Juntendo University researchers have made important discoveries about the human brain's fluid clearance system by modeling fluid movements using new MRI imaging methods (pictured).

WEAK WASTE REMOVAL IN THE BRAIN LINKED TO ALZHEIMER'S

A combination of advances in magnetic resonance imaging to help track THE MOVEMENT OF FLUIDS IN THE BRAIN and supercomputer-powered simulations are modifying our understanding of cognitive decline.

Koji Kamagata of Juntendo University in Tokyo, Japan, thinks that Alzheimer's disease may operate a little like a blocked drain. The disease is linked to a build-up of the protein amyloid beta in the brain, and he believes that this could be a symptom of a sluggish waste clearance system. If this proves correct, might there be a way to detect the problem long before any damage is done?

In 2022, Kamagata published a study that used the latest magnetic resonance imaging (MRI) methods to track the movement of fluids in the brain, which suggested a link between weak clearance of waste fluids and Alzheimer's disease.[1] He has since published further studies that link issues with the brain's waste clearance system to sleep problems, autoimmune disorders and other forms of cognitive decline.

IMAGING BRAIN FLUIDS

Although Kamagata has been imaging living human brains for a long time, looking at fluids isn't easy. Just as you can't see through the walls and into a pipe to find a plumbing problem, the brain is hidden behind layers of skin, bone and fluid, he explains.

Another layer of protection comes from the blood-brain barrier — which blocks toxins from entering the brain — and other membranes, such as the blood–cerebrospinal fluid barrier and the arachnoid barrier. These block contrast agents and other substances used to make imaging possible.

But Kamagata can see a way through. He is a specialist in 'diffusion MRI' at Juntendo University's Department of Diagnostic Radiology. This technique can look at the microstructural details of brains via dynamic water diffusion modelling. Kamagata is also leading an investigation into the brain's 'glymphatic system' — a structure discovered in 2013 that is similar to the body's lymphatic system, eliminating soluble proteins and metabolites from the central nervous system.

This project has already given him clues to better understand Alzheimer's disease, as well as the brain more broadly.

For example, studies in rodents had suggested that accumulation of the protein amyloid beta in the brain was related to problems with fluid clearance[2,3], but finding a similar link in humans is difficult without invasive surgery.

But Kamagata realized he could evaluate glymphatic system function using diffusion MRI.

Firstly, 'perivascular space volume' measurements could identify enlargements caused by the stagnation of cerebrospinal fluid in the glymphatic system, and something called an 'analysis along the perivascular space (ALPS) index' could track the fluid dynamics. It does this by analysing the three-dimensional motion of fluids using diffusion MRI — a feat requiring tensor mathematical analysis (the same technique that Einstein struggled with in the development of his Theory of General Relativity).

Better yet, he had access to data for 100 patients, to which he could apply the analysis techniques, from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal multicentre study founded in the United States, to develop early detection and tracking for Alzheimer's disease.

His team compared the fluid clearance processes of healthy subjects with those of Alzheimer's patients, and those with mild cognitive impairment, and found a possible link. The less the fluid appeared to move, the more the build-up of the amyloid beta and the greater the impairment of brain function. [1]

POTENTIAL PREVENTION

Kamagata is hopeful this may result in preventative treatments. "Amyloid beta deposition begins 10 years or more before cognitive impairment, so I hope this leads to new drugs that improve the glymphatic dysfunction before the onset of Alzheimer's disease."

But developing drugs for the brain is notoriously difficult. To bypass the blood-brain barrier requires administration via a painful injection into the spine, and measuring the effects is tricky without resorting to invasive surgical techniques.

A potential way around this problem is being developed elsewhere in Juntendo University. In the new Faculty of Health Data Science (see box), researcher, Zhe Sun, has the ambitious goal of creating a 'whole human brain simulation'.

With this incredible data-simulation tool researchers might be able to test drug mechanisms before clinical trials, potentially giving them a powerful head start.

The vision is bold: the tool would need to simulate the human brain's 86 billion neurons. In recent years, Sun and his colleagues have developed simulations of the brain's cerebral cortex, basal ganglia, cerebellum, and thalamus using one of Japan's supercomputers. Since then, the advent of Japan's newer Fugaku supercomputer — one of the five fastest supercomputers in the world — has provided a one hundredfold boost to the speed of the simulation.

Sun's team of software engineers has also improved the algorithms to the point where he believes they will have the ability to run an entire brain within the next five years.

The data to build the brain comes from a number of open MRI databases on the human brain. Different types of MRI provide data on the static brain components, while diffusion MRI data uses strong magnetic field gradients to show dynamic processes, and can highlight connections between areas.

Once the researchers add machine learning, to help reconstruct missing data points and tune the dynamic processes so they match the measured structural data, and they will have a formidable tool, says Sun. ■

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▲ Zhe Sun, Shigeki Aoki and Koji Kamagata (top, from left) of Juntendo University are all using MRI data (bottom) in ambitious modeling projects.

NEW HEALTH DATA SCIENCE FACULTY

Koji Kamagata has drawn on the extensive resources at Juntendo University's Faculty of Health Data Science to make important discoveries about the link between movement of fluid in the brain and disease.

Launched in 2023, the faculty is already a major hub for advanced Magnetic Resonance Imaging (MRI), a technology that produces three dimensional anatomical images of the body.

It boasts not only clinical specialists, but technicians, engineers, data scientists and software engineers, says Shigeki Aoki, a leading neuroradiologist, who moved to Juntendo to help guide the faculty's burgeoning Data Science team. "We are not large compared with some institutes in the United States, but the clinical and technical developers are very close — this leads to many breakthroughs, across many diseases," he says.

Health data science, says Aoki, can have a huge impact. For example, an ambitious project at Juntendo to simulate all of the brain's neurons should help researchers with drug discovery, and could also help neurosurgeons to remove tumours.

"Neurosurgeons want to take as much of the tumour as possible, every little bit that we can simulate is helpful," he says. Meanwhile, accelerated drug discovery could have huge implications for more than 55 million people with dementia globally.

Through their clinical collaborations, the faculty's breakthroughs already extend to psychiatry, cardiology and sport science, in addition to their contributions to neurological conditions, such as Alzheimer's disease and Parkinson's disease.

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