Theme 2

Neurosciences, Psychiatry and Mental Health
1.2 Biomarkers of response to psychological and pharmacological therapies in depression ........................................... 5
2.2 How environmental effects influence genetic risk for Autism Spectrum Disorder: addressing the 2-hit hypothesis in a rodent model. ........................................................................................................... 6
3.2 Evaluation of memory services for people living with Dementia ...................................................................................... 7
4.2 Astrocyte-derived exosomes in Alzheimer’s disease ........................................................................................................... 8
5.2 How well do people understand causal models of health and illness? Improving understanding of complex models of causation for medicine and health studies .............................................................................. 9
6.2 Understanding the neurobiology of psychosis using patient-specific induced pluripotent stem cells 10
7.2 Stress early in life and vulnerability or resilience to the development of psychiatric disorders: focus on epigenetic mechanisms ............................................................................................................. 11
8.2 Modeling of neurodevelopmental disorders in mouse/human ES and iP cells in 2D/3D culture system ........................................................................................................................................................................... 12
9.2 Astrocytes as mediators of synaptotoxic Abeta-tau interactions in Alzheimer’s disease ........................................... 13
10.2 Autophagy control of neurodevelopmental disorders ...................................................................................................... 14
11.2 Targeting mitochondrial signalling as a treatment for Parkinson’s disease .............................................................. 15
12.2 Maternal immune activation and their infants risk for autism .......................................................................................... 16
13.2 Investigating inflammation in blood, adipose and bowel tissues and their relation with psychopathology in obese patients undergoing bariatric surgery ............................................................................... 17
14.2 Anti-nociceptive effects of Brazilian Cnidarian venoms .................................................................................................. 18
15.2 MAPS-PD: Mitochondria, Associated Proteins and Synapses in Parkinson’s disease ..................................................... 19
16.2 Psychotic experiences in the flow of daily life – how does psychological therapy work? ........................................ 20
17.2 Cellular and Molecular mechanisms of Fat4-Dchs1 signalling during neurogenesis ............................................. 21
18.2 Development and psychometric testing of an implementation outcomes toolkit for use in physical health settings ...................................................................................................................................................... 22
19.2 Does maternal mood during pregnancy really affect early brain development? (A Developing Human Connectome Project) ........................................................................................................ 23
20.2 Novel Psychoactive Substance (NPS) initiation and user pathways and progression to alternative NPS or illicit drugs use ........................................................................................................................................ 24
21.2 Identifying novel targets for treating pain in Parkinson’s disease by unravelling the neuro-immune contribution ........................................................................................................................................ 25
22.2 Causal mechanisms of cancer chemotherapy-induced neurotoxicity .............................................................................. 26
23.2 Dynamics of presynaptic function at the first synapse in olfaction .................................................................................... 27
24.2 Investigating the migraine premonitory phase: neural networks regulating migraine initiation ................................ 28
25.2 Dissecting the genetic and environmental components of depression ............................................................................... 29
26.2 Motor relearning in rats and humans after stroke ................................................................................................................. 30
27.2 Childhood gender nonconformity and mental health problems ............................................................................................ 31
28.2 Cognitive Markers of Stigma on Mental Health Outcomes in Sexual Minority Youth ................................................... 32
29.2 Decomposing Emotion Regulation in Autism to Understand Its Role in Co-occurring Psychiatric Disorder .......................................................................................................................................................... 33
30.2 Measuring brain responses to anti-psychotic drugs in humans .......................................................................................... 34
31.2 Mobile App-Based Psychological Treatment for Headache: Development, User Involvement, and Pilot Testing .................................................................................................................................................. 35
32.2 Molecular basis of arthritic pain: roles of HCN ion channels and AT2 receptors ........................................................................ 36
33.2 Cognitive impairment in bipolar disorder: investigating promising new treatments ................................................. 37
34.2 Network asymmetry, callosal development and autistic behaviour ................................................................................... 38
35.2 Stress and early puberty: is the limbic brain the key? ............................................................................................................. 39
36.2 The Impact of Parental Mental Health on Offspring Development ..................................................................................... 40
37.2 Antenatal mental health disorders and infant birth outcomes ............................................................................................ 41
38.2 Brain, behaviour and genetics – why do some people develop neurodevelopmental disorders and other people don’t? ........................................................................................................................................ 42
39.2 Probing ER-mitochondria contact sites in vitro and in vivo: implications for ageing and neurodegeneration .......................................................................................................................................................... 44
40.2 Child mental health and neurodevelopmental disorders in Sierra Leone: a mixed methods study 45
41.2 White Matter Developmental Trajectories in the Neurotypical and Autistic Brain ........................................... 46
42.2 Thalamic inhibition in a mouse model of epilepsy ................................................................. 47
43.2 Creating a human iPSC-derived neuronal model for Bipolar Disorder using CRISPR /Cas9 gene editing ................................................................. 48
44.2 Youth gangs and mental health .................................................................................................. 48
45.2 Targeting α-synuclein-mediated synaptopathy in Parkinson’s disease ........................................ 49
46.2 Enhancing memory in old-age and dementia with visual imagery and neuro-stimulation .......... 51
47.2 Betting on boredom: Examining boredom’s impact on risk-taking and gambling ...................... 52
48.2 Application of routine data to assess the effectiveness and cost-effectiveness of pharmacological therapy for people experiencing psychotic major depression ........................................ 53
49.2 Pharmacological modulation of beliefs and values in people with schizotypy and healthy controls 54
50.2 Identifying target regions for neurofeedback treatment of auditory hallucinations using EEG of experimentally induced and pathological hallucinations. ................................................................. 55
51.2 Self-other control in social interaction: from psychological mechanisms to applications in autism 56
52.2 A feasibility study of training for mental health professionals in ‘Responding to Experienced and Anticipated Discrimination’ (READ) related to mental health ................................................. 57
53.2 Fear of cancer recurrence: understanding and ameliorating psychological distress in the aftermath of cancer ....................................................................................................................... 58
54.2 DETERMINING THE MECHANISM OF ACTION OF FIRST-IN-CLASS EXPERIMENTAL THERAPEUTICS IN PATIENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS ........................................ 59
55.2 Link between pathogen exposure, brain inflammation and disease course in dementia ........... 60
56.2 Acute effects of cannabis with different CBD:THC ratios in dependent users – An experimental study ..................................................................................................................................................... 61
57.2 Improving cognitive control over emotions through neuromodulation in eating disorders .......... 62
59.2 A novel approach to treating Fibromyalgia: Physiotherapy informed by Acceptance and Commitment Therapy (PACT) ........................................................................................................ 64
60.2 Neurodevelopmental trajectories and psychotic experiences: a longitudinal MRI study of young adults ............................................................................................................................................... 65
61.2 Turning the Curse into a Blessing: Using Mindfulness to Reduce Schizophrenia Vulnerability in Psychosis-Prone Individuals. .................................................................................................. 66
62.2 Employment on the pathway to recovery from mental disorders: Developing indicators of occupational functioning in CRIS (Clinical Record Interactive Search application) ............................................. 67
63.2 Using smartphone technologies to investigate the impact of the urban environment in psychosis .. 68
64.2 Development of disorder-specific imaging biomarkers of major depressive disorder ............. 69
65.2 Virtual reality assisted therapy for social difficulties in people with psychosis .......................... 70
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 Dr Sandrine Thuret

When choosing a project from this catalogue in the funding section of the online application form please enter MRCDT2016_Theme2

Deadline for application: 11 December 2016 23:59
Shortlisted candidates will be contacted in mid-January and invited to an interview on one of the two dates in February.

Interviews: 6 and 7 February 2017
The 2017/18 studentships will commence in September 2017.

For further information or queries relating to the application process please contact mrc-dtp@kcl.ac.uk

Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.
1.2 Biomarkers of response to psychological and pharmacological therapies in depression

Co-Supervisor 1: Prof Anthony Cleare  
Research Division/Department or CAG: Psychological Medicine/Centre for Affective Disorders  
E-mail: anthony.cleare@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk  
http://www.kcl.ac.uk/ioppn/depts/pm/research/CfAD/contact/contactcfad.aspx

Co-Supervisor 2: Dr James Stone  
Research Division/Department or CAG: Psychological Medicine/Centre for Affective Disorders  
Email: james.m.stone@kcl.ac.uk

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 randomised clinical trial comparing lithium and quetiapine in those who have not responded to initial antidepressant treatment (n=276)  

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/hair/saliva 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:


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

Co-Supervisor 1: Laura Andreae  
Research Division or CAG: Department of Developmental Neurobiology  
E-mail: laura.andreae@kcl.ac.uk  
Website: https://devneuro.org/cdn/group-overview.php?groupID=84

Co-Supervisor 2: Grainne McAlonan (Clinician)  
Research Division or CAG: Department of Forensic and Neurodevelopmental Disorders  
Email: grainne.mcalonan@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/grainne.mcalonan.html

For translational projects:  
Name of Collaborating Clinician Co-supervisor 2  
Research Division or CAG: Department of Forensic and Neurodevelopmental Disorders  
Email: grainne.mcalonan@kcl.ac.uk

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.
3.2 Evaluation of memory services for people living with Dementia

Co-Supervisor 1 : Dr Matthew Prina  
Research Division or CAG: HSPRD, IOPPN, KCL  
E-mail: matthew.prina@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/matthew.prina.html

Co-Supervisor 2: Dr Vanessa Lawrence  
Research Division or CAG: HSPRD, IOPPN, KCL  
Email: vanessa.c.lawrence@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/en/persons/vanessa-lawrence.html

Project description:

There are 850,000 people living with dementia in the UK, this number is expected to increase as the population ages. Dementia costs society £26 billion annually, making it a public health priority. Memory services play an important role in diagnosing dementia and providing post-diagnosis support to people living with dementia and their families; however, a large scale evaluation of memory services has yet to be conducted. To address this issue, this project will use mixed methods and has the overarching aim of evaluating South London & Maudsley NHS Trust memory services using routine data available on the Clinical Records Interactive Search application (CRIS).

The objectives of this study are to firstly gain a better understanding of care pathways for people living with dementia and subsequent outcomes including hospitalisation, moving to residential care and mortality. The second objective is to contextualise the quantitative findings by conducting focus group interviews with people living with dementia and their carers who have accessed memory services.

This study will provide valuable insight into the role of memory services in the care of people living with dementia and how this can be optimised.

Objectives
Year 1: literature review. Further training in quantitative and qualitative skills. Ethical approval.
Year 2: Data analysis of CRIS
Year 3: Qualitative component of the project
Year 4: final write-up, PhD submission

Both supervisors lead modules on epidemiological, statistical and qualitative methods at KCL. These modules will be available to the selected candidate.

Two representative publications from supervisors:


4.2 Astrocyte-derived exosomes in Alzheimer’s disease

Co-Supervisor 1: Dr Maria Jimenez-Sanchez
Research Division or CAG: Neuroscience
E-mail: maria.jimenez_sanchez@kcl.ac.uk

Co-Supervisor 2: Professor Diane Hanger
Research Division or CAG: Neuroscience
Email: diane.hanger@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Neurodegeneration/diane-hanger-dementia-tauopathies/Index.aspx

Project description:

In Alzheimer’s disease (AD), progressive neuronal degeneration results in memory loss and cognitive and behavioural changes. Pathologically, AD is characterized by the accumulation of extracellular plaques of β-amyloid (Aβ) and intracellular neurofibrillary tangles (NFT) of tau. While neurons have been the focus of research in AD, to design effective therapeutic strategies we need also to determine the effects of glial cells on neurodegeneration and disease progression. The aim of this project is to study how astrocytes protect neurons in AD.

This project will investigate exosomes as a form of communication between astrocytes and neurons in AD.

Year 1: exosomes will be isolated from mouse primary astrocytes. Protein content in exosomes from astrocytes treated with Aβ will be compared with those from untreated healthy astrocytes using SILAC proteomics.

Chaperones are a main constituent of exosomes and chaperones can be transferred between cells using exosomes as vehicles.

Year 2: primary cultures from wild type and transgenic AD mice will be used to determine whether chaperones in astrocyte-derived exosomes impact on tau pathology (phosphorylation, misfolding and aggregation).

Year 3: results will be validated in organotypic brain slice cultures from AD transgenic mice. These enable study of all brain cells in an integrated system and recapitulate the tau pathology observed in AD brains.

Techniques to be used will include biochemical and cell biology, western blotting, mammalian cell culture and use of siRNAs. This project will provide proof of principle for the use of chaperones as therapeutic targets for AD and exosomes as delivery vehicles.

Two representative publications from supervisors:


5.2 How well do people understand causal models of health and illness? Improving understanding of complex models of causation for medicine and health studies.

Co-Supervisor 1: Dr Nicola Byrom  
Research Division or CAG: Psychology  
E-mail: Nicola.byrom@kcl.ac.uk  
Website: [https://kclpure.kcl.ac.uk/portal/nicola.byrom.html](https://kclpure.kcl.ac.uk/portal/nicola.byrom.html)

Co-Supervisor 2: Dr Michael Aitken  
Research Division or CAG: Psychology  
Email: Michael.aitken@kcl.ac.uk  
Website: [https://kclpure.kcl.ac.uk/portal/michael.aitken.html](https://kclpure.kcl.ac.uk/portal/michael.aitken.html)

Project description:

The Problem:  
Reasoning about cause and effect is complex. We cannot observe causation, instead we infer causation from the contingency between events and outcomes. In terms of health, multiple causal factors combine and interact to produce outcomes (illness / wellbeing). Many health problems can be seen as “context-sensitive”; an intervention that works for one person may not work for another. This creates additional challenges for identifying causal relationships, diagnosing and treating illnesses. This is a real and immediate challenge for health research, as the Randomised Control Trial, the gold standard of medical research, fails to account for such individual variation and heterogeneity.

The Solution:  
This project will use an Associative Learning methodology to study causal reasoning with the aims of identifying how we reason about multiple causes, why we struggle to do so, and how information can be presented to facilitate such reasoning. Existing research shows that we can use multiple stimuli (or cues) to predict outcomes, but this ability is influenced by the relative salience of cues and individual difference in attentional factors.

Training:  
This project is suitable for individuals who have studied an introduction to associative learning as psychology students. The project will provide training and experience in computational models of causal reasoning, computer programme and statistical analysis.

Two representative publications from supervisors:  
6.2 Understanding the neurobiology of psychosis using patient-specific induced pluripotent stem cells

Co-Supervisor 1: Deepak P. Srivastava  
Research Division or CAG: Neuroscience  
E-mail: deepak.srivastava@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Cells-behaviour/srivastava-neuronal-circuitry/index.aspx

Co-Supervisor 2: Oliver Howes  
Research Division or CAG: Psychosis  
Email: oliver.howes@kcl.ac.uk

Co-supervisor 3: Prof Jack Price  
Research Division or CAG: Neuroscience  
Email: jack.price@kcl.ac.uk

Project description:

One of the most exciting developments in neuroscience has been the ability to generate neurons from stem cells derived from patients to model the illness: so called ‘disease in a dish’. This has the potential to revolutionise understanding of mental disorders. We are in a position to take this a step further by deriving neurons from patients in whom we have detailed functional imaging as well.

The 22q11.2 syndrome (also known as DiGeorge or VCSF) is a neurodevelopmental disorder where carriers have an increased risk of developing cognitive impairments, autism spectrum disorders and psychiatric disorders, such as schizophrenia. Although we understand the genetic underpinnings of the disorders, our understanding of the underlying and causative neurobiology is still relatively unclear. Recently, neuroimaging studies of individuals carrying the 22q11.2 deletion, have provided us with significant insight into the factors underlining the risk of developing psychosis in these patients. In this project, we propose to build directly on these findings, by using induced pluripotent stem cells derived from individuals carrying the 22q11.2 deletion, and generating specific neuronal cell types. This will allow us the ability to examine in detail the molecular and cellular mechanisms that are disrupted in this disorder. This project will utilize a combination of stem cell biology, in combination with advanced (including live) cell imaging, pharmacological and biochemical approaches to explore the underlying neurobiology of psychosis in this patient cohort.

Two representative publications from supervisors:

Deans et al. 'Psychosis risk candidate ZNF804A localizes to synapses and regulates neurite formation and dendritic spine structure'; Biological Psychiatry, 2015, In Press  

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

Co-Supervisor 1: Carmine M. Pariante
Research Division or CAG: Psychological Medicine
E-mail: carmine.pariante@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/carmine.pariante.html

Co-Supervisor 2: Patricia A. Zunszain
Research Division or CAG: Psychological Medicine
Email: annamaria.cattaneo@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/patricia.zunszain.html

Project description:

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

Two representative publications from supervisors:

Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis.

Interleukin-1β: A New Regulator of the Kynurenine Pathway Affecting Human Hippocampal Neurogenesis.
8.2 Modeling of neurodevelopmental disorders in mouse/human ES and iPS cells in 2D/3D culture system

Co-Supervisor 1: Dr. Setsuko Sahara  
Research Division or CAG: Neuroscience/Department of Developmental Neuroscience  
E-mail: setsuko.sahara@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/devneuro/Research/groups/sahara.aspx

Co-Supervisor 2: Prof. Oscar Marin  
Research Division or CAG: Neuroscience/Department of Developmental Neuroscience  
Email: oscar.marin@kcl.ac.uk  
Website: http://devneuro.org.uk/marinlab/Default.aspx

Project description:

The cerebral cortex plays an important role in cognition, so much so that the impairment of development is thought to underlie numerous neurodevelopmental disorders, including intellectual disability, autism and schizophrenia. Our research focuses on cortical development, in particular the developmental switch of progenitors from self-renewing to neurogenic and gliogenic fates, and the fate determination processes of progenitors that generate the various types of neurons and glia that make up the complex neural circuits of the brain.

In this 3-year project, the student will work on genes previously identified as potential regulators of cortical progenitor differentiation in human 2D and 3D ES differentiation models as well as in vivo mouse transplantation. We find that these genes are strongly associated with several neurodevelopmental disorders, including autism, polymicrogyria and schizophrenia, implicating them in the development of these mental disorders. In order to address the functional importance of the candidate genes described above, the student will employ various techniques, primarily focusing on 1) CRISPR genomic editing of mouse and human cells, 2) 2D and 3D culture of mouse ES/human iPSC-derived neuronal cultures, and 3) transplantation of human iPSC-derived neurons into mouse brains.

Two representative publications from supervisors:


9.2 Astrocytes as mediators of synaptotoxic Abeta-tau interactions in Alzheimer’s disease

Co-Supervisor 1: Dr Wendy Noble  
Research Division or CAG: Neuroscience  
E-mail: wendy.noble@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/wendy.noble.html; http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Neurodegeneration/wendy-noble-neurodegeneration/about-us.aspx

Co-Supervisor 2: Dr Beatriz Perez-Nievas  
Research Division or CAG: Neuroscience  
Email: beatriz.gomez_perez-nievas@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/beatriz.gomez_perez-nievas.html; http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Neurodegeneration/wendy-noble-neurodegeneration/about-us.aspx

Project description:

Synapse loss and cognitive decline in Alzheimer’s disease (AD) are correlated with the activation of astrocytes and mislocalisation of tau from the cytosol to synapses (Perez-Nievas et al., 2013). Aggregates of tau are transmitted across synapses in a neuronal activity-dependent manner, and these spread through diseased brain along anatomically connected pathways. The presence of this tau pathology underlies the synaptic dysfunction and neuron loss observed as AD progresses. Astrocytes are intrinsic components of tripartite synapses and play a role in basal synaptic functions, prompting speculation that astrocytes might play a role in the spread of tau pathology. We have previously shown that astrocytes can modulate the effects of Aβ on tau (Garwood et al., 2011), and this is likely to have important consequences for tau transmission in AD. This project will investigate the involvement of astrocytes in pathological tau transmission and has the following primary objectives:

1. To determine if specific species of tau are taken up by astrocytes in cell culture, and if this is dependent on changes in the local environment (Yr 1)
2. To study the effects of tau uptake on astrocyte morphology and function (Yr 1, 2)
3. To examine changes in communication between astrocytes and neurons following transmission of tau to astrocytes (Yr 2, 3)
4. To identify means to prevent tau transmission as a way of halting progression of AD (Yr 3).

The project will involve training in molecular/cellular neurosciences including preparation of organotypic brain slice cultures, and advanced microscopy techniques.

Two representative publications from supervisors:


10.2 Autophagy control of neurodevelopmental disorders

Co-Supervisor 1: Manolis Fanto  
Research Division/Department or CAG: Department of Basic and Clinical Neurosciences, IoPPN  
E-mail: manolis.fanto@kcl.ac.uk  
Website: https://www.kcl.ac.uk/ioppp/depts/bcn/Our-research/Neurodegeneration/fanto-molecular-mechanisms-neurodegeneration.aspx

Co-Supervisor 2: Heinz Jungbluth  
Research Division/Department or CAG: Department of Basic and Clinical Neurosciences, IoPPN and Child Health Clinical Academic Group  
Email: Heinz.Jungbluth@gstt.nhs.uk  
Website: https://kclpure.kcl.ac.uk/portal/heinz.1.jungbluth.html

Project description:

Autophagy is a key cellular process whose importance has been recognised by the 2016 Nobel Prize in Physiology and Medicine. While autophagy is known for its importance in cancer and neurodegeneration, its role in neural development is still relatively under-studied. However, increasing evidence suggests it is important at several stages.

Vici-Syndrome is a multisystem disorder due to mutation in EPG5, coding for a key regulator of autophagy. Vici patients have severe neurodevelopmental abnormalities and we have assembled an integrated approach to understanding how the mutations in EPG5 lead to defects in neural development.

This project relies on an exceptional multi-model approach focusing on the most recurrent missense mutation in EPG5, which also affects splicing. The student will study developmental defects in Drosophila models, in a mouse model (already generated) and in human fibroblasts to be used for human iPSC cells, to be later differentiated into neurons.

The student will focus on three aspects: neural stem cell renewal and differentiation, neurite extension and assembly of synapses. We will use Drosophila larval nervous systems for fast experiments and test predictions from Drosophila in mouse models and iPSC-derived neurons.

Beyond basic research, this process has a clear translational outlook. A collaboration is ongoing to be able to test in these models already approved drugs that will be selected through a screen on cells performed in the US. Such compounds will be tested in flies and mouse models, to be able to assess the level of organismic rescue and eventual side-effects.

Two representative publications from supervisors:


11.2 Targeting mitochondrial signalling as a treatment for Parkinson’s disease

Co-Supervisor 1: Dr Joseph Bateman  
Research Division or CAG: Wolfson Centre for Age-Related Diseases  
E-mail: joseph_matthew.bateman@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/research/bateman/index.aspx

Co-Supervisor 2: Professor Paul Francis  
Research Division or CAG: Wolfson Centre for Age-Related Diseases  
Email: paul.francis@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/research/neurodegeneration/staff/francispaul.aspx

For translational projects:  
Name of Collaborating Clinician: Professor Dag Aarsland  
Research Division or CAG: Department of Old Age Psychiatry  
Email: dag.aarsland@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/oldage/people/dag-arsland.aspx

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 (Gatt et al. Mov. Dis. 2016), 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 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 Drosophila and mammalian nervous system. They will use powerful genetic and transcriptomic approaches to identify new molecules and pathways activated by mitochondrial dysfunction in Parkinson’s disease. The ultimate aim is to identify new therapeutic targets for Parkinson’s disease.

The objectives are:  
Year 1 (or rotation project): Screening for novel molecules and pathways activated by mitochondrial dysfunction using Drosophila genetics and transcriptomics.  
Year 2: Characterisation and further analysis of novel pathways in Drosophila models.  
Year 3: Manipulation of pathways in human neuronal cellular models of Parkinson’s and analysis in Parkinson’s patient tissue.  
Year 4: Completion of human cell and patient tissue work, writing papers and thesis.

The student will be trained in and use: Drosophila genetics, behaviour and transcriptomics; cell line and primary cell culture studies; western and immunohistochemical analysis, imaging of CNS tissue and image analysis/quantification.

Two representative publications from supervisors:


12.2 Maternal immune activation and their infants risk for autism

Co-Supervisor 1: Professor Declan Murphy
Research Division or CAG: IOPPN, Sackler Institute for Translational Neurodevelopment. Behavioural and Developmental psychiatry CAG
E-mail: declan.murphy@kcl.ac.uk
Website: http://www.eu-aims.eu/the-group/consortium/king-s-college-london/

Co-Supervisor 2: Professor David Edwards
Research Division or CAG: Centre for Developing Brain; Child Health CAG; and Imaging CAG
Email: ad.edwards@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/devneuro/Scientists/David-Edwards.aspx

Project description:

If your first child has autism then the next one has a very increased risk (1:3) of also developing the condition. Parents want to know why that is – and to understand why some children go on to be affected – whereas others do not. To answer that question we need to identify the risk vs protective mechanisms that impact on their infants developmental outcome. We know that the very high risk is likely to be explained by an interaction between genetic and environmental factors. However nobody has directly addressed this issue during foetal and early infant development. Hence we will investigate how maternal physical health (including placental function and inflammatory processes) during pregnancy impacts on foetal brain development as measured using MRI and measures of autonomic function. We will then follow their infants through postnatal development and determine which do, and do not, develop autism. In this way we will be able to identify risk vs protective mechanisms; and so develop interventions that may improve outcome. This work brings a training opportunity to work with world leading experts in human brain development, neonatology, behaviour and mental health. Also it will link to major international networks led by Professors Murphy and Edwards, and to other Sackler Centres (e.g. Columbia, New York).

Two representative publications from supervisors:

Specialization and integration of functional thalamocortical connectivity in the human infant.

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

Co-Supervisor 1: Dr Valeria Mondelli
Research Division or CAG: Psychological Medicine
E-mail: valeria.mondelli@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/valeria.mondelli.html

Co-Supervisor 2: Professor Francesco Rubino
Research Division or CAG: Diabetes
Email: francesco.rubino@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/francesco.rubino.html

Project description:

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

Two representative publications from supervisors:


14.2 Anti-nociceptive effects of Brazilian Cnidarian venoms

Co-Supervisor 1: Professor Paul F. Long  
Research Division or CAG: Institute of Pharmaceutical Science  
E-mail: paul.long@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/paul.long.html

Co-Supervisor 2: Professor Stephen McMahon  
Research Division or CAG: Wolfson Centre for Age Related Diseases  
Email: stephen.mcmahon@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/stephen.mcmahon.html

Project description:

Chronic pain is prevalent, affecting 20% of adults (eg https://www.ncbi.nlm.nih.gov/books/NBK92525/). It is poorly controlled by existing therapies because of limited efficacy or very significant side effects. We know that most chronic pain be relieved – at least temporarily – by local anaesthetic blockade of peripheral nerves. Genetic studies have identified some ion channels that are specifically expressed in sensory neurones that, when mutated, cause either congenital analgesia (total absence of pain sensibility, specifically seen with mutations in Nav1.7) or episodic spontaneous pain. Natural occurring toxins and venoms have been found to have a range of actions on these peripherally expressed ion channels. For instance tetrodotoxins found in the flesh of marine puffer fish block sodium channels in peripheral nerves and block sensory and motor function. Ω-Conotoxin from cone snails is a selective calcium channel blocker that has found limited use (because of side effects) in the treatment of intractable pain. Cnidaria (jellyfish, corals etc.) are amongst the most iconic residents of the sea and are arguably the most primitive of venomous animals, yet their venoms have never been screened for neurotoxic compounds. In this project the student will learn how to culture primary rodent nociceptive neurones and will screen venoms extracted from cnidarians collected in the South Atlantic Ocean in the search for toxins that selectively reduce the excitability of these neurons and in particular target Nav1.7. Depending on interest, the student will then either biochemically isolate and characterise active toxin(s) or explore the potential therapeutic potential of these in whole animals.

Two representative publications from supervisors:


15.2 MAPS-PD: Mitochondria, Associated Proteins and Synapses in Parkinson’s disease

Co-Supervisor 1: Dr. Marios Politis (clinical scientist)
Research Division or CAG: Neuroscience / Basic & Clinical Neuroscience
E-mail: marios.politis@kcl.ac.uk
Website: www.nig-politis.com

Co-Supervisor 2: Dr Eugenii Rabiner
Research Division or CAG: Neuroimaging
Email: ilan.rabiner@imanova.co.uk
Website: www.imanova.co.uk/who-we-are/our-team/item/44-dr-ilan-rabiner

Project description:

The hallmark of Parkinson’s disease (PD) pathology is the aggregation of misfolded a-synuclein in Lewy bodies, which leads to loss of neuronal synapses and consequently, loss of neurons. The underlying mechanisms of neurodegeneration in PD are still unknown and there are no disease-modifying treatments to slow the neurodegenerative processes. A common finding in PD is the progressive mitochondrial dysfunction associated with a-synuclein aggregation, leading to energy deficits and synaptic loss, followed by cell death. Recent advances in positron emission tomography (PET) molecular imaging provide a unique opportunity for direct evaluation of mitochondria and synaptic function in vivo in patients with PD. In this study, we plan to use [18F]BCPP-EF, [11C]SA4503 and [11C]UCB-J PET molecular imaging aiming to investigate the availability of mitochondrial complex I, sigma receptors type-1 and synaptic vesicle glycoprotein 2A, respectively, in a cohort of early, untreated, de novo PD patients. We will compare cortical and subcortical [11C]UCB-J, [11C]SA4503, [18F]BCPP-EF PET binding between early de novo PD patients and a group of gender- and age-matched healthy volunteers, and we will investigate for correlations between mitochondrial and synaptic dysfunction and clinical measures of disease burden. Our study will provide the first in vivo evidence of mitochondrial and synaptic function, and their relevance to disease burden in patients with PD. Our findings may provide novel molecular markers to monitor disease progression and response to treatment, which could also serve as novel targets for drug development of disease-modifying therapeutics aiming to slow the progression of PD.

The PhD student will acquire the following skills & training in the duration of this project:
(a) Clinical and PET imaging applications on Parkinson’s disease
(b) Multi-modal imaging (PET & MRI)
(c) Methodology and analysis of different PET imaging techniques
(d) Cross-platform Neuroimaging skills & training through workshops, congresses and other scientific meetings
(e) Mechanistic interpretation of research finding and in relation to mitochondria, synapses and associated proteins
(f) Writing for publications

Annual over-arching objectives:
Year 1: Background reading / Methodology intense training / Set up of the study and study initiation
Years 2-3: Recruitment / PET scanning / data entry / methodology / initiation of data analysis / parallel neuroimaging techniques training
Year 4: Completion of scanning and data analysis / publications / PhD thesis

Two representative publications from supervisors:

16.2 Psychotic experiences in the flow of daily life – how does psychological therapy work?

Co-Supervisor 1: Dr Emmanuelle Peters  
Research Division or CAG: Psychology and Systems Sciences Division, Psychology Department, Psychosis CAG  
E-mail: Emmanuelle.peters@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/emmanuelle.peters.html

Co-Supervisor 2: Dr Juliana Onwumere  
Research Division or CAG: Psychology and Systems Sciences Division, Psychology Department, Psychosis CAG  
Email: juliana.1.onwumere@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/juliana.onwumere.html

Project description:

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

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

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

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

Two representative publications from supervisors:


17.2 Cellular and Molecular mechanisms of Fat4-Dchs1 signalling during neurogenesis

Co-Supervisor 1: Philippa Francis-West
Research Division or CAG: Craniofacial Development and Stem Cell Biology
E-mail: Philippa.francis-West@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/philippa.francis-west.html

Co-Supervisor 2: Clemens Kiecker
Research Division or CAG: Developmental Neurobiology
Email: clemens.kiecker@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/clemens.kiecker.html

Project description:

Van Maldergem syndrome is characterised by profound intellectual disability and is due to mutations in two protocadherins, Fat4 and Dchs1, that act as a receptor-ligand pair. Defects in humans include periventricular heterotopias, corpus callosum abnormalities and hypoplasia of the cerebellum. Despite the critical role of Fat4-Dchs1 signalling very little is known about how Fat4-Dchs1 regulates neurogenesis. To date, Fat4-Dchs1 signalling has been shown to regulate tangential neuronal migration via the regulation of collective cell polarity and progenitor cell proliferation in the cortex.

Aim 1 (year 1).
Characterisation of the development of the cerebellum and corpus callosum by morphological, histology and gene expression analysis in Fat4 and Dchs1 mouse mutants.

Aim 2 (year 2).
Characterisation of cellular mechanisms of Fat4-Dchs1 signalling through deletion of Fat4 or Dchs1 in specific cell types and in vivo and in vitro genetic mosaic approaches. Live imaging of cell behaviour and migration in tissue slices.

Aim 3 (year 3).

Aim 4 (Year 4).
Characterisation of transcriptional targets, their roles using in vivo and in vitro approaches.

Training: neurogenesis – neuronal stem cell development, neuronal migration, confocal imaging, mouse genetics, molecular biology, cell biology, tissue culture and bioinformatics.

The project will combine the expertise of two supervisors. Professor Francis-West is an expert in Fat4-Dchs1 signalling and Dr Albert Basson is an expert in brain development and using mouse models to study neurogenesis.

Two representative publications from supervisors:


18.2 Development and psychometric testing of an implementation outcomes toolkit for use in physical health settings

Co-Supervisor 1: Professor Nick Sevdalis
Research Division or CAG: Division of Psychology and Systems Sciences
E-mail: nick.sevdalis@kcl.ac.uk
Website: http://www.clahrc-southlondon.nihr.ac.uk/

Co-Supervisor 2: Dr Silia Vitoratou
Research Division or CAG: Division of Psychology and Systems Sciences
Email: silia.vitoratou@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/en/persons/silia-vitoratou(bfd49b60-0174-4c84-802c-e7361a516c94).html

Other supervisors:
Dr Louise Hull, Division of Psychology and Systems Sciences, louise.hull@kcl.ac.uk
Dr Zarnie Khadjesari, Division of Psychology and Systems Sciences, zarnie.khadjesari@kcl.ac.uk

Project description:
Implementing evidenced-based research into practice is a complex, challenging and time consuming task. Implementation of new treatments, practices, and services can be determined by measuring different aspects of the implementation process, termed implementation outcomes (IOs). These include: feasibility, acceptability, appropriateness, adoption, fidelity, implementation cost, penetration and sustainability. Accurate and precise measurement of IOs is vital in developing the evidence-base on effective implementation strategies, but to date there is no agreement on which measures to use. A systematic review of IO measures used in physical health settings, and their psychometric properties, is currently underway, which will identify where we need to develop and validate new measurement scales, before implementing them in physical healthcare settings.

The PhD candidate will receive support and training from internationally recognised experts from the Centre for Implementation Science (NS, LH, ZK), the Biomedical Research Centre (SV) and the IoPPN Psychometrics and Measurement Lab (SV).

The overall aim of this PhD is to develop and psychometrically test an implementation outcome toolkit for use across physical healthcare settings.
- Year 1: Familiarise with implementation science and measurement theory. Conduct a review of approaches to implementing core outcome sets into healthcare settings.
- Year 2: Develop new measurement scales to assess IOs. The scales may refer to practitioners and/or patients/carers. Explore barriers and facilitators to implementing the measures using mixed methods.
- Year 3: Conduct preliminary psychometric testing in physical healthcare settings within King’s Health Partners, through a proof-of-concept study of the new scales.
- Year 4: Conclude the studies and write-up thesis.

Two representative publications from supervisors:

Does maternal mood during pregnancy really affect early brain development? (A Developing Human Connectome Project).

Co-Supervisor 1: Dr Michael Craig PhD FRCOG FRCPsych
Research Division or CAG: Behavioural and Developmental Psychiatry Clinical Academic Group
E-mail: michael.c.craig@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/en/persons/michael-craig(1c1c83e1-d419-4ee1-b37e-8ad083fa9f7f).html

Co-Supervisor 2: Dr Suresh Victor PhD FRCPCH
Research Division or CAG: Child Health Clinical Academic Group; Imaging and Biomedical Engineering Clinical Academic Group.
Email: suresh.victor@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/suresh.victor.html

For translational projects:
Research Division or CAG: Child Health Clinical Academic Group; Imaging and Biomedical Engineering Clinical Academic Group.
Email: ad.edwards@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/en/persons/david-edwards(87af0614-bd26-4dd8-9d6c-722a619e0bdf).html

Project description:
10-15% of pregnant women suffer from depression and/or anxiety, which is associated with increased risk for serious problems in the offspring, including autism and ADHD. The biological basis for this is still poorly understood.

Using in vivo brain imaging we have found associations between antenatal depression/anxiety and key brain networks in infants and primary school children. These findings were important first steps but remain confounded by the postnatal environment (e.g. parenting, early life trauma).

The current project offers you a unique opportunity to better understand this relationship by analysing the effects of antenatal depression on (a) foetal and (b) neonatal brain (i.e. earlier than any previous researchers have been able to study). Your project will be part of the world famous ‘Developing Human Connectome Project’. This is an ambitious, multi-centred program funded by the European Research Council. Its aim is to apply MRI to create a dynamic map of human brain connectivity during early development.

The project will enable us to better fractionate the specific role of antenatal depressed mood on early brain development, helping to determine when to direct specific treatments.

Training in the analysis of neonatal and foetal brain MRI data.

YEAR 1: Assisting in the scanning of mothers and neonates; training in the analysis of neonatal and foetal brain MRI data. YEAR 2: Collection of data. YEAR 3/4: Analysis of findings; Presentation at International meetings; Writing up dissertation / papers.

Two representative publications from supervisors:

20.2 Novel Psychoactive Substance (NPS) initiation and user pathways and progression to alternative NPS or illicit drugs use.

Co-Supervisor 1: Dr Paolo Deluca
Research Division or CAG:
E-mail: Paolo.Deluca@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paolo.deluca.html

Co-Supervisor 2: Prof Colin Drummond
Research Division or CAG:
Email: Colin.Drummond@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/colin.drummond.html

Project description:

Over the past few years there has been increasing recognition from the EMCDDA, International Narcotics Control Board, the scientific community as well as the public and media of the major role that the Internet is now playing in shaping the recreational drugs market. Given the fast changes and opportunities provided with the development of new technologies, this will become an ever increasingly difficult phenomenon to understand, monitor and regulate. This new market is no longer restricted to just those groups of “learned psychonauts”, but is now targeted and marketed to a wider audience. The capacity for marketing novel compounds online is remarkable, and in the past few of years the case of Spice and synthetic cannabinoids, and the rise in popularity of mephedrone and related cathinones have emerged as key examples.

This PhD proposal focuses on studying the key reasons behind the surge in interest in legal highs and will track and user pathways and progression to alternative NPS or illicit drugs use. This will encompass, but not limited to, the monitoring of the web for emerging novel compounds, interviews/surveys with recreational drug users to understand the reasons behind their use of legal highs, an estimation of the prevalence across various sub-groups of the general population and reporting early short and medium term risks associated with their use.

The studentship will be linked with the ongoing EU funded CASSANDRA project.

Two representative publications from supervisors:


21.2 Identifying novel targets for treating pain in Parkinson’s disease by unravelling the neuro-immune contribution.

Co-Supervisor 1: Dr Susan Duty  
Research Division or CAG: Division of Neuroscience, Wolfson Centre for Age-Related Diseases  
E-mail: susan.duty@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/research/Duty-Lab/Duty-Lab.aspx

Co-Supervisor 2: Professor Marzia Malcangio  
Research Division or CAG: Division of Neuroscience, Wolfson Centre for Age-Related Diseases  
Email: marzia.malcangio@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/research/MalcangioLab/Index.aspx

For translational projects:  
Name of Collaborating Clinician: Professor K Ray Chaudhuri  
Research Division or CAG: Basic and Clinical Neuroscience  
Email: ray.chaudhuri@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/ray.chaudhuri.html

Professor Chaudhuri developed the first rating scale for pain in Parkinson’s. He will oversee the clinical pharmacology studies in Year 4, identifying suitable patients and delivering training in pain scoring.

Project description:

Parkinson’s disease is a neurodegenerative condition best known for its movement-related symptoms; tremors, slowed movement and postural instability. However, ‘non-motor’ symptoms are also present including depression, cognitive impairment and pain. Although pain in Parkinson’s impacts significantly on quality of life, it remains poorly understood and inadequately treated by currently-available analgesics. Neuroinflammation is implicated in the neurodegenerative side of Parkinson’s but its role in pain is unexplored. This project investigates the role of neuroinflammation, proposing that microglial activation in descending pathways from the brain modulates pain signalling at the spinal cord level and contributes to pain in Parkinson’s. This collaboration between pre-clinical experts in Parkinson’s (Dr Duty) and pain (Professor Malcangio) and leading clinical expert in pain in Parkinson’s (Professor Chaudhuri) aims to find novel analgesics for Parkinson’s patients.

Yearly Objectives:

• Year 1: Characterise pain responses in rodent models of Parkinson’s to identify the model that best reflects the human condition.
• Year 2: Establish degree of microglial and neuronal activation, and cytokine elevation, in pain pathways in brain and spinal cord from rodent model of Parkinson’s with pain and Parkinson’s patients with characterised pain.
• Year 3: Examine the efficacy of known analgesics (e.g. gabapentin, duloxetine, opioids) and novel microglial inhibitors (e.g. P2X7 receptor antagonists) to resolve pain and pain markers in rodent models of Parkinson’s.
• Year 4: Examine pain responses to different stimuli and their acute amelioration with single dose of different analgesics in Parkinson’s patients.

Skills training: rodent neurosurgery and behavioural assessment; immunohistochemistry; ELISA; clinical pharmacology and pain scoring.

Two representative publications from supervisors:


22.2 Causal mechanisms of cancer chemotherapy-induced neurotoxicity

Co-Supervisor 1: Dr. Sarah Flatters
Research Division: Wolfson Centre for Age-Related Diseases
E-mail: sarah.flatters@kcl.ac.uk
Website: www.kcl.ac.uk/flatterslab

Co-Supervisor 2: Dr. Roland Fleck
Research Division/Department or CAG: Centre for Ultra Structural Imaging
Email: roland.fleck@kcl.ac.uk
Website: http://www.kcl.ac.uk/innovation/research/corefacilities/majorrf/cui/index.aspx

For translational projects:
Name of Collaborating Clinician: Dr. Paul Farquhar-Smith
Research Division or CAG: Royal Marsden Hospital
Email: Paul.Farquhar-Smith@rmh.nhs.uk
Website: https://www.royalmarsden.nhs.uk/our-consultants-units-andwards/consultant-directory/dr-paul-farquhar-smith

Summary of role: Dr. Farquhar-Smith will provide samples from patients with chemotherapy-induced neurotoxicity for laboratory analysis and valuable insight into the patient presentation of CIN

Project description:

Chemotherapy-induced neurotoxicity (CIN) is the major dose-limiting side effect of several first-line cancer chemotherapeutics. 30-70% of patients will develop CIN, with neuropathic pain persisting following chemotherapy. Currently there is no treatment to prevent or treat CIN. Prevention of CIN would be greatly aided with a blood biomarker to identify patients susceptible to CIN 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 CIN identified atypical neuronal mitochondria (Flatters & Bennett 2006). Further work has shown the causal role of ROS and mitochondrial ETC activity to CIN (refs1&2 below). Ongoing work indicates that mtDNA content in blood is altered during CIN. This project will involve a multi-faceted experimental approach using ex vivo cells/tissues from translational rodent models of CIN and human blood samples from CIN patients. Thereby linking cellular mechanisms and whole animal behaviour through to clinical scenario.

Year 1/MRes: Behavioural assessment in rat models of CIN. Quantification of mitochondria/mtDNA in rat blood and tissues.
Year 2/3: Measure oxidative phosphorylation, glycolysis, elemental distribution in sensory neurones during CIN using state-of-the-art technology & ultrastructural EM techniques. Quantification of mitochondria/mtDNA in human blood samples.
Year 4: Evaluate novel therapeutic strategies for CIN 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:

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]

23.2 Dynamics of presynaptic function at the first synapse in olfaction

Co-Supervisor 1: Dr Matthew Grubb  
Research Division or CAG: IoPPN  
E-mail: matthew_grubb@kcl.ac.uk  
Website: www.grubblab.org

Co-Supervisor 2: Professor Juan Burrone  
Research Division or CAG: IoPPN  
Email: juan.burrone@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/devneuro/Research/groups/burrone.aspx

Project description:

The information sent from the sense organs to the brain has to be reliable. In many systems this reliability is achieved by synapses with extremely unusual structural properties. In the olfactory system the transmission of information from sensory neurons in the nose to their first sites of contact in the olfactory bulb is also highly reliable – the sensory neuron terminals have extremely high ‘release probability’. However, these synapses possess no unusual structural properties. This begs the question: how do these normal-looking synapses function so well? One clue may lie in a unique feature of this system: its extreme plasticity. Throughout life, olfactory sensory neurons are continually regenerated via a process of adult neurogenesis in the nasal epithelium, and these newly-generated cells must extend axons to form contacts with postsynaptic partners in the olfactory bulb. Could this constant arrival of new, immature inputs underlie the unusual functional properties of the first synapse in olfaction? Our project will address this question by combining the expertise of both supervisors, coupling the Grubb lab’s experience studying plasticity in olfactory sensory neuron inputs to the olfactory bulb, with the Burrone lab’s experience investigating the dynamics of presynaptic function. You will employ patch-clamp electrophysiological recordings together with cutting-edge functional imaging technology to explore how presynaptic terminals operate under conditions of extreme plasticity in the adult brain.

Two representative publications from supervisors:


24.2 Investigating the migraine premonitory phase: neural networks regulating migraine initiation.

Co-Supervisor 1: Dr Philip R Holland
Research Division or CAG: Basic & Clinical Neuroscience, IoPPN
E-mail: philip.holland@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/philip.holland.html

Co-Supervisor 2: Prof Peter J Goadsby (Collaborating Clinician)
Research Division or CAG: NIHR Biomedical Research Centre
Email: peter.goadsby@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/en/persons/peter-goadsby(daf66c47-179d-421c-af42-7e85d63f935a).html

Project description:
Migraine is one of the most common neurological conditions affecting humans; however our understanding of the mechanisms that lead to its initiation are limited. While head-pain often has dominated research approaches, the majority of patients suffer diverse neurological symptoms including light aversion (photophobia) and sleep disruption during the earliest premonitory phase (prior to pain). As such by studying this phase of the attack using functional neuroimaging we have identified several brain areas likely involved in attack initiation.

The current studentship will build upon this ground-breaking research to further investigate these early brain changes, combining human and preclinical imaging with cutting edge translational neuroscience methodologies.

The student will ideally have some knowledge of MRI techniques although full training will be provided. In addition the student will be trained in rodent surgery, preclinical imaging, in-vivo electrophysiology, pharmacogenetics (genetic manipulation of neural networks) and behavioural assessment.

Specific Objectives are:
Year 1/2:
• To expand on existing knowledge regarding key brain regions activated during the premonitory phase of migraine using functional MRI (0-24 months).
• To develop in vivo and pharmacogenetic tools to allow non-invasive modulation of targeted neural networks identified previously or from objective A in rodents.
• To assess the impact of this modulation of specific neural networks on migraine like phenotypes in rodents.

Year 3/4:
• To investigate the impact of modulation of identified brain regions on neural network activity in the rodent.
• To explore the impact of novel therapeutic targets in rodents to identify suitable translational targets that may act during the premonitory phase to prevent migraine related pain.

Two representative publications from supervisors:

25.2 Dissecting the genetic and environmental components of depression

Co-Supervisor 1: Professor Cathryn Lewis
Research Division/Department or CAG: MRC SGDP Centre & Genetics and Molecular Medicine
E-mail: Cathryn.lewis@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/gmm/departments/mmg/researchgroups/clewis/index.aspx

Co-Supervisor 2: Professor Barbara Maughan
Research Division/Department or CAG: MRC SGDP Centre
Email: Barbara.maughan@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/barbara.maughan.html

For translational projects:
Name of Collaborating Clinician: Dr Andrea Danese
Research Division or CAG: MRC SGDP Centre
Email: andrea.danese@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/andrea.danese.html

Summary of role: Dr Danese will contribute clinical expertise to ensure the hypotheses are well-formulated and enable translation into clinical practice. For example, gene-environment interactions may inform intervention studies for high risk subgroups.

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 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 (Danese) 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:


26.2 Motor relearning in rats and humans after stroke

Co-Supervisor 1: Dr Lawrence Moon
Research Division or CAG: Neurorestoration Group, Wolfson CARD, Guy’s Campus
E-mail: lawrence.moon@kcl.ac.uk
Website: www.lawrencemoon.co.uk/DTC

Co-Supervisor 2: Dr Diana Cash
Research Division or CAG: Neuroimaging Group, Denmark Hill
Email: diana.cash@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/diana.cash.html

For translational projects:
Name of Collaborating Clinician: Dr Stephen Ashford
Research Division or CAG: Cicely Saunders Institute of Palliative Care and Rehabilitation
Email: stephen.ashford@nhs.net
Website: https://kclpure.kcl.ac.uk/portal/en/persons/stephen-ashford(0ffaad18-c07a-41d8-a2a1-925a3fc1b3ce)/biography.html

Summary of role: Dr Ashford will introduce the student to clinical assessment of upper limb function and motor relearning. He has skills in the development and application of psychometrically robust instruments for clinical practice and the evaluation of rehabilitation programmes.

Project description:

Therapies are needed which improve motor relearning after stroke. Dr Moon and Dr Cash have shown that neurotrophin-3 (NT3) improves neuroplasticity and functional recovery after stroke 1,2 and it also reduces spasm after spinal cord injury 3 in rats. Dr Ashford is a clinician with special expertise in upper arm rehabilitation after stroke. He has developed a new scale used for assessing upper arm function following interventions to manage spasticity4,5. With the student, we will seek ways to move NT3 and rehabilitation towards clinical trials.

Objectives and skills training for the student:
Year 1: Clinical: Study principles of rehabilitation and assessment of motor relearning in stroke survivors4,5. Preclinical: Evaluate intensive rehabilitation of grasping in rats by novel in-cage devices after stroke (for methods see 1,2) with behavioural and neurophysiological assessments (see 3).
Year 2: Clinical: Undertake a systematic review of upper limb re-training programmes to identify best practice; Identify a comparator rehabilitation programme for application in a rat model for grasp. Preclinical: Evaluate NT3 in combination with intensive rehabilitation of grasping in rats after stroke.
Year 3: Clinical: Consider through literature review and secondary data analysis, the barriers to retraining the upper limb in stroke survivors to develop a model for clinical practice. Preclinical: Assess molecular and anatomical mechanisms of recovery in rats after NT3 and rehabilitation (see 1-3).

Two representative publications from supervisors:


27.2 Childhood gender nonconformity and mental health problems

Co-Supervisor 1: Dr Katharine Rimes
Research Division or CAG: Psychological Medicine and Integrated Care CAG
E-mail: Katharine.Rimes@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/katharine.rimes.html

Co-Supervisor 2: Dr Artemis Koukounari
Research Division or CAG: Department of Biostatistics
Email: artemis.koukounari@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/artemis.koukounari.html

Project description:

Childhood gender nonconformity - being more like the opposite sex in one’s interests / behaviour - is associated with more symptoms of psychological distress in adulthood. However previous research has generally relied on adult retrospective reports of childhood gendered behaviour, which are open to bias. This project will use a UK birth cohort study to investigate longitudinally the relationship between childhood gender nonconformity and psychological factors, addressing questions such as

1) Do young children higher in gender nonconformity go on to experience more mental health problems? If so, is this partly mediated by experiencing more negative interactions with others (e.g. bullying) and poorer self-image?

2) What are the psychological outcomes in childhood and adulthood for the children with extreme gender nonconformity?

3) Which factors are associated with maternal ratings of gender nonconformity in their child (e.g. birthweight, socioeconomic factors and maternal prenatal and postnatal depression)?

The PhD will also include a qualitative study to gain more in-depth understanding of experience of psychological distress in young people who identify as being high on gender nonconformity.

Skills training: Statistical analysis of longitudinal data, including structural equation models as well as modern mediation methods based on counterfactual theory. Training in statistical packages Mplus and / or STATA, SAS. Qualitative methodology. Testing and developing psychological models of mental health problems. Writing for publication.

Yearly objectives:
2: Continue data analysis. Qualitative study.
3: Complete quantitative and qualitative studies. Write-up and publish results.

Two representative publications from supervisors:


28.2 Cognitive Markers of Stigma on Mental Health Outcomes in Sexual Minority Youth

Co-Supervisor 1: Dr Qazi Rahman  
Research Division or CAG: Division of Psychology & Systems Sciences (IoPPN)  
E-mail: qazi.rahman@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/qazi.rahman.html

Co-Supervisor 2: Dr Helena Zavos  
Research Division or CAG: Division of Psychology & Systems Sciences (IoPPN)  
Email: helena.zavos@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/helena.1.zavos.html  
http://www.kcl.ac.uk/ioppn/depts/mrc/research/editlab/people/helena-zavos.aspx

Project description:

This project aims to quantify the cognitive signature of social stigma on mental health outcomes in young lesbian, gay, and bisexual (LGB) people (sexual minorities). LGB people are twice as likely as heterosexuals to suffer common mental health disorders (depression, anxiety, suicide) and this disparity is greater for LGB young people. Sexual minorities constitute approximately 4% of the population, and youth is a critical period for forming social identity; thus this disparity constitutes a major public health burden. Minority stress theory proposes that social stigma (e.g., antigay violence) causes this health disparity. However, the theory over simplifies the types of stigma and does not take account of the way the brain reacts to this stigma (e.g., through differences in cognition). This study will 1) develop novel experimental tasks to quantify general and group-specific (i.e., LGB specific) cognitive and emotional processing biases in LGB youth with and without psychological distress and 2) test their relationship to different types of stigma (enacted versus self-stigma). The student will receive training in complex statistical analysis, experimental methods, and working with underserved populations (through charity partners). The student will be trained in two experienced research groups in the IoPPN (EDIT Lab and LGBT Health). The project will significantly improve our understanding of how stigma cascades into poorer mental health through cognitive mechanisms more than any single discipline or method can do alone: cognitive experiments can reveal mechanisms that are potentially modifiable while social theory about stigma provides much-needed real-world validity for psychological constructs.

Two representative publications from supervisors:


29.2 Decomposing Emotion Regulation in Autism to Understand Its Role in Co-occurring Psychiatric Disorder

Co-Supervisor 1: Professor Emily Simonoff  
Research Division or CAG: Child and Adolescent Mental Health  
E-mail: Emily.Simonoff@kcl.ac.uk

Co-Supervisor 2: Professor Tony Charman  
Research Division or CAG: Child and Adolescent Mental Health  
Email: tony.charman@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/tony.charman.html

Project description:

People with autism spectrum disorders (ASD) have high rates of multiple, additional psychiatric disorders. These include anxiety, oppositional defiant disorder and ADHD. Many also experience aggression, severe noncompliant behaviour and/or self-injury – challenging behaviour. Emerging evidence suggests emotional regulation (ER) may be a particular problem for people with ASD and this raises the possibility that it may be an underlying mechanism for the high rates of psychopathology.

This PhD will investigate ER in people with ASD to understand whether variation within ASD is associated with psychopathology and which types. It will also compare the cognitive and biological underpinnings of ER in people with ASD and typical controls in order to determine whether there are qualitatively or quantitatively different processes in those with ASD.

The student will analyse data collected in several ASD cohorts: SNAP a population-based cohort of individuals with ASD initially seen at age 12, 16 and 23 years; QUEST a community sample initially studied at age 4 and followed up twice during adolescence. The predictors of dysregulated behaviours will be studied with longitudinal modelling and experimental tasks designed to challenge ER. Based on these initial findings, the student will then develop specific hypotheses and experiments to extend our understanding of the role of ER in ASD and associated psychopathology.


Two representative publications from supervisors:


30.2 Measuring brain responses to anti-psychotic drugs in humans

Co-Supervisor 1: Prof. Sukhi Shergill  
Research Division or CAG: King’s Centre for CNS Therapeutics  
E-mail: sukhi.shergill@kcl.ac.uk  
Website: www.kcl.ac.uk

Co-Supervisor 2: Dr. Isabella Premoli  
Research Division or CAG: Clinical Neuroscience  
Email: isabella.premoli@kcl.ac.uk  
Website: http://epilepsy-london.org

Project description:

A highly relevant challenge in psychiatry is to predict whether a patient will respond to pharmacological therapy. Despite the wide range of antipsychotic drugs, treatment is unsuccessful in 30% of cases. Treatment failures may occur because there is insufficient drug in the brain to exert a therapeutic effect, or because the pharmacological effect has no relevant therapeutic effect. We have recently demonstrated that the combination of transcranial magnetic stimulation and electroencephalography (TMS-EEG) is a powerful tool to measure pharmacological effect of drugs in the human brain. We identified TMS-EEG fingerprints associated with inhibitory (i.e. GABAergic) neurotransmission and with anti-epileptic activity. The PhD candidate will measure TMS-EEG responses before and after the intake of anti-psychotic drugs (clozapine and olanzapine, amisulpiride) in healthy volunteers. In a second step, he/she will measure TMS-EEG responses in patients with schizophrenia on monotherapy with these medications. We hypothesise that patients who are well-controlled by treatment will show a similar profile to the TMS-EEG fingerprint. In contrast, patients who are poor responders will show a different TMS-EEG response.

This project aims to reveal new biomarkers of anti-psychotic drug action, which associate with drug responsiveness in patients with schizophrenia. Finally, it will identify candidate biomarkers that could predict long-term success of treatment soon after it is commenced.

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

Year 1 – healthy volunteer data collection  
Year 2 – patient data collection  
Year 3 – analysis and write up

Two representative publications from supervisors:


31.2 Mobile App-Based Psychological Treatment for Headache: Development, User Involvement, and Pilot Testing

Co-Supervisor 1: Professor Lance McCracken
Research Division or CAG: Psychological Medicine
E-mail: Lance.McCracken@kcl.ac.uk

Co-Supervisor 2: Professor Leone Ridsdale
Research Division or CAG: Basic & Clinical Neurosciences
Email: Leone.Ridsdale@kcl.ac.uk

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 app-based treatment (with therapist support) 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: 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:


32.2 Molecular basis of arthritic pain: roles of HCN ion channels and AT2 receptors

Co-Supervisor 1: Professor Peter A McNaughton FMedSci
Research Division/Department or CAG: Wolfson CARD
E-mail: peter.mcnaughton@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/about/people/staff/McNaughtonPeter.aspx

Co-Supervisor 2: Dr Jon Robbins
Research Division/Department or CAG: Wolfson CARD
Email: jonathan.robbins@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/research/rcs/staff/robbinsjon.aspx

Project description:

Pain in rheumatoid arthritis and osteoarthritis is a significant clinical problem and a major target for the pharmaceutical industry. A scientific approach to the development of new and more satisfactory analgesics is hampered by our lack of knowledge of the molecular causes of arthritic pain.

In this PhD project we will investigate two major contributors to arthritic pain, for which we have evidence from studies in our group: HCN2 ion channels, and AT2 receptors. In work leading up to the application we have shown that HCN2 ion channels play a critical role in pain. We also have evidence that AT2 receptors may be coupled to HCN2 ion channels and therefore may also be important in arthritic pain. We aim to establish a clear role for HCN2 ion channels in arthritic pain, using mouse models of arthritis and a combined pharmacological approach to inhibit HCN2 ion channels using selective blockers, and a genetic approach to selectively delete HCN2 ion channels in pain-sensitive nerve fibres. We will then go on to investigate whether AT2 receptors modulate HCN2 ion channels and whether blockers of the AT2 receptor offer some relief in mouse models of arthritic pain.

Year 1: Develop mouse models of arthritis. Test blockers of HCN2 and AT2.
Year 2: Develop mouse strains with HCN2 and AT2 genetically deleted. Patch clamp of isolated sensory neurons
Year 3: Test arthritic models and patch clamp neurons from genetically deleted mice.

Skills: Mouse behavioural models, in vitro electrophysiology, mouse genetic models.

Two representative publications from supervisors:


33.2 Cognitive impairment in bipolar disorder: investigating promising new treatments

Co-Supervisor 1: Prof Allan Young
Research Division or CAG: Academic Psychiatry/Psychological Medicine and Integrated care CAG
Email: allan.young@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/allan.young.html

Co-Supervisor 2: Dr Paul Stokes
Research Division or CAG: Academic Psychiatry/Psychological Medicine and Integrated care CAG
E-mail: paul.r.stokes@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paul.r.stokes.html

For translational projects: Both Prof Young and Dr Stokes are clinical academic psychiatrists and are consultant psychiatrists with the National Affective Disorders Service, South London and Maudsley NHS Foundation Trust.

Project description:

Bipolar disorder is one 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 excellent translational skills training in the use of pharmacological functional MRI (fMRI) to examine experimental medicine treatment effects on brain function 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 in the assessment of cognitive impairment in bipolar disorder, systematically review studies in this area, and where possible gain expertise in recruiting and assessing research participants; the year 2 objectives are to develop expertise in the analysis of cognitive fMRI and clinical trial behavioral data; the year 3 objectives are to consolidate skills, present 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 pharmacological 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
34.2 Network asymmetry, callosal development and autistic behaviour

Co-Supervisor 1: Professor Marco Catani
Research Division or CAG: FANS
E-mail: m.catani@iop.kcl.ac.uk
Website: www.natbrainlab.com

Co-Supervisor 2: Professor Uwe Drescher
Research Division or CAG: Developmental Neurobiology
Email: uwe.drescher@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/devneuro/Research/groups/drescher.aspx

Project description:

Failure to develop neurotypical asymmetry has been postulated to underpin neurodevelopmental conditions such as Autism Spectrum Disorder (ASD). Indeed, loss of normal interhemispheric asymmetry mediated by the corpus callosum is one of the most replicated findings in ASD, with those white matter (WM) networks showing the greatest degree of lateralisation most affected (e.g. arcuate fasciculus). This PhD will investigate the structural connections of the corpus callosum (CC) and association white matter in mice and humans with the aim to test: (1) if non-typical development of the CC disrupts development of association pathways in mice; (2) if deficits of the CC correlate with those in association pathways of developing humans with ASD and if such deficits correlate with symptoms (3) investigate using the mouse as a model system a possible correlation between corpus callosum defects and ASD-like phenotypes.

The candidate will be trained in imaging methods to study connections both at the micro- (e.g. light sheet microscopy, CLARITY technique) and macrostructural level (MRI diffusion tractography).

Phase 1 aims to test the hypothesis that non-typical development of the CC disrupts development of association pathways. Given the experimental control they afford, mouse models provide a useful way to test this. Recently techniques have been developed to visualize axonal trajectories from the intact brain with unprecedented resolution (CLARITY) which – when combined with light sheet microscopy – enables an qualitatively better data collection with orders of magnitude higher than previous techniques. In the first phase the student will establish the CLARITY technique for wild type mice and its analysis using light sheet microscopy, focusing on CC formation and axonal projection pattern to its target structures.

Phase 2 aims to test the hypothesis that deficits seen in the CC of children with ASD correlate with those of association pathways, and to test if the intensity of deficits correlate with ASD symptoms. In parallel, the student will investigate now the formation of CC tracts in mice mutant in candidate autism genes (including neurexin1A, chd8).

Phase 3 aims to test the hypothesis that deficits seen in the CC of adults with ASD correlate with those of association pathways, and to test if the intensity of deficits correlate with ASD symptoms. The student will investigate the most promising mouse models further and will investigate in depth the innervation patterns of the neural structures which are connected in the CC.

Two representative publications from supervisors:


35.2 Stress and early puberty: is the limbic brain the key?

Co-Supervisor 1: Professor Kevin O’Byrne
Research Division or CAG: Women’s Health
E-mail: Kevin.o’byrne@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/wh/index.aspx

Co-Supervisor 2: Dr. Susan Pawlby
Research Division or CAG: Psychological Medicine
Email: susan.pawlby@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/pm/research/perinatal/index.aspx

Project description:

Life stress is associated with early puberty in girls which is a risk factor for anti-social behaviour, anxiety and other mental health disorders in addition to gynaecological disorders and cancers consequent to earlier sexual activity and first pregnancy. The combination of supervisors, Professor O’Byrne with expertise in neurobiology of puberty and stress animal models and Dr. Pawlby a child psychologist with vast research experience and comprehensive databases on child development will provide a unique environment and opportunity for PhD training in the neural mechanisms underlying precocious puberty and clinical sequelae. This project will test the hypothesis that the amygdala, a key limbic brain structure controlling emotional behaviour, stress responsivity and puberty, is a nodal site for corticotrophin-releasing factor (CRF) and related stress neuropeptide induced modulation of the key reproductive kisspeptin-gonadotrophin releasing hormone (GnRH) signalling system which is critical for timing of puberty.

Objectives:

MRes project: Surgery and experimental approaches necessary for measurement of plasma LH and gene expression (in situ hybridization/PCR) in brain tissue in models of advanced puberty.
Year 1 PhD: Determine expression profile of CRF and CRF receptors in the amygdala during the pubertal transition and correlate with kisspeptin and GnRH expression and LH pulses in advanced puberty.
Years 2/3 PhD: Functional studies examining the effects of intra-amygdala administration of CRF agonists and antagonists and neurotoxic lesions on the timing of puberty and anxiety behaviours. Analysis of clinical data on influence of childhood/maternal life events, stressors and psychopathology on pubertal development.

Two representative publications from supervisors:


The Impact of Parental Mental Health on Offspring Development

Co-Supervisor 1: Tom McAdams  
Research Division or CAG: SGDP Centre, IoPPN  
E-mail: tom.mcadams@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/mrc/research/editlab/people/tom-mcadams.aspx

Co-Supervisor 2: Fruhling Rijsdijk  
Research Division or CAG: SGDP Centre, IoPPN  
Email: fruhling.rijsdijk@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/fruhling.rijsdijk.html

Project description:

A family history of mental health problems 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, suggesting that being raised by a parent with mental health problems is a risk factor for the development of problems in offspring. Alternatively, it is well known that mental health problems are under genetic influence. As such, genetic transmission may explain the intergenerational transmission of mental health phenotypes. 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.

You will use data from studies of twins with children, and from Scandinavian population registries, to understand the relative importance of genetic and environmental routes of transmission in the intergenerational transmission of psychopathology. Further potential opportunities involve exploring the utility of multigenerational genomic datasets, and becoming involved in data collection in the children-of-TEDS project, a children-of-twins study based at the IoPPN.

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:


37.2 Antenatal mental health disorders and infant birth outcomes

Co-Supervisor 1: Professor Louise Howard  
Research Division: Section of Women’s Mental Health, Health Services and Population Research, Institute of Psychiatry, Psychology and Neuroscience  
CAG: Psychological Medicine and Women’s Health  
E-mail: louise.howard@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/hspr/research/CEPH/wmh/Staff/Professor-Louise-Howard.aspx

Co-Supervisor 2: Dr Dharmintra Pasupathy  
Research Division: Women’s Health  
CAG: Women’s Health  
Email: dharmintra.pasupathy@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/en/persons/dharmintra-pasupathy(d866bb79-0651-49ed-b6f3-ee6e00c3d2e1)/biography.html

Project description:

There is increasing evidence that many women experience mental health problems during pregnancy. Antenatal depression is associated with adverse outcomes in their infants and children, including low birth-weight and small for gestational age babies.

Evidence on the link between other antenatal mental disorders with birth outcomes is less clear. Recent research has shown an association between antenatal anxiety and increased risk of low birth-weight and preterm birth. Mental health problems during pregnancy such as anorexia nervosa and schizophrenia have also been associated with low birth-weight. However, relatively little is known about other mental health problems such as personality difficulties.

This PhD aims to investigate the association between antenatal anxiety disorders and other mental disorders with infant birth outcomes (birth-weight, gestational age, apgar scores).

The student will use a dataset from the WENDY cohort study (http://www.kcl.ac.uk/ioppn/depts/hspr/research/CEPH/wmh/projects/A-Z/WENDY-Well-being-in-pregnancy-in-an-inner-city-maternity-service.aspx), which is a representative sample of women recruited soon after their antenatal booking appointment. In year 1 the student will carry out a systematic review of antenatal mental disorders and birth outcomes; the student will then collect data from maternity notes and add this to the pregnancy cohort dataset. The student will be encouraged to develop their own additional ideas; for example a qualitative study on the experiences of services in women with anxiety disorders or personality problems. Data will be cleaned and analysed (year 2) and submitted for publication in a high impact journal (year 3). The student will gain skills in systematic reviewing, data collection and cleaning, advanced epidemiological skills and statistical analysis.

Two representative publications from supervisors:


38.2 Brain, behaviour and genetics – why do some people develop neurodevelopmental disorders and other people don’t?

Co-Supervisor 1: Eva Loth, PhD  
Research Division or CAG: Behavioural and Developmental Psychiatry  
E-mail: eva.loth@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/eva.loth.html

Co-Supervisor 2: Eileen Daly, PhD  
Research Division or CAG: Behavioural and Developmental Psychiatry  
Email: eileen.daly@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/eileen.daly.html

For translational projects:  
Name of Collaborating Clinician: Dr Clodagh Murphy, MRCPsych, PhD  
Research Division or CAG: Behavioural and Developmental Psychiatry  
Email: clodagh.m.murphy@kcl.ac.uk  
Website: www.national.slam.nhs.uk/about-us/our-experts/dr-clodagh-murphy

Summary of role: Clinical Scientist (Consultant Child & Adolescent Psychiatrist, Clinical Lead, Behavioural Genetics and Adult Autism Service, The Maudsley Hospital and Hon Consultant Psychiatrist, 22q Clinic, Great Ormond Street Hospital)

Project description:

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are common, complex and costly neurodevelopmental disorders that are impacted on by a variety of genes. However, some individuals with rare single gene disorders, such as 22q11.2 deletion syndrome (22q11.2DS) and Phelan McDermid Syndrome (PMS), have a significantly increased risk (30-50%) of developing ASD, ADHD and other neuropsychiatric disorders, while others remain well. This presents an intriguing opportunity to identify factors that increase the risk for - or protect - an individual from developing neurodevelopmental disorders.

This project will study individuals with 22q11.2DS and PMS across the lifespan to investigate neurobiological, genetic and environmental interactions that may contribute to some people developing neurodevelopmental and neuropsychiatric disorders, and others remaining well.

Skill training opportunities include: MRI brain imaging analyses across the lifespan (structural/functional MRI (sMRI, fMRI), DTI from infancy to adulthood), EEG, structured clinical assessment of ASD/ADHD, neuropsychology (cognitive testing and eye-tracking).

In year one, the successful candidate will be trained in clinical diagnostic assessments and neuroimaging acquisition. In years two, three & four, the candidate can choose training in up to two neuroimaging analyses methods, (e.g., EEG, structural/functional MRI, DTI/eye-tracking), and will closely link with ongoing large-scale European multi-centre projects investigating autism and related genetic disorders.

All supervisors will contribute to training in scientific writing, data presentation/dissemination. Additional contributions include: Dr Daly: sMRI/fMRI/DTI data acquisition and analysis, neuropsychological assessment, Dr Loth: EEG/eye-tracking data acquisition and analysis, neuropsychological assessment, Dr Murphy: sMRI/fMRI data acquisition and analysis, ASD/ADHD/ clinical assessment

Two representative publications from supervisors:


39.2 Probing ER-mitochondria contact sites in vitro and in vivo: implications for ageing and neurodegeneration.

Co-Supervisor 1: Alessio Vagnoni
Research Division or CAG: Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, IoPPN.
Present address: MRC Laboratory of Molecular Biology, Division of Cell Biology, Cambridge.
I will move to King’s in early 2017 as a tenure-track group leader.
E-mail: avagnoni@mrc-lmb.cam.ac.uk
Website: http://www.neuroscience.cam.ac.uk/directory/profile.php?avagnoni

Co-Supervisor 2: Chris Miller
Research Division or CAG: Department of Basic and Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, IoPPN.
Email: chris.miller@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Neurodegeneration/miller-cell-biology-als/about-us.aspx

Project description:
Many functions damaged in neurodegenerative diseases are regulated by specialised contact sites between the endoplasmic reticulum (ER) and the mitochondria. Restoring damaged ER–mitochondria associations is therefore an exciting therapeutic target to ameliorate neuronal functions in disease.
The protein complexes responsible for tethering ER and mitochondria in Drosophila are not known. By combining genetic manipulations in the fruit fly with a new in vivo functional assay and a validation step in mammalian primary cultures, the project aims to identify novel factors and/or modulators involved in tethering ER and mitochondria. Training will be provided throughout the PhD by both supervisors.

During Year 1 the candidate will perform an ethyl methanesulfonate screen in Drosophila to recover mutants that impact on the ER-mitochondria interaction. This approach involves producing transgenic flies to set up the screening platform. The desired phenotype will be assayed by Split-EGFP assay or ChiMERA method.
Target validation will be performed by tissue specific RNAi and CRISPR genome engineering.

During Year 2 the candidate will undertake a biochemical and functional characterisation of the validated targets. This will be performed in living flies and validated in mammalian neuronal primary cultures.

In Year 3 the candidate will test the relevance of the molecular target for neurodegeneration and ageing. This will be assayed by chronic and acute modulation of ER-mitochondria interactions in wild type and Drosophila disease models.

In Year 4 the student will consolidate the results obtained to then write a manuscript(s) for publications. He/she will write up the PhD thesis and submit.

Two representative publications from supervisors:
40.2 Child mental health and neurodevelopmental disorders in Sierra Leone: a mixed methods study

Co-Supervisor 1: Prof Martin Prince
Research Division or CAG: IoPPN/ Division of Psychology & Systems Sciences/ Department of Health Services & Population Research
E-mail: martin.prince@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/martin.prince.html

Co-Supervisor 2: Dr Rosa A Hoekstra
Research Division/Department or CAG: IoPPN/ Division of Psychology & Systems Sciences/ Department of Psychology
E-mail: Rosa.Hoekstra@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/rosa.hoekstra.html

Project description:

Conflict and disasters impact disproportionately on low income countries. Sierra Leone has been burdened by a 12 year civil war and a recent Ebola-virus outbreak. Such ‘population shocks’ with their attendant mortality, morbidity and societal disruption exacerbate chronic effects of poverty, limited resources, and poor governance. Half of Sierra Leone’s population are children; whilst mental health research has focused on child soldiers, little attention has been given to the overall burden of child and adolescent mental health (CAMH) problems.

In collaboration with King’s Sierra Leone Partnership, this project aims to provide an in depth study of child mental health and neurodevelopmental problems, to inform policy and practice and development of local CAMH services.

The project comprises:
• A quantitative epidemiological study estimating the prevalence of mental health and neurodevelopmental disorders in children and identifying the risk and protective factors related to these disorders.
• A nested qualitative study to provide an in-depth understanding of the recognition of mental health and neurodevelopmental disorders in children, and the challenges experienced by families caring for affected children.

After completion of the MRes the candidate will spend 6 months at IoPPN to prepare the fieldwork in Sierra Leone and acquire essential skills in qualitative and quantitative research methodology. The next 18 months will be primarily spent in Sierra Leone collecting and analysing data (with local research site visits from the supervisors); the final year, back at the IoPPN, will focus on final data analyses and completion of the PhD thesis.

Two representative publications from supervisors:


41.2 White Matter Developmental Trajectories in the Neurotypical and Autistic Brain

Co-Supervisor 1: Dr. Flavio Dell’Acqua  
Research Division or CAG: Division of Academic Psychiatry - Dept. of Forensic and Neurodevelopmental Sciences  
E-mail: flavio.dell’acqua@kcl.ac.uk  
Website: https://www.scopus.com/authid/detail.uri?authorId=24757840500  
https://kclpure.kcl.ac.uk/portal/flavio.dellacqua.html

Co-Supervisor 2: Dr. Andre Marquand  
Research Division or CAG: Division of Neuroscience - Dept. of Neuroimaging  
Email: andre.marquand@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/en/persons/andre-marquand.html

Project description:

In the UK, approximately 1% of the population has Autism spectrum disorder (ASD), which makes it one of the most common neurodevelopmental disorders. Despite the prevalence of ASD treatment options for the core deficits remain both ineffective and insufficient. The ability to classify individuals into stratified subpopulations would ultimately lead the way for advancing drug discovery and development.

To be able to achieve this, it is necessary to move away from classical case-control studies and develop novel methods that quantify how atypical neurodevelopment in ASD deviates from normality. The PhD candidate will construct normative models of typical development, using neuroimaging data collected from the EU-AIMS project. During the PhD, the candidate will apply and refine state-of-the-art, advanced methods to pre-process, analyse and integrate multi-modal (diffusion, structural and functional) imaging data. Using these data-driven models of typical development, the candidate will examine the full continuum of ASD and develop methods to classify atypical variation. These new procedures will be subjected to cross-validation, using independent datasets already available at the IoPPN (e.g. MRC-AIMS male and female datasets). To conclude, this project will devise innovative approaches to identify biological subgroups in ASD and path the way for enhanced drug development.

Objectives over the 4 years: The first and second year of the PhD will comprise of neuroimaging pre-processing, quality control, analysis and publishing results of typical neurodevelopment. The third and fourth year will focus on researching atypical neurodevelopment, cross-validation and thesis write-up.

Skills Training: The candidate will receive specialised training in data processing and analysis using advanced diffusion imaging modalities (including Spherical Deconvolution Tractography and novel tract specific indices) combined with state of the art multivariate and machine learning statistical analyses.

Two representative publications from supervisors:


42.2 Thalamic inhibition in a mouse model of epilepsy

Co-Supervisor 1: Dr Alessio Delogu  
Research Division or CAG: Neuroscience  
E-mail: alessio.delogu@kcl.ac.uk  
Website: [https://kclpure.kcl.ac.uk/portal/en/persons/alessio-delogu(2332d1f4-936a-4976-ab2a-83729c479283)/biography.html](https://kclpure.kcl.ac.uk/portal/en/persons/alessio-delogu(2332d1f4-936a-4976-ab2a-83729c479283)/biography.html)

Co-Supervisor 2: Prof Deb K Pal  
Research Division or CAG: Neurosciences  
Email: deb.pal@kcl.ac.uk  
Website: [www.childhood-epilepsy.org](http://www.childhood-epilepsy.org)

Project description:

The thalamus plays a critical role in defining the pattern of cortical excitation. Different activity modalities of GABAergic neurons in the thalamus explain asynchronous firing of cortical networks, typical of the wake state and the generation of synchronous oscillations, as seen when falling asleep and during deep sleep. Abnormal inhibitory function may lead to the occurrence of a pathogenic type of cortical activity that causes epilepsy. The project will focus on a mutant mouse line with impaired migration of GABA progenitors during early development. These mice are affected by early onset epilepsy and lack local thalamic interneurons, particularly in the visual thalamus. The student will perform cortical EEG recordings to monitor epileptiform discharges and seizures and correlate these with the sleep-wake cycle. Behavioural paradigms will be used to test if photic stimulation, loud sounds and stress can trigger the epileptic response. At the circuit level the project will use a reporter cre-line to selectively target local thalamic inhibitory neurons and study their connectivity and function with viral-based new technologies (trans-synaptic rabies, optogenetics, DREADDs). At the cellular level the project will look at the function of electrical junctions and their regulation by inhibitory afferents in the onset of epileptic seizures. Other techniques include laser microscopy, immunohistochemistry and mouse behavioural assays.

Two representative publications from supervisors:


43.2 Creating a human iPSC-derived neuronal model for Bipolar Disorder using CRISPR /Cas9 gene editing

Co-Supervisor 1: Robert Hindges  
Research Division or CAG: Centre for Developmental Neurobiology  
E-mail: robert.hindges@kcl.ac.uk  
Website: https://devneuro.org/cdn/group-overview.php?groupID=65

Co-Supervisor 2: Jack Price  
Research Division or CAG: Neuroscience  
Email: Jack.Price@kcl.ac.uk

Project description:

Bipolar disorder is a common and severe mental disorder causing dramatic mood swings from mania to depression. The exact causes are not known, but family and twin studies strongly suggest a significant genetic component in the aetiology of the disorder. A recent genome-wide association study has identified a genetic variation in the gene locus of teneurin 4 (ODZ4) as a highly significant susceptibility factor. Teneurins are large cell adhesion molecules expressed neuronal subpopulations in the brain. We have recently shown a critical role for teneurin 3 to establish the correct functional connectivity in the brain and found a strong synaptic localisation of all teneurin proteins, including Ten4, at synapses.

Functional and structural brain imaging of bipolar patients carrying the ODZ4 mutation have been inconclusive. However, no study has investigated so far the consequences of this intronic mutation in an in vitro system using human neurons. With this project we intend to re-create the tenm4 mutation in human iPSC-derived neurons through CRISPR/Cas9 gene-editing technology (Year 1). With this in vitro system we will assess in detail tenm4 protein localisation and gene expression levels (year 1& 2), as well as characterise the possible impact on neuronal structure, synapse formation and network connectivity (Year 2, 3 and possibly 4). Our findings have the potential to add important information on the molecular and cellular mechanisms underlying the aetiology of this mental disorder.

Two representative publications from supervisors:


44.2 Youth gangs and mental health

Co-Supervisor 1: Professor Craig Morgan
Research Division or CAG: Psychology and Systems Sciences
E-mail: craig.morgan@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/craig.morgan.html

Co-Supervisor 2: Dr. Stephani Hatch
Research Division or CAG: Academic Psychiatry
Email: stephani.hatch@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/stephani.hatch.html

Project description:

Violence is a major cause of mental health problems (1,2). In London, gang violence contributes to approximately 40% of shootings and 17% of stabbings (3). The Home Office has identified eight South London boroughs needing support with youth gang violence (4). Between 2009-2010 39% of gang-related offending in Southwark involved adolescents. Understanding adolescent gang membership is essential.

Epidemiological studies in adults suggest that mental health problems (e.g. psychosis) are associated with violence (5–7) and are more common among male gang-members (vs. violent non-gang members and non-violent men) (8). However, there is a dearth of literature on gang membership and adolescent mental health problems. A key issue that remains is determining the direction of any associations (i.e. do adolescents with mental health problems gravitate toward gangs; or does gang membership contribute to problems) and the mechanisms involved.

This project will capitalise on an established school-based cohort study of adolescent mental health in South London, REACH (n=~4000). The project aims to:
• Establish, in a large representative sample, the prevalence of gang membership (including differences across gender, age, ethnicities)
• Investigate the temporal relationship between mental health problems and gang membership
• Investigate how personal (e.g. self-beliefs), school (e.g. engagement) and community (e.g. social support) factors combine, over time, to influence gang membership
• Qualitatively investigate (in a subsample) the psychological processes that may underpin gang membership (e.g. moral disengagement).

Training: mixed methods research skills and advanced statistics, including longitudinal data analysis.

Objectives
• Y1-2: data collection, training
• Y3: data analysis, synthesis
• Y4: dissemination

Two representative publications from supervisors:


45.2 Targeting α-synuclein-mediated synaptopathy in Parkinson’s disease

Co-Supervisor 1: Dr Richard B. Parsons
Research Division or CAG: Institute of Pharmaceutical Science
E-mail: richard.parsons@kcl.ac.uk
Website: http://www.kcl.ac.uk/ism/research/divisions/ips/research/chembio/Staff/Parsons.aspx

Co-Supervisor 2: Dr Frank Hirth
Research Division or CAG: Institute of Psychiatry, Psychology and Neuroscience
Email: frank.hirth@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Neurodegeneration/frank-hirth-neural-circuits/Index.aspx

Project description:

Parkinson’s disease (PD) has been characterised as a synaptopathy, a process by which synaptic dysfunction leads to dying back-like neurodegeneration. α-synuclein (SYN) accumulation is a key feature of PD. SYN functions in synaptic transmission and DA neuron physiology - high energy demanding processes that rely on NAD+. We have evidence for a causal connection between SYN, NAD+ levels and PD-related synaptopathy which we aim to target by manipulating the expression of nicotinamide N-methyltransferase (NNMT), an enzyme we have shown to regulate NAD+ levels and to increase synapse formation. Our hypothesis is that the targeted expression of NNMT ameliorates SYN-mediated synaptopathy, breaking the pathogenic cycle and slowing the progression of both motor and non-motor symptoms of PD. In Part 1, using an in vivo Drosophila model in conjunction with an in vitro SH-SY5Y human cell-line model, we will determine whether NNMT expression can stop or at least ameliorate SYN-induced synaptopathy. In Part 2, we will determine target gene expression levels in SYN-positive human post mortem PD tissue to probe whether targeting this pathway is suitable for therapeutic intervention. The student will learn molecular cloning, Drosophila genetic manipulation, behavioural and biochemical analysis, quantitative Western blotting and immunohistochemistry.

Yearly objectives are:

Year 1: establish transgenic flies, carry out targeted expression of NNMT and perform comprehensive phenotypic analysis

Year 2: comprehensive biochemical, behavioural and pathological analyses

Year 3: establish transgenic SH-SY5Y cell-lines, perform comprehensive biochemical and functional analyses

Year 4: comprehensive analysis of target gene expression in SYN-positive post mortem PD brain tissue

Two representative publications from supervisors:


Enhancing memory in old-age and dementia with visual imagery and neuro-stimulation.

Co-Supervisor 1: Dr Charlotte Russell  
Research Division or CAG: Department of Psychology; Division of Psychology and Systems Sciences  
E-mail: charlotte.russell@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/charlotte.russell.html

Co-Supervisor 2: Prof. Robin Morris  
Research Division or CAG: Clinical Neurosciences CAG  
Email: robin.morris@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/robin-morris

For translational projects:  
Name of Collaborating Clinician Dr Paresh Malhotra  
Research Division or CAG: Faculty of Medicine, Imperial College London  
Email: p.malhotra@imperial.ac.uk  
Website: http://www.imperial.ac.uk/people/p.malhotra

Project description:

Precise episodic memory, our memory for personally experienced events, is central to our identity yet is a complex cognitive skill and among the first to show age-related decline. Here, we will analyse under-investigated visual-spatial imagery characteristics of episodic memory. Our recent fMRI data suggest regions of parietal cortex crucial for visual-spatial skills are implicated in critical aspects of episodic memory and are utilised differently across the lifespan. These exact regions are some of the first to show impairment in Alzheimer’s disease. This topic is ripe for exploration and as a route to ameliorate age related memory decline.

We will examine impairments in healthy ageing, in pathological aging and strategies for improving decline in both populations, developing novel techniques to examine the relationship between imagination and accurate memory. E.G., using head-mounted cameras we can probe and manipulate memory and virtual reality environments will be developed, thereby enabling an exceptional range of potential avenues for discovery.

Healthy participants aged from 30-90 years and patients reporting to a neurological ‘memory clinic’ will be recruited. In addition to establishing precise impairments, we will develop both behavioural and neuro-stimulation techniques (e.g., Transcranial Magnetic Stimulation) for boosting visual-spatial imagination and episodic memory. Skills training will include neuropsychological patient screening, experimental design, programming and neuro-stimulation. Year 1: Recruit healthy participants and run the first 3 behavioural experiments; Year 2: Start ‘Memory Clinic’ recruitment and establish suitable tests based on previous year’s results; Year 3: Focus on rehabilitation strategies, including visualisation techniques and neural stimulation.

Two representative publications from supervisors:

PA Malhotra, C Russell (2015) Does stroke imaging provide insights into the neural basis of cognition?  
Current neurology and neuroscience reports 15 (8), 1-8

47.2 Betting on boredom: Examining boredom’s impact on risk-taking and gambling

Co-Supervisor 1: Dr Wijnand A. P. van Tilburg  
Research Division or CAG: IoPPN, Department of Psychology  
E-mail: Wijnand.van_Tilburg@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/wijnand.van_tilburg.html and https://van.tilburg.socialpsychology.org/

Co-Supervisor 2: Dr Tim Rakow  
Research Division or CAG: IoPPN, Department of Psychology  
Email: tim.rakow@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/tim.rakow.html

Project description:

Many scholars identify boredom as a cause of high risk behaviours, including gambling, joy riding, and recklessness. If true, this is important: Boredom is a common experience, and any negative behavioural implications will permeate society. However, despite the intuitive appeal of the claim that boredom increases risk-taking, it is surprisingly unsubstantiated.

During your PhD project, we will pioneer the much needed investigation of whether boredom has its presumed detrimental impact on risk-taking choices. You will be part of an enthusiastic and committed international team that, besides yourself, consists of Dr Wijnand van Tilburg (KCL), Dr Tim Rakow (KCL), and Dr Eric Igou (University of Limerick). You will be working at Guy’s Campus in Central London.

We will tackle the following questions:

- Does boredom increase risk-taking (e.g., gambling)? Under what circumstances?
- What motivational and cognitive processes explain this effect (e.g., attention)?
- How can we counteract any detrimental impact of boredom on risk behaviour?

We will address these topics with behavioural experiments involving eye-tracking, gambling simulators, emotion measures, and virtual reality. You should aim to present your research at international conferences, and collaborate and publish internationally. Familiarity with social and cognitive psychology is essential. A good basis in experimental and statistical methods is an advantage and computer programming skills are helpful but not necessary. You receive relevant training (e.g., advanced methods and statistics, ethics, career development etc.) throughout.

Two representative publications from supervisors:


48.2 Application of routine data to assess the effectiveness and cost-effectiveness of pharmacological therapy for people experiencing psychotic major depression

Co-Supervisor 1: Professor Paul McCrone
Research Division or CAG: Psychology & Systems Sciences
E-mail: paul.mccrone@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paul.mccrone.html

Co-Supervisor 2: Dr Margaret Heslin
Research Division or CAG: Psychology & Systems Sciences
Email: Margaret.heslin@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/margaret.heslin.html

Project description:
Psychotic Major Depression (PMD) is a depressive disorder with the addition of delusions, hallucinations or depressive stupor. Although PMD is not uncommon, it is a largely under-researched disorder. Research has shown that people with PMD have a similar mortality risk as people with schizophrenia but might be more likely to attempt suicide and self-harm. Appropriate treatment for people with PMD is important to try to avoid or mitigate these outcomes. However, there is little high quality evidence on the best pharmacological treatment of PMD. This is reflected in the NICE guidelines: “For people who have depression with psychotic symptoms, consider augmenting the current treatment plan with antipsychotic medication (although the optimum dose and duration of treatment are unknown)”.

Therefore, the aim of the project is to close this knowledge gap by determining which antidepressant-antipsychotic combination is most effective & cost effective in the treatment of PMD. This research has the potential to lead to clear recommendations on what the first line of pharmacotherapy should be in people with PMD & could contribute to updates of the NICE clinical guidelines for depression.

Using a naturalistic design with a cohort of people with PMD identified (divided into groups according to pharmacotherapy given over the follow-up) via the Mental Health Electronic Health Records held by the BRC, effectiveness and cost effectiveness studies will be conducted.

This PhD will provide training in bioinformatics, statistics, epidemiology and health economics.

Two representative publications from supervisors:


http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0040808
49.2 Pharmacological modulation of beliefs and values in people with schizotypy and healthy controls

Co-Supervisor 1: Dr Mitul Mehta  
Research Division or CAG: Neuroscience  
E-mail: Mitul.mehta@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/neuroimaging/research/neuropharmacology/index.aspx

Co-Supervisor 2: Dr Vaughan Bell  
Research Division or CAG: Psychosis  
Email: Vaughan.bell@kcl.ac.uk  
Website: https://www.national.slam.nhs.uk/about-us/our-experts/dr-vaughan-bell/

Project description:

Abnormal beliefs are common in psychiatric symptomatology – such as delusions in schizophrenia, or odd beliefs, magical thinking, and paranoid ideas in schizotypy. Schizotypy shares some features of schizophrenia but is regarded as a personality variation and not a disorder. Recent models propose that the mesolimbic dopamine system mediates dispositions to believe, while its dysregulation underpins abnormal belief formation. However, its differential involvement in types of belief and aspects of belief in healthy and patient populations is poorly understood. Improved understanding would provide insights into belief formation, contribute to our understanding of abnormal belief formation and help identify treatment targets at a receptor (pharmacology) or systems level (neurofeedback).

This study investigates modulation of a) levels of agreement with; and the perceived b) self-relevance; and c) interest of propositions expressing beliefs and values relating to science, politics, ethics, religion, and paranormal beliefs in healthy male volunteers and people with schizotypy (n = 48) using i) a dopamine antagonist (the D2-blocker haloperidol), and (ii) a dopamine precursor L-Dopa. We will test the hypothesis that i) dopamine modulation is associated with greater changes in paranormal beliefs, and the perceived self-relevance of beliefs in general; (ii) that these effects are significantly greater in people with schizotypy – indicating a brain basis for susceptibility to abnormal beliefs.

The student will attend regular group meetings, departmental seminars, and primers for pharmacological studies, amongst other training opportunities.

Year 1: Develop study protocols, obtain ethics, attend training sessions for psychopharmacology and review literature. Collect pilot data (test-retest). Initiate drug study (~10 sessions)

Year 2: conduct drug study (~100 sessions)

Year 3 continue drug study (~50 sessions), all analyses, write up

Two representative publications from supervisors:


50.2 Identifying target regions for neurofeedback treatment of auditory hallucinations using EEG of experimentally induced and pathological hallucinations.

Co-Supervisor 1: Dr Quinton Deeley
Research Division or CAG: Forensic and Neurodevelopmental Sciences
E-mail: peter.q.deeley@kcl.ac.uk

Co-Supervisor 2: Dr Eamonn Walsh
Research Division or CAG: Neuroscience
Email: eamonn.walsh@kcl.ac.uk

Project description:

Models of auditory hallucinations in schizophrenia view them as inner speech misattributed to an external source. Most (but not all) fMRI studies indicate they are accompanied by reduced activity of supplementary motor area (SMA). However, fMRI has limited temporal resolution, while multiple factors potentially confound the detection of brain-symptom correlations in fMRI case-control studies. This study combines the improved temporal resolution of EEG with a symptom modelling approach and patient studies to delineate the relationship of SMA to auditory hallucinations. Convergent evidence of SMA involvement in auditory hallucinations would justify its selection as a target for neurofeedback. Study (i): suggestions for auditory hallucinations in highly hypnotically responsive individuals with EEG measurement before, during, and after hallucinations. We test the hypothesis that relevant EEG measures are reduced in frontotemporal leads immediately preceding hallucinations. We interpret this as an EEG marker of reduced activity of SMA and functional coupling with language generation regions as the proximate brain mechanism of auditory hallucinations. Study (ii): we adapt this design to patients with chronic auditory hallucinations, testing the same hypothesis.

The student will attend regular group meetings, departmental seminars, and primers for imaging and EEG methodology, and will have the opportunity to train MSc and PhD students amongst other training opportunities.

Year 1: Develop study protocols, obtain ethics, attend training sessions for hypnosis and suggestion and review literature. Conduct pilot study.

Year 2: conduct EEG study. Plan patient study, obtain ethics, pilot study, commence study

Year 3 complete patient study, all analyses, write up

Two representative publications from supervisors:


51.2 Self-other control in social interaction: from psychological mechanisms to applications in autism

Co-Supervisor 1: Caroline Catmur
Research Division/Department or CAG: Psychology
E-mail: caroline.catmur@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/caroline.catmur.html

Co-Supervisor 2: Geoff Bird
Research Division/Department or CAG: SGDP
Email: geoff.bird@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/geoff.bird.html

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 (de Guzman et al., 2016). 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 3) 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.

During years 1 and 2, 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 3 aims to pilot the effectiveness of self-other control training on social interaction in autism spectrum conditions. If the project is selected for the 0+4 pathway, the final year will be used to follow-up on the longitudinal study and carry out further tests on the effectiveness of self-other control training as an intervention to improve social interaction.

Two representative publications from supervisors:


52.2 A feasibility study of training for mental health professionals in ‘Responding to Experienced and Anticipated Discrimination’ (READ) related to mental health

Co-Supervisor 1: Dr Claire Henderson
Research Division or CAG: Psychosis
E-mail: Claire.1.henderson@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/hspr/research/ciemh/index.aspx

Co-Supervisor 2: Dr Jacqueline Sin
Research Division or CAG: Psychosis
Email: Jacqueline.sin@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/hspr/research/ciemh/index.aspx

Project description:

This project focuses on developing mental health professionals’ capability to respond to service users affected by mental health-related discrimination. ‘Responding to Experienced and Anticipated Discrimination’ (READ) is a training for community mental health team (CMHT) professionals under development. It is co-delivered by a mental health professional and a service user trainer. It aims to improve mental health professionals’ ability to:
- respond to users’ discrimination experiences
- reduce opportunity loss for service users e.g. for relationships, employment, or service access, due to patients’ anticipation of discrimination
- minimise their own behaviours that may be experienced by service users as discriminatory.

The project aims are to: (1) optimise the content of READ; (2) conduct a repeated measures cross-sectional feasibility study of READ including process evaluation.

Year 1
Intervention optimisation: Focus groups of people using South London and Maudsley NHS Foundation Trust CMHT services to discuss: experiences of discrimination; support received; and what support they would like from mental health professionals to address discrimination.

Programme evaluation design: Development of outcome measures using validated Kirkpatrick’s framework (Knowledge, Skills, Attitudes and Behaviours).

Regulatory approvals.

Year 2
Baseline assessments of professionals and service users from CMHTs recruited (by Dr Henderson) for training.

In vivo observation of READ for fidelity scoring and identification of potential implementation barriers.

Year 3
Follow up assessments, analysis and writing up.

Skills training
Application of: Kirkpatrick’s framework to evaluate complex training intervention; MRC (2015) process evaluation framework; implementation science concepts and metrics. Qualitative methods i.e. focus group and in-depth interviewing.

Two representative publications from supervisors:


53.2 Fear of cancer recurrence: understanding and ameliorating psychological distress in the aftermath of cancer

Co-Supervisor 1: Dr Colette Hirsch  
Research Division or CAG: Psychological Medicine  
E-mail: colette.hirsch@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/colette.hirsch.html

Co-Supervisor 2: Prof Rona Moss-Morris  
Research Division or CAG: Psychological Medicine  
Email: rona.moss-morris@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/rona.moss-morris.html

For translational projects:  
Name of Collaborating Clinician: Dr Jo Armes  
Research Division or CAG: Cancer  
Email: jo.armes@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/jo.armes.html

Summary of role: A clinical academic psychoncology specialist, with clinical and research expertise in FoR that will guide the research programme and facilitate recruitment, she will provide invaluable clinical insights into FoR.

Project description:

A diagnosis of cancer can be devastating and unfortunately, even after successful treatment, the psychological aftermath can be severe and ongoing. While it is understandable that cancer survivors may fear and worry about cancer coming back, for those with high levels of fear of recurrence (FoR) it causes great psychological distress, leading to difficulties in day to day functioning and poor quality of life.

Working at the interface between psychiatric and physical health, this pioneering cognitive research will pave the way for new treatments to help suffers improve their psychological well-being.

Drawing on our cognitive model of worry (Hirsch & Mathews, 2012), and using novel experimental methods, the PhD is designed to identify key cognitive processes (thinking habits) that maintain FoR by comparing cancer survivors with FoR to those with low FoR. Based on the findings, we will develop new methods to train survivors with FoR to develop new more helpful cognitive processes that characterise those with low FoR. This will help establish which processes maintain FoR and, importantly, identify novel interventions to overcome FoR. This will pave the way for new accessible treatments to reduce FoR in cancer survivors.

Year 1. Systematic review. Develop tailored materials and paradigms to assess cognitive processes that characterise those with FoR.
Year 2: Experiment to identify key cognitive processes that differentiate cancer survivors with high or low FoR. Develop paradigms to change key cognitive processes that may maintain FoR.
Year 3/4: Series of experiments to determine whether reducing unhelpful cognitive processes alleviates FoR.

Two representative publications from supervisors:


54.2 DETERMINING THE MECHANISM OF ACTION OF FIRST-IN-CLASS EXPERIMENTAL THERAPEUTICS IN PATIENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

Co-Supervisor 1: Paolo Fusar-Poli  
Research Division/Department or CAG: Department of Psychosis Studies  
E-mail: paolo.fusar-poli@kcl.ac.uk  
Website: https://scholar.google.co.uk/citations?user=UUBkAgEAAAAJ&hl=en

Co-Supervisor 2: Philip McGuire  
Research Division/Department or CAG: Department of Psychosis Studies  
Email: Philip.McGuire@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/ps/index.aspx

For translational projects:  
Name of Collaborating Clinician: Dr Paolo Fusar-Poli  
Research Division or CAG: Psychosis Studies and SLaM  
Email: paolo.fusar-poli@kcl.ac.uk  
Website: http://www.slam.nhs.uk/about-us/clinical-academic-groups/psychosis/oasis

Project description:

The onset of psychotic illness represents a potential personal disaster in the life-course of a young individual and current treatments offer minimal help. This PhD project will focus on understanding the mechanisms of action of first-in-class experimental therapeutics (modulators of NMDA receptors, n-acetyl cysteine, modulators of potassium channels, intranasal oxytocin) for the prevention of psychosis. During Y1 the candidate will learn how to acquire psychopharmacological imaging data (including fMRI, MRS, PET, EEG) as part of new pharmaco-imaging studies and how to assess patients at risk for psychosis. During Y2 the candidate will learn how to analyse imaging data in different modalities and how to integrate them. During Y3 the candidate will learn how to measure the impact of innovative treatments on neurocircuit-based models of psychosis onset and how to develop treatment efficacy biomarkers. During Y4 the candidate will learn how to validate these biomarkers in independent samples. The candidate will have the opportunity to train in one of the largest and most productive research groups on psychosis (approximately £20 million of research grant income, and over 1300 journal articles in the last 5 years), with high quality clinical services and teaching via the Psychosis Clinical Academic Group (CAG). The candidate will additionally have the opportunity to access large databases of patients at high risk from psychosis and collaborate with one of the largest clinical services for these patients (OASIS) worldwide. At the end of the PhD the candidate will have acquired advanced skills in cutting-edge pharmaco-imaging studies of early psychosis.

Two representative publications from supervisors:


55.2 Link between pathogen exposure, brain inflammation and disease course in dementia

Co-Supervisor 1: Dr. Angela Hodges  
Research Division or CAG: MHOA and dementia  
E-mail: angela.k.hodges@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/oldage/index.aspx  
https://kclpure.kcl.ac.uk/portal/en/persons/angela-hodges(c6af7937-17d1-4ca5-b3f6-dea760b48636).html

Co-Supervisor 2: Dr. Tibor Hortobágyi  
Research Division or CAG: MHOA and dementia  
Email: tibor.hortobagy@kcl.ac.uk  
Website: http://www.kcl.ac.uk/ioppn/depts/oldage/index.aspx

Project description:

Neuroinflammation is a feature of most late onset neurodegenerative diseases including AD. However, it isn’t clear whether all individuals or dementia types across the spectrum are equally vulnerable or whether neuroinflammatory risk can be established pre-clinically. Markers of microglia activation emerge in prodromal disease and are closely associated with pathology and clinical symptoms. Many risk genes including TREM2 are highly expressed in microglia and may mediate disease risk regardless of the primary disease pathology. Systemic infections can also modulate microglia behavior and exacerbate disease. This studentship will explore the relationship between variants in inflammatory risk genes, lifetime pathogen exposure measured from blood taken in-life, inflammatory markers measured in the same individuals at post mortem and the clinical course of disease. We will compare different dementia subtypes using the Brains for Dementia cohort. The goal is to establish which inflammatory markers are of clinical relevance and establish whether or not we can identify those people at greatest risk of disease due to vulnerability in their immune system. In time, this knowledge will be used to establish which people may benefit from treatments which modulate immune response.

Two representative publications from supervisors:


56.2 Acute effects of cannabis with different CBD:THC ratios in dependent users – An experimental study

Co-Supervisor 1: Prof Sir John Strang  
Research Division or CAG: Addictions  
E-mail: john.strang@kcl.ac.uk

Co-Supervisor 2: Professor Wayne Hall, Professor of Addiction Policy (part-time)  
Research Division or CAG: Addictions  
Email: wayne.hall@kcl.ac.uk

Project Description:

Cannabis contains at least 144 compounds unique to the plant called cannabinoids, of which the two main ones are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Currently, the majority of cannabis sold on the black market is high potency THC-dominant cannabis, which has been found to be more strongly related to negative outcomes such as addiction, cognitive impairment and psychosis. Conversely, CBD is found to be non-intoxicating and anti-psychotic in patients with schizophrenia. Our previous research has shown that a high dose of THC can induce psychotic symptoms and cognitive impairment in healthy volunteers, while these effects were negated by CBD. The proposed PhD project would run alongside an ongoing project being conducted by involved post-doc colleague Dr Amir Englund with Professor Philip Maguire which explores the cognitive and psychological effects of cannabis containing different CBD:THC ratios. In this study, healthy volunteers will attend 4 separate experimental visits in which they will inhale a cannabis preparation with the CBD:THC ratios: 0:1, 1:1, 2:1 and 3:1 in a randomised order.

The proposed PhD project would aim to perform the same experimental study, but in a group of cannabis dependent volunteers. Research to date has shown that this population are less susceptible to the acute effects of cannabis on cognition and psychopathology. Since it is likely that cannabis containing a greater amount of CBD is less harmful, this study will explore if dependent users are able to distinguish the different preparations apart and if the different ratios are equally rewarding and intoxicating.

Two representative publications from supervisors:


Hall, W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction, 2015, 110, 19-35.
57.2 Improving cognitive control over emotions through neuromodulation in eating disorders

Co-Supervisor 1: Prof Ulrike Schmidt
Research Division or CAG: Academic Psychiatry/Psychological Medicine
E-mail: ulrike.schmidt@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/ulrike.schmidt.html

Co-Supervisor 2: Prof Iain Campbell
Research Division or CAG: Academic Psychiatry/Psychological Medicine
Email: iain.campbell@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/iain.campbell.html

Co-Supervisor 3: Dr. Hubertus Himmerich
Research Division or CAG: Academic Psychiatry/Psychological Medicine
Email: Hubertus.himmerich@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/hubertus.himmerich.html

Project description:

Background: Significant progress has been made in delineating the neural mechanisms underlying emotion regulation (Ochsner et al., 2012). In eating disorders (ED) maladaptive emotion regulation (emotion suppression, little adaptive re-appraisal) is thought to be a key maintaining factor, with negative emotions triggering abnormal eating behaviour, (which in turn relieves distress). Neuromodulation techniques, e.g. transcranial direct current stimulation (tDCS) show promise for modulating emotion regulation in other disorders and increasingly are being applied in ED (McClelland et al., 2013). The project will assess whether tDCS applied to the dorsolateral prefrontal cortex (a key structure in emotion regulation) enhances adaptive emotion regulation in people with ED. The long term aim is to develop neuromodulation-enhanced emotion regulation training. Methods: In a series of experiments, people with ED will be exposed to illness-relevant or other socio-emotional cues, that elicit negative emotions (e.g. Cyberball paradigm). Then, they will undergo 20 min tDCS whilst also carrying out a structured writing task, designed to facilitate cognitive re-appraisal (Pennebaker, 2004). The impact of this on subjective distress, physiological variables (e.g. salivary cortisol), food choice behaviour and eating will be assessed. Objectives: Year 1: The student will learn the theoretical and practical basis of neuromodulation treatments, conduct a relevant systematic review (e.g. neuromodulation and emotion regulation) and undertake pilot studies, to finalise experimental paradigms; Year 2: She/he will conduct their main experiments, using an RCT design; Year 3: Complete experiments and write-up. Skills available: The supervisory team has substantial expertise in both translational and neuromodulation research in ED.

Two representative publications from supervisors:


58.2 Cognition and Obesity: The Roles of the systemic Environment and of hippocampal Neurogenesis. [Project C.O.R.E. Neurogenesis]

Co-Supervisor 1: Dr Sandrine Thuret
Research Division or CAG: Neuroscience
E-mail: Sandrine.1.thuret@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Cells-behaviour/thuret-adult-neurogenesis/about.aspx

Co-Supervisor 2: Dr Wendy Hall
Research Division or CAG: Diabetes and Nutritional Sciences
Email: wendy.hall@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/wendyhall.aspx

Project description:

Obesity is associated with impaired cognitive function and with the risk of dementia. The hippocampus is important for learning/memory and is one of the rare structures in the human brain where the production of new-neurons [neurogenesis] persists throughout life. Importantly, altered hippocampal-neurogenesis results in a deterioration of cognitive abilities.

Obesity-associated reduction of hippocampal-neurogenesis has been demonstrated in pre-clinical studies, and may contribute to obesity-associated cognitive impairment in human. Recent unpublished-work from our groups has shown that energy-restriction in obese human participants has improved their neurogenesis-associated memory. We have also shown that the human systemic environment modulates hippocampal-stem cells biology/neurogenesis. This can be assessed with a novel in-vitro assay using patients’ serum and a human hippocampal-stem cells line.

We hypothesize that the mechanisms underlying the association between obesity and cognition are mediated by the systemic environment and involves hippocampal stem cells biology/neurogenesis regulation.

Translational aspect and aims:
When we consider the growing population of overweight/obese people, understanding the pathophysiology of obesity on the central nervous system, and in particular sub-regions important in learning/memory, is essential. This project aims at uncovering the effect of the obese systemic environment on hippocampal stem-cells biology/neurogenesis and identifying modifiable molecular mechanisms linked to obesity and cognition affecting hippocampal neurogenesis.

Skills training:
Stem-cells culture, proteomics/molecular biology, immunohistochemistry, confocal-microscopy, high-throughput screening, statistical analyses/modelling.

Objectives:
Year1-Determine the effect of obese participants’ systemic environment [pre- and post-energy restriction intervention] on neurogenesis.
Year2-Identify systemic factors associated with improved Neurogenesis/Cognition.
Year3- Elucidate modifiable molecular-mechanisms underlying the role of identified-factors on hippocampal neurogenesis.

Two representative publications from supervisors:

MacLaughlin HL, Sarafidis PA, Greenwood SA, Campbell KL, Hall WL, Macdougall IC: Compliance with a structured weight loss program is associated with reduced systolic blood pressure in obese patients with chronic kidney disease. Am J Hypertens 2012, 25:1024-1029
59.2 A novel approach to treating Fibromyalgia: Physiotherapy informed by Acceptance and Commitment Therapy (PACT)

Co-Supervisor 1: Dr Emma Godfrey
Research Division or CAG: Psychological medicine
E-mail: emma.l.godfrey@kcl.ac.uk

Co-Supervisor 2: Professor Lance McCracken
Research Division or CAG: Psychological medicine
Email: lance.mccracken@kcl.ac.uk

Project description:

Background:
Fibromyalgia (FM) affects 1-3 % of the population and causes much suffering and disability. Acceptance and Commitment Therapy (ACT) has shown promise (McCracken. 2013), but has yet to be tested in a treatment delivered by physiotherapists. Physiotherapy informed by ACT (PACT) has been developed and tested in persistent low back pain.

Design:
This project will refine and test a bespoke ACT informed physiotherapy intervention to improve health outcomes in people with FM, based on the PACT model (Godfrey et al. 2016). A mixed methods approach will include a systematic review of current literature around using ACT for FM and semi-structured qualitative interviews exploring FM patient’s experiences of pain and current management strategies. 40 people with FM referred to physiotherapy services across King’s Health Partners will be recruited into a feasibility study to investigate the acceptability and feasibility of the PACT approach, as adapted for people with FM. Finally, focus groups will be undertaken to explore the experiences of the clinical staff who have delivered the PACT intervention.

Translational aspect:
Results may help improve health and quality of life in people with FM.

Description of the skills training available
a) Qualitative skills: interviews with patients and focus groups with staff
b) Quantitative skills: feasibility study and data analysis
c) Theory based intervention development and refinement

Objectives for each year:
a) Year 1: Conduct systematic review and semi-structured interviews
b) Year 2: Adapt PACT intervention and conduct feasibility study
c) Year 3: Conduct focus groups, analyse and write up all results

Two representative publications from supervisors:


60.2 Neurodevelopmental trajectories and psychotic experiences: a longitudinal MRI study of young adults

Co-Supervisor 1: Prof Anthony David
Research Division/Department or CAG: Academic Psychiatry; Psychosis Studies Dept/Psychological Medicine CAG.
E-mail: anthony.david@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/anthony.david.html

Co-Supervisor 2: Dr Paola Dazzan
Research Division/Department or CAG: Academic Psychiatry; Psychosis Studies / Psychosis Clinical Academic Group (CAG)
Email: paola.dazzan@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paola.dazzan.html

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:


61.2 Turning the Curse into a Blessing: Using Mindfulness to Reduce Schizophrenia Vulnerability in Psychosis-Prone Individuals.

Co-Supervisor 1: Prof Paul Chadwick
Research Division or CAG: Psychosis
E-mail: paul.chadwick@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paul.chadwick.html

Co-Supervisor 2: Dr Elena Antonova
Research Division or CAG: Psychosis
Email: elena.antonova@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/elena.antonova.html

Project description:

Main aim: To investigate the efficacy of mindfulness-based intervention (MBI) in psychosis-prone individuals (high positive schizotypy) in reducing the risk factors for schizophrenia (suspiciousness/paranoia), whilst preserving conditions promoting creativity.

Scientific basis: Schizotypy has been argued to present a latent schizophrenia-liability rather than a benign personality trait. Suspiciousness/paranoia, one aspect of positive schizotypy, has emerged as a significant predictor of schizophrenia, putting it at the forefront of prevention research. Positive schizotypy is associated with more open information processing style (i.e. less filtering), which in turn has been linked with creativity. Antipsychotic medication increases sensory filtering in people either with or vulnerable to schizophrenia. Alternative preventative interventions are needed that reduce psychosis-risk factors, whilst preserving decreased filtering associated with creativity. Our research on expert meditators showed that mindfulness is associated with lower suspiciousness and paranoia in the presence of decreased filtering, suggesting that mindfulness could be such intervention.

Translational aspect: This study is a first step in investigating MBI’s potential in psychosis prevention.

Methods: A wait-listed design with 20 high positive schizotypy participants randomly allocated to receive MBI and 20 serving as their controls. Creativity will be assessed using Alternative Uses Test. Electromyography (EMG) will be used to quantify the eye blink response during acoustic startle habituation paradigm to index sensory filtering. Creativity and sensory filtering will also be assessed in 40 individuals with low-to-moderate schizotypy to examine inter-relationships between schizotypy, filtering and creativity.

Skills training and Objectives: Year 1 – recruitment/screening of participants, psychophysiology methods training; Year 2 – data collection/analysis; Year 3 - data analysis and write-up.

Two representative publications from supervisors:


62.2 Employment on the pathway to recovery from mental disorders: Developing indicators of occupational functioning in CRIS (Clinical Record Interactive Search application)

Co-Supervisor 1: Dr J Das-Munshi  
Research Division or CAG: HSPRD, IOPPN, KCL  
E-mail: jayati.das-munshi@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/jayati.das-munshi.html

Co-Supervisor 2: Prof Rob Stewart  
Research Division or CAG: Psychological medicine, IOPPN  
Email: robert.stewart@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/robert.stewart.html

Project description:

The Clinical Records Interactive Search application (‘CRIS’) is a real-time research repository of electronic health records for patients under the care of South London & Maudsley NHS Trust. To date, CRIS has been instrumental in several landmark studies on mental disorders. More recent developments have included the incorporation of Natural Language Processing (NLP) to extract data from free text and structured fields. However, measures for employment have yet to be developed, despite employment being increasingly recognised as an important outcome in people living with mental disorders. Employment may provide a useful measure of ‘recovery’ for people living with severe mental illnesses and potentially has wide-ranging applicability to other mental health conditions.

The successful candidate will develop a measure for employment within CRIS using NLP and use the derived indicator as an outcome for studies on mental disorders. The PhD may for example assess employment as an outcome in people with severe mental illnesses, however there is flexibility to apply the derived measure as an outcome in other mental disorders, of the student’s choosing.

Objectives

Year 1: Literature reviews. Liaise with computational scientists. Attend training  
Year 2: Develop employment indicator  
Year 3: Analyses of employment indicator as an outcome in epidemiological studies on course of mental disorder  
Year 4: Complete write-up; Submit PhD

Training: The primary supervisor leads and teaches on modules in epidemiological and statistical methods and the candidate will be able to attend these if appropriate. The candidate will also be able to attend in-house training on Clinical Informatics.

Two representative publications from supervisors:


63.2 Using smartphone technologies to investigate the impact of the urban environment in psychosis

Co-Supervisor 1: Andrea Mechelli (clinical supervisor)  
Research Division or CAG: Psychosis  
E-mail: a.mechelli@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/a.mechelli.html

Co-Supervisor 2: Ioannis Bakolis (non-clinical supervisor)  
Research Division or CAG: Biostatistics  
Email: ioannis.bakolis@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/ioannis.bakolis.html

Project description:

People who live in urban environments are at higher risk of developing multiple episodes of psychotic illness - the fourth cause of disability worldwide. The aim of this project is to examine the impact of different aspects of the urban environment in people in the early stages of the illness. Two-hundred individuals in the early stages of psychosis and two-hundred healthy controls will be investigated using a smartphone app developed for this project. The app uses a technique called “ecological momentary assessment” to monitor the mental state and behaviour of participants as they go about their daily life. The results will be used to develop a smartphone-based prognostic tool for clinical use. This tool will monitor an individual’s reactivity to urban stressors in order to predict clinical and functional outcomes and optimise treatment. There is a critical need for such a tool, since at present clinicians are unable to predict who will and will not suffer a psychotic relapse on the basis of clinical presentation. Because urban environments are associated with higher risk for a range of severe mental illnesses, the tool could easily be adapted for use in other psychiatric populations. Students will receive training in the recruitment and assessment of individuals with psychosis, the statistical analysis of ecological momentary assessment data and the translation of research findings into a tool for clinical use.

Two representative publications from supervisors:


64.2 Development of disorder-specific imaging biomarkers of major depressive disorder

Co-Supervisor 1: Dr Roland Zahn (Senior Clinical Lecturer & Honorary Consultant Psychiatrist)
Research Division or CAG: Psychological Medicine, IoPPN
E-mail: roland.zahn@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/roland.zahn.html

Co-Supervisor 2: Professor Steve Williams (Director of the Centre for Neuroimaging Sciences)
Research Division or CAG: Neuroimaging/IoPPN
Email: steve.williams@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/steve.williams.html

Project description:

There is an urgent need to develop imaging biomarkers of major depressive disorder (MDD) to stratify patients into pathophysiologically more homogeneous subgroups. This serves the development of refined disease models and of novel treatments. Using a recently identified neural signature of guilt-selective abnormalities in functional connectivity, we employed a machine-learning-based classification algorithm and were able to distinguish MDD from healthy control participants with 78% accuracy irrespective of medication status. This demonstrates the high potential of our fMRI signature as a biomarker of MDD. It is unknown, however, whether our neural signature is specific to MDD, or a general marker of vulnerability to affective disorders. To address these shortcomings, the proposed project will gather independent fMRI data acquired using autobiographical cue-evoked guilt responses. The student will draw on data currently being collected in a clinical trial in MDD and recruit 1) patients with generalised anxiety disorder, but no MDD (year 1-2) and 2) a healthy control group (year 2-3) to determine the algorithm’s ability to identify distinctive neural signatures of MDD. This will also involve comparing other algorithms, and multimodal classification using fMRI, structural MRI and cognitive measures (year 3). The student will receive training in clinical assessment and design of neuropsychological tests (year 1), fMRI analysis (year 2), and machine-learning-based classification (year 3). The student will submit her/his results as papers to high-quality journals as first author (year 2&3). If successful, this project could lead to the first disorder-specific imaging biomarker that distinguishes MDD at an individual level.

Two representative publications from supervisors:


65.2 Virtual reality assisted therapy for social difficulties in people with psychosis

Co-Supervisor 1: Dr Lucia Valmaggia
Research Division or CAG: Psychosis CAG
E-mail: lucia.valmaggia@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/lucia.valmaggia.html

Co-Supervisor 2: Professor Philippa Garety
Research Division or CAG: Psychosis CAG
Email: philippa.garety@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/philippa.garety.html

Project description:

The aim of the project is to evaluate a newly designed Virtual Reality (VR) assisted therapy package for the treatment of social difficulties in people with psychosis. This new VR platform is flexibly programmed to allow personalised and carefully controlled therapy for persons with paranoia, and as such, has the potential to radically change the way we treat social difficulties in service users with psychosis; it will also improve the understanding of the mechanisms that lead to the onset of these problems. We have successfully tested the first version of the platform in a general population sample, confirming it elicits mild levels of paranoid thoughts, as intended and provides in vivo monitoring and evaluation of the service users progress. The project, in a series of studies, investigates mechanisms and social difficulties in persons with psychosis and evaluates the therapy outcome in phase II feasibility RCT study

Training

Training in using Virtual Reality; Advanced Statistics; Library and Database Usage; Attending weekly Seminars and Scientific talks; Access to all skill forge trainings.

Over-arching objectives:
Year 1: Systematic literature review; Ethical approval, Training in VR.
Year 2: Training in VR assisted therapy; Recruitment; Feasibility study.
Year 3: Pilot RCT; Quantitative and qualitative evaluation
Year 4: Complete RCT; analyses; and write-up

Two representative publications from supervisors:


Freeman, D & Garety, P 2014, 'Advances in understanding and treating persecutory delusions: a review' Social Psychiatry and Psychiatric Epidemiology, vol 49, no. 8, pp. 1179-1189., 10.1007/s00127-014-0928-7