Project Details	
Project Code	MRC23NMHBa Lancaster
Title	Integrating MRI network analysis and genomics to refine risk prediction in Alzheimer's disease
Research Theme	Neuroscience and Mental Health
Summary	Alzheimer's disease has a significant heritable component, yet we know little about this genetic risk affects the living human brain. The project will incorporate bioinformatic approaches using neuroimaging, genomic and clinical health record data to understand why we see increased brain cell death in individuals with heightened genetic for Alzheimer's disease.
Description	Background: Alzheimer's disease (AD) is a devastating and highly heritable neurodegenerative disorder, characterised by progressive brain atrophy starting in medial temporal lobe structures such as the hippocampus. Genome-wide association studies (GWAS) demonstrate AD risk is influenced by thousands of common genetic variants with a combined effect that are (in extreme cases) comparable to highly penetrant AD familial mutations (Sims, Hill & Williams, 2020). We have published numerous studies demonstrating that the combined effects of AD risk alleles (polygenic risk score; PRS) negatively influence hippocampal volume (Foley et al., 2017; Lancaster et al., 2019, Chandler et al., 2020). Furthermore, brain regions such as the hippocampus are heterogenous structures compromised of many sub-nuclei, supporting shared and distinct functional processes. Dr Lancaster's lab have recently further shown that AD-PRS has disproportionate effects on specific hippocampal sub-nuclei (Murray, Chandler & Lancaster, 2021). Hypotheses: Progressive brain atrophy observed in AD is exacerbated in individuals with high genetic AD risk, who have comparably fewer initial neural resources. We aim to understand the biological processes that explains how / which AD risk genes influence brain architecture. The student will combine advanced neuroimaging and bioinformatic approaches to provide these mechanistic explanations for the brain volume reduction observed in individuals with AD genetic risk. Project 1: Morphometric risk score analysis. Instead of measuring / assessing brain regions one-by-one (in a univariate approach), a morphometric risk score approach (Lancaster et al., 2022) will assess brain-wide liability to Alzheimer's disease. This data will be used to understand biology / pathophysiology or used as training data in forward inference approaches (e.g. machine learning for AD prediction, diagnosis and outcomes). This approach will be performed at two different scales. 1.1) Pre-acquired ultra-high resolution 7T MRI data collected at Cardiff University Brain Research Imaging Centre (CUBRIC), in fifty individuals with either extremely i) low or ii) high genetic risk for AD, from a wider large prospective cohort (PROTECT study: N=10,000) administered by Exeter University. This study will allow the student to learn principal methodologies / techniques to be applied at larger scale in: 1.2) Large, pre-existing 3T data (e.g. population-level, multimodal cohorts (e.g. UK Biobank, ADNI3, HCP-Aging; N=1,000-40,000). Project 2: AD genetic risk pathways. The student will use polygenic modelling to develop polygenic scores that reflect convergent biological pathways implicated in AD (e.g. immunity, protein-lipid, cholesterol transport; Kunkle et al.

	2019, Bellenguez et al. 2022) and link these to the AD morphometric risk scores in the MRI data analysed in Project 1.1 / 1.2. Project 3: Prospective outcomes. The student will assess prospective neurocognitive / psychiatric outcomes collected as part of PROTECT study network and link to MRI and genetic data collected during Project 1.1. This will include ongoing annual cognitive and neuropsychiatric assessments administered electronically and online using a detailed / validated battery across the PROTECT cohort. Planned outcomes: The proposed project is well-positioned / powered (> 80% power) to provide robust inference into how risk loci contribute to AD-linked brain atrophy. This will enable us to identify specific patterns of AD risk gene – mediated brain network disruption to be used in detection and prediction models and develop plausible biological mechanisms. The studentship will therefore help refine prediction for individual functional outcomes for future interventions and therapies.
Supervisory Team	
Lead Supervisor	
Name	Dr Thomas Lancaster
Affiliation	Bath
College/Faculty	Faculty of Humanities and Social Sciences
Department/School	Department of Psychology
Email Address	tml45@bath.ac.uk
Co-Supervisor 1	
Name	Dr Byron Creese
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Medical School
Co-Supervisor 2	
Name	Professor Valentina Escott-Price
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Division of Neuroscience and Mental Health, School of Medicine
Co-Supervisor 3	
Name	Dr Elizabeth Coulthard
Affiliation	Bristol
College/Faculty	School of Medicine
Department/School	Institute of Clinical Neurosciences