PhD studentships
Funded by the
NIHR Maudsley Biomedical Research Centre

Project Catalogue

Studentships to commence October 2018
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Introduction

Welcome to the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) project catalogue for potential candidates wishing to commence a PhD in October 2018 – 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 September 16 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 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 Anthony David

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 “pan-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

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**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 departments: 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 most 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 choice of project and project details are agreed after successful interview.
Projects

In this catalogue, the projects are listed in departmental order according to the department where the first 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.

When applying for the NIHR Maudsley Biomedical Research Centre PhD studentship programme, please ensure you state 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. BRC-031 Molecular effects of benzodiazepine on GABAergic function in people at clinical high-risk of psychosis
2. BRC-017 Investigating the potential of 5HT7 antagonists for the treatment for cognitive impairment in bipolar disorder: a proof of principle neuroimaging project
3. BRC-022 The role of subgenual frontal connectivity in predicting response to serotonergic medications

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.

The projects listed below are also available to apply for via the separate MRC Doctoral Training Partnership in Biomedical Sciences studentship programme. Applicants can apply for funding through both programmes but please note that separate applications are required. Please refer to the NIHR Maudsley BRC website for information about how to apply for the Maudsley BRC studentships.

BRC-001 Development and testing of novel electronic health interventions to alter drugs, alcohol and tobacco use patterns and trajectories in young people
BRC-010 Multi-modal objective measurement of mental health problems in autism
BRC-017 Investigating the potential of 5HT7 antagonists for the treatment for cognitive impairment in bipolar disorder: a proof of principle neuroimaging project
BRC-018 Gut Feeling: Probiotics as a Novel Treatment for Depression
BRC-022 The role of subgenual frontal connectivity in predicting response to serotonergic medications
BRC-034 Towards personalised medicine for antidepressant drugs: a machine learning approach
BRC-037 Identification of neurobehavioural predictors of eating disorders, weight gain and obesity
BRC-043 Elucidating the pathway from benign to pathological positive psychotic symptoms and back again: informing the next wave of psychological therapies
BRC-044 Improving treatment outcomes for sexual minority women with depression or anxiety

Please note: The final choice of funding, project and project details are agreed after successful interview.
BRC-001  Development and testing of novel electronic health interventions to alter drugs, alcohol and tobacco use patterns and trajectories in young people

Primary Supervisor:  Dr Paolo Deluca  
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Second Supervisor:  Professor Colin Drummond  
Academic Department: Addictions Sciences  
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Project Description

Background:  Systematic reviews report that opportunistic alcohol Screening and Brief Intervention (SBI) is effective and cost effective in reducing alcohol consumption, alcohol related harm, and NHS and criminal justice service use. The evidence base is strongest in the primary care setting, with further evidence of effectiveness in emergency departments and acute inpatient care (e.g. Kaner et al 2007). NICE (2010) recommends implementation of SBI in routine NHS care. However, only 2% of hazardous and harmful drinkers are identified annually in primary care in England, with significantly lower identification rates in 18-24 year olds than older patients. Therefore a cost effective and practical method of implementing SBI both in the NHS and delivered at a whole population level is urgently required.

Novelty and Importance:  SBI delivered via electronic media (eSBI) shows promise, with several clinical trials reporting positive outcomes. Currently most of this research has been via online or text message delivery. Recent reviews of the relevant literature (Donoghue et al 2014, Patton et al 2014) further supports the utilisation of eSBI to reduce alcohol consumption and related harms.

Primary aim(s):  This PhD proposal focuses on the development, implementation and evaluation of a purpose designed smartphone intervention app which would focus on a number of health and lifestyle behaviours such as: Alcohol, smoking, drugs use as well as obesity and self-harm. The app will be developed following proven brief intervention, gamification strategies, and augmented intelligence (ChatScripts) to personalise content, to promote healthier choices, to induce a reduction in quantity and frequency of substance use in adolescents, to provide a wider implementation and uptake of electronic brief interventions to the wider population, with associated health and cost benefits. The app development will involve qualitative research with target users through focus groups, interviews and product testing, in order to develop the most user friendly, credible and engaging intervention tool.

Planned research methods and training provided:  This PhD will be based on mixed methods, including qualitative analysis, focus groups, and quantitative analysis of app server usage data. The student will receive training in these research methods and analyses. In addition, we envisage a 6-month secondment to the industry partner.
**BRC-001 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: Literature review, PPI work

Year 2: Module development, PPI Work

Year 3: Data collection and analysis, writing up

Year 4: Writing up, dissemination of findings

**Two representative publications from supervisors:**


**Keywords:** Mobile Health; Addiction; Health and Lifestyle; Young People;

**BRC Theme/s:** Lifestyle Substance Use and Harms

Mobile Health
Project Description

Background: Harmful alcohol consumption poses a significant problem for public health. There is evidence to suggest that alcohol related frequent attenders pose a disproportionately large burden on health care services. Alcohol-related frequent attenders are patients with multiple attendances to primary and/or secondary care services relating to alcohol in a short period of time. This patient group may present with complex needs.

Novelty and Importance: Few studies have sought to determine the treatment needs of alcohol related frequent attenders in terms of complex and undiagnosed mental and physical health problems. Current treatment is often ineffective in terms of addressing the complex health needs of alcohol related frequent attenders. Findings from the proposed study will be of benefit to development of alcohol policy in the UK. With interventions targeting this patient group specifically and effectively, there is potential to reduce the huge costs imposed by this patient group.

Primary aim(s): The proposed study will characterise the physical and mental health harms amongst alcohol-related frequent attenders in primary and secondary care to estimate costs and treatment needs.

Planned research methods and training provided: Big data analysis and qualitative interview methods. The successful student will undertake training in alcohol addiction, alcohol policy, qualitative methods, big data analysis and writing papers and dissertation.

Objectives / project plan:

Year 1: During the first year, this project will conduct a systematic review of the research literature on the physical and mental health problems and costs relating to alcohol-related frequent attenders in primary and secondary care.

Year 2: During the first and second year, using large datasets, the research will characterise and compare alcohol-related frequent attenders presenting in primary care and secondary care (hospital admissions and A&E attendance) regarding physical/mental health problems, treatment and cost. In the second year, a qualitative interview study will be conducted recruiting 20 patients from GP surgeries and 20 patients from hospitals who are frequent alcohol attenders to compare these two patient groups. In the second year, the study uses data collected as part of the Alcohol Toolkit Study to investigate the use of health care services amongst dependent drinkers.

Year 3: In the third year, data analysis and writing up.
Two representative publications from supervisors:


Keywords: Alcohol; Primary care; Secondary care; Frequent alcohol attenders; Addiction;

BRC Theme/s: Lifestyle Substance Use and Harms
Bioinformatics & Statistics
Clinical & Population Informatics
BRC-003 Faster heroin/opioid overdose reversal with naloxone: The testing of accelerants

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Project Description

Background: Opiate overdose causes 100,000 deaths annually and is a major public health problem (WHO, 2015). Naloxone, a pure opiate antagonist, is a life-saving injection which rapidly reverses opiate overdose. In many countries, naloxone is now pre-provided to drug users and their family members (‘Take-Home Naloxone’) (Strang McDonald, EMCDDA, 2016).

However existing formulations are not well-suited. We identified deficiencies of improvised nasal naloxone kits (Strang, McDonald, Addiction, 2015) and have worked with industry to conduct pharmacokinetics analyses of concentrated nasal naloxone sprays (Mundin McDonald, Addiction, 2017; McDonald Lorch, Addiction, in press). In addition we explored other non-injectable naloxone options (Strang McDonald, Drug Alc Dep, 2016) and demonstrated feasibility of trans-buccal naloxone with prototype buccal wafers of lyophilised naloxone (AlQurshi Royall, Molecular Pharmaceutics, 2016; Courtney Royall, European Pharmaceutical Review, 2017).

Novelty and Importance: A major relative weakness of all current non-injectable formulations (especially compared with intravenous injection) is the slower speed of onset of effect which might not be sufficient to reverse acute respiratory arrest in time to prevent death. This concern is heightened by the spread of fentanyl overdose deaths with reportedly more rapid onset. Further research is now needed to investigate the accelerant effect of enhancers to achieve quicker naloxone absorption and central effect of reversal of respiratory arrest.

To address these issues we propose collaborative development with Professor Taylor and Forbes and Dr Royall in King’s Pharmaceutical Sciences to investigate combinations of naloxone and enhancers, and then to conduct preliminary first-in-human volunteer study, in our purpose-built Clinical Research Facility, to test actual speed of absorption and consequent opioid blockage and overdose reversal. In addition we wish to explore the potential value of decelerants also, which might open possibility of supplementary naloxone dosing, post-resuscitation, to achieve longer duration of reversal of respiratory arrest (to address the subsequent concern that the short-acting reversal effects of naloxone may wear off before the original overdose has passed, with risk of return of overdose). These areas, working with colleagues in Pharmaceutical Sciences and also with our Clinical Research Facility for the human volunteer study, will form the basis of this PhD proposal.
Primary aim(s): The primary aims are: to develop novel naloxone combinations with accelerants so as to produce emergency nasal and/or buccal naloxone with more rapid onset of action; and to conduct preliminary investigative first-in-man human volunteer study of naloxone+accelerant formulations.

Planned research methods and training provided: The two distinct component parts of the PhD are (a) the collaboration with colleagues in Pharmaceutical Sciences to develop and test the naloxone+accelerant combinations; and then (b) the preliminary investigative first-in-man human volunteer study of the naloxone+accelerant formulations with our Clinical Research Facility. Training opportunities will exist through our Addictions group, including material already provided through our Addictions Science MSc, and also through collaborations with senior colleagues working with patients and public engagement, with colleagues working in clinical services, and with joint working with health departments.

An opportunity will also exist for short-term industry placement to learn how such work can be taken forward to operational development and preparation for regulatory submission (an arrangement successfully arranged for recent PhD student): three potential Pharma partners are currently in discussion with us about this option.

Objectives / project plan:

Year 1: Develop and produce forms of naloxone+accelerant combination

Year 2: Test stability and product characteristics of the candidate naloxone+accelerant combinations; and also begin preparations for the investigative first-in-man human volunteer studies of the naloxone+accelerant formulations which will occur in Year 3 in our Clinical Research Facility.

Year 3: Conduct of the investigative first-in-man human volunteer studies of the naloxone+accelerant formulations in our Clinical Research Facility; and data analysis and interpretation.

Year 4: Write-up of thesis and project report, and preparation of scientific publications. There is also the option of an industry placement.

Two representative publications from supervisors:


Keywords: Naloxone; Overdose; Reversal; First-in-man; Patient and public involvement; PPI;

BRC Theme/s: Lifestyle Substance Use and Harms
Patient and Carer Involvement & Engagement
Translational Therapeutics
Clinical Research Facility
BRC-004  Investigating the effects of oxytocin on antisocial personality disorder and psychopathy using neuropsychological and functional imaging probes

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Project Description

Background: Violent crime has enormous financial and human costs. It is mostly committed by men with antisocial personality disorder (ASPD). Approximately 1/3 of these men are psychopaths (ASPD+P), characterised by reactive and instrumental aggression, and an inability to learn from punishment. By contrast, those without psychopathy (ASPD-P) exhibit mostly reactive aggression, and engage better in treatment programmes.

There are important structural and functional brain differences between these individuals. However we do not understand the neurochemical underpinnings of these differences, or if they can be modulated. The neuropeptide oxytocin is known to modulate social behaviour in healthy controls and in those with psychiatric conditions, but its effects on the brain in ASPD+/P have not been investigated.

This study will examine the effects of oxytocin in ASPD using:

i) a novel neuropsychology battery: developed by leading researchers in the field (Blair et al at NIMH) and aligned to core neuropsychological deficits in ASPD (including facial emotion recognition and processing of reward and punishment);
ii) fMRI: resting brain state and connectivity will be measured using cutting edge techniques (arterial spin labelling and multi-echo EPI).

The researcher will work with the forensic research group at Kings, and gain further experience with Professor James Blair in the United States.

Novelty and Importance: Current psychological and pharmacological treatments in ASPD have a very limited evidence base. Development of novel therapies has been hampered by a poor understanding of the underlying brain chemistry in this condition.

This study will help to address this issue by providing an understanding of the effect of oxytocin on the brain in ASPD+/P. Specifically, it will help to stratify ASPD according to the effects of oxytocin into more biologically homogenous subtypes. In this way, it will provide a platform for future studies investigating the effects of oxytocin and related pharmacological agents on behaviour in ASPD+/P, potentially alongside psychological therapies. Any intervention leading to reduced antisocial behaviours in this group, particularly a reduction in violence, would represent an important translational effect.

Further, ASPD+/P is increasingly understood as a neurodevelopmental condition, its precursors in childhood and adolescence being conduct disorder with or without callous-unemotional traits (CD +/- CU). Treatments targeting early deficits and altering the clinical trajectory of youths with CD would lead to an even greater potential impact.
BRC-004   Investigating the effects of oxytocin on antisocial personality disorder and psychopathy using neuropsychological and functional imaging probes

**Primary aim(s):** The study will test the following hypotheses:
there will be between-group differences in neuropsychological measures, resting state and connectivity; these will be modulated by oxytocin; and
this will facilitate stratification of ASPD into more biologically homogenous subgroups, and development of precision medicine approaches.

**Project plan:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Objectives</th>
<th>Planned research methods and training</th>
<th>Training and supervision provided</th>
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| 1    | ● Training in neuropsychology assessment and FMRI  
      ● Commence recruitment, neuropsychology and FMRI | ● Training in assessment of ASPD+/P (SCID-5 PD, PCL-R) and neuropsychology battery  
      ● Introductory FMRI/SPM Training | ● Training courses for SCID, PCL-R (external); neuropsychology battery (internal); introductory FMRI/SPM- Centre for Neuroimaging Sciences (CNS)  
      ● Supervision at IoPPN/CNS |
| 2    | ● Continued recruitment, neuropsychology assessment and FMRI  
      ● Training in computational modelling of FMRI data | ● Training in SPM  
      ● Training in Neuropsychology Battery analysis | ● Wellcome SPM training course  
      ● Neuropsychology Battery analysis at Boys Town campus (US)  
      ● Supervision at IoPPN/CNS |
| 3    | ● Completion of assessment and scanning  
      ● Thesis completion | ● Support on thesis and data analysis | ● Supervision at IoPPN/Centre for Neuroimaging Sciences |

**Two representative publications from supervisors:**


**Keywords:** Psychopathy; Personality disorders; Functional neuroimaging; Neuropsychology; Antisocial behaviour;

**BRC Theme/s:** Child and Neurodevelopmental Disorders  
Lifestyle Substance use and harms  
Obesity, Lifestyle and Learning from extreme populations  
Psychosis and Neuropsychiatry  
Biomarkers and Genomics  
Neuroimaging  
Translational Therapeutics  
BioResource  
Clinical Research Facility
BRC-005  Targeting Serotonin for the Treatment of Social Impairment and Repetitive Behaviours in Young Adults with Autism Spectrum Disorders and Hyperserotonaemia.

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Project Description

Background: Autism Spectrum Disorder (ASD) is a highly genetic neurodevelopmental condition affecting 1% of the population. There are no effective treatments for the core symptoms of repetitive behaviours, social function, and communication deficits – but our recent work suggests a novel way forward (targeting the serotonergic system). Evidence indicates that individuals with ASD have differences in brain serotonin (including increased serotonin). Yet, current drugs studies in ASD (e.g. selective serotonin reuptake inhibitors) aim to increase serotonin in all treated individuals, but the results have been mixed and the reasons why some individuals with ASD respond to treatment, whereas others do not, are unknown. Our recent work showed that current approaches might be wrong – in that they aim to increase brain serotonin – when in fact they should be aiming to reduce it. For example, we showed that people with ASD differ significantly from controls in brain activation patterns when performing social and repetitive behaviour tasks, but (crucially) that this is ‘normalised’ when we reduce brain serotonin. In this study, we will test the efficacy and safety of the Selective Serotonin Reuptake Enhancer (SSRE) tianeptine in a ‘fast fail’ clinical trial to translate measures of ‘serotonergic sensitivity’ towards the alleviation of core symptoms of ASD.

Novelty and Importance: The novelty of this project is the repurposing of the antidepressant tianeptine to target ASD deficits. There are no effective pharmacological treatments for the core symptoms, therefore, it is imperative to investigate treatments for the lifelong disabilities affecting people with ASD.

Primary aim(s): Our primary objective is to evaluate the pharmacodynamic/target engagement (i.e. fMRI effects) of tianeptine in adults with ASD.

Planned research methods and training provided: We will utilise pharmacological functional Magnetic Resonance Imaging (phMRI) in a 12-week double blind, placebo control “fast fail” trial of tianeptine. The student will be trained to employ and analyse both task and resting state functional MRI. The will also learn clinical and neuropsychological assessments applicable to autism.

Objectives / project plan:


Year 2: Develop expertise in neuroimaging, analysis of cognitive and resting fMRI and behavioural data.
Targeting Serotonin for the Treatment of Social Impairment and Repetitive Behaviours in Young Adults with Autism Spectrum Disorders and Hyperserotonemia.

Year 3: Complete recruitment, imaging and statistical analyses.
Year 4: Prepare and present data at international conference. Write dissertation thesis along with high quality peer-reviewed publications.

Two representative publications from supervisors:


Keywords: Autism; Neurodevelopment; Serotonin; Pharmacological fMRI; Tianeptine;

BRC Theme/s: Child and Neurodevelopmental Disorders
               Neuroimaging
               Translational Therapeutics
               BioResource
               Clinical Research Facility
The road not taken. Identifying how risk factors for Autism Spectrum and related conditions alter the path of perinatal brain development?

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Project Description

Background: The genes and environmental risk factors associated with autism act primarily prenatally or in the first year of life. Not everyone at-risk of Autism Spectrum Disorder (ASD) goes on to develop ASD, but early interventions work best. Thus, there is a compelling need to establish who is most likely to benefit from treatment; and to identify individual treatment targets within what is a very diverse population. To do this, powerful MRI techniques and careful behavioural phenotyping will provide the most detailed assessment ever of the growing brain in babies at risk of ASD. The overarching aim is to identify early divergence from typical maturation pathways in children who have a first degree relative with ASD, and therefore themselves a higher likelihood of developing autistic traits. This will reveal potential new treatment targets and guide early intervention to children most at risk of adverse outcomes.

Planned research methods and training provided: The student will be trained in analyses of resting state functional MRI measures of brain activity and functional connectivity. Approximately 800 typically-developing infants have already been scanned using state-of-the-art acquisition methods as part of the developing human connectome project (dHCP) which will provide a reference dataset. A number of foetuses and neonates at risk of ASD have also been scanned at the onset of the study and therefore the student will have access to data early in the project for training and exploration of the research questions.

Training will be provided in recruitment, screening and taking informed consent according to GCP standards. Behavioural measures are collected through the ages of 1-2 years old and the candidate will learn to conduct these assessments, including gold standard ASD assessments and thereby add to the at risk cohort during this study. This rolling timeline will allow comprehensive training from participant entry to data write-up within the PhD time-frame.

This project links to the EU-AIMS consortium, the world’s largest Autism grant, joining patient organizations, academia and industry across Europe to develop novel treatments. It will provide a unique opportunity to share ideas, gain multidisciplinary perspectives and network.

Objectives / project plan:
Year 1: Training in recruitment, behavioural and MRI methods.
Year 2: Analyses of existing datasets. Rolling recruitment, scanning and behavioural assessments of infants. Preparation of abstracts for conference (poster) presentations
BRC-006  The road not taken. Identifying how risk factors for Autism Spectrum and related conditions alter the path of perinatal brain development?

**Year 3:** Writing up initial analyses for publication. Explore novel multimodal methods (e.g. ‘machine learning’ techniques) to identify subgroups and predict outcome. Conference attendance – aiming at oral presentations.

**Year 4:** Complete analyses and write up publications alongside thesis preparation.

**Two representative publications from supervisors:**


**Keywords:** Autism Spectrum Disorder; foetal MRI; neonatal MRI; fMRI;

**BRC Theme/s:**  
Child and Neurodevelopmental Disorders  
Neuroimaging  
BioResource
**Project Description**

**Background:** Epilepsy and autism spectrum disorders are two common serious disorders of neurodevelopment. They can co-occur and are associated with structural and functional changes in the brain. Both disorders are complex, occur over neurodevelopment and, reflecting this, brain changes associated with these disorders can be highly variable from person to person. For infants and children especially, our ability to detect these atypical changes in the brain using neuroimaging are hampered by the ongoing typical neurodevelopment. This effectively means that the age of a child can determine the sensitivity of neuroimaging to pathology.

**Aims and Importance:** This project will aim to develop a dynamic atlas of the developing brain using magnetic resonance imaging (MRI) and statistical modelling. Using advanced quantitative MRI relaxometry, the project will expand this atlas to be adaptable to different MRI sites and scanners, ensuring that the resulting work can be used translated beyond specialist research sites. Finally, it will use this atlas to investigate tissue abnormalities in individual children with epilepsy and autism, two related neurodevelopmental disorders.

**Planned research methods and training provided:** The candidate will build statistical models of image intensity changes occurring over infancy and childhood, initially using pre-existing structural MRI data. They will receive training in image analysis and registration and neurobiological aspects of brain development. They will also be trained in supervised and unsupervised machine learning techniques applied to medical imaging. This project will be highly collaborative, involving interactions with clinicians, physicists, image scientists and statisticians.

**Objectives / project plan:**

- **Year 1:** Training in statistical packages (especially R) and image registration techniques. Begin collecting MRI data (T1 and T2 relaxometry) in children (both patients and healthy volunteers).
- **Year 2:** Completion of data collection. Build computational models of brain development from pre-existing data.
- **Year 3:** Optimise tissue pathology detection using quantitative MRI. Write-up results.
- **Year 4:** Finalise image analysis and complete write-up.
Two representative publications from supervisors:


Keywords: Epilepsy; Autism Spectrum Disorders; Neuroimaging; Neurodevelopment; Developmental Modelling;

BRC Theme/s: Child and Neurodevelopmental Disorders
Bioinformatics and Statistics
Biomarkers and Genomics
Neuroimaging
BRC-008 Novel plasma biomarkers for dementia in Down syndrome, a genetic cause of Alzheimer's disease

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Project Description

Background: Cognitive decline and dementia is a common part of the ageing process in Down syndrome (DS - trisomy 21) due to an extra copy of the amyloid precursor protein (APP) gene on chromosome 21, leading to Alzheimer’s disease (AD) brain pathology. DS can thus be viewed as a genetic form of AD, with a clinical presentation and age at onset that is similar to autosomal dominant causes of AD.

Novelty and Importance: DS is a critically important patient group for clinical trials of treatments to prevent and delay AD pathology and dementia symptoms, which could inform AD treatment in other patients. But they are currently excluded from treatment trials due to poor tolerability of invasive procedures and lack of markers of dementia progression. A reliable blood biomarker would overcome these issues and help to address disease burden in this vulnerable population. This proposal is to explore new plasma AD biomarkers in DS using cutting-edge methods including super-sensitive immunoassays using a Simoa analyzer and immuno-PCR. The results will have immediate impact by enabling early-phase clinical trials of new treatments to prevent or delay AD in DS.

Primary aim(s): To establish the utility of plasma biomarkers for cognitive decline in DS (including neurofilament light, a marker of neurodegeneration; modified Amyloidβ - pyroGlu-3 Aβ, a particularly sticky form of Amyloidβ believed to trigger plaque formation), by

- Exploring cross-sectional relationships of biomarkers with age and dementia symptoms
- Determining longitudinal change in biomarker levels and clinical correlates
- CSF will be available (n=15-20) to test relationships between peripheral and central biomarker levels.

Planned research methods and training provided: The student will have a unique opportunity to gain both clinical research skills (phlebotomy, cognitive assessments) and laboratory skills (processing and storing samples, using assays) as well as valuable transferable research skills (ethics, consent, working with vulnerable patient groups).
The student will benefit from working within an established consortium (The LonDownS Consortium) with genetics, biomarker and clinical expertise, while conducting longitudinal assessments with an existing DS cohort.

**Objectives / project plan:**

**Year 1:** training - research governance and ethics, cognitive assessments, phlebotomy. Start data and sample collection

**Year 2:** ongoing data/sample collection; training in laboratory techniques

**Year 3:** data/sample collection to month 6; analysis/write up month 7-12

**Year 4:** complete analysis/write-up

**Notable aspects:** The student will benefit from considerable input from Probiodrug, a drug company based in Germany (funding for pilot work, assays, and training).

**Two representative publications from supervisors:**

1: [https://www.nature.com/nrn/journal/v16/n9/abs/nrn3983.html](https://www.nature.com/nrn/journal/v16/n9/abs/nrn3983.html)

2: [https://doi.org/10.1016/j.freeradbiomed.2017.08.024](https://doi.org/10.1016/j.freeradbiomed.2017.08.024)

**Keywords:** Dementia; Down Syndrome; Alzheimer’s disease; Biomarkers;

**BRC Theme/s:** Child and Neurodevelopmental Disorders

Dementia and Related Disorders

Biomarkers and Genomics

Translational Therapeutics

BioResource

Clinical Research Facility
BRC-009  Brain stimulation and cognitive training as a new non-pharmacological treatment for ADHD

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Project Description

Background: ADHD patients are treated with stimulant medication which is very efficacious. However, not all patients respond to the medication, it has side effects and has limited longer-term efficacy. Therefore, new treatments that have longer-term efficacy and that are based on the underlying brain pathology may be more promising than treatments that were discovered by chance like stimulant medication. Brain modulation therapies like transcranial direct current stimulation when combined with cognitive training have shown to affect the plasticity of the brain and to have longer-term positive effects on cognition and behavior in other patient groups. A key target for brain stimulation in ADHD is the right inferior frontal cortex (rIFC) which mediates inhibition and attention and which has been shown to be consistently underfunctioning in patients with ADHD and to be upregulated with stimulant medication. Studies in healthy adults, and pilot studies in ADHD adults and adolescents have shown that stimulation of rIFC together with cognitive training enhances neuroplasticity and boosts the inhibition & attention training effects and can lead to improved performance and behavioural symptoms. Therefore, the project aims to use a promising safe and painless neuromodulation method, called transcranial direct current stimulation (tDCS), consisting of weak electrical currents, to modulate rIFC to boost inhibition/attention training in children with ADHD.

Novelty and Importance:  This is a very innovative proof of concept randomised controlled trial aiming to develop a novel, cost-effective, non-pharmacological brain-based therapy for ADHD. A few pilot studies have tested tDCS in ADHD children and found promising effects, but have not combined it with several sessions of cognitive training. This will be the first RCT of tDCS combined with cognitive training of inhibition and attention in ADHD children. The project is important clinically as if successful, it will provide a novel brain-based treatment for ADHD.

Primary aim(s):  This study aims to test for the first time in 40 ADHD children, whether stimulation of rIFC together with inhibition/attention training over 3 weeks will improve these and other cognitive functions mediated by rIFC and the clinical ADHD symptoms and whether the effects are still observed 6 months after the neurotherapy.

Planned research methods and training provided:  The PhD will be an opportunity to gain wide-ranging expertise in the neurobiology of ADHD, cognitive neuroscience, brain stimulation, clinical and neuropsychological assessments, EEG, and cognitive training.

1) Cutting-edge transcranial direct current stimulation methods.
2) Cognitive training (Use of a cognitive training task battery developed by Yale University)
3) Clinical and cognitive assessment of a child psychiatric disorder
Overarching objectives: To conduct a randomised clinical trial of a novel neuromodulation therapy in children and adolescents with ADHD, including patient recruitment & assessment, administration of therapy, testing outcome measures and analyzing and write-up of data.

Objectives / project plan:
- **Year 1**: Training in above mentioned skills; patient recruitment
- **Year 2**: Recruitment, assessment, treatment administration and data analysis
- **Year 3**: Recruitment, assessment, treatment administration and data analysis
- **Year 4**: Final analysis and write-up.

Two representative publications from supervisors:


Keywords: ADHD; Transcranial direct current stimulation; Cognitive training; Inhibition; Attention;

BRC Theme(s): Child and Neurodevelopmental Disorders
Neuroimaging
Translational Therapeutics
BRC-010 Multi-modal objective measurement of mental health problems in autism

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Project Description

Background: Co-existing mental health problems occur in three-quarters of people with autism and have a major impact on outcomes and quality of life. However, they are difficult to detect because of autism-specific problems with communication and lack of ‘emotional literacy’ – the ability to detect and describe one’s own emotions. We want to develop objective measures to identify and measure quantitatively emotional states in people with autism that can ultimately be translated into clinical practice for diagnosis and intervention.

Novelty and Importance: At present there are no validated objective measures of mental health in people with autism. This project would provide one of the first studies to identify anxiety and ADHD among children with autism through convergent multi-modal measurement, including both traditional and novel methodologies.

Primary aim(s): To assess the feasibility of reliably identifying anxiety and ADHD among children with autism and developing a validated battery for assessment and intervention monitoring.

Planned research methods and training provided: You will examine a wide range of concurrent behavioural and physiological responses to planned challenges. These include the structuring of challenges, software identified emotional states (Affectiva), galvanic skin response, heart-rate and heart-rate variability, observer-rated responses and parent questionnaires and interviews. Training will be provided in the presentation of challenges (the Autism Diagnostic Observation Schedule and computer based tasks), electrophysiological measurement from participant management and data capture to data extraction, processing and analysis. Training in study design principles will be provided for the proposed final year validation study.

Objectives / project plan:

Year 1: Literature review, familiarise with project cohorts (SNAP, QUEST and ASTAR), acquire experience and skills in electrophysiological data capture and processing, competence in methodology.

Year 2: Data analysis, Acquisition of advanced data analytic methods appropriate to each measure and assess their convergent validity.

Year 3: Publication of initial findings. Development of optimal measurement battery and of clinical validation study

Year 4: Complete clinical validation study, write-up of dissertation.
BRC-010 Multi-modal objective measurement of mental health problems in autism

The student will publish during the PhD and attend relevant international conferences. While much of the data will already be collected, there will be opportunities for the student to gain experience in data collection at the beginning of the study period and also through a smaller clinical validation study towards the end. For students with an interest in clinical aspects, there is the work programme can develop skills relevant to subsequent clinical training.

Two representative publications from supervisors:


Keywords: Autism; Biomarkers; e-Health; Anxiety; Clinical Outcomes;

BRC Theme/s: Child and Neurodevelopmental Disorders
Bioinformatics and Statistics
Biomarkers and Genomics
Mobile Health
Project Description

Background: Social difficulties are implicated in the onset and maintenance of eating disorders; although the underlying mechanisms for these issues have been scarcely investigated.

Novelty and Importance: This study will employ an experimental medicine approach to clarify the underlying mechanisms of social difficulties in patients with eating disorders. It will be the first study assessing the quality and complexity of social networks, and the cognitive processing of social stimuli depicting the risk of social rejection in a large population of adolescent patients. The findings from this study will be used to plan and develop a larger randomized-controlled trial testing a novel online and self-directed training to address biased cognitive processing of social stimuli and isolation in patients with eating disorders. The findings will also be used to plan for experimental medicine studies investigating the same topic in adolescents suffering from obesity.

Primary aim(s): The primary goals of this study are: i) to test the complexity and quality of social networks in adolescents with eating disorders, compared to healthy peers; ii) to develop and test the feasibility and preliminary effectiveness of a novel computerized, guided self-help intervention targeting biased cognitive processing of social stimuli and isolation in adolescents with eating disorders.

Planned research methods and training provided: A cross-sectional study and a longitudinal, randomized-controlled trial will be conducted. Training in the development of reaction-time based computerized tasks and in the online implementation of these tasks, using computer programs such as Inquisit and E-prime will be provided. Training in the clinical assessment of patients with eating disorders using structured clinical interviews will also be given. The study will entail training in conducting small-scale randomized controlled studies and in using advanced statistical analyses to analyse the quantitative data, such as linear mixed models. Finally, training will be provided in conducting novel online assessments to collect data on social networks.

Objectives / project plan:

Year 1: The objectives for the first year are: i) to conduct a systematic review and meta-analysis on interpersonal sensitivity, biased cognitive processing of social stimuli, and physiological reactivity to interpersonal stress in emotional disorders, ii) to develop and validate the testing and intervention materials, iii) to obtain ethics approval.

Year 2: The main objective for year 1 is the recruitment of participants and data collection.

Year 3: The main objectives are data analyses and dissemination of findings through peer-reviewed publications and conference presentations.

Two representative publications from supervisors:


Keywords: Eating Disorders; Social Processing; Cognitive Bias; Adolescents; Online interventions;

BRC Theme/s: Obesity, Lifestyle and Learning from Extreme Populations
Mobile Health
Patient and Carer Involvement and Engagement
From research to practice: Enhancing treatment response in depression through a stratified medicine model

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Project Description

Background: Potential predictors of non-response to treatments for depression have been extensively researched in past decades, since identifying predictors of treatment success has substantial implications for reducing the burden of this disabling illness. In spite of this, no personalized treatment program has yet reached clinical practice. This is partly a consequence of marked heterogeneity in previous findings. This heterogeneity is likely driven by the presence of many potential predictors, only a few of which are accounted for in individual studies. Variability between patients and treatment characteristics also contribute to inconsistent findings across investigations. While a difficult challenge to overcome, the magnitude of the literature and reliability of some factors across studies indicate that a ‘risk-factor’ measure (comprising a set of potential predictors) could provide a valuable pre-treatment pointer of which patients may require more intensive treatments to achieve remission from depression.

Novelty and Importance: This PhD project will progress the field substantially by amalgamating all previous evidence to systematically develop a prospective risk-factor measure for non-response. The measure will subsequently be validated in two novel, large studies. If successful, this can form the basis of a protocol for a stratified intervention trial.

Primary aim(s): To develop a testable method of prospectively predicting treatment response, such that the measure can be trialled in a stratified treatment design, which will markedly increase the rapidity with which this could be implementable widely, particularly in primary care services.

Planned research methods and training provided:
1) Literature review: training through available courses and supervisor expertise
2) Measure development: training through psychometrics course, liaison with academic collaborators
3) Validation data analysis: training through statistics courses and supervisor expertise

Objectives / project plan:
Year 1: Conduct systematic review of potential predictors of response to common treatments for depression. Predictors selected based on feasibility to measure in practice, as well as reliability and consistency of its relationship to subsequent response across evidence base.
Year 2: Measure development and finalisation. All data analysis preparation.
From research to practice: Enhancing treatment response in depression through a stratified medicine model

**Year 3:** Completion of data analysis and write-up

**Year 4:** *If possible, develop proposal for stratified trial (potentially as a post-doctoral fellowship or similar)*

The two projects planned for validation of the risk-factor measure both assess a large array of demographic, clinical, psychosocial and biological factors in patients with depression before and after treatment: *PROMPT study* (N=180; Grant et al., 2014); *LQD study* (N=276; Marwood et al., 2017).

**Two representative publications from supervisors:**


**Keywords:** Precision psychiatry; Depression; Treatment Response; Mood Disorders; Stratified treatment;

**BRC Theme/s:** Affective Disorders and Interface with Medicine Translational Therapeutics
BRC-013 Understanding the impact of psychiatric morbidity on employment and benefit changes: A data linkage project

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Project Description

Background: The largest cause of long term occupational disability is mental disorders. Closing the disability employment gap has become a focus for recent UK government social policy initiatives, as those being disabled are 32% less likely to be in employment compared to non-disabled people. 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 propose to link and analyse 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 (over 380,000) referred to psychiatric services in the UK and will enable a series of longitudinal studies to examine the relationship between occupational functioning, welfare receipt and psychiatric morbidity. The results can be used to inform policy on the provision of benefits and welfare to patients and to support their return to work as well as feed directly into patient care.

Primary aim(s):
- To understand the impact of psychiatric morbidity on benefit changes and occupational functioning
- To examine whether there is a differential impact between various clusters of disorders, benefit changes and occupational functioning

Planned research methods and training provided: The data linkage will be done by the DWP. The student is expected to apply quantitative data analyses techniques for longitudinal data in the statistical packages STATA and MPlus. Training will be predominantly provided by KCL, but some budget will be made available for external courses on a needs basis. The majority of the training will take place at the end of year 1 and the beginning of year 2.

Objectives / project plan:

Year 1: To conduct a thorough systematic literature review on occupational functioning and psychiatric morbidity, obtaining ethical approval, conduct a pilot data linkage, start data linkage, writing a statistical analyses plan.
Year 2: Finalise data linkage, extraction and cleaning of the CRIS/DWP data and conduct the quantitative data analyses.

Year 3: Finalise quantitative data analyses, writing up PhD thesis, writing for publication, dissemination of findings on conferences and stakeholder events.

Expected outputs (end of year 3):
- high quality database with combined CRIS/DWP data
- organisation of successful stakeholder meeting to disseminate results
- dissemination of results at (inter) national speaking events
- at least 3 peer-reviewed scientific publications published or in preparation

Two representative publications from supervisors:


Keywords: Mental health; Occupational health; data linkage; Statistics; 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
BRC-014  Identifying digital biomarkers of treatment response in patients with depression and anxiety disorders receiving psychological treatments.

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Project Description

Background:  Approximately 50% of people undergoing psychological therapies for depression do not respond within 3 months.  We have no way of identifying those who will respond and those who will not.  If one could identify who is likely to respond before committing to a prolonged course of CBT, this would improve patient care, meeting the precision psychiatry goal of the BRC.

Novelty and Importance:  IAPT services treat in the region of 800,000 individuals per year.  If the identification of digital biomarkers associated with likely treatment response allowed services to treat a smaller number of individuals with higher response rates, whilst other treatment modalities could be used for those unlikely to respond to CBT, the benefits would be enormous.

Primary aim(s):  To identify digital biomarkers associated with non-response to CBT in individuals with depression.

Planned research methods and training provided:  The student would be part of the RADAR-CNS team within KCL - a strong community of senior investigators and postdocs able to advise on issues ranging from PPI, clinical study protocol design, analytics and regular meetings/conferences.

A patient and professional involvement phase would consist of qualitative study using focus groups of IAPT patients and separate groups of IAPT practitioners, to solicit their views about the advantages of the approach and nature of variables to be collected.

The main study is an observational non-interventional study.  Participants will be recruited from an IAPT service, and followed over the course of 16 weeks.  Over that period they will be asked to wear a wrist-worn consumer fitness device and to download an app on their smartphone.  These technologies will passively harvest data on the individual’s activity levels, circadian rhythms using accelerometry and heart rate, and patterns of movement using de-identified GPS signals.
BRC-014 Identifying digital biomarkers of treatment response in patients with depression and anxiety disorders receiving psychological treatments.

We will further ask the participant to do a number of active tasks including speech, cognition and questionnaires on stress, mood and daily hassles using an experience sampling methodology protocol. Participants will complete an outcome schedule every 4 weeks.

Using methodologies developed in RADAR-CNS, we will identify patterns of signal from the smartphone and wearable which identify individual who do or do not respond to treatment.

Objectives / project plan

Year 1: Protocol development, focus groups of therapists and patients. Conduct literature review. Gain ethics approval

Year 2: Start main recruitment over 18 months period. Follow up of recruited participants.

Year 3: End recruitment. Complete data collection.

Year 4: Data-analysis and write up.

Two representative publications from supervisors:

1: Hepgul, N. King, S. Amarasinghe, M. Breen, G. Grant, N. Grey, N. Hotopf, M. Moran, P. Pariante, C.M. Tyleé, A. Wingrove, J. Young, A.H. Cleare, A.J. Clinical characteristics of patients assessed within an Improving Access to Psychological Therapies (IAPT) service: results from a naturalistic cohort study (Predicting Outcome Following Psychological Therapy; PROMPT) BMC Psychiatry 2016 16:52


Keywords: Mobile health; Depression; Mental health; Digital biomarker; Stratification biomarker;

BRC Theme/s: Affective Disorders and Interface with Medicine
Bioinformatics and Statistics
Mobile Health
Patient and Carer Involvement and Engagement
BRC-015  Repetitive transcranial magnetic stimulation (rTMS) in anorexia nervosa: An exploration of cognitive mechanisms of change

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Project Description

Background:  Treatment of anorexia nervosa (AN) in adults is problematic, as ‘talking’ therapies only lead to remission in 10-40%. Over time, key symptoms of AN, e.g. food restriction and excessive exercise, become highly habitual, which is thought to contribute to their persistence. Little is known about how to reverse these disorder-specific habits, but evidence suggests that new learning needs to occur.

rTMS is a non-invasive brain stimulation method, thought to be one of the most promising emerging treatments for AN in adulthood. We have shown in a proof-of-concept trial that high frequency rTMS leads to short-term reductions in AN symptoms and improvements in decision making (McClelland et al., 2016). We have also recently completed the first ever sham-controlled double blind RCT of rTMS in AN showing improvements in BMI and in mood compared to sham treatment.

Novelty and Importance:  Emerging understanding of the neurobiological effects of rTMS implicates synaptic plasticity and suggests rTMS could be used profitably in combination with other plasticity-inducing interventions, e.g. cognitive training (Cirillo et al., 2017). Very few studies have examined cognitive correlates and predictors of rTMS response in eating disorders (Dalton et al., 2017). We propose to conduct further studies into the effects of rTMS on neurocognition in AN (with a focus on disorder specific habit-learning and with the longer term aim of exploiting potential synergistic effects of rTMS and cognitive training).

Primary aim(s):  To improve our understanding of the short-term effect of rTMS on neurocognitive processes in AN, (particularly disorder-specific habit-learning) and how this relates to symptomatology.

Planned research methods and training provided:  The student will receive in-house training in the practicalities of delivering rTMS and using neuronavigation for localisation of the stimuli. They will also attend an established training course into theory and practice of rTMS.

Objectives / project plan:

Year 1:  The student will be introduced to theory and practice of different rTMS strategies (e.g. high and low frequency). They will carry out a systematic review of the effects of rTMS on neuro-cognition in psychiatric disorders, to identify the most promising neuro-cognitive targets for further study.
BRC-015  Repetitive transcranial magnetic stimulation (rTMS) in anorexia nervosa: An exploration of cognitive mechanisms of change

Year 2 and 3: The student will carry out a sham-controlled experimental RCT comparing one session of low- and high-frequency rTMS applied to the DLPFC in patients with AN. Neurocognitive outcomes and symptoms will be assessed. They will also conduct a case series of therapeutic LF-rTMS (20 session) (not yet studied in AN).

Year 4: Writing up.

Two representative publications from supervisors:


Keywords: Repetitive transcranial magnetic stimulation; Eating disorders; Anorexia Nervosa; Cognition; Habit learning;

BRC Theme/s: Obesity, Lifestyle and Learning from Extreme Populations
Translational Therapeutics
Co-prescribing in dementia: Providing an evidence base for clinical decision support

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Project Description

Background: As a late-life mental disorder, dementia naturally co-occurs with a range of other health conditions, and people with dementia are often receiving multiple medications for other conditions from the time of first diagnosis onwards. Polypharmacy in older people, particularly in people with dementia, is widely recognised as potentially problematic; however, the evidence base for avoiding and/or amending this when present is very limited. Using the CRIS data resource, we are able to assemble large cohorts of people at different stages of dementia, and have now developed a range of algorithms to standardize outcomes. In addition, colleagues at SLAM Pharmacy and SLAM MHOAD CAG, in collaboration with the Centre for Translational Informatics, have recently developed the Medichec app (www.medichec.com) which allows co-prescribed medications to be evaluated for one particular adverse feature (anticholinergic activity) and represents a novel platform for delivering decision support. It is now beginning to be used routinely in memory assessment services.

Novelty and Importance: The use of health records ‘big data’ for pharmacoepidemiological research is expanding and increasingly recognised. Dementia care stands to benefit in particular because of the high frequency of co-prescribing. SLaM CRIS has one of the largest cohorts of people with dementia receiving assessment and care, with an unrivalled range of linked data and natural language processing applications for case characterisation.

Primary aims:
1) To assemble published material on receptor occupancy and other characteristics of medications
2) To develop scales to allow identification of these characteristics in historic cohorts and investigate associations with dementia-relevant outcomes (e.g. rate of cognitive decline, mortality, fall/fracture hospitalisations
3) To pilot the development/enhancement of Medichec (or an equivalent app) to provide decision support and carry out early-phase evaluation of uptake effects on practice.

Planned research methods and training provided:
- Quantitative methodology
- ‘Big data’ analytics
- Natural language processing
- App development
Co-prescribing in dementia: Providing an evidence base for clinical decision support

Objectives / project plan:

Year 1: Review literature on available characteristics of prescribed medication with potential clinical relevance (e.g. receptor occupancy, propensity for sedation). Receive PPI on design and prioritisation. Develop methods for real-time characterisation.

Year 2: Carry out a series of analyses investigating associations with clinically relevant outcomes in cohorts of people with dementia.

Year 3: Translate findings from Year 2 analyses into clinical decision support initiatives via Medichec or an appropriate other platform. Complete and submit thesis

Two representative publications from supervisors:


Keywords: Clinical informatics; Epidemiology; Pharmacoepidemiology; Dementia; Polypharmacy;

BRC Theme/s: Dementia and Related Disorders
Clinical and Population Informatics
BRC-017 Investigating the potential of 5HT7 antagonists for the treatment for cognitive impairment in bipolar disorder: A proof of principle neuroimaging project

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Project Description

Background: Bipolar disorder is a serious mental health problem in which people experience repeated episodes of depression and elated mood. Bipolar disorder affects around 1.2 million people in the UK. Around 60% of people with bipolar disorder experience cognitive impairment, such as difficulties with attention and memory, which greatly affects the ability to work and hold relationships. Currently there are no effective drug treatments for cognitive impairment in bipolar disorder. However, drugs which block a type of brain chemical receptor, called the 5HT7 receptor, may be a promising new treatment.

Novelty and Importance: This innovative MRC funded study, in collaboration with Janssen Pharmaceuticals, will advance our understanding of the potential of 5HT7 antagonists for the treatment of cognitive impairment in bipolar disorder which may lead to the development of new treatments.

Primary aim(s): To understand the effect of 5HT7 antagonism on brain activity and cognitive performance in people with bipolar disorder.

Planned research methods and training provided:

Research methods: This project will provide excellent skills in the use of pharmacological functional MRI (fMRI) to examine the effects of the 5HT7 receptor antagonist, JNJ-18038683, and placebo on brain activity and cognitive performance in people with bipolar disorder and healthy controls. Participants will complete a screening visit where cognitive performance will be comprehensively assessed using the ISBD-BANC cognitive battery. Participants will be imaged on day 7 of each treatment using fMRI to determine drug effects on cognition and emotional processing related brain activations, and using the ISBD-BANC to determine effects on cognition. Drug related effects on brain function will be assessed using state of the art neuroimaging analysis infrastructure available at the Centre for NeuroImaging Sciences.

Training: Training will be provided in pharmacological neuroimaging, participant recruitment, cognitive and mood assessment, functional MRI imaging and analysis.
Investigating the potential of 5HT7 antagonists for the treatment for cognitive impairment in bipolar disorder: A proof of principle neuroimaging project

Objectives / project plan:

Year 1: Understand fMRI methodology in the assessment of cognitive impairment in bipolar disorder, systematically review previous studies, and gain expertise in recruiting and assessing participants.

Year 2: Develop expertise in MRI imaging, working with industry partners, and experience in the analysis of neuroimaging and behavioral data.

Year 3 / 4: Consolidate skills, complete participant imaging and data analysis, present results at an international conference, and submission of thesis and project publications.

Other notable aspects:

The student may also have an opportunity to work on further upcoming industry supported pharmacological fMRI studies in bipolar disorder led by Dr Stokes.

Two representative publications from supervisors:


Keywords: Bipolar Disorder; Neuroimaging; Cognition; Translational Therapeutics; Mood;

BRC Theme/s: Affective Disorders and Interface with Medicine Neuroimaging Translational Therapeutics BioResource Clinical Research Facility
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Project Description

Background: There is growing evidence that disturbances in the gut microbiome may play a direct role in development of brain-linked conditions including anxiety and depressive symptoms. Although there is extensive preclinical work to support these observations, human studies to date have generally been limited in scope; single species open-label supplements, and narrow clinical parameters. Importantly none have directly measured changes in gut microbiome resulting from probiotic administration, and correlated to clinical symptoms and relevant biomarkers. Furthermore, as previous studies have used a variety of different probiotic formulations (differences at a species and strain level are known to modulate very different physiological effects) this makes general conclusions difficult. Currently, there is no consensus as to which specific bacteria (at a strain level), would be most effective for reduction in depression and anxiety symptoms, which represents a significant barrier to wide-spread clinical implementation.

Novelty and Importance: This study will be the first double blind placebo controlled study to investigate the effect of a multi-strain probiotic administration on the gut microbiome in patients with depression, including specific biomarkers. It will provide the foundation for the design of larger multi-center studies, and the identification of specific bacterial strains that would be expected to target particular symptoms.

Primary aim(s):
1) To determine whether probiotic administration over 12 weeks leads to a significant change in gut microbiome diversity and colonization levels in patients with mild-moderate depression.
2) To investigate the effect of probiotic administration on psychological and blood-based biomarkers of depression (including emotional faces task and blood inflammatory markers).
3) To investigate the relationship between probiotic-induced change in gut microbiome (including colonisation levels) and clinical symptoms of depression and anxiety.

Planned research methods and training provided: Use of clinical rating scales, blood taking, use of the emotional faces task, 16S rRNA microbiome sample processing, sequencing and bioinformatics profiling, statistical modeling, Industrial placement.
Objectives / project plan:

Year 1: Commence recruitment of patients and enroll into study. Aim for 15 completed by end of year 1.

Year 2: Continue recruitment and enrollment of patients. Aim to complete 40 patients and commence microbiome and inflammatory marker analysis at Quadram Institute with LH.

Year 3: Finish analysis (including multivariate statistical framework analysis) and commence write up of thesis and papers arising. Aim to submit PhD thesis by middle of Year 3.

Year 4: Complete write up and corrections for PhD. Industrial placement.

Other notable aspects of the project: The study will have a third (non-KCL) supervisor (Lindsay Hall, Quadram Institute, Norwich) who will oversee and provide training in the microbiology and bioinformatics aspects of the study. The study will be receiving additional funding from a UK probiotics company (Protexin) who will be able to provide an industrial placement for 3 months of the study.

Two representative publications from supervisors:


Keywords: Depression; Anxiety; Probiotics; Experimental Medicine; Inflammation;

BRC Theme/s: Affective Disorders and Interface with Medicine
Biomarkers and Genomics
Patient and Carer Involvement and Engagement
Translational Therapeutics
Clinical Research Facility
BRC-019  Searching for cross diagnostic biomarkers in anorexia nervosa and autism spectrum disorder

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Project Description

Background:  Recent staging and maintenance models have postulated that difficulties in cognitive functioning play an important role in the maintenance of disordered eating in anorexia nervosa (AN). Research exploring thinking styles in individuals with AN have documented tendencies towards an inflexible thinking style and getting stuck in details. These characteristics are also defining symptoms of Autism Spectrum Disorder (ASD), which has led to research focusing on the overlap between AN and ASD. Indeed, recent findings demonstrate elevated prevalence of ASD symptoms among individuals with AN, and that these ASD traits are associated with poorer treatment outcomes.

Novelty and Importance:  Recent BRC-funded work from our lab demonstrated that relative to healthy individuals, adults with AN show greater inefficiency in neural processing during tasks involving central coherence and set shifting (Fonville et al. 2013; Lao-Kaim et al. 2015). However, since AN typically develops during adolescence, there is a pressing need for improved understanding of the mechanism involved during the early stages of illness. Thus, this study builds on these findings by examining the impact of comorbid ASD symptoms on various aspects of cognitive functioning in young people with AN, using neuropsychological assessments and functional neuroimaging during neurocognitive tasks.

Primary aim(s):  The study will recruit 200 young women with and without AN. The study will have two major components: 1) a cross-sectional assessment of differences in neuropsychological profile and neural processing between young women with AN and healthy young women as well as an investigation of the impact of comorbid ASD symptoms; 2) a longitudinal investigation exploring the impact of comorbid ASD symptoms along with neurofunctional profile on treatment response at a 6-month follow-up assessment.

Planned research methods and training provided:  
1.)  Assessment of psychopathology  
2.)  Neuropsychological assessments  
3.)  Collection and analysis of functional and structural MRI data  
4.)  Writing for publication, presentation skills for national and international conferences  
5.)  Communicating with main stakeholders: patients, carers, clinicians
6.) Developing psychoeducation materials
7.) Public engagement in research
8.) Possibility to collaborate with industry

**Objectives / project plan:**

**Year 1:** Develop skills and competency in assessment of psychopathology, neuropsychological assessment, and collection of fMRI data. Conduct and publish a systematic review of previous literature with help from collaborators.

**Year 2:** Finalise data collection and conduct data analysis under the guidance of collaborators. Present findings at international conferences.

**Year 3:** Publish results, present findings at conferences, and write thesis.

**Two representative publications from supervisors:**


**Keywords:** Anorexia Nervosa; Autism Spectrum Disorder; fMRI; Theory of mind; Set shifting;

**BRC Theme/s:** Child and Neurodevelopmental Disorders
Neuroimaging
BRC-020  A pilot randomized controlled trial of RESIST a computerized training intervention for binge eating: Testing the food addiction model.

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Project Description

Background: Bulimia Nervosa (BN) and Binge Eating Disorder (BED) are increasing in prevalence in young adults with a protracted course (32% symptomatic after 22 years)\(^3\). Current treatments are disappointing with a recovery rate of only 40\(^\%\)\(^4\). We have developed a novel approach to this problem. In collaboration with Dr Natalia Lawrence (University of Exeter) we have completed proof of concept studies using computerized training (RESponse Inhibition Training to food, RESIST) to inhibit approach to binge foods. The use of RESIST has shown benefits in overweight or obese participants, and in patients with binge eating.

Primary aim: To undertake a double-blind randomized trial to examine whether RESIST can reduce symptomatic behavior in people with BN and BED.

Planned research methods and training provided
1. Skills in conducting systematic review and meta-analysis
2. Skills in the design, delivery and analysis of randomized controlled clinical trials
3. Skills in neurocognitive assessments (FLARE, EEG)
4. Skills in data analysis using R
5. Skills in synthesizing process and quantitative data from RCT
6. The synthesis of the above in order to optimize and personalize treatment interventions.

Objectives / project plan:
Year 1: Systematic review of food addiction in BN, BED. Update theoretical model of BN and BED. Ethics approval in place (ethics for intervention completed, predictors to be added). Training in assessment of predictors (FLARE, EEG etc.).
Year 2: Completion of recruitment by 18 months. Completion of follow –up by 24 months.
Year 3: Data cleaning and analysis. Preparation of reports. PhD submission.
Year 4: Preparation of post-doctoral fellowship application.
A pilot randomized controlled trial of RESIST: a computerized training intervention for binge eating: Testing the food addiction model.

Two representative publications from supervisors:


Keywords: Bulimia nervosa; Binge eating disorder; Obesity; Food addiction; Response inhibition training;

BRC Theme/s: Obesity, Lifestyle and Learning from Extreme Populations
 Bioinformatics and Statistics
 Biomarkers and Genomics
 Mobile Health
 Patient and Carer Involvement and Engagement
 Translational Therapeutics
BRC-021  Cognition as a predictive biomarker in late-life depression

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Project Description

Background:  Depression and dementia are two of the most common conditions affecting the elderly population. The significant cognitive impairment which is common in late-life depression (LLD) often does not improve after remission of mood symptoms. Indeed, for some patients cognitive decline is progressive and is a prodrome for the development of dementia. Identifying which LLD patients will progress to dementia would allow new treatments to be tested in a highly enriched population and greatly increase the utility of translational studies in this area. One factor associated with the development of dementia among LLD patients is the age of onset of depression. However, a thorough investigation of the cognitive profile of people with LLD by age of onset and disease history has not yet been performed. Identifying any differences in cognitive profile between early and late-onset depression may be an important potential biomarker.

Novelty and Importance:  The mechanisms underlying the complex association between cognitive impairment and depression are unknown and there are no preventative treatments for progressive cognitive decline, thus presenting a major unmet clinical need. Early identification of those LLD patients with increased risk of dementia could allow for better targeted translational studies and clinical interventions (precision psychiatry). Further, this project will examine the utility of cognition as a biomarker predictive of treatment response in an open-label trial of Vortioxetine – a novel antidepressant with a unique mechanism of action that has been shown to improve both mood and cognition in the elderly (Katona et al. 2012).

Primary aim(s):
1. To improve our understanding of the association between cognitive impairment and depression;
2. To identify the differences in cognitive profile among LLD patients based on age of onset and disease history;
3. To assess cognition as a biomarker predictive of antidepressant treatment response in late life depression.

Planned research methods and training provided:  Systematic review, trial design and set-up, data collection & quantitative data analysis, academic writing.
BRC-021  Cognition as a predictive biomarker in late-life depression

Objectives/project plan:

Year 1: Systematic review of the existing body of literature on cognitive impairment in LLD;

Year 2: Analyses of data from the TWINS UK and PROTECT cohorts to explore the cognitive profile of people with LLD by age of onset and disease history;

Year 3: Open-label study of vortioxetine to assess cognition as predictive biomarker in LLD (set-up in years 1&2).

Two representative publications from supervisors:


Keywords: Depression; Late-life depression; cognitive impairment; Dementia; Cognition;

BRC Theme/s: Affective Disorders and Interface with Medicine
Dementia and Related Disorders
Translational Therapeutics
Clinical Research Facility
The role of subgenual frontal connectivity in predicting response to serotonergic medications

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Project Description

Background: There is an urgent need to develop imaging biomarkers of response to antidepressant medications in major depressive disorder (MDD). This serves the development of refined disease models and of novel treatments, as well as to develop decision support systems for individualized treatment algorithms. We have recently shown that subgenual frontal (SF) functional connectivity alterations predict subsequent recurrence in MDD patients whose symptoms were remitted. Dunlop et al., (2017) have shown that SF connectivity during resting state fMRI can be used to accurately predict non-response to antidepressant medications in treatment naïve patients. This demonstrates the high potential of SF connectivity as a biomarker of response to antidepressant treatment and recurrence risk in MDD.

Novelty and Importance: It is unknown, however, whether these findings generalise to patients with early treatment resistance as seen in UK primary care. Furthermore, the function of the SF cortex and its connectivity is still disputed. To address these questions, the student will acquire resting state fMRI data in patients independently recruited for an NIHR-funded randomised controlled trial comparing a novel computerised decision support algorithm for serotonergic medications with treatment as usual in primary care. Patients will all be non-responders to at least two serotonergic antidepressants in the current or previous episodes. We expect about 50% of patients to respond to treatment with serotonergic drugs over the 16 weeks of the trial. This will allow us to compare baseline MRI scans of treatment responders with non-responders.

Primary aim(s):
Aim 1: Determine whether resting state SF connectivity predicts subsequent response to treatment.
Aim 2: Determine whether SF connectivity is associated with individual differences on novel cognitive tests of blame attribution in social interactions

Planned research methods and training provided:
Training in clinical assessment of affective disorders including workshops on our MSc in Affective Disorders, as well as fMRI data acquisition and analysis will be provided.
Objectives / project plan:

Year 1: MRI scanning of n=9 patients with current MDD who are participating in an NIHR-funded clinical trial of antidepressant medication algorithms in primary care. Development of novel cognitive test.

Year 2: MRI scanning of n=20 patients with current MDD to complete total group of n=29 (including 5 lost to follow-up).

Year 3: Training in fMRI analysis and completing analyses, starting write up of manuscripts regarding cognitive and neuroimaging predictors of response to treatment.

Year 4: Write up of thesis and submission of journal manuscripts to high-quality journals.

Two representative publications from supervisors:


Keywords: fMRI; Guilt; Depression; Psychopharmacology; Biomarker;

BRC Theme/s: Affective Disorders and Interface with Medicine Neuroimaging
BRC-023 Exploring potential new therapies for psychiatric conditions and mood disorders: Retrospective pharmaco-epidemiological studies using the Clinical Practice Research Datalink

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Project Description

Background: Retrospective studies using patient data have become a useful tool to provide evidence for the therapeutic activity of drugs in new indications [1]. Given the paucity of new treatments, therefore, that have been developed for psychiatric and neurological conditions over recent years, the potential for securing these through drug re-positioning is clearly inviting.

With small-scale clinical studies showing that the oral antibiotic, minocycline, affords some benefit in early schizophrenia [2], we previously carried out this type of retrospective study and showed no effect of this drug on the likelihood of developing psychosis and other forms of severe mental illness (SMI) [3]. More generally, it is of interest to explore whether there are drugs like minocycline that might be re-positioned to help treat psychoses and/or mood disorders – drugs that are known to cross the blood-brain barrier, have anti-inflammatory and/or neuroprotective effects, and/or exert effects on glutamate and/or dopamine pathways. Drugs of potential interest, therefore, could include: celecoxib, diclofenac, indomethacin, tenoxicam, betaxolol, etc. Given that there are reports too of differences in SMI incidence between men and women [cf., 4] – a difference proposed due to estrogens – it is of interest too to determine whether there might be a protective effect in SMI gained through use of the contraceptive pill [5].

Novelty and Importance: Drug re-positioning is now accepted as a highly productive avenue of clinical exploration and is widely used within Pharma as an economic means to feed the drug discovery pipeline. The studies proposed here will hopefully provide much needed new leads for development of new and more effective treatments for SMI and mood disorders, and so could provide valuable evidence to support the mounting of clinical trials within the BRC of adjuvant therapies for these various conditions.

Primary aim(s): We propose to use patient data from the MHRA’s Clinical Practice Research Datalink (CPRD) to conduct pharmaco-epidemiological studies involving a series of retrospective cohort analyses to determine the beneficial effects that might be afforded by a range of drugs in treatment of SMI and mood disorders.
Exploring potential new therapies for psychiatric conditions and mood disorders: Retrospective pharmaco-epidemiological studies using the Clinical Practice Research Datalink

Planned research methods and training provided: Anonymized CPRD data will be obtained for patients who received treatment with drugs considered appropriate candidates (see list of illustrative examples given above), and the medical histories for these patients recorded. Validated code lists will then be employed to estimate the incidence of SMI, depression, and delirium, within each of the study cohorts. Poisson/negative binomial regression will subsequently be used to determine how the incidence rate for the test conditions is changed relative to the incidence in matched cohorts, adjusting for sex, age, socioeconomic status and year. The general population comparator cohorts will be identified matching 5:1 on sex, year of birth within ± 5 years, and medical history where applicable, to each individual in the given test cohort (cf., [6]). The student will be trained in interrogation of patient health care record data and in the use of statistical analyses and modelling in pharmaco-epidemiology (using Stata and Statistica software).

Objectives / project plan:

Year 1: Literature searches conducted to compile a list of candidate drugs for consideration; RCTs recently conducted for SMI, depression and dementia; recent pharmaco-epidemiological studies utilizing CPRD or similar data sources. Research protocol design for studies involving one candidate drug, eg, celecoxib. Preparation & submission of ISAC application to allow statistical analyses of the hypotheses pertaining to the effects of this candidate drug on the incidence of SMI, mood disorders and depression.

Year 2: Acquisition and analysis of CPRD data to test for the protective effects of the candidate drug in SMI, depression and dementia. (Costs for CPRD data access/use will be covered by the PIs and/or from Departmental funds.) Literature searches and research protocol designs for other drug studies.

Year 3: Preparation & submission of ISAC application(s) to allow statistical analyses of hypotheses pertaining to the other candidate drugs identified in year 1. Acquisition and analysis of CPRD data to test for the protective effects of these drugs in SMI, depression and delusion.

Year 3.5/4: Completion of work from Year 3, and preparation & submission of PhD thesis for examination

3. Herrero Zazo et al (2017) unpublished data (see references listed below)

Two representative publications from supervisors:


Keywords: Mood disorders; Severe mental illness; Pharmaco-epidemiology; Estrogen; Minocycline;

BRC Theme/s: Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Clinical and Population Informatics
BRC-024 Repairing a disordered sense of self: Neuromodulation in the treatment of depersonalisation disorder

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Project Description

Background: Depersonalisation disorder (DPD) is a psychiatric syndrome characterized by persistent and distressing feelings of unreality and alterations in a person’s sense of self. There are no established biological treatments. Case reports and small case series have reported promising responses to repetitive transcranial magnetic stimulation (rTMS) to prefrontal (ventro-medial prefrontal cortex: vmPFC) and temporo-parietal sites (temporoparietal junction: TPJ). The TPJ is thought to be important for somatosensory integration while the vmPFC plays a role in emotional regulation. As part of a BRC funded studentship we showed that a single rTMS session to both sites resulted in symptomatic improvement but only rTMS to vmPFC produced physiological changes (skin conductance reactivity) predicted to be related to treatment response. The time is ripe for a randomised controlled trial of multi-session rTMS in vmPFC versus Sham to study clinical efficacy. Further work has shown that transcranial direct current stimulation (tDCS) may also be promising as a therapeutic intervention on the basis of uncontrolled studies. We therefore plan to conduct controlled experiments using tDCS and can make use of the same measures of clinical and surrogate outcomes as used in the rTMS work.

Novelty and Importance: Our group is the only one in the UK carrying out such work and has an international profile. DPD affects around 1% of the population affecting young adults and tends to be chronic and disabling.

Primary aim(s): To test the efficacy of neuromodulation (rTMS and tDCS) as a therapeutic option in patients with DPD.

Planned research methods and training provided: This studentship will include the planning, conduct and writing up of such trials using patients linked to the DPD clinic at the Maudsley hospital. The project will examine possible mechanisms of action and will test a neuropsychological model of DPD using standard and novel cognitive tasks and will also include opportunities to develop fMRI paradigms relevant to the experience of Self. As well as learning about TMS the student will gain skills in neuroimaging, neuropsychological testing, clinical trials and psychiatric evaluation.
BRC-024 Repairing a disordered sense of self: Neuromodulation in the treatment of depersonalisation disorder

Objectives / project plan:

Year 1: Develop battery of test materials and physiological biomarkers (e.g., skin conductance) related to treatment response in DPD; recruit and characterize a group of patients seeking new treatments for DPD to be enrolled in studies.

Year 2: Carry out pilot and feasibility work of rTMS and tDCS to prepare for an RCT. Carry out a small RCT.

Year 3: Follow-up treatment groups; analysis of results; write-up.

Year 4: Prepare for postdoctoral fellowship and/or multicenter phase 3 trial of rTMS in DPD.

Two representative publications from supervisors:


Keywords: Depersonalisation disorder; rTMS; tDCS; Skin conductance; Neuropsychology;

BRC Theme/s: Affective Disorders and Interface with Medicine
Psychosis and Neuropsychiatry
Translational Therapeutics
Moving towards precision psychiatry: Identifying neuroimaging and blood-based markers of response to anti-inflammatory drugs in psychosis

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Project Description

Background: Antipsychotic medications are ineffective in approximately a third of patients with psychosis, but we do not have a reliable predictor of response to these treatments. However, alterations of brain morphology and connectivity, and activation of the immune system, seem particularly associated with this lack of response. On this basis, neuroimaging and immune markers could be useful to identify early on individuals less likely to respond to antipsychotics and who could benefit from other medications, such as anti-inflammatory drugs.

Novelty and Importance: Early treatment response is one of the strongest predictors of subsequent functional and clinical outcome in psychosis. There is therefore a crucial need to identify i. Markers of this early response and ii. Effectiveness of novel compounds for individuals who do not respond to existing drugs.

Primary aim(s): To use an innovative multimodal imaging and blood-based approach, to identify the brain morphological and neurofunctional, and immune response alterations associated with response to an anti-inflammatory drug in n=200 patients randomized to either the antibiotic minocycline or placebo as part of the BENEMIN trial (The Benefit of Minocycline on Negative Symptoms of Schizophrenia).

To specifically clarify whether basic static and dynamic functional connectivity, and inflammatory markers are associated with poor clinical response to minocycline over 6 months, and whether this relationship is mediated by the magnitude of the longitudinal changes in brain connectivity and immune function after treatment.

Planned research methods and training provided: All data have already been acquired. The student will be trained in basic and advanced methods of univariable and multivariable methods of analysis of neuroimaging and other biological and clinical variables, and in their interpretation as follows:
Objectives / project plan:

Year 1:
- Transfer of data from main database.
- Exploratory statistical analyses of data; preprocessing of structural and functional data.
- Training in analysis of brain morphology.

Year 2:
- Training and analysis of static and dynamic functional connectivity.
- Application of Graph Theory metrics including global network integration and global segregation to assess longitudinal changes in structural and functional brain connectivity and probe their relationships.

Year 3:
- Development of multivariable statistical models arising from the repeated measurements of subjects over time, and integrating patterns of change in immune biomarkers, to compare treatment groups.

Year 4:
- Submission of two papers for publication
- Writing up of the Thesis

Two representative publications from supervisors:


Keywords: Psychosis; Minocycline; Inflammation; Neuroimaging; Connectivity;

BRC Theme/s: Psychosis and Neuropsychiatry
- Neuroimaging
- Translational Therapeutics
Project Description

Background: Prevention of severe mental disorders such as psychosis is the most promising avenue for altering the course these conditions, saving the lives of many adolescents and young adults at risk for developing them.

Novelty and Importance: This PhD project will focus on identifying individuals at risk for developing mental disorders through e-Health individualised risk calculators and on treating them with first-in-class experimental therapeutics.

Primary aim(s): To improve the detection of individuals at risk for developing mental disorders, in particular psychosis. To develop first in class preventative treatment for these individuals.

Planned research methods and training provided: The candidate will learn how to use basic and advanced prediction modeling strategies to improve the detection of individuals at risk of developing psychosis. He/she will also learn how to integrate these algorithms into clinical routine through e-health apps. The student will also learn how to acquire imaging multimodal data and how to analyse them as part of mechanistic psychopharmacological experiments in these samples.

Objectives / project plan:

Year 1: During Y1 the candidate will learn how to develop individualised risk prediction tools and how to acquire psychopharmacological imaging data (including fMRI, MRS, PET, EEG) as part of experimental therapeutics studies conducted in at risk patients.

Year 2: During Y2 the candidate will learn how to integrate the individualised risk estimates with experimental therapeutics in at risk patients.

Year 3: During Y3 the candidate will learn how to measure the real world clinical benefits of stratification medicine and experimental therapeutics for the prevention of mental disorders. Candidate molecules may include: modulators of NMDA receptors, Phosphodiesterase-9 (PDE9) inhibitors, cannabidiol, modulators of potassium channels and intranasal oxytocin.

Year 4: During Y4 the candidate will learn how to validate these findings in independent samples.
Other notable aspects of the project:
The candidate will have the opportunity to train in one of the largest and most productive research groups on psychosis, with high quality clinical services and teaching. The candidate will additionally have the opportunity to access large databases of patients at high risk for developing mental disorders and collaborate with clinical services for these patients. At the end of the PhD the candidate will have acquired advanced skills in stratification medicine and cutting-edge experimental therapeutics in early psychosis.

Two representative publications from supervisors:


Keywords: Prevention; e-Health; Experimental Therapeutics; Neuroimaging; Risk;

BRC Theme/s: Psychosis and Neuropsychiatry
Bioinformatics and Statistics
Clinical and Population Informatics
Neuroimaging
Translational Therapeutics
BRC-027 Does altering synaptic function improve brain connectivity? An experimental medicine study with translation to schizophrenia and bipolar disorder.

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Project Description

Background: Abnormal brain network activity contributes to cognitive and behavioural impairments and it has been hypothesized that pharmacological modulation of abnormal network activity improves synaptic function, behavioural abnormalities and memory. In a number of neuropsychiatric illness, abnormal network activity has been ascribed but therapeutic interventions are currently not available. Levetiracetam (LEV), an antiepileptic drug, has been found to suppress aberrant network activity in preclinical models. Its mechanism of action is mainly attributed to its binding to the presynaptic vesicular protein SV2A. It is thought that SV2A has an important role in regulation neurotransmitter storage and release in vesicles. It has not been tested in humans and the dose-response relationship is unknown.

Novelty and importance: The discovery of a new PET tracer that binds to the brain SV2A ([11C]UCB-J) has given us the opportunity to evaluate a dose-response relationship with respect to its ability to modulate abnormal network activity. We will determine dose related occupancy of the SV2A protein in the human brain using Positron emission tomography (PET) and understand the relationship of levetiracetam’s ability to modulate brain networks using resting-state fMRI functional connectivity and associated behavioural paradigms. We will first use healthy volunteers to determine the dose-occupancy relationship and evaluate its safety. We will then evaluate the new experimental medicine in patients diagnosed with schizophrenia and bipolar disorder where abnormal brain connectivity has been hypothesized. If preclinical findings are proved then this will open a new class of therapeutics to treat neuropsychiatric illness where brain connectivity is altered.

Primary aim(s): The primary aim is to evaluate a new experimental medicine to modulate abnormal brain network activity in the context of neuropsychiatric illness.

Candidates will be trained in conducting functional MRI and PET imaging studies with provision of hands-on training in a group that is actively involved in these techniques. The project will also offer training in clinical and behavioural measures, statistical analysis, experimental medicine trial design and
BRC-027  Does altering synaptic function improve brain connectivity? An experimental medicine study with translation to schizophrenia and bipolar disorder.

Objectives / project plan:

Year 1: The goal will be to learn skills to conduct neuroimaging (both MRI and PET) as well start recruiting volunteers

Year 2: In the second year the goal will be to complete PET based target occupancy studies of levetiracetam in healthy volunteers to help determine dose-response relationships

Year 3: After obtaining occupancy data the goal will be to evaluate levetiracetam’s ability to modulate abnormal brain networks in patients diagnosed with psychotic illness using resting-state fMRI functional connectivity

Year 4: In the final year the goal will be to disseminate results through peer reviewed scientific journals and work towards submitting the thesis

Other notable aspects of the project: The new PET tracer has been standardized in healthy volunteers and the production of the tracer is now routinely available. Successful candidates will be supported hands on in these projects by an experienced team that work very closely with our industrial partner – IMANOVA

Two representative publications from supervisors: The project is new and hence there are no publications directly related to the project. The publications are representative of the techniques and skill set the team has to support the candidate.


Keywords: Schizophrenia; Bipolar disorder; Neuroimaging; SV2A; Brain connectivity;

BRC Theme/s: Psychosis and Neuropsychiatry
Biomarkers and Genomics
Neuroimaging
Translational Therapeutics
BioResource
BRC-028  Precision medicine in schizophrenia: Predicting response using genetic and imaging measures of glutamate dysfunction.

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Project Description

Background:  One third of patients with schizophrenia do not respond well to standard antipsychotic medication (treatment resistant schizophrenia (TRS)). The economic burden of TRS has been estimated as $11 Billion in the US, which approximates to around £2Bn in the UK.

The neurobiology of TRS is not yet understood, and this is a prerequisite for finding new medications to treat this very unwell patient group. Studies from our group have led to a novel neurochemical hypothesis of antipsychotic non-response, which involves dysfunction of glutamate neurotransmission. This hypothesis is supported by neuroimaging studies showing higher levels of glutamate in the brain of antipsychotic non-responders. It is also supported by genetic evidence linking genes implicated in glutamate pathways to antipsychotic response. This work is currently being extended with new data collection as part of a 5-year MRC-funded multi-centre program grant (STRATA), led by Dr MacCabe, and the TRIM study led by Dr Egerton. Lundbeck pharmaceuticals are funding further work to use these new data to derive combined biomarkers, using machine learning and other advanced statistical approaches. This project will combine genetic and neuroimaging approaches to discover, for the first time, how glutamate genetics and brain glutamate levels may together influence antipsychotic response, and to develop biomarkers of response for use in clinical trials, and ultimately, in clinical practice.

Novelty and Importance:  This research if successful, will lead to the first example of precision medicine in schizophrenia, and one of the first in psychiatry.

Primary aim(s):  This novel project will determine whether the elevated brain glutamate levels linked to antipsychotic non-response are driven by glutamate genetics, and whether the combined genetic-imaging approach can predict how well patients are likely to respond to antipsychotic treatment.

Planned research methods and training provided:  Skills training will include a) recruitment and assessment of patients with schizophrenia; b) acquisition and analysis of glutamate neuroimaging data using MRI scanning; c) training in genetics research; d) training in statistical analysis of imaging, genetic and clinical data including prediction modelling and machine learning; e) support in conference presentations and publishing results in journals.
**BRC-028  Precision medicine in schizophrenia: Predicting response using genetic and imaging measures of glutamate dysfunction.**

**Objectives / project plan:**

**Year 1:** Can glutamate genetic imaging discriminate between antipsychotic-responders compared to non-responders? (Cross-sectional sample of 100 patients from STRATA).

**Year 2:** Can glutamate genetic imaging predict response to clozapine in treatment resistant schizophrenia? (Longitudinal sample of 40 patients from TRIM with imaging at 2 time points plus genetics)

**Year 3:** Can glutamate genetic imaging predict antipsychotic response in first episode psychosis? (Longitudinal sample of 40 patients from STRATA, which the student would also participate in recruiting).

**Year 4:** The results of the three studies will be used to validate the results from each dataset in the other datasets, and combined to produce a predictive marker.

**Two representative publications from supervisors:**


**Keywords:** Precision medicine; Treatment resistant schizophrenia; Glutamate; Genetics; Neuroimaging;

**BRC Theme/s:**
- Psychosis and Neuropsychiatry
- Bioinformatics and Statistics
- Biomarkers and Genomics
- Neuroimaging
- Patient and Carer Involvement and Engagement
- Translational Therapeutics
- Clinical Research Facility
How does Cannabidiol act on the brain to improve psychotic and anxiety symptoms?

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Project Description
Background: Preclinical and experimental medicine studies indicate that CBD has antipsychotic and anxiolytic effects, yet has minimal adverse effects. A key outstanding issue is that its mechanism of action is still unclear.

Novelty and Importance: CBD is one of the most promising novel treatments in mental health, and represents a new class of pharmacological treatment.

Primary aim(s): To determine:
1. How CBD acts on the brain to produce its clinical effects.
2. The extent to which the therapeutic response to CBD is related to the polygenic risk score for schizophrenia

Planned research methods and training provided:
- Assessment of psychopathology
- Acquisition & analysis of neuroimaging data
- Acquisition & analysis of genetic data
- Development & evaluation of novel pharmaceutical compounds, in collaboration with industry

Objectives / project plan:

Design: Randomised placebo-controlled experimental medicine study. Participants (n=50) will be randomised to one of two treatment groups (n=25 per arm):
   i. Standard clinical care + Cannabidiol or
   ii. Standard clinical care + Placebo.
Randomisation will be double-blind. Standard clinical care involves psychological and practical support, provided by the OASIS service (Below).

Experimental Treatment: Oral cannabidiol, 600mg/day for 4 weeks. An identical placebo will be provided for the same period.
How does Cannabidiol act on the brain to improve psychotic and anxiety symptoms?

Participants: Adults (18-35 years) meeting the PACE criteria for being at Ultra High Risk (UHR) for psychosis will be recruited from OASIS, a well-established early detection service in the South London & Maudsley NHS Trust, which receives 200 new referrals per annum.

Assessments: Psychopathology will be assessed at baseline and at weeks 1, 2, 3 and 4 using the CAARMS. Substance use will be evaluated using the Cannabis Experience Questionnaire.

Neuroimaging data will be acquired in 2 sessions on a 3T MRI scanner, at baseline and at the end of treatment (week 4). Resting cerebral blood flow will be measured using Arterial Spin Labelling. Glutamate levels in the left hippocampus and GABA levels in the medial prefrontal cortex will be measured using MR Spectroscopy.

Venous blood will be collected for genetic analysis.

Analyses: Neuroimaging data will be analysed using established software. The polygenic risk score for schizophrenia will be estimated for each subject, using PRSice.

Timetable
Year 1: Engage with service users and OASIS. Obtain ethical approval. Secondment with industrial partner (BSPG). Co-ordinate shipment of CBD and placebo. Start subject enrollment and data collection.
Year 2: Data collection.
Year 3: Data analyses
Year 4: Dissemination of results; preparation for post-doc.

Two representative publications from supervisors:


Keywords: Cannabidiol; Psychosis; Biomarkers; Precision Psychiatry; Translation;

BRC Theme/s: Biomarkers and Genomics
Neuroimaging
Patient and Carer Involvement and Engagement
Translational Therapeutics
BioResource
BRC-030 Smartphone-based Interventions in Mental Health: Towards a Clinical Tool for Predicting and Preventing Psychotic Relapse

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Project Description

Background: Converging lines of evidence from animal and human models suggest that adult-life urban living can increase vulnerability to severe mental illness (Peen et al. 2010 Acta Psychiatr Scand. 12:84-93). Amongst all mental illnesses psychosis shows the strongest association with urbanicity, with epidemiological studies suggesting that more than 30% of all cases can be attributed to the detrimental impact of urban environments (Pedersen & Mortensen 2001 Arch Gen Psychiatry 58:1039-46). Remarkably, we still know very little about the mechanisms that underlie this effect.

Aim and Objectives: The overall aim of this project is to elucidate how the urban environment interacts with social stress reactivity to increase risk of psychosis. Specific objectives include:

To use smartphone technologies to measure reactivity to the urban environment in real time over a 2-week period, in 100 individuals with psychosis and 100 healthy people.

To follow-up participants for a period of 1 year to establish whether aberrant reactivity to the urban environment predicts future clinical outcomes (i.e. psychotic relapse).

To use the results to generate a smartphone-based assessment tool for clinical use; this tool will monitor an individual's reactivity to the urban environment for a period of 2 weeks and use this information to predict risk of future psychotic relapse.

Hypotheses: We hypothesize that people with psychosis show aberrant reactivity to their urban environment, including heightened negative response to adverse features (e.g. overcrowding) and blunted positive response to protective features (e.g. green spaces). In addition, we hypothesize that the degree of aberrant reactivity will be predictive of future psychotic relapse.

Project methods: Participants. A total of 200 individuals will participate in the project including 100 individuals with a diagnosis of psychosis and 100 healthy volunteers. Patients will be recruited through the Early Intervention Care Pathway within the South London and Maudsley NHS Foundation Trust. Study Design. We plan to use a naturalistic prospective design with 3 assessment points. At baseline, we will establish the clinical status of participants via face-to-face structured clinical interview and electronic clinical records and assess their reactivity to the urban environment via smartphone-based ecological momentary assessment. At 6 and 12 months, we will use face-to-face structured clinical interview and electronic clinical records to establish clinical outcomes in terms of psychotic relapse.
Smartphone-based Interventions in Mental Health: Towards a Clinical Tool for Predicting and Preventing Psychotic Relapse

Translational relevance: The translational relevance of the research is three-fold. First, from the perspective of health care technology, the research will lead to the development of a smartphone-based tool that could help clinicians predict clinical outcomes from an individual’s reactivity to their surrounding urban environment; there is a critical need for such instrument, since at present clinicians are unable to predict the onset and relapse of the illness on the basis of clinical presentation. Second, from the perspective of urban planning/design, the research will provide a much-needed evidence-base to inform future policies aimed at promoting mental health. There is an urgent need for such evidence-base since, at present, decisions about urban planning and design aimed at improving mental health tend to be based on “conventional wisdom” due to lack of robust scientific data. Third, in light of the cross-diagnostic association between urban living and mental illness, the tool could also be adapted for use in other psychiatric illnesses.

Student Training: The student will receive training in the recruitment and assessment of individuals with psychosis, the analysis and interpretation of smartphone-based data and the translation of research findings into a tool for clinical use. In addition, our industrial partner J&L Gibbons will provide training in GPS-based analysis of built and social features of the urban environment and the use of scientific research to influence policies and create impact.

Objectives / project plan:

Year 1:
- Recruitment and baseline assessment of 100 individuals with psychosis and 100 healthy volunteers
- Start of 6-month follow-ups assessments
- Statistical analysis of baseline data

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:


Keywords: Psychosis; Urban environment; Mobile Health; Social stress;

BRC Theme/s: Psychosis and Neuropsychiatry
Mobile Health
BRC-031 Molecular effects of benzodiazepine on GABAergic function in people at clinical high-risk of psychosis

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Project Description

Background: Psychosis is the fourth leading cause of disability in the world, and about 1.5 million people develop the disorder each year worldwide. However, the mechanisms leading to psychosis are still poorly understood. Post-mortem and preclinical studies have provided robust evidence for a key role of GABAergic dysfunction within a corticolimbic circuitry involving the medial prefrontal cortex and the hippocampus in the pathophysiology of psychosis. The critical role of GABA in the development of psychosis in this model is further illustrated by the effects of peripubertal administration of benzodiazepines at anxiolytic doses in a neurodevelopmental animal model of psychosis: this normalises hippocampal GABA function and prevents the emergence of elevated dopamine function and associated behavioural abnormalities in adulthood. These findings indicate that GABA dysfunction may play a critical role in the development of psychosis in humans, and suggest that clinical interventions targeting this pathway have the potential to reduce the risk of developing the disorder.

Novelty and Importance: Corticolimbic GABAergic dysfunction as key mechanism in the pathophysiology of psychosis has not been investigated in people at the putative premorbid stage of psychosis. As novel pharmacological imaging approach, the study will assess the effects of a benzodiazepine challenge on GABAergic function in participants at clinical high risk of psychosis (CHR). This will be achieved by using $[^{11}C]$Ro15-4513 Positron Emission Tomography (PET) to assess GABA-A$\alpha$5 receptors in the medial prefrontal cortex and the hippocampus.

Primary aim(s): To determine whether the acute administration of diazepam normalises medial prefrontal and hippocampal GABA-A$\alpha$5 binding in people at CHR of psychosis.

Planned research methods and training provided: The student will be trained in participant recruitment/ assessment (e.g., informed consent, the human tissue act, good clinical practice), and PET-MRI scanning. Training will also involve PET imaging methods and data analysis.
BRC-031 Molecular effects of benzodiazepine on GABAergic function in people at clinical high-risk of psychosis

Objectives / project plan:

Year 1: Obtaining ethical approval for the study (most regulatory approvals are already in place), setting up case report forms and databases. Start participant recruitment.

Year 2: Participant recruitment and scanning, preliminary data analysis.

Year 3: Complete participant recruitment and scanning, finalise data analysis and thesis write-up.

Year 4: This additional time would allow unplanned extensions in case of any delays in participant recruitment and/or offer a period of time following thesis submission for the student to support their transition into the post-doctoral phase.

Two representative publications from supervisors:


Keywords: Psychosis; GABA; PET-MRI imaging; Neuroimaging; Clinical high risk of psychosis;

BRC Theme/s: Psychosis and Neuropsychiatry
BioResource
Project Description

Background: Mental health faces many challenges in delivering the promise of precision medicine and is lagging behind some areas of physical health\(^1\).\(^2\). However, studies show that the large volume of data stored within psychiatric Electronic Health Records (EHRs) can provide valuable insight and high-quality indicators of recommended treatments\(^3\)\(^4\), inspiring the premise underpinning this project:

Precision medicine in psychiatry can be achieved by algorithmically matching a patient’s EHR longitudinal profile, including physical health comorbidities, with similar patients.

However, the EHRs are unstructured, heterogeneous, episodic and sparse, necessitating the creation of scalable, efficient, and interpretable computational models capable of automatically learning patient similarity.

Novelty and Importance: Automating the stratification of patients based on similarity between their EHR-mined digital phenotypes to identify likely treatment responses or prognosis for patient subgroups will allow for enormous benefits in terms of better outcomes and adversity minimization.

Primary aim(s): This project aims to:

a) Develop a suite of efficient and scalable deep learning models for automatically measuring similarity between patient longitudinal profiles mined from their unstructured mental and physical EHRs.

b) Build a proof-of-concept decision support tool to evaluate the models’ effectiveness in making personalized recommendations to mental health practitioners.

c) Evaluate the similarity measures and decision support prototype to predict outcome and drug-related adversity on patients with: a) rheumatoid arthritis with comorbid depression, b) anxiety

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Planned research methods and training provided:
1) Pattern recognition module at the Department of Informatics (DoI).
2) Machine learning module at the DoI.
3) Introduction to Natural Language Processing at the Department of Biostatistics & Health Informatics.

Objectives / project plan:
Year 1: Obtain a SLAM and KHP research passports. Conduct literature review. Complete the four taught modules. Mine CRIS and KCH data.
Year 2: Develop and evaluate computational models with evaluation on the two use cases
Year 3: Build decision support prototype and further evaluate models.
Year 4: Analysis & write-up.

Two representative publications from supervisors:
1: E Iqbal, R Mallah, R Jackson, M Ball, Z Ibrahim, M Broadbent, O Dzahini, R Stewart, C Johnston, R Dobson (2015). Identification of adverse drug events from free text electronic patient records and information in a large mental health case register. PloS one 10 (8), e0134208

2: C Ormandy, Z Ibrahim, R Dobson (2017). Learning Patient Similarity Using Joint Distributed Embeddings of Treatment and Diagnoses. Knowledge Discovery from Healthcare Data, Co-located with the International Joint Conference on Artificial Intelligence (KDH@IJCAI) 1891, 30-35.

Keywords: Health informatics; Machine learning; Text mining; Knowledge based Clinical decision support systems; Learning healthcare systems;

BRC Theme/s: Affective Disorders and Interface with Medicine
Child and Neurodevelopmental Disorders
Bioinformatics and Statistics
Clinical and Population Informatics
Translational Therapeutics
BRC-033  From cohorts to clinical prognosis: Identifying predictive factors for clinical outcomes in autism

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Project Description

Background:  While autism is a severe mental disorder linked to lifelong and pervasive impairments, there is nevertheless a very wide range of outcomes in adulthood which currently cannot be accurately predicted in early or mid-childhood, when clinicians and families are planning interventions. Clinical cohorts have been used extensively for testing specific hypotheses as to early markers of autism and the modelling of particular facets of development, such as language (e.g. Pickles et al. 2014). Now, with several cohorts being available (EDX, SNAP, QUEST, MoBa) and the progression of the participants into adulthood we are now in a position to provide a more general description of development and outcomes of more relevance to clinicians, services and parents. This project examines how this might be done.

Novelty and Importance:  Currently our ability to make prognoses about children with autism is very limited, even whether can be usefully done at all, if it can from what age and for whom. The development of personalized risk profiles should allow better planning of future assessments, interventions and services.

Primary aim(s):  To develop a meaningful clinical prediction tool through the following steps: To review the alternative approaches to using cohort data for prediction, to operationalize what clinicians and carers would find helpful to know about, to develop a prediction tool, assess its performance, internal and external validation.

Planned research methods and training provided:  Training will be provided in a range of methodologies including the fitting of growth curve and latent trajectory models. Learn about alternative approaches to out-of-sample prediction including empirical Bayes’, matching and regularised generalized linear models. Opportunities will be provided for consultation with clinicians and carers to guide the project development and interested students can gain direct clinical experience of autism and the associated impairments.
Objectives / project plan:

**Year 1:** Literature review, familiarise with project cohorts (EDX, SNAP, QUEST, MoBa), acquire experience and skills in longitudinal and prediction modelling.

**Year 2:** Identify and implement promising longitudinal and prediction methodology for developmental trajectories and adult educational, economic, social and behavioural outcomes. Assess internal validity.

**Year 3:** Cross-cohort assessment of external validity. Examination of scope for optimal adaptive assessment which would identify what measures would be most informative as to prognosis and at what age such measurements should be made.

**Year 4:** Development and testing of a decision support tool using clinical record data.

**Other notable aspects of the project:** The student will publish during the PhD and attend relevant international conferences.

**Two representative publications from supervisors:**


**Keywords:** Autism; Adult clinical outcomes; e-Health; Prognosis; Cohort;

**BRC Theme/s:**
- Child and Neurodevelopmental Disorders
- Bioinformatics and Statistics
- Biomarkers and Genomics
- Clinical and Population Informatics
BRC-034  Towards personalised medicine for antidepressant drugs: A machine learning approach

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Project Description

Background:  Individuals with depression differ in their response to treatment with antidepressants. It has been estimated that at least 40% of variation is attributable to genetic factors. Clinical factors showed a moderate role in predicting treatment response. The development of algorithms integrating genetic and clinical factors to predict treatment outcomes in depression may enable clinicians to select optimal medication for each patient.

Novelty and Importance:  Developing algorithms for treatment personalization from large datasets is a challenging task for which traditional statistics had limited success. Problems arise when the number of predictors exceeds the number of individuals, there are missing data, variables are highly correlated and effect sizes are small.

This PhD studentship will develop new algorithms to personalise antidepressant treatment based on Topological Data Analysis (TDA) a set of Multivariate machine learning techniques (MML) that have successfully been applied to precision medicine studies, but not yet in psychiatry. Algorithms will be applied to genetic and clinical data from 3899 subjects from two clinical trials (GENDEP, STAR*D) and three observational studies (MARS, MUESTER, PRN-AMPS). This research may produce clinically relevant predictive models to guide clinicians in antidepressant treatment selection.

Primary aim(s):  To develop new MML algorithms that combine genetic with clinical variables to improve prediction of antidepressant treatment response at the individual level.

Planned research methods and training provided: This PhD studentship will include an individualised training plan in methodology required for personalised medicine (e.g. statistical genetics, machine learning, longitudinal analysis of multivariate phenotypes and predictive modelling).

Objectives:

Year 1:  Develop and implement free standing code of a method for predictors selection based on the mapper TDA algorithm.

Year 2:  Develop and implement free standing code of a predictive algorithm based on the combination of a TDA method for predictors selection and a machine learning classifier.
BRC-034  Towards personalised medicine for antidepressant drugs: A machine learning approach

Year 3: Validate the predictive algorithm internally and externally, in GENDEP, STAR*D, MARS, MUENTSER and PRN-AMPS datasets.

Year 4: Apply the developed algorithms to assess the role that clinical and genetic variation plays in response to antidepressant treatment in GENDEP, STAR*D, MARS, MUENTSER and PRN-AMPS studies.

This project combines (a) the development of cutting-edge methods for treatment personalisation, using TDA as a novelty, plus (b) the practical application of the developed methods to a very relevant area, with a real potential to improve patients' health. We would welcome applications from students with a background in mathematics or other quantitative sciences (e.g. bioinformatics, computer science) and from biomedical with a strong commitment to developing statistical skills.

Two representative publications from supervisors:


Keywords: Antidepressant; Personalisation; Machine Learning; Topological Data Analysis; Genetics;

BRC Theme/s: Affective Disorders and Interface with Medicine
              Bioinformatics and Statistics
              Biomarkers and Genomics
BRC-035 The experience of people with dementia, carers and health professionals of problem adaptation therapy (PATH) for depression: Process evaluation of the PATHFINDER randomised clinical trial

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Project Description

Background: Depression is very common in people with dementia, reducing their quality of life and increasing mortality, risk of transfer into a care home and carer burden. Unfortunately, antidepressant drugs do not have clear effectiveness in these patients and it appears that the most commonly available psychological therapies are also not useful. Psychological therapy based upon the principle of problem-solving therapy (PATH) has been found to reduce depression among older people with mild cognitive deficits treated by senior therapists in a US healthcare setting.

Novelty and Importance: The PATHFINDER randomised controlled trial (RCT) will evaluate the clinical and cost-effectiveness of an adapted PATH intervention for people with mild-moderate dementia seen in the NHS. The process evaluation will examine the accessibility, acceptability, credibility and perceived value of the intervention and its delivery, thus supporting the interpretation of trial findings and helping to optimise implementation to the wider NHS.

Primary aim(s): To conduct a nested process evaluation within the PATHFINDER RCT to assess what was implemented and how; the importance of different intervention components; and contextual factors facilitating or inhibiting delivery and participation.

Planned research methods and training provided:

Implementation: All therapy sessions will be recorded and therapists will complete an anonymous qualitative satisfaction questionnaire to examine how PATH was delivered in practice (examining treatment fidelity, ease of delivery in people with dementia and therapist support needs). Individual interviews with therapists will examine motivation, views and experiences of delivering the intervention, training and supervision. Training sessions will be observed.

Mechanisms of impact: In-depth interviews with up to 40 people with dementia and 40 carers (across intervention and control sites) at 3 months and 12 months will explore experiences of participating in the trial and the perceived acceptability, feasibility, strengths and limitations of PATH and the methods of delivery.

Contextual factors: Socio-demographic and clinical data will be recorded at baseline and participants will be asked to complete pre and post intervention questionnaires about their treatment expectations and preferences. Qualitative interviews will explore the perceived impact of the person with dementia’s condition and circumstances.
The experience of people with dementia, carers and health professionals of problem adaptation therapy (PATH) for depression: Process evaluation of the PATHFINDER randomised clinical trial

Objectives / project plan:

Year 1: Systematic review and synthesis of qualitative and quantitative evidence. Further training in quantitative and qualitative skills. Ethical approval.

Year 2: Collection of process evaluation data.

Year 3: Ongoing data collection. Analysis of process evaluation data.

Year 4: Final write up. PhD submission. Fellowship applications.

Two representative publications from supervisors:


Keywords: Dementia; Depression; Problem Adaptation Therapy; Process evaluation; Psychological Therapy;

BRC Theme/s: Dementia and Related Disorders
Mobile Health
Translational Therapeutics
BRC-036  Efficacy and Neural and Cognitive Mechanisms of Mindfulness Based Interventions in ADHD

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Project Description

Background:  Spontaneous mind-wandering (MW) is an independent source of impairment in ADHD. Spontaneous MW and MW-associated neural processes, involving regulation of task positive and negative neural networks, are involved in generating core ADHD symptoms. Mindfulness based interventions (MBIs) improve regulation of the neural processes involved, and reduce core ADHD symptoms in randomized trials of ADHD adults. Yet, MBI is not an established treatment for ADHD and related neurodevelopmental disorders.

Novelty and Importance:  This project will evaluate the efficacy of MBIs on ADHD symptoms, identify neural moderators (targeting patient sub-groups), and mediators (monitor/optimize treatment by targeting directly the neural functions involved). This novel approach to treatment and neurobiology of ADHD, potentially leads to sustained treatment effects compared to the short-lived effects of current medications, and identifies neural-mechanisms that can be targeted by pharmacological and non-pharmacological (e.g. brain stimulation, neurofeedback) treatments.

Primary aim(s):
1. Evaluate the efficacy of mindfulness training in reducing core ADHD symptoms
2. Evaluate the efficacy of mindfulness training in normalising default mode network, and cortical control network activity, known to be dysregulated in ADHD.
3. Use structural equation modelling to identify moderator variables and mediating mechanisms during the treatment of ADHD with MBI.

Planned research methods and training provided:  These objectives will be achieved using a randomized control design to evaluate the efficacy of MBI in ADHD, and structural equation modelling to identify cognitive-EEG variables that moderate, and provide a mechanistic explanation at the neural level, of the clinical response. Training will be provided in assessment of ADHD; mindfulness training and psychoeducation for ADHD; conducting and analyzing cognitive-EEG data of default and cortical control network activity; and advanced statistical techniques for conducting efficacy, and moderator and mediator analyses, in the context of a randomized controlled trial.
Objectives / project plan:

Year 1: Training for all trial procedures, complete protocol, ethical application, initiate experimental trial *

Year 2: Data, and collection, and training in analysis of cognitive-EEG data.

Year 3: Complete data collection, advanced analysis of cognitive-EEG data and training in structural equation modelling

Year 4: Analysis of experimental trial data using structural equation modelling, and preparation of final publications and development of post-doctoral research.

* The research team has access to cognitive-EEG datasets relevant to this project. We also investigate drug effects on the same neural systems. The student project will be supported by a research assistant, trial coordinator and placement student during the data collection phase.

Two representative publications from supervisors:


Keywords: ADHD; Mindfulness; Default Mode Network; Cognitive control; EEG;

BRC Theme/s: Child and Neurodevelopmental Disorders
Bioinformatics and Statistics
Mobile Health
Neuroimaging
**Objective:** Identification of neurobehavioural predictors of eating disorders, weight gain and obesity

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**Project Description**

The eating disorders [anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED) and related sub-clinical syndromes] are common psychiatric disorders which affect up to 15% of young women and up to 4% of young men in high income countries. The peak age of onset of EDs is from mid adolescence into emerging adulthood (age 15 to 19), i.e. at a developmentally sensitive time. Moreover, one in 2-3 people with BN or BED are obese or will become obese, making them vulnerable to obesity-related complications.

While the aetiology of EDs is complex, there is a broad acceptance of EDs as being brain-based disorders and increasing evidence suggesting neurobiological overlaps between ED, anxiety disorders and addictions. Yet, most ED studies are based on small cross-sectional investigations of individuals who are either currently ill or have recovered from an ED, and thus any abnormalities displayed may reflect symptom severity, illness duration or ‘scarring’ effects. There have been no prospective studies for the neural risk factors of EDs, which precludes the establishment of a causal relationship between any associated factor and the development of disordered eating/EDs.

In this project, we propose to overcome these limitations using data from the IMAGEN project, a large population-based longitudinal cohort of adolescents, and a newly recruited clinical sample of emerging adults with an ED (AN or BED) diagnosis with complementary assessments. The aims of this project are to elucidate the neurobiological basis of EDs and identify predictor of EDs, weight gain and obesity in young adulthood.

**Plan:**

**Year 1:** The student will (i) familiarise themselves with the neurobiological basis of EDs and obesity and the IMAGEN project and database; (ii) conduct a relevant systematic review (e.g. on neurobiological predictors of EDs/obesity); (iii) utilise IMAGEN behavioural and BMI data (age 14 to 21) to identify and characterise different clusters of participants with distinct trajectories of disordered eating and body mass index (BMI) change.

**Year 2:** Using age 14 IMAGEN data, he/she will identify environmental, biological and psychological factors that characterize the different clusters previously derived.

**Year 3:** He/she will (i) study interactions between these factors to derive bio-behavioural risk/prediction models of EDs, weight gain and obesity and (ii) validate the results in a clinical sample of emerging adults with an ED (AN or BED) diagnosis.
Identification of neurobehavioural predictors of eating disorders, weight gain and obesity

Two representative publications from supervisors:


Keywords: Eating disorders; Obesity; Body Mass Index; IMAGEN; Biomarker;

BRC Theme/s: Obesity, Lifestyle and Learning from Extreme Populations
Bioinformatics and Statistics
Biomarkers and Genomics
Neuroimaging
BRC-038  Dissecting the genetic and environmental risk factors for major depressive disorder

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Project Description

Background:  Depression is a highly debilitating disorder, with an etiology involving both genetic and environmental risks.  Advances in genetic technology and the existence of large data-sets now provide unparalleled opportunities to identify risk factors and characterize their role in depression.

Novelty and Importance:  Research studies, led by the SGDP Centre, have finally begun to identify the genetic component of depression, with 44 loci now known.  Much further work is required to dissect the genetic and environmental contribution to depression, and explore how genetics could be used to identify those at high risk.

Primary aim(s):  This project will dissect the genetic and environmental contributions to depression, establishing how these factors confer risk across the life course; how they interact; and how they are implicated in heterogeneity associated with factors such as sex, age at onset, severity, recurrence, and diagnostic subtype.  Research studies in depression have diverse ascertainment (e.g. clinical, twin registry, population-based studies) and differing levels of phenotypic data, balancing the twin goals of achieving large sample sizes with detailed individual-level information.  The research will use key resources from the international Psychiatric Genomics Consortium and ongoing studies such as UK Biobank and the National Child Development Study, combining data across studies.  Sophisticated statistical methods will be used to fully exploit data sources to characterize the role of risk factors in depression.  The supervisors will contribute complementary expertise in genetics (Lewis) and epidemiology (Maughan) to inform translational potential, particularly from gene-environment interactions detected.

Planned research methods and training provided:  The student will develop cutting-edge statistical skills in the analysis of genetic and epidemiological studies, including genome-wide association studies, polygenic risk scores and gene-environmental interactions.  Training will be given from in house resources, peer-to-peer learning.
Objectives / project plan:

Year 1: Research rotation, developing skills in statistical genetics and psychiatric epidemiology

Year 2: Assimilate data sets, harmonizing environmental variables. Test for association with each risk factor and identify gene-environment interaction

Year 3: Assess how risk factors vary with heterogeneity in depression subtypes, applying polygenic risk scores from genome-wide association studies.

Year 4: Apply machine learning methods to assess predictive ability of risk factors.

Two representative publications from supervisors:


Keywords: Statistics; Genetics; Depression; Genome-wide association studies; GWAS; Psychiatry;

BRC Theme/s: Affective Disorders and Interface with Medicine
Biomarkers and Genomics
Evaluating genetic prediction of psychiatric disorders across ethnic groups

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Project Description

Background: Genetic studies have begun to identify variants associated with diseases and traits. However, most studies have been performed in populations of European ancestry, and we have limited information on the genetic predisposition to disease in other populations.

Novelty and Importance: Genomic medicine will become an important part of healthcare, but access to this must be open to all ethnicities. Risk prediction in individuals of non-European ancestry is difficult when genetic findings are generated in studies of European ancestry. For example, we can effectively use genetic information to predict outcome in first-episode psychosis cases in a sample European ancestry (9% of variance explained) but this reduces substantially in African ancestry (only 1% of variance explained).

This project will establish how the genetic contribution to psychiatric traits is transferrable across populations, and how information gained from multi-ethnic studies can be used effectively. Increasing the availability of non-European genetic data is of paramount importance: 1) to use genetic research findings globally, 2) to better understand biological mechanisms of disease, 3) to facilitate research of combining genetic with environmental data in different populations and 4) to allow clinical translation of the findings.

Primary aim(s): To understand sources of difference in genetic findings between populations of different ethnic background and investigate methods of improving disease risk prediction.

Planned research methods and training provided: This project will build on the findings of genome-wide association studies (GWAS), using polygenic risk scores, which provide a single measure of disease risk in an individual. Extrapolating genetic findings or making comparisons between individuals of different ancestry has a series of technical challenges, to be investigated as part of this PhD project: Africans, being a more ancient population than Europeans, have higher genetic diversity. In addition, allele frequencies differ between populations with an effect in measured effect sizes. Another challenge for individuals of different ancestry recruited in London is that they have all have a personal or family history of migration and therefore differential exposure to environmental stressors.

Training will be provided in the statistical analysis of genetic data. Note that this is a statistical, dry-lab project with no molecular component.
BRC-039  Evaluating genetic prediction of psychiatric disorders across ethnic groups

Objectives / project plan:

Year 1: Literature review, training in data management and genetic analysis, Polygenic Risk Scores analysis, development of methodology for multi-ethnic analysis.

Year 2: Methodology development for use of summary genetic data from GWAS of European population in risk prediction of populations of different ancestry across disorders.

Year 3: Validation of the above findings using GWAS data from non-European populations using data from PGC and other collaborations

Year 4: Publications and write-up of thesis

Two representative publications from supervisors:


Keywords: Statistics; Genetics; Ethnicity; Genome-wide association studies; GWAS; Psychiatry;

BRC Theme/s:  Biomarkers and Genomics
BRC-040 Developing the Next Generation of Symptom Assessments Tools for Negative Symptoms in Psychosis

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Project Description

Background: Despite significant investments in both pharmacological and psychosocial interventions the majority of the people with schizophrenia will experience long term disability. Negative symptoms are features typically observed in people with schizophrenia including 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 for not providing a sufficiently sensitive picture on how negative symptoms unfold and influence people’s everyday life. Recent technical developments enable the integration of VR with gaming techniques and allowed the development of VR environments to support advancement in mental health care.

Novelty and Importance: Assessment in mental health relies extensively on patients’ reports and clinicians’ impressions. Mental health professionals are rarely in a position where they can observe how symptoms impact on people’s lives. Psychologists have, for decades, asked clients to imagine themselves in difficult situations to elicit problematic thoughts, feelings and behaviours. However we know this only marginally equates to reality. To date this is one of the major limits of assessment methods and represent a barrier to the transfer of therapy gains to people’s everyday life. The proposed VR platform will enable, for the first time, to conduct a real-life assessment of negative symptoms and their impact on functioning. By reconstructing situations that trigger negative symptoms the new method we propose to develop will be important in developing therapies that can effectively tackle these symptoms and reduce disability. This approach could be also adapted for self-administration or remote support reducing the need of attending the clinic.

Primary aim(s):
1. Develop and refine experimental methods to assess negative symptoms using VR.
2. Assess the acceptability and feasibility of the new method.
3. Conduct a preliminary evaluation of the new assessment validity.
4. Explore the physiological correlates of negative symptoms during the new procedure.
Planned research methods and training provided: We propose to develop and test an innovative virtual reality environment in collaboration with our commercial partner Virtualware. This will consist of a front end, where the patient interacts with other Virtual humans (avatars), using the Oculus Rift headset and a gamepad navigate the environment, and a backend, where the researcher will control the 3D environment. The novel VR assessment will be based on a virtual social space environment (i.e. Virtual Café). We propose to conduct an iterative development of the procedures with service users feedback at multiple stages and trial the use of this new methodology for routine assessment on 20 service users with psychosis.

Training - Virtual Reality; Advanced Statistics; Library and Database Usage; Clinical interviews administration; Attending Seminars and Scientific talks; Access to all Skills Forge training courses.

Objectives / project plan:
Year 1: MSc, systematic review of the literature, ethic application, VR training
Year 2: VR environment familiarization, clinical assessment training; begin recruitment, statistic training
Year 3: Data collection
Year 4: Data collection, analysis and thesis writing

Two representative publications from supervisors:


Keywords: Psychosis; Virtual Reality; Negative Symptoms; Motivation; Disability;

BRC Theme/s: Psychosis and Neuropsychiatry
Mobile Health
Translational Therapeutics
BRC-041 Developing novel observational coding schemes of emerging infant inattention and hyperactivity/impulsivity as a potential outcome measure in a pre-emptive cognitive training of attention deficit/hyperactivity disorder (ADHD)

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Project Description

Background: Psychological treatments for ADHD initiated after disorder onset have had only limited success. Preventative psychological treatments for ADHD implemented in infancy have been championed but not tested or implemented successfully.

Novelty and Importance: We are conducting an RCT (n = 50) of a novel, developmental neuroscience approach to early intervention for 10-month-old infants at familial risk for ADHD (gaze contingent attention training). The primary 14 month endpoint will be complete in October 2018 and follow-ups at age 24 and 36 months in Spring 2020. However, there is currently a lack of well validated objective assessments of early emerging attention and behavior in the infants/toddlers and little is known about the cognitive and psychophysiological correlates of aberrant preschool behaviour and attention.

Primary aim(s): The project will (a) build on existing approaches to the objective assessment of ADHD in preschoolers to develop and validate a new index specifically designed for the infant/toddler period and (b) use these codes to examine the cognitive and psychophysiological correlates of preschool attentional difficulties. The potential for objective behavioural assessments to be outcomes in future pre-emptive trials will be tested within the context of the RCT.

Planned research methods and training provided: The student will be involved in the 24 and 36 month evaluations but will also have access to all materials collected at the infant timepoints. They will be trained in clinical assessments and neurocognitive experimental techniques (eye-tracking, EEG/ERP and psychophysiological arousal measures). They will develop and test the reliability and validity of coding schemes that these early-emerging behaviours and then combine these with experimental methods that simultaneously capture cognitive and biological indexes of underlying neurocognitive development. The PhD student will receive interdisciplinary training from a clinical developmental psychologist (Charman) and an international expert in ADHD developmental neuroscience (Sonuga-Barke) to promote translational developmental cognitive neuroscience.
BRC-041 Developing novel observational coding schemes of emerging infant inattention and hyperactivity/impulsivity as a potential outcome measure in a pre-emptive cognitive training of attention deficit/hyperactivity disorder (ADHD)

Objectives / project plan:

**Year 1:** Training on clinical and experimental assessments. Review of existing literature on the assessment of preschool behaviour and attention with special reference to early emerging ADHD. Development of novel coding schemes for infant/toddler ADHD.

**Year 2:** Analysis of the reliability and validity of the novel coding schemes.

**Year 3:** Training in statistical modeling and EEG, psychophysiological and eye-tracking analysis. Examination of the cognitive and psychophysiological correlates of early emerging attentional problems indexed by the new schemes.

**Year 4:** Analysis and paper writing. Completion of thesis.

Two representative publications from supervisors:


Keywords: Attention deficit hyperactivity disorder (ADHD); omised controlled trial (RCT); Observational measures; Cognitive neuroscience; Developmental psychology

BRC Theme/s: Child and Neurodevelopmental Disorders
Translational Therapeutics
**Project Description**

**Background:** Recurrent and chronic headaches, including migraine and tension headaches, are prevalent in the UK and represent a significant personal and societal burden. They are among the most disabling of all health conditions and cost billions of pounds each year in health care and lost productivity.

A psychological treatment called Cognitive Behavioral Therapy (CBT) is a potentially effective treatment for headache. However, this approach needs more development and research in the UK to assure accessibility and effectiveness. The aim of this study is to extend two recent treatment developments for application to headache treatment. These developments include a new theoretically-based form of CBT called Acceptance and Commitment Therapy (ACT) and a new mode of delivery, including limited contact, using mobile technology and the internet. The focus here is explicitly on disabling headaches because these are associated with the greatest costs and because ACT primarily aims to reduce disability.

**Novelty and Importance:** While there are some limited RCTs of ACT for headache, these include group-based treatments for participants with migraine and depression in the US, or women with migraine in Iran. None of the previous trials included mobile technology, individual delivery, or were conducted in the UK, where there is an almost complete absence of research on forms of CBT for headache.

**Primary aim(s):** The primary aims of this project are to design and pilot test a mobile app-based psychological treatment for headache based on ACT.

**Planned research methods and training provided:** The applicant will receive training in methods for systematic review, user involvement testing, trial design, skills for providing therapy support for participants in an "online" version of ACT, and pilot and feasibility testing.

**Objectives / project plan:**

**Year 1:** Systematic review and evidence synthesis focused on the role of psychological flexibility factors (including mindfulness) in headache

**Year 2:** Creation of a prototype app-based treatment (with therapist support) based on modification of a current previously treatment package (not yet developed for headache) and user acceptability testing of online interface, skills training modules, and assessment modules.
Year 3: Pilot testing of delivery of full "online" package and research methods in a small series of participants with headache recruited for headache services at KCH and GSTT.

Other notable aspects of the project: In addition to the training provided by these projects, a main research aim is to prepare for future research in the form or a RCT.

Two representative publications from supervisors:


Keywords: Headache; Migraine; Cognitive Behavioural Therapy; CBT; Internet based treatment; Acceptance and Commitment Therapy

BRC Theme/s: Pain
               Mobile Health
               Patient and Carer Involvement and Engagement
Elucidating the pathway from benign to pathological positive psychotic symptoms and back again: Informing the next wave of psychological therapies

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**Project Description**

**Background:** Up to 1/3rd of people with psychotic disorders continue to experience distressing positive symptoms despite available treatments. This project will inform the next wave of psychological therapies to help alleviate distress and improve recovery in such patients, by learning from people who are psychologically healthy and lead fulfilling lives despite the presence of positive symptoms, and by learning how Cognitive Behaviour Therapy for psychosis (CBTp) engenders successful change.

**Novelty and Importance:** This project will help us identify (1) key psychological factors that determine benign or pathological outcomes of positive symptoms, and (2) how psychological therapies can best build resilience in patients with positive symptoms to reduce distress and enable recovery.

**Aims:** We will use ESM to assess (1) resilience factors in individuals with benign PEs, and compare them to patients with distressing PEs; (2) a range of psychological factors in psychosis patients pre and post CBTp, comparing those who have a favourable, to those who have a poor, outcome.

**Planned research methods and training provided:**

**Study 1:** Non-clinical individuals with PEs (N=50) will be compared with psychosis patients (N=50) on a range of symptom dimensions and psychological variables and their interactions, using ESM.

The clinical group will fulfil additional criteria of: (a) ICD- 10 psychosis-spectrum disorders (F20-39); (b) under care of a clinical team; (c) having been referred for CBTp for distressing positive psychotic symptoms. The non-clinical group will be recruited from a research register held by the 1st supervisor.

**Study 2:** Patients will then undergo CBTp over 6-9 months, and be reassessed with ESM post-therapy (N=40; assuming 20% drop-out rate). Those who show a good outcome post CBTp, defined by increased scores on a recovery measure and individual goal achievement, will be compared to those who show a poor outcome.
Elucidating the pathway from benign to pathological positive psychotic symptoms and back again: Informing the next wave of psychological therapies

**Measures:** ESM: Participants will complete an ESM questionnaire, 10 times/day in response to a beep, over 6 consecutive days, to assess Affect; PEs; Delusions; Appraisals; Safety Behaviours; Social context; Self-esteem and resilience. Clinical: standardised interviews and questionnaires assessing psychotic symptoms; appraisals and safety behaviours; emotional problems; self-evaluation and resilience. Non-clinical individuals will complete ESM procedures once, and clinical individuals twice (pre-post therapy).

**Project plan:**

**Year 1:** Training in ESM methodology; therapy observations and recruitment

**Year 2:** Training in conducting systematic reviews, and multi-level modelling statistics for ESM analyses; recruitment, writing up systematic review

**Year 3:** Finish recruitment, analyse and write up clinical vs non-clinical paper

**Year 4:** Analyses of CBTp data, publishing of empirical paper(s), writing up thesis

**Other notable aspects of the project:** This project will form part of an ongoing collaboration with Prof Myin-Germeys’ group in Leuven University

**Two representative publications from supervisors:**


**Keywords:** Psychosis; Momentary assessment; Psychotic experiences; Cognitive Behaviour Therapy; CBT; Appraisal;

**BRC Theme/s:** Psychosis and Neuropsychiatry
Mobile Health
Translational Therapeutics
BRC-044  Improving treatment outcomes for sexual minority women with depression or anxiety

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Project Description

Background:  Sexual minority women have elevated rates of mental health problems such as depression and anxiety relative to heterosexual women. Furthermore, even adjusting for baseline levels of symptoms severity and other potential confounders, we found that lesbian and bisexual women show a smaller reduction in depression and anxiety after receiving psychological therapy in Improving Access to Psychological Therapy (IAPT) services than heterosexual women (Rimes et al., in press). This PhD will investigate reasons for this inequality in treatment outcomes and will apply these findings to develop a cognitive behavioural therapy intervention specifically for sexual minority women.

The primary supervisor has recently developed a group intervention for sexual minority individuals in Southwark IAPT but this group is mainly attended by men. The therapy needs of sexual minority women require specific attention given the evidence that these women (but not sexual minority men) have poorer treatment outcomes in routine clinical care.

Novelty and Importance:  The increased rates of mental health problems of sexual minority women and their poorer outcomes after psychological interventions for depression and anxiety in IAPT services is an important mental health inequality in the NHS. This is the first study to investigate factors that may be associated with poorer treatment outcomes for sexual minority women and to apply these findings to develop a new intervention specifically focused on their unique needs.

Primary aims:
1. To identify factors that may be contributing to poorer treatment outcomes after therapy for depression or anxiety in sexual minority women
2. To apply these findings to develop a new psychological intervention specifically designed for sexual minority women and test this in a feasibility study

Planned research methods and training provided:
- Qualitative methodology
- Quantitative methodology
- Psychological intervention development skills. If this is a group intervention the student will help deliver the intervention.
Improving treatment outcomes for sexual minority women with depression or anxiety

Objectives / project plan:

**Year 1:** Qualitative study investigating sexual minority women’s experiences of IAPT services and their treatment preferences for a new intervention.

**Year 2:** Quantitative study of IAPT data using the Clinical Record Interactive Search (CRIS) to investigate predictors of therapy outcome in sexual minority women.

**Year 3:** Applying the findings from the earlier studies, a feasibility study of a new psychological intervention for sexual minority women with depression or anxiety in IAPT services. This could be either an individual or group form of cognitive behavioural intervention, depending on findings from Years 1 and 2.

**Year 4:** Writing up for publication.

Two representative publications from supervisors:


Keywords: Mental health; Bisexual; Lesbian; Therapy; Sexual orientation;

BRC Theme/s: Affective Disorders and Interface with Medicine
Clinical and Population Informatics
Translational Therapeutics
BRC-045      Development of a smartphone app for Ecological Momentary Interventions (EMIs) in anxiety disorders

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Project Description

Background:  Cognitive behavioural treatments for anxiety disorders are effective but a significant minority of patients (30-50%) do not achieve treatment recovery. Treatment success typically depends upon the patient conducting unsupervised homework between sessions, e.g. exposure exercises and behavioural experiments. However patients encountering threat cues easily fall into old habits such as avoidance, use of safety behaviours, unhelpful attentional processes, use of alcohol or dissociation. Therapists typically have little or no visibility of such between-session processes, and therefore cannot offer timely corrective intervention.

Technological innovations show great promise for anxiety (e.g. Stott et al, 2013). One particular form of innovation is Ecological Momentary Interventions (EMIs), which provide patients with real-time tailored feedback (Schueller et al 2017), via a smartphone app. In addition, passive sensor technology (via smartphone and wristwatch) has advanced in recent years has the potential to identify relevant physiological and behavioural markers in real-time and inform the provision of a relevant, timely and personalised EMI.

This project will engage service users in the co-development of an EMI smartphone app for anxiety disorders, integrating passive sensor data. The project will examine feasibility in a sample of anxious patients, and assess efficacy using single case experimental design methodology.

Novelty and Importance:  Previous research has demonstrated that EMIs can increase homework adherence and reinforce therapy concepts (e.g. Aguilera & Munoz, 2011). However, little research has yet evaluated combining sensor data in a personalized EMI within anxiety disorders (Gee, Griffiths & Gulliver, 2016). This study could pave the way for a larger clinical trial to test the added value of this approach to treatment as usual in anxious patients.

Primary aim(s):
1) Identify the key digital signatures from passive monitoring in an anxiety disorder population which would inform an EMI app.
2) Develop an EMI app, with input from service users, which provides tailored feedback to anxious patients.
3) Assess feasibility with measurements of acceptability and adherence, as well as qualitative feedback.
4) Obtain preliminary efficacy data for the app using single case experimental design.

Planned research methods and training provided: Technologies: E4 wristband from Empatica (or equivalent). The open-source RADAR-CNS platform for a streaming passive data platform. Mixed methods including semi-structured interviews, observation, and single case experimental design.

Objectives / project plan:
Year 1: Ethics, literature review, training on technologies and methodologies and relevant clinical training to undertake patient assessments. Engage service user group in app functionality and design.
Year 2: Development of the app, recruitment of anxious patients and feasibility testing.
Year 3: Optimize app and conduct small efficacy study using N-of-1 methodology.

Two representative publications from supervisors:

Keywords: Technology; Wearables; Anxiety Disorders; Cognitive Behavioural Therapy; CBT; Smartphone App;

BRC Theme/s: Affective Disorders and Interface with Medicine
Mobile Health
Patient and Carer Involvement and Engagement
BRC-046  The role of maladaptive plasticity in causing seizures in humans with brain tumours

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Project Description

Background: Seizures are an extremely common symptom of brain tumours. These seizures diminish quality of life, and can cause injury or worse, death. To make matters worse, recent evidence suggests that the neural activity during seizures promotes tumour growth. Hence, abolishing seizures is vital.

Novelty and Importance: Tumour-associated seizures commonly do not respond to anticonvulsant medication. Investigations into how brain tumours cause seizures have failed to yield new treatments. The core problem is that we don’t know how the tumour affects neural circuitry in the surrounding cortex.

Brain tumours elicit a plastic response in the peritumoural cortex. Our hypothesis is that this plastic response is maladaptive and results in tumour-associated seizures.

Better treatment of tumour-associated seizures would reduce injury and death attributable to tumour-associated seizures; slow tumour growth; and improve quality of life for people with brain tumours.

Primary aim(s): The goals of this PhD are to explore what plastic changes occur in epileptogenic areas adjacent to the tumour. The student will focus on three main types of plastic changes to:
  1) Determine whether neurons in peritumoural cortex are hyperexcitable.
  2) Identify changes in synaptic strength or synapse number in peritumoural cortex.
  3) Assess whether there is aberrant rewiring of neural circuitry in peritumoural cortex

Planned research methods and training provided: The student will make ex vivo electrophysiological recordings from human brain tissue removed during neurosurgery to resect cerebral gliomas. The goal is to study the functional changes in excitatory circuitry of peritumoural cortex. In parallel, the student will investigate how brain tumours affect neuronal structure in peritumoural cortex. This will be done by a combination of 3D reconstructions of recorded neurons filled with fluorescent dye and immunocytochemistry.
The role of maladaptive plasticity in causing seizures in humans with brain tumours

**Objectives / project plan:** The initial aim is to identify the plastic changes affecting excitatory circuitry in human peri-tumoural cortex. The student will then investigate which plastic changes are maladaptive and cause seizures.

**Year 1:** Local field potential recordings to identify epileptic discharges in peritumoural cortex. This will be combined with patch clamp recordings from single neurons in peritumoural cortex to investigate changes in neuronal excitability.

**Year 2:** Investigate whether excitatory or inhibitory circuitry is altered in the peritumoural cortex. This will focus on evidence for changes in synaptic strength, synapse strength and rewiring.

**Year 3:** Use pharmaceutical agents that reverse the potentially maladaptive plasticity and assess whether this reduces epileptic discharges.

**Year 4:** Write up dissertation.

**Two representative publications from supervisors:**


**Keywords:** Brain tumour; Glioma; Seizure; Cortex; Plasticity;

**BRC Theme/s:** Dementia and Related Disorders
Psychosis and Neuropsychiatry
Biomarkers and Genomics
Translational Therapeutics
The role of Synaptic markers in patients with Parkinson’s disease dementia and Dementia with Lewy bodies: An in vivo positron emission tomography study

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www.kcl.ac.uk/ioppn/depts/oldage/people/dag-aarsland.aspx

Project Description

Background: Parkinson’s disease dementia (PDD) and Dementia with Lewy bodies (DLB) are highly disabling neurodegenerative disorders. In addition to classical motor symptoms, non-motor features such as cognitive decline and psychiatric disturbances are very important aspects of these diseases, as they bring an additional significant burden for patients and caregivers. The mechanisms underlying neurodegeneration and loss of synaptic signalling in these diseases are still only partially understood. Synaptic vesicle glycoprotein 2A (SV2A) is a transmembrane protein expressed ubiquitously in secretory vesicles in all brain areas which is critical for synaptic and mitochondrial function.

Novelty and Importance: $^{[11]}$CUCB-J is a novel PET radioligand, which has shown high specificity and selectivity for SV2A in vitro and in vivo. In this study, we aim to compare $^{[11]}$CUCB-J PET binding in PDD and DLB patients with a group of early Parkinson’s disease (PD) patients and healthy volunteers. We aim to investigate the integrity of molecular (PET imaging, cerebrospinal fluid and peripheral blood) synaptic markers (e.g. SV2A) in PDD and DLB patients and relative to healthy controls; and to investigate for correlations with clinical symptoms. This study would be of great benefit in understanding the role of synapses in patients with PDD and DLB. The successful application of $^{[11]}$CUCB-J PET imaging in PDD and DLB could also facilitate the development of potential new treatments and the development of diagnostic and/or prognostic markers.

Primary aim(s): By using $^{[11]}$CUCB-J PET imaging and CSF and peripheral blood markers we aim to explore in vivo synaptic levels in PDD/DLB patients compared to a group of age- and sex-matched healthy controls. We will also investigate correlations between synaptic markers and measures of disease severity.

Study design: Observational, cross sectional design of two cohorts: (a) PDD/DLB and (b) HCs  
Participants:  18 PDD/DLB subjects & 24 HCs  
Procedures: One SV2A PET scan; One 3T MRI scan; Clinical screening and assessments; LP/CSF and peripheral bloods
Sample size: There are no similar PET studies investigating in vivo SV2A in PD patients. [11C]UCB-J is kinetically a well-behaved tracer and we expect good reproducibility [Nabulsi et al., 2016]. A sample size of 16 will be sufficient to detect a minimum 15% group difference with 80% power and a 0.05 error in between group comparisons of SV2A.

Analytic methods: MIAKAT, Analyse and SPM software for the full quantification (and voxel by voxel analyses) of SV2A binding potential in vivo in the brains of PDD/DLB subjects compared to HCs. FSL/SPM for MRI analyses. Laboratory analyses for synaptic CSF and peripheral blood markers. SPSS for between group comparisons and interrogation of correlations between molecular (imaging and laboratory) and clinical markers (from clinical scales).

Planned research methods and training provided: PET methodology, Clinical assessments, CSF and blood biomarkers techniques

Objectives / project plan:
Year 1: Background reading, obtain relevant approvals, draft a review article, study initiation
Year 2: Recruitment, PET methodology, CSF and Blood Biomarkers techniques, scanning
Year 3: Data analysis, Publications, PhD Thesis

Two representative publications from supervisors:


Keywords: Positron Emission tomography; Synapses; Synaptic vesicle protein 2A; Parkinson's disease dementia; Lewy bodies;

BRC Theme/s: Dementia and Related Disorders
Biomarkers and Genomics
Neuroimaging
Clinical Research Facility
Precision Treatment for Persistent Pain: A Combined Examination of Neuroimaging and Therapeutic Mechanism in People with Fibromyalgia

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Project Description

Background: Fibromyalgia (FMS) affects between 1-4% of individuals. It is significantly disabling; sufferers experience symptoms including whole-body pain, fatigue, sleep disturbance, depression, cognitive impairment, and irritable bowel. Left untreated, few patients with FMS improve over time.

Psychological treatments are among the best current treatments for FMS, producing moderate reductions in symptoms and improved functioning. Acceptance and Commitment Therapy (ACT), a theoretically based and mechanism-focused form of Cognitive Behavioral Therapy, is a promising treatment for FMS.

A key challenge to improving treatments for conditions like FMS is to identify key therapeutic mechanisms that predict treatment outcome. Predictions based on conventional self-reported measures are generally imprecise, but advances in our understanding of pain mechanisms in the brain provided by neuroimaging may offer improved solutions.

We will use multiple kernel learning, a novel multivariate analytical technique that considers clinical, psychometric and neuroimaging data in concert to provide individualized predictions of treatment response to ACT. Each data type is represented by an individual kernel, the relative contribution of each informing the combination of assessments most predictive of treatment response.

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. We know that early intervention for patients contributes significantly to the likelihood of successful treatment. Knowing how to treat and why treatments are successful should enable timely and appropriate direction of healthcare resources.

Primary aim(s): To test the feasibility of a study of ACT treatment for FMS. Specifically, to perform a non-randomized feasibility study of predictors and mediation (mechanisms of change) of treatment outcome in 40 patients with FMS, using both self-report and neuroimaging data, focused on recruitment, retention, data quality, acceptability, and estimation of parameters for future study. We will use MKL and forward mapping procedures, respectively, to predict patient treatment outcomes and provide mechanistic insights.
Planned research methods and training provided: Acquisition and analysis of multimodal fMRI technologies (evoked-response and resting-state BOLD fMRI data, structural and perfusion MRI) alongside conventional clinical and self-reported outcome measures, using (mass) univariate and multivariate methodologies.

Objectives / project plan:
Year 1: Seek ethical approval and analyze existing RCT ‘mindfulness for FMS’ perfusion MRI data
Year 2: Data acquisition, perform interim analysis
Year 3: Complete data acquisition and analysis, dissemination of headline data to academic peers and patients, thesis submission
Year 4: Presentation of work at IASP conference, preparation of manuscripts

Other notable aspects of the project: Funding for delivery of ACT by a trained clinical psychologist and scanning costs are in place.

Two representative publications from supervisors:


Keywords: Pain; Fibromyalgia; Machine Learning; fMRI; Psychological Therapies;

BRC Theme/s: Pain
Biomarkers and Genomics
Neuroimaging
Clinical Research Facility
BRC-049 Precision Assessment of Difficult to Assess Metabolite Concentrations Using Magnetic Resonance Spectroscopy

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Project Description

Background: Developments in magnetic resonance spectroscopy allow in vivo measurement of low concentration neuro-metabolites. These have previously been difficult to disentangle from other, higher concentration metabolites that obscure their signatures in the spectrum. These low concentration metabolites include GABA, the predominant inhibitory transmitter within the brain and the antioxidant glutathione (GSH). Our adaptation of the HERMES sequence, allows simultaneous measurement of GABA and GSH within the same time as standard MEGAPRESS, with no reduction in spectral quality.

We will modify our implementation of HERMES measure other combinations of metabolites, starting with separating the neurotransmitter N-acetyl aspartate glutamate (NAAG) from N-acetyl aspartate (NAA).

Novelty and Importance: Accurate, reproducible assessment of metabolite concentrations is important in order to bring about the use of precision medicine MRS techniques in psychiatry. Current methods of assessing the concentrations of low concentration metabolites, are confounded by scanner frequency drift, which reduces the editing efficiency of MEGA-PRESS and HERMES, leading to inaccurate metabolite concentration measures. We aim to investigate the effects of scanner drift on quantitation, and to modify the acquisition sequence to monitor and correct for frequency drift. Similarly, CSDE leads to metabolites from outside the volume of interest. We intent to use a HERMES implementation of semi-LASER to alleviate this problem.

Primary aim(s):

1) To quantify, using density matrix simulations, and MEGA-PRESS and HERMES scans of both phantoms and volunteers, the effects of frequency drift during MRS, on quantitation of metabolite levels. In particular, those of macromolecule suppressed GABA, NAA & NAAG.

2) To test whether using information from the whole spectrum with LC model, makes GABA quantification more resistant to macromolecule contamination that fitting a single GABA peak.

3) To improve metabolite localization by implementing HERMES in the semi-LASER sequence.
Planned research methods and training provided:

- Quantum mechanical density matrix simulations of the pulse sequences used, using real pulse shapes and delays.
- Implementation of MEGA-PRESS HERMES and a semi-LASER implementation of HERMES, with real time frequency monitoring and correction.
- Creation and scanning of metabolite phantoms; scanning of human volunteers.

Objectives / project plan:

Year 1: Modification of HERMES to allow real time frequency monitoring and correction. Implementation of density matrix simulations.

Year 2: Data acquisition in phantoms and human volunteers; perform interim analysis.

Year 3: Implementation of the HERMES-semi-LASER sequence, phantom and human scanning. Application of the method to the measurement of NAAG in schizophrenia patients.

Year 4: Presentation of work at ISMRM conference, preparation of manuscripts.

Two representative publications from supervisors:


Keywords: Magnetic Resonance Spectroscopy; MEGA-PRESS; GABA; Glutathione; Programming;

BRC Theme/s: Pain
      Biomarkers and Genomics
      Neuroimaging
      Clinical Research Facility
The neural basis of psychosis in Parkinson’s disease.
Developing targets for understanding current treatments and developing novel treatments

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Project Description
Background: Parkinson’s disease is a neurodegenerative condition classically defined by the motor symptoms. In addition, many patients experience non-motor symptoms of which psychosis is amongst the most common. Progressive neurodegeneration is a significant risk factor, serotonergic dysfunction is thought to be a specific mediator. In addition to the loss of dopaminergic neurons, there is extensive loss of serotonergic raphe neurons and their projections. The 5-HT2a receptor is a candidate receptor here because it is the principal target of hallucinogenic drugs such, and 5-HT2a antagonists can reverse their effects. Indeed, two studies show increased 5-HT2a receptor binding in PD psychosis in the ventral visual pathway.

Functional neuroimaging evidence confirms dysfunctional ventral visual pathway activity in PD psychosis including our in-house pilot data from PD patients with and without hallucinations (ffytche). Outside of the ventral visual pathways, two studies have shown altered connectivity within the default mode network, pointing to more widespread abnormalities. The limited neuroimaging data in PD psychosis means that the functional consequences are poorly understood outside of a these few studies. Further work is urgently needed to identify these abnormalities such that their reversal can be used to test novel treatments. A proof of mechanism study for a new treatment using these methods would provide a strong platform to pursue symptom modification studies. We will use saracatanib here which acts downstream from 5-HT2a receptors.

Novelty and Importance: This study will test novel assessment tools for PD Psychosis (around 5M sufferers worldwide) and also test the impact of a completely novel therapeutic target on these outcomes.

Primary aim(s): The aim is to develop an neuroimaging protocol to test for whole brain impairment in PD patients with and without psychosis to:
1. Enhance understanding of the neural basis of PD psychosis,
   Estimate the magnitude of impairment both in predefined brain regions and across brain networks and
2. Test for drug effects in these networks.

Planned research methods and training provided: Task development, protocol development and implementation, GCP, imaging data processing, imaging data analysis, trial statistics.
BRC-050  The neural basis of psychosis in Parkinson’s disease. Developing targets for understanding current treatments and developing novel treatments

Objectives / project plan:

Year 1: Review literature, develop and pilot task battery, submit ethical approval (amendment), liaise with patient/carer group, liaise with parallel drug trial team to align measures, begin testing

Year 2: Recruitment and data collection

Year 3: Recruitment and data collection, data processing, analysis, conference attendance, write up

Year 4: Additional comparative analyses with drug study data set. Write up.

Other notable aspects of the project: The candidate will be part of the ‘industry liaison’ team to develop experience in working and partnering with industrial collaborators.

Two representative publications from supervisors:


Keywords: Parkinson’s disease; Psychosis; Neuroimaging; 5-HT2A; Serotonin;

BRC Theme/s: Dementia and Related Disorders  
Psychosis and Neuropsychiatry  
Neuroimaging  
BioResource  
Clinical Research Facility
Assessing the relationship between thalamo-cortical connectivity and psychiatric disorders in preterm children. What can we learn from high field MRI?

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Project Description

Background: Survivors of preterm birth are at an increased risk of developing behavioral and psychiatric disorders in adolescence. The underlying pathobiology of these disorders is not clear, but may be related to aberrant development of key thalamo-cortical connections. The thalamus comprises several nuclei, each with dense cortical or subcortical connections. Disruptions to the integrity and connectivity of the thalamus may modulate several core symptoms in psychiatric conditions and detailed characterization of thalamic nuclei and connecting cerebral cortex is crucial for our understanding of the pathophysiology associated with behavioral and psychiatric disorders associated with preterm birth.

Novelty and Importance: Up to 40% of preterm children display psychiatric disorders in childhood. High field strength MRI enables cortical and thalamic microstructure to be assessed in detail. There have been no studies assessing thalamic nuclei or cortical grey matter in children who were born preterm at high field strengths, and the relationship between detailed neuroimaging and psychiatric disorders has not been assessed. This project has the potential to identify novel targets for therapeutic interventions which can be applied in the neonatal period, prior to onset of psychiatric symptoms.

Primary aim(s): To take advantage of the improved signal to noise ratio and spatial resolution of 7 Tesla to elucidate the structural, microstructural and functional thalamo-cortical connectivity profiles in preterm children that are associated with a high risk of developing psychiatric disorders.

Planned research methods and training provided: Preterm children (aged 8-10, n = 60) will be recruited from our well characterized EPrime cohort who underwent neonatal neuroimaging. High resolution structural, diffusion and functional MRI will be obtained using the new 7 Tesla facility based at St. Thomas’ Hospital in Year 2. Neurocognitive and behavioural assessments will be undertaken in all children. The student will receive training in neuroimaging analysis and neurodevelopmental/neuropsychological assessments.
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Objectives / project plan:

Year 1: Using existing 7 Tesla HCP data, gain an understanding of thalamic and cortical structure and microstructure. Learn constrained spherical deconvolution tractography and graph-theory approaches to study thalamo-cortical connectivity, biophysical models to study cortical development and rfMRI to assess functional connectivity. Write-up Year 1 project.

Year 2: Collect structural, dMRI and rfMRI data in children using the newly installed 7 Tesla system at KCL. Apply techniques learnt in Year 1 to analyses these data. Undertake psychological assessments and analyze results

Year 3: Complete imaging and assessment analysis. Write-up results.

Year 4: Finalise image analysis and complete write-up.

Two representative publications from supervisors:


Keywords: Preterm; Neuroimaging; Psychiatric disorders; thalamo-cortical connectivity; High field MRI;

BRC Theme/s:  Child and Neurodevelopmental Disorders
Biomarkers and Genomics
Neuroimaging