Project Details	
Project Code	MRC23NMHCa Caseras
Title	Does common genetic risk for schizophrenia shape brain anatomy and function?
Research Theme	Neuroscience and Mental Health
Summary	Despite the assumption that common risk alleles for schizophrenia trigger brain changes that explain clinical symptoms, this association has not been clearly demonstrated. The lack of specificity in genomic approaches and the use of sub-optimal brain phenotypes have hindered progress. This project aims to implement innovative imaging and analytical methods to address this conundrum, potentially leading to improved diagnosis and new targets for treatment development.
Description	The heritability of schizophrenia (SZ) is estimated to be as high as ~80%, with hundreds of common alleles implicated and most risk genes highly expressed in the brain. Magnetic resonance imaging (MRI) research has confirmed widespread brain anatomical and functional differences between SZ participants and healthy controls, with some of these differences also shown in those genetically at risk but unaffected, therefore assumed to be associated with genetic risk. However, the association between common allele risk load for SZ and brain changes has yet to be demonstrated. Over the last 60 years, no novel therapeutic targets of proven efficacy for SZ have emerged, mostly due to the still largely unknown causes of the disorder. This project aims to implement novel approaches to uncover the association between common allele risk for SZ and brain changes associated with the disorder, advancing our knowledge on its pathogenesis to identify potential new therapeutic targets. We propose that increasing the precision of imaging phenotypes with 'closer-to-biology' metrics (e.g. indices of neurite density and myelin content rather than fractional anisotropy as white matter characterisation) and the specificity of polygenic scores (common risk allele load) through gene-sets rather than the standard genome-wide approach, is the key to uncovering the effects of genetic risk over brain anatomy/function. To this end, this project will exploit the wealth of data within existing large datasets: the UK Biobank, the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, the Human Connectome Project (HCP), and the Adolescent Brain Cognitive Development study (ABCD), along with high resolution data obtained through cutting-edge scanners/procedures in CUBRIC. The use of large cohorts will provide the study with the necessary statistical power to detect moderate/small effect sizes and provide an opportunity for replication, while the in-house data will provide with unique resolution. The combination of different cohorts will also allow to investigate the effects of age and gender. The student will first complete an in-depth review of the existing imaging literature in SZ along with neurobiological models to pre-select brain metrics of interest. The imaging space will be further reduced via clustering methods. Recent pilot data from our group using grey matter indices from UK Biobank suggested that these measures (>100) could be reduced to 14 factors accounting for >50% of the total variance while retaining biological meaning. It also highlighted that Principal Components was not an optimal procedure for reducing the genetic space due to linkage disequilibrium; therefore, the use of

	other methods such as Canonical correlations will be investigated. The student will use Machine Learning methods employing a variety of supervised and unsupervised tools to study the potential non-lineal associations between gene-risk and brain phenotypes. Identified gene-sets will be tested to determine whether they are part of known disease pathways or represent potential new pathways. Causal analyses, including Mendelian randomization (MR), will be employed to test if genetic liability to SZ causes brain changes. Pleiotropic effects of different gene-sets on multiple brain phenotypes will be investigated via multivariate MR. Within the framework of this PhD, the student will be able to tailor the work to best suit their own research interests. The novelty of the proposal and therefore the paucity of existing research in this area, the vast amount of available data (either public or inhouse), and the numerous methodological avenues that can be taken, brings the opportunity for the student to drive the project and widen their skill-set in many different directions.
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