Project Details	
Project Code	MRCNMH25Ba Lancaster
Title	Neuroimaging brain reward systems to stratify patients across the psychosis spectrum
Research Theme	Neuroscience & Mental Health
Summary	Severe mental illness with psychosis symptoms (e.g. bipolar disorder, schizophrenia) are reliably linked to alterations in brain reward circuitry. Neuroimaging techniques can predict diagnosis of individuals with/without psychosis by assessing neurophysiological alterations within key nodes of brain reward circuitry. However, little is known about the specificity, clinical correlates, or neurobiology of this biomarker. The candidate will join an established GW4-aligned mental health hub (Brain & Genomics UKRI Mental Health Platform) to assess how reward circuity is different in individuals with different diagnosis, medications, symptoms and genetic risk. This project will refine diagnosis and treatment strategies for individuals experiencing psychosis.
Description	**Background:** Individuals who experience severe mental illness across the psychosis spectrum (schizophrenia, schizoaffective disorder, bipolar disorder) require personalised interventions to address their specific symptoms. Precise diagnosis for these genetically and phenotypically overlapping syndromes is challenging and most treatment pathways are determined by trial and error, with significant opportunity for disagreement and sub-optimal outcomes. Current syndromic definitions of psychosis are too broad to offer biologically informed treatment targets. As a result, there is a pressing need for quantifiable and personalized biomarkers to better identify these targets, enhance prognoses, and deepen our understanding of pathophysiology across traditional diagnostic categories. Despite extensive research over the years, reliable biomarkers have yet to be identified. However, recent and reliable evidence suggests that targeting neural response in striatal reward circuitry may be a promising marker (PMID: 32251404; 38177349). **Aims:** The proposed project will aim to stratify patients, refine diagnosis, model clinical trajectories and link to genetic risk using a reliable assay of brain function linked to the mechanism of action for antipsychotics and a key node in the brain's reward circuitry (PMID: 38177349). The candidate will meet this objective using data that will be acquired as part of the newly established £4.3 million Brain and Genomics Hub as part of the National UKRI Mental Health Platform. Under the remit of the Brain and Genomics Hub's mission to combine data across multiple scales to improve patient stratification - the prospective candidate will assess neuroimaging data in over 600 people living with a diagnosis of either schizophrenia, bipolar disorder and schizoaffective disorder. The candidate will have the opportunity to combine the neuroimaging assessment with data simultaneously acquired, across a wide range of neurobiological scales (for example - clinical, cognitive, genetic, epigenomic, and immunometabolic assessments) to understand the neurobiological process by which alterations in the brain's reward circuitry are reliably altered in psychosis.

	The project will follow three broad objectives: 1) A functional striatal abnormality (FSA) index will be derived via intra- and extra-striatal functional connectivity and striatal fractional amplitude of low-frequency fluctuations imaging features, using an established support vector machine (SVM) classifier previously trained to discriminate between patients with non-affective psychosis (n=560) and controls (n=540). This 'FSA' score value will be compared individuals with different symptom, cognitive, immunological and (epi)genetic profiles to establish biological and clinical correlates of the biomarker. 2) The functional striatal abnormality (FSA) index collected in the psychosis patient cohort will be linked to ongoing / prospective treatment response / type data collected and measured as part of linked data such as e-health records collected as via SAIL. This will help establish the prognostic value of the biomarker, by linking FSA to intra-participant variation in illness severity in individual on different psychotic treatment pathways. As long-read NGS genomics sequencing will be collected, FSA could also be linked to variation in known pharmacogenes including CYP2D6, the major metaboliser of antipsychotics. 3) A functional striatal abnormality (FSA) will be created in previously established / collected normative samples such as an in house sample of healthy controls (Welsh Advanced Neuroimaging Database (WAND), N = 170, aged 18-63); and large open-access multimodal genetic-neuroimaging datasets across various stages of the lifespan (such as the CNP, HCP, ABCD, UKBB cohorts) and linked to common genetic risk across the psychosis spectrum. For example, establishing links between FSA and polygenic scores for psychosis (schizophrenia & bipolar disorder) and each diagnosis individually. Together, these three projects with dovetail together to provide novel insight into the aetiology of striatal dysregulation in individuals with psychotic symptoms, identifying specific clinical, cognitive and genetic profiles of individuals with FSA and provide insight to improve / refine diagnosis and optimises future treatment efficacy. Student ownership: As the 600+ cohort of psychosis patients will be collected across scale, in a deep phenotyping approach - there will be an extensive, eclectic range of opportunities to link FSA scores with genetic/epigenetic (with further availability based on NGS long read sequencing), clinical / cognitive data collected and linked to e-health records and immuno-metabolic markers collected via blood samples. The student could therefore further explore / gain expertise in any of these sub-specialities - liaising with the relevant Brain and Genomics Hub co-investigator. Furthermore, while the FSA score is derived using an established process/pipeline, we encourage the student to explore other striatal neuroimaging features to understand more about the specificity of the SVM model predictions. For example, as part of the WAND/HCP datasets - assess of neural responses to specific, probabilistic reward contingencies (such as monetary incentive or probabilistic reversal learning) could be explored. We would also support genome-wide association studies (GWAS) of FSA in larger cohort samples such as UKBB, ABCD to establish genetic architecture and genetic overlap with psychosis genomics. Together, available data will provide prospective

	students the opportunities to pursue expertise from a range of interdisciplinary skillsets.
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