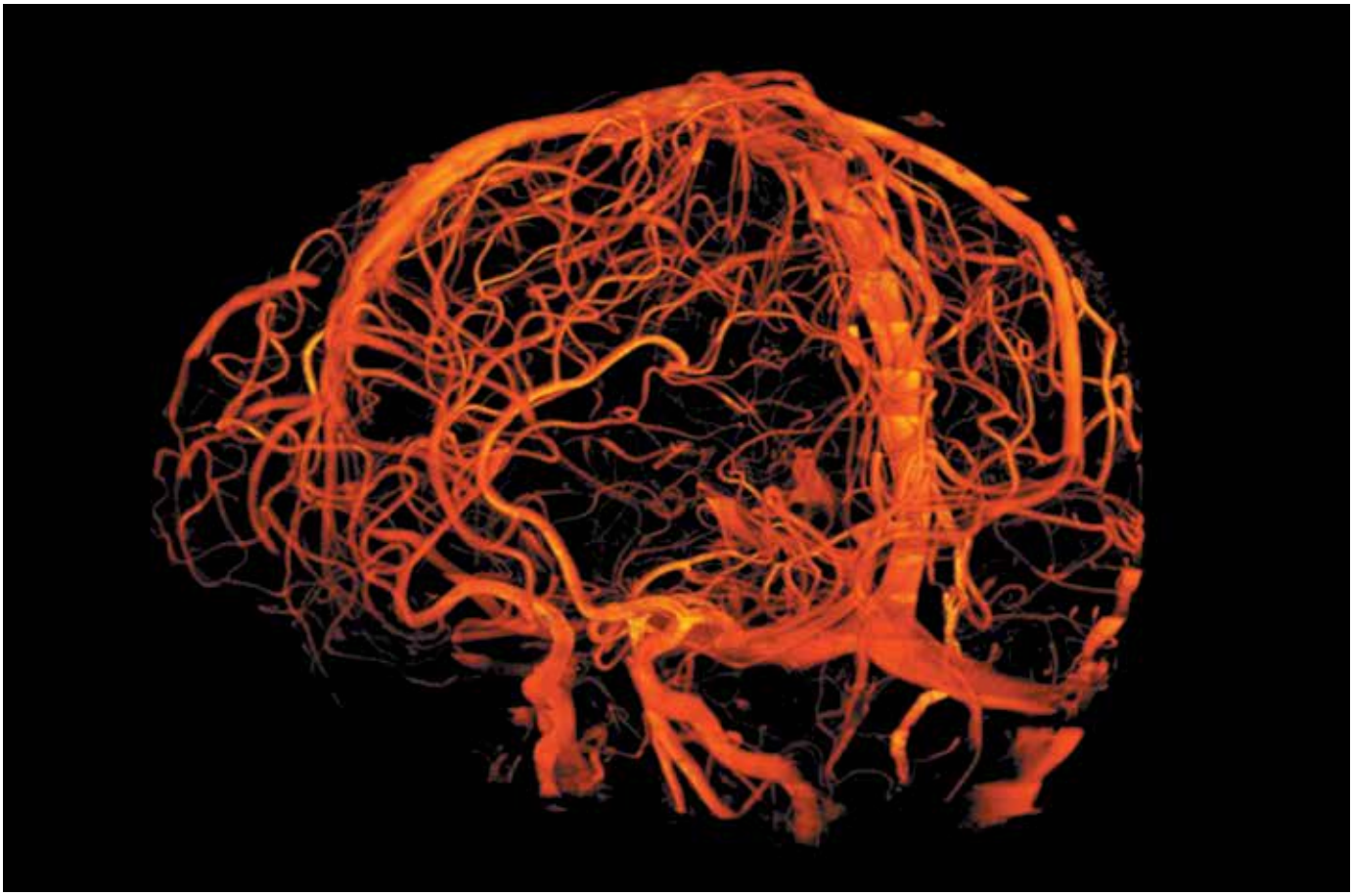

CENTRE FOR ADVANCED IMAGING, UNIV. QUEENSLAND

Cerebral blood vessels glow orange in this picture, generated by a 7-tesla magnetic resonance imaging scanner at the University of Queensland in Australia.

THE STRONGEST SCANNERS

Researchers are pushing non-invasive brain imaging to new limits.

BY JULIAN NOWOGRODZKI

On a cold morning in Minneapolis last December, a man walked into a research centre to venture where only pigs had gone before: into the strongest magnetic resonance imaging (MRI) machine built to scan the human body.

First, he changed into a hospital gown, and researchers made sure he had no metal on his body: no piercings, rings, metal implants or pacemakers. Any metal could be ripped out by the immensely powerful, 10.5-tesla magnet — weighing almost 3 times more than a Boeing 737 aeroplane and a full 50% more powerful than the strongest magnets approved for clinical use. Days earlier, he had passed a check-up that included a baseline test of his sense of balance to make sure that any dizziness from exposure to the magnets could be assessed properly. In the MRI room at the University of Minnesota's Center for Magnetic Resonance Research, he lay down inside a 4-metre-long tube, surrounded by 110 tonnes of magnet and 600 tonnes of iron shielding, for an hour's worth of imaging of his hips, whose thin cartilage would test the limits of the machine's resolution.

The centre's director, Kamil Ugurbil, had been waiting for years for this day. The magnet faced long delays because the liquid helium needed to fill it was in short supply. After the machine was finally delivered, on a below-freezing day in 2013, it took four years of animal testing and ramping up the field strength before Ugurbil and his colleagues were comfortable sending in the first human. Even then, they didn't quite know what they'd see. But it was worth the wait: when the scan materialized on screen, the fine resolution revealed intricate details of the wafer-thin cartilage that protects the hip socket. "It was extremely exciting and very rewarding," Ugurbil says.

The US$14-million scanner is one of a handful around the world that are pushing

MRI to new limits of magnetic strength. Today, hospitals routinely use machines with field strengths of 1.5 T or 3 T. But ultra-high-field scanners are on the rise. There are already dozens of 7-T machines in research labs around the world, and last year, the first 7-T model was cleared for clinical use in both the United States and Europe. At the extreme end are three scanners designed for humans that reach beyond 10 T. In addition to the University of Minnesota's machine, researchers are readying two 11.7-T devices for their first tests on people: a gargantuan one for whole-body scanning at the NeuroSpin Centre at CEA Saclay outside Paris, and a smaller one for head scans at the US National Institutes of Health (NIH) in Bethesda, Maryland. Germany, China and South Korea are considering building 14-T human scanners.

The appeal of ultra-high-field scanners is clear. The stronger the magnetic field, the greater the signal-to-noise ratio, which means the body can be imaged either at greater resolution, or at the same resolution, but faster. At 3 T, MRI machines can resolve details of the brain as small as 1 millimetre. That resolution can be as fine as 0.5 millimetres in a 7-T machine — enough to discern the functional units inside the human cortex and perhaps see for the first time how information flows between collections of neurons in a live human brain. Scanners with even higher field strengths are expected to have resolving power that is at least double that of the 7-T devices.

The push to achieve higher field strengths presents a range of challenges. The scanners are bigger, more expensive and more technically demanding. They also require more attention to safety. But work at 7 T has already resulted in gains, researchers say, for both neuroscience and clinical applications: clinicians can guide electrodes for deep-brain-stimulation treatments more accurately, and might also be able to detect osteoarthritis at an earlier stage than was possible before.

The scanners offer detail that was once seen only in thinly sliced postmortem samples imaged by powerful microscopes. "This is a window we've just never had in the intact human brain," says Ravi Menon, a neuroimaging scientist at Robarts Research Institute at Western University in London, Canada.

IF YOU BUILD IT

The nuts and bolts of MRI technology have not changed much since the first human scanner was developed in the mid-1970s. The heart of the MRI is still a tube-like superconducting magnet, which generates a static electromagnetic field that realigns a small fraction of the hydrogen protons inside water molecules. Once those protons are lined up, coils in the scanner emit a short burst of radio-frequency waves that cause the protons' magnetic fields to wobble. When the radio burst ends, the protons release energy, sending out a faint echo of the radio waves that is detected by receiver coils and gives a picture of the anatomy of the brain and other tissue.

The stronger the magnetic field, the greater the fraction of protons that become aligned, and the bigger the energy difference between them and those that remain unaligned. This produces a signal that can be better detected over background noise. But every jump in field strength comes with some uncertainty. "At the beginning of the MRI era, many scientists were thinking that 0.5 T would be the maximum magnet strength for MRI" because they thought the ion conductivity of live tissue would stop radio waves from penetrating far enough inside the body, says Victor Schepkin of the US National High Magnetic Field Laboratory in Tallahassee, Florida. Then, the 1980s saw the emergence of 1.5-T scanners for clinical use. And in 2002, 3-T scanners won approval. Even before then, researchers were pushing for higher field strength; the first 7-T research scanners began to emerge in 1999.

"EVEN THE STARTING IMAGES LOOK PRETTY SPECTACULAR."

The move from 3T to 7 T presented some challenges. Biological side effects, although temporary, are more pronounced: people can experience dizziness and vertigo when they move in and out of the scanner, researchers say. When people move inside the machine, they can sometimes taste metal, see white flashes or experience involuntary eye movements called nystagmus.

Tissue can also overheat. Because hydrogen nuclei resonate at higher frequencies as the field strength increases, ultra-high-field MRIs must use shorter-wavelength, and thus higher-energy, radio pulses to make the protons wobble. Human tissue absorbs more energy from these waves. So to avoid creating hotspots — and to make usable images — this energy must be smoothed out as much as possible inside the tube. Researchers have devised various ways of accomplishing this. One tactic, says Gregory Chang, a musculoskeletal radiologist at the New York University School of Medicine, is to generate the pulses using a ring of individually tunable transmitters arrayed around the patient.

The fine resolution is also a mixed blessing, because it makes scanners highly sensitive to the slightest motion. Some repetitive movements in the body, caused by breathing or heartbeats, can be modelled and removed. But Menon says that the biggest challenge at 7 T and above — one that is not present in lower-resolution scanners — is involuntary movements of the brain inside the skull. "If I stretch my toes while I'm in the scanner, my brain will move because my toes are connected through the spinal cord to the brain," Menon says. And thanks to the heartbeats, he adds, the brain pulsates "on the scale of half a millimetre to a millimetre". Tackling these artefacts is an ongoing area of research, he says.

Even so, scientists say, 7 T has already opened a new window onto the living brain, by revealing structures smaller than 1 millimetre. This regime, dubbed the mesoscopic scale by neuroscientists, is something that previously was accessible only by surgeons, says Klaus Scheffler, head of the magnetic-resonance centre at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany. With 7 T, Scheffler says, "you see all the details without opening the brain".

Among the structures that have been revealed are the six layers of the cerebral cortex, the 3-millimetre-thick outer region of the brain that is responsible for humans' high level of cognition. Each layer has a specialization: one handles inputs from other brain areas, some process information and still others convey the outputs of that processing to other parts of the brain. The jump to 7-T machines has enabled researchers to measure the relative activity in different layers, which can reveal how that information is travelling. "That's the huge advance over imaging at 3 T or 1.5 T," says Menon. "Normally, we just say A is connected to B, and we can't tell much about which way the information is flowing."

Some teams have used this capability to measure activity as people undergo verbal and behavioural tests, and the results are illuminating how activity in different layers alters how various areas of the cortex process experiences (S. J. D. Lawrence *et al. NeuroImage* http://doi.org/cwbr; 2017). "It's not just that area A is in charge of vision, but that it is modulated by attention, mood, memory," says Menon. "And those kinds of questions are extremely difficult to answer in animal models. They obviously don't think or verbalize the way we can." Now, with 7-T scans of humans, "a picture of human memory is emerging that was really unavailable before", he says.

Researchers also hope to learn more about the columnar organization of the brain. Cortical columns are thought to carry out computations and respond preferentially to particular stimuli, such as the orientation of objects, although there's fierce debate over their exact role in this context. Measuring roughly 500-micrometres across, the columns run perpendicular to the cortical layers and communicate with each other through connections in one of the middle layers. If MRI could measure brain activity at a columnar level, scientists might be able to use that to draw conclusions about computations in individual neurons. This would be exciting because one of the limitations of MRI is that it can't measure neuronal activity directly.

A 10.5-T magnet is delivered to the University of Minnesota in 2013.

CENTER FOR MAGNETIC RESONANCE RESEARCH, UNIV. MINNESOTA

MRI scans at 7 T also provide a better measure of brain connectivity, says Ugurbil, who is involved in the Human Connectome Project. The research effort, which aims to completely map links between neurons in the brain, has performed scans of 184 people at both 3 T and 7 T. At 7 T, they detected many more neural networks and connections between neurons than at 3 T. "In terms of what does that translate into, predicting or studying human diseases, this is still to come," says Ugurbil.

But Ugurbil says that the machines already show promise for clinical diagnosis and treatment. Deep-brain stimulation, which has been used to treat many people with Parkinson's disease, is often administered by inserting an electrode into the subthalamic nucleus, part of the basal ganglia deep inside the brain. MRI is used to help surgeons position the electrode, and once it seems to be in place, the electrode is activated to see whether it hit the correct target. But using 1.5- or 3-T machines, "it's a bit of a fishing expedition", says Ugurbil. "If you're not in the right place, you have to pull out your electrode and insert it again slightly differently." Each time, he says, there is a chance of hitting a blood vessel and causing bleeding. Images taken with 7-T scanners eliminate all this poking around. "You see your target, then you just go: one penetration and you have the result," he says.

Scans done with 7-T machines have also revealed more about the symptoms and progression of multiple sclerosis. New medications for the disease have helped to slow the advance of motor deficits, and the ensuing gain in patients' life expectancy and quality of life has meant that cognitive problems have been noticed for the first time. "A lot of these people have what they might describe as [attention deficit hyperactivity disorder]-like symptoms," says Menon. "We've never understood how that could be until now." Using a 7-T scanner, Menon's group has been able to spot lesions in areas where they previously had not been observed, including the dorsolateral prefrontal cortex, an area responsible for executive function and attention. "Historically, those were quite hard to see," he says. These lesions might explain why the patients develop cognitive symptoms. Menon is involved in a major project "looking at the relationship between cognitive function and the location of lesions", he says.

If greater resolution is not needed, clinicians can also use the higher signal-to-noise ratio in an ultra-high-field MRI to simply scan more quickly, creating images in seconds that would otherwise take minutes, and images in minutes that would otherwise take hours. For patients, this can make a big difference in comfort.

Researchers can also look beyond water. At field strengths of 7 T and higher, MRI can detect not only hydrogen nuclei, but also the nuclei of heavier elements, such as sodium, potassium, phosphorus and fluorine, which have a much lower intrinsic sensitivity to magnetic resonance than hydrogen nuclei do.

Chang has used New York University's 7-T scanner to look at sodium for biochemical changes that might presage osteoarthritis. The evidence suggests that in people with early stages of the disease, he says, "the sodium concentration in their cartilage goes down without any change in the structure of the cartilage". Several other groups have replicated the results in small studies. Chang hopes that if they hold up, the approach could be used to detect osteoarthritis early enough to prevent further damage by making lifestyle modifications and to allow researchers to perform clinical trials more quickly, because they get an early indicator of the disease.

BEYOND 7

The world's most powerful MRI scanner sits in the US National High Magnetic Field Laboratory. With an interior space just 10.5 centimetres in diameter, the 21.1-T machine is too small to be used on people. Schepkin and his colleagues there scan small animals instead. They have used the scanner to study, for instance, the sodium concentration in rat brain tumours, and their results suggest that the amount of sodium present in a tumour can indicate how resistant it would be to chemotherapy (V. D. Schepkin *et al. Magn. Reson. Med.* **67**, 1159–1166; 2012).

At first, Schepkin says, there was some hesitation around using the imager. "We had a rule that nobody can work near the magnet alone," he explains. That rule is no longer in place, but the group does still observe a strict 'no metal' policy.

It took years to prepare the scanner, which was not a fully commercial machine, for animal testing. The process has been similarly slow for many of the new human-research scanners beyond 10 T. The NIH, for example, is currently awaiting the return of its 11.7-T magnet. After it was delivered in 2011, the team turned some of the scanner components on and off too quickly, causing the magnet to overheat and damage some wiring, an imaging researcher at the agency says. The magnet needed a factory rebuild; it is expected back in 2019. The 5-metre-diameter magnet for the 11.7-T MRI at the NeuroSpin Centre in France was delivered last May. The scanner is slated to produce its first scans of live human brains in 2022.

Ugurbil received US Food and Drug Administration clearance in August 2017 to scan 20 people with his 10.5-T MRI (the man in December was the first). He expects to scan the first human brain in a few months. Scans at this field strength are at the point where researchers are not looking to answer any biomedical questions, but simply testing whether the process has any side effects. Still, he says, "even the starting images look pretty spectacular". He is part of a group discussing efforts to reach 20 T in humans.

The amount of heating generated by such machines could be even more problematic. Some researchers have speculated that scanners operating above 14 T could also cause nerve conductance to slow down, stimulate peripheral nerves or damage DNA, although Schepkin says he has seen none of these effects so far in animals, even at 21.1 T. Still, Scheffler thinks that at some point there will be a limit to field strength beyond which we can't go without damaging the body: "I don't think we can go higher and higher forever." ■

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