Project Details	
Project Code	MRCNMH26Ba Walton
Title	Bio-Computational Approaches to Understanding Transition to Psychosis
Research Theme	NMH
Project Type	Dry lab
Summary	This project aims to advance our understanding of psychosis by identifying the biological mechanisms that underlie its diverse symptom profiles. Moving beyond traditional diagnostic categories, it adopts a symptom-based framework to study features such as cognitive deficits, hallucinations, and delusions. Using large-scale multimodal datasets, the project will apply advanced computational methods—including machine learning and clustering techniques—to uncover biologically meaningful subtypes of psychosis. Integrating neuroimaging, (epi-)genomic, proteomic and inflammatory data, it will also explore the developmental and dynamic nature of these biological markers, with the goal of identifying people at risk as early as possible to enhance prevention and treatment.
Description	**Background** Psychotic disorders represent some of the most severe and debilitating forms of mental illness, significantly contributing to global disability, early mortality, and reduced quality of life. Despite extensive research efforts over the past decades, meaningful advances in treatment and prevention have remained limited. One critical barrier has been the reliance on traditional diagnostic categories, which group individuals into broad and often heterogeneous labels. These categories combine diverse symptom presentations—such as cognitive or emotional impairments, hallucinations, and delusions —into single diagnoses, potentially obscuring the underlying biological mechanisms that underlie these symptoms. To make progress in understanding and treating psychosis, the field is increasingly moving towards a dimensional framework. Instead of focusing solely on categorical diagnoses, this approach examines core symptom dimensions—such as cognitive deficits, mood dysregulation, or psychotic experiences—as biologically relevant features rather than diagnostic group. This shift allows for a more precise mapping between clinical presentation and underlying pathophysiology and holds promise for improving early identification, risk stratification, and the development of targeted interventions. Emerging evidence suggests that psychosis is associated with a range of biological abnormalities, including accelerated brain ageing, dysregulation in immune-inflammatory signalling, altered proteomic pathways and elevated (epi-)genetic risk burden. Many of these changes begin early in life and evolve across developmental stages, yet their interactions and contributions to illness onset, progression, and chronicity remain poorly understood. Addressing these knowledge gaps requires the integration of multimodal data—such as neuroimaging, (epi-)genomics, and proteomic/immunological markers—using advanced computational and statistical techniques. **Key Research Question** The central aim of this project is to identify and validate biologically meaningful subtypes of psychosis by refocussing on symptom domains

	(e.g. cognition) and by using large-scale, multimodal data and state-of-the-art computational approaches. Specifically, the project seeks to answer: How do (epi-)genetic, neuroimaging, and proteomic/inflammatory markers interact across development to shape vulnerability to psychosis, and how can these interactions inform prevention and treatment plans? By focusing on symptom dimensions and dynamic biological markers, this research aims to move beyond rigid diagnostic boundaries and contribute to a more nuanced and biologically informed understanding of psychosis. **Specific Objectives** The student has the opportunity to work toward a selection of the following interlinked objectives over the course of the studentship: 1) Characterise brain structural and age-related biomarkers of psychosis risk across the lifespan The first objective focuses on identifying neurodevelopmental and neurodegenerative patterns associated with psychosis risk. Using structural neuroimaging data, the student will compute markers such as brain-predicted age difference (brain-PAD) and regional developmental metrics to characterise deviations from normative brain trajectories in children, adolescents, and adults with or at risk for psychosis. This analysis will leverage large neuroimaging datasets (e.g., UK Biobank, ENIGMA, or local cohorts) and will apply machine learning models to estimate brain age and detect atypical neurodevelopmental signatures. 2) Investigate early-life biological predictors of brain aberrations in psychosis Building on the first objective, the second aim is to examine how early-life biological factors—such as (epi-)genetic risk (e.g., poly(epi-)genic risk scores, epigenetic age acceleration), proteomic or inflammatory markers (e.g., CRP, IL-6), and environmental exposures (e.g., early adversity)—influence brain development and psychosis risk. The student will integrate genetic and immunological data with neuroimaging metrics to test developmental models of vulnerability. This objective allows the student to explore mediation and interaction effects between genes, proteins, inflammation, and environmental variables, providing a systems-level view of early risk pathways. 3) Identify biological modifiers of brain and immune markers across time This objective focuses on the dynamic evolution of biological risk and resilience factors. The student will investigate how various modifiers—such as epigenetic changes, lifestyle factors (e.g., smoking, physical activity) —impact longitudinal trajectories of brain structure and inflammation. This work will involve analysing longitudinal datasets and applying advanced statistical models (e.g., mixed effects models, latent growth modelling) to characterise individual differences in illness progression and biological plasticity. Student Involvement and Opportunities for Ownership This project offers a wide scope for intellectual and methodological ownership. The student will have flexibility in shaping the direction of the analyses based on their interests—for example, focusing more deeply on specific symptom dimensions (e.g., hallucinations vs. cognitive

	deficits), developmental stages (e.g., adolescent vs. adult onset), or biological domains (e.g., inflammation vs. (epi-)genetics). Additionally, the project encourages the use and development of novel computational methods (e.g., proteomic age, multimodal integration), giving the student space to innovate and contribute to methodological advances. While the core objectives provide a structured framework, the student is encouraged to propose new research questions, develop independent hypotheses, and pursue follow-up analyses based on initial findings. There is also the opportunity to contribute to publications, attend international conferences, and engage with our interdisciplinary collaborators across neuroscience, psychiatry, and computational biology (e.g., at Oxford, Cambridge, UCL, Cardiff, Germany).
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