Neurodegenerative diseases that cause dementia constitute a major burden on society, both in terms of direct monetary costs and the suffering of patients and their relatives. The last decade witnessed significant progress into the understanding of neurodegenerative diseases such as Alzheimer's disease (AD), which is the most common form of neurodegenerative dementia. Currently, the only treatments for AD are for the symptoms and not their root cause, and a cure for AD is not yet on the horizon. However, there are numerous promising candidates for treatment currently in Phase II/III clinical trials, and tools are needed to test their safety and efficacy on patients. However, efficacy measurements are needed that provide evidence that these drugs are not just lessening symptoms but also actively modifying the course of the disease. Imaging biomarkers are currently the most promising of the available technologies for this purpose. Many trials that are currently enrolling were designed with endpoints based on longitudinal analysis of changes to structural magnetic resonance images (MRI).

The last two decades of research have seen major technological advances in MR imaging in dementia. MR-based imaging biomarkers in dementia now play a key role, enabling the robust and automatic measure of disease progression and potentially disease modification. Image acquisition advances must however go hand in hand with sophisticated and efficient image analysis techniques and appropriate computing infrastructure in order to maximize research potential and deliver the most robust imaging biomarkers.

Structural 3D T1-weighted sequences are standard in both clinical research and randomized trials, and can be used to track rates of brain atrophy due to their excellent tissue contrast. Much effort has been put into standardizing acquisition protocols for these sequences, in order to be able to group subjects across different research centres, scanner types and software platforms. In addition to 3D T1-w imaging, other types of structural imaging sequences, such as 3D T2 and FLAIR, can also provide extremely useful and complementary information relating to atrophy and the presence of brain lesions. More recently, there has also been increased interest in applying advanced MR imaging modalities to dementia: diffusion-weighted imaging to investigate structural connectivity; functional MRI to probe disruption of neuronal function and networks; T2*/susceptibility-weighted MRI to identify the presence of increased iron deposition and/or cerebral microbleeds; and arterial spin labelling to measure regional patterns of abnormality in cerebral perfusion. With this wealth of information potentially available from a single MR scanning session, the role of acquisition acceleration techniques such as parallel imaging and multi-banding is clear, to ensure that overall scan times are kept within limits that will be tolerated by elderly and potentially very unwell patients.

The resulting biomarkers that come out of these images can be used in numerous ways during clinical trials of dementia. First, they can be used to enrich trials, by improving patient selection and differentiating AD patients from those with a similar form of dementia that might not respond to the disease. An example of this is the use of hippocampal volumetry to identify patients more likely to have Alzheimer’s disease than other forms of dementia. This is especially important when moving earlier in the disease process to prodromal or even preclinical forms of the disease. Second, some potential drugs have been known to cause adverse effects that present first on imaging, often before any clinical manifestation of the patient. The Amyloid-related imaging abnormalities (ARIA) are well-documented and observed using FLAIR and T2* imaging, and the FDA have provided guidelines of how to use these sequences in trials. Finally, the most important applications of MRI-based biomarkers are as an endpoint to provide evidence that the drug is slowing down the neurodegenerative process. The most likely candidate for late phase endpoints are volumetric measures based on 3D T1 weighted images of grey matter atrophy in key regions of the brain (hippocampus, precuneus, entorhinal cortex). In addition, there are many new biomarkers that could provide additional, and perhaps earlier, information about the disease and how it is being modified by a potential drug. Diffusion imaging-based biomarkers could provide evidence of microstructural changes in the white matter, functional MRI could illustrate changes of connectivity between regions, and arterial spin labelling could provide evidence of decreased perfusion in key areas. All of these biomarkers show great promise, but need further validation for use in multi-site studies and are currently best suited for early phase single site studies to show proof of mechanism.

In this talk, we will present current and future imaging biomarkers under development, which could potentially lead to an early diagnosis of neurodegenerative diseases such as AD. In collaboration with the Dementia Research Centre (Institute of Neurology, Queen Square, UCL), we are developing novel imaging biomarkers for Alzheimer’s disease and related dementias using MR images. Some of these imaging biomarkers are currently used in many clinical trials, including large international activities, such as the ADNI and DIAN natural history studies of Alzheimer’s disease, which involve a large global collaboration to identify the timing and relationship of imaging biomarkers during the course of this prevalent and devastating disease.