Project Details	
Project Code	MRC21NMHBa Lancaster
Title	Integrating MRI network analysis and genomics to refine risk prediction in Alzheimer's disease
Research Theme	Neuroscience & 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 initial progressive brain atrophy 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, the hippocampus is a heterogenous structure 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, NBA: in revision). Hypotheses: Progressive hippocampal atrophy observed in AD patients is exacerbated in individuals with high genetic AD risk, who have comparably fewer initial hippocampal resources. We aim to formulate a biological explanation that explains how / which AD risk genes influence hippocampal architecture. The student will combine advanced neuroimaging and bioinformatic approaches to provide mechanistic explanations for the hippocampal volume reduction observed in individuals with AD genetic risk. Project 1: Hippocampal covariance. Instead of measuring / assessing hippocampal subfields one-by-one (a univariate analysis), a network-based approach will assess specific hippocampal sub-circuits. This approach reliably assays novel biological information and inter-state morphometry of hippocampal sub-nuclei (Ge et al., 2019; Kharabian et al., 2020). 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 polygenic 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) and link these to the AD hippocampal networks 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 hippocampal atrophy. This will enable us to identify specific patterns of AD risk gene – mediated hippocampal 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	School of Psychology
Email Address	tml45@bath.ac.uk
Co-Supervisor 1	
Name	Dr Byron Creese
Affiliation	Exeter
College/Faculty	Medicine and Health
Department/School	School of Medicine
Co-Supervisor 2	
Name	Professor Valentina Escott-Price
Affiliation	Cardiff
College/Faculty	Biomedical and Life Sciences
Department/School	Dementia Research Institute, School of Medicine
Co-Supervisor 3	
Name	Dr Elizabeth Coulthard
Affiliation	Bristol
College/Faculty	School of Medicine
Department/School	Institute of Clinical Neurosciences
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	