Human ultra-high field (7T) deuterium metabolic imaging

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Principal supervisor's CRUK CC theme: Advanced Cancer Imaging Programme

Department for student registration: Clinical Neurosciences / Wolfson Brain Imaging Centre
Department or institute where research will take place: Clinical Neurosciences / Wolfson Brain Imaging Centre

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Postgraduate scheme:
- **MRes + PhD (1 + 3-year non-clinical applicants)**
- **Part-time MRes + PhD (2 + 3-year clinical applicants)**

MRes project outline:

Background:
Deuterium metabolic imaging (DMI) is a new approach to probe brain metabolism in humans. Participants drink a tracer in which some hydrogen atoms are substituted for the non-radioactive isotope deuterium. Non-invasive deuterium MRI scans track uptake and metabolism of the tracer.
Human studies have so far used deuterated glucose as the tracer, which reveals probes the rates of aerobic metabolism via glucose conversion to glutamine/glutamate and anaerobic metabolism via conversion to lactate, which each appear as a separate peak. We are the first UK lab to perform human DMI with an ultra-high field (7T) MRI scanner which 3mL spatial resolution and 5-minute time resolution.
Aim: Show proof of concept for deuterated fumarate metabolic imaging.
Co-supervisor Prof Brindle has recently shown proof of concept for imaging necrotic tissue in an animal model using a new tracer: deuterated sodium fumarate. Oral sodium fumarate appears rapidly in the brain. The enzyme fumarase that converts fumarate to malate is normally strictly intracellular. However in necrotic tissue fumarase is released into the intercellular space where it converts any fumarate rapidly into malate within minutes. We hope that DMI maps of malate signal will visualise areas that respond effectively to therapy in brain tumours.

Objectives:
1. Demonstrate feasibility for human 7T DMI with sodium fumarate.
2. Re-optimise our scan protocols and analysis tools for sodium fumarate scans.

MRes experimental plan:

1. Adapt our established 7T DMI protocols to measure fumarate and malate.
We have established protocols for 7T DMI with deuterated glucose tracer using a world-leading 18-element deuterium RF array coil. We scan using 3D phase encoded chemical shift imaging and process the data using a custom Matlab tool. This pipeline will be re-optimised for fumarate and malate metabolic imaging using a phantom test object.

2. Trial deuterated sodium fumarate imaging in five volunteers.
We have ethical approval in place for human scans with deuterated sodium fumarate. The non-labelled form of sodium fumarate has a long history of safe use in the food industry. We will apply the optimised protocols from step 1 to image fumarate uptake in five volunteers. We do not expect to see a significant malate signal in these subjects because they should not have necrotic brain tissue. But by comparison with Prof Brindle's pre-clinical results, we will compute the dose required for a patient scan. We will assess the optimum time to scan after the oral sodium fumarate dose.

3. Adapt our analysis toolkit to plot maps of the fumarate to malate conversion rate.
We will adapt our Matlab DMI processing pipeline to fit water (HDO), fumarate and malate signals in readiness for patient scans.

Techniques: human ultra-high field (7T) MRI scanning, programming in Matlab.

PhD project outline:

Background:
Deuterium metabolic imaging (DMI) is a new approach to probe brain metabolism in humans. Participants drink a tracer in which some hydrogen atoms are substituted for the non-radioactive isotope deuterium. Non-invasive deuterium MRI scans track uptake and metabolism of the tracer.
Human studies have so far used deuterated glucose as the tracer, which reveals probes the rates of aerobic metabolism via glucose conversion to glutamine/glutamate and anaerobic metabolism via conversion to lactate, which each appear as a separate peak. We are the first UK lab to perform human DMI with an ultra-high field (7T) MRI scanner which 3mL spatial resolution and 5-minute time resolution.

Aim: Prove the value of 7T deuterium metabolic imaging for clinical research.

Objectives:

1. Measure metabolic heterogeneity and response to therapy in patients with glioblastoma brain tumours.

2. Measure energy uptake in patients with Mild Cognitive Impairment due to Alzheimer's pathology.

3. Refine sequences and analysis pipeline to maximise spatial resolution and sensitivity; to calibrate scans in quantitative mmol/kg wet weight units; and to map metabolic fluxes.
The long-term aim is to translate 7T DMI into a clinical tool for personalised medicine.

PhD experimental plan:
The project is articulated in three strands.

STRAND 1: clinical application in patients with brain tumours
Co-supervisors Prof Brindle (biochemist) and Prof Mair (neurosurgeon) have shown that pre-clinical DMI can track metabolic heterogeneity and early response to therapy in animal models with brain tumours.2,3 We will translate this into a human clinical study together, assessing the spatial patterns of metabolism in patients with glioblastoma and assessing necrosis after radiotherapy. This is important because some glioblastomas are resistant to treatment, recurring

aggressively soon after surgery or resisting radiotherapy. We have ethical approval for this work.

STRAND 2: clinical application in patients with mild cognitive impairment due to Alzheimer's Disease
The Brain Energy Metabolism hypothesis states that mitochondrial dysfunction causes a progressive impairment of neurons' cellular energy supply and leads to cognitive impairment in Alzheimer's Disease.4,8 This is supported by PET results from the ADNI consortium.
We will scan patients with early stage Alzheimer's ("mild cognitive impairment") in collaboration with Profs O'Brien and Rowe (neurologists specialising in dementia) and Dr Matys (neuroradiologist). We expect to see early metabolic changes in precuneus and posterior cingulate cortex since these areas are the first to show structural abnormality in Alzheimer's Disease.8
Our DMI scans are radiation-free, so in the future, we hope to track a cohort of patients with regular DMI scans to track the sequence of metabolic changes as Alzheimer's Disease progresses and whether this is halted by medicines.10

STRAND 3: refine sequences and analysis pipeline
We will develop scans that use modern signal processing approaches (e.g. random undersampling and regularised iterative reconstruction) to increase the spatial and temporal resolution. For example, we will implement the bSSFP DMI approach pioneered in preclinical studies by Prof Freedman.

We will refine our analysis pipeline to report quantitative metabolite concentrations, and to extract quantitative maps of the key metabolic rates: the rate of conversion of Glc --> Glx and of Glc --> Lac which quantify cellular energy supply via aerobic and anaerobic metabolism respectively. We will assess reproducibility in so that our applied clinical studies have the required statistical power.

Main techniques:

Ultra-high field (7T) deuterium metabolic imaging
Scientific programming in Matlab, C++, Python
Bayesian hierarchical modelling for analysis of metabolic fluxes

Key references:

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