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Deuterium metabolic imaging shows promise in detecting Alzheimer's disease

Deuterium metabolic imaging (DMI)[‡] is an emerging, novel MR multi-nuclei imaging (MNI) method for 3D mapping of metabolic activity in the body. It uses deuterium (^{2}H), a stable isotope of hydrogen, labelled to glucose (6,6-$^{2}H_2$) to enable the visualization of metabolic uptake and in vivo conversion of glucose to lactate, glutamate + glutamine (Glx). The deuterated glucose can be administered intravenously or orally prior to the scan.

Historically, ^{18}FDG-PET imaging has been the primary method for metabolic imaging. It provides maps on glucose uptake, but does not inform on glucose metabolism, and is radioactive, which can limit its use in repetitive scanning or longitudinal patient studies.

MNI is an alternative to PET metabolic imaging using MR to assess biological changes and metabolism in various diseases. Currently, hyperpolarized carbon-13 (HP ^{13}C) is an area of significant research in MNI, which allows in vivo tracking of the first pass metabolism, representing a different metabolic regime than ^{18}FDG-PET and DMI.

The MR Research Centre at Aarhus University, under the leadership of Christoffer Laustsen, DrMedSc, PhD, Professor, Department of Clinical Medicine, is investigating the use of DMI as a biomarker for brain tumors and Alzheimer's disease (AD). Professor Laustsen and colleagues have been collaborating with GE HealthCare on HP ^{13}C metabolic imaging for 15 years and he has published numerous manuscripts on the topic in peer-reviewed journals. Both HP ^{13}C and DMI are promising approaches for imaging of tissue metabolism that do not require the use of ionizing radiation. Aarhus is equipped with a Discovery™ MR750 3.0T system.

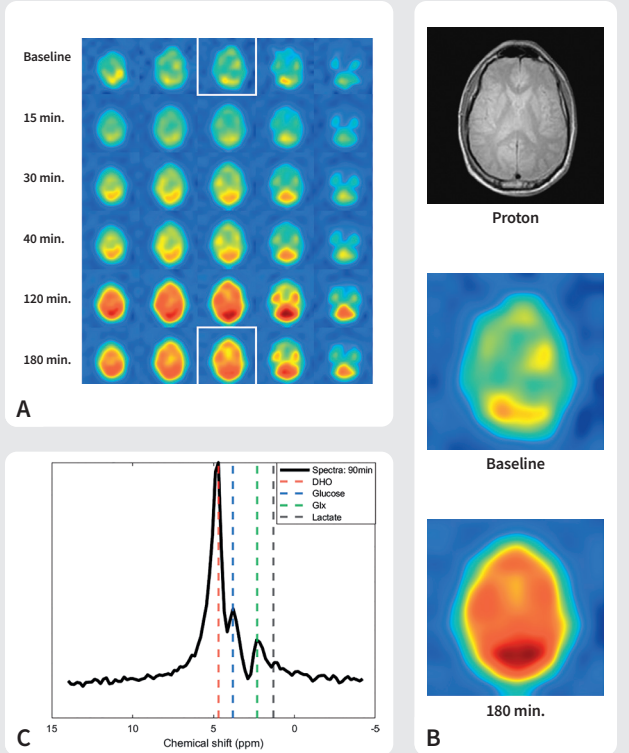

Figure 1. Illustration of deuterated glucose uptake and metabolism over time in a healthy subject. (A) Displays the total uptake of deuterated glucose over time. (B) Shows anatomical proton images of a central axial slice at baseline (pre-ingestion) and 180 minutes post-ingestion. (C) Presents a deuterium spectrum from a central voxel in the brain, illustrating glucose metabolism.

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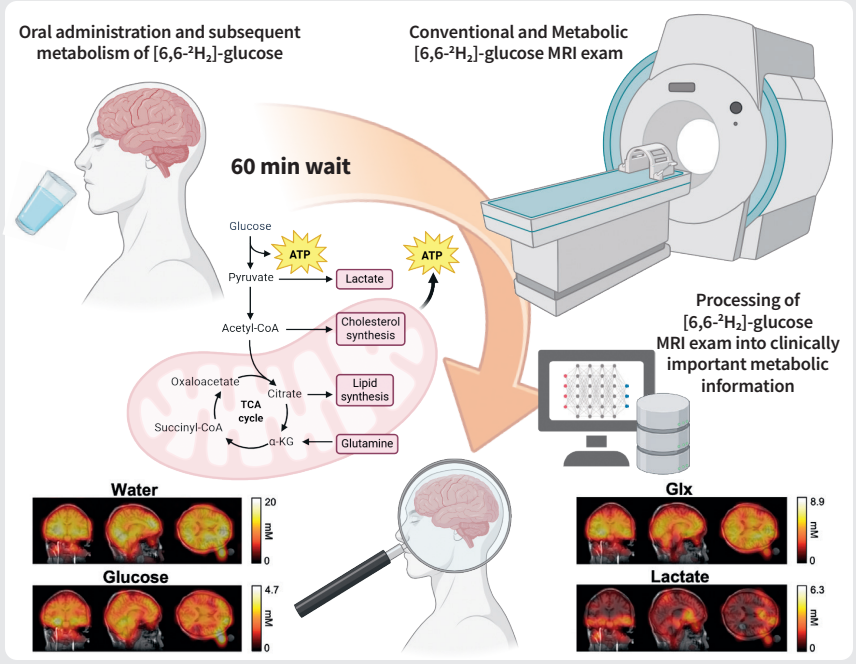

Figure 2. Sixty minutes after administration of the [6,6-$^2H_2$]-glucose, subjects undergo a conventional and metabolic glucose exam. The data is processed into clinical metabolic information.

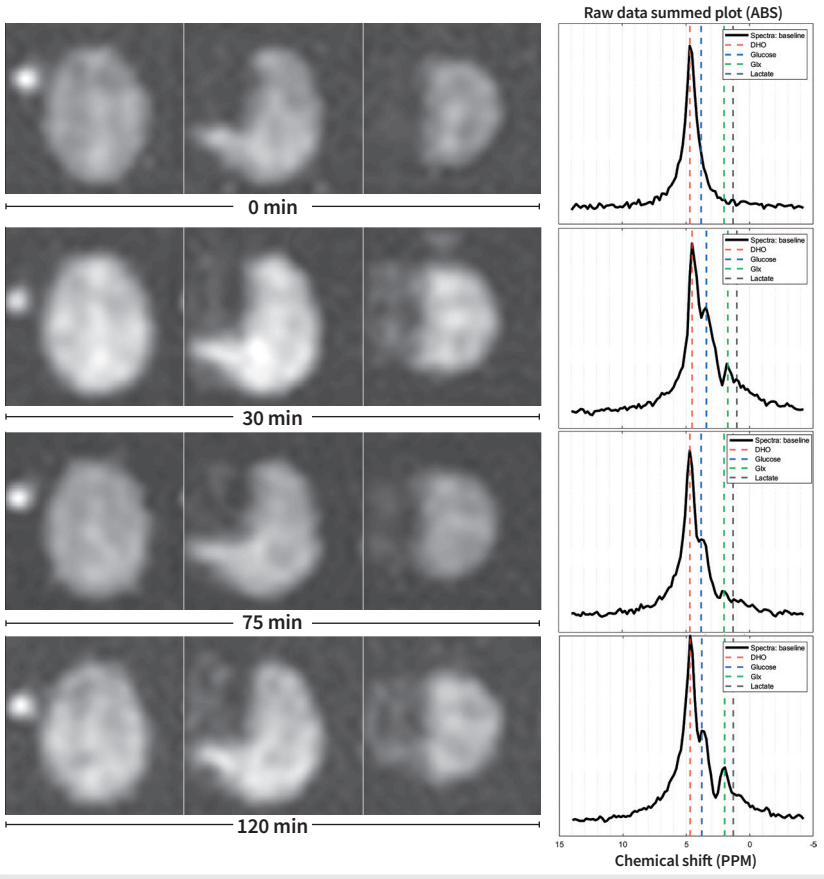

Figure 3. Evolution of the metabolic signal as a function of time.

Professor Laustsen first explored DMI in a pre-clinical study evaluating brown adipose tissue in rats.[1] His interest in DMI was piqued by a study from a group at Yale University describing the approach in vivo in rats and humans.[2]

"The fact they were able to demonstrate from mouse to man in the same paper was very strong," says Professor Laustsen.

The potential of DMI at 3.0T

De Feyter et al. demonstrated DMI's potential to map the metabolism of ^2H-labeled glucose or acetate in the liver and brain.[2] The authors also demonstrated the ability of DMI to visualize metabolism in the brain of a glioblastoma multiforme human patient beyond glucose uptake and map the Warburg effect, which is a potential target for cancer treatment.[2]

The Yale study used a custom-built 4.0T MR system, where ultra-high field systems previously were assumed to be required to achieve sufficient signal and the requisite spectral separation of the specific metabolites. The results sparked renewed interest in DMI for clinical translation as the field strength moved closer to commercial clinical 3.0T MR systems. Professor Laustsen believes that validating DMI on clinically available 3.0T MR systems would best advance its clinical utility.

"Deuterium is a cheaper alternative substrate to ^{18}FDG-PET and is slightly easier to implement," Professor Laustsen says. "With an existing clinical scanner, we had everything in place except the coil." He reached out to Rolf Schulte, PhD, from the Advanced Science Lab (ASL) Europe at GE HealthCare, who leads the company's MNI and multi-nuclear spectroscopy (MNS) research and development, to discuss feasible sequences and coil requirements. The group, which includes Michael Vaeggemose, PhD, MR Research Scientist, GE HealthCare, collaborated with Dr. Schulte to implement DMI to the MNS research software package (ASTM)‡ scanner's sequences to begin running experiments. Finally, with the hardware addition of a dual-tuned (^{1}H/^{2}H)

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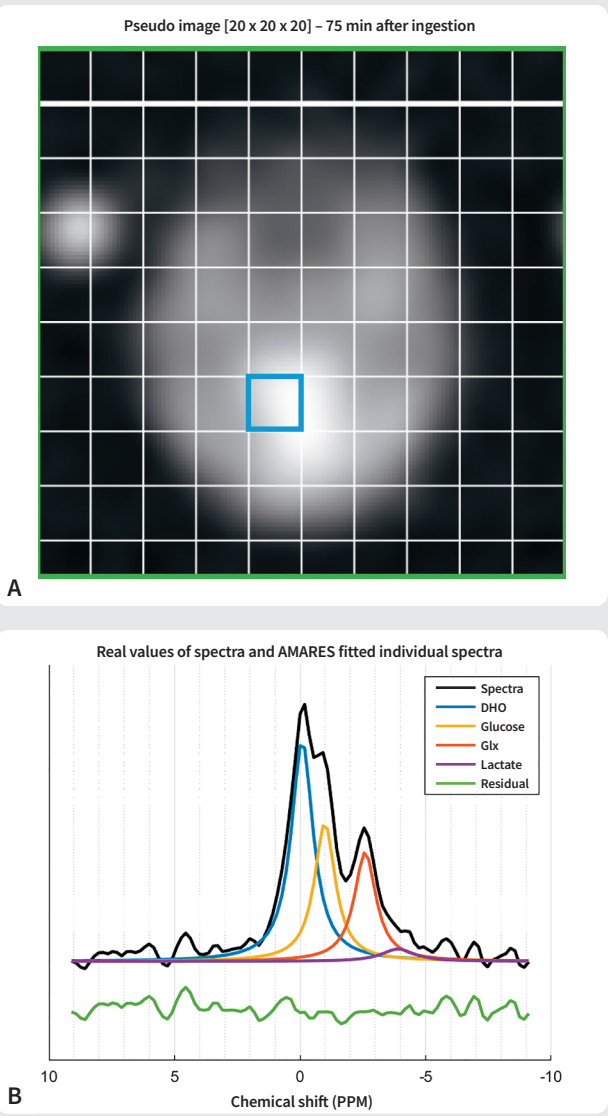

Figure 4. Quantification of spectral information in DMI MRSI images. (A) Pseudo image [20 x 20 x 20] 75 min. after ingestion. (B) Real values of spectra and AMARES fitted individual spectra of the voxel indicated with blue in (A).

quadrature head coil‡ (PulseTeq, UK), the group was ready to perform clinical trials.

Due to the simplicity of DMI compared to other MNS techniques (DMI relies on the use of oral deuterated glucose and not injection of a contrast agent) such as HP ^{13}C, Professor Laustsen and his team were able to reproduce some of the results reported in De Feyter et al. within a few months.

Another key difference of DMI from HP ^{13}C or pyruvate is that whereas HP ^{13}C or pyruvate examines the first pass uptake of metabolism (ultra-fast processes), DMI is an accumulation over time. Professor Laustsen likens it to ^{18}FDG-PET rather than other MNS approaches.

"DMI is complementary to other MNS techniques," Professor Laustsen explains. "The other positive aspect is there is signal that we can image before the deuterated glucose administration, providing internal references that might allow us to quantify the underlying biology."

Adds Dr. Vaeggemose, "We can measure the changes in deuterated water, glutamate, glutamine and lactate, which means we can actually investigate metabolism much deeper than just the glucose uptake into cells."

Previously, it was believed that the capability to investigate metabolism with MNS could only be performed on ultra-high field strength MR systems, the lowest field strength being 4.0T. In a 2022 ISMRM abstract, the group at Aarhus demonstrated the feasibility of DMI at 3.0T in a clinically acceptable scan time of 8:41 min.[3] The group is also acquiring the images with more averages to evaluate the impact of the signal in the Glx cohort with disease, which is expected to be lower than in healthy subjects.

Additionally, the group reported a peak imaging time for deuterium water signal at 120 minutes after glucose ingestion and an increase in Glx at 180 minutes after glucose ingestion, suggesting that Glx can be measured at 3.0T MR.

Demonstrating clinical feasibility, repeatability and reproducibility

For a novel imaging method to be clinically feasible, it must have clinically acceptable scan times and also be repeatable across patients and reproducible across institutions. The team also wanted to determine the appropriate timing to image the patient after administering the deuterated glucose.

To demonstrate feasibility and repeatability, the team performed a study in six healthy male volunteers, imaging the delivery of ^{2}H-glucose to the brain and its conversion to ^{2}H-Glx, ^{2}H-lactate, and ^{2}H-water at baseline and at 30, 70 and 120 minutes. The DMI scan was repeated after six weeks to ensure deuterium washout. The highest SNR and repeatability for water and Glx were obtained at 120 minutes post-deuterated glucose administration; for lactate and glucose, SNR plateaued between 75-120 minutes. Within-individual change in Glx or lactate greater than 25% was unlikely to occur, suggesting viability of test-retest clinical trials in brain tumors. Variation between individuals was small compared to differences between healthy brains and tumors, suggesting the feasibility of cross-sectional studies. They concluded that DMI is feasible and repeatable and could be used in larger cohort trials examining metabolism in various brain diseases.[4]

"We also wanted an approach that would not prolong the examination. We don't have unlimited scanner time in the clinic, so it was important to not add significantly longer scanning times to the conventional MR examination already performed."

Prof. Christoffer Laustsen

Increasing access to imaging for AD

In Denmark and many other countries, MR is one of the first imaging tests performed in patients with suspected dementia. ^{18}FDG-PET may also be used; however, it is typically more expensive, requires the use of a radioactive tracer that may not be readily available, often requires additional clinical expertise in nuclear medicine and is not as prevalent as MR systems in many countries worldwide.

"We look at DMI as a surrogate FDG scan. It is a very simple addition that extends MR into metabolic imaging. Then, we can reserve the more advanced ^{18}FDG-PET metabolic imaging for more difficult cases. It's a way to increase the number of patients we can examine without increasing costs and, therefore, increase the value to society."

Prof. Christoffer Laustsen

With currently approved treatments for AD, more people will require diagnostic imaging tests to detect the disease earlier, when these disease-modifying treatments are most effective. However, this increased patient demand may strain department resources both in terms of equipment availability and staffing.

"DMI is a way to potentially create more patient capacity by allowing us to combine these diagnostic imaging tests into a one-stop-shop MR scanning session that is not tremendously expensive when compared to utilizing two different modality examinations on the same patient," Professor Laustsen adds.

PET could then be reserved for more advanced imaging with more specific tracers, such as ones for tau or amyloid.

At ISMRM 2024, the team presented an abstract demonstrating that DMI correlates with ^{18}FDG-PET in detecting decreased metabolism in the temporal and parietal brain regions in patients with AD compared to healthy controls. The results suggested DMI could be used for metabolic imaging in suspected dementia and be added to conventional structural and vascular MR imaging examinations.[5]

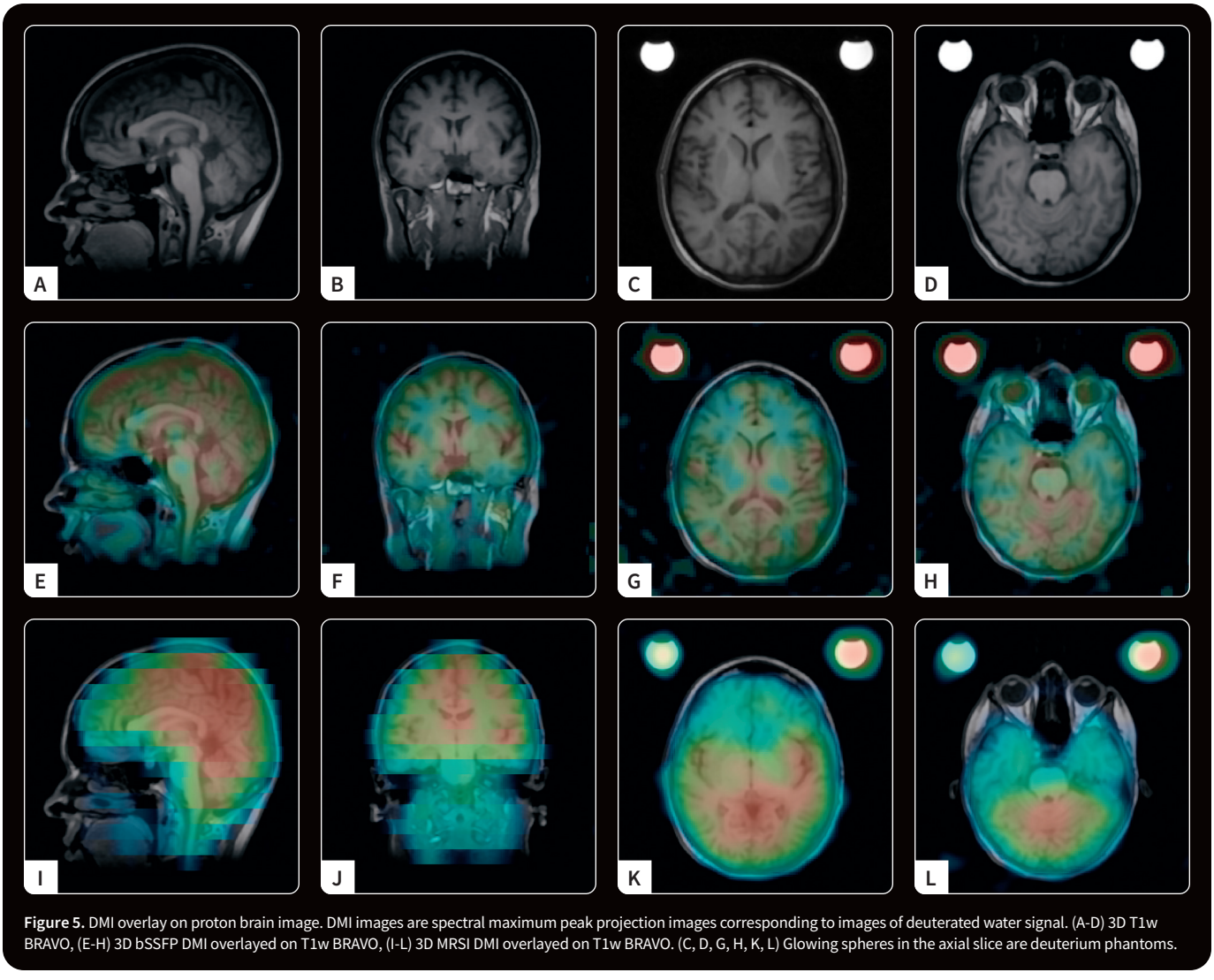

Figure 5. DMI overlay on proton brain image. DMI images are spectral maximum peak projection images corresponding to images of deuterated water signal. (A-D) 3D T1w BRAVO, (E-H) 3D bSSFP DMI overlayed on T1w BRAVO, (I-L) 3D MRSI DMI overlayed on T1w BRAVO. (C, D, G, H, K, L) Glowing spheres in the axial slice are deuterium phantoms.

These results are published in *Radiology*.[6] Although this prospective study using DMI found no significant difference in the lactate to glutamine + glutamate ratio between Alzheimer's patients (n=10) and age-matched controls (n=5), both lactate and glutamate + glutamine signals were reduced in the medial temporal lobe, showing a strong correlation between ^{18}FDG-PET and DMI in Alzheimer's patients.

"The Radiology study is benchmarking DMI against ^{18}FDG-PET by demonstrating the correlation in each patient."

Prof. Christoffer Laustsen

Researchers from Cambridge University recently published a similar study reporting that DMI at 3.0T could detect and localize metabolic changes in the brains of patients with a clinical diagnosis of AD, further supporting the clinical utility of DMI as a diagnostic tool in these patients.[7]

Professor Laustsen and his team are working on techniques to increase SNR and shorten scanning time in DMI. At ISMRM 2025, they will present their work on bSSFP, demonstrating 60% higher resolution (1.5 cm isotropic) in a shorter scan time (18 minutes down to 15 minutes), further demonstrating feasibility in the clinic and with a resolution comparable to ^{18}FDG-PET.

In addition to Alzheimer's patients, the Aarhus group is also examining downstream metabolism in glioblastoma and multiple sclerosis (MS) patients. In glioblastoma, they are looking at the changes in lactate to try to determine the impact of treatment in terms of restricting oxygen to the cancer cells. Low oxygen levels can promote growth and aggressiveness of glioblastoma tumors; however, hypoxia is being investigated as a potential therapeutic target for glioblastoma, as well as for its role in enhancing the efficacy of radiation and chemotherapy.[8] In MS patients, the Aarhus group hypothesizes there may be a correlation between Glx and lactate with the severity of the body's inflammatory response; however, they have only just begun recruiting patients to capture this data.

As more centers such as The MR Research Centre at Aarhus University continue to investigate the potential of DMI in different diseases and clinical scenarios, the science validating the technique will continue to expand the emerging field of MNI. The expansion of MR imaging into metabolism may provide a unique one-stop-shop for evaluating neurodegeneration diseases, cancer and more.

"It's science that will benefit patients and society," says Dr. Vaeggemose.

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