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REVIEW

Magnetic resonance elastography: a general overview of its current and future applications in brain imaging

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Abstract Magnetic resonance elastography (MRE) has been developed over the last few years as a non-invasive means of evaluating the elasticity of biological tissues. The presence of the skull has always prevented semeiotic palpation of the brain, but MRE now offers the possibility of "palpating by imaging" in order to detect brain consistency under physiological and pathological conditions. The aim of this article is to review the current state-of-the-art of MRE imaging and discuss its possible future diagnostic applications in neuroscience.

Keywords Brain imaging · Brain tumours · Elastography · Elasticity · Magnetic resonance elastography

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Introduction

Palpation is commonly used in clinical practice to make preliminary diagnosis (as in the case of breast lesions), but the presence of the skull obviously makes brain palpation impossible. Although neuroradiological techniques such as CT and magnetic resonance imaging (MRI) have made it possible to detect brain tumours, they do not provide any information about their consistency, which would be extremely useful when planning surgery because a number of tumours cannot be removed precisely because of the stiffness of the tissue. Furthermore, little is known about the viscoelastic properties of the brain, and so perceiving the differences between physiological and pathological tissue remains very subjective even for experienced surgeons.

The consistency of the brain has been investigated using a number of models, but such simulations often fail to reflect the rheological characteristics of the brain in vivo. The viscoelastic theory postulates that soft biological tissue subjected to an external force can be modelled by a combination of elastic and viscous elements that allow the specific rheological behaviour of the material to be characterised [24], and these principles have been used to develop non-invasive magnetic resonance elastography (MRE) as a means of evaluating the elasticity of biological tissues [42]. This innovative technique was introduced at the beginning of the 1990s by Muthupillai et al. [42] and offers the possibility of a kind of "palpation by imaging" [41, 42].

MRE is based on a transducer that transmits vibrations to the tissue of interest, a sequence of motion-encoding gradients to image tissue displacement and a mathematical reconstruction designed to reflect the mechanical properties of the tissue [41, 42]. In the case of mechanical excitation of the brain, vibration of the entire head indirectly induces shear waves that make it possible to acquire brain elasticity measurements in vivo despite the mechanical shielding of the skull. Acquiring a single MRE image captures a single directional component of motion, and so repeating the experiment in three orthogonal directions to capture all of the components of displacement can provide complex, three-dimensional information indicating the real differences in the shear moduli of the anatomical structures [33]. However, a number of computer science and mathematical problems remain in developing a sufficiently robust algorithm capable of deducing the distribution of elastic properties from these finely sampled three-dimensional displacement fields [70].

Principles and technical key points

MRE requires a wave driver to generate the mechanical excitation of target tissue, which must be positioned on the body surface as closely as possible to the scanned target. The driver vibrates at controllable frequencies and amplitudes, and each cycle is synchronised with a motion encoding sequence that is capable of measuring mechanical vibration. A shear modulus elastogram is calculated by processing the mechanical parameters of amplitude, wavelength, frequency and phase in the image volume using a three-dimensional linear elastic tissue model (see the workflow of MRE in Fig. 1). The calculation of the shear modulus may be inaccurate if the phase encoding sequence is not well synchronised with the source of the vibration, because a cumulative error in the wavelength estimate can be caused by phase lags between the vibration and the acquisition of the image.

The MRE compatibility and safety of the wave driver are main concerns in hardware design because it is positioned very closely to the image volume and in contact with the patient's body. MRE compatibility indicates the usability of the device in conjunction with MRI with minimal mutual interference. This is very important because any non-compatible devices can be a potential risk to both patients and clinician staff: ferromagnetic or paramagnetic materials can experience attractive forces and torques that elicit a "missile effect", and there have been frequent reports of chairs, pens and paper clips being pulled into an MR scanner to the danger of patients and staff [12, 14].

Eddy currents can be induced in conductive materials near to the scanner because of the fast switching gradients and radiofrequence pulses, creating image artefacts and possibly leading to the over-heating and malfunction of electronic components [7]. Any conductive parts of a device should be grounded with the scanner, but earthing loops must be avoided as this can lead to further sources of interference. Electrical and electronic components generate electromagnetic fields, which are picked up by the radio-frequence receive coil of the imager and cause signal degradation [7, 66], and so, they need to be carefully selected and tested according to the American Society for Testing Materials standard, which is a commonly used protocol, in the areas of artefact generation, magnetically induced force/torque and thermal effect to evaluate the MR compatibility of an introduced subject in the MR environment [1]. The conventional motors, transformers and AC–DC converters found in most medical devices use alternating currents which can cause electromagnetic interference, although appropriate shielding and low-pass

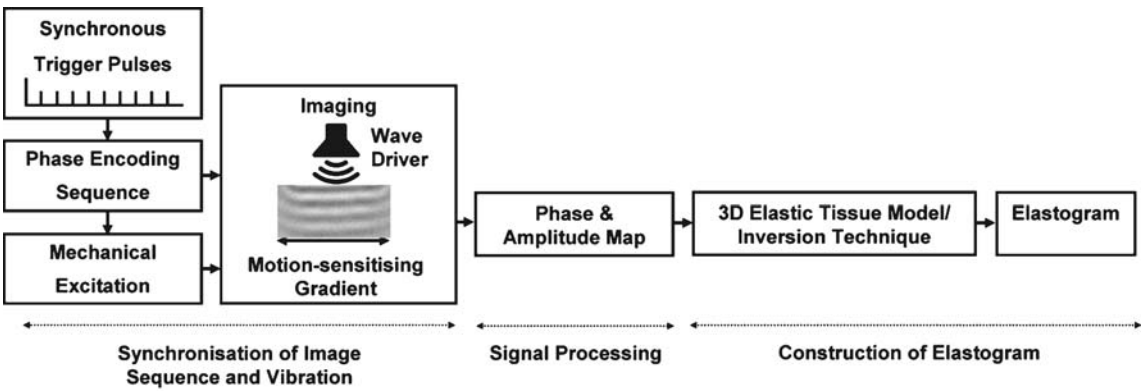

Fig. 1 Workflow of MRE: (1) mechanical excitation of the imaged tissue in terms of amplitude and phase which is measured by a phase-encoding sequence; (2) the mechanical actuator is triggered by the sequence to synchronise the produced wave propagation; (3) the acquired three-dimensional images are processed with the inversion technique, and an elastogram is then computed indicating the spatial distribution of the tissue stiffness

filtering of all signal cables can reduce the disturbance [11, 66]. The stringent MR compatibility requirements constrain the design of MRE devices and alternative methods have been investigated in an attempt to replace or minimise the use of traditional actuation methods.

The published actuation methods can be divided into three groups: (1) actuation using a remote excitation source, (2) electromagnetic actuation and (3) MR-compatible actuators.

In the first category, a passive end-effector is located near to the area of interest and linked to an excitation source positioned away from the imager in order to minimise electromagnetic interference [3, 49, 53, 63]. Talwalkar et al. developed a pneumatic device for liver elastography which consists of a passive driver placed directly on the chest, a loudspeaker located away from the magnetic field generating 60 Hz mechanical excitation and a plastic tube transmitting the excitation pneumatically from the active to the passive driver [63, 64]. Pneumatic actuation is a promising solution as it allows a non-MR compatible actuation system to be positioned away from or outside the scanner with air tubes linking it to a compatible end-effector in contact with the target area [13].

There are also remote actuation designs based on the use of electromagnetic vibrators and speaker-like devices [31, 51, 53].

In brief, electromagnetic designs have the benefit of good synchronisation but suffer from their relatively less flexible orientation to the main field and their location in the scanner and may generate artefacts, whereas pneumatic devices have the best MR compatibility but must take into account phase delays and may be less effective for very high frequencies (above 300 Hz).

The best MRE design is, therefore, a balanced compromise between MR compatibility, complexity, flexibility, cost and synchronisation and depends on the types of applications.

Overview of the current MRE applications in non-nervous systems

MRE of the breast In breast cancer imaging, MRE makes it possible to evaluate the elastic properties of tissues that reflect macroscopic alterations related to stromal reactions to a tumour, the remodelling of the normal extracellular matrix and the changes in cell density or extracellular matrix degradation induced by angiogenesis and tumour invasion [59] and may, therefore, overcome some of the limitations of conventional palpation. Manual palpation is a subjective technique and can only identify surface lesions that are at least 8–10 mm in diameter [39], whereas MRE non-invasively reveals the greater shear elasticity of breast tumours in comparison with normal breast tissue.

MRE of the liver Three-dimensional MRE has been used to estimate the viscoelastic properties of the liver in order to directly visualise and quantitatively measure propagating acoustic shear waves progressing through liver tissue [20–23, 50, 55, 62–64, 79, 82]. It has been suggested that hepatic MRE should be included among the morphological and perfusion imaging procedures used to detect liver cancer [72] and steatosis and assess liver function.

MRE of the prostate There is currently no standard imaging technique for the diagnosis or staging of prostate cancer [9], but MRE is one of the most promising although it still requires extensive validation. Kemper et al. have shown that in vivo MRE of the prostate gland is technically feasible insofar as the proposed experimental set-up allows the efficient use of the mechanical wave and successful MR data acquisition [25].

MRE of skeletal muscle In vivo measurements of the elastic properties of muscle could help evaluate muscle diseases early as well as during follow-up [2, 67]. Ultrasound elastography has been used to measure muscle elasticity but only within a limited range [67], whereas MRE enables the entire muscle to be studied and has no limitations in terms of penetration depth or the maximum resolvable field of view [46, 47, 52]. Although MRE cannot yet be used clinically, it does offer a unique means of measuring muscle tissue elasticity in situ, and there are already reports demonstrating significant differences in patients with paraplegia and a history of poliomyelitis.

MRE of other organs MRE has also been used to study the mechanical properties of lungs [15, 38], kidneys [34, 58], heart [10, 53], connective tissue [5, 6, 32] and blood vessels [74, 81], as well as for microscopic studies of frog oocytes and tissue-engineered adipogenic and osteogenic constructs for high-resolution assessments of the mechanical properties of developing tissues [45].

MRE of the brain

MRE imaging of the brain involves the generation of waves by means of an electromagnetic actuator attached to a bite-bar [19] or an electromechanical device such as a loudspeaker with a moving coil fixed to the head coil [53, 75–77], sequenced imaging and data acquisition, pre-processing and analysis (Fig. 1). In the suitable 59–1,000-Hertz range of mechanical excitation [34, 42], MRE is capable of measuring two-dimensional [28, 37, 68] and three-dimensional [4, 17, 19] shear waves fields in the brain.

Many studies have quantified shear modulus data in the brain under both physiological and pathological conditions, and propagating shear waves have been imaged and estimated using some specific sequences in volunteers (Figs. 2, 3). Xu et al. developed a modified phase-contrast gradient-echo sequence with motion-sensitising gradients and clearly demonstrated a difference in the elasticity of grey and white matter using a 3-T MR unit [77], and various authors have found shear module data ranging from 2.5 to 15.2 kPa for white matter and from 2.8 to 12.9 kPa for grey matter [8, 17, 18, 30, 37, 68, 77]. The data are generally consistent with the fact that cerebral white matter is significantly stiffer than grey matter in vivo [30, 37, 68, 75–77]; however, Nagashima et al. assumed grey matter to be stiffer than white matter for a finite element of brain oedema [43] and Green et al. found it was stiffer with MRE [16]. This variability suggests that there is no definite method of confirming brain stiffness estimates in vivo, but there is clearly a difference in the elasticity of grey and white matter [29, 30]. Potential symptomatic changes in global brain viscoelasticity may be attributable to diffuse effects of neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis [53]. Because of the small area of grey matter in comparison with shear wavelength and the difficulty in accurately determining shear wave velocity in different media, Hamhaber et al. [19] considered a mean shear modulus of 3.5 kPa (averaging grey and white matter). Kruse et al. estimated the rapid attenuation of wave propagation toward the centre of the brain in 25 healthy adult volunteers, and the increasing wavelength of the travelling shear wave that indicates that it is travelling through increasingly stiffer media [30].

Combining the echo-planar imaging and MRE acquisition technique with analysis of the propagating 3D wave fields, Hamhaber et al. found the largest deflection amplitude in all directions in parts of the cerebrum and the cerebellum adjacent to the tentorium cerebelli; the estimated mean shear wave velocity was about $1.88 \pm 0.58\ m s^{-1}$ [19]. Although 2D MRE provides a good approximation of 3D wave propagation in the brain, true 3D imaging would better account for its geometrically complex nature [29]. Klatt et al. used multi-frequency MRE to compare the rheological parameters of the brain and liver in five healthy volunteers and concluded that human brain is softer and more viscous than liver [27].

In relation to brain tumours, Xu et al. evaluated six patients with known solid brain tumours [76]: four meningiomas (two fibrous and two transitional; Fig. 4), one schwannoma and one hemangiopericytoma. The tumours were subjectively evaluated by a radiologist before surgery using MRE to visualise the propagating shear waves in the brain and the intra-tumour changes in their wavelengths in order to classify tumour elasticity as less than, more than or similar to that of the white matter of the brain; subsequently, the tumours were evaluated intra-operatively by the same surgeon (who was blinded to the MRE results), and their consistency was classified as soft (softer than white matter), hard (stiffer than white matter) or intermediate (similar to white matter). The elasticity of the tumours agreed with the neurosurgeon's assessment of consistency in all cases [76].

In relation to the changes of brain consistence due to gender and ageing, Sack et al. investigated 55 volunteers (23 females) ranging in age from 18 to 88 years, applying four vibration frequencies in an acoustic range from 25 to 62.5 Hz. By means of MRE, the authors revealed for the first time how physiological ageing changes the global viscosity and elasticity of the brain, showing that the healthy adult brain undergoes steady parenchymal "liquefaction"; moreover, it was shown a significant difference, showing female brain more "solid" than their male counterparts, rendering women more than a decade "younger" than men with respect to brain mechanics [54].

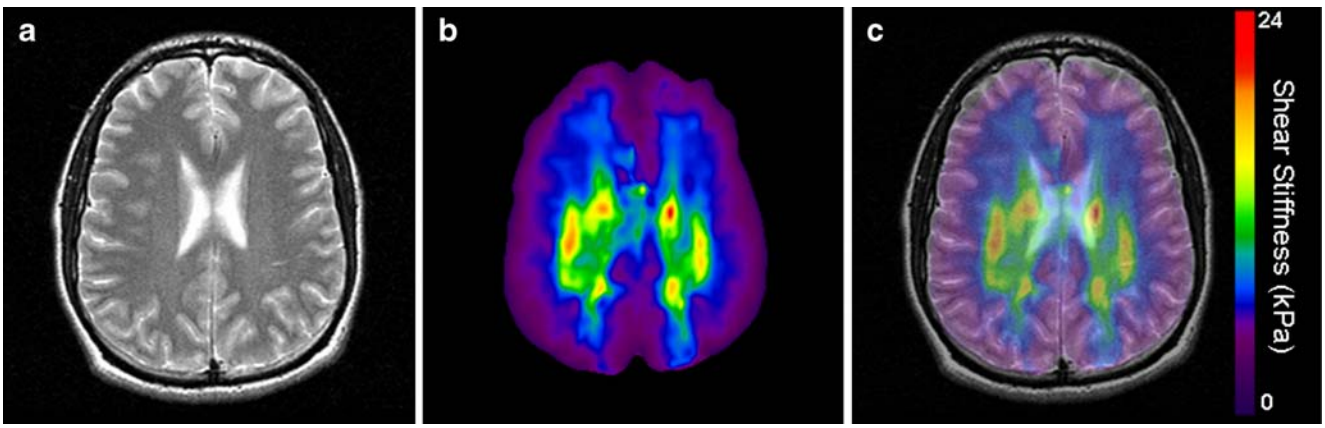

Fig. 2 MR elastography of the brain. **a** T2-weighted brain image for anatomical reference; **b** shear stiffness map, after the application of shear waves propagating in the brain; **c** fusion of images. The shear stiffness map overlaid on the anatomical reference illustrates the correlation of stiffness changes in anatomy. (Courtesy of Prof. Richard L. Ehman, MD, Department of Radiology, Mayo Clinic, Rochester, USA)

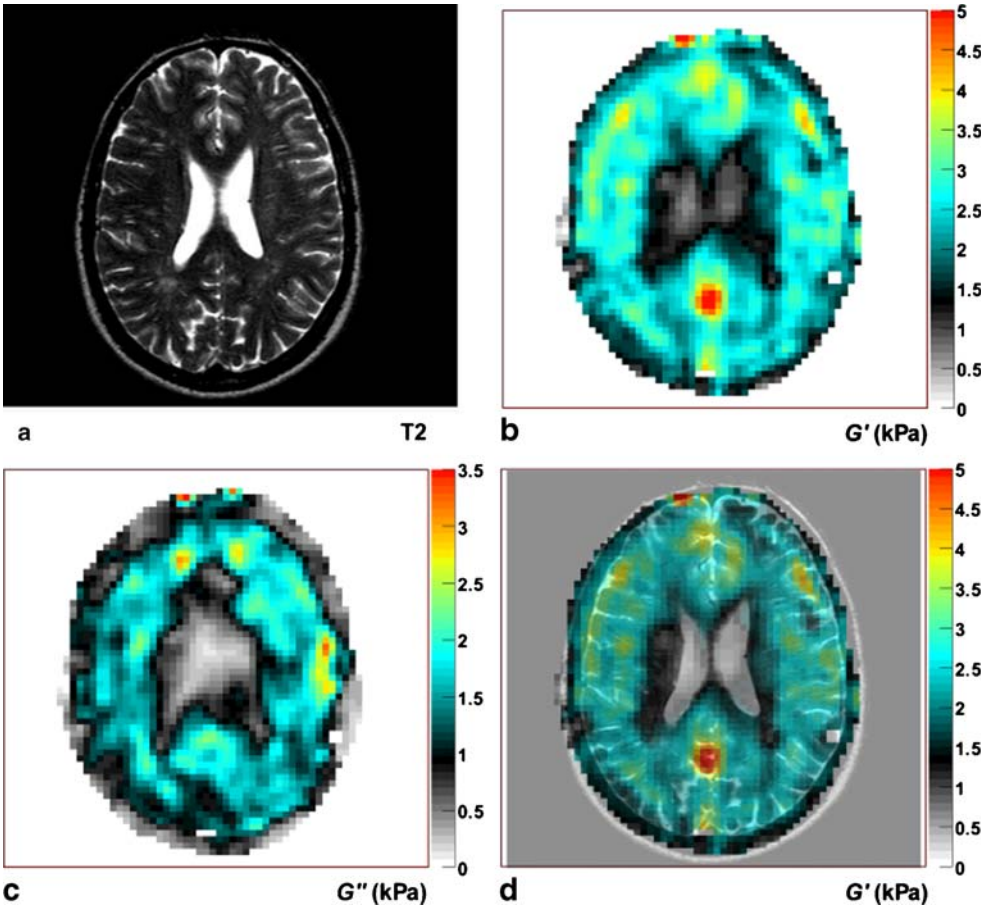

Fig. 3 MRE, example of in vivo reconstruction. **a** T2-weighted MR image; **b** G′ (kPa) image; **c** G″ (kPa) image; **d** elasticity overlaid with the T2-weighted image. Ventricles in the region of low elasticity are visible in the centre of the image. (Courtesy of Michael A. Green, PhD, Prince of Wales Medical Research Institute, Sydney, Australia)

Limitations

Estimates of physiological (normal) brain stiffness in vivo vary, and different image sequences or possible symptomatic changes in global brain viscoelasticity attributable to the widespread effects of neurodegenerative diseases or physiopathological states can change the results. Small tumours cannot be accurately evaluated because of the limited resolution of the image of elasticity; infratentorial tumours are also difficult to assess and the elasticity of tumours with cystic changes may not be evaluated properly because the shear waves cannot propagate through the cystic components [76].

The future of MRE in brain imaging

Once physiological values are known, MRE can detect changes in tissue stiffness that may indicate the presence of tumours or other diseases [60] and seems to be capable of preoperatively evaluating the consistency of a brain tumour. Knowledge of the consistency of a meningioma, in addition to its vascular and histopathological characteristics, could help in planning surgical strategy, particularly in patients with a tumour at the base of the skull-base or encasing cranial nerves and major blood vessels. The hardness of a meningioma correlates with its relative intensity on T2-weighted images [80], and a hard meningioma could benefit from preoperative endovascular embolisation as this induces necrosis and can make it soft enough to be removed safely and more easily [78].

The preoperative detection of a hard and highly fibrous pituitary macro-adenoma is important in planning surgery and avoiding multistage surgical procedures [65], because a hard pituitary adenoma cannot be successfully removed endoscopically and may require a more extensive trans-sphenoidal or a transcranial approach [48].

Furthermore, unaffected peritumoural tissue also has variable elastic properties due to compression by the lesion or perifocal oedema. An imaging method capable of reproducing these different elastic properties would provide useful detailed information concerning the composition of the lesion and the boundary between it and normal tissue [57].

Preoperative estimates of the tissue stiffness have also been correlated with some intra-operative data, as in the case of conventional sonographic imaging [44]. Vibrography using a signal-processing algorithm to calculate and display elastographic images in real time (sonography with real-time elastography) has been developed in order to make elastography more useful in brain surgery [56, 57].

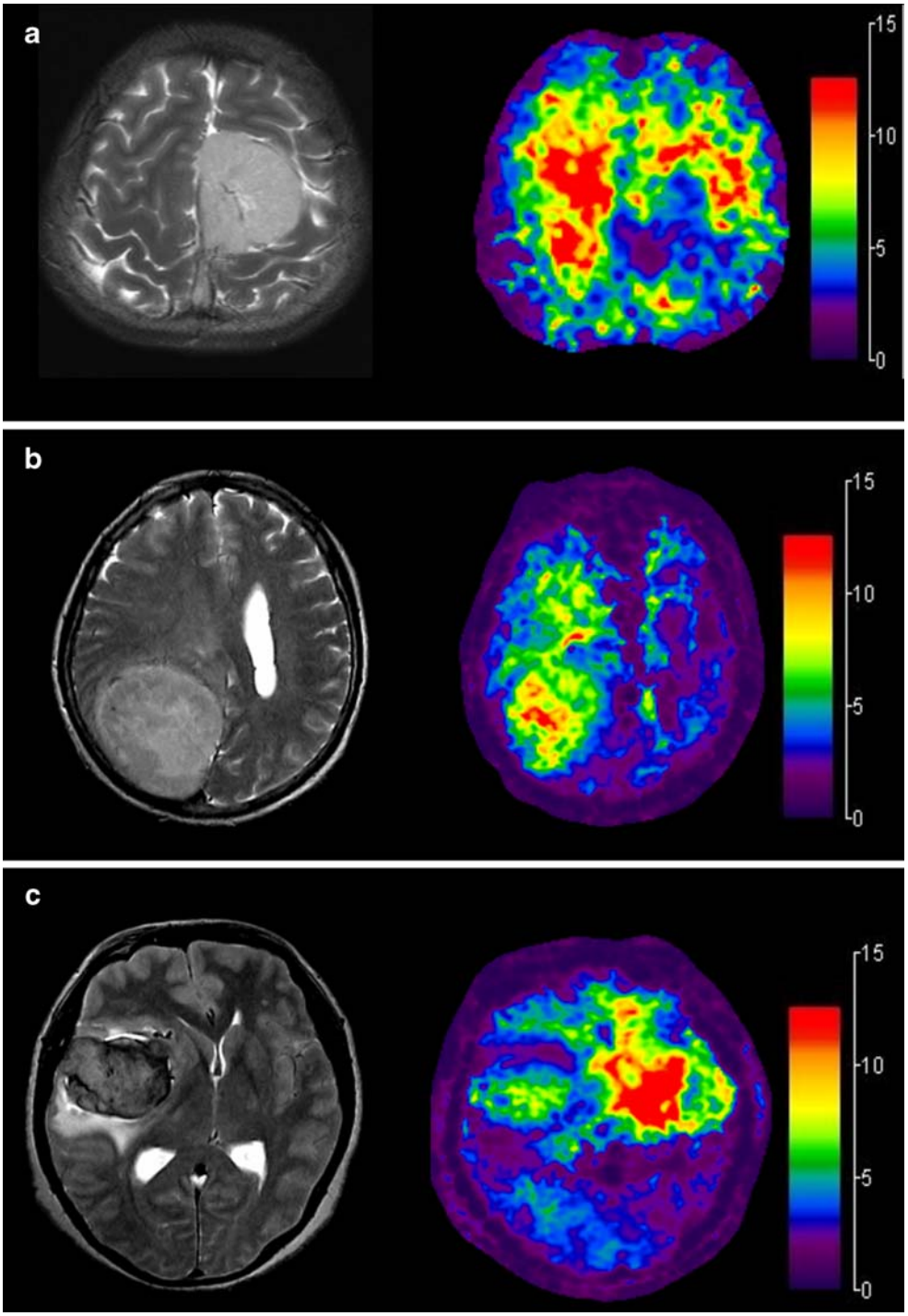

Fig. 4 Three cases of brain meningiomas (**a**–**c**). On the *left*, T2-weighted MR images, showing huge brain meningiomas. On the *right*, MRE. In the case (**a**), a transitional meningioma in the left parasagittal frontal lobe shows a lower elastic modulus compared to that of the white matter of the brain. In (**b**), a transitional meningioma located in the right parietal lobe, isointense to the cortex shows higher elastic modulus compared to that of the white matter. In the case (**c**), a fibrous meningioma, with an isointense signal to the cortex shows the elastic modulus to be similar to that of white matter. (Courtesy of Prof. Peiyi Gao, MD, Neuroimaging Center, Beijing Neurosurgical Institute, Beijing, China)

After the first experimental results in swine brain [56], Scholz et al. reported their experience on the use of the intra-operative vibrography in 20 patients affected by brain tumours. The authors detected brain tumours by means of intra-operative vibrography and differentiated them in three groups according to their stiffness values [57]. The colour coding of sonographic imaging provides a qualitative display of tissue elasticity (darker colours represent harder tissue and brighter colours softer tissue), although it is not quantitative [57]. Future studies of vibrography should not only characterise different strains in brain tumour tissue but also normal brain tissue with oedema or a high- or low-water content in different age groups [57]; the correlation of preoperative MRE data with intra-operative vibrographic estimates could provide new insights into the consistency of tissue and allow for the better treatment of diseases, although the results would need to be validated in a large study population in order to

assess the impact of MRE on therapeutic options and patient outcomes [65]. As suggested by Scholz et al., the combination of intra-operative vibrography and pre-surgical MRE could be integrated into a navigation system to provide useful information during the surgical procedure [57]. In this case, the quantitative values of stiffness measured by pre-surgical MRE could be compared to the qualitative analysis performed by means of vibrography during brain tumours surgery.

Considering that the mechanical behaviour of brain tissue is one of the most demanding and complicated to model [26], MRE could also improve biomedical engineering research as knowing more about the properties of the brain in order to develop materials which could aid our understanding of the mechanisms of concussion and other types of traumatic injury [36]. The mechanical properties of brain tissue govern its deformation during an impact or rapid acceleration. Margulies has developed an empirical correlation between critical shear strain and the onset of diffuse axonal injury in response to rotational inertial loading of the brain [35], and MRE could be useful in quantifying the necessary cut-off values. In addition, MRE could help in predicting the deformation of brain tissue during craniotomies or the insertion of needles and similar tools during routine neurosurgical procedures [40, 73]. In cadavers' specimens, it could be studied how formalin fixation or other techniques used in the anatomic laboratories affect white or grey matter preferentially [8]. Characterising the mechanical properties of the developing brain is also important for understanding the nature of brain development. Van Essen et al. have postulated that tension in axonal fibres pulls the cerebral cortex together to create outward folds and, although it is not yet clear whether the levels of tension generated in axons are sufficiently large to deform brain tissue, this question can be addressed by learning more about both axonal tension and tissue stiffness [69].

It is not yet known exactly how much (if at all) the stiffness of brain tissue changes during certain disease processes (e.g. Alzheimer's disease), but further improvements in data acquisition and processing techniques will improve the precision of brain MRE and may make it possible to distinguish normal and pathological tissue, or the physiological changes due to the ageing processes.

Changes in the water content of the brain parenchyma alter the stiffness of the tissue and could be measured by MRE, thus providing estimates of the biomechanical properties of the brain related to hydrocephalus or stroke or to the local concentration of drugs such as mannitol that alter water content. Three-dimensional MRE imaging would also allow studies of the possible anisotropic properties of white matter [29].

MR elastograms could aid surgery simulations by estimating tissue stiffness in order to allow the appropriate haptic control of surgical specimens by means of adapted forced feedback devices. In this way, more data can be added to the telemetric control of a robotic arm for neurosurgical operations in the next future. In this case, it is important that the estimates differentiate living and dead brain tissue and the temporal evolution of its post-mortem mechanical response [71].

Some studies aimed at obtaining the elastic modulus of whole human tissues by means of MRE are currently ongoing [61].

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Comments

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This is an interesting report on a novel imaging technology, explaining its engineering background, illustrating technical options and considerations during the image acquisition process and summarising a variety of clinical applications. The ability of magnetic resonance elastography (MRE) to capture elastic properties of tissue offers a new quality of information which will certainly complement current medical imaging techniques. Once the data are verified in larger series and image resolution has increased, MRE has the potential to allow accurate preoperative prediction of mechanical tissue behaviour, even of small lesions. This information could be extremely useful when planning the surgical corridor, considering the deformability of surrounding structures and deciding on the technique of dissection and resection. Together with structural, functional and molecular imaging MRE brings us one step closer to understand the inside without having been there.

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Magnetic resonance elastography (MRE) has been developed over the last years as a non-invasive means of evaluating the elasticity of tissues. The authors report an interesting review of a new possible MR application for the diagnosis of several brain pathologies and, in particular, of intracranial tumours. If confirmed by large clinical series, MRE could offer useful information regarding the consistency ("elastic modulus") of tumour, adding important preoperative and, if any, intra-operative data for the best surgical planning. Even if the limits of this application are still many, both in terms of affordability and of application, further technological evolution of MRE will give us the information about tumour stiffness we often need for a better surgical planning and for a more complete patient's preoperative consensus.