Deuterium Metabolic Imaging (DMI), a novel MR-based method for *in vivo* mapping of metabolism

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Introduction - Deuterium Metabolic Imaging (DMI) is a novel, non-invasive approach that combines deuterium (^{2}H) magnetic resonance spectroscopic imaging (MRSI) with oral intake or intravenous infusion of ^{2}H-labeled substrates to generate 3D metabolic maps [1]. Here we present examples of DMI applications in both animal models and human subjects, using ^{2}H-labeled glucose.

Methods - Data were acquired on preclinical 11.7T or clinical research 4T Magnex magnets interfaced to Bruker Avance III HD spectrometers, for animal and human studies, respectively. Custom-built radiofrequency (RF) coils included a four element Tx/Rx phased-array for ^{2}H RF integrated with a ^{1}H TEM volume coil for human brain studies. [6,6'-$^2H_2$]-glucose was administered orally at a dose of 0.75 g/kg of body weight. ^{2}H MR signal acquisition was achieved with a pulse-acquire sequence extended with 3D phase-encoding gradients in all three spatial directions (TR = 400 ms) for a nominal 8 mL resolution.

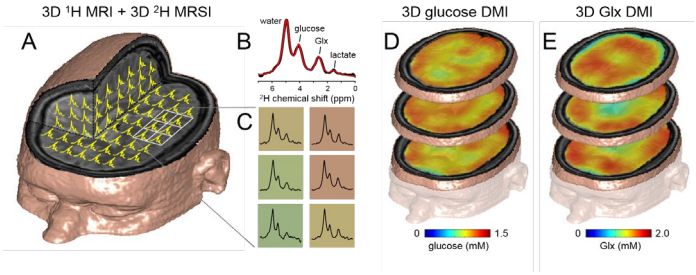
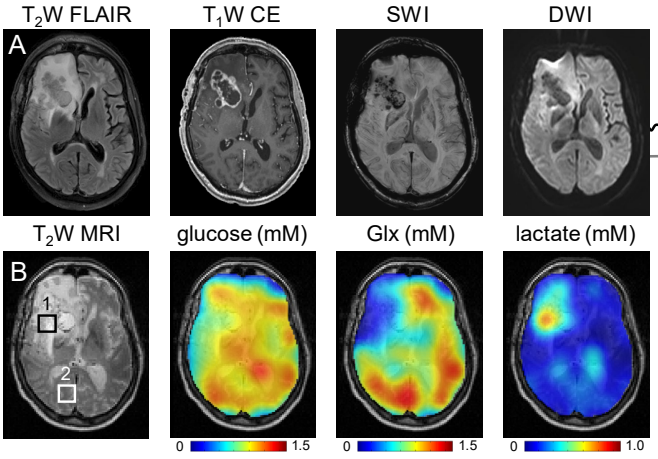


Figure 1. DMI in human brain after oral [6,6'-$^2H_2$]-glucose intake. A) 3D MRI overlaid with ^{2}H MR spectra from a 3D MRSI dataset (9x13x11 matrix) with 20x20x20 mm^3 nominal spatial resolution, acquired between 65 and 90 min after oral [6,6'-$^2H_2$]-glucose administration. B) A typical ^{2}H NMR spectrum from a single MRSI voxel overlaid with a spectral fit (red line) indicating the peaks from water, glucose, Glx and lactate. C) 2x3 grid extracted from the MRSI with data color-coded by the Glx intensity. D) 3D maps of ^{2}H-labeled cerebral glucose and E) Glx levels in mM, extrapolated from the 3D MRSI to the 3D MRI grid. Note the seemingly lower level of Glx in areas corresponding to the ventricles.

Results - Figure 1 illustrates DMI data acquisition and processing of a study in a healthy control subject, after oral intake of [6,6'-$^2H_2$]-glucose, with maps of ^{2}H-labeled glucose and glutamate+glutamine (Glx). Figure 2 shows DMI acquisition on a patient with an aggressive tumor in the right frontal lobe. The preferential anaerobic glucose utilization by the tumor, also known as the Warburg effect, is clearly visible by the elevated lactate and decreased Glx levels.



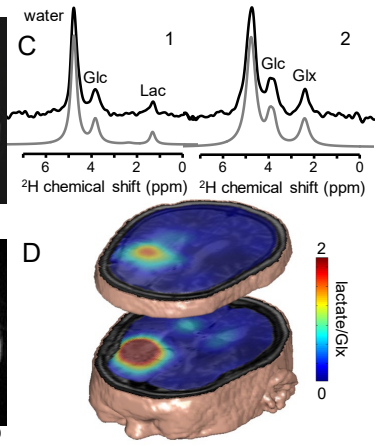


Figure 2. DMI on a patient with a GBM tumor after oral [6,6'-$^2H_2$]-glucose intake. A) Clinical MR images acquired as standard of care in a patient diagnosed with GBM in the right frontal lobe. The patient (man, 63 years old) had undergone sub-total resection of the lesion 9 months before the DMI study. B) T_2-weighted MRI and overlaid DMI maps in a slice that contains the tumor lesion. C) ^{2}H NMR spectra from selected locations depicted in the T_2W MR image, including tissue (1) within the lesion as seen on T_1W CE and (2) from normal-appearing occipital lobe. D) 3D illustration of combined MRI and DMI of the lactate/Glx ratio representing the spatial distribution of the Warburg effect.

Discussion - The use of ^{2}H-labeled substrates is a well-established technique for studying whole body metabolism, detecting the label in blood and tissue samples. DMI combines the administration of ^{2}H-labeled substrates with ^{2}H MRSI to establish a novel MR-based metabolic imaging technique. We illustrated the feasibility of DMI for human applications in brain, brain tumors and liver. Ongoing research is focused on improving absolute quantification of DMI, exploring DMI in animal models of disease and patient populations, and investigating ^{2}H-labeled substrates targeting pathways other than glucose metabolism. DMI is extremely well-suited to be implemented at ultra-high field because of the anticipated supralinear increase in signal-to-noise, DMI's very simple RF pulse sequence with very low SAR characteristics, and ^{2}H's low resonance frequency.

Conclusion - DMI is a versatile, robust and easy to implement technique that requires minimal modifications to existing clinical MRI scanners. DMI has great potential to become a widespread method for metabolic imaging in both (pre-)clinical research and the clinic.

References - [1] H. M. De Feyter, K. L. Behar, Z. A. Corbin, R. K. Fulbright, P. B. Brown, S. McIntyre, T. W. Nixon, D. L. Rothman, R. A. de Graaf, Deuterium metabolic imaging (DMI) for MRI-based 3D mapping of metabolism *in vivo*, *Science Advances* 2018; 4 : eaat7314