NIHR | Maudsley Biomedical Research Centre

KING'S College LONDON

PhD studentships

Funded by the

NIHR Maudsley Biomedical Research Centre

and

King's College London

Project Catalogue

Studentships to commence October 2019

Contents

Introduction **5**

NIHR Maudsley Biomedical Research Centre (BRC) **6**

NIHR Maudsley BRC Strategy 6

Clinical disorder focused research themes 7

Technology and methodology focused research themes 7

Cross cutting themes 7

Affective Disorders and Interface with Medicine Theme 8

Child and Neurodevelopmental Disorders 8

Dementia and Related Disorders 9

Lifestyle Substance Use & Harms (Substance Use) 9

Obesity, Lifestyle and Learning from Extreme Populations (Obesity) 10

Pain and headache 10

Psychosis and Neuropsychiatry 11

Bioinformatics and Statistics 11

Biomarkers and Genomics 12

Clinical and Population Informatics 12

Mobile Health 13

Neuroimaging 13

Patient & Carer Involvement and Engagement 14

Translational Therapeutics 14

BioResource 15

Clinical Research Facility 15

Institute of Psychiatry, Psychology and Neuroscience **16**

Projects **17**

Project-001 18

Drug pathway identification in overlapping heterogeneous neurodegenerative diseases through computational and statistical approaches applied to a large multiomics dataset 18

Project-002 20

Modelling Development and the Evolution of Morbidity 20

Project-003 22

Multimorbidity patterns in Severe Mental Illness: the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) Case Register 22

Project-004 24

Precision medicine and mechanism: How and for whom do psychological treatments work? 24

Project-005 26

Predicting diabetes in people with psychoses....26
Project-006....28
Transdiagnostic mechanisms in cognitive behavioural interventions for patients with Persistent Physical Symptoms: How do transdiagnostic psychological therapies work?....28
Project-007....30
Multi-modal objective measurement of emotional dysregulation in autism spectrum disorder and attention deficit hyperactivity disorder....30
Project-008....32
Predicting Neurodevelopmental Trajectories from EEG-based Brain Connectivity Assays....32
Project-009....34
Understanding the impact of psychiatric morbidity on employment and benefit changes: a data linkage project....34
Project-010....36
Adult phenotype associated with NRXN1 deletions....36
Project-011....38
Born Bad? - Can we treat children at risk of becoming psychopaths....38
Project-012....40
Can Targeting the serotonin (5-HT) system 'shift' the biology of Autism leading to a possible pharmacological treatment for core systems?....40
Project-013....42
Emerging brain networks in babies vulnerable to neurodevelopmental conditions (Autism Spectrum Disorder and ADHD): An MRI study of fetal and neonatal brain....42
Project-014....44
Shifting brain biology in Autism Spectrum Disorder.....44
Project-015....46
Using Neuroadaptive Bayesian Optimisation to identify biomarkers for Autism Spectrum Disorders....46
Project-016....48
Improving the care of people with diabetes and severe mental illness, using experience-based co-design.....48
Project-017....50
Investigating the interface between physical and mental health during adolescence among diverse communities in inner-city London....50
Project-018....52
Patterns of Brain Connectivity that Encourage Hallucinatory Percepts in the Auditory Domain....52
Project-019....54
Understanding Pain and Treatment Response in Neurodegenerative Disease....54
Project-020....56
Cannabidiol for psychosis in neurodegenerative disorders....56
Project-021....58
Mapping individual differences in the neuroanatomy of dementia....58
Project-022....60

The electrophysiology of synaptic potentiation in human visual cortex as a biomarker for prodromal dementia. 60
Project-023 62
How do resilient communities protect people with severe mental illnesses from death? Mixed methods study of local populations. 62
Project-024 64
Modelling patient mental, behavioural and somatic experiences using Natural Language Processing 64
Project-025 66
Developing the Next Generation of Mental Health Assessments Tools Using Virtual Reality 66
Project-026 68
Understanding psychosocial factors associated with distress in women survivors of breast cancer and assessing the efficacy of a mobile app-based intervention 68
Project-027 70
Biomarkers of Treatment Response in Schizophrenia 70
Project-028 72
Stratification of people at clinical high risk for psychosis 72
Project-029 74
Stratifying bipolar depression through its effects on the presynaptic dopamine system; an 18F-DOPA PET study 74
Project-030 76
The emotional clock: Balancing circadian rhythms and emotional regulation 76
Project-031 78
Using smartphone-based personal sensing to understand and predict risk of psychotic relapse at the individual level 78
Project-032 80
Using virtual reality to investigate sense of body ownership and agency in patients with functional neurological disorder 80
Project-033 82
Up-regulating positive affect in adolescence: exploring novel cognitive intervention strategies for depression and anxiety 82
Project-034 84
Mobile health and attention-deficit/hyperactivity disorder (ADHD): developing novel digital biomarkers to characterise clinical features and predict outcomes 84

Introduction

Welcome to the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) and King's College London project catalogue for potential candidates wishing to commence a PhD in October 2019 – we hope you will find a project which interests you.

The Maudsley BRC is a collaboration between the Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London – the largest collection of researchers in Europe investigating mental disorders, and the South London and Maudsley NHS Foundation Trust – a leading mental health trust with a long tradition in joining clinical and academic excellence. Most Maudsley BRC researchers, staff and students are based at the IoPPN at the King's College London Denmark Hill campus which is adjacent to the Maudsley Hospital. Within this setting we offer the opportunity to join a thriving group of interdisciplinary researchers with internationally recognised supervisors and we ensure our students benefit from an understanding of the context of their research, producing scientists with a strong translational ethos.

The Maudsley BRC is dedicated to developing better treatments for people with mental and neurological disorders, which collectively cause most of the disease burden in Western societies. Within the BRC we offer projects which are clinically relevant and attempt to bring new innovation to help treat people with mental disorders, dementia and other neurological conditions. This is the most exciting field in biomedical science, the least researched, the most important. And we offer an opportunity to gain research training in a vibrant and exciting centre where doctoral students are highly valued members of our team.

We hope we can look forward to receiving your application.

Professor Matthew Hotopf
Director
Maudsley Biomedical Research Centre

Professor Richard Brown
Training Lead
Maudsley Biomedical Research Centre

NIHR Maudsley Biomedical Research Centre (BRC)

NIHR Biomedical Research Centres are funded to support people and/or patient-focused early translational (experimental medicine) research, the aim of which is to translate discoveries from basic/discovery science into clinical research, and through to benefits for patients, the health system and for broader economic gain.

On 16 September 2016 the Secretary of State for Health announced that the Department of Health has awarded £66 million funding over the next five years to the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, Psychology & Neuroscience at King's College London.

The award represents a substantial uplift in funding compared to the previous BRC funding round, and demonstrates the government's continued commitment to the current NIHR Maudsley BRC, allowing the research centre both to build on its current work and expand into new areas including substance use, obesity, pain and mobile health technology.

The expanded NIHR Maudsley BRC will bring together scientists, clinicians, mental health professionals, service users and carers, to improve clinical care and services across the field of mental health. The investment in the NIHR Maudsley BRC will allow research into ground-breaking treatments and care for mental health and dementia.

NIHR Maudsley BRC Strategy

There are four major elements to the NIHR Maudsley BRC strategy for the coming 5 years, reflected in the aims of the 17 themes:

- **Precision psychiatry**: Bringing together insights from cognition, behaviour, genomics and brain imaging, we will develop biologically-informed strata of psychiatric syndromes, with the ambition to develop and provide more individually tailored treatment
- **Novel therapeutics**: Using the access to our large databases, electronic consent for contact procedures, and our dedicated experimental medicine Clinical Research Facility (CRF), we will undertake trials of new pharmacological, neuromodulation and psychological treatments
- **Translational informatics**: By using our bespoke natural language processing algorithms and 'smart agents', we will use informatics to influence treatment choice, increase adherence, improve health behaviours and increase patient empowerment, all of which will benefit patient outcomes and service delivery
- **Mental/physical interface**: We will decrease the 15 years of life lost to serious mental illness by using informatics to identify, prioritise and track the treatment of those with comorbid mental and physical disorders

Clinical disorder focused research themes

Seven clinical disorder focused research themes cover mental health and dementia from cradle to grave:

- Affective Disorders and Interface with Medicine
- Child and Neurodevelopmental Disorders
- Dementia and Related Disorders
- Lifestyle Substance Use & Harms (Substance Use)
- Obesity, Lifestyle and Learning from Extreme Populations (Obesity)
- Pain and headache
- Psychosis and Neuropsychiatry

Technology and methodology focused research themes

Seven technology and methodology focused research themes develop and deploy new approaches to clinical problems:

- Bioinformatics and Statistics
- Biomarkers and Genomics
- Clinical and Population Informatics
- Mobile Health
- Neuroimaging
- Patient and Carer Involvement and Engagement
- Translational Therapeutics

Cross cutting themes

Three cross cutting themes provide enabling infrastructure:

- BioResource
- Clinical Research Facility
- Training and Capacity Development

Affective Disorders and Interface with Medicine Theme

Lead: Professor Carmine Pariante

This theme focuses on developing new treatments for depression, bipolar and anxiety disorders, integrating multiple approaches beyond pharmacotherapy (including immunopsychiatry, neuroimaging, and psychological approaches) and addressing the mechanisms by which mental and physical illness interact.

Aims

1. Exploit cellular and clinical immunopsychiatry to maximise early diagnosis in individuals at risk for depression and drug repurposing opportunities for pharmacological treatments based on personalised algorithms
2. Deliver precise neuroimaging-based interventions addressing targetable psychological mechanisms and their neurofunctional underpinnings
3. Develop novel psychological treatments to address transdiagnostic mechanisms (e.g. cognitive and interpretation biases) in patients with depression, anxiety, and at the mental / physical health interface
4. Reach larger populations of difficult-to-engage patients using translational informatics (computer/web/app-based platforms for recruitment, assessment and interventions) and community cognitive behaviour therapy (CBT) workshops

Child and Neurodevelopmental Disorders

Lead: Professor Emily Simonoff

This theme focuses on improving early diagnosis and evaluating novel pharmacological and non-pharmacological interventions for neurodevelopmental disorders with childhood onset (especially autism and attention deficit hyperactivity disorder), and other mental disorders which occur in children (e.g., anxiety, depression, and conduct disorder). The theme takes a lifespan approach, with studies in children and adults.

Aims

1. Improve early diagnosis, reduce secondary complications and develop better treatment monitoring for children with mental disorders and people of all ages with neurodevelopmental disorders including autism, attention deficit hyperactivity disorder (ADHD) and childhood-onset neurodegenerative disorders.
2. For autism, our precision psychiatry research will identify early risk markers for the disorder and, amongst those with autism, markers that predict the poor mental health and adaptive functioning problems, which patients and families tell us are their greatest concern.
3. Evaluate novel therapeutics for autism, ADHD and neurodegenerative conditions in proof-of-concept trials. Our approach includes repurposed molecules, psychological interventions and neuromodulation.
4. Use mobile health technology to improve assessment and treatment monitoring in routine care and research studies.

Dementia and Related Disorders

Lead: Professor Dag Aarsland

The theme focuses on the improved identification, prevention and management of neuropsychiatric symptoms of dementia and other non-cognitive symptoms (e.g. agitations, depression, anxiety, psychosis, pain). The theme covers Alzheimer and non-Alzheimer dementia syndromes (including dementia with Lewy Bodies and Parkinson's dementia, Vascular dementia, stroke and white matter disease, and dementia in Down's syndrome). The theme investigates and brings to trial novel pharmacological, biological and psychological approaches to management in patients at all stages of dementia

Aims

1. Expand opportunities for online intervention studies to maintain cognitive health and prevent cognitive decline
2. Deliver innovative and novel intervention studies of a biological therapy
3. Launch new intervention studies focusing on treating priority mental health symptoms and pain in people with dementia
4. Use opportunities related to polygenic risk, candidate genes and specific risk factors to launch precision medicine RCTs
5. Deliver improved biomarker outcomes for clinical trials in Alzheimer's disease and dementia with Lewy bodies

Lifestyle Substance Use & Harms (Substance Use)

Lead: Professor Sir John Strang

This theme covers use of tobacco, alcohol and illegal substances in general populations outside addictions treatment, aiming to develop better understanding of the connections between substance use and harms, and to investigate novel interventions and specialist treatment options to address substance use before it causes substantial health problems, including addiction, or to reverse or reduce harms when incurred. It will take a precision medicine approach to cohorts from general healthcare, identifying critical transition points in LSU (Lifestyle Substance Use) to harmful substance use for stratified populations. It will devise and test novel therapeutic approaches (psychological, pharmacological, mobile health), and use translational informatics to test interventions embedded within systems of care.

Aims

1. Identify at-risk groups and investigate critical transition points in substance use trajectories
2. Develop behavioural interventions and novel therapies which alter substance use trajectories
3. Conduct experimental studies of harms and the potential to prevent

Obesity, Lifestyle and Learning from Extreme Populations (Obesity)

Lead: Professor Ulrike Schmidt

This theme focuses on behavioural research into obesity, and improving metabolic outcomes for people with mental disorders. It translates findings from neuroscience and mental health into treatments for obesity in the general population. It uses longitudinal cohorts established in early life and extreme weight phenotypes to determine neurobiological, psychological and behavioural underpinnings of disordered eating behaviour, weight gain and obesity, and to identify biomarkers.

Aims

1. Develop predictive models of obesity precursors and correlates (disordered eating behaviour, metabolic syndrome, weight gain) in different cohorts, facilitating stratified early risk detection and prognosis for obesity
2. Apply learning from extreme phenotypes in mental health to obesity in the general population by identifying biomarkers of treatment response (weight gain/loss) in bariatric surgery, anorexia nervosa and psychosis
3. Extend our expertise in complex interventions for mental health to obesity in the general population by evaluating novel therapeutics and translating into scalable interventions

Pain and headache

Lead: Professor Peter Goadsby

This theme focuses on the synergies between the neurobiology and psychology to understand the aetiology and transdiagnostic mechanisms of pain and mental (particularly mood) disorders, and to develop novel approaches to pain management

Aims:

1. Define the basis, mechanisms and biomarkers of chronic pain disorders to facilitate precision medicine approaches to treatment.
2. Use a cross-disciplinary approach to characterise the drivers of disability associated with chronic pain, and develop strategies to reduce the burden of chronic pain disorders.
3. Develop and test novel therapeutic targets for therapy including pharmacology, psychotherapy, neuromodulation and the use of devices.

Psychosis and Neuropsychiatry

Lead: Professor Philip McGuire

This theme focuses on developing new and repurposed methodologies and treatments (pharmacological, psychological and neuromodulation) for psychosis and schizophrenia, and for psychiatric and behavioural problems in neurological disorder. There will be particular focus on the therapeutic potentials offered by a transdiagnostic approach to features (e.g. 'amotivation') seen in psychosis and in neurological conditions, and approaches integrating mental and physical mental in neuropsychiatry.

Aims

1. Make use of multimodal methodologies to select the right treatment for the right patient with psychosis, moving towards precision psychiatry
2. Evaluate new (and repurposed) pharmacological, psychological and neuromodulatory interventions in neuropsychiatric disorders
3. Gain a new understanding of neuropsychiatric disorders by focusing on syndromes common across disorders with and without demonstrable brain abnormalities
4. Improve integration between mental and physical health in neurological and psychiatric disorders.

Bioinformatics and Statistics

Lead: Professor Andrew Pickles

This theme provides the computing infrastructure and expertise in statistics and bioinformatics required to integrate and use the complex multimodal data we have access to, particularly via our CRIS system, biomarkers, and data derived from our Mobile Health theme. We use advanced computer science approaches to improve patient care by developing a "self learning" healthcare system.

Aims

1. Deliver a "panor-omic" view of each patient through integration of –omics data with data derived from patient reports, electronic health records, exposures, social graphs, imaging and other emerging technologies, and to systematically exploit these data to explore precision psychiatry and the mental-physical health interface
2. Develop methodology and implement in-service designs for enhanced learning to optimise treatment selection and combination; where possible, to enable formal learning from routine practice, a key element in delivering a "self-learning" health care system
3. Deploy a programme of translational informatics Applied Intelligence software agents into routine practice to identify and communicate with patients and clinicians, and to monitor and evaluate the effects of novel therapies and changes in clinical practice, resulting in treatments and services that are cheaper, faster, more reliable or less intrusive than traditional methods

Biomarkers and Genomics

Lead: Professor Cathryn Lewis

The theme delivers analytical expertise in genomics, particularly in the methodology, analysis and implementation of polygenic risk scores (PRS), allowing us to exploit the potential of genomic medicine and multimodal biomarkers to predict progression, prognosis, and treatment response across a range of psychiatric disorders. The theme complements the laboratory and recruitment/recall infrastructure provided by our BioResource cross-cutting theme. A data-driven approach to psychiatry will enable us to move genetic discoveries from research towards patient care, integrating diverse data sources to develop multimodal predictive models that inform diagnosis and treatment.

Aims

1. Determine how to use polygenic risk scores (PRS) to predict clinical outcomes for psychiatric disorder and
2. Evaluate the most cost-effective combination of PRS with neuroimaging, -omics, and cognitive biomarkers to increase the power of predictive models
3. Identify novel pharmacogenetic variants of therapeutic response and adverse effects
4. Translate genetic findings into novel therapeutics and drug repositioning opportunities using large-scale genetic data and novel pathway analysis methods

Clinical and Population Informatics

Lead: Professor Robert Stewart

This theme is responsible for maintaining and developing applications of our Clinical Record Interactive Search (CRIS). This allows pseudoanonymised analysis of routine electronic medical records (EHR), using expertise in data security, record linkage and natural language processing, and linkages with internal and external datasets from a variety of sources, to maximise the research potential of these data.

Aims

1. Extend clinical and population mental health data resources through online recruitment platforms and enhanced clinical databases
2. Apply these data resources for improving physical health outcomes, supporting precision psychiatry and novel therapeutics, and delivering informatics-based interventions
3. Export data-generation / processing tools though a national e-network for mental health informatics

Mobile Health

Lead: Professor Richard Dobson

This theme exploits novel mobile health and remote sensing technology to enable nuanced, deep and continuous clinical phenotyping, by providing data on the patient experience throughout the disease continuum. Complementary to our other Informatics themes, it supplies the specific expertise and collaborations required in this emerging field to develop user experience, apply methodology for real-time streaming and predictive analytics, and platform development for data management.

Aims

1. Exploit mobile health (mHealth) and remote sensing technology, enabling a shift from sporadic clinical data capture, to a nuanced, deep and continuous clinical phenotype, allowing us to harness patient experience throughout the disease continuum – from at risk, through early diagnosis, to post-diagnosis
2. Establish mobile and remote sensing technology as essential translational informatics infrastructure for precision psychiatry, developing novel interventions including early diagnosis and anomaly detection, disease stage monitoring, therapeutic adherence, and treatment response
3. Explore the interface between physical and mental health (e.g. nutrition, exercise), linking with the electronic health record, –omics, and imaging to provide a more complete picture of health and a more objective phenotype

Neuroimaging

Lead: Professor Steven Williams

The Theme focuses on the research, development and application of a broad range of imaging techniques for clinical research of brain disorders using specialised PET and MRI equipment.. It establishes and supports a core standardised imaging protocol facilitating advanced image analysis, enabling data sharing between studies. A web-based brain imaging database (HiveDB) is linked to our Clinical Record Interactive Search (CRIS) electronic health record and BioResource for integration of imaging, clinical and genetic data.

Aims

1. Develop and implement neuroimaging (MRI, PET and EEG) for better diagnosis, improved understanding of disease biology, enhanced prediction of response heterogeneity and clearer patient stratification as critical technologies for precision psychiatry
2. Perform a wide range of neuroimaging studies in patients with psychiatric and other disorders of the brain, combining medicine with basic science to improve our understanding of brain pathology across the entire lifespan
3. Create novel imaging methods to visualise the central action of new medicines and extend our current efforts to visualise brain metabolism, inflammation, myelination and plasticity.

Patient & Carer Involvement and Engagement

Lead: Professor Dame Til Wykes

Focusing on patient-generated priorities for access, personalised care, novel treatments and avoiding the negative effects of treatment, this theme extends our existing work increasing diversity in research participation, developing participatory methods to contribute patient-valued outcome measures, and improving translation efficiency through patient assessments of feasibility and acceptability.

Aims

1. Increase diversity in research participation (age, gender and ethnicity)
2. Extend participatory methods to contribute further patient-valued outcome measures (PvROMs) and carer valued outcomes (CvROMs) to improve intervention tailoring
3. Improve translation efficiency through patient assessments of feasibility and acceptability of novel interventions and inventions, providing external validity for a range of disorders
4. Develop the next generation of an NHS patient portal to maximise patient benefit
5. Improve patient health and quality of life by reducing medication side effects

Translational Therapeutics

Lead: Professor Allan Young

The theme focus is to develop new, more efficacious and acceptable treatments for mental disorders and dementia by providing the infrastructure, training and expertise to develop new methodologies and analytical approaches for clinical trials. It supports the steady growth in scale and quality of experimental and translational studies and develops partnerships with industry. It provides methodological and analytical support for the NIHR-Wellcome Trust King's Clinical Research Facility (CRF), as well as new insights gained from working across clinical disorders

Aims

1. Support joint working and funding with the life sciences, biopharmaceutical and technology industries
2. Support Phase 1 / 2 trials, utilising validation by neuroimaging and surrogate measures, of novel pharmacotherapeutics based on new biological mechanisms
3. Design trials that use virtual reality (VR) based interventions and experimental psychological interventions to formulate new psychological treatments
4. Combine psychological interventions, especially cognitive and behavioural therapies, with biological interventions to enhance signal detection and efficacy signal

BioResource

Lead: Dr Gerome Breen

The BioResource provides infrastructure for the biological components of experimental medicine and clinical trials, driven by the needs of our clinical disorder and health behaviour themes, and combined with an efficient and adaptable patient-friendly recruitment and recall platform. Close integration with our new Biomarkers & Genomics theme allows us to maximise the potential of our strengths in database, data pipeline development and clinical data linkage, by providing integrated analytical and biomedical expertise.

Aims

1. Provide infrastructure for recruiting key patient populations and biological components of experimental medicine and clinical trials in our BRC
2. Provide a BioResource for mental health within the NIHR BioResource and a biobank allowing researchers access to samples for biomarker discovery or validation
3. Ensure that our BioResource is representative of the European, African and Black-Caribbean groups in our local patient population, enabling translational research in mental health that can meet their needs

Clinical Research Facility

Lead: Professor Peter Goadsby

The NIHR-Wellcome King's Clinical Research Facility (CRF) is a purpose-built facility to support clinical trials in mental health, neurology, and general medicine. It is situated within King's College Hospital, London, UK, on the Denmark Hill campus of King's College London, close to our partner South London and Maudsley NHS Foundation Trust. Our site houses high-quality experimental medicine facilities, where specialist clinical research and support staff work together on patient-orientated commercial and non-commercial studies.

The King's CRF is academically supported by King's Health Partners, an Academic Health Sciences Centre collaboration between King's College London, South London and Maudsley NHS Foundation Trust, Guy's and St Thomas' NHS Foundation Trust, and King's College Hospital NHS Foundation Trust.

We are one of 19 Clinical Research Facilities for Experimental Medicine supported nationally by the National Institute for Health Research (NIHR). Clinical Research Facilities exist to help speed up the translation of scientific advances for the benefit of patients, and work closely with related parts of the NIHR infrastructure, including our partner NIHR Maudsley Biomedical Research Centre.

Institute of Psychiatry, Psychology and Neuroscience

The Institute is organised into three academic divisions, each comprised of a number of cognate departments. Each Division includes academics and researchers from diverse scientific disciplines, working closely with colleagues across the faculty and our national and international partners:

- **Division of Academic Psychiatry** comprises 6 department: Addictions Sciences; Forensic & Neurodevelopmental Science; Child & Adolescent Psychiatry; Old Age Psychiatry; Psychological Medicine and Psychosis Studies (https://www.kcl.ac.uk/ioppn/divisions/academic-psychiatry/index.aspx)
- **Division of Psychology & Systems Science** comprises 4 departments: Biostatistics & Health Informatics; Health Service & Populations Research; Social Genetic & Developmental Psychiatry; Psychology; (https://www.kcl.ac.uk/ioppn/divisions/psychology/index.aspx)
- **Division of Neuroscience** comprises 4 departments: Basic & Clinical Neuroscience; Neuroimaging; Developmental Neurobiology; Wolfson Centre for Age-related Diseases (https://www.kcl.ac.uk/ioppn/divisions/neuroscience/index.aspx)

Successful applicants for these studentships will be registered for their MPhil/PhD with King's College London and will be based in the same department as their first supervisor. For all of the projects in this catalogue, the first supervisor is based in a department at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN).

Please note: The final allocation of project and supervisors will be agreed after successful interview.

Projects

In this catalogue, the projects are listed in departmental order according to the department where the lead supervisor for the project is based. Most projects fit with more than one of the Maudsley BRC themes and the relevant BRC themes are listed at the end of each project.

This document can be searched for both disorders and methodologies. Key words / key phrases for disorders and methodologies are provided with each project in this catalogue.

When applying for the NIHR Maudsley Biomedical Research Centre PhD studentship programme, please ensure you upload a separate, single side A4 document stating your three preferred PhD projects from those listed in this catalogue only. These should be listed in order of preference and include both the reference number and the project title.

For example:

1. Project-031 Using smartphone-based personal sensing to understand and predict risk of psychotic relapse at the individual level
2. Project-017 Investigating the interface between physical and mental health during adolescence among diverse communities in inner-city London
3. Project-022 The electrophysiology of synaptic potentiation in human visual cortex as a biomarker for prodromal dementia.

Below your project choices, please provide a statement explaining why you have chosen your **first choice** project and why you would like to take this forward as a PhD (**maximum 300 words**). This document is in addition to your application personal/supporting statement.

If you wish to discuss a project before you apply, you will find supervisors' names and their contact details listed with each project in this catalogue.

Further information about project supervisors can be viewed at the website address provided with the project details.

Please note: The final allocation of project and supervisors will be agreed after successful interview.

Project-001 | Drug pathway identification in overlapping heterogeneous neurodegenerative diseases through computational and statistical approaches applied to a large multiomics dataset

Supervisors: Professor Ammar Al-Chalabi and Doctor Alfredo Iacoangeli

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Project Description

Background: Frontotemporal Dementia (FTD) is a progressive degeneration of the frontal and temporal lobes. It is one of the most frequent dementia in people younger than 60. Amyotrophic lateral sclerosis (ALS, MND, motor neuron disease) is a devastating neurodegenerative disease that kills 1 in every 300 people, with a median survival of 3 years from diagnosis, and is the most common neurodegenerative disease of mid-life. There is a significant overlap between these conditions, and major heterogeneity within each, obstructing the development of new therapies. We now have an international dataset of thousands of patients, enabling us to study the clinical, genetic, epigenetic basis of ALS and FTD, to define the heterogeneity and overlap more precisely using biology, and therefore enabling the development of drugs targeted at specific pathways in specific groups of people.

Novelty and Importance: A comprehensive genetic, epigenetic and clinical approach on this scale, using machine learning (ML) and statistical methods, has never been attempted before in these diseases. Current classifications of ALS and FTD do not readily translate into meaningful subgroups for treatment, nor do they reliably predict clinically important factors like survival. The problem of correct classification potentially affects every patient, and is critical for the development of precision medicine and personalized treatments

Primary aim(s): To develop a biological classification of ALS and FTD subtypes to enable targeted drug design for precision medicine.

Planned research methods and training provided: The candidate will use powerful machine learning techniques and statistical methods to identify homogeneous patient subgroups based on the clinical phenotypes, genetic and epigenetic data, validated by correlation with biological outcomes such as survival. The candidate will receive training in big data, genetic association, rare variant analysis, Mendelian randomization, epigenetics, polygenic risk scoring, latent class cluster analysis and supervised machine learning methods. Bioinformatics and statistical genetic training will be provided by the Al-Chalabi group and industry collaboration with Rowanalytics. Machine learning training will be provided by the SLAM BRC Health informatics unit and industry collaboration with Benevolent AI.

Objectives / project plan:

Year 1: Bioinformatics and genetics training. Data acquisition, quality control and harmonisation of the dataset.

Year 2: Machine Learning training. Data analysis. Exploring the integration of the electronic health record (CogStack and CRIS) into the study.

Year 3: Data analysis. Translation of the analysis results into the development of models for the stratification of patients, prediction of clinical outcomes, and pathways analysis for drug discovery.

Project-001 Drug pathway identification in overlapping heterogeneous neurodegenerative diseases through computational and statistical approaches applied to a large multiomics dataset

Two representative publications from supervisors:

1: van Eijk RPA et al. Meta-analysis of pharmacogenetic interactions in amyotrophic lateral sclerosis c linical trials. Neurology. 2017 Oct 31;89(18):1915-1922

2: Iacoangeli A, Al Khleifat A, Sproviero W, Shatunov A, Jones AR, Opie-Martin S, Naselli E, Topp SD, Fogh I, Hodges A, Dobson RJ, Newhouse SJ, Al-Chalabi A.

Keywords / phrases

Clinical Area/s:	Frontotemporal Dementia Amyotrophic Lateral Sclerosis
Methodology	Machine Learning Bioinformatics Statistical genetics

BRC Theme/s:

Dementia and Related Disorders
Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Biomarkers and Genomics
Clinical and Population informatics
BioResource

Project-002 | Modelling Development and the Evolution of Morbidity

Supervisors: Professor Andrew Pickles and Doctor Rebecca Bendayan

Academic Department: Biostatistics & Health Informatics

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- https://kclpure.kcl.ac.uk/portal/en/persons/rebecca-bendayan(78ed6261-41ac-47af-bbee-f26f3467f3f7).html

Project Description

Background: This project is concerned with the formalization and statistical operationalization of the process of development of psychopathology; the dissipation and accretion of domains of symptoms that have long been recognized as occurring in childhood, but are now seen as commonly present in adulthood, particular at older ages. The project would formalize and explore concepts such as “developmental cascade”, which while long discussed, have never been operationalized into models that could be empirically tested or used for prognosis.

Novelty and Importance: In spite of the issues to be addressed being central to developmental psychopathology and a life course perspective on disease, the concepts used in the literature have remained poorly defined and sufficiently informal such that they have remained both largely empirically untested and, while influential, of little proven prognostic value to the clinician. This project would make a useful contribution to correcting this.

Primary aim(s): With assistance, to review the psychological literature for contributing concepts, and the survey the mathematical and statistical literature for formalizations of stochastic processes that could provide alternative formal and operationalizable frameworks. To develop estimation tools and present simulation and empirical exemplars using available population and clinical cohort studies**.**

Planned research methods and training provided: Attendance at appropriate internal BHI course modules and online courses

Objectives / project plan:

Year 1: Review literatures, gain programming skills, familiarize with target cohorts (e.g. Autism Early Diagnosis Study, National Child Development Study, Wirral Child Health and Development Study), begin to apply prototypical elements of models using both simulation and real data. Present preliminary findings.

Year 2: Elaborate prognostic implications from simulation and extend empirical analyses of cohort studies. Cross-cohort analysis. Paper submissions.

Year 3: For a single example evaluate scope for and implications of population and individual prediction. Thesis Write-up.

Two representative publications from supervisors:

1: Vidal-Ribas P, Pickles A, Tibu F, Sharp H, Hill J (2017) *Sex differences in the associations between vagal reactivity and oppositional defiant disorder symptoms.*
J Child Psychol Psychiatry. 58(9):988- 997. doi: 10.1111/jcpp.12750.

2: Salazar F, Baird G, Chandler S, Tseng E, O'sullivan T, Howlin P, Pickles A, Simonoff E. *Co-occurring Psychiatric Disorders in Preschool and Elementary School-Aged Children with Autism Spectrum Disorder.*(2015) Journal of Autism and Developmental Disorders 45(8) 2283-2294
DOI: 10.1007/s10803-015-2361-5

Keywords / phrases

Clinical Area/s:	Developmental cascade in childhood psychopathology Co-occurrence and multi-morbidity in adulthood Life course consequences of childhood adversity
Methodology	Stochastic process models Network transition model Multivariate growth

BRC Theme/s:
Affective Disorders and Interface with Medicine
Child and Neurodevelopmental Disorders
Dementia and Related Disorders
Lifestyle Substance use and Harms
Bioinformatics and Statistics
Clinical and Population Informatics

Project-003 | Multimorbidity patterns in Severe Mental Illness: The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) Case Register

Supervisors: Professor Richard Dobson and Doctor Rebecca Bendayan

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Project Description

Background: The Framework for Mental Health Research developed by the Department of Health (2017) has acknowledged the need to account for the interactions between mental and physical health to reduce the mortality gap between individuals with severe mental illnesses (SMI). Research to date in multimorbidity has been mainly focused in older adults and neglected this population. To identify underlying potential shared mechanisms in physical and mental health illness, we have first to identify common patterns of physical and mental health multimorbidity in this population and their progression patterns over time.

Novelty and Importance: From a clinical point of view, this project would allow to identify individuals at higher risk of complex multimorbidity (and consequently, disability and mortality) in SLaM, which could allow to develop targeted interventions earlier in time. From a methodological perspective, tools developed would be directly relevant and applicable to electronic health records collected by CRIS SLaM and other CRIS resources.

Primary aim(s): To identify the most common patterns of multimorbidity in individuals with SMI. This will provide an overview of which physical health conditions are more likely to appear in the first 5 and 10 years after diagnoses and whether these are associated with common risk factors such as age, sex, SMI medication, health behaviour and social and environmental factors at time of SMI diagnoses.
Specific objectives:

1. To develop data extraction tools using natural language processing techniques.
2. To explore which physical health conditions are more likely to develop at 5 and 10 years since SMI diagnoses.
3. To identify characteristics of individuals at higher risk of developing complex multimorbidity patterns at SMI diagnoses.

Planned research methods and training provided: BHI training and KCL early career training opportunities. Specific training on NLP and predictive statistical modelling (including machine learning techniques)

Objectives / project plan:

Year 1 (Objective 1): Literature review. CRIS data retrieval and preparation (including and NLP techniques).

Year 2 (Objective 2/3): Data analysis to identify the most common patterns of multimorbidity and associations with potential risk factors at time of SMI diagnoses. Paper submissions.

Year 3 (Objective 3): Data analysis to identify individuals at higher risk. Thesis and BRC report on potential clinical implications write up.

Project-003 Multimorbidity patterns in Severe Mental Illness: The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) Case Register

Two representative publications from supervisors:

1: Jackson, R. G., Patel, R., Jayatilleke, N., Kolliakou, A., Ball, M., Gorrell, G., ... & Stewart, R. (2017). Natural language processing to extract symptoms of severe mental illness from clinical text: the Clinical Record Interactive Search Comprehensive Data Extraction (CRIS-CODE) project. *BMJ open, 7*(1), e012012.

2: Wu, H., Toti, G., Morley, K. I., Ibrahim, Z. M., Folarin, A., Jackson, R., ... & Gorrell, G. (2018). SemEHR: A general-purpose semantic search system to surface semantic data from clinical notes for tailored care, trial recruitment, and clinical research. *Journal of the American Medical Informatics Association, 25*(5), 530-537.

Keywords / phrases

Clinical Area/s:	Multimorbidity Severe Mental Illness Lifestyle risk factors
Methodology	Natural Language Processing Longitudinal clustering techniques Machine Learning

BRC Theme/s:

Affective Disorders and Interface with Medicine
Obesity, Lifestyle and Learning from Extreme Populations
Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Clinical and Population Informatics

Project-004 | Precision medicine and mechanism: How and for whom do psychological treatments work?

Supervisors: Doctor Kimberley Goldsmith and Professor Rona Moss-Morris

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Project Description

Background: Understanding how treatments work (mechanisms) and for whom (in which subgroups) are key. Mediation and moderation analysis can answer such questions. Many mediation and outcome processes are longitudinal in nature and can be modelled using the structural equation modelling framework (SEM, Goldsmith et al, 2018 doi: 10.1037/met0000154). There is strong clinical interest in modelling overarching mediation and moderation processes, however these aspects are often studied separately and non-longitudinally. We will extend longitudinal mediation models to incorporate moderation transdiagnostically, using data from two large trials of cognitive behavioural therapies in chronic fatigue syndrome (PACE) and irritable bowel syndrome (ACTIB). This will include methods refinement and development for latent class moderating variable extensions, where individuals can be categorized according to clinically informative symptom groupings.

Novelty and Importance: Mediation and moderation analyses are necessary for targeting treatments to those who will best benefit, but these processes are often studied in isolation and cross-sectionally. This project would exploit datasets ideally designed for development of longitudinal explanatory precision medicine models incorporating mediation and moderation/latent variable moderators. Such models will have further scope to integrate adherence to treatment in a principled manner, realistically modelling processes together and allowing for the estimation of causal effects.

Primary aim(s): This cross-disciplinary project (psychology, statistics, medicine) will contribute to 1) methodological and clinical understanding of precision medicine and mechanisms relating to transdiagnostic cognitive behavioural treatments in chronic fatigue syndrome and irritable bowel syndrome and 2) will contribute more realistic and holistic mediation/moderation/adherence models, and code to run such models, to the literature.

Planned research methods and training provided: Translation of clinical questions into models/methods, R and Mplus software packages (or equivalent), and statistical simulation methods, as well as transferrable presentation, dissemination and collegial skills.

Objectives / project plan:

Year 1: Literature review, moderators added to longitudinal PACE mediation models, ACTIB mediation/moderation models in SEM.

Year 2: Inclusion of observed moderators, and methods for incorporating latent moderators, into mediation models.

Year 3: Simulation studies of model statistical properties of models and write-up of thesis.

Project-004 Precision medicine and mechanism: How and for whom do psychological treatments work?

Two representative publications from supervisors:

1: Goldsmith KA, Chalder TC, White PD, Sharpe M, Pickles A. Tutorial: Simplex, latent growth and latent change structural equation models for longitudinal mediation in the PACE trial of treatments for chronic fatigue syndrome. Psychological Methods, **2018,** 23(2):191-207. doi: 10.1037/met0000154.

2: Windgassen S, Moss-Morris R, Goldsmith K (joint last authors), Chalder T. Key mechanisms of cognitive behavioural therapy for irritable bowel syndrome: The importance of gastrointestinal specific cognitions, behaviours and general anxiety. Accepted by Journal of Psychosomatic Research. doi: 10.1016/j.jpsychores.2018.11.013

Keywords / phrases

Clinical Area/s:	Precision medicine Cognitive behavioural therapy Medically unexplained symptoms
Methodology	Mediation/Moderation Structural equation modelling Transdiagnostic

BRC Theme/s: Affective Disorders and Medicine
Obesity, Lifestyle and Learning from Extreme Populations
Bioinformatics and Statistics

Project-005 | Predicting diabetes in people with psychoses

Supervisors: Professor Daniel Stahl and Doctor Angus Roberts

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Project Description

Background: Diabetes diseases are a major cause of death, disability and reduction of quality of life for millions of people and treatment has placed a serious burden on healthcare systems. This situation is compounded for people with severe mental illness. 20-30% of patients with schizophrenia will develop diabetes or pre-diabetes during the course of psychiatric treatment, with up to 70% of cases are undiagnosed. This places a huge burden on patient, carer and the NHS.

Novelty and Importance: Integrated care initiatives in the NHS have paid insufficient attention to the relationship between physical and mental health. Current risk assessments underestimate the risk of cardiovascular related diseases such as diabetes in people with mental health problems. This project will develop a decision tool to screen for patients at risk of developing diabetes. This would allow monitoring persons at risk and to offer them early intervention

Primary aim(s): The aim of this project is to develop a decision support system to identify patients with severe mental health problems with a high risk for diabetes based upon routinely measured health records and existing databases from clinical studies in SLaM and KCL.

Planned research methods and training provided: The candidate will first establish a pipeline to link clinical databases and electronic patient health records data and develop a prediction model using machine learning methods to predict the risk of developing CVD and diabetes. Preliminary algorithms for identifying diabetes and risk were developed for CRIS data sets but need to be improved to obtain acceptable reliability. Two approaches will be compared: i) a regularized statistical modeling approach (lasso regression or boosted regression), which is easily interpreted and performs automatic variable selection and ii) random forests, which allow for implementation of more complex models at the expense of both interpretability and built in variable selection. The decision tool will be implemented in a web-based application at SLaM. Acceptance among clinicians will be assessed in a small feasibility study.

The student will gain relevant training in statistical methods, machine learning, and health informatics from the Department of Biostatistics and Health Informatics established education program.

Objectives / project plan:

Year 1: Development of pipeline between clinical databases, data extraction and preprocessing, upgrade proposal

- Training courses: Statistical programming, Prediction modelling, natural language processing

Year 2: Development of prediction models using machine learning methods

- Training courses: Machine learning

Year 3: Implementation of final decision tools as a web-based app, small pilot study of acceptance among clinicians, thesis write up.

Project-005 | Predicting diabetes in people with psychoses

Two representative publications from supervisors:

1: Iniesta, R. Stahl, D. and McGuffin (2016) Machine Learning, Statistical Learning and the Future of Biological Research in Psychiatry. Psychol Med. 2016 Sep;46(12):2455-65. doi: 10.1017/S0033291716001367.

2: Jackson, R. Kartoglu, I. Stringer, C. Gorrell, G. Roberts, A et al (2018) CogStack - experiences of deploying integrated information retrieval and extraction services in a large National Health Service Foundation Trust hospital. BMC Medical Informatics and Decision Making 18:47 doi: 10.1186/s12911-018-0623-9

Keywords / phrases

Clinical Area/s:	Psychosis Mental and physical health Diabetes
Methodology	Prediction modelling Machine learning Data linkage

BRC Theme/s: Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Clinical and Population Informatics

Project-006 | Transdiagnostic mechanisms in cognitive behavioural interventions for patients with Persistent Physical Symptoms: How do transdiagnostic psychological therapies work?

Supervisors: Professor Sabine Landau and Professor Trudie Chalder

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Project Description

Background: Persistent Physical Symptoms (PPS) such as chronic fatigue or pain are associated with profound disability and high health care costs. There is a body of evidence demonstrating that cognitive behavioural interventions can reduce levels of symptoms and improve functioning in a range of PPS. While it is standard clinical practice to adapt psychological therapies to the patient population it is not clear which components of the interventions are transdiagnostic, that is, address cognitive or behavioural responses shared by patients across the PPS spectrum, and which are disorder specific. Identifying such responses can help clinicians target core mechanisms and develop new psychological interventions for other PPS patient groups. This PhD project will develop and apply methods to model the similarities and differences in treatment mechanisms across PPS populations, and will provide an opportunity to develop knowledge of psychological theory and interventions and skills in biostatistics.

Novelty and Importance: The project will develop novel statistical modelling approaches so that existing data sources can be fully exploited to identify transdiagnostic mechanisms. The new methodology will be applied to understand how cognitive behavioural interventions work in patient populations with PPS, but the methodology will be relevant to the development of transdiagnostic psychological therapies more widely.

Primary aim(s): To identify components that represent transdiagnostic mechanisms of the cognitive and behavioural interventions in order to better target psychological interventions for patient groups with PPS.

Planned research methods and training provided: The student will have access research methods training provided by the BRC and to the programme of short courses on advanced statistical methodological provided by the Department of Biostatistics & Health Informatics. This will include training in structural equation modelling. In addition, the successful candidate will be able attend external training if required.

Objectives / project plan:

In year one, the student will carry out a systematic review of mechanistic theories in PPS and existing methods for assessing transdiagnostic mechanisms and will prepare individual participant data (IPD) from a number of CBT trials for pooling; likely to include the PACE trial for CFS (White et al 2011) and PRINCE Secondary trials for PPS in general. A number of putative mediators and effect modifiers have been measured across trials. This project will develop modelling techniques to assess whether mechanisms are shared across disorders or operate differentially. We envisage structural equation modelling and IPD meta-analysis/integrative data analysis techniques to play an important role (years 2 and 3).

Project-006 Transdiagnostic mechanisms in cognitive behavioural interventions for patients with Persistent Physical Symptoms: How do transdiagnostic psychological therapies work?

Two representative publications from supervisors:

1: Dunn G., Emsley E., Liu H., **Landau S.**, Green J., White I. & Pickles A. (2015) Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. *Health Technology Assessment* **19** (93) http://dx.doi.org/10.3310/hta19930

2: **Chalder T**., Goldsmith KA, White PD, Sharpe M, Pickles AR. (2015) Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *Lancet Psychiatry* **2** (2):141-52. doi.org/10.1016/S2215-0366(14)00069-8

Keywords / phrases

Clinical Area/s:	Persistent Physical Symptoms Cognitive Behavioural Therapy Transdiagnostic psychological therapies
Methodology	Integrative data analysis Mechanisms Trials

BRC Theme/s: Affective Disorders and Interface with Medicine
Bioinformatics and Statistics

Project-007 | Multi-modal objective measurement of emotional dysregulation in autism spectrum disorder and attention deficit hyperactivity disorder

Supervisors: Professor Emily Simonoff, Professor Tony Charman and Doctor Virginia Carter Leno

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Project Description

Background: Emotional dysregulation has been proposed as a trans-diagnostic construct that may underpin many forms of psychopathology. In particular, certain symptoms often present in neurodevelopmental disorders such as ASD and ADHD are theorized to be due to difficulties in emotion regulation. The nature of emotional dysregulation, and the underpinning neurocognitive and biological mechanisms are unknown. This project will take a trans-diagnostic approach to emotional dysregulation by exploring the presentation and underpinning mechanisms in ASD and ADHD.

Novelty and Importance: Symptoms related to emotional dysregulation are typically highly impairing and difficult to treat. Objectively measured emotional dysregulation has not been well studied in neurodevelopmentally disordered populations and from a transdiagnostic perspective. Conclusions will improve understanding of drivers of these symptoms and offer novel intervention strategies.

Primary aim(s): To delineate the neurocognitive mechanisms that underpin emotional dysregulation among children with ASD and ADHD, and test whether similar or distinct mechanisms of dysfunction are present across the two disorders.

Planned research methods and training provided: The candidate will examine a wide range of concurrent behavioural and physiological responses to challenges designed to elicit arousal/regulation. The RDoC framework will be used to guide the selection of specific tasks. Training will require consideration of how best to structure experimental challenges, measurement of arousal/regulation through both behavioural and neurocognitive (using electroencephalography; EEG) modalities, observer-rated responses and parent questionnaires and clinical interviews. Training will be provided in experimental design, measurement of neurocognitive functioning, and processing and analysis of experimental data.

Objectives / project plan:

Year 1: Literature review, strategically review existing datasets (SNAP, QUEST), acquire experience and skills in experimental programming and data capture, competence in EEG methodology.

Year 2: Refine programming ability, design and pilot experimental paradigms, data collection from ASD and ADHD populations.

Year 3: Data analysis, publication of initial findings and write up of dissertation.

The student will publish during the PhD and attend relevant national and international conferences. While there is already collected data available for analysis, there is much scope for the student to select cognitive domains of interest and design appropriate experiment tasks to assess cognitive functioning. The student will also receive specialized training in the use of brain imaging techniques (EEG) in clinical populations. For students with an interest in clinical aspects, the work programme can develop skills relevant to subsequent clinical training.

Project-007 Multi-modal objective measurement of emotional dysregulation in autism spectrum disorder and attention deficit hyperactivity disorder

Two representative publications from supervisors:

1: **Simonoff, E.**, Jones, C. R., Pickles, A. , Happé, F. , Baird, G. and **Charman, T.** (2012). Severe mood problems in adolescents with autism spectrum disorder. *Journal of Child Psychology and Psychiatry, 53:* 1157-1166.

2: Mikita N, Hollocks MJ, Papadopoulos AS, Aslani A, Harrison S, Leibenluft E, et al. (2015). Irritability in boys with autism spectrum disorders: an investigation of physiological reactivity. *Journal of Child Psychology and Psychiatry, 56:* 1118-1126.

Keywords / phrases

Clinical Area/s:	Autism spectrum disorder Attention deficit hyperactivity disorder Emotional dysregulation
Methodology	Electroencephalography (EEG) Neurocognitive tasks RDoC approach

BRC Theme/s: Child and Neurodevelopmental Disorders
Biomarkers and Genomics
Patient and Carer Involvement and Engagement

Project-008 | Predicting Neurodevelopmental Trajectories from EEG-based Brain Connectivity Assays

Supervisors: Doctor Charlotte Tye and Doctor Rosalyn Moran

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Project Description

Background: The past decade has witnessed an increase in the awareness of significant overlap between autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). Diverse behavioural and neurocognitive profiles identified in ASD and ADHD may reflect underlying abnormalities in brain circuitry, supported by findings from studies of neural connectivity. The majority of studies have focused on idiopathic (no known cause) cases of ASD and ADHD. An important line of enquiry involves investigation of brain circuitry in comparatively well-understood single-gene disorders that carry a high risk for neurodevelopmental impairment, such as tuberous sclerosis complex (TSC). In order to determine which abnormalities lie on the causal pathway from gene-brain-behaviour, the effect of TSC-associated brain lesions (cortical tubers) on the reorganization of neural networks needs to be clarified. Dynamic causal modeling (DCM) is a state-of-the-art technique that estimates the influence one brain system exerts over another and enables an evaluation of the impact of lesions on downstream functional connections (c.f. diaschisis). This approach is ideal for teasing apart the influence of structural brain differences on connectivity and neurocognitive markers of ASD/ADHD, to enable complementary parallel studies of idiopathic and syndromic cases and translation of findings into clinical care.

Novelty and Importance: A demonstration that the same connectivity markers associated with idiopathic cases of ASD and ADHD are shown in TSC and predict neurodevelopmental outcome from early in life will provide important insights into the biological alterations that underpin neurodevelopmental impairments. Ultimately this will inform early intervention approaches, which require objective brain-based markers that predict neurodevelopmental outcome, before ASD/ADHD behaviours can be reliably measured.

Primary aim(s): The aims of the PhD are to (i) map atypicalities in brain networks in idiopathic ASD and ADHD; (ii) investigate changes to brain networks that result from cortical tubers in TSC; (iii) identify predictive brain network markers of ASD and ADHD in TSC that account for cortical tubers using longitudinal data.

Planned research methods and training provided: The project involves a combination of analysis of large existing EEG datasets of ASD (n=400 from the EU-AIMS Longitudinal European Autism Project) and TSC (n=50) and collection of new data in infants and toddlers with TSC in an ongoing longitudinal study (n=60). The student will be trained in conducting connectivity analyses using DCM, infant behavioural, clinical and neurocognitive measures and longitudinal data analysis, to provide a unique interdisciplinary skillset.

Project plan:

Year 1: Training in EEG, DCM and neurodevelopmental measures; literature review; analysis of ASD/ADHD data.

Project-008 | Predicting Neurodevelopmental Trajectories from EEG-based Brain Connectivity Assays

Year 2: Analysis of TSC data; clinical/neurocognitive assessment of toddlers; feasibility study for early intervention.

Year 3: Longitudinal analysis of infant data; presentation of results; thesis completion.

Two representative publications from supervisors:

1: Tye, C. & Bolton, P. (2013). Neural connectivity abnormalities in autism: insights from the tuberous sclerosis model. BMC Medicine, 11(1), 55.

2: Tye, C. Varcin, K.J., Bolton, P., & Jeste, S.S. (2016). Early developmental pathways to autism spectrum disorders in tuberous sclerosis complex. Advances in Autism, 2(2).

Keywords / phrases

Clinical Area/s:	Autism ADHD Genetic syndromes
Methodology	EEG Dynamic causal modeling Longitudinal design

BRC Theme/s: Child and Neurodevelopmental Disorders
Bioinformatics and Statistics
Neuroimaging

Project-009 | Understanding the impact of psychiatric morbidity on employment and benefit changes: a data linkage project

Supervisors: Doctor Johnny Downs and Doctor Sharon Stevelink

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Project Description

Background: The biggest cause of long-term occupational disability is mental disorders. Research suggests that people with a disability (e.g. mental health, musculoskeletal conditions) are 32% less likely to be employed than those without. Further, only 3 in 100 of those who receive employment and support allowance stop receiving this each month. Therefore, it is important to understand the complex relationship between welfare, benefits and occupational needs of patients presenting with a mental health disorder.

Novelty and Importance: We have received ministerial approval to link Department for Work and Pensions (DWP) welfare and employment data with SLaM mental health electronic record data via Case Record Interactive Search (CRIS). These linked data sources will provide the largest clinical cohort of adults (> 380,000) referred to psychiatric services in the UK.

The student will contribute to accelerating our understanding about the dynamics between patients presenting with mental disorders, their occupational status and receipt of welfare benefits. Results will be promoted nationally and locally to directly impact NHS and DWP policies and current patient care.

Aim: To understand the impact of psychiatric morbidity on benefit changes and employment status.

Specific research questions include:

1. What are the underlying health reasons for those on incapacity benefits?
2. How does the likelihood of returning to work vary for different mental health diagnoses?
3. What patient or treatment characteristics are predictive of return to work?

These questions can be tailored to fit with the student's interest after discussion with the supervisors.

Planned research methods and training provided: The data linkage will be undertaken by the DWP. The student will be trained in how to apply quantitative data analyses techniques for longitudinal and cross-sectional data in the statistical packages STATA and MPlus. Training will be provided by KCL, but budget will be made available for external courses on a needs basis.

Project plan:

Year one
- Conduct literature review on 'what components of psychiatric morbidity predict occupational outcomes?'
- Write statistical analyses plan
- Preliminary analyses

Project-009 | Understanding the impact of psychiatric morbidity on employment and benefit changes: a data linkage project

Year two
- Submit systematic review for publication
- Continue data analyses

Year three:
- Finalise data analyses
- Write up thesis
- Write up scientific output

Expected outputs (end of year three):
- Organisation of successful PPI and stakeholder meetings at different stages throughout the PhD
- Dissemination of results at (inter) national speaking events
- At least three peer-reviewed scientific publications published or in preparation
- At least one policy brief written and circulated among stakeholders

Two representative publications from supervisors:

1: Perera G, Chang C, Broadbent M, Callard F, **Downs J**, …. Stewart R. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 2016, 6,3, 1-22.

2: **Stevelink SAM**, Jones N, Jones M, Dyball D, …. Fear, NT. Do serving and ex-serving personnel of the UK Armed Forces seek help for perceived stress, emotional or mental health problems? European Journal of Psychotraumatology 2019, online first.

Keywords / phrases

Clinical Area/s:	Mental health Psychiatry Occupational Health
Methodology	Data linkage Quantitative methods Big data

BRC Theme/s:

Affective Disorders and Interface with Medicine
Lifestyle Substance Use & Harms
Obesity, Lifestyle and Learning from Extreme Populations
Pain
Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Clinical and Population Informatics
Patient and Carer Involvement and Engagement
Translational Therapeutics

Project-010 | Adult phenotype associated with NRXN1 deletions

Supervisors: Professor Andre Strydom and Doctor Marija Petrinovic

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Project Description

Background: Deletions at 2p16.3 involving the NRXN1 gene are associated with autism, psychosis, seizures, and intellectual disability due to effects at synapses and transmission at both glutamatergic and GABAergic synapses via altered expression of neurexins and other proteins. Although the links with neurodevelopmental disorders have now been established, the penetrance and phenotype varies, and the clinical phenotype in adults (when psychiatric co-morbidity tend to develop) remain poorly defined. Furthermore, animal model studies have suggested a strong association with specific behavioural phenotypes, particularly aggression.

Novelty and Importance: There have been very few studies providing an in-depth description of the adult phenotype associated with NRXN1 mutations. We plan to fill this gap by using a translational approach linking findings in genetic and animal model studies with cognitive, behavioural, psychiatric and EEG assessment of affected individuals to better understand the adult characteristics of this disorder, with a particular focus on aspects such as aggression. Through this study, the student will identify cognitive and biological markers for adult behavioural phenotypes and inform treatment guidance, which can be later be back-translated into animal models to gain insights into mechanisms and to examine potential treatments.

Primary aim(s): This student will take a translational approach to undertaking an in-depth characterization of the adult phenotype of NRXN1 mutation using established assessment protocols from a NRXN1 child study in Ireland and the AIMS-2-TRIALS study, thus allowing for comparison with other cohorts.

Planned research methods and training provided: The student will gain transferable skills in specialist clinical, cognitive and EEG assessment and genetic analyses of neurodevelopmental disorders. S/he will benefit from input from clinical/neuroscience supervisors, and close collaboration with other researchers.

Objectives / project plan: Establish a cohort of ~30 individuals with NRXN1 mutations, recruited through clinical services, previous studies in ID individuals and a patient organization (Unique). Collect clinical, behavioural, cognitive and EEG data to explore specific hypotheses informed by animal model literature; phenotypes will be related to genetic factors (e.g. isoforms, exons involved, inheritance, additional CNVs).

Year 1: Training in assessments; setting up data and sample collection pipeline; starting recruitment.

Year 2: Ongoing recruitment and detailed assessment of participants; training in analysis

Year 3: Additional genotyping (using SNP arrays or other methods); EEG preprocessing and combined analyses.

The student will benefit from collaborations with Dr Louise Gallagher's group in Dublin and geneticists (Dr Andrew McQuillin, UCL).

Two representative publications from supervisors:

1: Thygesen, J. H., Wolfe, K., McQuillin, A., Viñas-Jornet, M., Baena, N., Brison, N., … **Strydom, A.** & Ruiz, A. (2018). Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders.
The British Journal of Psychiatry, *212*(5), 287-294.

2: Horder* J, **Petrinovic*** MM, Mendez MA, Bruns A, Takumi T, Spooren W, Barker GJ, Künnecke B, Murphy DG (2018). Glutamate and GABA in autism spectrum disorder-a translational magnetic resonance spectroscopy study in man and rodent models.
Translational Psychiatry. 8(1):106. doi: 10.1038/s41398-018-0155-1.

Keywords / phrases

Clinical Area/s:	Autism Psychosis/ schizophrenia Intellectual disability/ cognitive impairment
Methodology	Clinical studies Genotyping, using aCGH, SNP arrays, etc. EEG

BRC Theme/s: Child and Neurodevelopmental Disorders
Biomarkers and Genomics
Translational Therapeutics
BioResource

Project-011 | Born Bad? - Can we treat children at risk of becoming psychopaths

Supervisors: Doctor Michael Craig, Doctor Nigel Blackwood and Doctor Marija Petrinovic

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Project Description

Background: Conduct Problems (CP) are the commonest paediatric mental disorder and a huge burden to the affected individual and society.

'Parent training' programs are the primary interventions used to treat CP. However, RCTs report approximately 40% of children under 12-years-old still have significant CP after treatment completion (with poorer outcome in older children).

Medications are sometimes prescribed to CP children, particularly when psychological treatments fail, but their effect size, and the quality of supporting studies, is poor.

Consequently, there is a critical unmet need for research to develop new effective treatments for CP.

Novelty/Importance: CP comprise a heterogeneous group of conditions and targeting specific subgroups may optimise treatment success. Probably the most clinically important CP subgroup is defined by the presence, or absence, of callous unemotional traits (i.e. CU+/CU- respectively). CP/CU+ children are particularly unresponsive to established treatments, commit more violent crimes when younger and have high risk for developing adult psychopathy.

CP/CU+ children have a specific cognitive and neurological profile that contributes to their antisocial behaviour. For example, CP/CU+ individuals have reduced autonomic responsivity to stressful stimuli & hypo-sensitivity to punishment cues, and abnormalities in brain function in regions involved in processing of i) reward & punishment, and ii) facial emotion recognition & empathy.

One of the candidates that has been proposed to best account for these cognitive and neurological differences is the oxytocin (OXT) system.

However, no-one has tested whether modulating the OXT system in CP/CU+ children can 'shift' the abnormal neural processing towards 'normal'.

Primary aim(s): You will study, for the first time, whether 'single dose' intranasal OXT can modulate the abnormal neural processing (i.e. using *f*MRI), and/or behaviour (i.e. using Taylor Aggression Paradigm), in CP/CU+ children.

If your results are positive, they will form the basis of further work to accelerate the translation into the first therapeutic intervention(s) that target the OXT system in CP/CU+ children.

Training: Training in cutting edge, structural and functional brain imaging techniques with world leaders in this field at IoPPN(UK),UCL(UK), NIMH(USA).

Project-011 Born Bad? - Can we treat children at risk of becoming psychopaths

Project Plan:

Year 1: Recruit/scan children from pre-developed pipeline;

Year 2: Completion of recruitment and preliminary analysis;

Year 3: Completion of analysis; Writing up dissertation/papers; Present at International meetings.

Two representative publications from supervisors:

1: Anatomy of the dorsal default-mode network in conduct disorder: Association with callous-unemotional traits. Sethi, A., Sarkar, S., Dell'Acqua, F., Viding, E., Catani, M., Murphy, D. G. M. & Craig, M. C., Apr 2018, In: Developmental Cognitive Neuroscience. 30, p. 87-92.

2: The effect of intranasal oxytocin on neural response to facial emotions in healthy adults as measured by functional MRI: a systematic review. Tully, J., Gabay, A. S., Brown, D., Murphy, D. G. M. & Blackwood, N., 28 Feb 2018, In: Psychiatry Research. Neuroimaging. 272, p. 17-29.

Keywords / phrases

Clinical Area/s:	Conduct Disorder Callous Unemotional Oxytocin
Methodology	fMRI Pharmacological challenge Within-group balanced crossover design

BRC Theme/s:

Child and Neurodevelopmental Disorders
Biomarkers and Genomics
Neuroimaging
Translational Therapeutics
Clinical Research Facility

Project-012 | Can Targeting the serotonin (5-HT) system 'shift' the biology of Autism leading to a possible pharmacological treatment for core systems?

Supervisors: Doctor Eileen Daly and Dr Mark Tricklebank

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Project Description

Background: Autism Spectrum Disorder (ASD) is a highly genetic neurodevelopmental condition affecting 1% of the population with no effective drug treatments for the core symptoms of repetitive behaviours, and social/communication deficits. However, our recent work suggests a novel way forward by targeting the serotonin (5-HT) system.

One of the most consistently reported abnormalities in ASD is hyperserotonaemia (elevated blood levels of 5-HT ~30%) [1]. This study will provide proof of concept that attentuation of 5-HT differentially 'shifts' brain functional deficits in a subset of ASD individuals with hyperserotonaemia.

We've established that reduction in brain 5-HT by Acute Tryptophan Depletion (ATD) 'normalises' brain response in ASD when performing social and inhibition tasks during fMRI [2, 3]. However, it is not feasible to use ATD in a clinical setting. Hence, we tested the impact of a single dose of tianeptine (an atypical antidepressant enhancing synaptic reuptake of 5-HT) on brain function in ASD during performance of the same tasks. Like ATD, tianeptine abolished most functional brain deficits in ASD (Figure 1), and the degree of normalisation correlated with 5-HT blood levels and symptom severity [4].

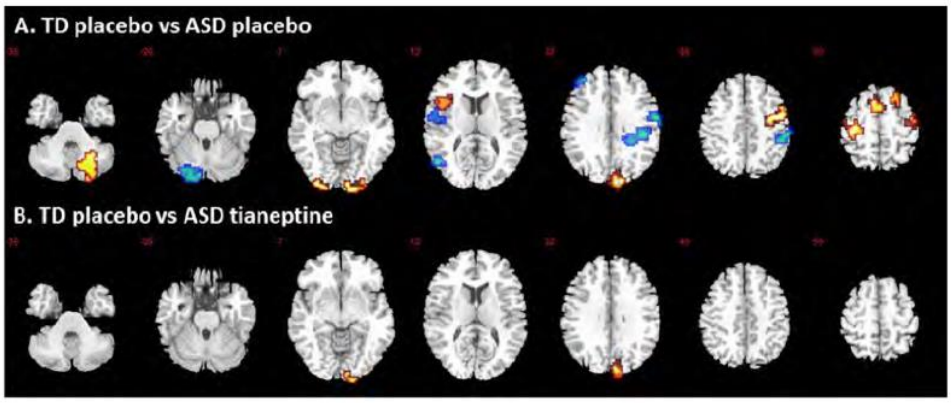

Figure 1. A./B. Brain activation map showing abnormally activated regions during successful response inhibition in ASD that were 'normalised' by tianeptine. Location of BOLD signal changes between groups. Blue: TD<ASD; Red: TD>ASD. Numeric label = z Talairach coordinate. Right hemisphere of brain is on the right side of the image.

Now we'll test potential 'personalised medicine' approach based on blood serotonin. In this study, we will stratify ASD individuals into normal and elevated serotonin and conduct the same fMRI tasks to evaluate if serotonin level is a precision biomarker of 'serotonergic sensitivity'.

Novelty and Importance: It is imperative to develop tools for individualized, precise pharmacological treatments for core symptoms of ASD. Novelty is proof of concept that circulating serotonin levels is a biomarker for response to tianeptine targeting ASD brain deficits. Hopefully, 'serotonergic sensitivity' biomarker can lead to 'fast fail' clinical trials to translate alleviation of core symptoms of ASD by prolonged drug treatment.

Primary aim(s): To evaluate if 'serotonergic sensitivity' (hyperserotonemia) as a biomarker for stratifying tianeptine's pharmacodynamic/target engagement (i.e. fMRI effects) in adults with ASD.

Project-012 Can Targeting the serotonin (5-HT) system 'shift' the biology of Autism leading to a possible pharmacological treatment for core systems?

Planned research methods and training provided: Pharmacological fMRI (phMRI). Randomised, double blind, placebo-controlled, 'shiftability' study of tianeptine to compare the brain functional response in 40 adults with ASD (20 with hyperserotonaemia).

Training on phMRI MRI as well as ASD clinical and neuropsychological assessments.

Objectives / project plan:

Year 1: Systematic review of ASD/5-HT. Develop expertise in patient recruitment & assessment. Learn phMRI, analysis of imaging and behavioural data.

Year 2: Complete recruitment, imaging and statistical analyses.

Year 3: Prepare and present data at international conference. Write PhD thesis along with high quality peer-reviewed publications.

This project is a clinical study within the European Commission IMI2 AIMS-2-TRIALS.

Two representative publications from supervisors:

1: Daly E, Deeley Q, Ecker C, et.al., (2012). Serotonin and the Neural Processing of Facial Emotions in Adults with Autism. An fMRI Study Using Acute Tryptophan Depletion. *Archive of General Psychiatry*. 69, 1003-1013.

2: Daly, E., Ecker C, Hallahan B, et.al., (2014). Response Inhibition and Serotonin in Autism: a Functional MRI Study Using Acute Tryptophan Depletion. *Brain*. 137, 2600-2610.

Keywords / phrases

Clinical Area/s:	Autism Neurodevelopment Serotonin
Methodology	Pharmacologic shiftability Tianeptine Task based fMRI

BRC Theme/s:

Child and Neurodevelopmental Disorders
Biomarkers and Genomics
Neuroimaging
Translational Therapeutics
BioResource

Project-013 | Emerging brain networks in babies vulnerable to neurodevelopmental conditions (Autism Spectrum Disorder and ADHD): An MRI study of fetal and neonatal brain.

Supervisors: Professor Grainne McAlonan and Doctor Dafnis Batalle

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Project Description

Background: Constant neural adjustments are needed to control the different brain states which support thinking, emotions and behavior. This Dynamic functional connectivity (dFC) can be captured at rest using functional (f)MRI. Abnormalities in dFC have been proposed to underpin cognitive and behavioural difficulties of neurodevelopmental conditions (NDD) such as autism spectrum disorder (ASD and ADHD); but, the evidence comes from individuals already diagnosed. This is problematic, because even in children it is very challenging to separate the primary mechanisms of a disorder from the secondary consequences and/or compensatory effects of living with a disorder. To truly understand the biology of these conditions we must look early, when the foundations of cognition and behaviour are established, and pathology linked to NDD emerges. Our group at King's is the first to use MRI look at the brain of individuals vulnerable to NDD in fetuses and shortly after birth.

Novelty and Importance: This will help us to: establish how genetic and/or prenatal environmental insults disrupt the emergence and function of fundamental brain networks; and ii) determine whether abnormalities in emerging neural networks at birth predict later outcomes. This will inform future tailored prevention efforts, reveal new treatment targets and identify those most in need of intervention at the earliest opportunity.

Primary aim(s): With access to the world's most advanced fetal and neonatal brain MRI protocols, the student will investigate how fetal and/or neonatal brain dFC is linked to NDD symptoms (or not) later in childhood. This will provide a means to subgroup the at-risk population earlier than ever before.

Planned research methods and training provided: We will use conventional analyses and graph theory approaches to fMRI to determine if there are underlying patterns in fetal and/or neonatal brain network organization and function which relate to childhood outcomes. Using machine learning approaches we will also identify predictors of specific NDD traits in childhood.

Objectives / project plan:

Year 1: Training in neuroimaging, graph theory and machine learning. Preliminary assessment of the data. Characterisation of brain network characteristics during early development. Hands-on involvement in on-going data collection. Training in relevant aspects of ASD and ADHD and mental health. Becoming confident in working with participants and their families.

Year 2: Characterisation of changes associated with ASD phenotypes. Exploration of novel graph theoretical features.

Year 3: Writing up analyses for publication. Explore novel multimodal methods (e.g. machine learning) to identify subgroups and predict outcome.

Project-013 Emerging brain networks in babies vulnerable to neurodevelopmental conditions (Autism Spectrum Disorder and ADHD): An MRI study of fetal and neonatal brain.

Two representative publications from supervisors:

1: Annual Research Review: Not just a small adult brain: understanding later neurodevelopment through imaging the neonatal brain. Batalle, D., Edwards, A. D. & O'Muircheartaigh, J., 2018, In : Journal of child psychology and psychiatry.

2: Ciarrusta, J, O'Muircheartaigh, J, Dimitrova, R, ……..McAlonan, GM. 2019 'Social Brain Functional Maturation in Newborn Infants With and Without a Family History of Autism Spectrum Disorder.' In Press *JAMA Network Open*

Keywords / phrases

Clinical Area/s:	Autism ADHD Perinatal Brain Development
Methodology	MRI Functional networks

BRC Theme/s: Child and Neurodevelopmental Disorders
Neuroimaging
BioResource

Project-014 | Shifting brain biology in Autism Spectrum Disorder.

Supervisors: Professor Declan Murphy and Professor Grainne McAlonan

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Project Description

Background: Treatment of Autism Spectrum Disorder (ASD) is challenging. Its etiology is poorly understood, and there are no means to 'fractionate' the spectrum into biologically homogeneous sub-groups to target with specific interventions. However, there is fresh hope, based on evidence that multiple risk factors for ASD converge to disrupt excitatory glutamate (E) and inhibitory GABA (I) neurochemical pathways in brain; which controls behavior and cognition.

We can now safely measure glutamate and GABA in the living human brain using [1H]Magnetic Resonance Spectroscopy (MRS). We can also measure the activity of circuits controlled by glutamate and GABA using functional (f)MRI. Finally, we can look at sensory processes thought to depend on glutamate and GABA using sensory tasks out of the scanner. This has enabled us to show that E/I chemistry and brain function is altered in different ways in ASD by the anti-glutamate and pro-GABA drug riluzole. Thus, for the first time, we have 'turned-the dial' on a potential pathological mechanism in ASD.

However, riluzole has broad effects across glutamate and GABA, and impacts on both neuronal and glial targets. Hence we now wish to better dissect the specific receptor pathways involved using more directed pharmacological probes of particular GABA receptor sub-types.

Primary aim(s): We are collaborating with industry (Astra Zeneca and Roche) and autism research charities (SFARI and Autistica) to test the impact of specific GABA receptor drugs on brain chemistry, fMRI, and sensory discrimination in adults with and without ASD.

Planned research methods and training provided: Glutamate and GABA levels in the prefrontal lobe will be measured using MRS; and whole brain functional connectivity measures will be acquired using fMRI. Data will be acquired 1 hour after active drug or placebo. Scans will be at least 1 week apart with drug/placebo order randomized and double-blind.

Objectives / project plan:

Year 1: Training in neuroimaging, neuropharmacology and statistics. Training in sensory testing. Preliminary assessment of the data. Hands-on involvement in data collection. Training in relevant aspects of ASD and and mental health. Becoming confident in working with participants and their families.

Year 2: Characterization of response differences/similarities in ASD and relationship with autistic traits.

Year 3: Writing up analyses for publication. Explore novel multimodal methods to identify responsivity differences.

Through-out: The student will be linked to EU-AIMS-2-TRIALS a consortium of industry and academic partners throughout Europe which will provide unmatched opportunities for training, networking and career development.

Project-014 | Shifting brain biology in Autism Spectrum Disorder.

Two representative publications from supervisors:

1: Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder. Pretzsch, C. M., Freyberg, J., Voinescu, B. I., Lythgoe, D. J., Horder, J., Mendez, M. A., Wichers, R. H., Ajram, L. A., Ivin, G., Heasman, M., Edden, R. AE., Williams, S. C. R., Murphy, D. G., Daly, E. & McAlonan, G. M., 6 Feb 2019, In : Neuropsychopharmacology.

2: Shifting brain inhibitory balance and connectivity of the prefrontal cortex of adults with autism spectrum disorder. Ajram, L. A., Horder, J., Mendez, M. A., Galanopoulos, A., Brennan, L. P., Wichers, R. H., Robertson, D. M., Murphy, C. M., Zinkstok, J., Ivin, G., Heasman, M., Meek, D., Tricklebank, M. D., Barker, G. J., Lythgoe, D. J., Edden, R. A. E., Williams, S. C., Murphy, D. G. M. & McAlonan, G. M., 23 May 2017, In: Translational psychiatry. 7, 5, e1137.

Keywords / phrases

Clinical Area/s:	Autism ADHD Psychopharmacology
Methodology	MRI MRS Sensory processing

BRC Theme/s: Child and Neurodevelopmental Disorders
Neuroimaging
Translational Therapeutics
BioResource

Project-015 | Using Neuroadaptive Bayesian Optimisation to identify biomarkers for Autism Spectrum Disorders

Supervisors: Doctor Eva Loth and Professor Robert Leech

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Project Description

Background: There is great interest in applying precision medicine to autism to target therapies based on an individual's neurobiological profile. Progress depends on availability of reliable biomarkers for patient stratification and sensitive 'surrogate end-points' to test treatment effects (including in young children and individuals with intellectual disability). This PhD is embedded in our larger efforts to develop/ validate these tools by combining novel conceptual approaches with cutting-edge AI methods. We capitalize on our recently developed Bayesian Adaptive Optimization methodology to create individual neurocognitive fingerprints of weaknesses/ strengths across six fundamental social/emotional/motivational/cognitive domains and map those onto particular symptom profiles/trajectories, as well as underlying mechanisms. We adopt a brain-circuit approach to identify individual neurofunctional profiles for use as stratification markers, and a more scalable behavioural approach to measure treatment effects.

Novelty and Importance: 1. We are currently combining age-appropriate cartoons with BAO to optimize a behavioural tablet battery that spans the six domains across ages and (dis)ability ranges. 2. We are also creating a cognitive task space tapping two key networks implicated in autism and use BAO with real-time fMRI to find tasks that maximally dissociate the networks.

Primary aim(s): Building on this existing work: apply BAO to (1) optimize a novel tablet task battery for use as surrogate end-point; and (2) to identify robust neuro-functional stratification biomarkers.

Planned research methods and training provided: Over the PhD, the student will be trained in core behavioural and neuroimaging skills and the BAO approach; fMRI and behavioural data acquisition with healthy and ASD populations, clinical measures of autism, and psychometric analyses.

Objectives/project plan:

Year 1: Create normative ranges of the tablet tasks, providing the input for the BAO algorithm; and establish test-retest and construct validity of the tests. Contribute to recruitment and behavioural testing of neurotypical and autistic volunteers (3-45 years).

Year 2: (i) Behavioural testing of the optimized BAO version with ASD individuals (recruited through AIMS-2-TRIALS). Link individual bio-behavioural fingerprints to symptom severity. **(ii)** Building on the existing fMRI BAO work, the student will apply this approach to 30-40 autistic people, quantifying atypicalities in specific networks, relating individual neurofunctional fingerprints to behavioural/clinical profiles.

Year 3: Assess 'sensitivity to change' of the relevant BAO tablet tests by include them in a AIMS-2-TRIALS funded 'fast fail' trial, which tests the effect of a pharmacological treatment on brain function and a clinical outcome.

By leveraging the AIMS-2-TRIALS cohorts, the project is viable and cost-effective.

Project-015 Using Neuroadaptive Bayesian Optimisation to identify biomarkers for Autism Spectrum Disorders

Two representative publications from supervisors:

1: Lorenz, R., Hampshire, A., & Leech, R. (2017). Neuroadaptive Bayesian Optimization and Hypothesis Testing. *Trends Cogn Sci, 21*(3), 155-167. doi:10.1016/j.tics.2017.01.006

2: Loth, E., Spooren, W., Ham, L. M., Isaac, M. B., Auriche-Benichou, C., Banaschewski, T., . . . Murphy, D. G. (2016). Identification and validation of biomarkers for autism spectrum disorders. *Nat Rev Drug Discov, 15*(1), 70-73. doi:10.1038/nrd.2015.7

Keywords / phrases

Clinical Area/s:	Biomarkers Autism Neurodevelopmental Disorders
Methodology	Neuroimaging Neuroadaptive Bayesian Optimization Psychometric validation

BRC Theme/s:

Child and Neurodevelopmental Disorders
Bioinformatics and Statistics
Biomarkers and Genomics
Neuroimaging

Project-016 | Improving the care of people with diabetes and severe mental illness, using experience-based co-design.

Supervisors: Professor Alan Simpson and Doctor Sara Donetto

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Project Description

Background: People with a severe mental illness (SMI) such as schizophrenia or bipolar disorder have an increased risk of developing type 2 diabetes mellitus (T2DM), which is attributed to physical inactivity, obesity, anti-psychotic medications and high rates of smoking. Those with T2DM and SMI face significant health inequalities compared to those with T2DM alone, such as premature death, increased T2DM complications and considerable variations in diabetes care. Those with SMI may be less likely to receive a range of screening, treatments and diabetes education, and are also less likely to receive hospital care. The primary supervisor led a programme of mixed-methods research with service users and healthcare staff to explore these inequalities and identify facilitators and barriers to self-management of T2DM in people with SMI. These results were mapped against the TDF to identify potential behavioural change targets for inclusion in future interventions.

Novelty/Importance: The student will draw on our theory-informed research and undertake a systematic review of related literature to inform discussions about the design of an intervention. Employing the innovative experienced-based co-design (EBCD) approach, the student will engage service users, carers and healthcare staff to 1) develop an intervention to improve self-management of T2DM in people with SMI, and 2) co-design components of a feasibility study. Implementation and delivery of the intervention will then be feasibility tested, and the process evaluated with participants.

Recent well-designed UK trials, PRIMROSE, STEPWISE and IMPaCT, aimed to improve the physical health of people with SMI however, failed to achieve significant results on their primary outcomes illustrating the importance of further study to address this urgent and costly healthcare challenge.

Primary aim(s): The aim is to create and feasibility test a theoretically- and evidence-based intervention, to improve self-management of T2DM in people with SMI.

Planned research methods/training:

- Systematic literature review
- Theoretical Domains Framework
- Experience-based co-design
- Qualitative/quantitative research methods/analysis

Objectives/project plan:

Year 1: Identify evidence and develop theory: systematic literature review; experienced-based data gathering with service users, carers and healthcare staff.

Project-016 Improving the care of people with diabetes and severe mental illness, using experience-based co-design.

Year 2: Modelling intervention: EBCD events to develop intervention(s) and co-design components of feasibility study.

Year 3: Feasibility study and process evaluation with participants: identify key components/changes required for full-scale RCT.

Two representative publications from supervisors:

1: Mulligan, K., McBain, H., Lamontagne-Godwin, F., Chapman, J., Flood, C., Haddad, M., Jones, J. & **Simpson, A.** (2018). Barriers to effective diabetes management - a survey of people with severe mental illness.
BMC Psychiatry, 18(1). doi:10.1186/s12888-018-1744-5.
https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-018-1744-5

2: McBain, H., Lamontagne-Godwin, F., Haddad, M., **Simpson, A.,** Chapman, J., Jones, J., Flood, C. & Mulligan, K. (2018). Management of type 2 diabetes mellitus in people with severe mental illness: An online cross-sectional survey of healthcare professionals.
BMJ Open, 8(2). doi:10.1136/bmjopen-2017-019400. https://bmjopen.bmj.com/content/8/2/e019400

Keywords / phrases

Clinical Area/s:	Type 2 diabetes mellitus Psychosis Integration of metal and physical healthcare
Methodology	Theoretical Domains Framework/Behaviour Change Techniques Experience-based co-design Mixed methods feasibility studies

BRC Theme/s:
Lifestyle Substance Use & Harms
Obesity, Lifestyle and Learning from Extreme Populations
Psychosis and Neuropsychiatry
Patient and Carer Involvement and Engagement

Project-017 | Investigating the interface between physical and mental health during adolescence among diverse communities in inner-city London

Supervisors: Professor Craig Morgan and Doctor Gemma Knowles

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Project Description

Background: Our understanding of the directionality and mechanisms of relationships between physical health, mental health, and health behaviours is limited. As a result, it is unclear when or how to intervene to prevent declines in physical health and to improve health behaviours in those with mental health difficulties, and vice versa.

Adolescence is a critical period of emotional, behavioral and physical development. It is the period in which many lifelong health behaviors are established (e.g., smoking, physical activity, diet) and many mental health difficulties (e.g., worry, low mood) and sub-clinical physical health problems (e.g., obesity, high blood pressure) emerge. Prospective data on the physical-mental health interface during this key development phase could, then, be crucial in informing the timing and design of interventions.

Novelty and Importance: Around 12-18% (£8-13 billion) of annual NHS expenditure on long-term physical conditions is linked to poor mental health, and those with mental health problems have an average life expectancy of around 10-20 years lower than those without mental health problems. This is a public health tragedy. The evidence suggests that around a third of this premature mortality is due to impaired cardiovascular health in those with mental health problems. Preventing declines in cardiovascular health and health behaviors among those with mental health problems is a public health priority.

REACH provides a unique platform to examine the physical-mental health interface through adolescence and the transition to adulthood. REACH is a highly diverse cohort and the largest of its kind in the UK (n>4000, 11-14y at baseline; >80% minority ethnic groups). Those taking part have provided detailed information on physical health (e.g., BMI, existing health conditions), mental health (e.g., worry, mood, behaviour, self-harm) and health behaviours (e.g., physical activity, sleep, substance use, smoking) at three timepoints. Hair cortisol and DNA collection, and linkage to education and health records, are ongoing. The fourth wave of data collection (16-18yrs) will begin in 2020.

Primary aim(s): To examine prospective associations between physical health, mental health, and health behaviours during adolescence, and variations by age, gender and ethnic group.

Planned research methods and training provided: The student will receive training in the advanced statistical methods required for this project: multi-level modelling, structural equation modelling, growth mixture modelling.

Objectives/project plan:

Year 1:
- Training
- Writing: literature review; methods; analysis plan
- Data collection: Wave 4 physical health measures

Project-017 Investigating the interface between physical and mental health during adolescence among diverse communities in inner-city London

Year 2:
- Data cleaning
- Analyses

Year 3:
- Write-up
- Dissemination

Two representative publications from supervisors:

1: Das Munshi, J., Ashworth, M., Dewey, M., Gaughran, F., Huss, S., **Morgan, C.**, Nazroo, J., Petersen, J., Schofield, P., Stewart, R., Thornicroft, G., Prince, M. (2017) Type 2 diabetes mellitus in severe mental illness; inequalities by ethnicity and age. Cross-sectional analysis of 588,408 records from the UK. *Diabetic Medicine*, 34, 916-924.

2: Das-Munshi, J., Ashworth, M., Gaughran, F., Hull, S., **Morgan, C.**, Nazroo, J., Roberts, A., Rose, D., Schofield, P., Stewart, R., Thornicroft, G., & Prince, M. (2016) Ethnicity and cardiovascular health inequalities in people with severe mental illnesses: protocol for the E-CHASM study. *Social Psychiatry and Psychiatric Epidemiology*, 51(4), 627-38

Keywords / phrases

Clinical Area/s:	Mental health Physical activity Obesity
Methodology	Accelerated cohort study Growth mixture modelling Structural equation modelling

BRC Theme/s: Lifestyle Substance Use & Harms
Obesity, Lifestyle and Learning from Extreme Populations
Clinical and Population Informatics

Project-018 | Patterns of Brain Connectivity that Encourage Hallucinatory Percepts in the Auditory Domain

Supervisors: Doctor Rosalyn Moran, Professor Sukhi Shergill and Doctor Erik Fagerholm

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Project Description

Background: Synchronization of information across disparate parts of the brain is required to process auditory inputs such as speech and music. Desynchronization – i.e. isolating only relevant brain connections, is a second critical mechanism. It is thought that this inability to suppress connections, particularly those within and between the temporal lobes may underlie the hallucinations observed in patients with schizophrenia. In this project we will use a recently developed model of brain synchronization (Fagerholm et al. 2018) to understand how connectivity profiles depend on the content of an auditory signal (i.e. its semantic features) and how they are distinct from those connections responsible for isolating self-generated 'internal' audition. As well as the presence or absence of connections within the brain, the project will examine the direction of connections.

Novelty and Importance: To date, several studies have shown that temporal lobe connections to prefrontal cortex are abnormal in patients with psychosis and in animal models of psychosis (Moran at al 2014). However, whether the abnormalities are context-dependent, and under what conditions they may be exacerbated remains unknown. In this study we will take advantage of a novel imaging protocol – so-called 'silent' fMRI to test for changes in networks that configure and reconfigure for particular classes of auditory stimuli. We will also develop an in silico model of the patient network to demonstrate putative benefits of targeted stimulation based interventions.

Primary aim(s), Objectives / project plan: We will use a 2x2 task design to test for hierarchical network activity patterns that underlie complex vs. simple and internally vs. externally generated sounds. Our complex stimuli will involve semantically rich spoken sentences aimed to evoke strong left temporal – frontal connections and will be compared to frequency-matched tone-based stimuli of similar duration and predictability designed to elicit lower-level temporal activations. For the internally generated stimuli we will ask participants to silently read those same sentences and letters (matching for tones), to test for motor suppression effects in auditory regions.

We hypothesize that controls use inhibitory top-down connections to suppress auditory regional activities during silent reading and that these connections are weaker or absent in patients.

Planned research methods and training provided:

Year 1: Literature review, training in MRI data acquisition & data acquisition.

Year 2: Training in computational modeling & model-based data analysis. Comparison of connectivity modeling methods.

Year 3: Develop in silico model of the patient network and test connectivity changes of targeted stimulation-based interventions

Project-018 Patterns of Brain Connectivity that Encourage Hallucinatory Percepts in the Auditory Domain

Two representative publications from supervisors:

1: ***Moran R***, Jones* M, Blockeel A, Adams RA, Stephan KE, Friston K. (2015). Losing control under ketamine: suppressed cortico-hippocampal drive following acute ketamine in rats. *Neuropsychopharmacology 40:* 268-277.

2: **Moran RJ**. (2018) Disease strays to evolution's bounds. *Nature Neuroscience,* doi: 10.1038/s41593-018-0199-9.

Keywords / phrases

Clinical Area/s:	Psychosis Schizophrenia Mental Health Intervention
Methodology	fMRI Computational Modeling In Silico tDCS

BRC Theme/s: Psychosis and Neuropsychiatry
Neuroimaging

Project-019 | Understanding Pain and Treatment Response in Neurodegenerative Disease

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Project Description

Background: There are currently 35 million people worldwide living with dementia. Estimates suggest that between 30-60% of these individuals live with daily pain, but pain is often overlooked when considering their treatment. Existing pharmacological therapies offer limited efficacy, irrespective of any side effects. Our understanding of how these treatments work remains relatively poor, nor do we fully understand how neurodegenerative diseases perturb how the brain represents pain and responds to treatment. The proposed project, using functional magnetic resonance imaging (fMRI), aims to characterise the experiences of evoked and ongoing pain in patients with two common neurodegenerative disorders, Alzheimer's and Parkinson's disease. We will compare these patients to healthy, pain free individuals. We will also study the analgesic effects of remifentanil, a potent opioid, in these three groups.

Novelty and Importance: Chronic pain is a major burden worldwide. The prevalence of patients with chronic pain continues to increase and we struggle to treat them quickly and effectively. To date we work under the assumption that treatment response to opioids is not affected by neurodegenerative disease, but preclinical evidence suggests that opioidergic tone may well be altered in these patients. Improving our understanding of how the brain in AD and PD represents the pain experience and responds to treatment should enable more timely and appropriate future direction of healthcare resources.

Primary aim(s): To understand the brain representation of evoked and ongoing pain in AD and PD;
To understand how the effect of acute opioid administration on evoked and ongoing pain in these patients;

Planned research methods and training provided: The successful candidate will have the opportunity to work at the heart of three vibrant, pioneering KCL research groups, specialising in pain and neuroinflammation (Malcangio), neurodegeneration (Chaudhuri) and neuroimaging (Howard). The student will receive interdisciplinary training in fMRI acquisition, analysis and interpretation, psychometric, psychophysical and clinical investigative techniques.

Objectives / project plan:

Year 1: Within the first year, the student will have optimised a multimodal protocol for examining evoked and background pain in patients with neurodegenerative disease.

Year 2: In year two, further investigation of modulation of pain in these patients using remifentanil will be undertaken.

Project-019 | Understanding Pain and Treatment Response in Neurodegenerative Disease

Year 3: In year three, the student will disseminate their findings to their public and their academic peers. The candidate will be expected to present at relevant international conferences (e.g. IASP) and author publications in high impact journals.

Two representative publications from supervisors:

1: Hodkinson, D. J., Khawaja, N., O'Daly, O., Thacker, M., Zelaya, F. O., Wooldridge, C. L., **Howard, M. A.** (2015). Cerebral analgesic response to non-steroidal anti-inflammatory drug ibuprofen. Pain, 156(7), 1301-1310.

2: Aman, Y., Pitcher, T., Simeoli, R., Ballard, C. & **Malcangio, M.** (2016) Reduced thermal sensitivity and increased opioidergic tone in the TASTPM mouse model of Alzheimer's disease. Pain. 157, 10, p. 2285-2296

Keywords / phrases

Clinical Area/s:	Pain Parkinson's disease Alzheimer's disease
Methodology	Resting state fMRI Evoked-response fMRI Psychopharmacology

BRC Theme/s:

Dementia and Related Disorders
Pain
Neuroimaging
Translational Therapeutics
Clinical Research Facility

Project-020 | Cannabidiol for psychosis in neurodegenerative disorders

Supervisors: Doctor Latha Velayudhan and Doctor Sagnik Bhattacharyya

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Project Description

Background: No approved treatments are available for psychosis in patients with Alzheimer's disease (ADP) and Parkinson's disease (PDP), which are particularly disabling, and cause much suffering. Existing antipsychotics have only modest benefits and significant side-effects.

Randomised clinical trials (RCTs) in people with psychosis indicate that cannabidiol has antipsychotic effects and is well-tolerated. Work from Bhattacharyya's group has shown that a single dose of cannabidiol partially normalises brain function abnormalities in the striatum and medial temporal cortex in early psychosis. Whether cannabidiol may have a similar effect in people with PDP and ADP remains unclear. The present proposal aims to investigate this.

Novelty and Importance: Cannabidiol is one of the most promising novel treatments in mental health, and its mechanism of action especially in psychosis associated with neurodegenerative disorders remains unclear.

Primary aim(s): To investigate-

1. The neurophysiological mechanisms underlying the antipsychotic effects of cannabidiol in ADP and PDP.
2. The relationship between effects of cannabidiol on brain function and symptomatic response.

Planned research methods and training provided: Acquisition & analysis of neuroimaging and cognitive data. Evaluation of novel treatments; clinical research in neurodegenerative disorders; industrial collaboration.

Objectives / project plan:
The proposed PhD will involve 2 components. Projects 1 and 2 will be nested within RCTs in ADP and PDP respectively, with identical designs.

Design: Double-blind, parallel-arm, placebo-controlled RCT. Participants (n=32 in each RCT) will be randomised to one of two treatment arms (n=16 per arm) in each RCT (in ADP and in PDP). In each RCT, patients will receive:

i. Treatment as usual (TAU) + Cannabidiol or
ii. TAU + Placebo.

TAU will involve routine treatment in AD or PD.

Experimental Treatment: Oral cannabidiol, 600mg/day or matched placebo for 6 weeks.

Participants: Adults (50-85 years) meeting the diagnostic criteria for AD and PD with psychosis will be recruited from those participating in 2 separate RCTs at KCL.

Assessments: Neuroimaging data (verbal learning and resting state fMRI) will be acquired on a 3T MRI scanner using established protocols twice: at baseline and at the end of 6-week treatment. Psychopathology and cognition will be assessed at same timepoints. The PhD student will investigate the effect of CBD treatment on the fMRI BOLD signal.

Analyses: Neuroimaging data will be analysed using established software.

Timetable;

Year 1: Liaison with RCT team; subject enrolment; data collection.

Year 2: Data collection; Industrial secondment.

Year 3: Data analyses; Dissemination; Submission of PhD

Two representative publications from supervisors:

1: Bhattacharyya S, Wilson R, Appiah-Kusi E, et al. Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. *JAMA Psychiatry.* 2018;75(11):1107-1117.

2: Velayudhan L, Van Diepen E, Marudkar M, Hands O, Suribhatla S, Prettyman R,Murray J, Baillon S, Bhattacharyya S. Therapeutic Potential of Cannabinoids in Neurodegenerative Disorders: A Selective Review. *Curr Pharm Des*. 2014;20(13):2218-30.

Keywords / phrases

Clinical Area/s:	Alzheimer's dementia Parkinson's disease Psychosis
Methodology	Randomised controlled trial fMRI

BRC Theme/s: Dementia and Related Disorders
Neuroimaging
Translational Therapeutics
Clinical Research Facility

Project-021 | Mapping individual differences in the neuroanatomy of dementia

Supervisors: Professor Dag Aarsland, Doctor James Cole and Professor Andre Marquand (Radboud University)

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Project Description

Background: Currently, dementia trials are designed to detect group-level differences in MRI biomarkers (e.g., whole-brain or hippocampal atrophy) between treatment and placebo groups, making the flawed assumption of within-group neuroanatomical homogeneity. Moreover, this does not match clinical practice, where treatments must be allocated individually to patients. Positive findings are scarce, potentially because this approach does not capture individual neuroanatomical differences in neurodegeneration. Given the pronounced heterogeneity in the clinical presentation of diseases like Alzheimer's, Parkinson's, or Lewy body dementia, methods are needed to characterise the underlying heterogeneity in brain structure, that likely better map to the observed clinical variability.

Novelty and Importance: Here, we will move beyond simple group-averages towards mapping individual differences, utilising advanced statistical methods for normative modelling of neuroimaging data pioneered by **Dr Marquand**. These methods have already provided new insights into the diverse neuroanatomical consequences resulting from psychosis and autism; this project will be the first application in dementia. By overcoming the assumption of homogeneity in clinical trials of dementia treatments, which may have led to numerous false negatives, we have an important opportunity to reconsider the efficacy of previously failed interventions, using a more sensitive and appropriate statistical approach.

Primary aim(s):

i. Map the individualised neurobiological fingerprints in people with neurodegenerative diseases.
ii. Relate measures of neuroanatomical deviation (from the norm) to the risk of cognitive decline and disease progression in pre-symptomatic patients.
iii. Revisit clinical trial MRI biomarker data, to investigate how treatments influence individual differences in brain structure, rather than group averages.

Planned research methods and training provided: Visit to Donders Institute, student to learn normative modelling method (Dr Marquand). Student will receive training in advanced statistics and neuroinformatics (Dr Cole) and attend IoPPN courses (e.g., *Predictive Modelling*). Expertise in dementia and clinical trials will be provided by Prof. Aarsland.

Objectives/project plan:

Year 1: Donders visit (normative modelling training). Apply normative models to dementia patients from public (Alzheimer's Disease Neuroimaging Initiative [ADNI]; Parkinson's Progressive Markers Initiative [PPMI]) and local datasets (Norwegian Dementia Disease Initiation study; European Dementia Lewy Body cohort; Maudsley BRCAD).

Year 2: Apply normative models to pre-symptomatic or mild cognitive impairment patients (from ADNI, PPMI, Maudsley BRCMEM/BRCDEM studies). Relate deviations from normative models to disease progression risk.

Project-021 | Mapping individual differences in the neuroanatomy of dementia

Year 3: Apply to clinical trial data to re-evaluate treatment effectiveness. Treatment data obtained from ADNI, BRCAD (linked to CRIS), the Global Alzheimer's Association Interactive Network and through collaboration with academic and industrial partners.

Two representative publications from supervisors:

1: Wolfers, T., Doan, N. T., Kaufmann, T., Alnæs, D., Moberget, T., Agartz, I., . . . **Marquand, A. F.** (2018). Mapping the Heterogeneous Phenotype of Schizophrenia and Bipolar Disorder Using Normative Models. JAMA Psychiatry, 75(11), 1146-1155.

2: Litvan, I., Kieburtz, K., Tröster, A. I., & **Aarsland, D**. (2018). Strengths and challenges in conducting clinical trials in Parkinson's disease mild cognitive impairment. Movement Disorders, 33(4), 520-527.

Keywords / phrases

Clinical Area/s:	Neurodegenerative disease Dementia Pre-symptomatic
Methodology	Neuroimaging Normative modelling Precision health

BRC Theme/s: Dementia and Related Disorders
Biomarkers and Genomics
Neuroimaging

Project-022 The electrophysiology of synaptic potentiation in human visual cortex as a biomarker for prodromal dementia.

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Project Description

Background: Synapses, the chemical junctions between brain cells, provide the route of information transfer in the brain. They can change in strength to store memory and dysfunction of this process is thought to be the earliest dysfunction in neurodegenerative disease. Studies of synaptic neurophysiology rely on pre-clinical animal models as there is currently an absence of methods to explore synaptic-level alterations within specific cortical circuits non-invasively in man. However, recent reports of long-term potentiation-like (LTP) enhancement of sensory evoked potentials after simple stimulation in human studies offer promise of a translational bridge between pre-clinical and clinical studies.

Novelty and Importance: The project would be the first to explore the detailed cortical circuitry of LTP non-invasively in man and apply the findings to clinical populations with prodromal dementia. The importance of the project would be in providing a new clinical measure of synaptic change at the earliest stage of dementia that could be used to detect neurodegenerative disease before the onset of measurable symptoms and as a target for drug trials of new dementia treatments.

Primary aim(s): To develop a clinical assay of synaptic function for use in neurodegenerative disease

Planned research methods and training provided: The project will develop novel measures of LTP in specific visual circuits using electroencephalography (EEG) and event-related potentials (ERPs). The measures will be based on responses to standard visual stimuli presented before and after brief periods of tetanic (high frequency) visual stimulation. The basic methodology has already been used in the Ffytche lab for pharmacological studies but will be adapted in the studentship based on pre-clinical work in the Cooke lab using monocular and binocular stimulation at different visual field locations to investigate specific cortical circuits. The assay will be developed and tested with the help of patients with prodromal Alzheimer's disease, dementia with Lewy bodies and age matched controls recruited from BRC dementia cohorts. Training will be provided in EEG acquisition and analysis, synaptic neurophysiology and clinical assessments.

Objectives / project plan:

Year 1: Develop the synaptic plasticity assay and adapt it for clinical populations in collaboration with patients. Explore links between visual synaptic function and measures of cognitive and higher visual function.

Year 2: Cross-sectional study of prodromal dementia cohorts and age-matched controls.

Year 3: Follow-up of participants to examine progression of synaptic changes over a year.

The focus of the study is on visual plasticity but it is envisaged an equivalent assay will be developed for the auditory and somatosensory systems within the studentship to examine similarities and difference in synaptic dysfunction across different cortical systems.

Project-022 The electrophysiology of synaptic potentiation in human visual cortex as a biomarker for prodromal dementia.

Two representative publications from supervisors:

1: Cooke SF, Komorowski RW, Kaplan ES, Gavornik JP and Bear MF (2015) Visual Recognition Memory, Manifested as Long-term Habituation, Requires Synaptic Plasticity in V1. Nature Neuroscience. 18: 262-271.

2: Cooke SF and Bliss TVP (2006) Plasticity in the Human Central Nervous System. Brain. 129(7): 1659-73.

Keywords / phrases

Clinical Area/s:	Prodromal dementia Mild cognitive impairment LTP
Methodology	EEG Evoked potentials

BRC Theme/s: Dementia and Related Disorders
Biomarkers and Genomics

Project-023 | How do resilient communities protect people with severe mental illnesses from death? Mixed methods study of local populations.

Supervisors: Doctor Jayati Das-Munshi, Professor Dame Til Wykes and Professor Craig Morgan

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Project Description

Background: People with severe mental illnesses (SMI) such as schizophrenia experience an 11-17 year reduction in life expectancy compared to the general population, mostly from preventable physical causes. This excess risk of death shows strong variation by geographical area and for example is lower for certain ethnic minority groups in areas of higher own group density.

The aim of this mixed-methods proposal is to understand this variation, by using data to map areas of higher/ lower mortality in SMI, followed by qualitative interviews with people with SMI living in these areas, and with community-based organisations, helping to identify factors contributing to **'community-level resilience'**.

Novelty and Importance: Current interventions to address premature mortality in SMI have focused on addressing individual-level risk factors, however, an emerging body of work has suggested that social factors (such as social capital, networks and support) situated in resilient communities, could play a role in buffering against the risk of premature deaths in this group. The project will utilize data from the Clinical Records Interactive Search (CRIS) to map mortality patterns in SMI across southeast London, informed by qualitative interviews. This topic has mainly been addressed by separate disciplinary approaches (epidemiology and social science at the community level) and will combine the two to provide a seamless approach to the problem and therefore have a greater chance of impact.

Primary aims:

1. In a cohort of people with SMI (defined as schizophrenia-spectrum, bipolar disorders and non-organic psychoses) to assess area-level correlates, and geographically map all-cause and cause-specific mortality rates, in southeast London.
2. Use these data to sample people with SMI purposively who reside in areas of higher versus lower mortality and conduct qualitative interviews with them, to assess what types of factors (such as social capital, social support and social networks) may enhance resilience in these communities and buffer against premature mortality. This will be supplemented with interviews with community organisations and leaders, to identify resources which may play a role in this inequality as well as mapping potential risks or protections within communities (e.g. available food outlets).

Planned research methods and training provided: Training will include advanced statistical methods, methods to visualize spatial data and qualitative/ mixed methods training.

Project-023 How do resilient communities protect people with severe mental illnesses from death? Mixed methods study of local populations.

Objectives / project plan:

Year 1: Training. Systematic reviews relating to topic area. Ethics application for qualitative study/ approvals to access CRIS. Data cleaning/ analysis. MPHIL upgrade at 9 months.

Year 2: Quantitative data analysis/ mapping. Qualitative interviews.

Year 3: Synthesis of qualitative and quantitative findings. Finalise analyses, submit PhD.

Two representative publications from supervisors:

1: **Das-Munshi J,** Chang CK, Dutta R, Morgan C, Nazroo J, Stewart R, Prince MJ. Ethnicity and excess mortality in severe mental illness: a cohort study. *The Lancet Psychiatry.* 2017; 4(5) p389-399

2: Bécares L., Dewey M.E., **Das-Munshi J.** Ethnic density effects for adult mental health: Systematic r eview and meta-analysis of international studies. *Psychological Medicine.* 2017 14:1-19.

Keywords / phrases

Clinical Area/s:	Schizophrenia/ psychosis Population health Preventative medicine
Methodology	Psychiatric epidemiology/ quantitative/ data science methods Qualitative methods Mixed methods research

BRC Theme/s:

Affective Disorders and Interface with Medicine
Lifestyle Substance Use & Harms
Obesity, Lifestyle and Learning from Extreme Populations
Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Clinical and Population Informatics
Patient and Carer Involvement and Engagement
BioResource

Project-024 | Modelling patient mental, behavioural and somatic experiences using Natural Language Processing

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Project Description

Background: Clinicians are taught that when recording the 'presenting complaint' in the psychiatric history they should give a brief description in the patient's own words. Although some patients use symptom terms, (e.g. 'I feel depressed'), many describe their experiences in their own words (e.g. 'my head feels heavy'). For accurate diagnostic formulation and appropriate treatment planning, clinicians condense and interpret the information they glean from the patient interaction, often focusing on symptoms and risk issues, whereas patients are more concerned with challenges and experiences of daily living, well-being, relationships and social issues.

Natural language processing (NLP) algorithms have been successfully applied to extract clinically relevant information from clinical text, such as CRIS, and social media. Examples include extracting symptom profiles, treatments and exposures. However, the subjective experience of the patient, which might be expressed as lay phrases, idioms and figures of speech has not been widely modeled using NLP on CRIS. Such algorithms could be very important for understanding the correlation between experiences, symptoms and subsequent diagnoses and treatments.

Novelty and Importance: The BRC already has a substantial lead in novel NLP approaches translatable to healthcare. As well as innovations in NLP application across a wide range of clinical use cases, modeling more complex non-compositional representations that capture patient experiences transdiagnostically remains an understudied area. To make advances in shared decision making and to translate this to care that improves outcomes for patients it is essential that the focus shifts to patient relevant experiences.

Primary aim(s):

1. To review scientific publications related to patient reported mental, behavioural and somatic experiences and how they can be modeled using state-of-the-art NLP, particularly with contextualized embedding models.
2. To develop methods for defining and extracting patient reported experiences from CRIS and other clinically relevant text, including creating reference standards and annotation guidelines.
3. To involve patients and clinicians in the evaluation of these methods.

Planned research methods and training provided:

- Quantitative methodology
- Natural language processing
- Data Science
- Co-design and collaborative methods involving patients

Project-024 Modelling patient mental, behavioural and somatic experiences using Natural Language Processing

Objectives / project plan:

Year 1: Review literature and analyze existing approaches to model patient experiences from clinical text in collaboration with NLP researchers and data scientists, as well as patients and clinicians to gain a deeper understanding of their needs.

Year 2: Method development, define appropriate datasets.

Year 3: Finalize method development and carry out extensive evaluation with patients and clinicians. Complete and submit thesis.

Two representative publications from supervisors:

1: **Velupillai S**, Suominen H, Liakata M, Roberts A, Shah AD, Morley K, Osborn D, Hayes J, Stewart R, Downs J, Chapman W, **Dutta R**. Using clinical Natural Language Processing for health outcomes research: Overview and actionable suggestions for future advances.
J Biomed Inform. 2018 Dec;88:11-19. doi: 10.1016/j.jbi.2018.10.005. Epub 2018 Oct 24

2: **Velupillai, S**., Mowery, D., Conway, M., Hurdle, J., and Kious, B. Vocabulary Development To Support Information Extraction of Substance Abuse from Psychiatry Notes.
In Proceedings of BioNLP 2016, pages 92–101, Berlin, Germany, August 2016. Association for Computational Linguistics.

Keywords / phrases

Clinical Area/s:	Patient experience Symptoms Mental disorder
Methodology	Natural Language Processing Machine learning Text Analytics

BRC Theme/s:

Affective Disorders and Interface with Medicine
Child and Neurodevelopmental Disorders
Dementia and Related Disorders
Lifestyle Substance Use & Harms
Obesity, Lifestyle and Learning from Extreme Populations
Psychosis and Neuropsychiatry
Clinical and Population Informatics
Patient and Carer Involvement and Engagement

Project-025 | Developing the Next Generation of Mental Health Assessments Tools Using Virtual Reality

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Project Description

Background: Despite significant investments in both pharmacological and psychosocial interventions the majority of the people affected by schizophrenia will experience long term disability. Negative symptoms are features typically observed in people with schizophrenia and include poor motivation, social withdrawal, difficulties in experiencing pleasure, blunted affect and reduced communication. Despite their importance to illness prognosis and functioning, the development of interventions for negative symptoms received only very limited attention. An issue that has significantly hampered this process is assessment. Methods currently available to measure negative symptoms rely exclusively on observer rated or self-assessed methods. These have been criticised as they cannot provide an accurate picture on how negative symptoms unfold and influence people's everyday life.

Recent technical developments enabled researchers to use Virtual Reality (VR) and gaming techniques in clinics and research settings. This project will bring together these strands of evidence with the ultimate goal of developing a novel and effective assessment tool for people with psychosis. Once developed this assessment can be validated also for other mental health problems like bipolar disorder or severe depression.

Novelty and Importance: This project will introduce a new paradigm for mental health assessment. The standardised VR assessment could be ultimately delivered by less specialist staff, this will reduce the waiting times for assessment and potentially contribute to personalise care and improve its cost-efficiency.

The novel VR platform will represent a clear step towards the integration of new technologies into mental health care. The new VR assessment has the potential to radically change the way we assess mental health problems.

Primary aim(s):

1. Develop and refine experimental methods to assess negative symptoms using VR. This will be achieved by an interactive development process involving technology experts, researchers, service users and the general public.
2. Assess the acceptability and feasibility of the new method. This will be achieved by testing the VR methodology both in participants from the general population and people with schizophrenia.
3. Conduct a preliminary evaluation of the new assessment validity. This will be achieved by evaluating the new method concurrent validity with existing interview-based measures of symptoms.
4. Explore the physiological correlates of negative symptoms during the new procedures. This will be achieved by measuring sympathetic and parasympathetic functioning using wearable devices while participants undertake the new assessment.

Project-025 Developing the Next Generation of Mental Health Assessments Tools Using Virtual Reality

Planned research methods and training provided: The project will provide training opportunities for: systematic literature review skills and meta-analysis, a variety of assessment tools for people with mental health problem, statistics and data management, VR programming and VR use in clinical settings and an industry placement and training.

Objectives / project plan:

Year 1: Complete systematic literature review and meta-analysis; placement period with industry; begin adaptation process for the VR software; Ethics amendments and R&D in place.

Year 2: Service user feedback, data collection for main empirical study; data analysis training

Year 3: Complete main data collection; data analysis; thesis and papers write-up.

Two representative publications from supervisors:

1: Cella, M., Bishara, A., Swan, S., Medin, E., Reeder, C., & Wykes, T. (2014). Identifying cognitive remediation change through computational modelling – effects on reinforcement learning in schizophrenia. Schizophrenia Bulletin, 40(6):1422-32

2: Cella, M., Preti, A., Edwards, C., Dow, T., & Wykes, T. (2017). Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis. Clinical Psychology Review, 52, 43-51.

Keywords / phrases

Clinical Area/s:	Psychosis Schizophrenia Mood Disorders
Methodology	Virtual Reality Assessment Digital Technology

BRC Theme/s: Affective Disorders and Interface with Medicine
Psychosis and Neuropsychiatry
Translational Therapeutics
Clinical Research Facility

Project-026 | Understanding psychosocial factors associated with distress in women survivors of breast cancer and assessing the efficacy of a mobile app-based intervention

Supervisors: Doctor Lyndsay Hughes, Professor Rona Moss-Morris and Doctor Zoe Moon

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Project Description

Background: Improvements in cancer detection and treatment have increased the number of breast cancer survivors. However, there are important psychosocial needs associated with breast cancer survivorship which are not currently well supported during ongoing clinical management. For example, around 48% of breast cancer survivors experience significant depression and anxiety, which is compounded by side-effects associated with adjuvant hormone therapy (HT). HT is prescribed to reduce the risk of cancer recurrence, and is associated with menopausal-related side-effects including hot flushes and loss of libido.

Depression and symptom burden appear to be higher in women from Black, Asian and Minority Ethnic (BAME) groups, but the mechanisms for this are not understood. Higher depression results in worse treatment adherence, quality of life and increased healthcare utilization.

Novelty and Importance: Utilising mhealth, an innovative new app-based intervention may improve daily symptom management and distress, particularly for women who feel embarrassed discussing sexual dysfunction and mental health. This translational research has the potential to directly improve daily living for the growing number of breast cancer survivors.

Planned research methods and training provided: This project will use a mixed-methods approach and provide advanced training in; intervention development and framework mapping; multilevel modelling; qualitative data analysis and provides an opportunity to gain insight into randomized controlled trials.

Objectives/project plan: The aim of this studentship is to better understand the relationship between symptom experience and distress in women prescribed HT, and to adapt an existing app-based intervention to improve distress in these women. Specific attention will be paid to identifying the needs of women from BAME backgrounds.

Year 1: Using advanced statistical analysis, e.g. multilevel modelling, identify clinical, sociodemographic and psychosocial factors that mediate/moderate the relationship between symptoms and distress in an existing dataset (n=2000).

Following training in semi-structured interviewing and thematic analysis, use interviews to investigate the specific needs of BAME women around symptom management and distress.

Year 2/3: Work with service users to design an adaptation to an existing app to focus on distress and symptom management, ensuring it meets the needs of BAME women.

Assess the efficacy of this app-based intervention in reducing symptom-related distress in a feasibility study.

Project-026 Understanding psychosocial factors associated with distress in women survivors of breast cancer and assessing the efficacy of a mobile app-based intervention

Using Normalisation Processing Theory, work with charities and patient representatives to explore implementation of the app.

This project provides an exciting opportunity to join the e-PATH trial, showcasing mhealth and translational research in a dynamic team.

Two representative publications from supervisors:

1: Moon, Z., Hunter, M. S., Moss-Morris, R., & Hughes, L. D. (2017). Factors related to the experience of menopausal symptoms in women prescribed tamoxifen. *Journal of Psychosomatic Obstetrics & Gynecology*, 38(3), 226-235. DOI: 10.1080/0167482X.2016.1216963.

2: Moon, Z., Moss-Morris, R., Hunter, M. S., Hughes, L. D. (2017) More than just side effects: the role of clinical and psychosocal factors in non-adherence to tamoxifen. *British Journal of Health Psychology*, 22, 998-1018. doi:10.1111/bjhp.12274

Keywords / phrases

Clinical Area/s:	Interface between physical and mental health Breast cancer
Methodology	Mobile health Patient engagement

BRC Theme/s: Affective Disorders and Interface with Medicine
Mobile Health
Patient and Carer Involvement and Engagement

Project-027 | Biomarkers of Treatment Response in Schizophrenia

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Project Description

Background: The goal of precision medicine is to integrate biological and clinical information to in order to predict individual disease risk, understand disease aetiology, identify disease subcategories, improve diagnosis, and provide personalized treatment strategies. This is especially important in Schizophrenia (SZ) a heterogeneous and aetiologically complexity disease where roughly one third of patients do not respond to treatment.

Neuroimaging has greatly improved understanding of SZ primarily through the use of hypothesis driven, single modality methods. However, the selection of individual imaging markers a priori can bias observations and may discard the rich data available from multiple imaging modalities. Presently, new approaches to data-driven image analysis allow for non-subjective analysis of multimodal datasets to discover new imaging markers and their relation to clinical events and outcomes.

This project will utilize data driven, multivariate approaches to identify biomarkers of treatment response (TR) in SZ with multimodal neuroimaging. The project will use retrospective data collected as part of the MUTRIP study. The data from MUTRIP is ideal for identifying biomarkers as it comprises data from two clinical populations including a chronic cohort and a longitudinal first episode psychosis (FEP) cohort. Both cohorts have undergone the same high-quality imaging protocols making them well suited for data driven approaches. Biomarkers will first be identified in the chronic cohort with well-established clinical profiles and then validated on the FEP cohort.

Novelty and Importance:
Identifying biomarkers that can be used as diagnostics or predictors of treatment response in people with SZ will be an important step towards being able to provide personalized treatment. Moreover, the search for biomarkers may enhance our current understanding mechanisms of disease and help in developing more effect drug treatments.

The novelty of this project is that it focuses on a data driven multimodal approach which may be better suited to discovering biomarkers of TR given the complexity of SZ.

Primary aim(s):

1. Identify biomarkers of treatment (TR) response in schizophrenia using data driven approaches to fuse imaging modalities and relate to clinical, behavioral and genomic data.
2. Quantify how these TR biomarkers provide insight for the disease trajectory in FEP.
3. Assess whether a single imaging modality or combination is most informative in assessing treatment response in SZ or in understanding different facets of SZ throughout disease course.

Planned research methods and training provided: The student will get extensive training in neuroimaging methods. This project focuses on use of multimodal imaging, and will include training in different structural, functional and diffusion modalities. Training on data decomposition and related statistical methods and programing will also be provided in order to carry out the data driven analyses.

Project-027 | Biomarkers of Treatment Response in Schizophrenia

Objectives / project plan:

Year 1: Training and application of data-driven multimodal neuroimaging data fusion techniques to the chronic cohort to identify biomarkers.

Year 2: Application of biomarkers from Year 1 to the FEP cohort to validate the findings from the chronic cohort**.**

Year 3: Exploration of which imaging modalities are most information in SZ and write up

Two representative publications from supervisors:

1: Vanes, L.D.**,** Mouchlianitis, E., Woods, T., & Shergill, S.S. (2018). White matter changes in treatment refractory schizophrenia: does cognitive control and myelination matter? NeuroImage: Clinical, 18, 186–191.2.

2: Vanes, L.D., Mouchlianitis, E., Collier, T., Averbeck, B. B., & Shergill, S. S. (2018). Differential neural reward mechanisms in treatment responsive and treatment resistant schizophrenia. Psychological Medicine, 1–10.

Keywords / phrases

Clinical Area/s:	Schizophrenia Treatment Response Psychosis
Methodology	Neuroimaging Machine learning Genomics

BRC Theme/s:

Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Biomarkers and Genomics
Clinical and Population Informatics
Neuroimaging
BioResource

Project-028 | Stratification of people at clinical high risk for psychosis

Supervisors: Doctor Paolo Fusar-Poli and Professor Philip McGuire

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Project Description

Background: At present, the treatment of psychosis is not initiated until after the first episode of the disorder. The onset of psychosis is usually preceded by the clinical high risk (CHR) state, characterised by 'attenuated' psychotic symptoms coupled with functional impairments similar to those of established mental health disorders. Because the way that CHR individuals are ascertained varies depending on the referral pathway and the type of service engaging them, there is a variable level of risk for psychosis at the time of presentation3. Clinical outcomes are also heterogeneous.

Novelty and Importance: Stratifying the baseline risk of psychosis at the time of their initial presentation would help to reduce the logistical challenges associated with the recruitment of CHR samples. In a subsequent step, using biomarkers to stratify the CHR population according to clinical outcomes would allow the subgroup that is especially likely to develop psychosis to be selectively offered preventative treatment. A stepped stratification of recruitment and clinical outcomes of CHR population would permit a more personalised approach to clinical care that would be more ethical and cost effective. It would also allow novel interventions designed to prevent the onset of psychosis to be selectively offered to the subgroup of CHR individuals who are at most risk, increasing statistical power and reducing the size of samples required to detect a treatment effect.

Primary aim(s):

- Validate a stratification system to optimise recruitment and risk enrichment of CHR samples.
- Validate a set of biomarkers that robustly stratify CHR subjects according to clinical outcomes.
- Identify biomarkers that predict the response to treatment with CBD in CHR subjects.

Planned research methods and training provided: The candidate will have the opportunity to train with world-leading experts in the field of clinical prediction modelling, patients' stratification and precision psychiatry and preventive interventions in psychosis. The research methods will include biostatistical and machine-learning approaches to the development and validation of risk estimation algorithms, Electronic Health Records and bioinformatics, neuroimaging methods, peripheral biomarkers and e-Health.

Objectives / project plan:

Year 1: Finalisation of the STEP study protocol, training on the assessment of individuals at risk of psychosis and on the acquisition of biomarkers.

Year 2: Acquisition of multimodal predictors, training on methods to develop and validate risk prediction models, follow-up.

Year 3: Completion of the follow-up, analyses and publication of the results.

The candidate will have the opportunity to work in a large international research network.

Two representative publications from supervisors:

1: Fusar-Poli P, et al. *JAMA Psychiatry.* 2013;70(1):107-120.

2: McGuire P, et al. *American Journal of Psychiatry.* 2018;175(3):225-231.

Keywords / phrase

Clinical Area/s:	Clinical High Risk for Psychosis Early Intervention Schizophrenia
Methodology	Clinical prediction modelling and machine learning Biomarkers acquisition Bioinformatics

BRC Theme/s:

Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Biomarkers and Genomics
Clinical and Population Informatics
Mobile Health
Neuroimaging
Patient and Carer Involvement and Engagement
Translational Therapeutics
BioResource
Clinical Research Facility

Project-029 | Stratifying bipolar depression through its effects on the presynaptic dopamine system; an 18F-DOPA PET study

Supervisors: Professor Oliver Howes, Doctor Sameer Jauhar and Professor Allan Young

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Project Description

Background: Bipolar disorder (BD) has significant morbidity, UK data indicating at least 12 times increased suicide risk (more than schizophrenia) and 50 times the risk of self-harm (Hayes et al., 2017). The main cause of morbidity is depression (Judd et al., 2002), with few efficacious treatments licensed for treatment of BD depression (Jauhar and Young, 2019). Amongst these pharmacological treatments are antipsychotics, though it is unclear whether these effects are mediated through the dopamine system (as seen for psychosis) or other neurotransmitter systems. From examining the pharmacology of effective antipsychotics there is a suggestion that non-dopaminergic mechanisms underlie bipolar depression, though effectiveness of some dopamine agonists in unipolar depression makes this distinction difficult, on the basis of clinical evidence. This suggests a role for understanding the underlying neurobiological basis of bipolar depression. In comparison to psychosis, there has been little examination of the dopamine system in BD-and no molecular imaging studies conducted in bipolar depression.

Novelty and Importance: The dopamine system in bipolar depression has yet to be examined in-vivo. Given the interest in novel antipsychotics in treatment of bipolar depression, the proposed study is topical.

Primary aim(s):
Determine whether there is an underlying dopaminergic abnormality (indexed as dopamine synthesis capacity, Ki_{cer}, in bipolar depression, compared to matched controls.
Determine if a relationship exists between Ki_{cer} and depression symptoms, in people with bipolar depression.

Design Case-control ^{18} F-DOPA PET study

Population inclusion criteria: Case group; bipolar disorder with melancholy features (DSM-5 criteria), N=20. Fully-matched controls taken from existing database, collected using same imaging protocol and scanner.

Population exclusion criteria:
Recent history substance misuse/dependence;
Significant medical co-morbidity
Positive pregnancy test.
Nb antipsychotic medication will not be an exclusion, as this will affect recruitment, and recent evidence suggests no effects of antipsychotics on Ki_{cer} (Jauhar et al., 2019)

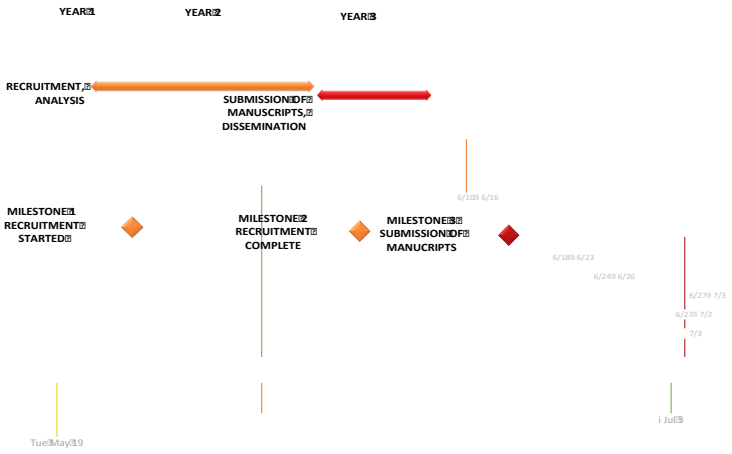
Clinical measures: Structured Clinical Interview for DSM 5, the Montgomery-Asberg Depression Rating Scale.

Image acquisition and analysis: This will be in line with our previous studies (Jauhar et al., 2017).

Project-029 | Stratifying bipolar depression through its effects on the presynaptic dopamine system; an 18F-DOPA PET study

Statistical power: Ki^{cer} bipolar depression vs controls. There are no prior studies in BD depression, and therefore we aim to recruit 20 subjects, based on prior PET studies conducted by our group in disease states (Jauhar et al, 2017).
The project will utilise skills in PET data analysis, using quantification methods validated in studies from our laboratory. It will involve assessment of depression using clinical measures.

Objectives / project plan: Ethical approval for this study has already been given.
Therefore, the applicant will be able to start recruitment from the beginning of their PhD.



Two representative publications from supervisors:

1: Ashok, A.H., Marques, T.A.R., **Jauhar, S**., Nour, M., Goodwin, G.M., **Young, A., Howes, O.D**., 2017. The dopamine hypothesis of Bipolar Affective Disorder: the state of the art and implications for treatment. Molecular Psychiatry 22, 666–679.

2: **Jauhar, S.**, Nour, M.M., Veronese, M., Rogdaki, M., Bonoldi, I., Azis, M., Turkheimer, F., McGuire, P., **Young, A.H., Howes, O.D**., 2017. A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. JAMA Psychiatry 74, 1206–1213.

Keywords / phrases

Clinical Area/s:	Bipolar disorder
Methodology	Positron Emission Tomography

BRC Theme/s: Psychosis and Neuropsychiatry
Neuroimaging

Project-030 The emotional clock: Balancing circadian rhythms and emotional regulation

Supervisors: Doctor Theresa D'Oliveira and Professor Sukhi Shergill

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Project Description

Background: Sleep is one of the most basic and essential circadian rhythms with disruptions impacting behaviour and mood in both vulnerable and healthy populations.
The association between sleep disturbances and mood disorders such as major depression, bipolar disorder, and seasonal affective disorder, was noted over 50 years ago (Kim et al, 2017). Nearly all people suffering from mood disorders have significant disruptions in circadian rhythms and the sleep/wake cycle (Ketchesin et al., 2018); disturbed sleep patterns are a major diagnostic criterion of affective disorders (McClung, 2013).

In healthy participants, fMRI studies highlighted the impact of sleep deprivation on emotions with an increased emotional reactivity to negative information and impaired emotional regulation; good night of sleep is proposed to provide an opportunity for an emotional "reset" (Walker, 2009).

Novelty and Importance: Despite these results, research with healthy participants is plagued with methodological constraints resulting from the use of cross-sectional designs and laboratory settings. To overcome these ecological threats, the project adopts a naturalistic approach and monitors healthy participants in a continuous period of 14 days. Data on potential disturbances to sleep and daily affective events are assessed using nonintrusive wearable devices (i.e., actigraphs), sleep and emotional dairies and using experience sampling methods resulting in an integrative approach to mental and physical health.

Primary aim(s): The main objective of the project is to study the mutual influence between sleep and emotions in healthy participants. The project is part of a vaster collaboration with an industry partner and we expect future phases to include participants with sleep disorders and affective disorders.

Planned research methods and training provided: Training on multivariate longitudinal analysis, such as structural equation modelling, latent variable models, multi-levelling modelling, latent growth modelling will be required.

Objectives / project plan:

Year 1: Summarise the findings of previous literature associating sleep and emotions. As most daily activities of healthy participants involve work, we are particularly interested in emotions in the workplace;

Year 2: Examine the influence of distinct working time patterns in the association between sleep and emotions; Sleep and emotions of healthy participants will be monitored in a continuous period of 14 days using nonintrusive wearable devices (i.e., actigraphs), sleep and emotional dairies and experience sampling methods.

Year 3: In collaboration with an industry partner, Kokoon, explore the impact of a sleep intervention developed by Kokoon that combines EEG data and CBT inspired exercises in the association between sleep and emotions.

Project-030 The emotional clock: Balancing circadian rhythms and emotional regulation

Two representative publications from supervisors:

1: D'Oliveira, T. C. (2016). Markers of circadian disturbances in cabin crew: Combining cortisol and melatonin responses with self-reporting measures. Brain, Behavior, and Immunity, 57, e13-e14, 57, doi: 10.1016/j.bbi.2016.07.047

2: Joyce, D. W., & Shergill, S. S. (2018). Integration is not necessarily at odds with reductionism. International Journal of Social Psychiatry, 64(7), 626-627. https://doi.org/10.1177/0020764018770476

Keywords / phrases

Clinical Area/s:	Sleep disorders Affective disorders Emotional regulation
Methodology	Wearables devices (e.g. actigraphs) Experience sampling methods Structural equation modelling

BRC Theme/s: Affective Disorders and Interface with Medicine
Lifestyle Substance Use & Harms
Bioinformatics and Statistics
Mobile Health

Project-031 | Using smartphone-based personal sensing to understand and predict risk of psychotic relapse at the individual level

Supervisors: Professor Andrea Mechelli and Doctor Stefania Tognin

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Project Description

Background: The application of smartphone technologies in mental health care has the potential to fundamentally change the way in which psychiatric patients are assessed, treated and monitored. It allows the close monitoring of people across multiple contexts, time-points and locations, providing access to a wealth of ecologically valid information that would have been impractical to collect only a decade ago.

Novelty and Importance: The present project has several novel aspects: (i) it involves the use of smartphone technologies to investigate a key putative mechanism underlying psychotic relapse i.e. social stress; (ii) it uses machine learning to generate a dynamic and responsive individualised risk score for psychotic relapse; (iii) it will lead to the development of an individualised risk score for psychotic relapse which could be integrated in electronic health records nested within routine clinical care.

Primary aim(s): Over the past 3 years, we have been developing a smartphone app that allows the fine-grained monitoring of mental states and behaviours in real time (www.urbanmind.info). In this project, we will use an updated version of this app to investigate social stress as a putative mechanism that underlies psychotic relapse in people with a first episode of the illness.

Planned research methods and training provided: We will use a prospective longitudinal design. Firstly, we will employ our smartphone app, face-to-face interviews and electronic health records to monitor 200 patients with first episode psychosis over a period of 12 months. Secondly, we will use the data to develop a predictive model linking measures of social stress sensitivity and social withdrawal with risk of future psychotic relapse. The output of this predictive model will be an individualised risk score for psychotic relapse that could be used to inform clinical assessment of individual patients.

Training provided. The student will receive training in the recruitment and assessment of individuals with psychosis, the analysis and interpretation of smartphone-based data using machine learning methods, and the translation of research findings into a tool for clinical use.

Objectives / project plan:

Year 1:
- Recruitment and baseline assessment of participants
- Start of 6-month follow-ups assessments
- Statistical analysis of baseline data

Project-031 Using smartphone-based personal sensing to understand and predict risk of psychotic relapse at the individual level

Year 2:

- Completion of 6-month follow-up assessments
- Start of 12-month follow-up assessments
- Statistical analysis of 6-month follow-up data

Year 3:

- Completion of 12-month follow-up assessments
- Statistical analysis of 12-month follow-up data
- Dissemination of results amongst academics and the general public

Two representative publications from supervisors:

1: Bakolis I, Hammoud R, Smythe M, Gibbons J, Davidson N, Tognin S, **Mechelli A** (2018). Urban Mind: Using Smartphone Technologies to Investigate the impact of Nature on Mental Wellbeing in Real Time. *Bioscience* 68(2):134-45.

2: Vieira S, Pinaya WHL, **Mechelli A** (2017). Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: methods and applications. *Neuroscience & Biobehavioral Reviews* 74:58-75

Keywords / phrases

Clinical Area/s:	Psychosis Social stress Relapse prediction
Methodology	Digital health Personal sensing Machine learning

BRC Theme/s: Psychosis and Neuropsychiatry
Mobile Health

Project-032 | Using virtual reality to investigate sense of body ownership and agency in patients with functional neurological disorder.

Supervisors: Professor Sukhi Shergill and Doctor Paul Shotbolt

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Project Description

Background: Functional Neurological Disorder (FND) is one of the commonest causes of neurological disability; it is the second most common diagnosis in neurology outpatient clinics (Carson & Stone, 2015). A key clinical feature of FND is that motor symptoms, although similar to voluntary movements, are subjectively reported by patients as involuntary (Edwards, 2012). This may be explained by differences in self-recognition of motor actions, mediated by an altered sense of body ownership and agency.

Novelty and Importance: Previous attempts to study these constructs in FND patients using experimental paradigms such as the rubber hand illusion have led to conflicting results. In the proposed study, state-of-the-art VR environments designed by the industrial partner (Mesmerise Global) will be used. We anticipate that the fully immersive nature of these experiences, plus the possibility of manipulating them to change experimental conditions, will allow for more precise and valid investigation of both sense of body ownership and agency.

Primary aim(s): The aim of the proposed study is to investigate sense of body ownership and agency in patients with FND, using immersive virtual reality environments.

The hypotheses are that patients with FND will; 1. be more susceptible to manipulation of sense of body ownership ('virtual body illusion') as compared to non-FND controls. 2. show reduced agency over the movements of an avatar ('virtual mirror') as compared to non-FND controls.

Planned research methods and training provided: 10 individuals diagnosed with FND and 10 healthy control participants will be recruited. All will undergo assessment in two immersive VR environments; firstly a 'virtual mirror' avatar environment (participants will see an avatar directly in front of them that follows their movements), and secondly a 'virtual body illusion' in which participants see a projected true image of their body from the back.

In both environments, experimental conditions will be manipulated using active and passive movement, incongruous avatar positions and time delays.

Sense of body ownership and agency will be assessed in the different VR conditions using a modified version of Kalckert and Ehrsson's Moving Rubber Hand Illusion (mRHI) Questionnaire.

Training: The student will receive training in; 1. assessment and management of FND patients within the neuropsychiatry service 2. VR design for clinical and non-clinical applications in secondment with Mesmerise 3. all aspects of relevant research methods and data analysis.

Objectives / project plan:

Year 1: Finalise design and VR environments, engage patient groups (FND Hope/FND Action) prepare final protocol, regulatory approval, start recruitment.

Year 2: Run and complete study, secondment with Mesmerise Global

Project-032 Using virtual reality to investigate sense of body ownership and agency in patients with functional neurological disorder.

Year 3: Write up thesis and publications, disseminate results at conferences (e.g. British Neuropsychiatry Association, UK Functional Neurological Symptoms meetings). Next steps with funding – fellowships / further collaborative grants with industry sponsor (Mesmerise Global).

Two representative publications from supervisors:

1: Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study. McCormack R, Moriarty J, Mellers JD, Shotbolt P, Pastena R, Landes N, Goldstein L, Fleminger S, David AS. J Neurol Neurosurg Psychiatry. 2014 Aug;85(8):895-900

2: Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia. Shergill SS, White TP, Joyce DW, Bays PM, Wolpert DM, Frith CD. JAMA Psychiatry 2014 Jan;71(1):28-35.

Keywords / phrases

Clinical Area/s:	Neuropsychiatry / Neurology Functional Neurological Disorder Psychopathology
Methodology	Virtual reality Novel investigation/assessment

BRC Theme/s:
Psychosis and Neuropsychiatry
Patient and Carer Involvement and Engagement
Translational Therapeutics
Clinical Research Facility

Project-033 | Up-regulating positive affect in adolescence: exploring novel cognitive intervention strategies for depression and anxiety

Supervisors: Professor Andrea Danese, Doctor Katherine Young and Doctor Jennifer Lau

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Project Description

Background: Theoretical models of anxiety and depression, such as the tripartite model (Watson & Clark, 1991), have long recognized the separable constructs of negative and positive affect. However, existing psychological interventions, such as cognitive behavioural therapy, focus on reducing of symptoms of negative affect, without aiming to increase positive affect. While these treatments can be effective, estimates suggest that up to 50% of individuals fail to achieve clinically significant improvements in symptoms or functioning (March et al., 2005; Loerinc et al., 2015; Hollon et al., 2006). Novel strategies aiming to enhance positive affect may offer a potential to reduce this treatment gap.

Adolescence may be an optimal window to intervene to impact long-term trajectories for psychological health. The neural systems involved in experience and regulation of positive and negative affect continue to develop across childhood and into adolescence (Casey, 2018). In particular, neurocircuitry implicated in the regulation of positive affect has peak sensitivity to rewarding stimuli in mid-late adolescence (Braams et al., 2015). Experimental evidence demonstrating the efficacy of cognitive strategies for regulating emotional experiences comes from self-report, behavioural and neuroimaging paradigms investigating negative affect (Ochsner et al., 2012; Young et al., 2018). There is a lack of comparable research exploring regulation of positive affect, with very few studies investigating these processes in adolescence (Young et al., 2019).

Novelty and Importance: Cognitive strategies for regulating experiences of positive affect are not well understood and may provide an avenue for reducing the treatment gap for depression and anxiety.

Primary aim(s): This project involves three main aims: 1) PPI research exploring the strategies adolescents use to enhance/maintain positive affect; 2) investigating the impact of cognitive regulation strategies on behavioural measures of positive affect; 3) investigating the impact of these strategies on neurophysiological measures of positive affect (i.e., reward system functioning in the brain).

Planned research methods and training provided: This project will involve a range of techniques (PPI research, behavioural assessments, neuroimaging) for which training will be provided. The student will benefit from being based in the SGDP and having collaborations with the Department of Psychology to ensure support across these methodologies.

Objectives / project plan:

Year 1: Conduct PPI exploring strategies adolescents use to enhance/maintain positive affect, develop behavioural paradigm and collect data

Project-033 Up-regulating positive affect in adolescence: exploring novel cognitive intervention strategies for depression and anxiety

Year 2: Analysis of data from behavioural paradigm, development of neuroimaging study and data collection

Year 3: Neuroimaging data analysis, manuscript preparation

Two representative publications from supervisors:

1: Young KS, Sandman CF, Craske MG (2019). Positive and Negative Emotion Regulation in Adolescence: Links to Anxiety and Depression. PsyArXiv. February 12. doi:10.31234/osf.io/uwy6q

2: Young KS & Craske MG. (2018) The cognitive neuroscience of psychological treatment action for depression and anxiety, Current Behavioral Neuroscience Reports, 5(1), 13-25

Keywords / phrases

Clinical Area/s:	Depression Anxiety Psychological treatment
Methodology	Meta-analysis Experimental behavioural research Neuroimaging

BRC Theme/s:

Affective Disorders and Interface with Medicine
Neuroimaging
Patient and Carer Involvement and Engagement
Translational Therapeutics

Project-034 | Mobile health and attention-deficit/hyperactivity disorder (ADHD): developing novel digital biomarkers to characterise clinical features and predict outcomes

Supervisors: Professor Jonna Kuntsi and Professor Richard Dobson

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Project Description

Background: Remote measurement technology (RMT) is changing the way in which many conditions are assessed and managed, shifting the focus from 'diagnose and treat' to 'predict and prevent'. King's investigators are leading international RMT developments in relation to disorders such as depression and epilepsy (RADAR-CNS.org; RADAR-base.org). Benefiting from the RADAR-base platform, supervisors Kuntsi and Dobson have recently started developing a novel remote assessment system for adults and adolescents with ADHD. While the initial measures now under development focus on the remote application of commonly used measures, such as clinical symptom questionnaires and cognitive tasks, further significant untapped potential lies in smartphone-based passive monitoring data. Digital phenotyping is a new approach to measuring behavior from smartphone sensors and keyboard interaction, which can be used to measure, for example, aspects of cognition (reaction time, attention, memory), sociability and activity (Insel 2017, *JAMA*). Benefiting from digital phenotyping developments in RADAR, this studentship will focus on developing novel passive monitoring measures for ADHD and investigating their potential as digital biomarkers to characterise clinical features and predict outcomes.

Novelty and Importance: ADHD is associated with an increased risk for detrimental outcomes. Yet outcomes are highly variable, with some individuals remitting in young adulthood. A better understanding of predictors and markers of different long-term ADHD outcomes is required for developing interventions that aim to halt adverse developmental trajectories. RMT offers unprecedented opportunities for long-term research and clinical monitoring of individuals with ADHD. The core symptoms in ADHD of distractibility and impulsivity are strong targets for smartphone-use biomarkers.

Primary aim(s):

Aim 1 is to develop and pilot smartphone-based passive monitoring measures for adults/adolescents with ADHD.

Aim 2 is to apply the new measures to our existing follow-up sample of adults with ADHD and controls, to investigate how well they characterise clinical features and predict outcomes (remission/persistence of ADHD, and co-occurring symptoms). Longer term, these developments will feed into a subsequent phase where the utility of the measures for clinical decision making, optimisation of treatment effects and supporting self-management will be assessed.

Planned research methods and training provided: The RADAR-base platform (www.radar-base.org) is highly scalable and allows rapid development and integration of new sensors/devices and third party apps. Passive monitoring measures will be developed that obtain data from smartphone sensors and keyboard interaction on aspects of cognition, sociability and activity. Training in both study-specific and academic skills will be provided. We will work closely with health informatics SMEs (e.g. the Hyve) that supervisor Dobson is already collaborating with in the RADAR projects.

Project-034 Development and testing of novel electronic health interventions to alter drugs, alcohol and tobacco use patterns and trajectories in young people

Objectives / project plan:

Year 1: Development and piloting of the measures

Years 2-3: Application of the new measures to our follow-up sample of adults with ADHD and controls

Two representative publications from supervisors:

1: Cheung CH, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, Kuntsi J (2016). Cognitive and neurophysiological markers of ADHD persistence and remission. Br J Psychiatry, 208(6), 548-555. doi: 10.1192/bjp.bp.114.145185.

2: Ranjan Y, Rashid Z, Stewart C, Kerz M, Begale M, Verbeeck D, Boettcher S, Conde P, The Hyve, Dobson R, Folarin A, The RADAR-CNS Consortium (2018). RADAR-base: An open source mHealth platform for collecting, monitoring and analysing data using sensors, wearables, and mobile devices. JMIR Preprints, 29/08/2018:11734. doi: 10.2196/preprints.jmir.org/preprint/11734.

Keywords / phrases

Clinical Area/s:	Attention-deficit/hyperactivity disorder (ADHD) Neurodevelopmental disorders Psychiatry
Methodology	Mobile health Remote measurement technology Passive monitoring

BRC Theme/s: Child and Neurodevelopmental Disorders
Mobile Health