Theme 2

Neurosciences, Psychiatry and Mental Health
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Neurosciences, Psychiatry and Mental Health

Priorities in this theme are linking developmental, molecular, cellular & systems neuroscience to clinical research; sensory disorders (including pain); neurodevelopmental disorders; neurodegeneration; experimental medicine in psychiatry; and the social sciences interface.

Lead: Professor Francesca Happe and Professor Jonathan Cooper

Projects beginning with K are KBI projects for example K1.2
1.2 The Role of Social Networks and Psychological Processes in Treatment Outcome in Alcohol Related Frequent Hospital Attenders

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Project description:  
The cost of alcohol misuse to the NHS is £2.7 billion, over 78% of which is incurred as hospital based care. Alcohol related frequent attenders to acute and mental health NHS services (AFA patients) are of significant cost to the NHS, and patients have severe, complex and long lasting co-morbidities. Assertive community treatment (ACT) is an effective treatment for people who do not engage well with services but are in urgent need of support. Interventions focussed on social components, an essential component of ACT, are effective for people with alcohol dependence. However, it is not clear what social network and psychological factors are involved in successful treatment outcome within the AFA population, which intervention components are most effective, and the interplay between social and psychological processes have not been explored. This PhD will explore this interplay in determining treatment outcome for AFA patients, in the context of a funded trial that compares treatment as usual with ACT.

Over-arching objectives:  
• Year 1: to review social theories of recovery and effects of social network interventions for alcohol dependence  
• Year 2: to explore AFA patient perceptions of their social networks and their impact on help seeking  
• Year 3: to model assertive outreach trial data to predict the impact of social networks and psychological processes, and interactions between them, have on clinical outcomes  
• Year 4: to explore how data from this project fits with existing theoretical models  

Skills training would include systematic review and qualitative research methods in applied health research and statistical modelling.

Two representative publications from supervisors:  

2.2 New protein involved in Amyotrophic lateral sclerosis (ALS): biochemical characterization of annexin11 interacting with calcyclin

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Project description:

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder. Great efforts have been carried out to identify new genes related to ALS. Professor Shaw’s laboratory has screened a large number of families affected by ALS leading to the identification of 10 novel mutations in AnnexinA11 in 12 individuals. We are particularly interested in the novel mutations D40G (n=6) (absent in >60,000 control exomes) and G38R (n=2) (a rare variant). These mutations are clustered in the N-terminus of annexinA11, which seems to be a hot spot for mutations. Interestingly it was shown that, in-vivo, AnnexinA11 D40G mutant disrupts binding to its binding partner calcyclin.

Analyzing the AnnexinA11 N-terminus, we identified putative domains, which include the mutation hot spot region. The PhD project will start with the cloning, expression and purification of all domains identified. The student will then carry out a biophysical and biochemical characterization using CD and NMR to verify their folding states. The student will repeat the analysis on the AnnexinA11 D40G mutation. This should allow the student to discriminate if the effect of this mutation on calcyclin binding is due to a structural or functional alteration. The student will also carry out in vitro and in vivo pull-down assays with the newly identified domains and calcyclin to characterize their ability to retain interaction. In vivo pull-down assays will be carried out in cells transfected with AnnexinA11 with different tagged-domains. Biolayer interferometry and/or isothermal titration calorimetry will be used to obtain more detailed information on their binding affinities.

Two representative publications from supervisors:
Ferredoxin, in conjunction with NADPH and ferredoxin-NADP reductase, transfers electrons to the IscS/IscU complex to promote iron-sulfur cluster assembly.  

Exome-wide rare variant analysis identifies TUBA4A mutations associated with familial ALS.  
3.2 Cognitive impairment in bipolar disorder: investigating promising new treatments

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Project description

Bipolar disorder is one of the most disabling mental health disorders and is associated with widespread cognitive deficits that are present not only during mood episodes but also during remission. Foremost amongst these deficits are working memory impairments which can significantly impair patients' social and vocational functioning. Improving working memory and other cognitive symptoms is a key treatment target in bipolar disorder. The goal of this project is to use neuroimaging and clinical trial studies to investigate the effects of promising new treatments for cognitive impairment in bipolar disorder. This project will provide the student with skills training in the use of pharmacological functional MRI (fMRI) to examine glucocorticoid antagonist treatment effects on brain activations and the use of clinical trial methodology to assess the efficacy of cognitive remediation in bipolar disorder. The year 1 objectives are to understand fMRI and clinical trials methodology and gain expertise in recruiting and assessing research participants; the year 2 objectives are to develop expertise in practical aspects of neuroimaging and cognitive clinical trials; the year 3 objectives are to gain expertise in the analysis of fMRI and cognitive data; the year 4 objectives are to consolidate skills, present study data at an international conference, and submit the dissertation thesis along with high quality publications. The project provides a fantastic opportunity to work within a highly respected multidisciplinary research team directed by Prof Allan Young, a world leader in mood disorders, and Dr Paul Stokes an expert in neuroimaging and clinical trials.

Two representative publications from supervisors:

Stokes PRA, Rhodes RA, Grasby PM & Mehta MA  
The effects of the COMT val108/158met polymorphism on BOLD activation during working memory, planning and response inhibition: a role for the posterior cingulate cortex?  
Neuropsychopharmacology 2011 36 763-71

A Randomized Trial to Examine the Effect of Mifepristone on Neuropsychological Performance and Mood in Patients with Bipolar Depression.  
4.2 Childhood adversity, its association with adult health, cortisol and somatic symptoms in their offspring

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Project description:

Childhood adversities have been linked repeatedly to adult mental health, in particular post traumatic stress disorder (PTSD) and chronic fatigue syndrome (CFS). One of the proposed biological mediators is a decreased level of cortisol resulting from disturbed HPA axis functioning. This study aims to answer the question whether childhood adversities are trans-generational phenomena in the sense that childhood adversities lead to poor mental health in adulthood which in turn might interfere with the challenges of parenthood and could eventually lead to an increased reporting of somatic symptoms in their offspring. The results of this study will help in developing better evidence based treatments for both the adults and their offspring. Two cohorts of patients will be recruited: men who have served in the military with PTSD and patients with chronic fatigue syndrome.

The student in this project will develop methodological and analytic skills. They will also develop competence in analysing biological samples and will liaise closely with experts in the BRC for the biological aspects of the study. The student will develop some knowledge in the clinical presentations of the disorders studied but will also develop therapeutic skills in interviewing vulnerable people.

Objectives:
Year 1: To conduct a systematic review of the literature on the effects of trauma transgenerationally and to start recruiting participants for the cohort study
Years 2 and 3: To collect data for the cohort study and examine the relation between trauma, cortisol and symptoms in their offspring cross sectionally.
Year: complete analysis and write up.

Two representative publications from supervisors:
5.2 Investigating the role of TRPV4 and monocytes in cancer chemotherapy-induced pain

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Project description:

The therapeutic use of the anti-cancer agent vincristine is limited by its major side-effect, a pronounced peripheral neuropathy causing substantial pain. We have recently identified evidence that the pain is caused by vincristine stimulating the infiltration of monocytes into peripheral sensory nerves, and activating them by production of reactive oxygen species. Previous work in other labs suggests that deletion of the cation channel TRPV4 can reduce pain caused by vincristine and other chemotherapeutic agents. There is little evidence that TRPV4 is expressed by sensory nerves, but it is expressed by macrophages and is suggested to regulate their ROS production. Our preliminary data suggests that although monocytes infiltrate normally into sensory nerves in vincristine-treated TRPV4 knockout mice, they develop pain more slowly than their wild type counterparts.

In this project we will further investigate the mechanism by which TRPV4 regulation of macrophage activity can contribute to vincristine pain, then extend the study to determine whether a similar mechanism is also involved in the pain caused by other chemotherapeutic agents.

Year 1: Learn techniques to assess pain behaviours in mice; how to produce mouse primary macrophage cultures; confirm reduced pain with normal monocyte infiltration in TRPV4 knockout mice.

Years 2-3: Pharmacogenetic investigation of TRPV4-induced Ca2+ influx & ROS production (fluorescent / luminescent quantification) in cultured macrophages; Effect of TRPV4 antagonists on behaviour in vincristine-treated mice.

Years 3-4: Use techniques above to investigate the TRPV4-macrophage contribution to other chemotherapeutic neuropathies (e.g. oxaliplatin, paclitaxel).

Two representative publications from supervisors:


6.2 The importance of social cognition for cognitive health in old age: Explorations in autism, dementia and healthy ageing

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Project description:

Cognitive decline is common in older age. While usually a healthy part of ageing, decline may also be a precursor to dementia, a devastating condition that affects 850,000 people in the UK. Finding early markers and understanding risk factors is vital to enable tailoring of large-scale public health interventions.

Social cognition - the ability to understand and interact with others - is often affected in people with dementia, and in the neurodevelopmental disorder, autism. However, little is known about how social decline may be linked to dementia, or whether social interventions could slow cognitive decline. Similarly, little is known about cognitive function in old age in autism.

This PhD project will seek to:
1. Establish the cognitive profile of older adults with current (and/or developmental) impaired social cognition, using an online cohort of 10,000 people
2. Develop and test the feasibility of:
   a) online measurement of social cognition (e.g. ‘theory of mind’) in older adults, with the aim of informing future tests for decline in social cognition;
   b) online intervention and support for social cognition and remote interaction in older adults, with and without existing impairment.

The project will involve working with individuals with autism spectrum disorder, cognitive decline, and typical development. The student will be trained in an exciting combination of methods, including analysis of large datasets, working with patient representatives, interviewing and assessing individuals with ASD and/or dementia, development of novel online technology, and establishing evidence-based assessments and piloting new interventions within important clinical groups.

Two representative publications from supervisors:

Ferreira N, Owen A, Mohan A, Corbett A, Ballard C. Associations between cognitively stimulating leisure activities, cognitive function and age-related cognitive decline. Int J Geriatr Psychiatry. 2015 Apr;30(4)

7.2 Improving cognitive control over emotions through neuromodulation in eating disorders

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Project description:

Background. Progress has been made in identifying brain mechanisms underlying emotion regulation (Ochsner et al., 2012). In eating disorders (ED), poor emotion regulation is believed to be a key maintaining factor, e.g. negative emotions trigger abnormal eating behaviour, which in turn relieves distress. In other disorders, neuromodulation techniques (e.g. transcranial direct current stimulation, tDCS) have shown promise in improving emotion regulation. These are now being studied in ED (McClelland et al., 2013). This project will assess whether tDCS enhances adaptive emotion regulation in people with ED. The long-term aim is to develop neuromodulation-enhanced emotion regulation training to improve treatment outcomes.

Methods. In a set of experiments, people with ED will be exposed to illness-relevant or emotional cues that produce negative emotions (e.g. Cyberball game). Then they will receive 20 minutes of tDCS. The tDCS will be applied to the prefrontal cortex, a key structure in emotion regulation. During the tDCS, they will complete a writing task designed to facilitate cognitive reappraisal (Pennebaker, 2004). The impact of this on subjective distress, physiological variables (e.g. cortisol), food choice behaviour and eating will be assessed.

Objectives. Year 1: The student will learn about eating disorders and the theoretical and practical basis of neuromodulation treatments. She/he will conduct a relevant systematic review and carry out pilot studies to finalise experimental designs. Year 2: She/he will conduct their main experiments using an RCT design. Year 3: She/he will complete experiments and write-up.

Skills available. The supervisors have expertise in translational and neuromodulation research in ED.

Two representative publications from supervisors:

U Schmidt:  

I Campbell:  

H Himmerich:  
8.2 Neurodevelopmental trajectories and psychotic experiences: a longitudinal MRI study of young adults

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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.

Two representative publications from supervisors:


10.2 Improving Social Cognition in Schizophrenia using Brain Stimulation.

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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

Two representative publications from supervisors:
Dr Rachel Mitchell  

Prof Veena Kumari  
11.2 Developing eHealth Methods for Social Functioning Assessment in Schizophrenia

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Project description:

People with schizophrenia experience significant social functional difficulties as a result of their illness. These difficulties are associated with cognitive problems and considered a barrier for recovery. The assessment of social functioning problems and cognition is often conducted using interviews, performance based tests or questionnaires. These assessments rely on memory, informants and may only capture limited information. The current project aims to capitalise on recent developments in mobile phones and wearables technology to develop a novel eHealth assessment of social functioning and cognition in people with psychosis. This new assessment will capture information in its natural environment. This knowledge will contribute to explain the mechanism driving functional problems and introduce a novel methodology to evaluate these difficulties routinely in people with schizophrenia. The eHealth assessment will also allow characterising individualised pathway to functional problems and provide valuable information for personalised care. This will be important in translating assessment information in individualised therapy recommendations.

The project will provide training in the following areas: qualitative analysis; systematic reviews; eHealth devices optimisation and tailoring; basic clinical skills to work with the target population; neuropsychological assessment; quantitative statistical techniques.

Overarching objectives for the student will be:
Year 1 – MRes rotation ; Year 2 – Select and optimise eHealth devices for data collection and acceptability/usability evaluation, statistic training; Year 3 – Data collection; Year 4 – Data collection, analysis and thesis writing.

Supervisors’ contribution:
Cella: eHealth; assessment and statistic; clinical skills.
Wykes: Service user evaluation; recruitment support; research skills.

Two representative publications from supervisors:


12.2 Functional and mechanistic analysis of autism-associated genes

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Project description:

Recent advances in human genetics have led to the identification of several candidate genes for autism and associated neurodevelopmental disorders. To fully understand the aetiology of these disorders, a functional characterisation of these candidates is imperative. This project will capitalise on complementary expertise in our laboratories (Kiecker: chick embryology, functional screening approaches; Basson: modelling neurodevelopmental disorders in the mouse) to investigate the function of two autism-associated genes: SETD5 and PTCHD1.

Mutations in SETD5 are associated with intellectual disability (ID), obsessive-compulsive disorder and autism spectrum disorder (ASD)\(^1\); mutations in PTCHD1 with ID and ASD\(^2\). SETD5 encodes a putative methyltransferase, but its cellular substrates are not known. PTCHD1 is hypothesised to regulate Hedgehog signalling, a pathway essential for embryonic development and adult homeostasis.

To characterise the functions of SETD5 and PTCHD1, the student will:

- perform an overexpression screen for SETD5 methylation targets in cultured cells (year 1) and putative targets will be validated in Setd5\(-/-\) neural progenitors generated in the Basson lab (years 2+3);
- investigate the neurodevelopmental roles of Setd5 by examining cell patterning, proliferation and differentiation in neural-specific Setd5 conditional mouse mutants (years 1+2);
- investigate the putative role of PTCHD1 as a regulator of Hedgehog signalling using electroporation in chick embryos and reporter assays (years 1-3).

The student will be trained in a variety of techniques, including cell culture, proteomics, chick and mouse embryology, mouse genetics, in situ hybridisation and immunohistochemistry.


Two representative publications from supervisors:


13.2 Multidisciplinary Approaches to Translational Research In Conduct Syndromes (MATRICS)

Co-Supervisor 1: Dr Michael Craig
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Co-Supervisor 2: Prof Steven Williams
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Project description:

Conduct Disorder (CD), is characterised by persistent aggression and is the commonest childhood mental health condition. It is heterogeneous, and our understanding of the neurobiology to subtype aggression is limited. The current project is nested within a multidisciplinary European Union consortium that focuses on the subtyping of aggression.

The project will test the hypothesis that reactive and instrumental aggression result from aberrant autonomic reactivity coupled to the differential impairment of three basic neural functions:

1) Regulation of control mechanisms of aggression,
2) Emotional value rating of others, and
3) Empathy and moral decision-making.

The project will employ the same psychological tasks assessing 1), 2) and 3) in animal aggression models (led by Prof Williams, Basic Scientist) and human CD samples (led by Dr Craig, Clinical Academic) concurrent with the assessment of neural, neurochemical, (epi)-genetic and autonomic nervous system markers.

The project will identify new potentially 'druggable' targets, develop novel animal models and conduct pilot medication in rodents (and high-risk and CD patients).

Year 1 & 2: Collection of anatomical, structural and functional MRI data and MRS data in
(a) Two appropriate rodent models of aggression.
(b) CD children and controls

Year 3 (&4): Pharmacological stimulation (drug challenge) in rodents during the imaging session. Map the effect on brain activation and functional networks, and see how they differ over time in rodent models of aggression vs shams.

Skills training available: Training in several different types of brain imaging techniques in human and rodent models and development of appropriate analytical skills.

Two representative publications from supervisors:
1. Longitudinal in vivo maturational changes of metabolites in the prefrontal cortex of rats exposed to polyinosinic-polycytidylic acid in utero Vernon, A. C., So, P-W., Lythgoe, D. J., Chege, W., Cooper, J. D., Williams, S. C. R. & Kapur, S. 21 Oct 2015 In : European Neuropsychopharmacology.
14.2 Does elevated expression of the synaptic protein CSPalpha prevent neurodegeneration and memory impairment in a mouse model of Alzheimer’s disease?

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Project description:

We propose to test a novel strategy to protect neurons in Alzheimer’s disease (AD) brain. This strategy is based on observations as to how neurons die in the brain of patients with the disease. In most parts of the brain, neurons die after losing synapses, the connections between neurons. However, in cerebellum, a brain region important for motor coordination, synapses and neurons are protected. Whilst this neuroprotection is very little understood, our recently published work (Tiwari et al., 2015) suggests that elevated levels of a protein called CSPalpha in AD cerebellum are protective. This idea has been confirmed in htau mice, a mouse model of AD tau pathology, where elevated CSPalpha correlates with lack of neuronal loss. However, the impact of CSPalpha upregulation needs closer analysis to evaluate its usefulness for protecting synapses, neurons and memory. Here, we propose to carry out such analysis in htau mice. In this model we will examine the effect on disease progression of blocking CSPalpha upregulation in htau mice using an shRNA-expressing, knockdown adeno-associated virus. This virus will be be injected into organotypic brain slice cultures prepared from htau pups. Long term culture of htau brain allows accelerated de
development of their neurodegenerative phenotype. The virus will also be injected into htau hippocampus to allow in vivo examination of the relationship between prevention of CSPalpha upregulation, tau pathology, synapse loss, neuronal death and spatial memory. Thus, this project will test whether or not CSPalpha overexpression is neuroprotective in a model of Alzheimer’s disease.

Two representative publications from supervisors:


15.2 Role of Teneurins on hippocampal structure and function

Co-Supervisor 1: Robert Hindges
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Co-Supervisor 2: Juan Burrone
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Project description:

We are interested in the mechanisms that lead to a correct establishment of neural connectivity ensuring normal brain function. This project is based on our preliminary data indicating that the loss of the synaptic adhesion molecule Teneurin-3 in mice leads to a series of defects in neurons of the hippocampus (a region important for learning and memory), including cell position, synapse arrangement and dendritic tree morphology. It is not clear, however, if these phenotypes are specific to the cells that normally express Teneurin-3 and if they lead to differences in synaptic function and/or animal behaviour. Mutations in human teneurin genes have been linked to different disorders, including mental retardation, bipolar disorder and cerebellar ataxia. We therefore anticipate our results to give important insight in the underlying molecular mechanisms.

With this project, we will investigate in a first step the detailed changes in cell migration, the morphology of the dendritic trees and the number and density of synapses of hippocampal neurons. In a second step we will then characterise the synaptic properties of teneurin-3 deficient neurons using state of the art physiological methods, and compare them to the wild-type situation. Finally, in collaboration with experts at the IoPPN, we will perform mouse behavioural experiments to describe any defects on learning and memory function in the mutant mice.

The student will be trained in the use of genetically altered mouse lines, brain histology, imaging (brightfield, fluorescent, confocal), structural and functional (electrophysiology) characterisation of neurons, as well as performing behavioural tests.

Two representative publications from supervisors:

16.2 Development and evaluation of a decision aid on help-seeking and disclosure for health professionals experiencing a mental health problem

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Co-Supervisor 2: Dr Ira Madan
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Project description:
Scientific basis
Decision aids have been shown to improve decision related outcomes e.g. uncertainty and satisfaction with the decision. Mental health problems are the commonest reason for sickness absence from work, but research shows that health professionals with mental health problems face barriers to help. These include: difficulty identifying mental health problems; stigma regarding mental illness, the discourse of professional competence; workload pressures; confidentiality expectations; and delayed access to help. However, health professionals must adhere to guidance on help-seeking from professional regulatory bodies. Disclosure is therefore essential to people in roles such as occupation health, but decisions about whether to be open to other colleagues are usually more difficult. Health professionals may therefore benefit from a decision aid to make informed decisions on help-seeking and disclosure based on: information on available support; personal values, and professional guidance, potentially reducing sickness absence and/or presenteeism.

This project builds on research into two decision aids: CORAL (Conceal or ReveAL), regarding disclosure of a mental health problem (see publications); and DASH, a decision aid for young people who self-harm about help-seeking options.

Skills training
Development and evaluation of complex interventions in health, and specifically decision aids, including qualitative research, feasibility testing, design and conduct of a randomised controlled trial (RCT) including process evaluation; writing for the PhD and academic publications.

Project Objectives
Year 1 Development of the decision aid. PhD upgrade.
Year 2 Feasibility testing; decision aid revision.
Year 3: RCT: recruitment, decision aid delivery.
Year 4 RCT completion; thesis write up and submission.

Two representative publications from supervisors:

17.2 New perspectives on neuronal polarity using non-classical neurons.

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Co-Supervisor 2: Dr Richard Wingate  
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Project description:

Neuronal polarity is a central organising principle of nervous system. It is vital for normal brain cell function and its disruption can lead to a range of developmental disorders. The interdependence of processes underlying the establishment of an anatomical polarity in brain cells is poorly understood. In particular, in “classical” neurons the asymmetric segregation of intracellular proteins is coincident with somatodendrite/axon compartment boundaries. It is unclear whether both are regulated by the same mechanisms? Evidence that this is not the case comes from non-classical neurons where, for example, the axonal origin is on a dendrite. These cells give the opportunity to investigate the minimum requirement for protein trafficking independent of other features of the somatodendritic/axon boundary.

This project will study compartment boundary proteins and the patterns of protein trafficking in non-classical neurons to determine the minimum requirements for intracellular neuronal polarity.

Objective 1 Study the anatomy of polarized proteins in non-classical neurons.
Objective 2 Study the development of pre-synaptic/axonal and post-synaptic/dendritic compartment using live imaging approaches.
Objective 3 Study changes in polarized proteins in atypical cell types following knock down of orthologues of AIS master regulator gene AnkyrinG.

The project will utilise a range of tools developed in Drosophila that exploit the GAL4/UAS system to infer intrinsic distributions of intracellular proteins in a defined range of vertebrate and invertebrate neurons:

- Primary sensory neurons of the trigeminal and acoustic nerves (chick)
- Mesencephalic trigeminal neurons in (chick)
- Rohon-Beard cells (zebrafish)
- Larval motor neurons (Drosophila)
- Larval interneurons (Drosophila)

Two representative publications from supervisors:

An ESCRT module is required for neuron pruning  
Loncle, N., Agromayor, M., Martin-Serrano, J. & Williams, D. W. 13 Feb 2015 In : Scientific Reports. 5, , 8461

An Interaction Screen Identifies headcase as a Regulator of Large-Scale Pruning  
Loncle, N. & Williams, D. W. 28 Nov 2012 In : Journal of Neuroscience. 32, 48, p. 17086-U513


18.2 Mechanisms underlying motor neuron disease

Co-Supervisor 1: Sarah Guthrie
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Co-Supervisor 2: Diane Hanger
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Project description:

Scientific basis: This project will examine the possible reasons why some groups of neurons are resistant to motor neuron disease. The dysregulation of the cytoskeleton is a key factor in the pathogenesis of neurodegenerative disorders. Our recent work shows that mutations in the motor neuron disease (MND) gene TDP-43 lead to dysfunction of the cytoskeleton and neuronal toxicity. These experiments were carried out in spinal motor neurons, which are MND-susceptible, whereas oculomotor neurons in the head are resistant to disease progression. This project will explore the differential effects of TDP-43 pathogenesis in spinal and oculomotor neurons, focusing on the cytoskeleton. We will determine mechanisms whereby oculomotor neurons resist disease progression.

Skills training: chick embryo model system, primary neuronal cultures, immunohistochemistry, electroporation and transfection, molecular biology, toxicity assays, live imaging of cytoskeleton, biochemistry

Yr1 objectives:
If rotation project - training in chick electroporation and successful targeting of the oculomotor nucleus with TDP-43 constructs.
If year full-time – quantitation of TDP-43 toxicity, axon projections and synapse formation.

Yr2 objectives:
Determination of whether TDP-43 mutant isoforms cause pathogenesis and cytoskeletal dysfunction in oculomotor neurons in vivo, using chick embryo model. Quantitation of neuronal death, cytoskeletal integrity.

Yr3 objectives:
More detailed evaluation of resistance to disease progression using primary oculomotor neurons. Quantitation of TDP-43 protein localisation and phosphorylation, and cytoskeletal function using live imaging and biochemistry.

Yr4 objectives:
Evaluation of candidate cytoskeletal-regulatory proteins (identified in a proteomics screen) in MND progression by comparison of expression in spinal and oculomotor neurons.
Writing up thesis.

Two representative publications from supervisors:

19.2 Investigating the comorbidity of ADHD with obesity and depression

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Co-Supervisor 2: Dr Paul O’Reilly
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Project description:

This project focuses on the comorbidity of attention-deficit/hyperactivity disorder (ADHD) with obesity and depression. The risk for comorbid obesity and major depressive disorder is increased both in adolescents and adults with ADHD, and adolescent ADHD predicts adult obesity and major depressive disorder. The PhD project will augment and complement a major new EU study starting in 2016 (KCL PI Prof Kuntsi), called ‘CoCA’ (comorbid conditions of attention-deficit/hyperactivity disorder). The EU study incorporates a randomized clinical trial that will investigate the effectiveness of bright light therapy and exercise, in combination with m-Health based monitoring and reinforcement, in participants with ADHD, targeting the prevention of obesity and depressive symptoms. While the student will have the opportunity to contribute directly to this study, and exploit its resources and data, a particular focus here will be on additionally testing for mediators of these comorbidities in the general population. The student will exploit both publicly available genome-wide association study data and cognitive measures in our in-house data sets to interrogate these relationships. Dr O’Reilly will provide training in statistical genetics, and in particular in his multivariate and polygenic methods (MultiPhen and PRSice) that will be exploited to disentangle these complex comorbidities (including testing for direction of effects with a method under development). Prof Kuntsi will provide training on ADHD and will guide the integration of this project with the EU study. In addition, consultant psychiatrist Prof Asherson (also CoCA investigator) will provide training in clinical assessments and interpretation.

Two representative publications from supervisors:


20.2 Brain Network Ictogenicity in Juvenile Myoclonic Epilepsy

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Project description:

Juvenile Myoclonic Epilepsy (JME) is a common incurable disorder affecting young adults, requiring lifelong treatment. The BIOJUME project, funded by the Canadian Institutes for Health Research, aims to use endophenotypes and statistical approaches to understand the biological basis of JME. Endophenotypes are clinically unobserved heritable characteristics linked to the underlying aetiology. Using mathematical methods applied to EEG, we have shown that an endophenotypic measure of Brain Network Ictogenicity (BNI) varies between JME patients, controls and relatives and can be used as a quantitative trait for genomewide association analysis. Seizures and EEG discharges also show propensity for the early morning, suggesting a diurnal rhythm of cortical excitability, which might be useful to target therapeutically.

In this project, the candidate will investigate the diurnal variability of BNI and electrographically visible discharges within and across several hundred subjects testing the hypothesis of a circadian rhythm underlying cortical excitability. S/he will seek correlations between BNI and demographic, clinical and genetic variables.

In addition to transferable skills, the candidate will receive training in clinical epilepsy and the basics of clinical and experimental electroencephalography; the genetics of epilepsy; network modelling; graph theory; and neuropsychological assessment.

Objectives Year 1: Theoretical training; Transferable skills; Literature review
Objectives Year 2: Measure BNI from >100 EEG JME patient recordings and assess variability
Objectives Year 3: Correlate BNI with patient measures and in a subset examine 24hour variability and relation with sleep-related markers.
Objectives Year 4: Write-up thesis and present work at conferences.

Two representative publications from supervisors:
21.2 The role of NNMT and NAD+ levels in synaptic function in Parkinson’s disease: Jekyll and Hyde?

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Project description:
Parkinson’s disease (PD) is characterized by the degeneration of dopaminergic (DA) neurons in the brain. There is mounting evidence that mitochondrial dysfunction and reduced energy levels are causally related to synaptic deficits and subsequent neurodegeneration of DA neurons. Nicotinamide N-methyltransferase (NNMT), which we showed is increased in PD patients, regulates the synthesis of NAD+ via the availability of its precursor, nicotinamide. Decreased cellular NAD+ results in the onset of axonal degeneration and synaptopathy, hallmarks of PD disease onset and progression. We hypothesize that NNMT and thus NAD+ levels are causally related to DA neurodegeneration. The project will test this hypothesis in an in vivo model of PD. The successful student will investigate phenotypic alterations caused by altered NNMT and NAD levels induced by targeted misexpression of transgenic NNMT in our Drosophila model of PD. Systematic phenotypic analyses will cover all aspects, from genes to circuits and behaviour. The student will learn molecular cloning, Drosophila genetics & behaviour, biochemical endpoint analysis, and immunohistochemistry. We expect to gain fundamental insights into the mechanisms underlying NNMT/NAD+-related cellular energy regulation and neuronal function, identifying new targets that will guide the development of novel therapeutic strategies for the treatment of PD and related neurodegenerative diseases.

Yearly objectives:
1: establish transgenic NNMT flies, carry out targeted expression in developing and adult Drosophila  
2: determine NAD+ and ATP content  
3: comprehensive phenotypic, behaviour and pathologic analyses  
4: comprehensive protein expression and metabolism analyses, and the effect of pharmacological application of nicotinamide on these processes (drug-mediated rescue attempt)

Two representative publications from supervisors:


Anorexia nervosa (AN) affects 1-2% of the population and is a leading cause of death in young women. There are no effective medications, owing largely to our poor understanding of the underlying mechanisms. New analyses of genomic data from the Psychiatric Genomics Consortium (PGC) AN group (co-chaired by supervisor Breen) point to a strong role of genetic risk for metabolic factors (e.g. low BMI and high insulin sensitivity) as well as psychiatric genetic risk in the development of AN.

Aims by year:

i. Using access to the PGC dataset of 20,000 AN cases and >100,000 controls with genomewide association data, the student will establish how genetic risk for metabolic and psychiatric phenotypes influences risk for AN, and the interactions between them.

ii. The student will identify whether there are distinct groups of AN cases showing differing patterns of metabolic and psychiatric genetic risks and explore this in available cohorts with detailed phenotype information (>15,000 cases).

iii. Using access to the Twins Early Development twin dataset of >9000 pairs of twins, the student will establish the shared heritability between metabolic (BMI) and psychiatric (emotional/behavioural symptoms) in childhood and adulthood with eating disorders traits.

iv. The student will establish how AN polygenic scores, metabolic and psychiatric risk factors influence eating behaviour in a cohort of 170,000 with detailed eating and food intake information from UK Biobank.

The student will receive all necessary training in a supportive environment and will be strongly encouraged to publish with the aim of thesis submission by publication.

Two representative publications from supervisors:


23.2 Pathway dependent pathogenesis in fatal childhood degenerative disorders: going beyond the brain

Co-Supervisor 1: Professor Jonathan D Cooper  
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Project description:  
An important first step towards devising effective therapies for neurodegenerative diseases is to identify which parts of the brain are affected, and the mechanisms that underlie these events. We have been studying Batten disease (neuronal ceroid lipofuscinosis, NCL), which is the most common cause of childhood dementia, but also involves a range of sensory and motor problems. Each form of NCL is due to inherited mutations that cause lysosomal dysfunction, resulting in a devastating fatal disease. Since this disease appeared to mostly affect the brain, we have been directing most of our attention and therapy there, but have recently discovered surprisingly substantial pathology in the spinal cord of NCL mice. The effects of disease appear early in the cord, before moving along connected pathways to the rest of the brain. This raises important questions about how this happens and what we can do about it. In this project we will study the extent to which sensory pathways that lead into the cord, and motor pathways that descend the cord are affected, and study the timing of these events. The project will involve anatomical, biochemical, and electrophysiological methods to explore the spinal cord and peripheral nervous system, and the impact upon sensory and motor function. We shall also test methods for delivering therapy to these structures in order to assess their overall contribution to disease, and for improving therapeutic efficacy. This is a collaboration between two world-leading labs, with expertise in childhood degenerative disorders (Cooper) and spinal cord repair (Bradbury).

Two representative publications from supervisors:  

26.2 Effects of preeclampsia on fetal brain development

Co-Supervisor 1: Prof Guillermina Girardi  
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Project description:

FETAL BRAIN DEVELOPMENT DURING PREECLAMPSIA  
During pregnancy, a defect in the placenta leads to dangerously high blood pressure in the mother, causing injury to the blood vessels, kidneys and heart, which threaten the lives of mother and baby. Yearly, preeclampsia costs the lives of 1,000 babies in Britain. It is known that preeclampsia is associated with excessive intrauterine inflammation and that this might affect the neurodevelopment of the foetus with long-term adverse neurological outcomes. We will use a mouse model of preeclampsia that resembles the clinical cases to investigate neurological complications after preeclampsia and evaluate strategies for prevention. Statins will be used to prevent preeclampsia and the associated risks in the mother and offspring. We will use MRI-based imaging methods and immunohistochemical studies to follow up brain development before, during and after a preeclamptic pregnancy as well as the placenta. In particular, we will use imaging methods to detect complement components (biomarkers of inflammation) in utero that can help us predict fetal outcomes. We will also use proton magnetic resonance spectroscopy to evaluate the brain metabolism in the foetus and offspring.

This study has strong translational potential as it will provide a model of the long term influences of preeclampsia on the child and a potential therapeutic strategy for prevention. A major advantage is that these studies - in comparison with human studies- can provide information on long term effects over a short time span.

Two representative publications from supervisors:


27.2 Functional dissection of the brainstem circuitry regulating REM sleep.

Co-Supervisor 1: Alessio Delogu  
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Co-Supervisor 2: Philip Holland  
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Project description:

The brain requires sleep for optimal function and sleep disturbances play a pivotal role in many neurological disorders. Mammalian sleep consists of NREM sleep—a state of deep disconnection with restorative function, and REM sleep—of unknown function and characterised by dreaming. The complex organisation of the subcortical circuitries that control the NREM to REM switch rely on GABAergic neurons in the mesopontine and medullar brainstem (see: Control of REM sleep by ventral medulla GABAergic neurons Nature 2015). The Delogu Lab described a disrupted circadian rhythmicity (Delogu et al., Neuron 2012) and abnormal sleep (unpublished) in the Sox14 knockout mouse. Our hypothesis is that neurons genetically defined by Sox14-expression in the mesopontine and medullar region of the brainstem are required for REM sleep. The Holland Lab investigates the link between migraine—a common neurological disorder- and the sleep system. NREM to REM transitions are disrupted in a mouse model of migraine (see: Unilateral cortical spreading depression affects sleep need and induces molecular and electrophysiological signs of synaptic potentiation in vivo Cerebral Cortex 2010)

The aim of the project is the functional characterisation of Sox14 GABAergic neurons in the context of REM sleep and migraine.

The project will first map the connectivity of Sox14 neurons, using Sox14cre mice and viral tracing (year 1-2) and subsequently apply optogenetics/DREADD’s and EEG/EMG recordings to disrupt the normal progression through the sleep cycle (year 2-3). A panel of preclinical electrophysiological and behavioural migraine models will be used to assess the impact of altered brainstem neural circuitry on migraine biology (year 3-4).

Techniques: recombinant virus, stereotaxic brain surgery, in vivo optogenetics/DREADD’s, EEG/EMG recordings, preclinical migraine models, confocal microscopy and IHC.

Two representative publications from supervisors:  
29.2 The role of sleep in neuroinflammation

Co-Supervisor 1: Dr Ivana Rosenzweig  
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Co-Supervisor 2: Dr Diana Cash  
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Name of Collaborating Clinician: Dr Rosenzweig is also a Sleep Consultant/Consultant Neuropsychiatrist at the NHS Sleep Disorders Service, Guy’s

Project description:
Neuroinflammation is a highly dynamic and complex adaptive process to preserve and restore the central nervous system (CNS) homeostasis, where resident microglia and infiltrating immune cells from the periphery have important roles.1 Common diseases of the CNS, such as stroke, depression and neurodegeneration, elicit a neuroinflammatory response with the goal to limit the extent of the disease and to support repair and regeneration. However, various disease mechanisms lead to neuroinflammation contributing to the disease process itself. Sleep deprivation and its fragmentation have also been suggested to lead to neuroinflammation, and by doing so to aid or trigger neurodegenerative processes, such as Alzheimer’s disease (Rosenzweig et al., in preparation). This project will aim to elucidate the role for specific sleep stages in the process of neuroinflammation and adult neurogenesis in animal model by immunocytochemistry, electrophysiology and MR and PET neuroimaging.

Translational aspect: therapeutical utilization of sleep in a number of neuropsychiatric/neurodegenerative diseases is potentially very lucrative model with direct clinical translational value.
Core skills training: neuroimaging (MR: structural, rsfMRI, ASL; PET) and electrophysiology (ECoG).

Over-arching objectives:
Year 1 experimental set-up and core skills training. Study 1 (exploration of neuroinflammatory and microglial changes in the CNS, Response to targeted sleep stage loss2)
Year 2 Study 2 (nREM versus REM sleep stage role in neurogenesis in adult rat hippocampus3) and Study 3 (potential neuroinflammatory role for the deep brain stimulation of thalamic nuclei during sleep4).
Year 3 data analyses (1/2 Year3) and thesis and papers write up (2/2 Year 3).


Two representative publications from supervisors:
30.2 Inequalities in access to high quality treatments in people with schizophrenia. Mixed methods study.

Co-Supervisor 1: Dr Jayati Das-Munshi  
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Co-Supervisor 2: Professor Diana Rose  
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Project description:

Description:  
Concerns have been expressed about high rates of psychosis and compulsory treatment among people from ethnic minority communities. This is a mixed-methods study to establish if ethnic minority service users with schizophrenia experience disparities in access to psychological therapies and high quality pharmacotherapies, and to determine underlying reasons.

Objectives by year of PhD:

Years 1-2: Using data from the National Audit for Schizophrenia (NAS) (approximate sample size n=10,000), a random sample of service users from all UK mental health Trusts, to determine if there are inequalities in access to psychological therapies and prescribing quality, by ethnicity, in people with schizophrenia. Systematic reviews will supplement data analyses.

Year 2-3: To determine healthcare experiences, help-seeking and barriers to accessing care, from the perspectives of ethnic minority service users with psychosis, which may account for inequalities identified in quantitative data analyses, using qualitative methodologies (focus groups).

Training: The primary supervisor co-leads an MSc module on ‘Advanced statistical methods in psychiatric epidemiology’, which the student can attend. The primary supervisor will support all quantitative data analyses. The student will be able to attend other relevant MSc modules (e.g. qualitative methods). Both supervisors will provide support in the conduct of focus groups and analyses of qualitative data and integration with quantitative findings.

Translational aspects:
Access to NAS data has been negotiated with Professor Mike Crawford, Director for the Royal College of Psychiatrists’ Centre for Quality Improvement at the Healthcare Quality Improvement Partnership (HQIP) programme. Findings could have a direct impact on care standard guidelines.

Two representative publications from supervisors:

31.2 Dissecting the genetic and environmental contribution to depression

Co-Supervisor 1: Professor Cathryn Lewis
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Co-Supervisor 2: Professor Barbara Maughan
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Name of Collaborating Clinician: Dr Argyris Stringaris
Research Division/Department or CAG: Child and Adolescent Mental Health Clinical Academic Group
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Project description:

Depression is a highly debilitating disorder, with an etiology involving both genetic and environmental risks. Advances in genetic technology and the existence of large-scale data-sets now provide unparalleled opportunities to identify risk factors and characterize their role in depression. 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), supported by clinical input (Stringaris) to inform translational potential, particularly from gene-environment interactions detected.

Year 1: Research rotation, developing skills in statistical genetics and psychiatric epidemiology
Year 2: Assimilate data sets, harmonizing environmental variables. Test for association and gene-environment interaction
Year 3: Assess how risk factors vary with heterogeneity in depression subtypes
Year 4: Apply machine learning methods to assess predictive ability of risk factors. Design intervention studies based on findings.

Two representative publications from supervisors:


K32.2 Identifying biomarkers and causal mechanisms of chemotherapy-induced painful peripheral neuropathies

Supervisor 1: Dr. Sarah Flatters
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Co-Supervisor 2: Dr. Roland Fleck
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Name of Collaborating Clinician (if relevant): Dr. Mark Harries
Research Division or CAG: Cancer CAG
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Project description:

Chemotherapy-induced painful peripheral neuropathy (CIPPN) is the major dose-limiting side effect of several first-line chemotherapeutics. 30-70% of patients will develop CIPPN, which often persists following chemotherapy. Currently there is no treatment to prevent or treat CIPPN. Prevention of CIPPN would be greatly aided with a blood biomarker to identify patients susceptible to CIPPN accompanied with knowledge of the causal mechanisms to develop novel targeted pharmacotherapy.

An electron microscopy (EM) study on nerves from a translational rat model of CIPPN identified atypical neuronal mitochondria (Flatters & Bennett 2006). Further work has shown the causal role of ROS and mitochondrial ETC activity to CIPPN (refs1&2 below). Ongoing work indicates that mtDNA content in blood is altered during CIPPN. This project will involve a multi-faceted experimental approach using ex vivo cells/tissues from translational rodent models of CIPPN and human blood samples from CIPPN patients. Thereby linking cellular mechanisms and whole animal behaviour through to clinical CIPPN.

Year 1/MRes: Behavioural assessment in rat models of CIPPN. Quantification of mitochondria/mtDNA in rat blood and tissues.

Year 2/3: Measure oxidative phosphorylation, glycolysis, elemental distribution in sensory neurones during CIPPN using state-of-the-art technology & ultrastructural EM techniques. Quantification of mitochondria/mtDNA in human blood samples.

Year 4: Evaluate novel therapeutic strategies for CIPPN using techniques used in year 2/3.

Training: Diverse range of in vivo and ex vivo experimental techniques, data analysis, presentation skills, project organisation and time management. Application support & specialist microscope training from Jeol and Leica Microsystems. Seminars, workshops, journal clubs through Wolfson CARD and CUI.

Two representative publications from supervisors:

1. Fidanboylu M, Griffiths LA and Flatters SJL (2011) Global inhibition of reactive oxygen species (ROS) inhibits paclitaxel-induced painful peripheral neuropathy. PLoS ONE 6(9):e25212 [The first author of this paper completed his experimental contribution to this paper during a 3-month MRes rotation project]


33.2 Self-other control in social interaction: from mechanisms to applications

Co-Supervisor 1: Caroline Catmur
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Co-Supervisor 2: Geoff Bird
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Project description:

Fundamental to social cognition is the ability to control representations of the self and other people. This is essential for skills such as perspective-taking, empathy, and theory-of-mind. Previous research by the two supervisors has demonstrated how self-other control is implemented by specific brain regions (Sowden & Catmur, 2015) and how training to enhance self-other control in one social domain transfers to other areas of social interaction (Santiesteban et al., 2012). The present project builds on this work by establishing: 1) whether self-other control uses mechanisms that are specialised for social cognition; and 2) the longevity of self-other control training effects; with a view to implementing such training to improve social interaction in the longer term, both in typical development and in neurodevelopmental disorders.

The project will provide training in specific (neurostimulation, response time measurement) and generic (ethics, programming, experimental design, participant recruitment and testing, data analysis, scientific writing, research dissemination) research skills.

Year 1 will involve a behavioural study establishing a non-social counterpart to the social tasks hitherto used to investigate self-other control. During years 2 and 3, neurostimulation and behavioural training techniques will be used to uncover the social and non-social mechanisms that underlie self-other control; and a 2-year longitudinal study will establish the longevity of self-other control training. Year 4 aims to pilot the effectiveness of self-other control training on social interaction in autism spectrum conditions.

Two representative publications from supervisors:

34.2 Exploring the Intergenerational Transmission of Psychopathology Using Genetically Informative Databases

Co-Supervisor 1: Dr Tom A. McAdams PhD  
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Co-Supervisor 2: Dr Fruhling V. Rijsdijk PhD  
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Project description:

Mental health problems run in families. Indeed, a family history of psychopathology is a major predictor of mental health related outcomes. However, it is not yet clear why this is. Many theories highlight the role that parents play in offspring development. Such theories suggest that being raised by a parent with mental health problems is itself a risk factor for the development of problems in offspring. Alternatively, it is well known that genetic factors play a role in explaining variance in psychopathology within populations. As such, it could be that the intergenerational transmission of psychopathology can be attributed to genetic transmission. These two possibilities are not mutually exclusive, but understanding the relative importance of genetic vs environmental routes of transmission can help in the design of interventions and policy. Using children-of-twins data and data from Scandinavian population registries, this project will be focused on understanding the relative importance of genetic and environmental routes of transmission in the intergenerational transmission of psychopathology.

Skills Training
Data management and training in structural equation modelling using OpenMx and other statistical methods; SGDP Centre Summer School 2017; Workshop on Statistical Genetic Methods for Complex Traits 2018 (Boulder, CO).

Objectives

Two representative publications from supervisors:


35.2 Patient activation, decision-making and Psychological status in people with motor Neuron Disease (MND)

Co-Supervisor 1: Professor Laura Goldstein
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Co-Supervisor 2: Professor Ammar Al-Chalabi
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Project description:
Motor Neuron Disease (MND) refers to several life-limiting devastating neurodegenerative diseases. Our interdisciplinary group has shown that while illness-related factors predicted those patients needing to make a medical intervention decision to help prolong survival, patients’ formal cognitive and education status, and level of everyday executive (i.e. cognitive/behavioural) dysfunction were associated with decision-making and acceptance/refusal of these interventions. Patients’ understanding of their illness, their early approach to considering interventions and carer-related factors were also associated with treatment decisions (Martin et al 2014).

This project will extend understanding of factors involved in care choices by MND patients by exploring the role of levels of patient activation in decision-making, health status and psychological outcome. ‘Patient activation’ describes the knowledge, skills and confidence a person has in managing their own health and health care. The study will employ the Patient Activation Measure, a reliable patient-reported measure that has been validated in the United Kingdom. The project will test the hypothesis that patient activation scores will predict a number of health behaviours and will be related to clinical outcomes, the types of health care use and MND patients’ ratings of their experience. The study will also explore the relationship between patient activation and other psychological outcomes (e.g. mood) and neuropsychological status, in the context of physical symptom severity.

Objectives for the student if 0+4: experience/skills in ethics/R&D applications/PPI and systematic reviews (year 0-1); knowledge of neurodegenerative disease and neuropsychology (year 0-4); quantitative and qualitative methodology (years 1-4); submission of papers to journals/conference presentations (years 1-4).

Two representative publications from supervisors:


36.2 Exploring clinical and neurocognitive characteristics of patients with eating disorders with and without autistic traits: are phenotypes disorder specific?

Co-Supervisor 1: Dr. Kate Tchanturia  
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Co-Supervisor 2: Dr. Catherine Stewart  
Research Division/Department or CAG: CAMHS  
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Name of Collaborating Clinician Dr. Mima Simic  
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Project description:

This project will provide a unique opportunity for students to work within a multidisciplinary team with a variety of academic and clinical skills.

The project will build upon the work the supervisors have started exploring the links between Anorexia Nervosa (AN) and Autism Spectrum Disorder (ASD). Research shows phenotypic similarities in adults, however less is known about the development of these in childhood.

This project will focus on screening young people receiving clinical care for an AN for co-morbid ASD, and using a series of clinical interviews, neuropsychological assessments and questionnaires to compare specific characteristics of this group (AN+ASD) with young people with an ASD diagnosis without AN. Further longitudinal assessment of a small cohort of participants with AN post-treatment will assess treatment response differences in AN/AN+ASD. Findings will be highly translational; informing the tailoring of treatment for AN+ASD and increasing understanding and identification of ASD in females.

The project will allow the student to develop a repertoire of skills to enable them to pursue a career as independent researchers or to prepare for future clinical training. These will include literature reviews, study design, clinical interviewing, neuropsychological assessment (first year), data analysis (second year) and research presentation both internally and at national and international conferences (third year).

They will also have the opportunity to enhance their clinical skills by attending clinical skills workshops that the senior team provides regularly (e.g. Multifamily groups, Cognitive Remediation Therapy, Emotion Skills Training), and by receiving supervision from a prominent clinical psychologist in eating disorders.

Two representative publications from supervisors:
37.2 Limited Contact Psychological Treatment for Headache: Development, User Involvement, and Pilot Testing

Co-Supervisor 1: Professor Lance McCracken
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Co-Supervisor 2: Professor Leone Ridsdale
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Project description:

Recurrent and chronic headaches, including migraine and tension headaches, are prevalent in the UK and represent a significant personal and societal burden. They cost billions of pounds each year in health care and lost productivity.

A psychological treatment called Cognitive Behavioural 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 the internet. The focus here is explicitly on disabling headaches because these are the most costly and because ACT primarily aims to reduce disability.

This programme of PhD studies will include training in the following:
(a) Year 1: systematic review and evidence synthesis focused on the role of psychological flexibility factors (including mindfulness) in headache
(b) Year 2: creation of a prototype treatment based on modification of a current treatment package (not yet developed for headache)
(c) Year 2: user acceptability testing of online interface, skills training modules, and assessment modules
(d) Years 3 & 4: pilot testing of delivery of full online package in a small series of participants with headache.

In addition to the training provided by these projects, the main research aim is to prepare for future research in the form or a Randomized Controlled Trial.

Two representative publications from supervisors:

38.2 Anxiety, Alcohol and Adolescence (AAA project): Risk and resilience, and interventions

Co-Supervisor 1: Jennifer Lau
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Co-Supervisor 2: Clare Mackie
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Project description:

Adolescence is a period of social, biological and psychological transition, with many persistent mental health problems first emerging at this developmental juncture. Among these are social anxiety and problematic alcohol use. While each condition can occur independently, adult data show significant co-occurrence, with some suggestion that each condition can exacerbate the other across time. These links have been studied less in adolescence, despite both conditions being associated with significant impacts on health, social and educational functioning. This project will use multidisciplinary techniques to investigate questions that extend our understanding of these links during development, risk factors for these conditions and how we can enhance resilience.

Study 1 (Year 1) will use a genetically-informative longitudinal design to investigate the emergence of social anxiety and alcohol use across adolescence; when reciprocal links between these conditions first become apparent; and whether reciprocal links are explained by common genetic and environmental factors.

Study 2 (Year 1-2) will use developmental cognitive neuroscience methods to investigate whether exaggerated threat learning predicts social anxiety; those with greater reward sensitivity will develop problematic alcohol use, and a combination of exaggerated emotional learning will interact to influence both problem-behaviours. Neural data will be used to investigate between-group differences on emotional brain networks that correlate with behavioural differences.

In Study 3 (Year 2-3), a novel training program (in the form of a health app) that teaches adolescents new emotion regulation strategies for controlling attention/behaviour away from threatening cues (for social anxiety) or immediate reward cues (for alcohol use) will be piloted.

Two representative publications from supervisors:


39.2 A systematic investigation of the role of the oxytocin system in the pathophysiology of bulimia nervosa: a new target for treatment?

Co-Supervisor 1: Professor Janet Treasure
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Co-Supervisor 2: Dr Yannis Paloyelis
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Project description:
Preclinical evidence demonstrates the key role the oxytocin system plays in the regulation of eating behaviour, whether directly impacting on feeding processes or modulating the reward value of food. Evidence from human studies, including many from our group, implicates genetic and functional abnormalities in the oxytocin system in eating disorder pathophysiology, identifying this system as a key target for efforts to understand the pathophysiology of eating disorders and develop new therapeutic approaches.

This project benefits from supervisors who combine expertise in the pathophysiology of eating disorders (JT) and the function, organisation and pharmacological manipulation of the oxytocin system in the human brain (YP). This new project aims to characterise the involvement of the oxytocin system in the pathophysiology of bulimia nervosa and its possible role as a target for treatment. We will directly (administering oxytocin) and indirectly (examining the impact of known functional genetic variants of the oxytocin receptor or of epigenetic regulation) manipulate the function of oxytocin system to investigate its involvement in appetite, feeding behaviour and neurocognitive processes underlying bulimia nervosa.

The PhD student leading this project will develop both theoretical expertise in this area and acquire skills in neuroimaging, psychopharmacological, genetic and neuropsychological research, paving the pathway for a promising career in interdisciplinary experimental medicine.

Objectives by year:
1: Develop theoretical understanding through literature review and project planning. Ethics and participant recruitment.
1&2: Acquiring advanced skills in statistics, neuroimaging, neuropsychological testing and pharmacological research.
2&3: Leading the experimental project/data acquisition.
3&4: Data analysis & dissemination. Thesis writing.

Two representative publications from supervisors:
40.2 Use of Performance and Image Enhancing Drugs

Co-Supervisor 1: Dr Paolo Deluca
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Co-Supervisor 2: Prof John Marsden
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Project description:

Performance and Image Enhancing Drugs (PIEDs) are substances taken by people with the intention of improving their physical appearance and/or to enhance their sporting performance. PIEDs can be grouped in substances aimed to:
1. Change the structure and function of muscle
2. Lose weight
3. Change the cosmetic appearance of the skin and hair
4. Improve sexual behaviour and function
5. Enhance cognitive processes
6. Improve mood and social behaviours

Those taking PIEDs are at risk of physical and mental harm. The rapid growth of the Internet has made the purchase of illegal PIEDs easier, however, the product received may be counterfeit with unknown harms associated with its ingredients.

Currently little is known about what factors may influence the use of PIEDs, therefore the aim of this research is to:
i. Identify factors that influence the uptake and continuation of PIEDs use
ii. Categorise the effects and user typologies and develop an understanding of how new trends in PIEDs use are communicated and adopted by users.
iii. Develop a tool for the measurement of reasons for PIEDS use and related behaviours
iv. Assess knowledge, attitudes, and reasons for use and how they are associated with different user typologies, patterns of use, and outcomes.
v. Examine the natural history of PIEDs use.

Greater understanding of these aspects of PIEDs will facilitate the development of interventions to help raise awareness of the harms of these drugs and reduce their availability and use.

Training in Addictions, online research methods, qualitative/quantitative analysis will be provided.

Two representative publications from supervisors:


41.2 Neurophysiological networks in the brain: a window to the study of treatment response in schizophrenia.
Co-Supervisor 1: Dr Alice Egerton
Approximately 1/3 of patients with schizophrenia do not respond to medication, termed treatment-resistant schizophrenia (TRS). Clozapine is the most effective medication for TRS, but only half of TRS patients will respond to clozapine. This PhD will determine 1) whether neuroimaging can predict how well an individual patient will respond to clozapine and 2) the neurobiological mechanisms underlying clozapine response. This could lead to personalised approaches to treatment, development of new medications, and better clinical outcomes.

The PhD will involve collection, analysis and integration of state-of-the-art, multimodal magnetic resonance imaging (MRI) data in patients with TRS before and after 12 weeks of clozapine.

Year 1: Will determine whether brain network activity (resting state functional MRI, rs-fMRI) can predict clozapine response and changes during clozapine treatment.
Year 2: Will determine the influence of regional blood flow (arterial spin labeling, ASL) on brain network activity and clozapine response.
Year 3: Will determine the influence of regional glutamate and GABA neurotransmission (magnetic resonance spectroscopy, MRS) on brain network activity and clozapine response.
Year 4: Will combine multi-modal imaging data in a machine-learning algorithm to predict clozapine response.

Skills training: Patient recruitment and assessment; MRI acquisition; MRI analysis; machine learning. Training will be provided by the supervisors and through dedicated training courses. The Departments run weekly seminar series, providing a broader understanding of psychiatric research and neuroimaging. The student will be wholly supported in publishing their PhD research in leading journals, attending international scientific conferences, and in progressing to the next steps in their career.

Two representative publications from supervisors:
42.2 Autism around the globe: exploring culturally universal and culturally specific characteristics of autism

Co-Supervisor 1: Dr Rosa A. Hoekstra (RAH)
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Co-Supervisor 2: Dr Ioannis Bakolis (IB)
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Project description:
Existing quantitative measures for autism have all been developed in high-income and primarily Western countries. There is an urgent need for autism measures that can be applied globally (Durkin et al., 2015). While it is generally assumed that the core symptoms of autism are universal, subtle cultural differences in the expression, recognition and interpretation of autism symptoms exist (Freeth et al., 2013). Because most research to date has been conducted in Western countries little is known about these cultural influences on autism symptomatology. This project aims to systematically explore the culturally universal and culturally specific characteristics of autism. Benefiting from a collaboration with Cambridge University’s Professor Simon Baron-Cohen and international partners providing access to existing multinational data on autistic traits, detailed cross-cultural comparisons will be made using a range of statistical techniques.

Throughout the project, the PhD candidate will gain a deep understanding of the behavioural and cognitive characteristics of autism and how cultural factors might affect these symptoms (under prime supervision of RAH) and learn and apply a range of state-of-the-art statistical techniques, including multi-group factor analyses and item response theory (under main supervision of IB).

Yr1: Training on quantitative assessment of autism and (in 0+4 pathway) review previous cross-cultural autism studies;
Yr2: Explore whether ‘red flags’ for autism (items most predictive of autism) are culturally universal;
Yr3: Conduct a cross-cultural examination of the latent structure of autism;
Yr4: Synthesise findings and draft a list of recommendations informing the development and validation of a global autism screening tool.

Two representative publications from supervisors:
43.2 Statistical and Clinical Validation of Outcome Measures in the Paediatric Autism Communication Trial – Generalised (PACT-G)

Co-Supervisor 1: Prof. Tony Charman  
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Co-Supervisor 2: Prof. Andrew Pickles  
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Project description:  
Considered to be lifelong neurodevelopmental condition autism significantly impacts on individuals, families and carers. In 2016 we will be starting the largest psychological intervention trial conducted to date in the autism field. The Paediatric Autism Communication Trial – Generalised (PACT-G) is an MRC/NIHR EME funded randomised trial of a parent- and teacher-mediated social communication intervention for pre-school and school-age children with autism. After decades of neglect a new-wave of trials have been conducted over the past few years that hold promise for improving outcomes. However, a number of conceptual and methodological challenges remain and whilst our new trial has much strength – builds on a previous successful trial; includes a large sample – some of these challenges apply to our new study. The PhD student will receive interdisciplinary training from a clinical developmental psychologist (Charman) and a statistician (Pickles) to address some of these in the context of a world-leading trial.

Recently developed, the Brief Observation of Social Communication Change (BOSCC) is intended to extend the measurement of social communication abilities beyond that measured by the widely-used Autism Diagnostic Observation Schedule (ADOS). Using statistical modelling techniques the student will test the properties of the two measures and their mapping to measures of ‘real-world’ adaptive functioning. This will inform the primary outcome to be used in the main trial.

Year 1: Training on BOSCC and ADOS alongside trial staff. Year 2: Training in trial methodology and statistical modelling  
Year 3: Analysis of extant datasets. Year 4: Analysis of main trial data.

Two representative publications from supervisors:


45.2 The effect of polygenic risk score on brain function before and during the development of psychosis

Co-Supervisor 1: Dr Matthew Kempton  
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Co-Supervisor 2: Dr Andrea Mechelli  
Research Division/Department or CAG: Department of Psychosis Studies  
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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) and has collected rich longitudinal data including neuropsychology, neuroimaging data, childhood environment, social factors 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/Rotation-Preparation of data, attending MSc courses, training in polygenic risk
Yr2-Baseline data analysis, participant recruitment in PSYSCAN
Yr3/4-Longitudinal data analysis, write-up

While we are particularly interested in the above project, the wide range of data collected means there would be some flexibility for the student to mould the project to their own interests.

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

Both supervisors have expertise in ARMS, neuroimaging and cognition

Two representative publications from supervisors:


46.2 Effect of contingency management and a high nicotine delivery electronic cigarette on smoking cessation among people with severe mental illness

Co-Supervisor 1: Prof Ann McNeill  
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Co-Supervisor 2: Dr Sara Hitchman  
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Website: http://www.kcl.ac.uk/ioppn/depts/addictions/people/profiles/DrSaraHitchman.aspx

Project description:

Smoking prevalence among people with severe mental illness (SMI) is estimated at 36-56% (Royal College of Physicians, 2013) and has changed little over the last 2 decades. There is evidence that contingency management (CM) may be effective for smoking cessation among people with SMI (Roll et al. 1998; Tidey et al. 2002, 2011). CM for smoking cessation involves monitoring smoking using biological markers and rewarding abstinence, and withholding reward when smoking is detected. There is also evidence from a pilot trial of smokers with schizophrenia (Caponnetto, et al., 2013) and a sub-sample analysis of people with MI from a randomised control trial that electronic cigarettes (EC) could be effective for smoking cessation among people with MI (O’Brien, et al., 2015); additionally factors involved in sustaining smoking among people with SMI suggest that novel treatments such as EC could be effective (Tidey et al., 2015). Thus, this project will be a feasibility study and pilot that will use CM for smoking cessation among people with SMI with EC as a cessation aid. A high nicotine delivery EC will be used in contrast to previous studies. Year 1: Literature review and begin running feasibility study of CM and EC use among people with SMI, including qualitative research with service users. Year 2: Continue running feasibility study and write-up. Set-up and begin running pilot. Year 3/4: Finalise pilot, write-up pilot findings and dissertation. Skills training: literature reviews, qualitative research, feasibility and pilot study management and monitoring, data analysis, and communication of research findings.

Two representative publications from supervisors:  

47.2 A project using machine learning theory to develop and test the construct validity of a prediction model identifying high risk of depression in people with type 2 diabetes.

Co-Supervisor 1: Daniel Stahl (basic scientist)
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Project description:
Depression is associated with increased mortality in people with type 2 diabetes. The underlying mechanisms include a complex relationship between psychological, biological and social factors, but whether they are independent, mediating or moderating effects has not been studied. We are following up a cohort of 1750 newly diagnosed type 2 diabetes patients collecting a wide range of variables spanning the bio-psycho-social construct. Data have been collected at baseline (diagnosis), 1, 2 and 10 years follow-up and has been linked to routine clinical data from acute trusts and primary care databases. This provides an unprecedented opportunity to use machine learning techniques (i.e. regularized regression or Bayesian network models) to develop prediction models of the effect of depression on the progression of type 2 diabetes and risk of diabetes complications, dementia and mortality. The findings would have direct translation to clinical practice. DS will provide training in statistics and machine learning and KI in the clinical aspects.

Timetable and overarching aims
Year 1:
Acquiring during supervision and by formal teaching:
- Research methods and design
- Machine learning and statistical computing methods
- Clinical knowledge about the nature and course of type 2 diabetes, depression and its complications

Year 2:
- Learning about prediction modelling, mediation and moderation
- Building and comparing prediction models

Year 3:
- Building a process model using Bayesian networks
- Assessing the construct validity of the prediction models in clinical settings

Year 4:
- Developing user-friendly software code
- Writing of thesis and viva
- Writing publications and report findings to NHS and primary care Clinical Commissioning Groups

Two representative publications from supervisors:

48.2 Is there a functional role for the schizophrenia susceptibility gene, ZNF804A, at synapses?

Co-Supervisor 1: Deepak P. Srivastava
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Co-Supervisor 2: Anthony Vernon
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Project description:
Schizophrenia is a devastating disorder, affecting ~1% of the population worldwide and current treatments for schizophrenia are only partially effective. Recent advances in understanding the complex genetics of schizophrenia provide a unique opportunity to increase our understanding of the aetiology of this complex disease, which will accelerate development of safer and more effective treatments. Variations in the gene encoding zinc finger binding protein 804A (ZNF804A) have been shown to have significant association with schizophrenia and related psychoses. However, this gene is predicated to have several isoforms, and our knowledge of the biological roles of the ZNF804A protein is sparse. Recently, we have found that ZNF804A can be found in several specialized subcellular compartments in neurons. This includes localization of the protein at small sub-micron structures called dendritic spines. These structures are the post-synaptic compartment of excitatory synapses, and are believed to be highly specialised signalling compartments. The aim of this PhD is to build on these exciting novel findings by examining the function of a) different isoforms of ZNF804A, and b) to determine the biological function of ZNF804A in these specialized subcellular compartments. This project will utilize a combination of in vitro preparations, to allow advanced live cell and superresolution imaging, in addition to in vivo approaches to dissect the role of this protein within the brains of mice. In addition, the student will also use a combination of cellular, biochemical and advanced imaging techniques to dissect the biological function of this protein.

Two representative publications from supervisors:

49.2 Assembly of inhibitory circuits in health and disease

Co-Supervisor 1: Prof. Beatriz Rico
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Co-Supervisor 2: Dr. Andrew Lowe
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Project description:

Neuronal circuits underlying the function of the mammalian cerebral cortex collectively constitute one of the most complex biological systems. Thus, unraveling the mechanisms that control their development represents one of the most challenging questions in science. The cerebral cortex contains two main classes of neurons: excitatory pyramidal cells and inhibitory interneurons. The output of excitatory neurons is fine-tuned and synchronized by the function of inhibitory neurons. Most notably, different classes of interneurons target different subcellular compartments of pyramidal cells. Since the location of synaptic contacts largely determines their influence on the postsynaptic cell, it has been suggested that this elaborate organisation of inhibitory inputs greatly increases the computational power of individual neurons. The overall goal of this project is to elucidate the molecular mechanisms controlling the GABAergic synaptic targeting, and to study how disruption of this process leads to disease. Increasing evidences suggest that abnormalities in the function of interneurons contribute to major developmental disorders, including schizophrenia, autism and epilepsy.

Year-1: Screen for genes involved in interneuron synaptic targeting and corroborate expression
Year-2 and 3: Undertake gain/loss of function experiments of identified candidates (Student-driven phase of PhD)
Year-4: Contingency and full-time write up of thesis and manuscript(s) for publication.


Two representative publications from supervisors:


50.2 Emerging principles in the organisation of inhibitory circuits in the cerebral cortex of the mouse

Co-Supervisor 1: Prof. Oscar Marin
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Co-Supervisor 2: Dr. Setsuko Sahara
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Project description:

One of the major goals of neuroscience is to understand how brain function emerges through the assembly of specific neuronal circuits. This is particularly challenging for the cerebral cortex, where many different classes of neurons converge during development to establish specific microcircuits. The cerebral cortex contains two main classes of neurons: excitatory pyramidal cells and inhibitory interneurons. One of the most fascinating aspects of the assembly of cortical circuits is that pyramidal cells and interneurons are generated in distant germinal zones during embryonic development, and yet they have to converge with great precision to form functional circuits in specific layers of the cortex. The overall goal of this project is to elucidate the molecular mechanisms controlling the precise allocation of different classes of interneurons into specific layers of the cortex and to study how disruption of this process leads to disease. Increasing evidence suggest that abnormalities in the function of interneurons contribute to major developmental disorders, including schizophrenia, autism and epilepsy.

Year-1: Perform screen for genes involved in interneuron distribution and corroborate gene expression
Year-2 and 3: Carry out gain and loss of function experiments with selected candidates
Year-4: Write up Thesis project and submit a manuscript for publication; address revisions.

Skill training abilities: mouse genetics, especially conditional mouse models (Cre/LoxP), in vivo manipulation of gene expression through conditional overexpression (in utero electroporation or viral delivery of full length plasmids) or loss of function (in utero electroporation or viral delivery of shRNA, CRISPR-Cas9) experiments. Molecular biology techniques (gene screens, cloning, biochemistry). Cell Biology (primary neuronal cultures, immunohistochemistry, in situ hybridisation, confocal imaging). Electrophysiology, including optogenetics. Time-lapse imaging.

Two representative publications from supervisors:

51.2 Epigenetics factors predicting brain state and disease risk

Co-Supervisor 1: Sylvane Desrivières  
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Project description:

The highly complex structure of the human brain is strongly shaped by genetic influences. Subcortical brain regions form circuits with cortical areas to coordinate movement, cognition, learning, memory, and motivation. To investigate how genetic variations affect the structure and function of the brain, we have conducted genome-wide association studies of magnetic resonance imaging (MRI) brain measures within the context of two international consortia (e.g., Hibar et al. 2015). These analyses indicated that genetic variations exert localised and lasting influences on brain structures and functions associated with behaviour and predisposition to disease. We are complementing these studies by investigation the effects of epigenetic processes such as DNA methylation that may explain an important proportion of the gene-environment contribution to expression of many common diseases of the brain (e.g., Ruggeri et al., 2015). To date, we have aggregated methylation data from 9,000 people, of whom 5,000 have both methylation data and MRI. The aim of this project is to investigate the impact of DNA methylation on brain structure and function. The following objectives with serve this aim:

1) perform epigenome-wide association studies of MRI measures (years 1 & 2).
2) perform the analyses by prioritizing the DNA methylation sites based on their effect on gene expression or association with stress- and anxiety-related phenotypes, as stress influences DNA methylation and later life disease (years 2 & 3).
3) investigate age-related epigenetic changes, which may predict all-cause mortality as well as physical and cognitive performance (years 3 & 4).

Two representative publications from supervisors:

*Equally contributing authors  
This study analysed data from 29,037 people from 48 cohorts on 4 continents—the largest study of this kind worldwide—to discover the genetic basis of brain structure. Times Cited: 18 (Scopus): Expected to be in the top 1% in the world for the general subject area of Medicine

*Equally contributing authors:
52.2 Mental disorders and risk of domestic violence perpetration

Co-Supervisor 1: Prof Sabine Landau
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Co-Supervisor 2: Dr Siân Oram
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Project description:

Domestic violence (DV) affects over 2 million people in England and Wales each year. Improving our understanding of why some people are more likely to be violent towards their partners and family members would help violence prevention efforts. Mental disorders are known to be associated with an increased risk of violence towards others, but little is known about a possible link with DV.

Two studies will be conducted. First, the research will combine and harmonise international psychiatric epidemiology studies to create a combined dataset of >70,000 participants and investigate whether (1) individuals with mental disorders are more likely to be DV perpetrators and (2) this is because of their mental health problem or because of other factors such as alcohol, drugs, and social deprivation. Second, it will systematically review qualitative studies investigating barriers to mental health services responses to DV. Students pursuing the 0+4 route will be encouraged to develop an additional research component, e.g. interviews with mental health professionals or secondary analyses of Domestic Homicide Review data.

The student will acquire expertise in advanced epidemiology and statistics; conducting systematic reviews, individual participant data meta-analysis, and meta-ethnography; and qualitative analysis.

Objectives include:
• Year 1 –skills training, develop collaborative relationships and data sharing agreements with researchers contributing international datasets;
• Year 2 –acquire, harmonise, and combine contributed datasets; conduct systematic review searches; analyse systematic review data using meta-ethnography;
• Year 3 – analyse combined dataset; conduct additional research component;
• Year 4 - write up; publication and dissemination activities.

Two representative publications from supervisors:

53.2 Biomarkers of response to psychological and pharmacological therapies in depression

Co-Supervisor 1: Prof Anthony Cleare
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Co-Supervisor 2: Dr James Stone
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Website:

Project description:

Inflammatory, endocrine and neurotrophic disturbances have an important role in the aetiology of depression, and may predict who responds to which treatments. This project involves studying two longitudinal cohorts of patients. Cohort-1 is patients (n=600) undergoing psychological therapies for depression within the IAPT services (Grant et al 2014). Cohort-2 is patients with “treatment resistant depression” who are part of a trial comparing lithium and quetiapine in those who have not responded to initial antidepressant treatment (n=260).

Recruitment is underway for these cohorts, and training will be provided for the student to be involved in clinical assessments according to their interest. All patients have a range of specimens taken at baseline, including blood samples, which will allow the testing of specific hypotheses about biomarkers that may predict response to both psychological and pharmacological therapies. The student will develop an appropriate project utilising these samples. Current interests of the supervisors include inflammatory measures (such as C-reactive protein or cytokines), novel endocrine markers (such as cortisol gene expression) or neurotrophic factors (such as BDNF), but other biomarkers could be included. Lab training for analysing blood samples could be included depending on interests. Biological measures will be integrated with psychological measures allowing a full understanding of factors predicting response to these treatments. Results will help form a potential basis for a more efficient and personalised choice of antidepressant therapies in the future.

Year 1: training, clinical assessments, development of specific hypotheses
Year 2: clinical assessments, measurement of biomarkers
Year 3: analysis and write up
Year 4: optional (e.g. paper write up, or as part of 1+3)

Two representative publications from supervisors:

54.2 HCN ion channels as initiators of itch: mechanisms and signalling pathways

Co-Supervisor 1: Professor Peter A McNaughton FMedSci
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Co-Supervisor 2: Dr Jon Robbins
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Project description:

We have recently found that HCN2 ion channels, known as “pacemaker” ion channels, are critical for chronic pain. We have preliminary evidence to show that these same ion channels are also critical for itch, particularly when it is exacerbated by inflammation. The PhD student joining our labs will have the opportunity to investigate this novel idea, using a range of methods available in our labs, including patch clamp electrophysiology, calcium imaging, molecular biology, a range of novel HCN2 blocking drugs that we have developed, and the use of transgenic and mouse models to investigate the impact of gene deletion on behavioural responses to itch.

Itch and pain share many characteristics: they are both poorly understood and both can have very adverse effects on the lives of those who suffer from them. Itch is greatly exacerbated by the ongoing inflammation present in conditions such as eczema and psoriasis. In preliminary experiments we have found that scratching in mice is enhanced by inflammation, and that drugs blocking HCN2 ion channels alleviate itch. We will use isolated neurons to determine cellular signalling pathways important in itch; we will use genetic methods to achieve targeted deletion of HCN2 and other ion channels; and we will also use novel HCN2 blocking drugs that we have developed to examine whether they are effective in mouse models of itch. The ultimate aim will be to achieve a better scientific understanding of itch and to lay the foundation for the development of novel treatments effective for pathological itch.

Two representative publications from supervisors:


55.2 Communication Needs of Vulnerable Individuals during Mass Casualty Emergency Decontamination

Co-Supervisor 1: Dr James Rubin
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Co-Supervisor 2: Dr Alison Wright
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Project description:
In a recent review by the Global Health Security Initiative’s Chemical and Radiological/Nuclear Working Groups (Cibulsky et al., 2015), the need for further research on behavioural, communication and privacy issues was identified, with the goal of improving casualty adherence to emergency interventions during chemical, biological, radiological, or nuclear (CBRN) incidents, whether deliberate (e.g. terrorist attack) or accidental (chemical spill) in nature. There remains a gap in the emergency guidance literature as to what constitutes an effective communication strategy and how best to communicate with vulnerable casualties, such as children, the elderly, pregnant women, non-English speakers, those with visual, hearing, or physical impairment, those with cognitive impairment, those with mental illnesses, those from different social or cultural backgrounds, and those with pre-existing medical conditions (Carter & Amlôt, in preparation).

In Year 1 of this project, the student will conduct a systematic literature review to identify knowledge gaps pertaining to communication in general and communication with vulnerable groups in particular, during emergencies.
In Years 1 to 2, following focus group facilitation training, the student will conduct focus group interviews with members of the lay public (including vulnerable individuals) to identify information needs in the event of an on-scene prehospital decontamination scenario.
In Year 3, the student will design and conduct an online experiment to test the relative effectiveness of different communication messages and methods at improving casualties’ adherence.
In Years 3 to 4, the student will conduct a field trial to put the communication strategies tested in the online experiment into practice.

Two representative publications from supervisors:

56.2 Psychopathology in the offspring of mothers with adverse pregnancy: understanding the role of oxidative stress

Co-Supervisor 1: Dr Patricia A. Zunszain
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Project description:

Exposure to maternal depression in utero has been shown to increase the risk of offspring psychopathology in later life. However, the underlying biological causes are not clear. This project will examine the role of oxidative stress. Oxidative stress can inflict cellular damage affecting the neuronal environment, potentially disturbing brain development and with detrimental consequences in offspring. Markers of oxidative damage are increased in depression (Black 2015), but it remains to be established whether maternal depression affects the oxidative status of offspring. This project aims to determine the existence of such an association, which would warrant interventions during pregnancy and/or early life to control oxidative stress and thereby minimise the transmission of depression, by studying two cohorts:

1) 125 families followed for 25 years as part of the South London Child Development Study, where we have longitudinal data on maternal antenatal depression, offspring childhood maltreatment, adolescent antisocial behaviour and depression (at ages 11 and 16) and blood samples to extract RNA (at age 25).

2) 150 mother-baby dyads, with pregnant maternal blood samples for RNA extraction and babies saliva samples to extract DNA (with clinical and biological data available).

This PhD project will evaluate levels of expression of oxidant and defence genes (years 1-2), and epigenetics regulation of Nrf2 and Keap1 which orchestrate the cascade of antioxidant events (years 2-3). Year 4 will involve data analysis and writing.

Two representative publications from supervisors:


57.2 TRP channel control of pain and analgesia

Co-Supervisor 1: Dr David Andersson  
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Co-Supervisor 2: Prof Stuart Bevan  
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Chronic pain affects up to 20% of the population, but current therapies are either ineffective or produce intolerable side effects in many patients. An improved understanding of the mechanisms underpinning pain to aid the development of improved therapeutic agents is therefore urgent. We have demonstrated that the ion channel TRPA1 (the mustard/wasabi receptor) is of central importance for pain and for the ability of animals to respond to cold and touch. During this studentship, the mechanisms by which TRPA1 controls pain will be elucidated using electrophysiological, behavioural and molecular techniques. Our pilot data suggest that TRPA1 acts through transcriptional changes, rather than by simply acting as receptor for mechanical or cold stimulation.

In year one, the student will use a skin-nerve preparation to explore whether the behavioural phenotype of TRPA1 knockout mice in vivo can be translated to an isolated tissue preparation. In years 2 and 3, the student will study the molecular profiles of isolated sensory neurons from wildtype and TRPA1 knockout mice and their sensitivities to cold and mechanical stimulation using Ca2+-imaging and patch-clamp methods.

In year 3 the student will examine if TRPA1 plays a modulatory role in synaptic transmission. The student will study spinal cord slices electrophysiologically, to determine whether TRPA1 controls pain via spinal mechanisms.

We anticipate that additional lines of investigation will be encountered and that year 4 will be spent completing studies, writing manuscripts, thesis and fellowship applications. The student will be encouraged to present her/his findings to national and international meetings.

Two representative publications from supervisors:


58.2 The epigenetics of clozapine therapy in schizophrenia: a window into the mechanisms of treatment resistance in schizophrenia.

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Co-Supervisor 2: Prof John Powell
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Project description:
1/3 of patients with schizophrenia are resistant to treatment with conventional antipsychotics, consuming 25% of the NHS mental health budget. The only treatment with proven efficacy in treatment-refractory patients is clozapine, but this is associated with severe adverse effects. Its mechanism of action is unclear, limiting progress in drug discovery.

The student will investigate the effects of clozapine on DNA methylation and gene expression in an observational, longitudinal study of 30 patients with schizophrenia initiated on clozapine. The patients will be studied at 0, 3, 6 and 12 weeks post-initiation with clozapine, with detailed clinical data and biospecimens collected at each time-point. Genome-wide patterns of DNA methylation and gene expression will be quantified using cutting-edge technology and correlated with changes in gene expression, clinical course and adverse reactions. Costs will be met through existing grants held by the supervisors.

The supervisors combine expertise in clozapine and treatment refractory schizophrenia (MacCabe) and epigenetics (Powell). They have completed pilot work showing the feasibility of this approach in 12 patients and have shown clear longitudinal changes in DNA methylation associated with clozapine exposure. The student will gain skills in epigenetic and gene expression data, bioinformatics and longitudinal data analysis with opportunities to explore prediction modelling. (S)he will be trained in the assessment of psychotic symptoms and adverse events and in phlebotomy skills.

Yr 1: Literature review, training in clinical and lab skills, setup, start data collection; Yr 2: Data collection; Yr 3: analysis and write-up.

Two representative publications from supervisors:


59.2 Evaluating wearable technologies for use in the psychopharmacological monitoring of rare diseases

Co-Supervisor 1: Dr Paramala Santosh
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Website:

Co-Supervisor 2: Dr Andrea Danese
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Project description:

The overarching aim of the project is to evaluate the use of wearable technologies for the psychopharmacological monitoring of rare diseases, namely Rett Syndrome (RTT) and Mucopolysaccharidoses (MPS). Dr Paramala Santosh leads a translational clinical research programme at the Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD) with the needs of patients with rare diseases at the core.

Patients with RTT and MPS will be recruited from the CIPPRD, and their functional outcomes monitored using wearable technology and HealthTrackerTM. HealthTrackerTM is an established platform for online collection and storage of medical data that allows multi-modal presentation of questionnaires.

The wearable technologies part of the study will be used to illuminate patterns between behavioural, cognitive and physiological aspects in individuals with RTT or MPS. Through the use of the E4/Embrace wristband, we will be able to receive real-time streaming of physiological data including continuous heart rate (heart rate variability, stress and relaxation), electrodermal activity (skin conductance) and movement in individuals in RTT / MPS, and be able to correlate these physiological signatures with the behavioural aspects of the diseases.

This bench-to-bedside technology will improve the care pathway of individuals with these rare diseases, empowering clinicians to improve the treatment trajectory in individuals with RTT and MPS. The project focus will be to develop alert systems to identify autonomic storms and panic attacks based on psychophysiological measures.

Project Timeline:
Year 1: Literature review and questionnaire development / selection; Ethics Approval
Year 2&3: Questionnaire and wearable technologies stage (creation of database); write up protocol for publication
Year 4: Final output – completion of data analyses and project write up

Two representative publications from supervisors:


60.2 Inequalities in access to high quality treatments in people with schizophrenia. Mixed methods study.

Co-Supervisor 1: Dr Jayati Das-Munshi  
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Co-Supervisor 2: Professor Diana Rose  
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Project description:

Description:
Concerns have been expressed about high rates of psychosis and compulsory treatment among people from ethnic minority communities. This is a mixed-methods study to establish if ethnic minority service users with schizophrenia experience disparities in access to psychological therapies and high quality pharmacotherapies, and to determine underlying reasons.

Objectives by year of PhD:
Years 1-2: Using data from the National Audit for Schizophrenia (NAS) (approximate sample size n=10,000), a random sample of service users from all UK mental health Trusts, to determine if there are inequalities in access to psychological therapies and prescribing quality, by ethnicity, in people with schizophrenia. Systematic reviews will supplement data analyses.
Year 2-3: To determine healthcare experiences, help-seeking and barriers to accessing care, from the perspectives of ethnic minority service users with psychosis, which may account for inequalities identified in quantitative data analyses, using qualitative methodologies (focus groups).

Training: The primary supervisor co-leads an MSc module on ‘Advanced statistical methods in psychiatric epidemiology’, which the student can attend. The primary supervisor will support all quantitative data analyses. The student will be able to attend other relevant MSc modules (e.g. qualitative methods). Both supervisors will provide support in the conduct of focus groups and analyses of qualitative data and integration with quantitative findings.

Translational aspects:
Access to NAS data has been negotiated with Professor Mike Crawford, Director for the Royal College of Psychiatrists’ Centre for Quality Improvement at the Healthcare Quality Improvement Partnership (HQIP) programme. Findings could have a direct impact on care standard guidelines.

Two representative publications from supervisors:

61.2 Does contingency management engineered behavior change cause an accompanying change in attitude and drug craving?

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Co-Supervisor 2: Dr. Mitul Mehta
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Project description:

We are currently conducting a NIHR clinical research programme to study contingency management in the treatment of opiate-dependent patients. For this programme we are examining the use of contingency management (CM) (voucher reinforcement to encourage positive behaviour change) to reduce street heroin use in heroin addicts receiving opiate substitution treatment. We have already seen striking findings with this approach (Weaver, Metrebian et al 2014). To improve understanding of the mechanism of action of this psychological treatment we propose a “reverse translational” approach. Little is known about whether contingency management (positive reinforcement) engineered behavior change is accompanied by a change of attitude toward drugs and a reduction in cue-evoked craving as measured by self-report, physiological responses and cerebral activity related to the craving network (by fMRI). Craving is one of the most important characteristics of addiction. Craving refers to the general desire and urges to experience the effect of a previously experienced drug (general craving) and can be an instant desire triggered by internal or external cues (instant craving). Craving is an important mediator of continued drug use and relapse after abstinence. The robustness of this behaviour change is critical to the fuller impact of CM, and the findings from the proposed study will build upon existing work in this area.

Objectives include: Year 1 – to assess feasibility of inducing craving and measuring response through self-report physiological measures and fMRI. Year 2&3 - Pilot RCT to evaluate the extent to which artificially-engineered change in behaviour (through Voucher-Based CM) alters behaviour and cue responsivity.

Two representative publications from supervisors:


62.2 Mental health problems associated with childhood gender nonconformity and sexual orientation

Co-Supervisor 1: Dr Katharine Rimes
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Co-Supervisor 2: Dr Artemis Koukounari
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Project description:
Childhood gender nonconformity (being more like the opposite sex in one’s interests / behaviour) and lesbian, gay or bisexual (LGB) sexual orientation are both associated with increased mental health problems. Gender nonconformity and sexual orientation are partly related; children higher on gender conformity are more likely to later identify as LGB. This study will use an existing longitudinal dataset to investigate:
1) Do young children higher in gender nonconformity go on to experience more negative interactions with others (e.g. bullying) and poorer self-image, and do these factors account for higher levels of subsequent mental health problems?
2) Do people who identify as LGB at age 15 go on to experience more negative interactions with others and poorer self-image, and do these factors account for higher levels of mental health problems in early adulthood?
3) Do higher levels of childhood gender nonconformity contribute to increased distress, negative interpersonal experiences and poorer self-image between LGB and heterosexual youth?

Finally the student will conduct pilot study of a new online psychoeducation intervention for adolescents with high gender non-conformity to help them maintain self-esteem and self-acceptance.

Skills training:
Supervisor 1: Training in developmental models of mental health problems and intervention methods.
Supervisor 2: Statistical analysis of longitudinal data, including path and structural equation models. Training in the statistical packages Mplus and STATA.

Yearly objectives:
2: Continue data analysis. Develop and begin pilot intervention study.
3: Complete intervention study. Write-up.

Two representative publications from supervisors:


63.2 Association between daily variation in mood and symptoms and long-term adherence and outcomes in rheumatoid arthritis

Co-Supervisor 1: Sam Norton
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Co-supervisor 2: John Weinman
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Name of Collaborating Clinician: Dr James Galloway
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Project description:
Rheumatoid arthritis (RA) is a chronic inflammatory condition causing inflammation and swelling of the joints, and leading to pain and limited function. Despite advances in the treatment, rates of disability and depressive disorder remain high. To enable improved medicines adherence as well as better targeting of non-pharmaceutical treatments, there is a need to understand the dynamic processes and causal mechanisms underlying psychological and physical outcomes in RA.

To date, most research addressing this issue has used longitudinal observational studies with a small number of assessments over months or years. There is a growing interest in the use of short-term high-frequency studies with assessments on a daily basis to examine intra-individual fluctuations in factors such as pain and mood. The research will involve combining data from both types of study to examine how inter-individual differences in intra-individual variability on daily assessments are related to illness related behaviours (e.g. medication adherence) and symptoms (e.g. pain and fatigue) in the long-term.

Over the course of the studentship the student will initially conduct a systematic review of short-term high frequency longitudinal studies in RA. This will inform the design and analysis of a 'measurement burst' longitudinal study combining routinely collected data from outpatient appointments with a nested short-term high-frequency follow up study with daily assessments of mood, symptoms and illness-related cognitions over a six-week period. Routine data are from the Rheumatology Department at King's College Hospital, which includes patient reported outcomes, such as mood, pain, fatigue and adherence.

Skills training will focus on health psychology and advanced quantitative methods, specifically concerning use of routinely captured health data for research and longitudinal data analysis using latent variable modelling approaches.

Two representative publications from supervisors:


64.2 Food intolerance - a new way forward: developing and testing a novel intervention to help patients manage their symptoms more effectively

Co-Supervisor 1: Dr Emma Godfrey
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Co-Supervisor 2: Dr Stephen Till
Research Division/Department or CAG: Division of Asthma, Allergy & Lung Biology, King’s College London and Department of Allergy
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Project description:

Food intolerance (FI) describes a range of food-related complaints of varying aetiology. In contrast, food allergy (FA) is a specific reaction involving the immune system (IgE-mediated). FI is becoming increasingly prevalent and can have a major impact on people’s health and lifestyle. We have conducted a cross-sectional study of 200 new patients referred to the Adult Allergy Service at Guy’s and found that the majority of patients were diagnosed with FA, but 25 per cent of attendees presented with undefined FI. These patients reported significantly more symptoms, higher anxiety levels, more health care use and lower quality of life than those with FA.

Aim: to understand and model the role of psychological processes in the experience of FI and then develop and pilot a new intervention delivered in the clinic to help patients manage their symptoms more effectively.

Year 1: theoretical development and scoping exercises. Conduct a systematic review, recruit a PPI group and create a theoretical model to underpin an intervention in undefined FI.

Year 2: pilot work to design and test an intervention. Use of experimental methods and questionnaire study to facilitate the development of a theory-based intervention. Patient and professional focus groups will input into the design to ensure feasibility and acceptability.

Year 3: feasibility study to evaluate feasibility and acceptability, recruitment rate, effect size, and any unforeseen adverse events. Interview participants and clinicians.

Year 4: write up and grant application for RCT to test the intervention.

Training available: Quantitative and qualitative methods, systematic review, experimental methods

Two representative publications from supervisors:


65.2 Explaining the Mechanisms underlying treatment response in Psychosis

Co-Supervisor 1: Prof Sukhi S Shergill  
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Co-Supervisor 2: Dr Chiara Nosarti  
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Project description:

Schizophrenia is characterised by a broad range of symptoms, including positive symptoms such as hallucinations and delusions; negative symptoms such as amotivation and social withdrawal; and cognitive symptoms such as impaired memory and cognitive flexibility. Despite optimal treatment, between a third and half of these patients fail to achieve adequate symptom control in one or more of these domains. The aim of this project is to clarify the neural mechanism underlying treatment response in psychosis in order to guide treatment in a more effective manner. The key hypothesis is that individuals with psychotic illness who don’t respond adequately to their medication have specific behavioural cognitive deficits indexed by anatomical and/or functional differences in the ‘connectivity’ of pathways connecting the frontal lobes to the basal ganglia. The identified MRI biomarker could be used to stratify patients and refer to appropriate treatments earlier in their care.

The student, along with the team, will recruit 100 patients with a first onset of psychosis and assess them longitudinally using our experimental paradigms.

The student will develop key skills in cognitive and clinical assessment of patients with psychosis and advanced functional and structural imaging analysis.

First year:
• Training in imaging analysis, clinical and neuropsychological assessments
• MRI safety training
• Patient recruiting and data acquisition

Second Year:
• Patient recruiting and data acquisition
• Preliminary analysis of data
• Dissemination in conferences

Third Year:
• Completion of patient recruiting and data acquisition
• Final data analysis
• Thesis Write up

Two representative publications from supervisors:

Functional Magnetic Resonance Imaging of Impaired Sensory Prediction in Schizophrenia  

Alterations in cortical thickness development in preterm-born individuals: Implications for high-order cognitive functions  
66.2 The impact of childhood adversity on stress reactivity and treatment outcomes in individuals with paranoia.

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Project description:

At least 10% of the general population regularly experience paranoid thoughts and persecutory delusions are a frequent symptom of psychosis. According to the vulnerability stress model, the likelihood of psychotic symptoms is a function of the extent of vulnerability and stress that someone encounters. Adverse childhood life events, especially when occurring repeatedly and chronically, show a strong association with alterations in adult stress reactivity, potentially predisposing for later mental disorders. Previous studies suggest chronic victimization as a possible cause of paranoid symptoms, involving interpretations of everyday information as personally threatening.

We are conducting the first study (NIHR funded) investigating the effectiveness of a new therapeutic procedure, ‘Cognitive Bias Modification for paranoia’ (CBM-pa). CBM-pa involves participants reading 4 stories on a computer screen, completing missing words and answering questions in a way that encourages more helpful beliefs about themselves and others.

The PhD candidate will work closely with the team in recruiting participants (Year 1); measuring psychophysiological response to everyday stress (i.e heart rate, saliva cortisol, blood pressure) in individuals with persistent distressing paranoia, before and after receiving CBM-pa (Year 2) and investigating the association between childhood adversity, response to environmental influences and resilience to stress using psychobiological measures (Year 3).

Two representative publications from supervisors:  

The long-term effectiveness of cognitive behavior therapy for psychosis within a routine psychological therapies service  
67.2 The electrophysiology of visual hallucinations in neurodegenerative disorders

Co-Supervisor 1: Dr Dominic ffytche
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Co-Supervisor 2: Professor Dag Aarsland
Research Division/Department or CAG: Old Age Psychiatry

Project description:

Visual hallucinations (seeing something that is not actually there) are a common symptom in neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease and rarer but related dementias such as Dementia with Lewy Bodies. In these contexts, visual hallucinations are indicators of worse outcome in that they are associated with more rapid cognitive decline and trigger the move from independent living to a care home. This contrasts with visual hallucinations occurring in eye disease (the Charles Bonnet Syndrome) where hallucinations seem unrelated to cognition or long-term prognosis. Why might the same symptom be associated with very different outcomes? This PhD project will set out to answer this question by investigating the brain mechanism underlying visual hallucinations in such disorders using electroencephalography (EEG), scalp recorded electrical potentials reflecting underlying brain oscillations. Scalp EEG and cognitive potentials will be recorded to characterise similarities and differences in people with and without susceptibility to visual hallucinations across different clinical contexts with a specific translational goal to explore EEG biomarkers of Dementia with Lewy bodies.

The student will be trained in the recording and analysis of EEG and cognitive evoked potentials, gamma EEG signals and in the clinical assessment of: hallucinations and related perceptual symptoms; higher visual function; cognition and behaviour. Dr ffytche will supervise the clinical and visual science aspects of the study while Dr Nottage will supervise EEG and gamma electrophysiology. There is opportunity for the student to develop and pilot their own perceptual/cognitive EEG paradigm for use in the study and depending on their interests and background, it is envisaged the final thesis will contain work related to resting EEG, gamma-band EEG, EEG connectivity, evoked potentials, trans-diagnostic EEG differences, biomarker characterisation and perceptual neurophysiology.

Year 1  Year 2 /3  Year 3 /4
Developing skills in clinical assessment and EEG recording, application for ethical approval, paradigm development  EEG acquisition in the patient groups  Analysis and write-up

Two representative publications from supervisors:

ffytche DH The hodology of hallucinations Cortex 2008; 44: 1067-83.

68.2 Treatment pathways for veterans who access secondary mental health care services.

Co-Supervisor 1: Professor Sir Simon Wessely
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Project description:
Estimates of the veteran population, here defined as those who have served in the military (e.g. one day of employment in the Armed Forces) and subsequently have left, range from approximately three to five million. A minority of the veterans may experience physical and mental health problems, some resulting from their experiences in the line of duty. The majority of veterans with mental health problems do not seek formal medical help for their problems. Limited evidence is available about veterans who do seek help from secondary mental health care services.

This project aims to provide insight into
i. the number of veterans accessing secondary NHS mental health care services,
ii. the type of mental health problems they present with,
iii. what kind of treatment they receive,
iv. the duration of their involvement with services,
v. how this compares to the general population who access the same services,
vi. how this compares to veterans who receive care from Combat Stress (a national mental health charity for veterans).

This project will involve the analysis of large datasets from different sources
1) South London and Maudsley (SLAM) BRC case register: this is an anonymised register that includes electronic clinical records of patients who access the secondary mental health care services provided by SLAM. Based on a pilot search earlier this year, we expect to identify at least 300 eligible veterans in this register and they will be matched with the same number of civilians.
2) Combat Stress case register: the case register from Combat Stress is extensive and last year they received over 2000 new referrals. The register will be used to extract patient data from approximately 300 veterans.

This project will provide the PhD student to develop the skills and experience in creating and managing large datasets, conduct advanced quantitative analyses, write scientific output and gain insight in the treatment pathways of veterans.

Two representative publications from supervisors:

K69.2 A translational approach to neurodevelopmental disorders associated with defective autophagy.

Co-Supervisor 1: Manolis Fanto  
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Co-Supervisor 2: Heinz Jungbluth  
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Project description:

What does it take for your nervous system to develop properly and maintain its functions during your life? Cell maintenance and quality controls mechanisms, like autophagy, have been proven fundamental, and a cause for neurodevelopmental and neurodegenerative disorders, when they fail.

Genetic childhood-onset neurological disorders are associated with a substantial individual and societal disease burden. Many of these conditions are fatal and for the vast majority there is currently no cure. Whilst individually rare, these disorders are often linked in the same cellular pathways, suggesting feasible targets to develop therapies potentially suitable to cure a wide range of human disease. Defects in autophagy have recently emerged as a common cause of Vici syndrome and related disorders. The aim of the present project is to assemble a translational pipeline for 3 neurodevelopmental disorders recently attributed to primary autophagy defects.

You will generate disease models in the fruitfly Drosophila melanogaster, an excellent model organism to study autophagy abnormalities. Initial experiments will be done with RNAi knock down, which can be performed during first year rotations.

This will be complemented with a state-of-the-art iPSC models to apply Drosophila-derived knowledge and potentially investigate drugs to ameliorate these neurological disorders. This project may lead to therapy developments potentially applicable to a wide range of neurodevelopmental and neurological disorders.

In this project, you will learn techniques related to basic cell biology in vivo and in petri dish and work within a translational perspective that integrates basic science and clinical outlook.

Two representative publications from supervisors:

Unpublished yet but important and available upon request:
K70.2 Targeting mitochondrial retrograde signalling as a treatment for Parkinson’s disease

Co-Supervisor 1: Dr Joseph Bateman, PhD
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Project description:
Mitochondria have vital functions in the generation of cellular energy, apoptosis, calcium buffering and the generation of reactive oxygen species. Mitochondrial dysfunction plays a clear role in Parkinson’s disease, but there are currently no treatments that target mitochondria. Mitochondria communicate with the cell through a mechanism known as mitochondrial retrograde signalling. We have recently shown that inhibition of mitochondrial retrograde signalling, by knock-down of the gene HIFalpha, restores function in a Drosophila model of Parkinson’s disease (Cagin et al. PNAS, 2015). The PhD student will investigate mitochondrial retrograde signalling in the mammalian nervous system. They will also test whether genetic and pharmacological inhibition of HIFalpha has therapeutic potential in mammalian models of Parkinson’s disease. The ultimate aim is to develop a HIFalpha inhibitor as a preventative treatment for Parkinson’s.

The objectives are:
Year 1 (or rotation project): Test HIFalpha inhibitors in neuronal cell lines and primary neuronal models of Parkinson’s disease.
Year 2: Test HIFalpha inhibitors in mammalian in vivo chemical lesion models of Parkinson’s disease using behavioural and immunohistochemical analysis.
Year 3: Determine whether conditional deletion of HIFalpha in neurons improves function in a mammalian genetic model of Parkinson’s disease and use microarray analysis to characterise mitochondrial retrograde signalling in this model.
Year 4: Completion of behavioural and microarray analyses, writing papers and thesis.

The student will be trained in and use: cell line and primary cell cultures; generation and analysis of animals models of Parkinson’s; microarray analysis of CNS tissue from Parkinson’s models; western and immunohistochemical analysis of CNS tissue. Additional consumables costs for the project will be covered through Prof Ballard’s ongoing grant funding, including funding from the Edmund J Safra foundation.

Two representative publications from supervisors:
(2) Cummings, J. et al. (Ballard senior author) Phase 3 Placebo-Controlled Trial of Pimavanserin for Parkinson’s Disease Psychosis (2014). Lancet, 383, 533-540.
K71.2 Functional characterisation of a novel cytoplasmic RNA binding protein mutated in Amyotrophic Lateral Sclerosis

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Project description:
Amyotrophic Lateral sclerosis (AKA Motor Neuron Disease) is a fatal neurodegenerative disorder causing progressive paralysis and death within ~3 years. We have identified 10 novel mutations in an RNA binding protein in 22 ALS cases, providing powerful evidence that these mutations are pathogenic. There are strong parallels with two RNA binding proteins, TDP-43 (Sreedharan, 2008) and FUS (Vance, 2009), that we previously published in the journal Science with past PhD students as first author and >1,000 citations each. Very little is known about the new and unpublished ALS gene other than it is greatly enriched in the brain. While TDP-43 and FUS are predominantly nuclear the new gene is largely cytoplasmic. Recent studies have shown that vital aspects of RNA regulation occur within axons and dendrites. The discovery of mutations in this gene places abnormal non-nuclear RNA regulation centre stage as a disease mechanism. The Houart lab has established the zebrafish as a powerful model to study RNA regulation in motor axons in vivo (Thomas-Jinu 2015).

The successful candidate will be responsible for exploring the function of the normal protein and the pathological effects of mutations using the tools of cellular and molecular biology including; gene cloning, mutagenesis, genome editing with CRISPR/Cas9 and live cellular and molecular imaging of patient stem cells (Shaw lab) and zebrafish lines (Houart lab) lacking the gene or carrying ALS associated mutations. The student will lead the functional characterisation of this newly discovered gene and learn state-of-the-art molecular neurobiological techniques in two world-famous Neuroscience laboratories.

Two representative publications from supervisors:
K72.2 How do cortical circuits rewire?

Co-Supervisor 1: Dr Gerald Finnerty (clinical academic)
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Co-Supervisor 2: Dr Matthew Grubb (basic scientist)
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Project description:

The mechanisms that enable our brains to adapt to changes in our environment, to learn and to form memories are poorly understood. In the neocortex, three broad groups of cellular plasticity mechanism underpin these capacities: altered neuronal excitability, synaptic plasticity and rewiring of neural circuits. All of these mechanisms alter the output of neural circuits. However, rewiring is the only plasticity mechanism that allows reconfiguration of cortical circuits by forming entirely new connections between neurons or by losing existing connections. The goal of this PhD project is to work out how rewiring occurs.

The first part of the project focuses on excitatory connections between pyramidal neurons (Finnerty). Rewiring is induced by manipulating whisker sensory experience. The student will use a combination of patch-clamp electrophysiology, high-resolution confocal imaging and electron microscopy (collaboration with Dr Graham Knott) to study the functional and structural changes at connections facing impending loss (Years 1 - 2). The second part of the project investigates how interneurons are incorporated into mature neural circuits. The student will use the same techniques in combination with stereotaxic injection of viral vectors to study the olfactory bulb, where adult-born interneurons are wired into olfactory bulb circuitry continuously. Armed with an understanding of the mechanisms underlying rewiring, the student will selectively manipulate these processes to assess whether this prevents or slows reorganization (Year 3 - 4).

Two representative publications from supervisors:

K73.2 How environmental effects influence genetic risk for Autism Spectrum Disorder: addressing the 2-hit hypothesis in a rodent model.

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Co-Supervisor 2: Grainne McAlonan (Clinician)
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Project description:

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder affecting communication and social interaction, with repetitive behaviours. There are currently no treatments for its core symptoms, and the search for therapies is hampered by poor understanding of causal mechanisms. Genetic predisposition is important, but environmental exposures also play a role. For example, altering the immune system in the prenatal period, including by maternal infection, increases the risk of ASD. In this project, we will use rodent models to examine how brain development is altered when risk genes for ASD interact with early life immune activation. Using the immune stimulant PolyIC, we will activate the immune system in pregnant mice with or without a genetic mutation linked to ASD. In mice with 2 copies of a risk gene (homozygous), 1 copy (heterozygous) or 0 copies (control), we will examine how high or low dose immune activation and/or stage of pregnancy influences postnatal brain development of offspring. Brain structure and function can be measured at a macroscopic level using MRI and behaviour testing; and at a microscopic level using high resolution imaging, including 3D imaging of transparent brains (CLARITY), functional imaging and/or electrophysiology. The first year will involve learning technical skills and beginning to examine changes in the adult brain. In the second and third years, the objectives will be to examine in more detail the neurodevelopmental trajectory. This multidisciplinary project therefore provides outstanding breadth of skills training and has the potential to rapidly impact upon our understanding of a costly common condition.

Two representative publications from supervisors:
Andreae LC* and Burrone J. Spontaneous neurotransmitter release shapes dendritic arbors via long-range activation of NMDA receptors. Cell Reports, 2015; 10(6):873-82

Q Li, YO Leung, I Zhou, LC Ho, W Kong, P Basil, R Wei, S Lam, X Zhang, ACK Law, SE Chua, PC Sham EX Wu and GM McAlonan*. Dietary supplementation with n-3 fatty acids from weaning limits brain biochemistry and behavioural changes elicited by prenatal exposure to maternal inflammation in the mouse model. Transl Psychiatry (2015) 5, e641; doi:10.1038/tp.2015.126
K74.2 From bench to bedside: the BBB in health and Alzheimer’s disease.

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Name of Collaborating Clinician (if not one of the two co-supervisors)  
Dr Suzanne J. Reeves (Clinical Senior Lecturer and NIHR Clinician Scientist)  
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Project description:  
There is considerable interest in blood-brain barrier (BBB) dysfunction in the Alzheimer’s disease (AD) process and its impact on drug delivery. This may have particular relevance for antipsychotic medication. Research into amisulpride use in people with AD implicates central (neuro) as well as peripheral (renal) pharmacokinetic (PK) mechanisms in antipsychotic sensitivity, as high central dopamine receptor occupancy is observed following very low doses. (Int J Ger Psychiatry 29 (2014) 1001-1009 Reeves S senior author). The proposed studentship aims to test the hypothesis that both influx and efflux transporters contribute to brain delivery of second generation antipsychotic drugs. Preliminary (ARUK funded) studies have revealed that there are multiple transporters involved in amisulpride uptake and efflux at the BBB, which may be equally relevant for other antipsychotic drugs. Furthermore, the increased central occupancy observed with administration of low doses of amisulpride, and correspondingly low blood levels (confirmed in the applicant’s current study – unpublished data) could be related to age and/or disease-specific changes in expression of the uptake and efflux transporters of amisulpride. The overall objective of this proposal will be to understand the relative contributions of individual transporters to atypical antipsychotic drug CNS delivery using in vitro BBB models, in vivo physiology and animal models of AD. The work is highly translational and will direct future research in the clinical population.


Two representative publications from supervisors:  
K75.1 Dissecting the genetic and environmental contribution to depression

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Co-Supervisor 2: Professor Barbara Maughan
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Name of Collaborating Clinician: Dr Argyris Stringaris
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Project description:

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

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), supported by clinical input (Stringaris) to inform translational potential, particularly from gene-environment interactions detected.

Year 1: Research rotation, developing skills in statistical genetics and psychiatric epidemiology
Year 2: Assimilate data sets, harmonizing environmental variables. Test for association and gene-environment interaction
Year 3: Assess how risk factors vary with heterogeneity in depression subtypes
Year 4: Apply machine learning methods to assess predictive ability of risk factors. Design intervention studies based on findings.

Two representative publications from supervisors:


K76.2 Endoplasmic reticulum (ER)-mitochondria associations in fronto-temporal dementia and amyotrophic lateral sclerosis (FTD/ALS)

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**Project description:**

FTD is the second most common cause of presenile dementia after Alzheimer’s disease and ALS is the most common form of motor neuron disease. FTD and ALS are now known to be clinically, genetically and pathologically linked. There are no cures for FTD/ALS. Mitochondria and the ER form close physical associations that permit signalling between the two organelles. This signalling regulates many cellular functions including ATP production, Ca2+ homeostasis, ER stress and the unfolded protein response, axonal transport and autophagy. All these functions are damaged in FTD/ALS. Recently, we identified the mechanism by which regions of ER become tethered to mitochondria and showed that this is disrupted in FTD/ALS. Our findings reveal a new therapeutic target for FTD/ALS and have generated much interest being highlighted by MRC and ALZFORUM (http://www.mrc.ac.uk/news/browse/molecular-e28098scaffold-e28099-could-hold-key-to-new-dementia-treatments/ http://www.alzforum.org/news/research-news/no-mam-als-protein-breaks-mitochondria-endoplasmic-reticulum-bond).

Mutations in C9ORF72 cause most familial forms of FTD/ALS. This project is to investigate how mutant C9ORF72 insults affect ER-mitochondria associations and linked functions. It will also involve studies of potential therapeutics that we have identified in collaboration with pharmaceutical companies. The aims are:-

**Year 1/2.** To determine how mutant C9ORF72 insults affect ER-mitochondria associations. We already have data that these disrupt ER-mitochondria associations.

**Year 2.** To determine whether C9ORF72 insults affect Ca2+ homeostasis and ATP production.

**Year 3.** To investigate the mechanisms by which C9ORF72 damages ER-mitochondria associations.

**Year 4.** To study the therapeutic potential of drugs that might correct C9ORF72 induced ER-mitochondria damage.

The work will involve cell and molecular approaches including advanced imaging (super-resolution microscopy), proteomics/mass spectrometry and use of iPS cells.

Two representative publications from supervisors:
