National Institute for Health Research

NIHR Maudsley Biomedical Research Centre

PhD Studentships

Project Catalogue

Affective Disorders & Interface with Medicine

Studentships to commence October 2017

Contents

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

Projects

When applying for the NIHR Maudsley Biomedical Research Centre PhD studentship in the **Affective Disorders and Interface with Medicine** 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. ADIM-2.04 Investigating inflammation in blood, adipose and bowel tissues and their relation with psychopathology in obese patients undergoing bariatric surgery
2. ADIM-2.01 Stress early in life and vulnerability or resilience to the development of psychiatric disorders: focus on epigenetic mechanisms

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.

ADIM-2.01 Stress early in life and vulnerability or resilience to the development of psychiatric disorders: focus on epigenetic mechanisms

Primary Supervisor: Professor Carmine Pariante

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Second Supervisor: Dr Annamaria Cattaneo

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Project Description

Stressful life events, especially when experienced early in life, represent a major risk factor for the onset of psychiatric disorders, but, not all people that experience traumatic events during childhood manifest psychiatric disorders in adulthood. The identification of the mechanisms underlying stress-vulnerability or stress-resilience may lead to the identification of novel pharmacological targets. The overall aim of this project will be to investigate the epigenetic mechanisms underlying early life stressful events that could mediate the vulnerability or the resilience to stress-related disorders in adulthood. We will reach this goal by developing a multidisciplinary project based on a cross-tissues approach and by using whole genome analyses, focusing on stress-, inflammation and HPA axis-related genes. Analyses to be conducted include: 1) DNA methylation and miRNAs in the blood of control subjects exposed to childhood trauma, and stratified for being vulnerable or resilient to psychiatric disorders; and 2) testing in vitro possible treatments to reverse these putative epigenetic alterations found associated with stress vulnerability, inducing or silencing genes or miRNAs, or treating cells with relevant agonists or antagonists, in our established model of 'human depression in a dish', that is, human hippocampal progenitor stem cells treated with cortisol, a stress condition that has been associated with impaired neurogenesis defects. The multidisciplinary training opportunities will include clinical interviews, collection and analysis of human biological samples, cell cultures, epigenetics, molecular biology and pharmacology.

Keywords: stress; depression; epigenetics; inflammation; neurogenesis;

Two representative publications from supervisors:

1: Absolute Measurements of Macrophage Migration Inhibitory Factor and Interleukin-1-β mRNA Levels Accurately Predict Treatment Response in Depressed Patients. Cattaneo A, Ferrari C, Uher R, Bocchio-Chiavetto L, Riva MA; MRC ImmunoPsychiatry Consortium., Pariante CM. Int J Neuropsychopharmacol. 2016 Oct;19(10).

2: Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. Anacker C, Cattaneo A, Musaelyan K, Zunszain PA, Horowitz M, Molteni R, Luoni A, Calabrese F, Tansey K, Gennarelli M, Thuret S, Price J, Uher R, Riva MA, Pariante CM. Proc Natl Acad Sci U S A. 2013 May 21;110(21):8708-13.

ADIM-2.02 Oxidative stress and the pathogenesis of depression: molecular insights and clinical translation

Primary Supervisor: Dr Patricia Zunszain

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Second Supervisor: Professor Giovanni Mann

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Project Description

Oxidative stress is a pathological state arising from an imbalance in the generation of reactive oxygen species (ROS) and protection afforded by endogenous antioxidant defence enzymes. The hippocampus, implicated in the development and recovery from depression, is particularly vulnerable to oxidative stress, where excess of ROS, known to alter the structure and function of cells, contributes to lower neuroplasticity and reduced neurogenesis, both of which have been linked to depression. This project links Dr Zunszain's expertise in cellular models of depression with Prof Mann's expertise in redox signaling. The main aim is to induce oxidative stress in cultures of human hippocampal progenitor cells and evaluate drugs that can reverse or prevent damage. There will be a particular focus on the role of the master redox-sensitive transcription factor Nrf2, which activates detoxifying/antioxidant defenses, and has been linked to stress-induced vulnerability in depression. Treatment of cells will be evaluated through a series of outcomes, each providing acquisition of novel biochemical techniques. These include neurogenesis using immunostaining, measurement of mitochondrial superoxide production and nitric oxide release/action during Year 1. Year 2 will include acquiring expertise in nuclear transactivation assays, electrochemiluminescence assays and gene expression analysis using transcriptomics and validation by qPCR. Year 3 will provide a translational phase, involving a comparison of gene expression changes and production of cytokines with clinical data from depressed patients, with a specific emphasis to determine whether responders and non-responders can be clustered according to their redox status.

Keywords: depression; oxidative stress; hippocampus; neurogenesis;

Two representative publications from supervisors:

1: Bakunina N, Pariante CM, Zunszain PA. Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology. 2015 Jan 10. doi: 10.1111/imm.12443

2: Ishii T, Mann GE. Redox status in mammalian cells and stem cells during culture in vitro: critical roles of Nrf2 and cystine transporter activity in the maintenance of redox balance. Redox Biol. 2014 Apr 18;2:786-94. doi: 10.1016/j.redox.2014.04.008.

ADIM-2.03 In search of better antidepressants: a human in vitro and clinical study

Primary Supervisor: Dr Patricia Zunszain

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Project Description

Major depressive disorder is one of the leading causes of disability worldwide. However, the many pharmacological treatments available are far from ideal, with one-third of all depressed patients not responding to available antidepressants. We propose modeling depression in vitro using human hippocampal progenitor cells to test the mode of action of currently prescribed drugs and specifically dissect differential effects according to initial dysfunctions in the cells. We will then translate results to clinical data, comparing with alterations in biomarkers of patients who respond or fail to respond to treatment, aiming to enhance options towards personalised medicine. Cells will be treated with two depressogenic insults known to trigger depressive episodes: cortisol, to model the effect of stress, and IL-1beta, to represent inflammatory alterations. We will evaluate how antidepressants of different classes can rescue the detrimental effects caused by these insults by looking at: (a) potentiation of synaptogenesis, dendritic outgrowth and expression of synaptic proteins using immunostaining and confocal microscopy; (b) production of inflammatory cytokines using electrochemiluminescence MSD technology; and (c) modulation of gene expression, using mRNA microarrays. Observations from (a) will provide a platform in which to test new drugs which could be repurposed; results from (b) and (c) will be used to compare with data from patients. In vitro experiments will be done during years 1-2, while analysis of results from (b) and (c) in conjunction with clinical data will be done in year 3.

Keywords: depression; hippocampus; inflammation; stress;

Two representative publications from supervisors:

1: Horowitz MA, Wertz J, Zhu D, Cattaneo A, Musaelyan K, Nikkheslat N, Pariante CM Zunszain PA. Antidepressant compounds can be both pro- and anti-inflammatory in human hippocampal cells. Int J Neuropsycopharmacol, 2014 Oct 31. pii: pyu076. doi: 10.1093/ijnp/pyu076.

2: P.J. Michael Deans, Pooja Raval, Katherine J. Sellers, Nicholas J.F. Gatford, Sanjay Halai, Rodrigo R.R. Duarte, Carole Shum, Katherine Warre-Cornish, Victoria E. Kaplun, Graham Cocks, Matthew Hill, Nicholas J. Bray, Jack Price, Deepak P. Srivastava. Psychosis risk candidate ZNF804A localizes to synapses and regulates neurite formation and dendritic spine structure. Biological Psychiatry. DOI: http://dx.doi.org/10.1016/j.biopsych.2016.08.0 38. Published online: September 15, 2016

ADIM-2.04 Investigating inflammation in blood, adipose and bowel tissues and their relation with psychopathology in obese patients undergoing bariatric surgery

Primary Supervisor: Dr Valeria Mondelli

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Second Supervisor: Dr Francesco Rubino

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Project Description

This is an exciting opportunity for students interested in multidisciplinary work as the project spans across different fields (psychiatry, surgery, immunology and basic science). Physical health can influence mental health and vice versa. Unfortunately the co-existence of both physical and mental health problems is usually associated with worse prognosis. A striking example is the bidirectional association between obesity and depression, with obesity increasing the risk for depression and depression increasing the risk of obesity. One biological system suggested playing a role in the association between obesity and depression is increased inflammation. The aims of this PhD project are to investigate inflammation across different peripheral tissues (blood, stool, adipose and bowel) in obese patients undergoing bariatric surgery and the association of inflammation across the tissues with psychopathology and clinical outcome. The PhD student will have the opportunity to 1) be trained and recruit and assess obese patients from the bariatric clinic; the assessment would involve psychiatric interviews and collection of blood samples; 2) be trained and perform immunophenotyping analyses on blood, adipose and bowel tissue (cytokine analyses, immunostaining and flow cytometry), 3) be trained and perform statistical analyses and writing manuscripts. During the first year the student will focus on the recruitment and assessment of patients, during the second part of the first year and second year the student will focus on laboratory analyses for immunophenotyping. The third year will be dedicated to the statistical analyses of the data and writing up.

Keywords:

Two representative publications from supervisors:

1: D. Baumeister, R. Akhtar, S. Ciufolini, C.M. Pariante, **V. Mondelli**. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Molecular Psychiatry. 2016, May;21(5):642-9.

2: Chakravartty S, Tassinari D, Salerno A, Giorgakis E, Rubino F. What is the Mechanism Behind Weight Loss Maintenance with Gastric Bypass? Curr Obes Rep. 2015 Jun;4(2):262-8.

ADIM-2.05 Imaging activation of microglia in humans by the experimental challenge, interferon-alpha, using the novel TSPO tracer [11C] PBR 28

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Second Supervisor: Dr Valeria Mondelli

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Third co supervisor: Dr Mattia Veronese, Department of Neuroimaging, King's College London

Project Description

Increasing evidence has emerged over the last few years supporting presence of increased inflammation in blood of patients with depression. However, we still do not know if inflammation in the blood can cause inflammation in the brain. This project will investigate inflammation in the brain, using PET and MRI, before and after activation of the immune system. We will activate the immune system by giving the subjects an immune challenge (injection of interferon-alpha). The main aims of this PhD project are 1) to assess if "inflammation in the blood" is associated with "inflammation in the brain" in five healthy subjects, and 2) to identify specific peripheral molecular inflammatory pathways associated with central inflammation. The project has been funded by NIHR SLaM BRC and has recently gone through ethical approval. The PhD student will have the opportunity to 1) be trained and perform analyses on PET and MRI data, 2) be trained and perform laboratory analyses; specifically cytokine analyses and RNA extraction and gene expression analyses, 3) be trained and perform statistical analyses and writing manuscripts. It is likely that the collection of data will be concluded by summer 2017, therefore the student will focus mainly on data already collected. During the first year the student will focus on the analyses of the PET and MRI images acquired longitudinally. During the second year the student will focus on laboratory analyses of (cytokines and gene expression). The third year will be dedicated to the statistical analyses of the data and writing up.

Two representative publications from supervisors:

1: D. Baumeister, A. Russell, C.M. Pariante, V. Mondelli. Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors. Social Psychiatry and Psychiatric Epidemiology. 2014 Jun;49(6):841-9

2: N. Hepgul, A. Cattaneo, K. Agarwal, S. Baraldi, A. Borsini, C. Bufalino, D.M. Forton, **V. Mondelli**, N. Nikkheslat, N. Lopizzo, M.A. Riva, A. Russell, M. Hotopf, C.M. Pariante. Transcriptomics in interferon-alpha treated patients identifies inflammation-, neuroplasticity- and oxidative stress-related signatures as predictors and correlates of depression. Neuropsychopharmacology. 2016 41(10):2502-11

ADIM-2.06 Can we encourage male students to seek mental health help?

Primary Supervisor: Dr Emma Godfrey

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Men are more reluctant than women to seek help for mental health problems, especially depression (Moller-Leimkuhler 2002). Different health beliefs affect this, including adhering to masculinity beliefs (Seidler et al 2016) and having less confidence in mental health professionals (Kessler et al 1981). Anti stigma campaigns also tend to affect men less (Clement et al 2014). House et al (submitted) has shown that shame is consistently experienced by men who experience depression, whether or not they sought help. It was recommended more positive messages about help-seeking and the effectiveness of treatments could increase help-seeking. The main aim is to quantitatively and qualitatively evaluate an intervention designed to support male university students seek help for mental health problems and designed to evaluate an intervention using Acceptance Commitment Therapy (ACT) designed to reduce self-stigma and shame for those demonstrating high levels of shame. ACT has been shown to reduce self-stigma but only among those with substance abuse problems (Luoma et al 2008). Comparisons will be made of quantitative changes before and after the self-stigma intervention. Qualitative interviews will also be conducted. The PhD student will have the opportunity to learn: a) Systematic review; b) Quantitative skills: statistical analysis training for assessing change and C) Qualitative skills. During first year, the student will assess shame and help-seeking among male students. During second year, the student will evaluate programme, quantitate and qualitatively. Third year the student will analyse and write-up results.

Keywords: men; reluctance; help-seeking; self-stigma; acceptance and commitment therapy (ACT);

Representative publications from supervisors:

1: Luoma, Jason B. et al (2008) Reducing self-stigma in substance abuse through accdeptance and commitment therapy: Model, manual development and pilot outcomes. Addiction, Research and Theory, 16(2), 149-165.

2: Moller-Leimkuhler, A.M. (2002) Barriers to help-seeking by men: a review of sociocultural and clinical literature with particular reference to depression. Journal of Affective Disorders, 71, 1-9.

3: Seidler, Zac E. et al (2016) The role of masculinity in men's help-seeking behavior for depression: a systematic review. Clinical Psychology Review. 49, 106-118.

ADIM-2.07 Why do university students seek help from counselling services

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Primary Supervisor: Dr Nicola Byrom

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Project Description

Most mental health problems develop in early life, with 75% of lifetime mental disorders beginning by age 25 years [1]. University students form a substantial group of young people, with just under 50% 18-19 year olds applying for university. University students are therefore at high risk of developing mental health problems due to their age. While previously thought to be different from their non-university peers, the psychiatric morbidity of students is similar [2].

There is considerable concern about rising stress among university students [3]. University counselling services, which usually offer 1:1 sessions, are reporting dramatic increases in demands for their services. One university reported a 136% increase among undergraduates seeking counselling services between 2003-4 and 2013-14 [3].

It is not clear what the reasons for the increased demand for counselling service is. Some possible reasons may be decreased stigma about seeking help, more students coming with mental health issues, greater pressures at university (financial pressures, larger classes).

The main aim of this research to investigate possible reasons for increased demand for university counselling services by interviewing and gathering data from students applying for the counselling service. Mixed methods design to qualitatively investigate this question through interviews as well as quantitatively through the use of self-report questionnaires. The PhD student will have the opportunity to gain: a) Systematic review skills; b) Qualitative skills e.g. semi-structured interviews to ask students about expectations of counselling and C) Quantitative skills e.g. using self-report distress questionnaires as well as student self-defined measure of problems (PSYCLOPS). During first year the student will do a systematic review, second year qualitative skill; use of quantitative measures and third year analyse data and write-up.

Keywords: University students; mental health; counselling; stress;

Representative publications from supervisors:

1: Kessler R, Amminger PG, Aguilar-Gaxiola S, al e: **Age of onset of mental disorders: a review of recent literature**. *Curr Opin Psychiatry* 2007, **20**(4):359-364.

2: Blanco C, Okudo M, Wright C, Hasin DS, Grant BF, Liu S-M, Olfson M: **Mental health of college students and their non-college attending peers: results from the national epidemiological study of alcohol and related conditions**. *Archives of General Psychiatry* 2008, **65**(12):1429-1437.

3: Grove J: **Oxford students' demand for counselling shoots up**. In: *Times Higher Education.* London: TES Global Limited; 2015.