Project title: AI-based assessment and validation of brain mineral deposition in its different forms detected from routine clinical brain magnetic resonance images

Abstract: Iron is essential for maintaining a healthy body function. But an excess of it can lead to oxidative stress damage to biomolecules, as well as cellular dysfunction causing cell death. This process is apparent with increasing age, where iron gets accumulated in the brain, leading to cognitive decline and increasing the risks of neurodegenerative diseases. Iron-containing macromolecules can aggregate forming calcified clusters, and are visible using magnetic resonance images (MRI). While work has been done in the development of MRI sequences that allow quantifying these mineral accumulations, work is needed to assess this mineralisation process from conventional MRI for prognostic purposes and for identifying pre-clinical stages of neurodegenerative diseases like Alzheimer's and Parkinson's diseases. Moreover, given the ferromagnetic (iron) vs. paramagnetic (calcium) nature that these deposits have in different proportions throughout the brain -which varies according to the underlying disease-, the validation of the accuracy of the assessment methods from MRI requires the use of complementary methods that may range from the development of physical MRI phantoms to the analyses of histological images (tissue samples) or body fluids (blood). This project will develop a method for segmenting brain iron and calcium accumulation throughout the whole brain and in its different forms (tissue deposition, brain microbleeds, superficial siderosis, and haemorrhagic transformations from ischaemic lesions) using AI, in a large sample of MRI images acquired from different patient groups, assess the degree of mineral accumulation in the areas segmented offering a proxy for insoluble iron/calcium concentration and degree of aggregation (i.e., clustering) in different subregions (also using AI methods), and validate the AI-based imaging computational assessments using complementary biomedical analysis methods in a sample of individuals with both brain MRI and tissue samples.

Introduction: Iron is involved in oxygen transport, DNA synthesis, and cell division, metabolism and neurotransmission, which are essential for maintaining a healthy body's function. But while the ability of iron to circulate in an oxidative state in the body is fundamental to these biological functions, an excess of it can lead to oxidative stress damage to biomolecules, as well as cellular dysfunction. This occurs mainly due to metabolic failure in processing iron at the cellular level (1), mainly due to iron catalysing liposomal peroxidation of highly expressed unsaturated fatty acids on cell membranes, thereby inducing cell death. This process is apparent with increasing age, where iron gets accumulated in the brain, and it increases the risks of neurodegenerative diseases (1). Brain iron accumulation occurs not only this via, but also due to spillage from rupture of small blood vessels (2), and from other clinical events. Overall, it is the strongest factor influencing cognitive decline in normal ageing (3). Although this process occurs gradually, it can be detected using magnetic resonance images MRI (4) in the preclinical stages when minor cognitive concerns are starting to appear and before any other clinical symptom (Figure 1).

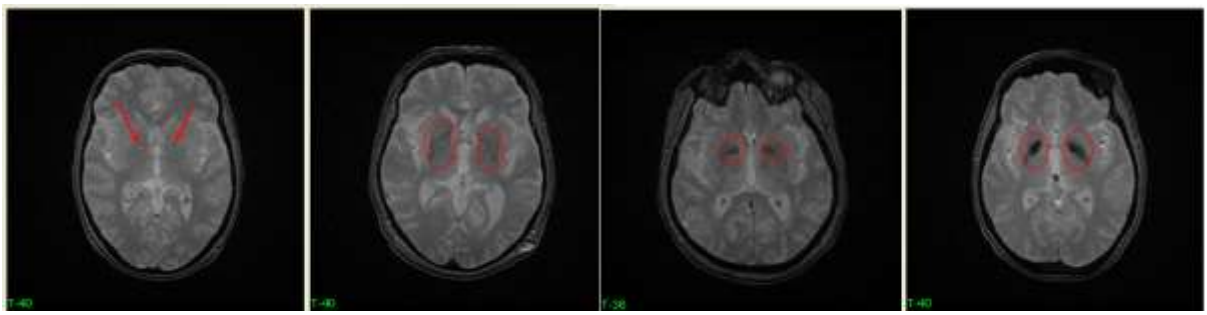

Figure 1. Different degrees of mineralisation of the basal ganglia, as described in Penke et al. Neurobiol Aging 33, pp 510-517(2012)

This important topic is an active area of research. MR scientists have developed special sequences and techniques that allow this brain accumulation to be quantified, but these special sequences are not part of the routine clinical MRI protocols, and the quantification from using these sequences has been only validated using iron concentration curves obtained from post-mortem samples. Based on this information, we previously developed an automatic method (the only existent so far) to identify and segment the areas of iron deposits from routine clinical MRI (5), and validated it with a physical phantom (Figure 2). But we could not establish (it is not possible using only MRI) the degree of iron accumulation in the segmented areas, most important for predictive medicine. Moreover, our method was only limited to assess iron accumulation in a small brain region, given the computational power available at the time (i.e., 10 years ago). Proteomics allow to investigate altered molecular interactions between different cellular constructs. Comparing proteomes from bodily fluids (e.g. blood samples) from different individuals allows scientists to identify the molecular changes undergoing the cells of these individuals. Therefore, it can be useful for validating the stage of iron accumulation if is used to analyse blood samples from the same individuals whose brains is imaged using MRI.

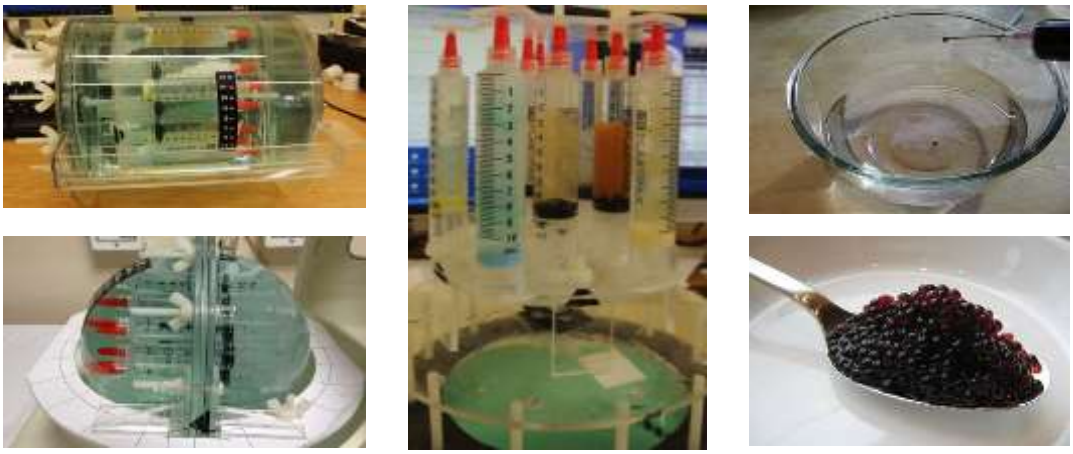

Figure 2. Physical phantom developed to validate the identification and segmentation of mineral deposition in the basal ganglia (https://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.721183)

Aims: This project builds on our previous works in brain MRI processing and tissue analyses to

1) Assess the extent of brain iron accumulation (i.e., segmentation of the regions containing any degree of mineral deposition) throughout the whole brain and in its different forms (tissue deposition, brain microbleeds, superficial siderosis, and haemorrhagic transformations from ischaemic lesions) using artificial intelligence (AI)
2) assess the degree of iron accumulation in the areas segmented offering a proxy for insoluble iron concentration and degree of aggregation (i.e., clustering) in different subregions, also using AI methods and reflecting patterns related with clinical outcomes
3) validate the AI-based imaging computational assessments using histological samples from individuals with also brain MRI

Data and Methodology:

The student will use well-phenotyped data with carefully-generated ground truth from studies conducted at the Centre for Clinical Brain Sciences to develop the iron deposition assessment method, which will give as output differential probabilistic masks of the various forms of iron deposits throughout the whole brain. The breadth of data available for the project includes routine clinical MRI, vascular function and blood-brain-barrier permeability measurements, clinical, demographic, and cognitive information from each of the studies' participants (approximately 1200). Tissue samples from which derive iron concentration curves are from ~20 brains from the study on cognitive ageing which also has brain MRI, these acquired in different (i.e., five) assessment waves every three years. The samples were imaged at 7T MRI and the co-supervisor has aligned both modlaities. The external partner collaborator has experience in proteomics analyses in relation to small vessel disease, which imaging phenotypes involve different forms of iron deposition. Therefore, preliminary data hold by the collaborator may be useful in further validating the developed method. More tissue-MRI pair samples have been also acquired from tissue banks, reaching a total of 80 samples.

Once the AI assessment method is validated using the in-house data from different studies, MRI data from online repositories will be downloaded to test are re-train the AI model for increased robustness. Finally, and given the strong association between these deposits and dementia progression, we will upload the model to the National Safe Heaven to apply it to the National Scottish Registry MRI data to estimate dementia prediction accuracy, over the estimation achieved using currently available methods, which have been applied as part of an ongoing multicentre project.

Responsible AI/ Ethical considerations: All primary studies providing data have been approved by the ethical regional and national ethical committees, and the imaging and data acquisition have been acquired following the declaration of Helsinki. Induction on responsible AI, data security, and privacy regulations will be given to the student. All data will be managed in the secure servers at the CMVM. Permission will be requested for the student to work in the National Safe Heaven, after the student has passed the relevant MRC-approved courses to handle the data. All data will be, nevertheless fully anonimised for the project.

Expected outcome and Impact: This project offers a rare opportunity of working in a clinically relevant theme to address a clinical need and work with a breadth of data from different modalities and nature. It goes beyond the conventional use of computational descriptors for validating the AI-based method, to use clinically relevant data to ensure its impact and further applicability in clinical research and practice.

Key References:

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