

## **Debbie Scientific Abstract:**

Novel biomarkers that reliably detect the disease onset before any clinical symptoms occur, are crucial for research of Alzheimer's disease (AD) and related dementias. One of the earliest pathological alterations in AD is the loss of the Blood-Brain-Barrier (BBB) integrity, which can be directly imaged and mapped using positron emission tomography (PET) or magnetic resonance imaging (MRI). Of these methods, arterial spin labeling (ASL) MRI is the only candidate for mapping local changes in BBB integrity without the use of contrast-enhancing agents or radioactive tracers. Currently, ASL cannot be reliably applied in a clinical setting due to the rather long scan times and high sensitivity to patient-specific physiological/hemodynamic variability, a lack of a standardized analysis approach, and a lack of a normal reference map for finding pathological BBB patterns.

In the project DEBBIE we propose to develop a direct non-invasive clinical imaging biomarker called 'BBB-ASL' that maps BBB integrity loss in preclinical stages of AD.

The DEBBIE consortium consists of a unique combination of pioneers in the field of contrast-free physiological imaging with a focus on neurodegenerative pathology, with an expertise in MR sequence development, image post-processing, biophysical modelling, AD imaging, and biomarker validation.

The overall goal of this project is to establish quantitative BBB-ASL analysis for scientific group studies of the human brain, ultimately improving healthcare delivery in clinical applications and benefiting individual patients suffering from early dementia. We propose to develop a clinically ready non-invasive MRI biomarker for BBB integrity mapping by focusing on automatic Calibration (WP1) of MRI acquisition parameters based on the patient's hemodynamic status, Standardization (WP2) of image processing for atlas-based correction of between-scanner and between-patient physiological confounders, Validation (WP3) of this integrated BBB-ASL MRI solution by comparing it with PET, and Application (WP4) in several ongoing longitudinal AD studies to evaluate its clinical value. This work will allow the DEBBIE consortium to provide a sensitive, non-invasive, and early biomarker of AD.