Project Details	
Project Code	MRCNMH24Ba Lancaster
Title	Investigating the biological intersection between Alzheimer's risk genetics and cognitive reserve
Research Theme	Neuroscience & Mental Health
Summary	The genetic architecture for Alzheimer's disease (AD) overlaps substantially with the genetics variants that influence individual differences in intelligence and cognition, supporting a hypothesis that 'cognitive reserve' is protective against AD. This project will employ an array of bioinformatic tools to identify how these processes overlap and how it manifests at a neurobiological level and across the lifespan.
Description	Background: Alzheimer's disease (AD) risk is partly explained by a network of genetic variants with small effects, operating via neurobiologically distinct, molecular pathways (PMID:32112059). The cumulative impact of these risk loci has been assessed, demonstrating i) high predictive capacity for identifying individuals with AD (PMID:34301930) and ii; robust associations with indices of brain health such as cognition or metrics derived via neuroimaging (PMID: 36070676; PMID:33227567). However, limited advances have been made to parse the distinct aspects of neurobiology that confer risk for AD to understand how these genetic features shape risk for AD. Research demonstrates a shared genetic aetiology between AD and cognition / intelligence (PMID:30820047) with evidence for a causal link (PMID:32003800). However, the specific molecular characterisation of this overlap has yet to be investigated. Furthermore, AD genetic loci within genes expressed in specific cell types, such as microglia may have a disproportionally large influence (PMID:37115753). Here, the student will triangulate evidence using an array of biostatistics (PMID: 32915962;34493297), neuroimaging (PMID:33875891) and psychometric (PMID:33414549) data and tools to map the specific molecular composition of genetically mediated cognitive reserve in AD and it neural/cognitive profile. This series of investigations will provide novel understanding into process by which cognitive reserve may protect against future AD. Hypothesis: We anticipate identifying precise links between common (in combination) / rare AD risk alleles and cognition across the lifespan. The methods employed will uncover the molecular intersection between AD and cognition that will provide novel insight into the process of cognitive reserve. This will include the identification of gene networks, molecular pathways to cognition profiles and neural correlates. We will map these AD genetic features to specific aspects of cognition and / or brain structure and function. P1: What is the molecular intersection between the genetic architecture for cognition and AD? This project will employ a range of novel biostatistical techniques to parse the heterogeneity in the genetic architecture of AD and cognition identified via genome-wide association (GWAS) to establish locus / pathways across the genome with common aetiology. This will be accomplished by leveraging recent GWAS summary statistics for AD and cognitive traits and novel methods able to parse the shared (but mixed) genetic signal (PMID:29220677,30962613,32915962) and established AD pathways such as variants within genes preferentially expressed in microglia (PMID:35379992). P2: Can this overlap make

	reliable and valid inference in AD and beyond? Polygenic risk scores (PRS) for cognition and AD will be created based on evidence of this intersectionality. The performance of these gene / pathway specific instruments will be tested in independent cohorts such as HCP,ADNI and PROTECT to assess suitability as a prediction tool for AD liability and cognitive function. P3: How do rare AD risk alleles relate to cognition and the brain across the lifespan? This project will utilise large neuroimaging-genetic large data sets across the lifespan (ABCD,ALSPAC/HCP, UKBB) to understand how rare SNPs in genes with known immune/microglia function shape cognition/brain health. This project will provide the first comprehensive assessment of functionally protective/risk conferring variants with known impact on immune system physiology across the lifespan. Outcomes: The project will lead to the formulation of new evidence for plausible, causal mechanisms of cognitive reserve in AD (P1). These could be used to refine risk prediction of AD (P2) as well as be investigated to identify potential treatment / intervention targets to mitigate cognitive deficits/decline in individuals with high genetic risk for AD (P1-3).
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