7 T MR: From Basic Research to Human Applications

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The recent ultra-high field magnetic resonance (UHF MR, ≥7 T) scanners are demonstrating incredible potential, especially in the analysis of cerebral tissues. The technological achievements and the principles associated with the use of 7 T MRI systems are now being turned to applications on human, increasing both physiological and physiopathological knowledge as prelude to future clinical applications.

23.1 Ultra-High Field (UHF) MR

From the early days of magnetic resonance imaging, great interest was shown in obtaining ever stronger static magnetic fields since, according to the principles of NMR, all physical quantities are functions of the magnetic field applied B_0. It was therefore not by chance that in 1981, the same year in which the first clinical MR scanner was introduced to the biomedical market, Lauterbur and Budinger attempted to build the first superconductor magnet with a magnetic field of 6 T, the strongest magnetic field ever created at that time for human applications. Neither the time nor technology was right for such an undertaking; however, it is not difficult to see how in the 30-years history of magnetic resonance and its applications in medicine, there was an inexorable and very rapid increase in the strength of the static magnetic fields used in the medical context with 0.3–0.5 T systems seen in the early 1980s, 1–1.5 T in the early 1990s and the 3 T introduced between the late 1990s and the early 2000s. The same period also saw the development of revolutionary technologies in terms of image acquisition such as phased array systems and parallel imaging techniques. The power of these new approaches allowed the promises of ultra-high field MR (≥7 T magnetic field, ultra-high field, UHF), which had been predicted 20 years before, to be made possible, and led to the development of suitable tools for resolving many hypothetical and real problems which had been encountered in terms of the quality of images and safety.

In the late 1990s, 3 T systems were introduced to clinical practice. In the same period, in 1998, the first 8 T system for human applications was installed in Ohio State University, followed in 1999 by the installation of a 7 T scanner in the Magnetic Resonance Research Center of the

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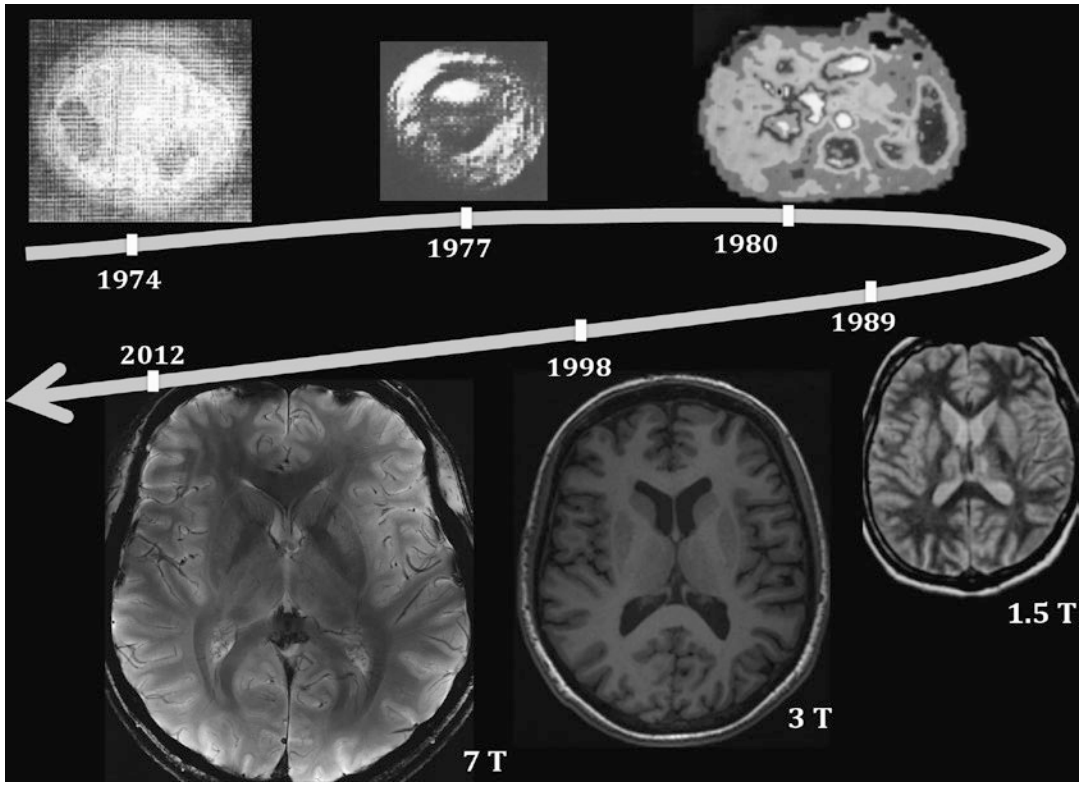

Fig. 23.1 The evolution of MR images over time. In 1974, the first image of a small animal was obtained by Lauterbur using a technique called zeugmatography at that time. The Mansfield's group obtained the first human anatomical image in vivo, an axial cross section of a finger (1977). On 28 August 1980 in Aberdeen, the first clinical image of a cross section of the abdomen was obtained. In the late 1980s, the use of 1.5 T magnetic resonance began to spread around the world followed in the late 1990s by 3 T systems. In the 21st century the MR image acquired at 7 T has an in-plane resolution of 192 μm *in plane*

University of Minnesota. Both these systems were for experimental purposes only and were assembled with great effort and dedication by research laboratories using components made on-site.

The incredible results obtained opened the road to the main manufacturers at that time, Siemens, General Electric and Philips, to develop ultra-high field magnetic resonance (UHF MR) technologies, which led to the first Siemens 7 T system being installed in Massachusetts General Hospital in Boston and, in rapid succession, a General Electric scanner at the Bethesda National Institute of Health (NIH). Today, around the world, there are more than 60 systems with ≥7 T magnetic fields installed and dedicated to the development and use in experimental protocols for human clinical research.

In retrospect, given the history of the discoveries in MR, the progress made towards the use of UHF technology would appear no less than logical (Fig. 23.1).

The trend forward high magnetic fields derives from the quite low sensitivity of MRI. This originates from the small difference in the population of two consecutive Zeeman energy levels caused by the difference in energy of these levels. The slight excess of spin in the fundamental state generates a small polarisation, which depends on the temperature and the magnetic field applied, and it is only from this small fraction of sample that the whole absorption signal is detected in correspondence with the radio frequency associated with the nuclear transition. One direct method for increasing the low sensitivity was identified as increasing the static magnetic field B_0. In more detail, the MR

signal increases in quadratic mode with the strength of the static magnetic field, while the associated noise demonstrates linear dependence. Therefore, the use of MR 7 T equipment allows a significant increase in the signal-to-noise ratio (SNR) in comparison with lower fields. For example, an image obtained with a clinical 1.5 T or even a 3 T system has a spatial resolution limit of about 1 cubic millimetre, while the combination of the benefits of ultra-high field can lead to a resolution of some hundredths of microns with similar signal-to-noise ratio. The significant increase in SNR produces a great improvement of all the imaging parameters and can be used not only in terms of spatial resolution but also in terms of sensitivity to modifications of the composition of the tissue or in terms of temporal resolution for dynamic phenomena or in terms of spectral resolution of signals. In addition, many other benefits could come out from the potential of new sources of mechanisms of contrast. Particularly in the brain, but also generally in the human body, there are potential sources of signal which cannot be fully explored using standard magnetic fields, because of low SNR, poor spatial resolution and/or their scarcity. It is the case of myelin, iron or metabolites which contain nuclei that differ from hydrogen (^{13}C, ^{23}Na, ^{31}P) that can be in principle detected by MR. These further signal sources can be extremely useful for providing additional and complementary information about molecular structure and/or the physiological, metabolic and functional dynamics of physiopathological processes. Moreover, the improvement in SNR and consequently in the intrinsic sensitivity of MR experiment can make possible the study of spontaneous distribution of nuclei different from proton that are normally found within structures of biological interest. For the same reason, it becomes possible to explore the distribution and the metabolic dynamics of molecular probes that are artificially enriched with stable isotopes that are visible in MR.

Increasing the magnetic field however causes some physical and instrumental problems that must be considered and fully investigated so that the potential of an ultra-high field MR system can be fully exploited. The major issues are related to the signal losses associated with the effects of magnetic susceptibility and inhomogeneities of the static magnetic field B_0, to the increase of chemical shift artefacts and to the variations in the relaxation times T_1 and T_2, which completely change the semeiotics of the images and the strategies of signal acquisition.

Moreover, the wavelength and dielectric effects of the radio frequency (RF) signal produce an uneven excitation and can cause an inhomogeneous distribution of radio frequency energy deposition on tissues. At 7 T, the resonance frequency for hydrogen is 298 MHz. Raising the operating frequency leads to the so-called wavelength effect: the radio frequency wavelength becomes comparable with the dimensions of the sample being investigated (limbs, brain and trunk) which per se brings stationary wavelength effects to the whole sample. The experiment becomes more complicated due to the dielectric properties of the sample irradiated by the radio frequency that further decreases the radiation wavelength (e.g. at 7 T, the wavelength in anatomical tissue with a high concentration of water is about 12 cm). This effect shows up as inconsistencies in the RF field transmitted (B_1) distribution, which is known as dielectric resonance. This generates peculiar artefacts in images that present hypo- and hyperintense zones caused by the presence of peaks and dips in the RF magnetic field B_1 and as a consequence generates locally different flip angles. The inhomogeneities in the B_1 magnetic field inevitably translate into inhomogeneous depositing of energy on the patient and give rise to possible "hot spots" of energy deposited. Specific absorption rate (SAR) is the parameter that measures this energy and forms the basis for both national and international patient safety standards. Commercial UHF MR systems monitor this parameter and use acquisition thresholds to do not exceed the abovementioned standards. However, given the uneven distribution of the transmitted fields and the possible presence of "hot spots", new methods for assessing variations in local magnetic field are mandatory. These may involve the simulation of electromagnetic fields and experimental measures [1], as well as the development of sensors for the real-time monitoring of SAR specifically for each individual patient (Fig. 23.2).

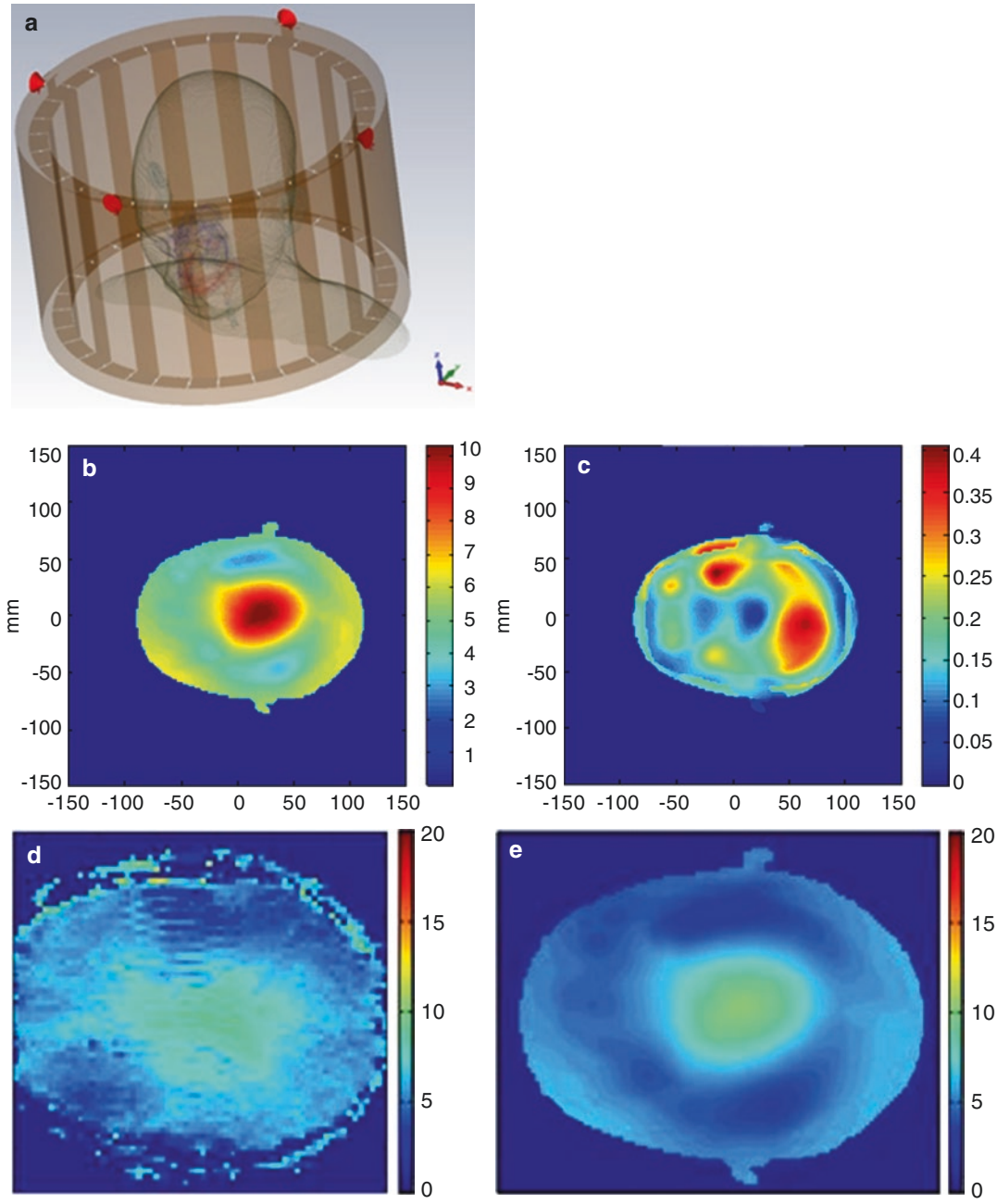

Fig. 23.2 The use of UHF MR in human needs a very careful safety assessment. In this context, calculating the specific absorption rate (SAR) becomes vitally important. SAR is a measure of the rate at which energy is absorbed by the tissue when exposed to radio frequency (RF) magnetic field per unit of mass. At ultra-high field, the distribution of the SAR within a patient becomes very uneven; this lack of uniformity is associated with the high-radio frequency (RF) output of the coil (298 MHz at 7 T). The calculation of RF fields and SAR is usually performed using full-wave electromagnetic simulators. In our case, we used the CST MW suite to simulate the volume transmitter in quadrature loading it with anatomical models of the human body (Hugo, Virtual Family, Virtual Classroom). In all the models, the voxel discretization has a resolution of 1 mm^3, whereas the dielectric properties of tissue are taken from literature. Figure (**a**) shows Ella's head (female Virtual Family model) within the volume transmitter in quadrature. Figures (**b**) and (**c**) show the map of B1+ (magnitude, in [μT]) and the SAR [W/kg] on the axial section passing through the eyes. Lastly, simply to validate the simulator, Figures (**d**) and (**e**) show the map of B1+ measured on a volunteer with characteristics similar to Ella [μT] and the appropriately scaled map of Ella [μT], respectively [11]

In recent years, huge technological progress has been made in attempting to resolve the problem of inhomogeneities in the excitation and in the receiving of RF signals in terms of both hardware and software. Rewriting the pulse sequence for UHF to enable the use of less sensitive sequences and eliminate errors in the flip angles applied to prevent sequence "refocusing" has proved extremely difficult. As the use of multichannel coils for signal receiving revolutionised MRI by allowing increased SNR and reduction of acquisition times, the introduction of parallel transmission opened new scenarios for UHF, creating a fundamental turning point in the use of UHF. Parallel transmission uses and controls a multichannel array system for the signal transmission, adjusting independently phase and amplitude of signals sent to each channel, with the aim of producing uniform excitation inside the sample. This led to what is now known as "RF shimming" (radio frequency calibration). Recently, parallel transmission systems allow to manage the different channels of signal transmission not only by adjusting the phases and amplitudes of signals but also by sending completely independent signals to single channels, increasing the spatial selectivity of the RF pulses. Thanks to this technological advance, it is possible to compensate specific B_1 inhomogeneities induced by specific geometry and dielectric properties of each single human body exanimated. Corrections of B_1 are therefore "customised" and allow the quality of imaging to be improved while at the same time minimising the depositing of energy for each patient with his or her specific characteristics (gender, age, dimensions such as weight and height, muscle mass and the presence of physiopathological signs).

As described above, some physical key UHF MR phenomena are not favourable for the application of 7 T in a clinical context such as inhomogeneities in B1 and the corresponding distribution of SAR. Moreover, the shortening of the RF wavelength used at UHF can interfere more strongly with metal objects increasing the heating effect. For this reason, the presence of implanted metal objects remains the main cause of exclusion from UHF MR exams.

With knowledge of above-mentioned limits and the significant results expected from awareness of the physical phenomena of UHF MR, the encouraging results of experimental studies carried out on patients suffering from diseases of the central nervous system have recently started to arrive.

23.2 Applications of UHF MR

From its first introduction into clinical practice in the 1980s, MRI has become a key tool for studying the anatomy and function of the central nervous system (CNS). At present, 7 T scanners around the world are used only for experimental purposes, and most of these experiments involve improving both hardware and software of the systems, in order to overcome the technological limitations intrinsic in the ultra-high field.

Studies about the applications to diseases of the CNS are still limited and are aimed to assess the diagnostic-clinical benefits of UHF with respect to clinical scanner, as well as to investigate safety aspects of application of UHF in humans (Fig. 23.3).

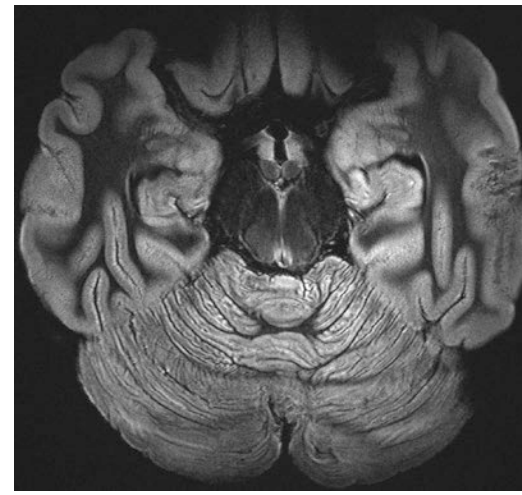

Fig. 23.3 Ex vivo 7 T cerebellum. Ex vivo imaging of the cerebellum at 7 T: a gross specimen from a human cadaver was fixed in a 10 % aqueous solution of formaldehyde, placed in a perfluoropolyether suspension and imaged with an IR sequence. The image resolution was about 100 microns and allows the appreciation of extremely fine details of the human anatomy such the cerebellar folia

The physical phenomena of UHF MR regulate the diagnostic possibilities obtainable with these scanners in a counteracting manner and provide benefits in some cases and disadvantages in others. The limited diffusion of UHF, the high costs involved and the presence of artefacts in the images limit its use in experimental studies, but at the same time push the development of new signal treatment methods and technological development. The possibility of obtaining new contrasts acts as a stimulus for the development of a new imaging semeiotics of the CNS in both healthy and unhealthy subjects. This is a true challenge for future clinical applications.

In effect, with increase of the applied magnetic field, relaxation times vary, particularly lengthening T1 while shortening T2 and T2*. In some applications, such variations can be beneficial, e.g. an increase in T1 which favours the saturation of stationary spins or a decrease in T2 which provides faster sequences. On the other hand, as relaxation times do not change uniformly in different parts of the CNS, contrasts between different structures can vary. Based on new signal treatment methods, new signal semiotics must be redefined and new imaging techniques can be discovered [2, 3].

An increase in SNR allows spatial resolution (in the order of hundredths of micron) able to provide anatomical imaging never seen in vivo. The phenomena of magnetic susceptibility have pros and cons for the clinical application of UHF. On the one hand, they allow greater sensitivity in detecting paramagnetic and diamagnetic substances such as haemosiderin in microhaemorrhages, calcium in tumoural calcifications and iron in degenerated portions of the CNS, while on the other hand, they increase distortions in anatomical images and decrease diagnostic quality. Greater sensitivity to the effects of magnetic susceptibility however allows new types of contrast to be obtained (susceptibility-weighted imaging, phase mapping, susceptibility mapping) (Fig. 23.4) which allow to distinguish anatomical components with different susceptibilities within an anatomical structure such as the laminar aspect of the cerebral cortex.

At the same time, the increased sensitivity to deoxyhaemoglobin in the veins causes greater sensitivity to the blood oxygenation level-dependent (BOLD) effect. This effect exploits the magnetic properties of the blood and of haemoglobin in particular, as an endogenous source of contrast, and forms the basis of the classical detection techniques of cortical activation. The functional magnetic resonance imaging (fMRI) technique is considered as one of the main applications that benefits from the use of UHF, thanks to the two simultaneous advantages of increased SNR and increased sensitivity to the BOLD effect. The improvement of both these factors can be exploited to study cerebral function with greater spatial resolution and greater sensitivity. It has been demonstrated that an increase in the spatial resolution of UHF fMRI can allow the definition of the functional architecture of the cerebral cortex at columnar level. In addition, the increase in the sensitivity of fMRI at 7 T allows to obtain statistically significant functional maps of cerebral activation not only in group of subjects but also for individual patients and individual events, opening new perspectives in the use of fMRI for clinical purposes.

The increase in the static magnetic field produces also an increase of the phenomenon of chemical shift, which can be also a negative effect, by worsening the chemical shift artefact typical of the fluid-fat interface. However, the increase of chemical shift forms the basis of a better spectral resolution of the frequency signal obtainable with UHF MR spectroscopy. The applicability of proton spectroscopy in a medical context is limited by the low concentration of most of the cerebral metabolites of interest compared with the quantity of water present in the tissue (over 50 mM). As the SNR and chemical shift are proportional to the strength of the static magnetic field, 7 T MR systems allow the quantification of about 13 brain metabolites, and thanks to spectral editing techniques, the direct detection

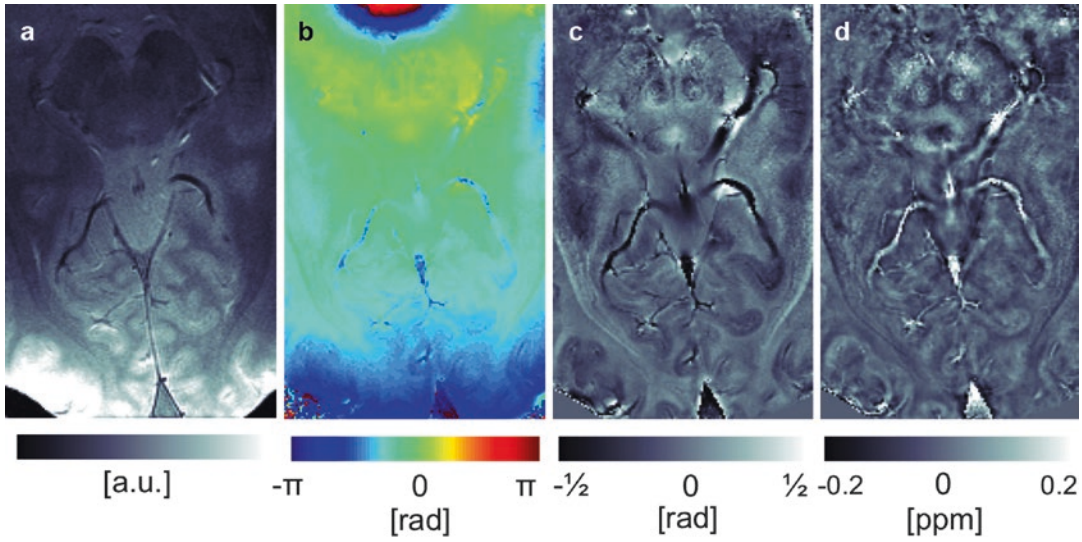

Fig. 23.4 From the acquisition of signal (real and imaginary component), the phase can be extracted, and therefore information can be obtained regarding the physical measurements associated with the static magnetic field which affect the precession frequency. In other words, it is possible to obtain a map of the magnetic susceptibility of the tissue being examined. The latter physical property has proven to be a new and powerful endogenic contrast agent that can detect significant tissue characteristics in clinical practice. Susceptibility is in fact directly proportional to the presence of iron and inversely proportional to myelin density – two key parameters in the study of neurodegenerative diseases for example. The extraction of susceptibility maps is performed starting from the signal (**a**) and the reconstruction of phase images (**b**) which are processed in order to isolate the contributions of phase from the large-scale ones caused by inhomogeneities of the static magnetic field. From these maps of local phase variations (**c**), frequency variation maps and therefore quantitative magnetic susceptibility maps QSM (**d**) can be reconstructed and applied in clinical protocol [12]

of important neurotransmitters such as glutamate in few minutes (Fig. 23.5 MRS).

Thanks to an increase in the sensitivity of spectral resolution, the introduction of UHF systems also opens new horizons for the study of other nuclei such as ^{31}P, and significant results have also been obtained with ^{13}C, ^{23}Na and ^{17}O, which are key elements in the study of cerebral metabolism and metabolism energy balance.

7 T scanning offers huge benefits when investigating structures and ultrastructures in vivo in human as in the field of neurometabolic studies and of cortical activation, improving our knowledge about anatomy and normal physiology in vivo. It is also for this reason that part of the research carried out at the UHF MR centres is aimed at fine-tuning sequences, identifying new contrast and optimising acquisition protocols on healthy volunteers. Moreover, the use of UHF offers a great potential for improving the characterisation of a wide spectrum of diseases of the CNS such as multiple sclerosis, neurodegenerative diseases, cerebral neoplasms and epilepsy.

The evaluation of multiple sclerosis at UHF allows to better clarify the underlying inflammatory process. In particular, the high resolution combined with the sensitivity to susceptibility of UHF allows to reveal the development of plaques along the perivenular white matter as a marker of MS in the differential diagnosis with other demyelinating disorders. Moreover, susceptibility-weighted imaging seems to detect paramagnetic rims at the lesion edge reflecting the expanding inflammatory phenomena of acute MS plaques [4].

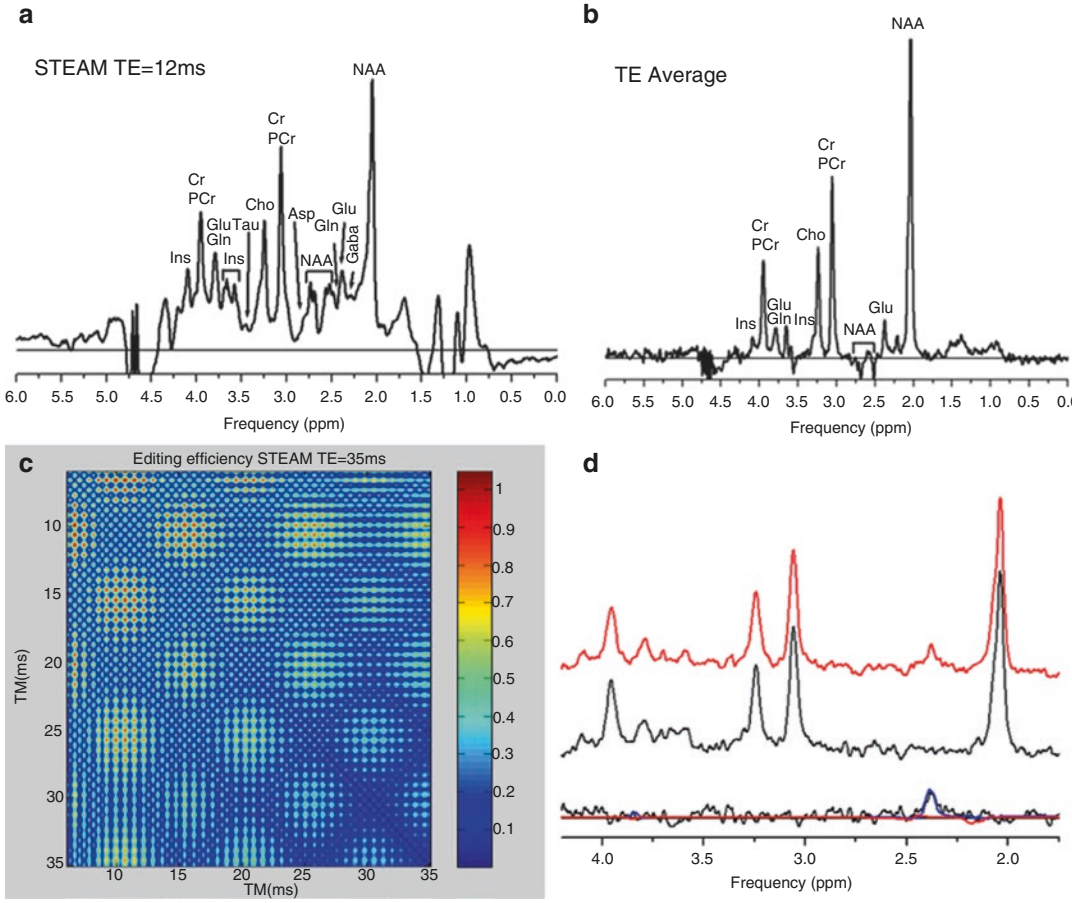

Fig. 23.5 MR spectroscopy in vivo. Thanks to the use of UHF systems, and the subsequent increases in SNR and spectral resolution, signals from a larger number of cerebral metabolites can be detected and separated than with clinical magnetic fields. (a) Example of standard acquisition with stimulated echo acquisition mode (STEAM) short echo time sequence for detecting the greatest number of metabolites. (b) The technique of spectral simplification, which allows the detection of metabolites of interest by eliminating the spectral components of multiplets. (c) The simulation of the quantum evolution of spins for optimising acquisition parameters (TE, TM) to detect particularly weak signals and/or signals that are spectrally overlapped with others (STEAM-MiTis, *mixing time subtraction* technique). The STEAM-MiTis technique is optimised for detecting glutamate, an important neurotransmitter involved in numerous pathological processes [13]

As regards neurodegenerative diseases, most of the attention is focused on Alzheimer-type dementia, Parkinson's disease and, to a smaller extent, amyotrophic lateral sclerosis.

The studies on Alzheimer's are aimed at evaluating hippocampal formations at high resolution (Fig. 23.6) to measure substructures of the Ammon's horn such as the reticular or lacunosum moleculare layer sites of the initial phase of the neurodegenerative process. In comparison with normal subjects, these studies also regard hippocampal morphology in patients with mild cognitive impairment. Thanks to the combination of high resolution and sequences that are sensitive to magnetic susceptibility, other studies are dedicated to detecting amyloid plaques that are the pathological substrate of the disease. Such consistent results in ex vivo animal experiments are however a matter of debate when applied to humans in vivo.

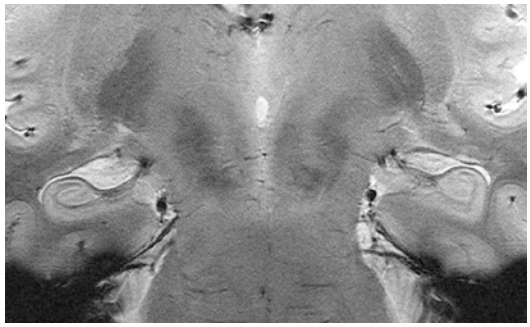

Fig. 23.6 Images acquired with the MR 7 T system with very high spatial resolution (200 μm *in plane*) by using a gradient-recalled echo (GRE) sequence targeted on the hippocampus regions. This portion of the brain plays an important role in long-term memory and in spatial navigation. Simultaneous research into high spatial resolution and contrast in the hippocampus is aimed at measuring fine substructures of the Ammon's horn such as the reticular layers and incomplete molecular sites and locations of the initial phase of the neurodegenerative process of Alzheimer's disease

In Parkinson's disease, UHF MR has shown its additional value compared with clinical MR systems at conventional field strength, using targeted sequences sensitive to susceptibility. For the first time in vivo, UHF MR has allowed the identification of components of the substantia nigra including that responsible for the disease [5]. The disappearance of the pars compacta of the substantia nigra, containing the nigrosome, demonstrates its degeneration, which is the pathological counterpart of dopaminergic deficit. Moreover, UHF MRI allows identifying patients in the initial phase of Parkinson's disease with great diagnostic accuracy. These radiological signs are not specific of Parkinson's disease but constitute a hallmark of nigrostriatal degeneration common to other forms of atypical parkinsonisms. In addition, the possibility of obtaining quantitative maps of magnetic susceptibility will also provide more information about the pathogenesis of the neurodegeneration seen in Parkinson's disease.

In amyotrophic lateral sclerosis, high-resolution UHF imaging of the motor cortex has revealed an unusual accumulation of iron in the deeper layers of the cortex corresponding with what can be detected by an anatomopathological examination. This accumulation would seem to correspond with the severity of the disability [6]. In the field of motor neuron diseases, however, there are great expectations for high-resolution imaging of the spinal cord. This is currently under study to resolve hardware problems associated with the receiving of MR signals in an anatomically complex region and to increase the sensitivity of MRI in identifying the ultrastructure of the spinal cord.

In the evaluation of cerebral neoplasia, conventional MR, proton spectroscopy and advanced techniques such as diffusion and perfusion are currently the techniques used for neoplasia grading and for defining the bioptic target. The new contrasts that can be obtained with UHF (intratumoural susceptibility signals) seem to provide additional elements that are indicative of greater aggressiveness such as the presence of micro-haemorrhages or venographic studies, which, thanks to the sensitivity of the UHF for deoxyhaemoglobin, have become an index of oxygen consumption. Specific patterns of neoplasia in differential diagnostics with radionecrosis or expansive lesions of another nature have not yet been studied, but there are great hopes for the demarcation of neoplastic tissue, which remains a challenge unresolved at conventional fields. Moreover, a great expectancy is about the differential diagnosis and grading of gliomas. Sodium MR imaging greatly improved at 7 T for the increased SNR. Sodium signal has been shown to increase in brain tumours, and it seems to be a probe of tissue viability able to differentiate low- and high-grade gliomas [7]. 1H-MR spectroscopy provides a benefit for measuring metabolic markers of tumours for the increased spectral resolution and metabolite sensitivity compared with conventional magnetic field strength.

In epilepsy, the introduction of UHF allows to identify more epileptogenic lesions than those detectable with lower magnetic field strength, so that the number of patients with secondary focal epilepsy increases, reducing the incidence of patients with cryptogenic focal epilepsy. 7 T MR

shows structural and biochemical abnormalities in greater detail to delineate seizure foci and probably could contribute to the surgical planning and to the improvement of patients outcome [8, 9].

Lastly, for all the experimental protocols on humans, many studies have been carried out about safety and tolerability of 7 T MR, providing encouraging results regarding the absence of significant side effects. Only annoying sensations have been reported, such as vertigo result, the most frequent at high magnetic fields [10].

Based on the laws of physics which govern it, UHF magnetic resonance has created great expectations and hopes for the creation of new semeiotics of many diseases of both the CNS in the first instance and in the future of many other regions of the body, e.g. the musculoskeletal system. In recent years, there have been numerous efforts made to provide 7 T scanners with coils and sequences for application on human to thus gain greater physiological and physiopathological knowledge as a prelude to future clinical applications. Many problems have been resolved but many others still remain to be fixed, before the full potential of UHF could be exploited at all. Only through continuous research, multidisciplinary synergy and the comparison of expertise from different sectors (physics, chemistry, engineering and medicine), the effective diagnostic progress of UHF in comparison with conventional fields can be demonstrated in different diseases, a fundamental step for putting UHF MR at the service of medicine.

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