https://doi.org/10.1038/s41551-023-01020-6

Making MRI increasingly useful

New strategies for enhancing the sensitivity and resolution of contrast in magnetic resonance imaging will broaden its applicability.

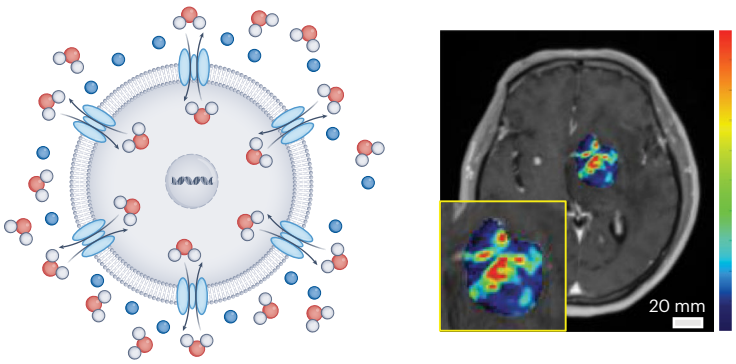

Fig. 1 | Transmembrane water-efflux rates quantified by MRI can be used as a biomarker of proliferative glioma. The water-efflux rates correlate with the expression levels of the water-channel protein aquaporin-4 (blue; left), and can be measured via dynamic-contrast-enhanced MRI (by using a gadolinium-based contrast agent; single blue spheres). The MRI image on the right shows a map (magnified in the inset) of the rate of transmembrane water transport overlaid on a brain scan of a patient with a glioma. Figure adapted with permission from the News & Views article by T. Ruan and K. Keshari; originally adapted with permission from the Article by R. Bai, Y. Liu and co-authors.

In magnetic resonance imaging (MRI), the hydrogen atoms (or protons) of water molecules in the tissue of the person laying still in the scanner align with the direction of the spatially varying magnetic field generated by a gradient coil. On brief excitation by radio waves generated by a radiofrequency coil, the protons release weak electromagnetic energy, which the scanner's gradient-coil system detects, amplifies and digitizes before the output is computationally processed to reconstruct the signal into an image of the tissue. By adjusting the strength and timing of the radio and magnetic pulses, a typical clinical MRI scanner can resolve tissue structures of a few millimetres. The actual spatial resolution also depends on the strength of the magnetic field, the characteristics of the receiving coil, and the size and spacing of the imaging voxels, which are constrained by a range of considerations, such as image quality, scan time and patient comfort.

During disease diagnosis or monitoring, the spatial resolution may be less limiting than the contrast sensitivity (the detection of structural abnormalities or other changes within the same tissue) and contrast resolution (the discrimination of tissues with different contrast) that the MRI scanner can provide. Both types of contrast can be enhanced by using better coils or higher magnetic-field strengths, which increase the signal-to-noise ratio, by developing imaging sequences and protocols to capture more information from the imaged tissue (such as water diffusivity) and by leveraging post-processing methods such as image registration and segmentation, most recently with the aid of machine-learning models.

Two commonly used contrast-enhancement strategies are multi-parametric MRI (that is, the acquisition of multiple complementary sources of contrast in a single scan), and the use of contrast agents[1]. Specifically, MRI can detect differences in proton density, and in the protons' longitudinal and transverse relaxation times. It can also use exogenous sources of contrast via paramagnetic or superparamagnetic agents that affect the relaxation properties of neighbouring water protons. For example, gadolinium compounds and iron oxide nanoparticles are typically used to enhance the contrast of blood vessels (and hence they can aid the detection of lesions; however, gadolinium contrast agents may cause nephrogenic systemic fibrosis in people with diseased kidneys[2]). And nanoparticles of iron oxide and of manganese oxide can be used to detect lymph-node, liver and spleen tissue[3], as well as brain and heart tissue[4]. Beyond being magnetically susceptible, contrast agents can be designed to bind to specific disease biomarkers, or to alter their magnetic properties in response to environmental changes. In this issue of *Nature Biomedical Engineering*, three research Articles report the use of these strategies to broaden the applicability of MRI.

In one Article, Haiming Fan and colleagues report the development of a manganese-containing ultrasmall nanoparticle with high specificity for hepatocytes as a contrast agent for imaging the liver and the biliary tree (the gallbladder, bile ducts and pancreatic ducts). The nanoparticle improved the sensitivity and resolution of contrast with respect to gadoxetate disodium, which is the typical contrast agent used in the clinic for hepatobiliary MRI. In rabbits, pigs and macaques, the nanoparticle allowed for a higher detection rate of early-stage liver tumours and for a more accurate assessment of biliary obstruction. Liver-specific MRI contrast agents may better inform the diagnosis of liver tumours, particularly in patients with liver cirrhosis and hepatitis.

Ruiliang Bai, Yingchao Liu and co-authors show in another article that water-exchange dynamic-contrast-enhanced MRI — which can detect the diffusion of water molecules across cell membranes by leveraging a gadolinium-based contrast agent — can be used to quantify the degree of expression of the transmembrane water-channel protein aquaporin-4 in gliomas. The authors show that the rates of transmembrane water efflux across the water channels correlate with the proliferation stages of the tumours in rodent and human gliomas, and hence that the measured water-efflux rate can be used as a diagnostic and prognostic biomarker of this cancer (Fig. 1). Water-exchange dynamic-contrast-enhanced MRI might also aid the identification of gliomas that are resistant to therapies. Indeed, in an accompanying News & Views article, Thomas Ruan and Kayvan Keshari write that the quantification of the expression of aquaporin-4 might be used to guide treatment in patients with glioma, because tumours with high water-efflux rates would be more susceptible to chemotherapy.

In another research Article, Alan Jasanoff and colleagues show that, by using specially designed photosensitive nanoparticle probes, MRI can be used to map the spatial distributions of light in living tissue. The probes consist of a reservoir of a gadolinium-based paramagnetic contrast agent enclosed by a liposomal membrane incorporating photosensitive lipids, whose photoisomerization by incident light alters the longitudinal-relaxation-weighted contrast of the paramagnetic molecules (via variations in hydrodynamic exchanges between the paramagnetic metal centres and the surrounding solvent across the membrane). By injecting the nanoparticle probes into the brains of rats, the authors mapped the magnetic responses to illumination profiles relevant to photostimulation, photometry and phototherapy. As highlighted by Aruna Singh and Michael McMahon in an accompanying News & Views article, the MRI-based light-mapping approach "may be useful to plan experimental procedures and to interpret experimental findings when using optical imaging for the characterization or manipulation of brain circuits".

When combined with other clinical imaging modalities, in particular positron emission tomography (PET), MRI can reveal insights into the interplay between diseases, such as atherosclerosis and immune disorders (for instance, how changes in bone-marrow metabolism affect the levels of atherosclerotic plaque), as Zahi Fayad, Willem Mulder and co-authors discuss in a Perspective article. PET/MRI can in fact help guide the development of immunomodulating drugs targeting atherosclerosis and its associated comorbidities.

Imaging modalities considered to be mature may not be so in all respects. Indeed, as exemplified by research included in this issue, the applicability of MRI can continue to be broadened as a result of resolute technological advances.

Published online: 23 March 2023

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