Project Details	
Project Code	MRCNMH26Ex Tyrrell
Title	Severe mental illness, brain iron and adverse metabolic consequences
Research Theme	NMH
Project Type	Dry lab
Summary	This exciting PhD combines big data and genetics to understand the role of brain iron in metabolic psychiatry. This is important has people with severe mental illness are more likely to have adverse metabolic health problems and we don't know why. Preliminary results from the supervisory team suggest brain iron may be a crucial factor. This PhD will test this in more detail using novel brain iron metrics and new imaging methodology. The student will train in 3 world leading centres and will gain skills in brain imaging, statistics and genetic epidemiology.
Description	This interdisciplinary PhD offers a unique opportunity to build expertise in metabolic psychiatry—an emerging field investigating the shared biological mechanisms linking mental illness and metabolic disorders. This area is of growing clinical importance, as individuals with severe mental illness (SMI)—such as schizophrenia, bipolar disorder, and severe depression—have significantly higher rates of obesity, type 2 diabetes, and cardiovascular disease. Despite this, many mechanistic links remain poorly understood. This PhD will focus on the role of brain iron in SMI and its potential contribution to metabolic dysregulation, using data from MRI imaging, genetics, and electronic health records (EHRs). Iron plays a vital role in brain function, but its dysregulation is implicated in neurodevelopmental and neurodegenerative conditions. Smaller studies suggest altered brain iron levels in schizophrenia, but broader, large-scale investigations are lacking. This PhD will build on preliminary data from the supervisory team, which found potential bidirectional causal relationships between schizophrenia and brain iron—especially in the substantia nigra—as well as associations between brain iron accumulation and bipolar disorder or major depression. This project aims to explore these findings further across more brain regions and at larger scale, while investigating the causes and consequences of brain iron accumulation in SMI. The overarching goal is to understand how brain iron dysregulation interacts with SMI and contributes to downstream metabolic outcomes. Three interlinked work packages will address this: Work Package 1: Brain Iron and SMI – Observational and Genetic Analyses Using the UK Biobank, the student will analyse associations between brain iron levels—estimated using a range of methods developed by the supervisory team from MRI data—and SMI diagnoses using epidemiological methods. They will then perform genome-wide association studies (GWAS) to identify genetic variants linked to brain iron levels (if not already published), followed by Mendelian randomisation (MR) to test for causal relationships between brain iron and psychiatric conditions. The MR will use individual level data within the UKB and publicly available summary statistics from the Psychiatric Genomics Consortium. This will cover both cortical and subcortical brain regions, offering insights into regional specificity. Work Package 2: Replication in Diverse Cohorts

	To test the generalisability of findings, the student will replicate genetic analyses in All of Us (US) and Our Future Health (UK). While these cohorts currently lack MRI data, their larger size and greater ethnic and socioeconomic diversity will improve external validity for the MR analyses. These analyses will confirm whether genetic associations with brain iron and SMI are consistent across populations. Work Package 3: Causes and Consequences of Brain Iron in SMI The student will systematically identify causal risk factors for high iron levels which may also contribute to SMI. For example, our work has highlighted the potential role of higher BMI and higher triglyceride levels on brain iron. The student will take this forward and unpick potential shared causal risk factors to improve our understanding of the links between iron and SMI. The student will also consider the downstream consequences of SMI with and without brain iron overload on adverse outcomes (e.g. mortality, dementia, cardiovascular problems). They will use a broad range of genetic epidemiological methods including but not limited to GWAS, genetic correlations, partial LDSC, MR and mediation methods. Skills Development The student will gain advanced training across multiple areas: • MRI brain imaging: Techniques to estimate iron levels in different brain regions. • Genetic epidemiology: GWAS, MR, mediation analysis, polygenic risk scoring. • Statistical methods: Regression, lifecourse approaches, handling collider bias. • Clinical science: Insights into psychiatric assessment and metabolic health. • Data science: Analysis of large-scale datasets including MRI, genetics and EHRs. The project is designed to be flexible, allowing the student to tailor aspects to their interests—such as focusing on one SMI, a specific brain region, or stratified analyses by sex or age. The student will work across disciplinary boundaries, with their supervisors and external collaborators coming from molecular/genetic, epidemiological, clinical psychiatric, neuroscience and brain imaging, and advanced biostatistical backgrounds. The student will benefit from their supervisors networks with all of the supervisory team involved in 2 of the Mental Health Hubs - providing the student with amazing opportunities for collaboration. This PhD offers a rich and varied training environment and the opportunity to contribute to a cutting-edge area of research with high clinical relevance. By investigating the intersection of brain biology, mental health, and metabolic disease, this work has the potential to reveal novel mechanistic insights and inform future approaches to precision psychiatry and prevention.

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