Project Details	
Project Code	MRC22NMHCa Bray
Title	Exploring the early genetic origins of schizophrenia at the cellular level
Research Theme	Neuroscience & Mental Health
Summary	Schizophrenia is a severe psychiatric disorder with an unclear biological basis. This project will combine single cell sequencing technology with the latest data on genetic risk factors for schizophrenia to identify cell types and mechanisms within the developing human brain mediating genetic risk for the condition. The project will provide training in state-of-the-art laboratory and bioinformatic techniques for analysing cellular gene expression.
Description	Schizophrenia is a severe psychiatric disorder affecting ~1% of the population. Recent large-scale genomic studies have identified hundreds of schizophrenia genetic risk loci, paving the way for much-needed biological insights into the condition. Our own research (e.g. 1-3) and that of others (e.g. 4) has indicated that many of these genetic risk variants operate in utero, substantiating long-held neurodevelopmental theories of the disorder. However, the prenatal brain regions and cell types through which these genetic risk variants operate remain unclear. This PhD project will build upon a current MRC project grant to lead supervisor Bray which is using single-cell sequencing to assess gene expression and its regulation in the constituent cell types of the human foetal brain. The student will combine use of this cutting-edge wet-lab technology with the latest genetic data for schizophrenia (available through the host MRC Centre for Neuropsychiatric Genetics & Genomics) to identify cell types of the prenatal brain mediating genetic risk for the disorder. Through the two host centres, they will be trained in both state-of-the-art laboratory techniques for profiling cellular gene expression and sophisticated biostatistical methods for its analysis and integration with large-scale genetic data. The student will additionally benefit from use of related epigenomic and transcriptomic data generated by the Cardiff and Exeter supervisors' groups (from both foetal and adult human brain) as well as from established international collaborations (e.g. with the Psychiatric Genomics Consortium, PsychENCODE). The impact of the student's research will be maximised through their regular attendance at international conferences (e.g. World Congress on Psychiatric Genetics, Society for Neuroscience), publication in leading journals and dissemination through data-sharing repositories. 1. Hill MJ, Bray NJ (2012) Evidence that schizophrenia risk variation in the ZNF804A gene exerts its effects during fetal brain development. Am J Psychiatry 169: 1301-8. 2. Hannon E,…Bray NJ, Mill J (2016) Methylation QTLs in the developing brain and their enrichment in schizophrenia risk loci. Nature Neurosci. 19: 48-54. 3. O'Brien HE, Hannon E,….O'Donovan MC, Mill J, Bray NJ (2018) Expression quantitative trait loci in the developing human brain and their enrichment in neuropsychiatric disorders. Genome Biol. 19: 194. 4. Walker RL,…Geschwind DH (2019) Genetic control of expression and splicing in developing human brain informs disease mechanisms. Cell 179: 750-771. Year 1 (Cardiff) Training in single cell transcriptomics / epigenomics using human foetal brain tissue (wet-lab and data analysis), advanced computing and psychiatric genetics.

	Principal aim: identify cell types within the developing human brain mediating genetic risk for schizophrenia. Year 2 (Exeter) Training in epigenomics and further bioinformatics, including integration with / comparisons against other cell-specific epigenomic and transcriptomic data generated by Mill's group (e.g. from adult brain). Principal aim: refining neurodevelopmental mechanisms mediating genetic risk for schizophrenia (e.g. specific cellular processes, developmental time-points). Year 3 Depending on findings and interest of student, could have a wet lab or bioinformatic focus (e.g. spatial transcriptomics or potential refinement of schizophrenia subtypes associated with genetic risk operating prenatally).
Supervisory Team	
Lead Supervisor	
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