The effect of the *APOE* genotype on brain function

Genes explain between 60% and 80% of the predisposition to develop Alzheimer's disease (AD) and the *APOE* gene is the best established risk-factor. *APOE* has three allelic variants (e2, e3, and e4). The e4 variant has been shown to both increase the prevalence and lower the age of onset in AD patients. Imaging studies in humans have reported reduced hippocampal volumes and glucose metabolism in both AD patients and healthy controls carrying the e4 allele relative to non-carriers.

Here, I will present a series of MRI experiments I carried out in my research, as part of my PhD program and Post-Doc, to investigate the effect of *APOE* on the brain. In our own laboratory, using functional MRI (fMRI) based on the Blood-Oxygenation-Level-Dependent (BOLD) signal, I was able to detect increased brain activity in young (20-35 years old) healthy subjects with the e4-form when compared to people with the e3-form decades before any possible cognitive decline or impending disease. Subsequently, I investigated the role of *APOE* in an older (50-75 years old) group of participants by repeating the same experiment and found that the increased activity of brain function observed in young subjects with the e4-form was disproportionately reduced with advancing age even before the onset of measurable memory decline. This suggests that: 1) the *APOE* gene is changing something about the way the brain ages and 2) our MRI approach is sensitive enough to detect these effects long before we are expecting any abnormalities associated with AD. However, because the BOLD signal is largely dependent on cerebrovascular components (i.e. cerebral blood flow, cerebral blood volume and vascular compliance), cerebral oxygenation and the coupling between these measures, any change in one of these factors may affect both the amplitude and the magnitude of the BOLD signal.

In order to start addressing this question, I set up a multi-methodological MRI protocol involving a memory task, a CO_2-inhalation challenge (to investigate the impact of *APOE* on cerebral vasomotor reactivity) and resting and task-related measures of blood flow and volume (acquired with arterial spin labelling - ASL) in young healthy e2-, e3- and e4-carriers. This multi-modal approach confirmed my previous results, showing that the e4 allele is associated with the greatest task-related BOLD percentage signal change relative to non-carriers. Moreover, using the CO_2-inhalation challenge, I made the novel observation that the *APOE* genotype differentially modulates small-vessel cerebrovascular reactivity (CO_2-CVR), reporting an allele-specific decrease in CO_2-CVR (widespread throughout the brain), from e2 to e4, in a pattern that mirrors the lifetime risk for AD (AD-risk: e4>e3>e2).