



*National Institute for
Health Research*

Maudsley Biomedical Research Centre

**PhD Studentship
Project Catalogue**
Psychosis and Neuropsychiatry

Studentship to commence February 2018

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

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

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

NIHR Maudsley BRC Strategy

There are four major elements to the NIHR Maudsley BRC strategy for the coming 5 years, reflected in 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

Projects

When applying for the NIHR Maudsley Biomedical Research Centre PhD studentship in **Psychosis and Neuropsychiatry** theme, please ensure you state your two preferred PhD projects from those listed in this catalogue only. These should be listed in order of preference and include the number that is assigned to the project and the project title.

For example:

1. PSNE-2.04 Enhancing cognitive training and assessment in schizophrenia using a virtual reality environment
2. PSNE-2.01 Can an individual's Gamma and Beta neural oscillations inform treatment choice for Psychotic Disorders?

Important: With your application, in addition to the personal statement, please upload a separate single-side A4 document listing your first and second choice projects with a statement explaining why you have chosen your **first choice** project and why you would like to take this forward as a PhD (**maximum 300 words**).

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 in the [King's College London Research Portal](#). Under **Researchers**, type the name of the person you wish to view information about.

Please note: The final choice of funding, project and project details are agreed after successful interview.

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.

PSNE-2.01 Can an individual's Gamma and Beta neural oscillations inform treatment choice for Psychotic Disorders?

Primary Supervisor: Dr Paul Morrison

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Second Supervisor: Dr Judith Nottage

Academic Department: Neuroimaging

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Project Description

This project will explore high frequency neural oscillations in first-episode psychosis. There is considerable interest in whether abnormal high frequency oscillations underlie disorders such as schizophrenia and whether abnormal oscillations can predict how an individual will respond to antipsychotic medication. Recent advances in EEG analysis, many of which have been implemented in our own lab (Nottage et al 2013, 2016), have made high frequencies of the EEG, such as the gamma band (>30 Hz) more accessible to investigators. We have now implemented these methods in a new, professional-level, user-friendly BRC-funded software package, which will be used for this research. In addition to interest in the gamma band in schizophrenia, it has recently emerged from animal studies that synchronised higher beta waves (>20-30Hz) in the parietal and frontal cortex are crucial for reward processing in mammals. Drugs which impact upon dopamine transmission or lesions to the main dopamine centres in the basal ganglia have a marked effect on these reward-related cortical oscillations. Given that dopamine is intrinsic to psychosis, we plan to extend the animal findings by investigating higher beta oscillations for the first time in man, and will compare first-episode patients versus matched controls. There are two parts to this project, which will involve EEG data collection and analysis in patients suffering psychosis, and where appropriate, matched healthy controls: 1. A longitudinal study tracking gamma and reward-related beta oscillations as first-episode psychotic in-patients move from an un-medicated, symptomatic state to being treated with antipsychotics. 2. A cross-sectional study of out-patients diagnosed with a psychotic disorder investigating gamma and reward-related beta oscillations using tasks which probe reward systems.

Training: Within this project, professional-level training will be provided in two main areas: the recording / analysis of EEG, and the measurement of psychopathology / cognitive function in major mental illness.

Yearly Objectives:

- Year 1: Obtain approvals for the project (e.g. ethics). Research and publish a literature review of the field in collaboration with Dr Nottage and Dr Morrison. Develop skills and competency in EEG recording and analysis under the guidance of Dr Nottage. Develop skills and competency in measuring psychopathology and cognitive function under the guidance of Dr Morrison. Begin data collection for the project.
- Year 2. Carry out the majority of the data collection and analysis.
- Year 3. Complete data collection and analysis, publish results and write thesis, present findings at International conferences.

Keywords: Psychosis; EEG; antipsychotics; personalised;

Two representative publications from supervisors:

- 1: Nottage, J. F., J. Stone, et al. (2015). "Delta-9-tetrahydrocannabinol, neural oscillations above 20 Hz and induced acute psychosis." *Psychopharmacology (Berl)* 232(3): 519-528.
- 2: Ranlund, S., J. Nottage, et al. (2014). "Resting EEG in psychosis and at-risk populations--a possible endophenotype?" *Schizophr Res* 153(1-3): 96-102.

PSNE-2.02 Can the polygenic risk score for bipolar disorder predict diagnosis and outcome of patients with psychosis?

Primary Supervisor: Professor Sir Robin Murray

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Second Supervisor: Dr James MacCabe

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Third co-supervisor: Dr James Walters. Cardiff University, UK.

Project Description

Molecular genetics is revolutionising our understanding of psychiatric disorders. For example, polygenic risk scores (PRS) have been developed for schizophrenia (PRS-Sz) and bipolar disorder (PRS-BP). In this project, the student will measure the diagnostic, and predictive, value of the PRS-BP in 2500 patients who have been followed-up for two to 10 years since first contact with mental health services for psychosis. The patients will come from the STRATA-G study which is currently completing the follow-up and GWAS from 12 participating centres.

AIMS

1. How effective is the polygenic risk score for bipolar illness (PRS-BP) in distinguishing between patients with (a) bipolar disorder, b) schizophrenia spectrum disorders, and c) depressive psychosis?
2. Does the PRS-BP predict manic and depressive symptom dimensions among patients with schizophrenia?
3. Does the PRS-BP predict long-term outcome?
4. Is there evidence of interaction between the PRS-BP, and environmental risk factors e.g. childhood adversity, stressful life events, use of illicit drugs.

In the first year, the student will participate in cleaning the data, and integrating phenotypic data in the 2500 patients from a) baseline, and b) follow-up. In the second year, she/he will participate in the calculation of the PRS-BP score under supervision of Paul O'Reilly, and will learn to apply the PRS-BP to the phenotypic data of interest, and to study the interaction with environmental factors. The third year will focus on analysis and the student will learn the application of advanced statistical techniques such as STATA, 'R', and machine learning.

Keywords: molecular genetics; bipolar; psychosis; diagnosis; outcome;

Two representative publications from supervisors:

- 1: Di Forti, Marta; Marconi, Arianna; Carra, Elena....Murray Robin M Proportion of patients in south London with first-episode psychosis attributable Di Forti M et al, Proportion of first episode psychosis attributable to use of high potency cannabis: a case-control study LANCET PSYCHIATRY, 2015, 2, 233-238
- 2: Legge et al GWAS and rare variant analysis provides novel insights into clozapine- associated neutropenia. Molecular psychiatry. Published On-line 12 July 2016

PSNE-2.03 Developing a Virtual Reality Paradigm to Assess and Treat the Negative Symptoms of psychosis

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Third co-supervisor: Dr Maria Rus-Calafell. Health Service & Population Research, KCL.

Project Description

Despite the availability of antipsychotic medications that reduce psychotic symptoms in most people with psychosis levels of functional disability have changed little over the past decades. Negative symptoms, such as social withdrawal, amotivation and anhedonia, are the major predictors of marked functional disability and place an enormous strain on people with psychosis, carers and health care services. Negative symptom assessment is usually carried out in a clinic room with the interviewer asking the patient to recall their symptoms experience in the the past week or month. This method provides very limited information of the service user experience of the symptoms and how they affect their life. Virtual Reality (VR) has been increasingly used in mental health research to provide a standardized assessment of actual symptom occurrence.

This project aims to develop a new VR paradigm to assess key behavioural negative symptoms and test its acceptability and feasibility in people with psychosis. The new assessment method will also use an mHealth device to investigate, for the first time, the psychophysiological signature of specific negative symptoms. The project will evaluate the validity and reliability of the new method but also explore clinical applications.

Training

Virtual Reality; Advanced Statistics; Library and Database Usage; Clinical interviews administration; Attending Seminars and Scientific talks; Access to all skill forge trainings. Overarching objectives for the student will be: 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.

Keywords: Psychosis; Virtual reality; Negative Symptoms; Assessment; Mobile Health;

Two representative publications from supervisors:

1: Valmaggia, L., Day, F., Rus-Calafell, M. (2016) Using virtual reality to investigate psychological processes and mechanisms associated with the onset and maintenance of psychosis: a systematic review. *Social Psychiatry and Psychiatric Epidemiology*, 51, 7, 921-936.

2: Cella, M., Edwards, C., Wykes, T. (2016). A question of time: A study of time use in people with schizophrenia. *Schizophrenia Research*, 76(2-3):480-4.

PSNE-2.04 Enhancing cognitive training and assessment in schizophrenia using a virtual reality environment

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Project Description

Assessment of real-life functioning is a crucial aspect of clinical mental health assessment, with relevance for clinical diagnosis, but also in determining the impact of real change secondary to any therapeutic intervention. This real-life assessment has been recognized as a problem and the US Food and Drug Administration (FDA) has recently mandated that that all studies of cognitive function should also include evidence of functional relevance. Cognitive dysfunction is a key yet under recognized feature of schizophrenia; and performance-based assessments of functioning have demonstrated higher correlations with cognitive test performance than patient self-reports derived from interview-based measures. Recent technological development has made 3-D immersive virtual reality (VR) assessment feasible for routine use, and through a novel collaboration with two external industrial partners -a brain training game development company and the other specializing in developing 3D immersive software - we have developed a computerized virtual reality assessment that contains all of the components of real-life functional performance in patients with schizophrenia. The first phase of this project will test feasibility and optimize this VR resource; the second phase will use the optimised version as part of the assessment of a pilot study of a brain training intervention in patients with schizophrenia. Interested candidates can consider incorporating a neuroimaging component to examine brain mechanisms underlying the cognitive training.

0-9 months – ethics and testing in healthy participants

9-18 months – testing in patients

18-24 months – pilot study of cognitive training in patients

24-36 – analysis/write up papers

Keywords: virtual reality; cognition; schizophrenia;

Two representative publications from supervisors:

1: A systematic review of the effects of low- frequency repetitive transcranial magnetic stimulation on cognition. / Lage, Claudia; Wiles, Katherine; Shergill, Sukhwinder; Tracy, Derek K.

2: Computerized cognitive remediation training for schizophrenia: An open label, multi-site, multinational methodology study Murthy, N. V., Mahncke, H., Wexler, B. E., Maruff, P., Inamdar, A., Zucchetto, M., Lund, J., Shabbir, S., Shergill, S., Keshavan, M., Kapur, S., Laruelle, M. & Alexander, R. Aug 2012 In : Schizophrenia Research. 139, 1-3, p. 87-91

PSNE-2.05 Improving Social Cognition in Schizophrenia using Brain Stimulation.

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Second Supervisor: Professor Sukhwinder Shergill

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Project Description

Social cognition concerns how we think about others and how this influences our behaviour and social interactions. In schizophrenia, social cognition is profoundly impaired, which impacts on patients' ability to function in everyday life. In this pilot study you would test a brain stimulation intervention designed to improve social-cognition deficits. Everyday functioning relies on recognising and correctly interpreting associations between stimuli or events. In schizophrenia, the time windows used for identifying events as being linked together are less precise and this imprecision can lead to impaired social interactions. The project will assess whether 'brain training' (time perception exercises) can improve patients' ability to judge social intentions. The effects will be enhanced with non-invasive brain stimulation to the brain regions that calculate physical causality. Training effects will be measured with EEG recordings, to clarify the brain mechanism involved. Scores on clinical measures will be compared before and after training, to determine improvements in symptoms and well-being.

Objectives: Overall: To test whether damaged representations of timing cues in the brain transmit unreliable information about causal relations between events, which then leads to incorrect interpretations that there was a social intention or purpose behind these events.

Year1: Gain permissions and approvals, review literature, develop and test methods. Year2: Recruit healthy adults and patients with schizophrenia, baseline test sessions. Year3: Treatment and evaluation test sessions, data analysis.

Skills training:

- (i) Assessing patient populations
- (ii) Cognitive Remediation Therapy
- (iii) Neurostimulation methodology
- (iv) Use of EEG and analysis of EEG data
- (v) Assessment of psychological well-being

Keywords: Schizophrenia; Social cognition; Neurostimulation; Cognitive remediation; Sensory processing;

Two representative publications from supervisors:

1: Mitchell R, Phillips LH (2015) "The overlapping relationship between emotion perception and theory of mind". *Neuropsychologia*, Vol. 70, pp 1-10.

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

PSNE-2.06 Inflamed brain: testing the role of neuroinflammation in schizophrenia

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Project Description

Schizophrenia is a chronic and disabling psychiatric illness. Antipsychotics have been the only treatment for schizophrenia but they are ineffective or not tolerated in three-quarters of patients. Therefore there is an urgent need for alternative and better treatments for schizophrenia. Converging lines of evidence suggest that neuro- inflammation has an important role in the pathophysiology of schizophrenia. Microglia are the main immune cells in the brain and microglial activity can be measured using PET imaging. PET imaging has shown an increase in microglia activity in schizophrenia. However, it is still unknown if activated microglia play a primary role in the disorder or is a secondary phenomenon. The key test is to reverse microglial activation and determine the effect on symptoms and brain functional measures. This exciting project will use multi-modal imaging and a monoclonal antibody challenge to specifically target reduce microglial activation in patients to test the following main hypotheses: i) reducing microglial activation reduces symptoms ii) reducing microglial activation reduces altered brain connectivity.

The student will acquire the following skills & training:

- a) Clinical assessment
- b) Evaluation of a new potential pharmacological intervention
- c) Analysis of PET, structural, MRS and fMRI data
- d) Writing for publication and presentation skills
- e) Project Management

Annual objectives:

Year 1: Background reading / Imaging training / Set up and study initiation/ Begin recruitment

Year 2: Recruitment / PET, MRS, structural and fMRI scanning / data entry / initiation of data analysis

Year 3: Completion of scanning and data analysis / publications / PhD thesis

Keywords: PET; microglia; schizophrenia; neuroinflammation; antipsychotics;

Two representative publications from supervisors:

1: Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo A, Owen DR, Bloomfield MA, Bonoldi I, Kalk N, Turkheimer F, McGuire P, de Paola V, Howes OD. Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [(11)C]PBR28 PET Brain Imaging Study. *Am J Psychiatry*. 2016 Jan;173(1):44-52

2: Marques TR, Natesan S, Niccolini F, Politis M, Gunn RN, Searle GE, Howes O, Rabiner EA, Kapur S. Phosphodiesterase 10A in Schizophrenia: A PET Study Using [(11)C]IMA107. *Am J Psychiatry*. 2016 Jul 1;173(7):714-21.

PSNE-2.07 Neurodevelopmental trajectories and psychotic experiences: a longitudinal MRI study of young adults

Primary Supervisor: Professor Anthony David

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Second Supervisor: Professor Paola Dazzan

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Project Description

This project will provide the opportunity to participate in a unique study. This is a collaboration between several UK universities, the Avon Longitudinal Study of Parents and Children (ALSPAC) using multimodal brain imaging. Over 250 people from the ALSPAC birth cohort have already undergone structural and functional MRI at age 20 in the Cardiff University Brain Imaging Centre. ALSPAC contains a wealth of data on physical and mental health, cognitive development, DNA, personality and environmental exposures on over 6000 people who have been followed-up intensively since birth. Studies undertaken so far have concentrated on psychotic experiences (PEs) and these show subtle correlations with altered brain connectivity. The study team are planning to re-scan 250 participants to gain information on trajectories of brain development. This project will focus on neuroimaging predictors of persistence or remission of PEs and possible mediating factors. There will be ample opportunities to develop a PhD project around other symptoms, clinical outcomes, personality factors, genetics or cognition combining multi-modal imaging with these measures. The student will acquire skills in image analysis, longitudinal research, cognitive development and psychiatric disorders and will work with a multidisciplinary team of academics on a truly cutting edge piece of work.

Prof David will supervise all aspects of the study, will facilitate visits to collaborating labs, and guarantee access to data. Dr Dazzan will provide training and supervision in MR imaging and longitudinal data analysis and in interpretation of findings.

Keywords: Neuroimaging; ALSPAC; development; Psychotic experiences; MRI;

Two representative publications from supervisors:

- 1:** (1). Drakesmith M, Dutt A, Fonville L, Zammit S, Reichenberg A, Evans CJ, Lewis G, Jones DK, David AS. (2016). Mediation of developmental risk factors for psychosis by white matter microstructure in young adults with psychotic experiences. *JAMA Psychiatry*, 73(4):396-406. doi:10.1001/jamapsychiatry.2015.3375. (2). 1. Fonville L, Kadosh KC, Drakesmith M, Dutt A, Zammit S, Mollon J, Reichenberg A, Lewis G, Jones DK, David AS. (2015) Psychotic experiences, working memory and the developing brain: a multimodal neuroimaging study. *Cerebral Cortex*. doi: 10.1093/cercor/bhv181
- 2:** Reinders AA, Fearon P, Heslin M, Zanelli J, Jones PB, Murray RM, Dazzan P. Bilateral hippocampal increase following first-episode psychosis is associated with good clinical, functional and cognitive outcomes. *Psychol Med*. 2014 Apr;44(6):1279-91. doi: 10.1017/S0033291713001712. Epub 2013 Jul 18. (2). Palaniyappan L, Marques TR, Taylor H, Handley R, Mondelli V, Bonaccorso S, Giordano A, McQueen G, DiForti M, Simmons A, David AS, Pariante CM, Murray RM, Dazzan P. Cortical folding defects as markers of poor treatment response in first-episode psychosis. *JAMA Psychiatry*. 2013 Oct;70(10):1031-40. doi: 10.1001/jamapsychiatry.2013.203.

PSNE-2.08 Pharmacological modulation of sensorimotor symptoms in people with functional neurological symptoms and healthy controls

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Second Supervisor: Dr Mitul Mehta

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Project Description

Suggestion has been proposed as a mechanism underlying the formation of functional neurological symptoms such as sensorimotor loss and non-epileptic seizures (Deeley 2017). Also, suggestions have been used in healthy individuals to create experimental models of the brain correlates of functional neurological symptoms and the cognitive processes that produce them (Deeley 2017). However, the role of neuromodulatory systems in mediating suggested effects in healthy individuals, and psychopathology, remains unknown. It has been proposed that the mesolimbic dopamine system mediates suggestive processes at a neural level. However, its differential involvement in types of suggestion, and functional neurological symptom formation, is poorly understood. Improved understanding would provide insights into the relationship between suggestibility and functional symptom formation, and help identify treatment targets at a receptor (pharmacology) or systems level (neurofeedback).

Study 1 investigates modulation of responses to verbal and non-verbal suggestions in healthy male volunteers (n = 48) using i) a dopamine antagonist (the D2- blocker haloperidol), and (ii) a dopamine precursor L- Dopa. We will test the hypothesis that dopamine antagonism is associated with decreased, and potentiation increased, response to both verbal and non-verbal suggestions.

Study 2 investigates the effects of haloperidol and L-dopa on i) response to verbal and non-verbal suggestions, and ii) symptoms, in patients with sensorimotor symptoms. We test the hypothesis that dopaminergic modulation of response to non-verbal suggestions mediates symptom modulation in this group.

The student will attend regular group meetings, departmental seminars, and primers for pharmacological studies, amongst other training opportunities. **Year 1:** Develop study protocols, obtain ethics, attend training sessions for hypnosis and suggestion and review literature. Conduct pilot study. **Year 2:** Conduct study. **Year 3:** Complete study, all analyses, write up.

Keywords: suggestion; expectancy; functional neurological symptoms; dopamine; pharmacology;

Two representative publications from supervisors:

1: 2017 Deeley Q. Hypnosis as a model of functional neurologic disorders. *Handb Clin Neurol.* 2017;139:95-103.

2: 2015 Stone, J., Kotoula, V., Dietrich, C., De Simoni, S., Krystal, J. H., & Mehta, M. A. (2015). Perceptual distortions and delusional thinking following ketamine administration are related to increased pharmacological MRI signal changes in the parietal lobe. *Journal of Psychopharmacology*, 29(9), 1025-1028.

PSNE-2.09 Precision medicine for the individualised prediction of psychosis in high risk patients

Primary Supervisor: Dr Paolo Fusar-Poli

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Second Supervisor: Dr Daniel Stahl

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Project Description

The onset of psychotic illness represents potential personal disaster in the life-course of a young individual and current treatments offer minimal help. The PhD project will focus on the development and clinical validation of individualized predictive models and risk stratification in patients at high risk for psychosis. During Y1 the candidate will learn about research methodology and how to develop predictive models with cutting-edge analytical methods including machine-learning approaches by attending specific courses including the IoPPN summer school "Prediction modelling". During Y2 the candidate will apply these models to complex multimodal databases acquired as part of ongoing international studies that comprise clinical, neuroimaging, and electrophysiological measures. During Y3 the candidate will learn validating these predictive models in independent samples to maximize their translational impact. During Y4 the candidate will implement these models in clinical practice to improve clinicians' ability to predict psychosis onset. The candidate will have the opportunity to train in one of the largest and most productive research groups on psychosis (approximately £20 million of research grant income, and 1300 journal articles in the last 5 years), with high quality clinical services and teaching via the Psychosis Clinical Academic Group and to receive high-quality methodological supervision by the Department of Biostatistics and Health Informatics. The candidate will additionally collaborate with one of the largest clinical services for these patients (OASIS) worldwide. At the end of the PhD the candidate will have acquired advanced skills in stratification medicine studies of early psychosis.

Keywords: Psychosis; Machine Learning; Prediction; Neuroimaging; Translational;

Two representative publications from supervisors:

1: The psychosis high-risk state: a comprehensive state-of-the-art review. Fusar- Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, Keshavan M, Wood S, Ruhrmann S, Seidman LJ, Valmaggia L, Cannon T, Velthorst E, De Haan L, Cornblatt B, Bonoldi I, Birchwood M, McGlashan T, Carpenter W, McGorry P, Klosterkötter J, McGuire P, Yung A. JAMA Psychiatry. 2013 Jan;70(1):107-20.

2: Machine Learning, Statistical Learning and the Future of Biological Research in Psychiatry Iniesta, R., Stahl, D. R. & McGuffin, P. Sep 2016 In : Psychological medicine. 46, 12, p. 2455-2465

PSNE-2.10 Predicting clinical and functional outcomes in adulthood among children at-risk for psychosis: a transdiagnostic approach using multivariate disease signature analysis with multimodal data.

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Second Supervisor: Professor Philip McGuire

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Third co-supervisor: Dr Kristin Laurens. University of New South Wales.

Project Description

Background: Over the past decade, novel strategies for identifying children at elevated risk for psychosis in the community have been implemented in research centres internationally. Whilst the majority of these children will not develop psychosis, other psychiatric disorders and functional impairments will likely be common. Thus, a transdiagnostic approach, identifying predictors of poor outcome irrespective of disorder, may maximise opportunities for early intervention. Using existing multimodal data (neuroimaging, cognitive, HPA axis, and genomic markers) acquired from longitudinal high-risk cohorts, the current study will determine the predictive utility of these markers for poor clinical and functional outcomes in early-adulthood.

Training: The student will complete a comprehensive training package and gain exposure to cutting-edge methodologies. Our collaborators (Dr Joyce and Professor Lewis) will facilitate the development of skills in multivariate disease signature (MDS) analysis and analysing and interpreting polygenic risk scores (PRS), respectively. Project supervisors will provide training in conducting systematic reviews/meta-analyses, analysing HPA axis biomarkers, and assessing clinical/functional outcomes.

Objectives: In the first year, associations between neuroanatomical features and HPA axis biomarkers, and possible mediation by PRS, will be examined in a large cohort of at-risk youth (Objective 1). During year two, a systematic review will be performed to compare the performance of different multivariate prediction models in psychosis (Objective 2), thereby informing subsequent analyses. In the final year, the student will apply MDS methods to multimodal data (neuroimaging, PRS, cognitive function, HPA axis biomarkers) acquired during childhood/adolescence to identify patterns of neurobiological features predictive of outcome in early-adulthood (Objective 3).

Keywords: Psychosis risk; Schizophrenia; Predictive models; Neuroimaging; Machine learning;

Two representative publications from supervisors:

- 1:** Laurens KR, Cullen AE (2016) Toward earlier identification and preventative intervention in schizophrenia: Evidence from the London Child Health and Development Study. *Social Psychiatry and Psychiatric Epidemiology*, 51, 475-491.
- 2:** Young J, Kempton MJ, McGuire P (2016) Using machine learning to predict outcomes in psychosis. *Lancet Psychiatry*, 3, 908-909.

PSNE-2.11 Predicting treatment response in psychosis using TMS-EEG

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Project Description

Antipsychotic drug treatments are unsuccessful in approximately 30% of cases. Treatment failures may occur because there is insufficient drug in the brain to exert a therapeutic effect, or because the pharmacological effect has no relevant therapeutic effect. These factors may differ between individual patients. Recent work has demonstrated that the combination of transcranial magnetic stimulation and electroencephalography (TMS-EEG) can measure the pharmacological effect of drugs in the human brain. Our pilot work at King's has shown that TMS-EEG can identify fingerprints of the pharmacological effects of specific psychotropics (lamotrigine and levetiracetam) in healthy subjects. In this project, the student will initially measure TMS-EEG fingerprints of well known antipsychotic medication (olanzapine, amisulpiride, clozapine) in the healthy brain. In a second step, they will measure TMS-EEG response in patients on monotherapy with these medications, to test the hypothesis that patients who respond to treatment will show a similar profile to the TMS-EEG fingerprint, while patients who are poor responders will show a different TMS-EEG response. This will develop a tool that can measure whether an antipsychotic has entered the brain, is functioning in a desired way, and therefore might predict future treatment outcome.

The student will develop a strong working knowledge of tms and eeg analysis. Further expertise will be gained in neuropharmacology and psychosis in the CSI Lab in the Department for Psychosis Studies. Training will be provided in neuropsychological and clinical assessment.

Year 1 – healthy volunteer data collection

Year 2 – patient data collection

Year 3 – analysis and write up

Keywords: psychosis; treatment response; tms; EEG;

Two representative publications from supervisors:

1: Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., et al. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. *Neuroimage*. (2014), 103:152-62.

2: Dysfunctional Striatal Systems in Treatment- Resistant Schizophrenia. / White, Thomas; Wigton, Rebekah; Joyce, Daniel William; Collier, Tracy; Fornito, Alex; Shergill, Sukhwinder S. In: *Neuropsychopharmacology*, Vol. 41, 2016, p.1274–1285.

PSNE-2.12 Psychotic experiences in the flow of daily life – how does psychological therapy work?

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Third co-supervisor: Professor Inez Myin-Germeys. Leuven University, Belgium.

Project Description

Psychotic experiences (PEs) are not necessarily associated with distress or requiring care from mental health services. Cognitive models of psychosis suggest that it is the way individuals appraise and cope with their PEs, rather than their presence, that determines how much distress is associated with the PEs. Psychological therapies aim to reduce distress by changing threatening appraisals of, and unhelpful responses to, psychotic symptoms, as well as increasing resilience and self-esteem.

Experience Sampling Method (ESM) is a structured diary technique, using a Smartphone App over a 1-week period, permitting 'in-the-moment' measurement of PEs, appraisals, and emotions within their social and environmental context as they unfold in daily life.

In this project we will use ESM to monitor progress of psychosis patients undergoing therapy, and compare them to individuals with benign PEs. This will allow us to elucidate (1) psychological factors that determine benign or pathological outcomes of PEs, (2) mechanisms of change in therapy. This will improve our understanding of resilience and inform the next wave of therapies. The successful candidate will have access to the required populations through the supervisor's psychological therapies for psychosis clinic and a research register of individuals with persistent, benign PEs in the general population.

Year 1: Training in ESM design and methodology; therapy observations and recruitment to the study; Year 2: training in conducting systematic reviews, and multi-level modelling statistics for ESM analyses; recruitment, writing up systematic review; Year 3: Analyses, publishing of empirical paper(s), writing up thesis.

Keywords: Psychosis; Experience Sampling Method (ESM); Cognitive Behaviour Therapy; Non-clinical psychotic experiences;

Two representative publications from supervisors:

- 1: Peters et al (16) Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a 'need-for- care'. *World Psychiatry*, 15(1), 41-52.
- 2: Peters et al (12) Appraisals, psychotic symptoms and affect in daily life. *Psychological Medicine*, 42, 1013-1023.

PSNE-2.13 Restoring a disordered sense of self: neuromodulation in the treatment depersonalisation disorder

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Project Description

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 treatments. Single case reports and one 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, hence both sites may be credibly involved in the disorder. The time is ripe for a randomised controlled trial of rTMS. This studentship will include the planning, conduct and writing up of such a trial using patients linked to the DPD clinic at the Maudsley hospital. The project will also 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 perception and experience of the self. As well as learning about TMS the student will gain skills in neuroimaging, neuropsychological testing, clinical trials and psychiatric evaluation.

Keywords: depersonalisation disorder; TMS; self; prefrontal cortex; neuropsychology;

Two representative publications from supervisors:

1: (1). Jay E-L, Sierra M, Van den Eynde F, Rothwell JC, David AS. (2014). Testing a neurobiological model of depersonalization disorder using repetitive transcranial magnetic stimulation. *Brain Stimulation*, 7: 252-9.(2). Jay EL, Nestler S, Sierra M, McLelland J, Kekic M, David AS. (2016). Ventrolateral prefrontal cortex repetitive transcranial magnetic stimulation in the treatment of depersonalization disorder: A consecutive case series. *Psychiatry Research*, 240: 118–122. DOI:<http://dx.doi.org/10.1016/j.psychres.2016.04.027>.

2: 527 Tracy DK, Shergill SS, David AS, Fonagy P, Zaman R, Downar J, Elliott E, Bhui K. (in press) Self-harm and suicidal acts: a suitable case for treatment of impulsivity-driven behaviour with repetitive transcranial magnetic stimulation (rTMS). *BJPsych Open*.

PSNE-2.14 Rumination, depression and distress in Parkinson's disease

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Project Description

Rumination is a common thinking style defined as 'compulsively focused attention on the symptoms of one's distress, and on its possible causes and consequences, as opposed to its solutions'. Rumination is common in (and may serve to maintain) anxiety and depression, while as a trait it can increase vulnerability and risk of relapse. This has led to the development of new rumination focused therapies that offer considerable promise in the management of chronic depression.

Parkinson's disease a progressive neuro-degenerative disorder with a wide range of motor and non-motor symptoms. Depression, frequently co-morbid with anxiety, is common and is frequently chronic, persisting for many years. Antidepressant medication and CBT can be helpful but their effectiveness is limited. We have shown previously that rumination is strongly associated with depression in Parkinson's disease and that it may predict subsequent distress.

Building on such evidence the project will assess the potential and feasibility of rumination-focussed approaches for the management of chronic depression and distress in people with Parkinson's disease. It will provide scope to learn a variety of research methods to investigate the nature rumination and its relationship to depression and distress, and its potential as a therapeutic target. It will use qualitative (Year 1) and quantitative methods with both on-line survey (Year 1) and real-time Experience Sampling Method approaches (Year 2). Combining this evidence it will assess the short-term malleability of ruminative thinking style through a single-session controlled experimental intervention (Years 2 and 3), providing the foundation for a future clinical trial.

Keywords: Parkinson's disease; Rumination; Depression; Distress; Experimental psychopathology;

Two representative publications from supervisors:

1: Anxiety and anxious-depression in Parkinson's disease over a 4-year period: a latent transition analysis. Landau S, Harris V, Brown RG. Psychological Medicine. 2016;46:657-667. DOI:10.1017/S0033291715002196

2: Rumination and behavioural factors in Parkinson's disease depression. Julien CL; Rimes, KA; Brown RG. Journal of Psychosomatic Research 2016;82:48–53. DOI: 10.1016/j.jpsychores.2016.01.008

PSNE-2.15 The effect of polygenic risk score on brain function before and during the development of psychosis

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Project Description

Patients with psychotic disorders such as schizophrenia usually experience prodromal symptoms 1–5 years prior to the first episode of frank psychotic illness. This is described as an ‘at risk mental state’ (ARMS), as these individuals have a high risk of developing psychosis, and 20-30% will develop the illness within 2 years.

For the last 5 years the IoPPN has led a large longitudinal study of ARMS in 12 international centres (EU-GEI high risk study, PI Philip McGuire, Coordinator Matthew Kempton) and has collected rich longitudinal data including neuropsychology, neuroimaging data, childhood environment, and genetic samples.

Genetic influences may have an early and late effect on cognitive deficits in psychosis. The aim of the study is to examine the effect of polygenic risk score (provided) on cognition at 1) baseline when ARMS first report to clinical services and 2) changes in cognition in those individuals who transition to psychosis. It may also be possible to relate how cognitive deficits are associated with parallel changes in brain function.

Yr1-Preparation of data, attending MSc courses, training in polygenic risk

Yr2-Baseline data analysis, participant recruitment in PSYSCAN Yr3- Longitudinal data analysis, write-up

Training would be provided in on the analysis of cognitive data and the interpretation of polygenic risk scores and strategies to combine multicentre data. In addition to analysing data from the EU-GEI study, the student would have the choice of undertaking data collection in a new longitudinal high-risk study, PSYSCAN

Keywords: Psychosis; schizophrenia; high-risk; longitudinal;

Two representative publications from supervisors:

1: Kempton MJ, Bonoldi I, Valmaggia L, McGuire P, Fusar-Poli P (2015) Speed of Psychosis Progression in People at Ultra-High Clinical Risk: A Complementary Meta- analysis. *JAMA Psychiatry*. 2015 Jun;72(6):622-3

2: Young J, Kempton MJ, McGuire P (2016) Using machine learning to predict outcomes in psychosis. *Lancet Psychiatry*. 2016 Oct;3(10):908-909.

PSNE-2.16 Dissecting the heterogeneity of psychosis outcome with a multimodal approach: can we generate accurate, cost-effective models clinically useful for the individual patient?

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Third co-supervisor: Dr Lena Palaniyappan, Prevention & Early Intervention Program for Psychoses (PEPP), Ontario, Canada.

Project Description

Up to 50% of patients initially diagnosed with schizophrenia develop unfavourable clinical and functional outcomes, despite available pharmacological and psychosocial treatments. Although many potential factors (illness course, socio-demographic variables, brain alterations) have been identified that could predict these outcomes to some extent, it remains unclear whether using them in combination improves the predictive accuracy, or rather adds more noise to the models. This PhD aims to go beyond recent applications of machine learning to single data (features) types and focus on multivariate combination that could generate accurate, cost-effective models clinically useful for the individual patient. The aim in Year 1 is to examine existing datasets to identify the set of data that are significantly associated with prognosis (clinical, structural MRI, Diffusion Tensor Imaging, functional MRI, blood-based biomarkers), and rank them according to 'accessibility' (ease of obtaining and cost); in Year 2, to estimate the incremental validity of each additional set of variables; this work will involve a period of time spent in Ontario (Canada), working in the Prevention & Early Intervention Program for Psychoses (PEPP) under the supervision of Prof Palaniyappan; and finally in Year 3, to estimate the accuracy of a parallel test that includes all variables in the feature space and to test its validity in a newly acquired dataset. The candidate will develop skills in the evaluation of clinical outcome in psychosis and in advanced multivariate statistical approaches, particularly machine learning and its application for clinical utility.

Keywords: Psychosis; Outcome; Neuroimaging; Machine Learning; Neuroinflammation;

Two representative publications from supervisors:

- 1: Palaniyappan L, Marques TR, Taylor H, Mondelli V, Reinders AA, Bonaccorso S, Giordano A, DiForti M, Simmons A, David AS, Pariante CM, Murray RM, Dazzan P. Globally Efficient Brain Organization and Treatment Response in Psychosis: A Connectomic Study of Gyrification. *Schizophr Bull.* 2016 Nov;42(6):1446-1456.
- 2: Mourao-Miranda J, Reinders AA, Rocha-Rego V, Lappin J, Rondina J, Morgan C, Morgan KD, Fearon P, Jones PB, Doody GA, Murray RM, Kapur S, Dazzan P. Individualized prediction of illness course at the first psychotic episode: a support vector machine MRI study. *Psychol Med.* 2012 May;42(5):1037-47.

PSNE-2.17 Pharmacogenetics and pharmacoepidemiology of clozapine induced haematological side effects

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Project Description

Around one third of patients with schizophrenia fail to respond to treatment. The only drug with evidence of efficacy in such patients is clozapine. However, clozapine is associated with agranulocytosis, a severe drop in the white blood cell count, a rare but serious adverse effect, which limits the use of clozapine. A better understanding of the predictors of agranulocytosis and neutropenia would allow it to be used more effectively and more safely, and potentially with less blood monitoring. This would open the door to the introduction of personalised medicine in schizophrenia, a key objective of the SLAM-BRC.

We have linked an anonymised database of 1500 patients from the clozapine monitoring service to our Clinical Records Interactive Search (CRIS) system. Through a collaboration with the University of Cardiff, we will be able to link most of these records to genetic data. This allows us to conduct anonymised research on the genetic and clinical determinants of haematological problems on clozapine.

The student will spend the first year reviewing the literature, learning data management skills and linking the genetic data. The second year will be spent analysing the data, learning advanced statistical techniques. The third year will be spent publishing and writing up the project.

Keywords: Schizophrenia; Clozapine; Pharmacogenetics; Pharmacoepidemiology; Genetics;

Two representative publications from supervisors:

1: Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia Legge, S. E. , Hamshere, M. L. , Ripke, S. , Pardini, A. F. , Goldstein, J. I. , Rees, E. , Richards, A. L. , Leonenko, G. , Jorskog, L. F. , Chambert, K. D. , Collier, D. A. , Genovese, G. , Giegling, I., Holmans, P. , Jonasdottir, A. , Kirov, G. , McCarroll, S. A. , MacCabe, J. H. , Mantripragada, K. , Moran, J. L. & 9 others 12 Jul 2016 In : Molecular Psychiatry.

2: Reasons for discontinuing clozapine: A cohort study of patients commencing treatment Legge, S. E., Hamshere, M., Hayes, R. D., Downs, J., O'Donovan, M. C., Owen, M. J., Walters, J. T. R. & MacCabe, J. H. 1 Jul 2016 In : Schizophrenia Research. 174, 1-3, p. 113-119

PSNE-2.18 The epigenetics of Treatment Resistance and Clozapine response in schizophrenia

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Second Supervisor: Dr Alice Egerton

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Third co-supervisor: Professor Jonathan Mill. University of Exeter, UK.

Project Description

Approximately one third of patients with schizophrenia do not respond to antipsychotics, and are described as having 'treatment resistant schizophrenia'. For these patients, clozapine is the recommended treatment, with around 50% of otherwise treatment resistant cases responding to clozapine. However we do not understand what determines (a) response to antipsychotics, or (b) response to clozapine. Understanding this would improve our ability to predict in advance which treatment a particular patient is likely to respond to, a key goal of personalised medicine. It may also allow us to elucidate the mechanism of action of clozapine, opening the possibilities of developing new effective treatments. Epigenetics refers to dynamic changes in the methylation of DNA that influence gene expression. Our previous work has shown that treatment with clozapine is associated with epigenetic changes. However, studies with TRS populations face the challenge of separating out the effects of schizophrenia status, length of illness, treatment-resistant physiology, clozapine exposure and clozapine response. We propose a collaborative project, bringing together epigenetic data generated at the University of Exeter from multiple studies conducted by KCL, to address this issue. Four studies of schizophrenia (STRATA, TRIM, CRESTAR, IMPACT) have all collected blood samples for DNA methylation profiling, and include the following patient groups: 50 patients with TRS who have been exposed to clozapine; 50 patients with TRS, who have never been exposed to clozapine; 50 patients with schizophrenia who are responsive to conventional antipsychotics, who have never been exposed to clozapine; 50 patients with TRS who have had longitudinal samples collected before and after clozapine exposure – among these patients, we have data on response to clozapine. The student will use data from all these sources to disentangle the effects of disease status, treatment resistance, clozapine treatment and clozapine response. In doing so, we hope to develop epigenetic signatures that will allow prediction of response to standard antipsychotics and clozapine, with clear translational potential, furthering the goals of the stratified theme of the BRC to introduce stratified psychiatry into clinical practice.

Keywords: Schizophrenia; Epigenetics; Clozapine; Psychopharmacology; Treatment;

Two representative publications from supervisors:

1: Lally J., MacCabe JH. (2016) Personalised approaches to pharmacotherapy for schizophrenia. *BJPsych Advances* 22(2): 78-86

2: Hannon, E Dempster, E Viana, J Burrage, J Smith, AR Macdonald, R St Clair, D Mustard, C Breen, G Therman, S Kaprio, J Touloupoulou, T Hulshoff Pol, HE Bohlken, MM Kahn, RS Nenadic, I Hultman, CM Murray, RM Collier, DA Bass, N Gurling, H McQuillin, A Schalkwyk, L Mill, J. (2016) An integrated genetic-epigenetic analysis of schizophrenia: evidence for co-localization of genetic associations and differential DNA methylation. *Genome Biol* 17(1): 176