S. Moeller, J. Xu, E.J. Auerbach, M.W. Woolrich, C.F. Beckmann, M. Jenkinson, J. Andersson, M.F. Glasser, D.C. Van Essen, D.A. Feinberg, E.S. Yacoub, K. Ugurbil, Temporally-independent functional modes of spontaneous brain activity, Proc. Natl. Acad. Sci. USA 109 (2012) 3131–3136.
[124] B.T. Yeo, F.M. Krienen, M.W. Chee, R.L. Buckner, Estimates of segregation and overlap of functional connectivity networks in the human cerebral cortex, Neuroimage 88 (2014) 212–227.
[125] H.L. Lee, B. Zahneisen, T. Hugger, P. LeVan, J. Hennig, Tracking dynamic resting-state networks at higher frequencies using MR-encephalography, Neuroimage 65 (2013) 216–222.
[126] D. Vidaurre, S.M. Smith, M.W. Woolrich, Brain network dynamics are hierarchically organized in time, Proc. Natl. Acad. Sci. USA 114 (2017) 12827–12832.
[127] A.G. Garrity, G.D. Pearlson, K. McKiernan, D. Lloyd, K.A. Kiehl, V.D. Calhoun, Aberrant "default mode" functional connectivity in schizophrenia, Am. J. Psychiatry 164 (2007) 450–457.
[128] S. Han, J.P. Son, H. Cho, J.Y. Park, S.G. Kim, Gradient-echo and spin-echo blood oxygenation level-dependent functional MRI at ultrahigh fields of 9.4 and 15.2 Tesla, Magn. Reson. Med. 81 (2019) 1237–1246.
[129] S.P. Lee, A.C. Silva, S.G. Kim, Comparison of diffusion-weighted high-resolution CBF and spin-echo BOLD fMRI at 9.4 T, Magn. Reson. Med. 47 (2002) 736–741.
[130] J. Hua, Q. Qin, P.C. van Zijl, J.J. Pekar, C.K. Jones, Whole-brain three-dimensional T2-weighted BOLD functional magnetic resonance imaging at 7 Tesla, Magn. Reson. Med. 72 (2014) 1530–1540.
[131] T. Jin, S.G. Kim, Improved cortical-layer specificity of vascular space occupancy fMRI with slab inversion relative to spin-echo BOLD at 9.4 T, Neuroimage 40 (2008) 59–67.
[132] H. Lu, X. Golay, J.J. Pekar, P.C. Van Zijl, Functional magnetic resonance imaging based on changes in vascular space occupancy, Magn. Reson. Med. 50 (2003) 263–274.
[133] L. Huber, J. Goense, A.J. Kennerley, R. Trampel, M. Guidi, E. Reimer, D. Ivanov, N. Neef, C.J. Gauthier, R. Turner, H.E. Moller, Cortical lamina-dependent blood volume changes in human brain at 7 T, Neuroimage 107 (2015) 23–33.
[134] Y. Cheng, Q. Qin, P.C.M. van Zijl, J.J. Pekar, J. Hua, A three-dimensional single-scan approach for the measurement of changes in cerebral blood volume, blood flow, and blood oxygenation-weighted signals during functional stimulation, Neuroimage 147 (2017) 976–984.

[135] S.N. Krieger, L. Huber, B.A. Poser, R. Turner, G.F. Egan, Simultaneous acquisition of cerebral blood volume-, blood flow-, and blood oxygenation-weighted MRI signals at ultra-high magnetic field, Magn. Reson. Med. 74 (2015) 513–517.
[136] Y. Yang, H. Gu, E.A. Stein, Simultaneous MRI acquisition of blood volume, blood flow, and blood oxygenation information during brain activation, Magn. Reson. Med. 52 (2004) 1407–1417.
[137] L. Huber, D.A. Handwerker, D.C. Jangraw, G. Chen, A. Hall, C. Stuber, J. Gonzalez-Castillo, D. Ivanov, S. Marrett, M. Guidi, J. Goense, B.A. Poser, P.A. Bandettini, High-resolution CBV-fMRI allows mapping of laminar activity and connectivity of cortical input and output in human M1, Neuron 96 (2017) 1253–1263, e1257.
[138] J.R. Polimeni, B. Fischl, D.N. Greve, L.L. Wald, Laminar analysis of 7T BOLD using an imposed spatial activation pattern in human V1, Neuroimage 52 (2010) 1334–1346.
[139] R. Scheeringa, P. Fries, Cortical layers, rhythms and BOLD signals, Neuroimage (2017).
[140] K.E. Stephan, F.H. Petzschner, L. Kasper, J. Bayer, K.V. Wellstein, G. Stefanics, K.P. Pruessmann, J. Heinzle, Laminar fMRI and computational theories of brain function, Neuroimage (2017).
[141] J.F. Schenck, The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds, Med. Phys. 23 (1996) 815–850.
[142] W. Li, K. Grgac, A. Huang, N. Yadav, Q. Qin, P.C. van Zijl, Quantitative theory for the longitudinal relaxation time of blood water, Magn. Reson. Med. 76 (2016) 270–281.
[143] X. Li, S. Mangia, J.H. Lee, R. Bai, C.S. Springer Jr., NMR shutter-speed elucidates apparent population inversion of (1) H2O signals due to active transmembrane water cycling, Magn. Reson. Med. 82 (2019) 411–424.
[144] J.H. Duyn, J. Schenck, Contributions to magnetic susceptibility of brain tissue, NMR Biomed. 30 (2017).
[145] A. Deistung, F. Schweser, J.R. Reichenbach, Overview of quantitative susceptibility mapping, NMR Biomed. 30 (2017).
[146] S. Liu, S. Buch, Y. Chen, H.S. Choi, Y. Dai, C. Habib, J. Hu, J.Y. Jung, Y. Luo, D. Utriainen, M. Wang, D. Wu, S. Xia, E.M. Haacke, Susceptibility-weighted imaging: current status and future directions, NMR Biomed. 30 (2017).
[147] Y. Wang, P. Spincemaille, Z. Liu, A. Dimov, K. Deh, J. Li, Y. Zhang, Y. Yao, K. M. Gillen, A.H. Wilman, A. Gupta, A.J. Tsiouris, I. Kovanlikaya, G.C. Chiang, J.W. Weinsaft, L. Tanenbaum, W. Chen, W. Zhu, S. Chang, M. Lou, B.H. Kopell, M.G. Kaplitt, D. Devos, T. Hirai, X. Huang, Y. Korogi, A. Shtilbans, G. H. Jahng, D. Pelletier, S.A. Gauthier, D. Pitt, A.I. Bush, G.M. Brittenham, M.R. Prince, Clinical quantitative susceptibility mapping (QSM): Biometal imaging and its emerging roles in patient care, J. Magn. Reson. Imaging 46 (2017) 951–971.
[148] C. Liu, R. Bowtell, J. Schenck, Editorial for special issue on MRI phase contrast and quantitative susceptibility mapping, NMR Biomed. 30 (2017).
[149] S. Eskreis-Winkler, Y. Zhang, J. Zhang, Z. Liu, A. Dimov, A. Gupta, Y. Wang, The clinical utility of QSM: disease diagnosis, medical management, and surgical planning, NMR Biomed. 30 (2017).
[150] X. Guan, M. Xuan, Q. Gu, P. Huang, C. Liu, N. Wang, X. Xu, W. Luo, M. Zhang, Regionally progressive accumulation of iron in Parkinson's disease as measured by quantitative susceptibility mapping, NMR Biomed. 30 (2017).
[151] N. He, P. Huang, H. Ling, J. Langley, C. Liu, B. Ding, J. Huang, H. Xu, Y. Zhang, Z. Zhang, X. Hu, S. Chen, F. Yan, Dentate nucleus iron deposition is a potential biomarker for tremor-dominant Parkinson's disease, NMR Biomed. 30 (2017).
[152] S. Ropele, C. Langkammer, Iron quantification with susceptibility, NMR Biomed. 30 (2017).
[153] F.W. Wehrli, A.P. Fan, Z.B. Rodgers, E.K. Englund, M.C. Langham, Susceptibility-based time-resolved whole-organ and regional tissue oximetry, NMR Biomed. 30 (2017).
[154] J. Lee, Y. Nam, J.Y. Choi, E.Y. Kim, S.H. Oh, D.H. Kim, Mechanisms of T_2^* anisotropy and gradient echo myelin water imaging, NMR Biomed. 30 (2017).
[155] C. Liu, W. Li, G.A. Johnson, B. Wu, High-field (9.4 T) MRI of brain dysmyelination by quantitative mapping of magnetic susceptibility, Neuroimage 56 (2011) 930–938.
[156] S. Puwal, B.J. Roth, P.J. Basser, Heterogeneous anisotropic magnetic susceptibility of the myelin-water layers causes local magnetic field perturbations in axons, NMR Biomed. 30 (2017).
[157] A.L. MacKay, C. Laule, Magnetic resonance of myelin water: an in vivo marker for myelin, Brain Plast. 2 (2016) 71–91.
[158] J.G. Sled, Modelling and interpretation of magnetization transfer imaging in the brain, Neuroimage 182 (2018) 128–135.
[159] J.G. Sled, G.B. Pike, Quantitative imaging of magnetization transfer exchange and relaxation properties in vivo using MRI, Magn. Reson. Med. 46 (2001) 923–931.
[160] N. Stikov, J.S. Campbell, T. Stroh, M. Lavelee, S. Frey, J. Novek, S. Nuara, M.K. Ho, B.J. Bedell, R.F. Dougherty, I.R. Leppert, M. Boudreau, S. Narayanan, T. Duval, J. Cohen-Adad, P.A. Picard, A. Gasecka, D. Cote, G.B. Pike, In vivo histology of the myelin g-ratio with magnetic resonance imaging, Neuroimage 118 (2015) 397–405.
[161] D. Mao, Y. Li, P. Liu, S.L. Peng, J.J. Pillai, H. Lu, Three-dimensional mapping of brain venous oxygenation using R_2^* oximetry, Magn. Reson. Med. 79 (2018) 1304–1313.
[162] A. Panda, B.B. Mehta, S. Coppo, Y. Jiang, D. Ma, N. Seiberlich, M.A. Griswold, V. Gulani, Magnetic resonance fingerprinting – an overview, Curr. Opin. Biomed. Eng. 3 (2017) 56–66.
[163] F.G. Goncalves, S.D. Serai, G. Zuccoli, Synthetic brain MRI: review of current concepts and future directions, Top. Magn. Reson. Imaging 27 (2018) 387–393.
[164] S.J. Riederer, J.N. Lee, F. Farzaneh, H.Z. Wang, R.C. Wright, Magnetic resonance image synthesis, Clin. Implement., Acta Radiol. Suppl. 369 (1986) 466–468.
[165] X. Li, L. Chen, K. Kutten, C. Ceritoglu, Y. Li, N. Kang, J.T. Hsu, Y. Qiao, H. Wei, C. Liu, M.I. Miller, S. Mori, D.M. Yousem, P.C.M. van Zijl, A.V. Faria, Multi-atlas tool for automated segmentation of brain gray matter nuclei and quantification of their magnetic susceptibility, Neuroimage 191 (2019) 337–349.
[166] Y. Zhang, H. Wei, M.J. Cronin, N. He, F. Yan, C. Liu, Longitudinal atlas for normative human brain development and aging over the lifespan using quantitative susceptibility mapping, Neuroimage 171 (2018) 176–189.
[167] W. Li, C. Liu, T.Q. Duong, P.C. van Zijl, X. Li, Susceptibility tensor imaging (STI) of the brain, NMR Biomed. 30 (2017).
[168] W. Li, C. Liu, Comparison of magnetic susceptibility tensor and diffusion tensor of the brain, J. Neurosci. Neuroeng. 2 (2013) 431–440.
[169] P.A. Bottomley, J.R. Griffiths, Handbook of Magnetic Resonance Spectroscopy In Vivo: MRS Theory, Practice and Applications, Wiley & Sons Ltd, Chichester, U.K., 2016.
[170] A.D. Harris, M.G. Saleh, R.A. Edden, Edited (1) H magnetic resonance spectroscopy in vivo: methods and metabolites, Magn. Reson. Med. 77 (2017) 1377–1389.
[171] D.L. Rothman, O.A. Petroff, K.L. Behar, R.H. Mattson, Localized 1H NMR measurements of gamma-aminobutyric acid in human brain in vivo, Proc. Natl. Acad. Sci. USA 90 (1993) 5662–5666.
[172] G. Oz, J.R. Alger, P.B. Barker, R. Bartha, A. Bizzi, C. Boesch, P.J. Bolan, K.M. Brindle, C. Cudalbu, A. Dincer, U. Dydak, U.E. Emir, J. Frahm, R.G. Gonzalez, S. Gruber, R. Gruetter, R.K. Gupta, A. Heerschap, A. Henning, H.P. Hetherington, F.A. Howe, P.S. Huppi, R.E. Hurd, K. Kantarci, D.W. Klomp, R. Kreis, M.J. Kruiskamp, M.O. Leach, A.P. Lin, P.R. Luijten, M. Marjanska, A.A. Maudsley, D.J. Meyerhoff, C.E. Mountford, S.J. Nelson, M.N. Pamir, J.W. Pan, A.C. Peet, H. Poptani, S. Posse, P.J. Pouwels, E.M. Ratai, B.D. Ross, T.W. Scheenen, C. Schuster, I.C. Smith, B.J. Soher, I. Tkac, D.B. Vigneron, R.A. Kauppinen, M.R.S.C. Group, Clinical proton MR spectroscopy in central nervous system disorders, Radiology 270 (2014) 658–679.
[173] M. van der Graaf, In vivo magnetic resonance spectroscopy: basic methodology and clinical applications, Eur. Biophys. J. 39 (2010) 527–540.
[174] M. Wilson, O. Andronesi, P.B. Barker, R. Bartha, A. Bizzi, P.J. Bolan, K.M. Brindle, I.Y. Choi, C. Cudalbu, U. Dydak, U.E. Emir, R.G. Gonzalez, S. Gruber, R. Gruetter, R.K. Gupta, A. Heerschap, A. Henning, H.P. Hetherington, P.S. Huppi, R.E. Hurd, K. Kantarci, R.A. Kauppinen, D.W.J. Klomp, R. Kreis, M.J. Kruiskamp, M.O. Leach, A.P. Lin, P.R. Luijten, M. Marjanska, A.A. Maudsley, D.J. Meyerhoff, C.E. Mountford, P.G. Mullins, J.B. Murdoch, S.J. Nelson, R. Noeske, G. Oz, J.W. Pan, A.C. Peet, H. Poptani, S. Posse, E.M. Ratai, N. Salibi, T.W.J. Scheenen, I.C.P. Smith, B.J. Soher, I. Tkac, D.B. Vigneron, F.A. Howe, Methodological consensus on clinical proton MRS of the brain: review and recommendations, Magn. Reson. Med. 82 (2019) 527–550.
[175] S.S. Gurbani, E. Schreibmann, A.A. Maudsley, J.S. Cordova, B.J. Soher, H. Poptani, G. Verma, P.B. Barker, H. Shim, L.A.D. Cooper, A convolutional neural network to filter artifacts in spectroscopic MRI, Magn. Reson. Med. 80 (2018) 1765–1775.
[176] R.A. de Graaf, D.L. Rothman, K.L. Behar, State of the art direct 13C and indirect 1H-[13C] NMR spectroscopy in vivo. A practical guide, NMR Biomed. 24 (2011) 958–972.
[177] R. Gruetter, E.J. Novotny, S.D. Boulware, G.F. Mason, D.L. Rothman, G.I. Shulman, J.W. Prichard, R.G. Shulman, Localized 13C NMR spectroscopy in the human brain of amino acid labeling from D-[1-13C]glucose, J. Neurochem. 63 (1994) 1377–1385.
[178] A.D. Sherry, C.R. Malloy, Isotopic methods for probing organization of cellular metabolism, Cell Biochem. Funct. 14 (1996) 259–268.
[179] Z.J. Wang, M.A. Ohliger, P.E.Z. Larson, J.W. Gordon, R.A. Bok, J. Slater, J.E. Villanueva-Meyer, C.P. Hess, J. Kurhanewicz, D.B. Vigneron, Hyperpolarized (13)C MRI: state of the art and future directions, Radiology 291 (2019) 273–284.
[180] A. Cho, J.Y.C. Lau, B.J. Geraghty, C.H. Cunningham, K.R. Keshari, Noninvasive interrogation of cancer metabolism with hyperpolarized (13)C MRI, J. Nucl. Med. 58 (2017) 1201–1206.
[181] R.L. Hesketh, K.M. Brindle, Magnetic resonance imaging of cancer metabolism with hyperpolarized (13)C-labeled cell metabolites, Curr. Opin. Chem. Biol. 45 (2018) 187–194.
[182] J. Kurhanewicz, D.B. Vigneron, J.H. Ardenkjaer-Larsen, J.A. Bankson, K. Brindle, C.H. Cunningham, F.A. Gallagher, K.R. Keshari, A. Kjaer, C. Laustsen, D.A. Mankoff, M.E. Merritt, S.J. Nelson, J.M. Pauly, P. Lee, S. Ronen, D.J. Tyler, S.S. Rajan, D.M. Spielman, L. Wald, X. Zhang, C.R. Malloy, R. Rizi, Hyperpolarized (13)C MRI: path to clinical translation in oncology, Neoplasia 21 (2019) 1–16.
[183] C. Najac, S.M. Ronen, MR molecular imaging of brain cancer metabolism using hyperpolarized 13C magnetic resonance spectroscopy, Top. Magn. Reson. Imaging 25 (2016) 187–196.
[184] P.J. Rayner, S.B. Duckett, Signal amplification by reversible exchange (SABRE): from discovery to diagnosis, Angew. Chem. Int. Ed. Engl. 57 (2018) 6742–6753.
[185] W.S. Warren, E. Jenista, R.T. Branca, X. Chen, Increasing hyperpolarized spin lifetimes through true singlet eigenstates, Science 323 (2009) 1711–1714.
[186] I. Marco-Rius, S.E. Bohndiek, M.I. Kettunen, T.J. Larkin, M. Basharat, C. Seeley, K.M. Brindle, Quantitation of a spin polarization-induced nuclear Overhauser

effect (SPINOE) between a hyperpolarized (13) C-labeled cell metabolite and water protons, Contrast Media Mol. Imaging 9 (2014) 182–186.
[187] H.M. De Feyter, K.L. Behar, Z.A. Corbin, R.K. Fulbright, P.B. Brown, S. McIntyre, T.W. Nixon, D.L. Rothman, R.A. de Graaf, Deuterium metabolic imaging (DMI) for MRI-based 3D mapping of metabolism in vivo, Sci. Adv. 4 (2018) eaat7314.
[188] K.M. Jones, A.C. Pollard, M.D. Pagel, Clinical applications of chemical exchange saturation transfer (CEST) MRI, J. Magn. Reson. Imaging 47 (2018) 11–27.
[189] M.T. McMahon, A.A. Gilad, J.W.M. Bulte, P.C.M. van Zijl, Chemical Exchange Saturation Transfer Imaging: Advances and Applications, Pan Stanford, Singapore, 2017.
[190] P.C.M. van Zijl, A.A. Sehgal, Proton chemical exchange saturation transfer (CEST) MRS and MRI, eMagRes 5 (2016) 1307–1332.
[191] P.C.M. van Zijl, W.W. Lam, J. Xu, L. Knutsson, G.J. Stanisz, Magnetization transfer contrast and chemical exchange saturation transfer MRI. Features and analysis of the field-dependent saturation spectrum, Neuroimage 168 (2018) 222–241.
[192] W. Ling, R.R. Regatte, G. Navon, A. Jerschow, Assessment of glycosaminoglycan concentration in vivo by chemical exchange-dependent saturation transfer (gagCEST), Proc. Natl. Acad. Sci. USA 105 (2008) 2266–2270.
[193] J. Zhou, J.F. Payen, D.A. Wilson, R.J. Traystman, P.C. van Zijl, Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI, Nat. Med. 9 (2003) 1085–1090.
[194] K. Cai, M. Haris, A. Singh, F. Kogan, J.H. Greenberg, H. Hariharan, J.A. Detre, R. Reddy, Magnetic resonance imaging of glutamate, Nat. Med. 18 (2012) 302–306.
[195] L. Chen, P.B. Barker, R.G. Weiss, P.C.M. van Zijl, J. Xu, Creatine and phosphocreatine mapping of mouse skeletal muscle by a polynomial and Lorentzian line-shape fitting CEST method, Magn. Reson. Med. 81 (2019) 69–78.
[196] M. Haris, A. Singh, K. Cai, F. Kogan, J. McGarvey, C. Debrosse, G.A. Zsido, W.R. Witschey, K. Koomalsingh, J.J. Pilla, J.A. Chirinos, V.A. Ferrari, J.H. Gorman, H. Hariharan, R.C. Gorman, R. Reddy, A technique for in vivo mapping of myocardial creatine kinase metabolism, Nat. Med. 20 (2014) 209–214.
[197] F. Kogan, M. Haris, C. Debrosse, A. Singh, R.P. Nanga, K. Cai, H. Hariharan, R. Reddy, In vivo chemical exchange saturation transfer imaging of creatine (CrCEST) in skeletal muscle at 3T, J. Magn. Reson. Imaging 40 (2014) 596–602.
[198] S. Jiang, C.G. Eberhart, M. Lim, H.Y. Heo, Y. Zhang, L. Blair, Z. Wen, M. Holdhoff, D. Lin, P. Huang, H. Qin, A. Quinones-Hinojosa, J.D. Weingart, P.B. Barker, M.G. Pomper, J. Laterra, P.C.M. van Zijl, J.O. Blakeley, J. Zhou, Identifying recurrent malignant glioma after treatment using amide proton transfer-weighted MR imaging: a validation study with image-guided stereotactic biopsy, Clin. Cancer Res. 25 (2019) 552–561.
[199] A. Nishie, Y. Asayama, K. Ishigami, Y. Ushijima, Y. Takayama, D. Okamoto, N. Fujita, D. Tsurumaru, O. Togao, K. Sagiyama, T. Manabe, E. Oki, Y. Kubo, T. Hida, M. Hirahashi-Fujiwara, J. Keupp, H. Honda, Amide proton transfer imaging to predict tumor response to neoadjuvant chemotherapy in locally advanced rectal cancer, J. Gastroenterol. Hepatol. 34 (2019) 140–146.
[200] O. Togao, A. Hiwatashi, K. Yamashita, K. Kikuchi, J. Keupp, K. Yoshimoto, D. Kuga, M. Yoneyama, S.O. Suzuki, T. Iwaki, M. Takahashi, K. Iihara, H. Honda, Grading diffuse gliomas without intense contrast enhancement by amide proton transfer MR imaging: comparisons with diffusion- and perfusion-weighted imaging, Eur. Radiol. 27 (2017) 578–588.
[201] J. Zhou, H.Y. Heo, L. Knutsson, P.C.M. van Zijl, S. Jiang, APT-weighted MRI: techniques, current neuro applications, and challenging issues, J. Magn. Reson. Imaging. (**50**, 2019, 347-364).
[202] J. Zhou, E. Tryggestad, Z. Wen, B. Lal, T. Zhou, R. Grossman, S. Wang, K. Yan, D. X. Fu, E. Ford, B. Tyler, J. Blakeley, J. Laterra, P.C. van Zijl, Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides, Nat. Med. 17 (2011) 130–134.
[203] M. Haris, K. Nath, K. Cai, A. Singh, R. Crescenzi, F. Kogan, G. Verma, S. Reddy, H. Hariharan, E.R. Melhem, R. Reddy, Imaging of glutamate neurotransmitter alterations in Alzheimer's disease, NMR Biomed. 26 (2013) 386–391.
[204] C. Li, S. Peng, R. Wang, H. Chen, W. Su, X. Zhao, J. Zhou, M. Chen, Chemical exchange saturation transfer MR imaging of Parkinson's disease at 3 Tesla, Eur. Radiol. 24 (2014) 2631–2639.
[205] K.A. Davis, R.P. Nanga, S. Das, S.H. Chen, P.N. Hadar, J.R. Pollard, T.H. Lucas, R. T. Shinohara, B. Litt, H. Hariharan, M.A. Elliott, J.A. Detre, R. Reddy, Glutamate imaging (GluCEST) lateralizes epileptic foci in nonlesional temporal lobe epilepsy, Sci. Transl. Med. 7 (2015) 309ra161.
[206] O. Cohen, S. Huang, M.T. McMahon, M.S. Rosen, C.T. Farrar, Rapid and quantitative chemical exchange saturation transfer (CEST) imaging with magnetic resonance fingerprinting (MRF), Magn. Reson. Med. 80 (2018) 2449–2463.
[207] H.Y. Heo, Z. Han, S. Jiang, M. Schar, P.C.M. van Zijl, J. Zhou, Quantifying amide proton exchange rate and concentration in chemical exchange saturation transfer imaging of the human brain, Neuroimage 189 (2019) 202–213.
[208] Z. Zhou, P. Han, B. Zhou, A.G. Christodoulou, J.L. Shaw, Z. Deng, D. Li, Chemical exchange saturation transfer fingerprinting for exchange rate quantification, Magn. Reson. Med. 80 (2018) 1352–1363.
[209] J.I. Friedman, M.T. McMahon, J.T. Stivers, P.C. Van Zijl, Indirect detection of labile solute proton spectra via the water signal using frequency-labeled exchange (FLEX) transfer, J. Am. Chem. Soc. 132 (2010) 1813–1815.
[210] J. Xu, N.N. Yadav, A. Bar-Shir, C.K. Jones, K.W. Chan, J. Zhang, P. Walczak, M.T. McMahon, P.C. van Zijl, Variable delay multi-pulse train for fast chemical exchange saturation transfer and relayed-nuclear overhauser enhancement MRI, Magn. Reson. Med. 71 (2014) 1798–1812.
[211] Z. Zu, K. Li, V.A. Janve, M.D. Does, D.F. Gochberg, Optimizing pulsed-chemical exchange saturation transfer imaging sequences, Magn. Reson. Med. 66 (2011) 1100–1108.
[212] G. Liu, S.R. Banerjee, X. Yang, N. Yadav, A. Lisok, A. Jablonska, J. Xu, Y. Li, M.G. Pomper, P. van Zijl, A dextran-based probe for the targeted magnetic resonance imaging of tumours expressing prostate-specific membrane antigen, Nat. Biomed. Eng. 1 (2017) 977–982.
[213] N.N. Yadav, X. Yang, Y. Li, W. Li, G. Liu, P.C.M. van Zijl, Detection of dynamic substrate binding using MRI, Sci. Rep. 7 (2017) 10138.
[214] L. Knutsson, J. Xu, A. Ahlgren, P.C.M. van Zijl, CEST, ASL, and magnetization transfer contrast: how similar pulse sequences detect different phenomena, Magn. Reson. Med. 80 (2018) 1320–1340.
[215] B.E. Dewey, C. Zhao, J.C. Reinhold, A. Carass, K.C. Fitzgerald, E.S. Sotirchos, S. Saidha, J. Oh, D.L. Pham, P.A. Calabresi, P.C.M. van Zijl, J.L. Prince, DeepHarmony: a deep learning approach to contrast harmonization across scanner changes, MRI (2019), https://doi.org/10.1016/j.mri.2019.05.041 [Epub ahead of print].
[216] Quantitative Imaging Biomarkers Alliance, <https://www.rsna.org/en/research/quantitative-imaging-biomarkers-alliance>.
[217] European Imaging Biomarker Alliance (EIBALL), <https://www.eibir.org/initiatives/>.
[218] C.R. Jack Jr., J. Barnes, M.A. Bernstein, B.J. Borowski, J. Brewer, S. Clegg, A.M. Dale, O. Carmichael, C. Ching, C. DeCarli, R.S. Desikan, C. Fennema-Notestine, A.M. Fjell, E. Fletcher, N.C. Fox, J. Gunter, B.A. Gutman, D. Holland, X. Hua, P. Insel, K. Kantarci, R.J. Killiany, G. Krueger, K.K. Leung, S. Mackin, P. Maillard, I. B. Malone, N. Mattsson, L. McEvoy, M. Modat, S. Mueller, R. Nosheny, S. Ourselin, N. Schuff, M.L. Senjem, A. Simonson, P.M. Thompson, D. Rettmann, P. Vemuri, K. Walhovd, Y. Zhao, S. Zuk, M. Weiner, Magnetic resonance imaging in Alzheimer's Disease Neuroimaging Initiative 2, Alzheimers Dement 11 (2015) 740–756.
[219] M.W. Weiner, D.P. Veitch, P.S. Aisen, L.A. Beckett, N.J. Cairns, J. Cedarbaum, R. C. Green, D. Harvey, C.R. Jack, W. Jagust, J. Luthman, J.C. Morris, R.C. Petersen, A.J. Saykin, L. Shaw, L. Shen, A. Schwarz, A.W. Toga, J.Q. Trojanowski, I. Alzheimer's disease neuroimaging, 2014 update of the Alzheimer's disease neuroimaging initiative: a review of papers published since its inception, Alzheimers Dement 11 (2015) e1–120.
[220] D.C. Van Essen, K. Ugurbil, The future of the human connectome, Neuroimage 62 (2012) 1299–1310.
[221] B.J. Casey, T. Cannonier, M.I. Conley, A.O. Cohen, D.M. Barch, M.M. Heitzeg, M. E. Soules, T. Teslovich, D.V. Dellarco, H. Garavan, C.A. Orr, T.D. Wager, M.T. Banich, N.K. Speer, M.T. Sutherland, M.C. Riedel, A.S. Dick, J.M. Bjork, K.M. Thomas, B. Chaarani, M.H. Mejia, D.J. Hagler Jr., M. Daniela Cornejo, C.S. Sicat, M.P. Harms, N.U.F. Dosenbach, M. Rosenberg, E. Earl, H. Bartsch, R. Watts, J.R. Polimeni, J.M. Kuperman, D.A. Fair, A.M. Dale, A.I.A. Workgroup, The Adolescent Brain Cognitive Development (ABCD) study: imaging acquisition across 21 sites, Dev. Cogn. Neurosci. 32 (2018) 43–54.
[222] K.L. Miller, F. Alfaro-Almagro, N.K. Bangerter, D.L. Thomas, E. Yacoub, J. Xu, A. J. Bartsch, S. Jbabdi, S.N. Sotiropoulos, J.L. Andersson, L. Griffanti, G. Douaud, T.W. Okell, P. Weale, I. Dragonu, S. Garratt, S. Hudson, R. Collins, M. Jenkinson, P.M. Matthews, S.M. Smith, Multimodal population brain imaging in the UK Biobank prospective epidemiological study, Nat. Neurosci. 19 (2016) 1523–1536.
[223] B.R. Howell, M.A. Styner, W. Gao, P.T. Yap, L. Wang, K. Baluyot, E. Yacoub, G. Chen, T. Potts, A. Salzwedel, G. Li, J.H. Gilmore, J. Piven, J.K. Smith, D. Shen, K. Ugurbil, H. Zhu, W. Lin, J.T. Elison, The UNC/UMN Baby Connectome Project (BCP): an overview of the study design and protocol development, Neuroimage 185 (2019) 891–905.
[224] G. Litjens, T. Kooi, B.E. Bejnordi, A.A.A. Setio, F. Ciompi, M. Ghafoorian, J. van der Laak, B. van Ginneken, C.I. Sanchez, A survey on deep learning in medical image analysis, Med. Image Anal. 42 (2017) 60–88.
[225] V.S. Parekh, M.A. Jacobs, Deep learning and radiomics in precision medicine, Expert. Rev. Precis. Med. Drug. Dev. 4 (2019) 59–72.
[226] J. Schmidhuber, Deep learning in neural networks: an overview, Neural Netw. 61 (2015) 85–117.
[227] H.J. Aerts, E.R. Velazquez, R.T. Leijenaar, C. Parmar, P. Grossmann, S. Carvalho, J. Bussink, R. Monshouwer, B. Haibe-Kains, D. Rietveld, F. Hoebers, M.M. Rietbergen, C.R. Leemans, A. Dekker, J. Quackenbush, R.J. Gillies, P. Lambin, Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach, Nat. Commun. 5 (2014) 4006.
[228] P. Lambin, E. Rios-Velazquez, R. Leijenaar, S. Carvalho, R.G. van Stiphout, P. Granton, C.M. Zegers, R. Gillies, R. Boellard, A. Dekker, H.J. Aerts, Radiomics: extracting more information from medical images using advanced feature analysis, Eur. J. Cancer 48 (2012) 441–446.