Theme 2

Neurosciences, Psychiatry and Mental Health

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: Prof Francesca Happé and Dr Sandrine Thuret

When choosing a project from this catalogue in the funding section of the online application form please enter **MRCDTP2019_Theme2**

Deadline for application: Sunday 25th November 2018
Shortlisted candidates will be contacted in mid-January.

Interviews: 30th January
The 2019/20 studentships will commence in September 2019.

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 Translational Systems Biology of Neurodegenerative diseases using brain-microbiome interactions and diet intervention

Co-Supervisor 1A: Prof. Dag Aarsland
Research Division or CAG: Institute of Psychiatry, Psychology & Neuroscience, Department of Old Age Psychiatry
Email: dag.aarsland@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/oldage/about/index.aspx

Co-Supervisor 1B: Dr. Saeed Shoaie
Research Division or CAG: Translational Systems Biology group, Centre for Host-Microbiome Interactions, Dental Institute
E-mail: saeed.shoaie@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/saeed.shoaie.html

Project description:

The bi-directional microbiome-brain axis involves neural, immune, endocrine, and metabolic pathways which are highly relevant for the risk of neurodegenerative disease. Available treatments are only symptomatic, affecting cholinergic and glutamatergic neurotransmission with modest clinical effect[1]. There are no disease-modifying treatments available, and recent phase-III trials with anti-amyloid agents have failed. It is therefore crucial to explore alternative disease mechanisms.
To observe if there is a signature in oral and gut microbiome as a predictive marker of age-related cognitive decline we will perform quantitative systems biology approach. The aim of this project is to discover the evidence for the potential of host-microbiome-diet interactions to prevent cognitive decline and dementia in at-risk people, explore the potential role of the microbiome in mediating this effect and translating these finding s to propose new translational intervention[2]. Therefore, during this PhD project, we aim to:

1. Investigate the association between microbiome, lifestyle, medical, genetic factors and cognition in ageing.
2. Explore the mediating role of host-microbiome interactions on the effects of diet on cognition in people with an increased risk for dementia.
3. Study the predictive role of microbiome on the cognitive effects of diet and anthocyanins.

During this PhD, student will learn physiology of dementia and neuro diseases. The student will learn novel systems biology and bioinformatics concepts to analyse host and microbiome multi-omics data[1,2] This project will also use cutting-edge methods to integrate the multi-omics data using systems biology approach to discover new biomarkers and novel interventions.

Two representative publications from supervisors:

1. **Synaptic markers of cognitive decline in neurodegenerative diseases: a proteomic approach**,
Erika Bereczki, Rui M Branca, Paul T Francis, Joana B Pereira, Jean-Ha Baek, Tibor Hortobágyi, Bengt Winblad, Clive Ballard, Janne Lehtiö, **Dag Aarsland**, 2018/1/9, **BRAIN JOURNAL**, doi:10.1093/brain/awx360.

2. **Quantifying Diet-Induced Metabolic Changes of the Human Gut Microbiome**
Shoaie, S., Ghaffari, P., Kovatcheva-Datchary, P., Mardinoglu, A., Sen, P., Pujos-Guillot, E., de Wouters, T., Juste, C., Rizkalla, S., Chilloux, J., Hoyles, L., Nicholson, J. K., Dore, J., Dumas, M. E., Clement, K., Bäckhed, F., Nielsen, J. & MICRO-Obes Consortium 4 Aug 2015 **CELL METABOLISM**. *22*, 2, p. 320–331

2.2 Putting experience into context: cognitive training for depression

Co-Supervisor 1A: Dr Michael Aitken
Research Division/Department or CAG: Psychology
E-mail: Michael.aitken@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/michael.aitken.html

Co-Supervisor 1B: Dr Nicola Byrom
Research Division/Department or CAG: Psychology
Email: Nicola.byrom@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/nicola.byrom.html

Project description:

Episodic memory, our memory for life events, shapes our sense of self. This memory is usually context dependent, capturing unique configurations of "what, where and when." However, individuals with depression show deficits in episodic memory, recalling the gist of memories, without the depth and breadth of a unique "what, where, when" configuration. This deficit contributes to the over-generalisation of negative experience, characteristic of depressive cognition and can cause irrational and inaccurate appraisals. Current theory suggests that factors relating both to attention at the time of encoding and the way information is represented mentally contribute to the context dependence of memory.

Working in the field of associative learning, this project will (a) develop and experimentally test an associative framework for how individual differences in context-dependent memory develop, and (b) assess, in a non-clinical group, whether cognitive training, based on this framework, can improve context dependent memory and mood.

This project provides the opportunity to develop an understanding of learning theory and its practical application for clinical interventions. The project will develop skills in experimental psychology, computer programming, quantitative statistical analysis and eye-tracking.

Two representative publications from supervisors:

Byrom, N. C., & Murphy, R. A. (2016). Individual difference in configural associative learning. *Journal of Experimental Psychology: Animal Learning and Cognition*, 42(4), 325.

Tobias-Webb, J., Limbrick-Oldfield, E. H., Gillan, C. M., Moore, J. W., Aitken, M. R., & Clark, L. (2017). Let me take the wheel: Illusory control and sense of agency. *The Quarterly Journal of Experimental Psychology, 70*(8), 1732-1746.

4.2 Dissecting the mechanisms underlying altered excitatory: inhibitory balance in mouse models of autism and executive dysfunction

Co-Supervisor 1A: Prof M. Albert Basson
Research Division or CAG: DI/Craniofacial and Regenerative Biology
E-mail: albert.basson@kcl.ac.uk
Website:https://www.kcl.ac.uk/dentistry/research/divisions/craniofac/ResearchGroups/BassonLab/BassonLab.aspx

Co-Supervisor 1B: Dr Laura Andreae
Research Division or CAG: IoPPN / Centre for Developmental Neurobiology
Email: laura.andreae@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/laura.andreae.html

Project description:

Neurodevelopmental disorders, including autism spectrum disorders (ASDs), are widely attributed to disturbances to the balance between excitation (E) and inhibition (I) in critical brain circuits. We have recently found evidence for E/I imbalance in the frontal cortex of mouse models for two neurodevelopmental disorders. The overall aim of this project will be to identify the underlying mechanisms that account for these changes.

Year 1: Using electrophysiology and calcium imaging in live, acute brain slices, a developmental time course of synaptic and circuit development will be established.
Year 2: Excitatory and inhibitory synapses will be visualised and their density and volumes quantified at key developmental time points. Once the critical time points have been identified, RNA sequencing will be performed to identify dysregulated genes that may be responsible for these phenotypes.
Year 3-4: A combination of conditional genetic, region/cell-type specific gene knockdown approaches will be employed to validate specific mechanistic hypotheses.

The student will receive training and develop expertise in state-of-the-art approaches that include mouse genetics, neuronal and brain slice generation / culture, electrophysiology, structural and functional high-resolution imaging, Next generation sequencing and bioinformatics, and a range of molecular biology and epigenetic techniques.

Two representative publications from supervisors:

Suetterlin, P., Hurley, S., Mohan, C., Riegman, K.L.H., Pagani, M., Caruso, A., Ellegood, J., Galbusera, A., Crespo-Enriquez, I., Michetti, C., Yee, Y., Ellingford, R., Brock, O., Delogu, A., Francis-West, P., Lerch, J.P., Scattoni, M.L., Fernandes, C. & **Basson, M.A.** (2018). Altered neocortical gene expression, brain overgrowth and functional over-connectivity in Chd8 haploinsufficient mice. *Cereb. Cortex*. 28:2192-2206. https://doi.org/10.1093/cercor/bhy058

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
https://www.cell.com/cell-reports/fulltext/S2211-1247(15)00057-1

5.2 Investigating mitochondrial transport and function in ageing and neurodegeneration

Co-Supervisor 1A: Dr Joseph Bateman
Research Division or CAG: IOPPN/Neuroscience
E-mail: joseph_matthew.bateman@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/bcn/our-research/neurodegeneration/bateman/index.aspx

Co-Supervisor 1B: Prof Chris Miller
Research Division or CAG: IoPPN/Neuroscience
Email: chris.miller@kcl.ac.uk
Website:https://www.kcl.ac.uk/ioppn/depts/bcn/our-research/neurodegeneration/miller-cell-biology-als/index.aspx

Project description:

Mitochondrial dysfunction plays a clear role in healthy ageing and in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Mitochondria are also central regulators of neuronal function and the nervous system is particularly sensitive to defective trafficking of these organelles. Interventions that increase transport and function of mitochondria might delay the onset of age-related neuronal dysfunction. However, the molecular mechanisms that link mitochondrial transport and function to specific neuronal functions are poorly understood. We have recently identified novel mechanisms by which mitochondrial transport/function and signal transduction are regulated in ageing neurons and neurodegenerative disease models. The PhD student will utilise *in vivo Drosophila* neuronal and human induced neuronal models to investigate the relationship between mitochondrial transport and function in the nervous system. They will use powerful genetic and transcriptomic approaches to identify new molecules and pathways activated by defects in mitochondrial transport and function.

Objectives:
Year 1 (or rotation project): Testing novel optogenetic tools and probes to acutely inactivate mitochondrial membrane potential or interfere with mitochondrial transport in neurons and monitor mitochondrial and cytoplasmic Ca2+ dynamics.
Year 2: Transcriptomic analysis of the stress response activated by reduced neuronal mitochondrial transport.
Year 3: Characterisation of genes/pathways identified from the transcriptomic analysis and their role in mitochondrial transport/function using imaging tools (see year 1).
Year 4: Validation of *Drosophila* work in human induced neurons, writing papers and thesis.

The student will be trained in and use: *Drosophila* genetics, behaviour and transcriptomics; generation of human induced neurons; imaging of neurons and image analysis/quantification.

Two representative publications from supervisors:

Duncan OF, Granat L, Ranganathan R, Singh VK, Mazaud D, Fanto M, et al. (2018) Ras-ERK-ETS inhibition alleviates neuronal mitochondrial dysfunction by reprogramming mitochondrial retrograde signaling. *PLoS Genet* 14(7): e1007567. https://doi.org/10.1371/journal.pgen.1007567

Stoica, R., De Vos, K.J., Paillusson, S., Mueller, S., Sancho, et al. (2014). ER-mitochondria associations are regulated by the VAPB-PTPIP51 interaction and are disrupted by ALS/FTD-associated TDP-43. *Nature Comm*. 5 3996. https://www.ncbi.nlm.nih.gov/pubmed/?term=24893131

6.2 Novel methods of plasticity to recover normal breathing and fight infection after spinal cord injury

Co-Supervisor 1A: Prof. Elizabeth Bradbury
Research Division or CAG: Wolfson Centre for Age-Related Diseases, IOPPN
E-mail: elizabeth.bradbury@kcl.ac.uk
Website: http://bradburylab.org/www.kcl.ac.uk/bradburylab

Co-Supervisor 1B: Dr. Lawrence Moon
Research Division or CAG: Wolfson Centre for Age-Related Diseases, IOPPN
Email: lawrence.moon@kcl.ac.uk
Website: www.larencemoon.co.uk

Project description:

Respiratory failure is the leading cause of morbidity and mortality following spinal cord injury. These deficits make recovery from immune challenge (e.g. pneumonia) unmanageable, increasing mortality. This project will use an innovative gene---based regenerative treatment strategy for spinal cord injury to determine if respiratory recovery will alter the response to immune challenge in a clinically relevant animal model. The student will be trained in a range of cutting-edge surgical, behavioural, neurophysiological, molecular and anatomical techniques in a stimulating research environment and will be part of an interdisciplinary team at the forefront of developing regenerative therapies to treat spinal cord injury.

Year 1: Assess the respiratory effects of immune challenge through nasal bacterial infection inoculation following spinal cord injury and determine through EMG and other electrophysiological recordings of the respiratory muscles. Examine spinal cord tissue after injury for cell body changes and alterations in genetic expression.

Year 2: Chronically injured rats will be treated with a novel viral method for inducing neuroplasticity and recovery following spinal cord injury. 1-2 months following treatment, animals will undergo immune challenge, and respiratory parameters, cell body, and expression changes will be assessed to determine the effects these protocols have upon the recovered activity.

Years 3-4: Use inducible DREADDs and electrophysiology to turn on and off the pathways responsible for respiratory motor recovery to assess the mechanisms for functional recovery and effects of immune challenge and determine if the respiratory outcomes following insult to the immune system can be improved using genetic techniques.

Two representative publications from supervisors:

E. R. Burnside et al., (2018) Immune-evasive gene switch enables regulated delivery of chondroitinase after spinal cord injury. *Brain, Epub ahead of print*; doi:10.1093/brain/awy158.

C. Kathe et al., (2016) Intramuscular Neurotrophin-3 normalizes low threshold spinal reflexes, reduces spasms and improves mobility after bilateral corticospinal tract injury in rats. *eLife*, 5: e18146.

7.2 A neuroimaging assessment of brain metastability changes in Epilepsy

Co-Supervisor 1A: Dr David Carmichael
Research Division or CAG: FoLSM/School of Biomedical Engineering
E-mail: david.carmichael@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/david.carmichael.html

Co-Supervisor 1B: Prof Mark Richardson
Research Division or CAG: IoPPN/Neuroscience & Neuroscience CAG
Email: mark.richardson@kcl.ac.uk
Website: www.epilepsy-london.org

Project description:

We have been engaged in understanding epilepsy as disease where the brain is considered a complex network with a resulting repertoire of dynamics. Neuroimaging methods such as EEG and fMRI both measured individually and simultaneously can provide a window onto these dynamics. We have a hypothesis that epilepsy has an effect on the brain where its dynamics become more stable, and the brain becomes 'stuck' in certain states where brain networks are in synchrony. This has important implications because the brain being in a metastable (switching between stable states) regime is thought to be a desirable property that underpins attentional changes, cognitive flexibility and consciousness.
In this project, we will use EEG and fMRI to characterise focal and generalised epilepsy patients in terms of their brains synchrony and metastability both during and in the absence of ongoing epileptic activity and alterations related to treatment effects.

YR1: Training in neuroimaging and associated analysis methods
YR2: Characterise brain metastability and synchrony at the whole brain and network level for focal and generalised epilepsy patients using fMRI data. Measure differences associated with epileptic discharges.
YR3: Relate metastability and synchrony to treatment effects including drug effects comparing drug naïve to treated cohorts and focal epilepsy syndromes.
YR4: The main objective will be to complete and write up scientific papers and thesis.

This project will give a strong training in neuroimaging analysis methodology and its application to brain dynamics. It will provide strong computational abilities and an introduction to a range of mathematical concepts as applied to neuroscience.

Two representative publications from supervisors:

Dynamic brain network states in human generalized spike-wave discharges.
Tangwiriyasakul C, Perani S, Centeno M, Yaakub SN, Abela E, Carmichael DW, Richardson MP.
Brain. 2018 Aug 28.

Combined electroencephalography-functional magnetic resonance imaging and electrical source imaging improves localization of pediatric focal epilepsy.
Centeno M, Tierney TM, Perani S, Shamshiri EA, St Pier K, Wilkinson C, Konn D, Vulliemoz S, Grouiller F, Lemieux L, Pressler RM, Clark CA, Cross JH, Carmichael DW.
Ann Neurol. 2017 Aug;82(2):278-287.

8.2 Enhancing episodic memory with neurostimulation and reward

Co-Supervisor 1A: Dr Caroline Catmur
Research School/Division or CAG: Department of Psychology, Division of Psychology & Systems Sciences
E-mail: caroline.catmur@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/caroline.catmur.html

Co-Supervisor 1B: Dr Charlotte Russell
Research School/Division or CAG: Department of Psychology, Division of Psychology & Systems Sciences
Email: charlotte.russell@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/charlotte.russell.html

Collaborating Clinician: Dr Paresh Malhotra
School/Division or CAG: Faculty of Medicine, Imperial College London
Email: p.malhotra@imperial.ac.uk
Website: https://www.imperial.ac.uk/people/p.malhotra

Project description:

Episodic memory, our memory for personally experienced events, is central to our identity: your memories make you an individual. Unfortunately, this form of memory declines as people get older and its loss is a core feature of common dementias. Research suggests that not all aspects of this complex cognitive function deteriorate at the same time. As an example of these aspects, for us to remember a summer picnic on the beach last year we need to reconstruct what we saw and experienced, where these elements were in relation to us and to correctly tag this memory in time- when it occurred. This project will examine whether these critical contextual elements – the 'where' and 'when' within our memories – decline at different rates. Using the information discovered we will then develop methods for enhancing memory across the lifespan. The first of these methods will use reward – investigating how manipulations that stimulate neural reward circuits affect memory for these different contextual elements. The second is neurostimulation, again we will use the information gained from our behavioural studies, along with evidence from Dr Russell's neuropsychological research, to develop targeted intervention protocols.

Skills: experimental design, quantitative analysis, neuropsychological testing, neurostimulation

Year 1: Behavioural studies on changes to contextual elements of episodic memory
Year 2: Intervention strategies – reward and neurostimulation– in health and in pathological ageing (Mild Cognitive Impairment (MCI) and dementias)
Year 3: Continuation of neurostimulation intervention strategies and writing up.

Two representative publications from supervisors:

Malhotra, P. A., Soto,D., Li, K. & **Russell, C.** (2013) Reward modulates spatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84 (4): 366-369.

Santiesteban, I., Kaur, S., Bird, G. & **Catmur, C.** (2017). Attentional processes, not implicit mentalizing, mediate performance in a perspective-taking task: Evidence from stimulation of the temporoparietal junction. *NeuroImage*, 155: 305-311.

9.2 Does combining neurocognitive and behavioural markers improve our ability to predict trajectories and outcomes in infants at familial risk of ASD and ADHD?

Co-Supervisor 1A: Prof. Tony Charman
Research Division or CAG: PASS, Psychology Department
E-mail: tony.charman@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/tony.charman.html

Co-Supervisor 1B: Prof. Andrew Pickles
Research Division or CAG: PASS, Biostatistics and Health Informatics Department
Email: andrew.pickles@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/andrew.pickles.html

Project description:

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders with high heritability and high rates of co-occurrence. This allows prospective study of infants at familial risk for ASD and ADHD due to having a first degree relative with a diagnosis. By studying neurocognitive and behavioural profiles of infants in the two risk groups (and low-risk controls with no family history) it will be possible to identify common and distinct mechanisms that lead to the two clinical disorders. However, to date most work has focused on single antecedent markers. Variability in both aetiology and presentation of these disorders suggests that different neurodevelopment risk factors will act in combination, and further that these combinations will differ between individuals. As part of the MRC-funded BASIS network (http://www.basisnetwork.org/) we study infants at familial risk of ASD and ADHD using multiple methods (EEG, eye-tracking, electrophysiology, behavioural experiments, clinical measures) at multiple timepoints from 6 months of age to 7 years. The PhD student will develop expertise in statistical modeling approaches (e.g. SEM, LCA, MIMIC) to test whether combinations of risk markers better predict developmental trajectories and clinical outcomes than single markers alone. Identifying mechanisms of atypical development will inform translational approaches to early intervention.

Skills: Complex statistical modelling. Clinical assessments of infants and toddlers. Training in EEG, eye-tracking and electrophysiological data collection and analysis.
Year 1: Training on assessments. *Year 2:* Training in statistical modelling *Year 3:* Analysis and paper writing. *Year 4:* Completion of thesis.

Two representative publications from supervisors:

Shephard, E., Bedford, R., Milosavljevic, B., Gliga, T., Jones, E. J. H., Pickles, A., Johnson, M. H., **Charman, T.**, & The BASIS Team. (in press). Early developmental pathways to childhood symptoms of attention-deficit hyperactivity disorder (ADHD), anxiety, and autism spectrum disorder (ASD). *Journal of Child Psychology & Psychiatry*.

Pickles, A., Harris, V., Green, J., Aldred, C., McConachie, H., Slonims, V., Le Couteur, A., Hudry, K., Charman, T. & The PACT Consortium. (2015). Treatment mechanism in the MRC Pre-school Autism Communication Trial: Implications for study design and parent-focused therapy for children. *Journal of Child Psychology and Psychiatry*, 56, 162-170.

11.2 Identifying neuroimaging predictors of neurodevelopmental disorders in children with congenital heart disease

Co-Supervisor 1A: Professor Serena Counsell
Research Division or CAG: School of Biomedical Engineering & Imaging Sciences
E-mail: serena.counsell@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/serena.counsell.html

Co-Supervisor 1B: Professor Mary Rutherford
Research Division or CAG: School of Biomedical Engineering & Imaging Sciences
Email: mary.rutheford@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/mary.rutherford.html

Project description:

Congenital heart disease (CHD) affects almost 1% of UK births, and is the most frequent congenital malformation. Up to half of childhood survivors experience difficulties in learning, memory, inattention, hyperactivity, and survivors have an increased risk for autism spectrum disorders. Despite the significant and growing public health problems associated with survivors of CHD, research into the underlying causes of cognitive and behavioral disorders in these children has been limited. We have acquired a unique and growing cohort of neonates with CHD who have undergone high quality quantitative multimodal neuroimaging (HARDI diffusion MRI, measures of cortical folding, cerebral oxygen delivery, brain volumes, NIRS) and who have neurodevelopmental assessments at 2 years. We will undertake neurodevelopmental assessments at 4 years in a sub-group of 60 children. The aim of this project is to increase our understanding of the neural substrate underpinning neurodevelopmental disorders in children with CHD by performing detailed analyses of these brain imaging data and undertaking neurodevelopmental assessments in early childhood.

Objectives

- Training in fetal and neonatal neuroanatomy, quantitative imaging analysis techniques, neurodevelopmental assessments (Training by Counsell & Rutherford)
- Analyses of multimodal neuroimaging datasets (blinded to subject ID) (Counsell)
- Undertake 4 year old neurodevelopmental assessments (Rutherford)
- Assess relationships between neonatal neuroimaging and 2 and 4 year outcome including exploring novel ways to predict outcome (e.g. machine learning approaches) (Counsell).

Skills training: The student will be trained in fetal and neonatal neuroimaging analysis, in undertaking neurodevelopmental assessments and in preparing data for presentations and publications.

Two representative publications from supervisors:

D Batalle, EJ Hughes, H Zhang, J-D Tournier, N Tusor, P Aljabar, L Wali, DC Alexander, JV Hajnal, C Nosarti, AD Edwards, SJ Counsell. Early development of structural networks and the impact of prematurity on brain connectivity. NeuroImage 2017 Jan 30. Apr 1;149:379-392. doi: 10.1016/j.neuroimage.2017.01.065.

Kyriakopoulou V, Vatansever D, Davidson A, Patkee P, Elkommos S, Chew A, Martinez-Biarge M, Hagnerg B, Melissa D, Allsop J, Fox M, Hajnal. JV, Rutherford MA. Normative biometry of the fetal brain using magnetic resonance imaging. Brain Structure & Function. 2017 Jul;222(5):2295-2307. doi: 10.1007/s00429-016-1342-6.

12.2 Altering Behaviour in Children (ABC)

Co-Supervisor 1A: Dr. Michael Craig
Research Division/Department or CAG: Behavioural and Developmental Psychiatry Clinical Academic
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 1B: Dr Nigel Blackwood
Research Division/Department or CAG: Behavioural and Developmental Psychiatry Clinical Academic
Email: nigel.blackwood@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/nigel.blackwood.html

Project description:

Understanding the cause(s) conduct problems (CP) in childhood is important because such children are persistently aggressive, break rules and frequently have continued problems in adulthood.

The underlying cause(s) for CP is complex but there is compelling evidence that children with CP have differences in brain anatomy and function from normally developing children. However, no-one has ever analysed whether there are specific brain differences that: a) predict resistance to change; and/or b) are 'reversible'.

To complete this studentship you will be trained to use cutting-edge brain imaging techniques to study CP children before and after a parent training intervention, which reduces antisocial behaviour in about 1/3rd of CP children.

You will personally visit, and work alongside, International Leaders in CP, parenting and brain imaging in the UK and USA including Profs. Scott, Murphy & Williams (IoPPN), Viding (UCL) and Blair (NIMH (USA)). You may also be part of a TV documentary currently being planned around this study.

TRANSLATIONAL ASPECT OF THE PROJECT: It is anticipated that our findings will assist in focusing future research into the molecular basis of CP, and ultimately lead to better treatments.
SKILLS TRAINING AVAILABLE IN THE PROJECT: Training in cutting edge structural and functional brain imaging techniques.
OVER-ARCHING OBJECTIVES: YEAR 1: Recruit/scan children; Collection of data; Brain image analysis training. **YEAR 2**: Completion of recruitment and preliminary analysis. **YEAR 3**: Completion of analysis; Presentation at International meetings; Writing up dissertation/papers.

Two representative publications from supervisors:

Sethi, A., Sarkar, S., Dell'Acqua, F., Viding, E., Catani, M., Murphy, D. G. M., & **Craig, M. C**. Anatomy of the dorsal default-mode network in conduct disorder: Association with callous-unemotional traits. Developmental Cognitive Neuroscience 30 (2018) 87–92.

Gregory S, Blair RJR, Ffytche D, Simmons A, Kumari V, Hodgins S, **Blackwood N** (2015) Punishment and psychopathy: a case-control functional MRI investigation of reinforcement learning in violent antisocial personality disordered men. Lancet Psychiatry 2, 153-60.

13.2 Can targeting the serotonin (5-HT) system 'shift' the biology of Autism?

Co-Supervisor 1A: Dr Eileen Daly
Research School/Division or CAG: IoPPN/Academic Psychiatry & Behavioural Disorders CAG
E-mail: Eileen.daly@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/eileen.daly.html

Co-Supervisor 1B: Dr Mark Tricklebank
Research School/Division or CAG: IoPPN/Neuroimaging
Email: mark.tricklebank@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/mark.tricklebank.html

Project description:

At present, there are no medications for the treatment of Autism core or comorbid symptoms. One of the most consistently reported abnormalities in Autism Spectrum Disorder (ASD) is the occurrence of hyperserotonaemia (elevated blood levels of serotonin (5-HT)) in ~ 30% of individuals. This PhD will provide proof of concept that modulation of 5-HT differentially 'shifts' brain functional deficits in the subset of ASD individuals with hyperserotonaemia. If successful project will help validate hyperserotonaemia as a candidate stratification biomarker, and provide evidence for translation to Fast-Fail Clinical trial.

This randomised, double blind, placebo-controlled biomarker 'shiftability' study will compare the brain functional response in both adults with ASD (N=40, 20 with hyperserotonaemia and 20 without hyperserotonaemia) and healthy adults without ASD (N=20). Specifically, we will test the impact of an acute dose of citalopram/tianeptine (using fMRI and EEG) on resting and active brain functional connectivity. Our design will allow us to both test case-control differences in brain function, and to determine if citalopram/tianeptine differentially 'normalises' deficits within hyperserotonaemic ASD individuals.

Skills Training: Phlebotomy, Autism Diagnostic Interview (ADI-R), Autism Diagnostic Observational Scale, Neuroimaging Paradigms and Analyses (EEG, fMRI, resting state and active tasks).

Objectives:
Year 0 or 1 –Learn Phlebotomy. Complete MRI safety training. Become familiar with departments database of participants and start recruiting subjects. Initiate testing of subjects for serotonin blood levels. Learn and begin MRI scanning.
Year 1 or 2 –continue/complete scanning of N=60. Analysis of collected data.
Year 3 or 4 - presenting results at meetings and through publications. Thesis.

Two representative publications from supervisors:

Daly, E. 2014, Response inhibition and serotonin in autism: a functional MRI study using acute tryptophan depletion. *Brain*.

Ticklebank, M. 1992, Centrally active 5-HT receptor agonists and antagonists. *Neuroscience and Biobehavioral Reviews.*

14.2 Residential instability and psychosis risk – a cross-national study using electronic health records

Co-Supervisor 1A: Dr Jayati Das-Munshi
Research School/Division or CAG: IOPPN/ Psychological Medicine (formerly HSPRD)
E-mail: jayati.das-munshi@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/jayati.das-munshi.html

Co Supervisor 1B: Dr Peter Schofield
Research School/Division or CAG: School of Population Health & Environmental Sciences
Email: peter.schofield@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/peter.schofield.html

Project description:

A growing body of evidence has indicated strong social risk factors for the onset of psychosis, particularly those experienced in childhood / adolescence when the developing brain may be more prone to environmental insults. Residential instability in childhood and adolescence is one such factor [Paksarian 2015, Mok 2016] with a recent study showing double the later psychosis incidence for those experiencing frequent moves, hazard ratio 1.99 (95% CI 1.30-3.05) [Price et al 2018]. These findings raise important questions about the role of home and neighbourhood in young people's lives and their risk of psychosis.

Using large linked datasets from the UK (the SLaM-BRC CRIS dataset linked to UK census 2011) and Denmark (Danish population register data), this study will permit a fine-grained analysis of residential instability (i.e. type of moves) and other predictive factors related to moves (e.g. childhood adversity/ familial instability) shedding light on possible causal pathways for this increased psychosis risk.

This would suit a candidate with a strong quantitative background (e.g. statistics / epidemiology) wishing to develop expertise within data science focusing on the social determinants of severe mental illness. The studentship would include analytical methods training and time spent in the two study centres in Denmark and London.

Annual objectives: Year 1: undertake systematic reviews, gain study approvals, at least one site visit to Denmark, data cleaning / commence analyses, upgrade to PhD from MPhil at 9 months; year 2: conduct analyses in UK and Denmark; year 3: finalise all analyses for publication and PhD submission.

Two representative publications from supervisors:

Schofield, P., Thygesen, M., Das-Munshi, J., Becares, L., Cantor-Graae, E., Agerbo, E., Pedersen, C., 2017. Ethnic density, urbanicity and psychosis risk for migrant groups – A population cohort study. Schizophrenia Research 190, 82–87.

Das-Munshi J, Chang CK, Dutta R, Morgan C, Nazroo J, Stewart R, Prince MJ. Ethnicity and excess mortality in severe mental illness: a cohort study. *The Lancet Psychiatry*. 2017; 4(5) p389-399

16.2 Effects of Aberrant Light on Mood and Cognition

Co-Supervisor 1A: Dr Alessio Delogu
Research School/Division or CAG: Neuroscience
E-mail: alessio.delogu@kcl.ac.uk
Website:https://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Cells-behaviour/delogu-subcortical-circuitries-sleep-arousal.aspx

Co-Supervisor 1B: Dr Samuel Cooke
Research School/Division or CAG: Neuroscience
Email: samuel.cooke@kcl.ac.uk
Website:https://www.kcl.ac.uk/ioppn/depts/bcn/our-research/cells-behaviour/cooke-experience-dependent-plasticity/index.aspx

Project Description:

Night-time use of back-lit computers and shift work are two examples of factors in modern life that cause aberrant light exposure. There is now considerable evidence that this type of aberrant light can contribute to disruptions of mood and cognition that manifest as depression, a psychiatric condition that causes much suffering and provides a major economic burden for society. To understand the biological mechanisms that underlie the effect of aberrant light on cognition, mice can be subjected to a 7-hour dark/light schedule that transitions every 3.5 hours, known as T7, and compare its effects to a normal T24 schedule. It is documented that T7 leads to disrupted hippocampus-dependent learning and memory and other behaviours that are consistent with disrupted mood, such as increased immobility and reduced sucrose consumption, as well as increased release of the stress hormone corticosterone. However, the circuit and transmitter mechanisms mediating this effect are not fully understood. It is known that an unusual population of photosensitive retinal ganglion cells that express melanopsin are the key receptors that deliver information about light cycles, including aberrant light, to mood centres in the brain. It is also known that the habenula, a midbrain structure that responds to negative outcomes of behaviour, is chronically hyperactive in depressed patients and has emerged as a candidate target for new treatment approaches. In this project, we aim to develop the mouse T7 model to understand the key circuit intermediaries between melanopsin-expressing retinal ganglion cells, habenular activation and hippocampal plasticity/hippocampus-dependent cognition.

Two representative publications from supervisors:

Jager P, Ye Z, Yu X, Zagoraiou L, Prekop HT, Partanen J, Jessell TM, Wisden W, Brickley SG, **Delogu A**. (2016) Tectal-derived interneurons contribute to phasic and tonic inhibition in the visual thalamus. Nat Communications. 7:13579

Cooke SF, Komorowski RW, Kaplan ES, Gavornik JP, Bear MF (2015) Visual recognition memory, manifest as long-term habituation, requires synaptic plasticity in V1. Nature Neuroscience. 18(2): 262-71

17.2 Evaluating the effectiveness of public health interventions to reduce the harms related to anabolic-androgenic steroids in the United Kingdom

Co-Supervisor 1A: Dr Paolo Deluca
Research School/Division or CAG: IoPPN, Addictions Department
Email: Paolo.Deluca@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paolo.deluca.html

Co-Supervisor1B: Prof John Marsden
Research School/Division or CAG: IoPPN, Addictions Department
Email: John.Marsden@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/john.marsden.html

Project description:

Anabolic-androgenic steroids (AAS) are synthetic versions of the hormone testosterone, with clinical applications in the treatment of conditions like male hypogonadism, breast cancer and anemia. However, in the light of the escalating number of healthy men and women making use of AAS in order to promote the growth of muscle size and strength and to lower body fat, the increasing use in the general population and related harms have made it a public health concern.

The global overall prevalence of AAS use is 3.3%, being 6.4% for males and 1.6% for females. There are a number of potential harms associated with AAS, including cardiovascular problems, hepatic dysfunction, and psychological disorders (e.g. reduction in mood upon cessation).
Although AAS have been used in larger groups in the general population, evidence to determine the effectiveness of existing policies, including prevention and harm reduction interventions, is very limited.

The aim of the proposed study is to fill the gap in current knowledge by investigating the effectiveness of currently implemented policies and interventions to reduce harm related to AAS. The study comprises five work packages: WP1 Literature review, WP2 Online survey of AAS users, WP3 Interviews with service providers, WP4 service review of AAS users in harm reduction services, and WP5 a scale to estimate the harm of taking AAS. Each work package will produce a body of knowledge of its own, whilst working together to build a solid and forward-looking perspective to inform future development of policy relevant to AAS use.

Two representative publications from supervisors:

Kimergård, A., Foley, M., Davey, Z., Wadsworth, E., Drummond, C., & Deluca, P. (2017). The challenge of complex drug use: associated use of codeine containing medicines and new psychoactive substances in a European cross-sectional online population. DOI: 10.1002/hup.2611

Mephedrone: Use, subjective effects and health risks. Adam Winstock, Luke Mitcheson, John Ramsey, Susannah Davies, Malgorzata Puchnarewicz, John Marsden. Addiction 05/2011; 106(11):1991-6. DOI:10.1111/j.1360-0443.2011.03502.x

18.2 Identification of neurobehavioural predictors of eating disorders, weight gain and obesity

Co-Supervisor 1A: Dr Sylvane Desrivières
Research School/Division or CAG: Social Genetic & Developmental Psychiatry
Email: Sylvane.desrivieres@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/sylvane.desrivieres.html

Co-Supervisor 1B: Prof Ulrike Schmidt
Research School/Division or CAG: Psychological Medicine and Integrated Care Clinical Academic Group Email: ulrike.schmidt@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/ulrike.schmidt.html

Project description:

Eating disorders (EDs) are disabling psychiatric disorders, with a peak age of onset of 15–25 years. One in every six or seven young women has an eating disorder that, if untreated, has lasting effects on brain, body, behaviour and life expectancy. Furthermore, 30-40% of people with bulimia nervosa or binge eating disorder (i.e. the most common EDs) are or will become obese, making them susceptible to obesity-related complications. Early intervention is key in achieving full recovery. Yet very little is known about neurobiological predictors of EDs that might allow targeted prevention or early intervention.

This project will elucidate the neurobiological basis of EDs and identify predictor of EDs, weight gain and obesity in young adulthood. The student will
Year 1. (i) Familiarise themselves with the neurobiological basis of EDs (Prof. Schmidt's area of expertise) and the IMAGEN database (Dr. Desrivières, one of the IMAGEN PIs, will provide access and support); (ii) conduct a systematic review (e.g. on neurobiological predictors of EDs/obesity); (iii) utilise IMAGEN behavioural and body mass index (BMI) data (age 14 to 21) to identify and characterise distinct trajectories of disordered eating and BMI change.
Year 2. Use age 14 IMAGEN data to identify environmental, biological and psychological factors characterizing the different trajectories.
Year 3. (i) Study interactions between these factors to derive bio-behavioural risk/prediction models of EDs, weight gain and obesity, and (ii) validate results in a clinical sample of emerging adults with an ED diagnosis.

Trainings for statistical, neuroimaging and genomics analyses will be provided.

Two representative publications from supervisors:

Bartholdy S, Dalton B, O'Daly OG, Campbell IC, Schmidt U. A systematic review of the relationship between eating, weight and inhibitory control using the stop signal task. Neurosci Biobehav Rev. 2016 May;64:35-62.

Xu B, Jia T, Macare C, Banaschewski T, Bokde ALW, Bromberg U, Büchel C, Cattrell A, Conrod PJ, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Ittermann B, Martinot JL, Paillère Martinot ML, Nees F, Orfanos DP, Paus T, Poustka L, Smolka MN, Walter H, Whelan R, Schumann G, Desrivières S; IMAGEN Consortium. Impact of a Common Genetic Variation Associated with Putamen Volume on Neural Mechanisms of Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry. 2017 May;56(5):436-444

19.2 The nature and natural history of health harm, health inequalities, and treatment-seeking in adolescents attending hospitals for alcohol-related health conditions.

Co-Supervisor 1A: Professor Colin Drummond
Research School/Division or CAG: Addictions CAG, SLAM/IOPPN BRC
E-mail: Colin.Drummond@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/colin.drummond.html

Co-Supervisor 1B: Professor Michael Lynskey
Research School/Division or CAG: IoPPN/ Academic Psychiatry/ Addictions
Email: Michael.lynskey@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/addictions/people/profiles/professor-lynskey.aspx

Project description:

Alcohol use is typically initiated during early adolescence and is associated with considerable morbidity and mortality across the lifespan. National data indicate that over 11,000 people under age 18 are admitted to hospital for an alcohol related condition each year. Little is known about the characteristics of these people, their presenting health problems or their longer-term outcomes. This project will access national data on patterns of health service utilization to identify a large cohort of young people admitted to hospital for an alcohol related problem. Linking across multiple years of HES data and to data on specialist alcohol and drug treatment and mortality will improve understanding of longer term outcomes within this group and the relationship to deprivation. This project will involve ongoing training in statistical analysis and would be ideally suited to a candidate with strong interests in quantitative methods.

Year One: Attend course on analysis of HES Data.
Conduct systematic review on alcohol related hospital admissions among youth.
Obtain permissions for access to HES data and for linkage to NDTMS and ONS data.
Year Two: Construct ten-year national data set of alcohol related admissions among youth.
Write paper identifying sociodemographic characteristics and morbidity among this group.
Year Three: Construct in silico 10-year cohort of youth initially admitted to hospital for an alcohol related condition.
Write paper identifying 10-year patterns of health care utilization over a 10-year period.
Year Four: Conduct analyses describing specialist drug treatment utilisation and mortality over 10 years.
Finalise and submit Thesis based on papers described above.

Two representative publications from supervisors:

Donoghue, K., Rose, H., Boniface, S., Deluca, P., Coulton, S., Alam, M.F., Cohen, D., Gilvarry, E., Kaner, E., Lynch, E., Maconochie, I., McArdle, P., McGovern, R., Newbury-Birch, D., Patton, R., Phillips, C., Phillips, T., Russell, I., Strang, J., Drummond, C. Alcohol consumption, early-onset drinking, and health-related consequences in adolescents presenting at emergency departments in England. Journal of Adolescent Health, 2017. doi.org/10.1016/j.jadohealth.2016.11.017

Degenhardt L, Stockings E, Patton G, Hall WD, Lynskey M. The increasing global health priority of substance use in young people. Lancet Psychiatry. 2016 Mar;3(3):251-64.

20.2 Targeted drug repurposing to find neuroprotective treatments for Parkinson's.

Co-Supervisor 1A: Dr Susan Duty
Research School/Division or CAG: Wolfson CARD; Division of Neuroscience
E-mail: susan.duty@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/wolfson/research/Duty-Lab/Duty-Lab.aspx

Co-Supervisor 1B: Dr Gareth Williams
Research School/Division or CAG: Wolfson CARD; Division of Neuroscience
Email: Gareth.2.williams@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/wolfson/research/Williams/Index.aspx

Project Description:

Scientific Basis:

Parkinson's disease is a neurodegenerative condition best known for its movement-related symptoms but increasingly for related dementia. Given current treatments do not tackle the cause of the progressive symptoms, there is urgent need for better drug treatments. Drug repurposing is an exciting drug discovery strategy that interrogates drugs already shown to be safe in man or efficacious in one disease, for potential for use in another. By combining bioinformatics with cell and whole animal studies, we recently used targeted repurposing to identify drugs (e.g. the anti-asthmatic, salbutamol) to preserve dopaminergic neurones in Parkinson's by boosting transcription of FGF-20, a protein we discovered had protective properties. This project will adopt similar strategies to identify FDA-approved drugs that boost production of other proteins of therapeutic interest (e.g. GDNF; protective when infused into patients' brains) or suppress transcription of genes that are upregulated or risk-associated in Parkinson's and dementias (e.g. alpha-synuclein).

Yearly Objectives:

- Year 1: To use bioinformatics to identify drugs that boost GDNF production then confirm production in cell systems and brains of treated mice.
- Year 2: To investigate the therapeutic potential of GDNF-boosting drugs in animal models of Parkinson's (e.g. 6-OHDA mouse)
- Year 3-3.5: To identify novel transcriptional targets for early intervention and apply bioinformatics to select promising FDA-approved drugs to test for correction of identified early pathological changes.

Skills training:
bioinformatics; cell culture; microarray techniques; ELISA; transgenic and toxin models of Parkinson's disease and related dementia ; behavioural assessments; immunohistochemistry.

Two representative publications from supervisors:

Boshoff EL, Fletcher EJR, Duty S. (2018). Fibroblast growth factor 20 is protective towards dopaminergic neurons in vivo in a paracrine manner. Neuropharmacology. 137:156-163.

Williams G. (2012). A searchable cross-platform gene expression database reveals connections between drug treatments and disease. BMC Genomics 13(1): 12.

21.2 Glutamate, inflammation and clinical outcome in schizophrenia.

Co-Supervisor 1A: Dr Alice Egerton
Research School/Division or CAG: Dept. Psychosis Studies, Academic Psychiatry, IoPPN.
E-mail: alice.egerton@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/alice.egerton.html

Co-Supervisor 1B: Dr Valeria Mondelli
Research School/Division or CAG: Dept. Psychological Medicine, Academic Psychiatry, IoPPN
Email: valeria.mondelli@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/valeria.mondelli.html

Project description:

Both inflammation and brain glutamate neurotransmission play an important role in schizophrenia but have so far mainly been investigated separately. This novel project will test the hypotheses that inflammation and glutamate dysfunction are linked, and that together they may mediate how well schizophrenia symptoms will respond to treatment with antipsychotic medication. The project will involve analysis of brain scans, blood samples and clinical data from patients with schizophrenia. The associations between inflammation and glutamate will be determined cross-sectionally (comparing good versus poor responders to antipsychotic treatment), as well as prospectively (to determine whether these biomarkers can predict antipsychotic response). This research will increase understanding of the neurobiology of schizophrenia and will provide information that may help develop new treatments.

Skills training can include a) lab-based training in blood cytokine measurement; b) acquisition and analysis of brain glutamate, myo-inositol and choline using MRI neuroimaging; c) recruitment and assessment of patients with schizophrenia; d) training in statistical analysis; e) support in preparing conference presentations and publishing results in journals.

Year 1: To determine the associations between blood inflammatory cytokine levels and brain glutamate, myoinositol and choline levels in good versus poor antipsychotic responders

Year 2: To determine the associations between inflammation and glutamate in predicting response to the antipsychotic clozapine

Year 3: To determine the associations between inflammation and glutamate in predicting response to antipsychotic treatment in first episode psychosis

Two representative publications from supervisors:

Response to initial antipsychotic treatment in first episode psychosis is related to anterior cingulate glutamate levels: a multicentre 1H-MRS study (OPTiMiSE).
Egerton A, Broberg BV, Van Haren N, Merritt K, Barker GJ, Lythgoe DJ, Perez-Iglesias R, Baandrup L, Düring SW, Sendt KV, Stone JM, Rostrup E, Sommer IE, Glenthøj B, Kahn RS, Dazzan P, McGuire P.
Mol Psychiatry. 2018 Jun 7. doi: 10.1038/s41380-018-0082-9.

Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis.

Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, Giordano A, Marques TR, Zunszain PA, Morgan C, Murray RM, Pariante CM, Dazzan P.

Schizophr Bull. 2015 Sep;41(5):1162-70. doi: 10.1093/schbul/sbv028. Epub 2015 Mar 31.

22.2 Chronic Fatigue Syndrome, occupation and mental health; what enables people with CFS to re-join the work force?

Co-Supervisor 1A: Professor Nicola Fear
Research School/Division or CAG: Academic Psychiatry
E-mail: Nicola.t.fear@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/nicola.t.fear.html

Co-Supervisor 1B: Professor Sir Simon Wessely
Research School/Division or CAG: Academic Psychiatry
Email: simon.wessely@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/simon.wessely.html

Project description:

Chronic Fatigue Syndrome (CFS) is characterised by feeling extremely tired and generally unwell and affects over 250,000 people. Only 5-30% of people appear to fully recover. People with CFS find it difficult to carry out everyday tasks and activities. Still, little is known about how this impacts their ability to work, and more importantly, what predicts return to work if their symptoms subside and how we can support people with CFS to stay in employment during the early course of their illness. Your PhD will focus on addressing these questions, and aims, in the long term, to contribute to the quality of life of those affected by CFS. Further, we anticipate that your PhD will inform the development and implementation of employment support programs. We envisage the successful PhD student to work closely with experts by experience and other stakeholders in this important field of study.

You will use readily available large quantitative datasets in combination with qualitative interviews with CFS patients (conducted by the student). Training opportunities will be provided, mostly by King's, to develop your quantitative and qualitative research methods skills. Budget will be made available for external courses.

Year 1:

- Conduct a literature review on occupational outcomes in CFS patients
- Set up a stakeholder advisory group including an expert by experience
- Conduct data cleaning
- Start quantitative data analyses

Year 2:

- Submit systematic review for publication
- Conduct, transcribe and start analysing the qualitative interviews
- Finalise quantitative data analyses

Year 3:

- Finalise qualitative analyses
- PhD write up
- Prepare manuscripts for publication
- Present at stakeholder event and (inter)national conferences

Two representative publications from supervisors:

Thandi G, **Fear NT,** Chalder T. A comparison of the Work and Social Adjustment Scale (WSAS) across different patient populations using Rasch analysis and exploratory factor analysis (2017). Journal of Psychosomatic Research 92.

Holgate ST, Komaroff AL, Magan D, **Wessely S**. Chronic fatigue syndrome: understanding a complex illness 2011. Nature reviews neuroscience 12;9

23.2 Mechanisms of seizures in humans with brain tumours

Co-Supervisor 1A: Dr Gerald Finnerty
Research School/Division or CAG: IoPPN/ Neuroscience, Dept Basic and Clinical Neuroscience
E-mail: gerald.finnerty@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/bcn/our-research/neurology/finnerty-cortical-plasticity.aspx; https://geraldfinnerty.wixsite.com/finnertylab

Co-Supervisor 1B: Professor Keyoumars Ashkan
Research School/Division or CAG: IoPPN/ Neuroscience, Dept Basic and Clinical Neuroscience
Email: k.ashkan@nhs.net
Website: https://www.kch.nhs.uk/profiles/40239/keyoumars-ashkan

Project description:

Seizures are an extremely common symptom of brain tumours. Recent evidence suggests that neural activity during seizures may promote tumour growth. Hence, controlling tumour-associated seizures is vital. However, current treatments are frequently ineffective. Rational development of new therapies is hampered by our limited knowledge of how the tumour affects brain circuitry and, thereby, causes seizures.

The goal of this PhD is to establish the cellular mechanisms that cause tumour-associated seizures in humans. Our hypothesis is that the seizures are due to maladaptive plasticity. The student will focus on three main types of plastic changes to:

1. Determine whether neurons in peritumoural cortex are hyperexcitable.
2. Identify changes in synaptic strength or synapse number in peritumoural cortex.
3. Assess whether there is aberrant rewiring of neural circuitry in peritumoural cortex

The student will make ex vivo electrophysiological recordings from human brain tissue removed during neurosurgery.

Year 1: Local field potential recordings to identify epileptic discharges in peritumoural cortex. This will be combined with patch clamp recordings from single neurons in peritumoural cortex to investigate changes in neuronal excitability. In parallel, the student will investigate how brain tumours affect neuronal structure in peritumoural cortex with a combination of 3D reconstructions of recorded neurons filled with fluorescent dye and immunocytochemistry.

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

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

Two representative publications from supervisors:

Albieri G, Barnes SJ, Alonso B, Cheetham CE, Edwards CE, Lowe AS, Karunaratne H, Dear JP, Lee KC, **Finnerty GT** (2015) Rapid bidirectional reorganization of cortical microcircuits. Cereb Cortex 25:3025-3035

deSouza R, Shaweis H, Han C, Sivasubramiam V, Brazil L, Beaney R, Sadler G, Al-Sarraj S, Hampton T, Logan J, Hurwitz V, Bhangoo R, Gullan R, **Ashkan K.** Has the survival of patients with glioblastoma changed over the years? Br J Cancer. 2016;114(2):146-50.

24.2 Predicting susceptibility to cancer chemotherapy-induced neuropathy

Co-Supervisor 1A: Dr Sarah Flatters
Research School/Division or CAG: IoPPN / Wolfson CARD
E-mail: sarah.flatters@kcl.ac.uk
Website: www.kcl.ac.uk/flatterslab

Co-Supervisor 1B: Dr Angela Swampillai
Research School/Division or CAG: Guy's Cancer Centre
Email: Angela.Swampillai@gstt.nhs.uk

Collaborating Clinician: Nicola Peat - Clinical Specialist Physiotherapist
School/Division or CAG: Therapies Directorate, Physiotherapy
Email: nicola.peat@gstt.nhs.uk

Project description:

Chemotherapy-induced neuropathy (CIN) is a serious side effect of first-line chemotherapeutics for breast cancer and glioma. There is no treatment to prevent/treat CIN, therefore CIN development often curtails cancer treatment. CIN markedly affects patients' quality of life due to persistent painful, neurological symptoms following chemotherapy. Prevention would become possible with a biomarker to identify patients susceptible to CIN accompanied with novel treatments. Additionally, knowledge of CIN incidence in different patient populations would provide clinicians with vital information to determine personalised treatment strategies. Research led by Dr Flatters has established mitochondrial dysfunction as causal factor in CIN rat models. Recent data indicates mitochondrial changes in blood prior to CIN – which is being translated to patient samples as part of SUSPECT (SUSceptibility to Pain Evoked by ChemoTherapy) study. Clinical data suggests skin mitochondrial changes associated with development of other neuropathies, which will be explored using CIN rat skin. This translational, interdisciplinary project has a bench-to-bedside and back approach to determine CIN susceptibility and evaluate possible treatments underpinned by scientist-clinician-physio collaboration at Guy's.

Year 1/MRes: Retrospective CIN incidence audit on Guy's breast/glioma patients. Mitochondrial assessment in CIN rat blood.
Year 2: Database creation; neuropathy data collation from SUSPECT questionnaires. Mitochondrial assessment in patient blood samples and CIN rat skin samples.
Year 3/4: Evaluate preventative therapeutic strategies in preclinical and clinical settings.
Training: Diverse range of experimental techniques, clinical audit procedures, patient database creation, data analysis, experimental design, presentation skills, project organisation, time management. Seminars, journal clubs through Wolfson CARD and Guy's Cancer Centre.

Two representative publications from supervisors:

Duggett NA, Griffiths LA, Flatters SJL (2017) Paclitaxel-induced painful neuropathy is associated with changes in mitochondrial bioenergetics, glycolysis, and an energy deficit in dorsal root ganglion neurons. *Pain* Aug 158(8):1499-1508

Morris KA, Golding JF, Blesing C, Evans DG, Ferner RE, Foweraker K, Halliday D, Jena R, McBain C, McCabe MG, Swampillai A, Warner N, Wilson S, Parry A, Afridi SK. Toxicity profile of bevacizumab in the UK Neurofibromatosis type 2 cohort. *J Neurooncology* 2017;131(1):117-124

https://www.kcl.ac.uk/ioppn/depts/bcn/our-research/cells-behaviour/giese-memory-mechanisms.aspx

26.2 Precision medicine and mechanism: How and for whom do psychological treatments work?

Co-Supervisor 1A: Dr Kimberley Goldsmith
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience/Division of Psychology and Systems Sciences
E-mail: kimberley.goldsmith@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/kimberley.goldsmith.html

Co-Supervisor 1B: Prof Rona Moss-Morris
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience/Division of Psychology
Email: rona.moss-morris@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/rona.moss-morris.html

Name of Collaborating Clinician: Hazel Everitt
School/Division & CAG: Medicine, University of Southampton
Email: hae1@soton.ac.uk
Website: https://www.southampton.ac.uk/medicine/about/staff/hae1.page

Project description:

Understanding how treatments work (mechanisms) and for whom (in which subgroups) is key. Mediation and moderation analysis can answer such questions. Many mediation and outcome processes are longitudinal in nature, and can be modelled using the structural equation modelling framework (SEM, Goldsmith et al, 2018 doi: 10.1037/met0000154). There is strong clinical interest in modelling overarching mediation and moderation processes, however these aspects are often studied separately and non-longitudinally. We will extend longitudinal mediation models to incorporate moderation transdiagnostically, using data from two large trials of cognitive behavioural therapies in chronic fatigue syndrome (PACE) and irritable bowel syndrome (ACTIB). This will include methods refinement and development for latent class moderating variable extensions, where individuals can be categorized according to clinically informative symptom groupings.

This cross-disciplinary project (psychology, statistics, medicine) will contribute to methodological and clinical understanding of precision medicine and mechanisms relating to transdiagnostic cognitive behavioural treatments. There are future back-translational precision medicine implications for the application of such treatments, whereby the biological bases of important moderating factors of treatment mechanisms could be sought.

Skills training will include: translation of clinical questions into models/methods, R and Mplus software packages (or equivalent), and statistical simulation methods, as well as transferrable presentation, dissemination and collegial skills.

Years:

1. literature review, moderators added to longitudinal PACE mediation models, ACTIB mediation/moderation models in SEM.
2. incorporation of observed moderators, and methods for incorporating latent moderators, into mediation models.

3. simulation studies of model statistical properties of models and write-up of thesis.

Two representative publications from supervisors:

Goldsmith KA, Chalder TC, White PD, Sharpe M, Pickles A. Tutorial: Simplex, latent growth and latent change structural equation models for longitudinal mediation in the PACE trial of treatments for chronic fatigue syndrome. Psychological Methods, **2018,** 23(2):191-207. doi: 10.1037/met0000154.

Sibelli A, Chalder T, Everitt H, Chilcot J, **Moss-Morris R**. Positive and negative affect mediate the bidirectional relationship between emotional processing and symptom severity and impact in Irritable Bowel Syndrome. Journal of Psychosomatic Research, 2018 105: 1-13. 10.1016/j.psychores.2017.11.016

27.2 Getting nosey about brain repair: how does presynaptic plasticity aid functional integration in regenerating olfactory nerve terminals?

Co-Supervisor 1A: Dr Matthew Grubb
Research School/Division or CAG: Centre for Developmental Neurobiology, IoPPN
E-mail: matthew.grubb@kcl.ac.uk
Website: www.grubblab.org

Co-Supervisor 1B: Prof Juan Burrone
Research School/Division or CAG: Centre for Developmental Neurobiology, IoPPN
Email: juan.burrone@kcl.ac.uk
Website: https://devneuro.org/cdn/people-detail.php?personID=1039

Project description:

The adult brain is generally terrible at repairing itself. One exception to this rule is the projection from the nose to the olfactory bulb – the olfactory nerve – whose component cells are continually produced throughout life. This ongoing generation of new inputs to the brain means that the olfactory nerve can also naturally regenerate after injury. However, although olfactory nerve regrowth can be effective, the success of functional contacts made by regrowing axons with their target cells in the brain remains unclear. There are crucial unanswered questions regarding the strong inhibitory influence that target circuits usually have on olfactory nerve terminals, questions that will form the basis for your PhD project with us. Year 1: Is presynaptic inhibition still strong when inputs are actively regenerating, or is it lowered during regrowth? Year 2: In either case, does the level of feedback inhibition on nerve terminals aid, or hinder their re-connection with post-synaptic partners? And Year 3: Can we modulate this process to aid brain repair? Your project will combine both laboratories' expertise, coupling the Grubb lab's experience studying plasticity in the olfactory bulb, with the Burrone lab's experience investigating the dynamics of presynaptic function. You will employ electrophysiological recordings together with cutting-edge functional imaging including 2-photon microscopy in vivo, to explore how presynaptic terminals adapt during regeneration. Importantly, your findings will not only inform basic understanding of brain function, but will also be relevant to approaches trying to repair circuits in all areas of the nervous system.

Two representative publications from supervisors:

Galliano E, Franzoni E, Breton M, Chand AN, Byrne DJ, Murthy VN, **Grubb MS** (2018) Embryonic and postnatal neurogenesis produce functionally distinct subclasses of dopaminergic neuron. *eLife*, 7:e32373.

Grillo FW, Neves G, Walker A, Vizcay-Barrena G, Fleck RA, Branco T, **Burrone J** (2018) A Distance-Dependent Distribution of Presynaptic Boutons Tunes Frequency-Dependent Dendritic Integration. *Neuron* 99:275-282.

28.2 Ultra-high field MRI in MR-negative, PET-positive refractory focal epilepsies

Co-Supervisor 1A: Professor Alexander Hammers
Research School/Division or CAG: School of Biomedical Engineering & Imaging Sciences; Imaging and Biomedical Engineering CAG
E-mail: alexander.hammers@kcl.ac.uk
Website:https://kclpure.kcl.ac.uk/portal/alexander.hammers.html; http://www.sthpetcentre.org.uk/

Co-Supervisor 1B: Dr Enrico De Vita
Research School/Division or CAG: School of Biomedical Engineering & Imaging Sciences, Imaging and Biomedical Engineering CAG
Email: enrico.devita@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/enrico.devita.html

Collaborating Clinician Dr Colm McGinnity
School/Division & CAG: Biomedical Engineering & Imaging Sciences
Email: colm.mcginnity@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/colm.mcginnity.html; http://www.sthpetcentre.org.uk/

Project description:

Epilepsies affect 1/200 people. In focal epilepsies, seizures start in one part of the brain; 1/3 patients continue seizures despite medication. Identification and removal of the epileptogenic zone can stop seizures. MRI can detect epileptogenic lesions (notably focal cortical dysplasias, FCDs, and hippocampal abnormalities). However, **not all are visible on 3T MRI (up to 50% of FCDs).** In such MRI-negative patients, positron emission tomography (PET) can detect both hippocampal abnormalities and FCDs. **7T MRI may reveal abnormalities invisible at lower fields** (Veersema et al. 2017).

The student will test the **hypothesis that additional sensitivity results from detailed 7T imaging of "PET-positive" regions,** i.e. those with decreased glucose metabolism.
Starting from existing high-resolution MR sequences, we will evaluate accelerated and motion-resilient sequences being developed in the School, to find specific signal signatures that can potentially be back-translated to standard clinical field strengths. Synergistic reconstruction of multi-parametric data and analyses including deep learning and generative adversarial networks will be implemented to extract maximal feature information from sub-millimetre images.

- Year 1 – pilot established sequences alongside novel acquisitions/reconstructions
- Year 2 – MR sequence optimisation/selection; commence data acquisition (40/70 subjects with epilepsy; 20/30 controls) and analyses (ROI based, voxel based, machine learning)
- Year 3/3.5 – complete data acquisition, analyses, writing-up

MRes students will acquire pilot data in controls and generate a machine-specific atlas of hippocampal subfields for subsequent analyses.

Full training in MR imaging, image analysis, and clinical background provided by the supervisors and collaborators. Success could allow more people with epilepsy to be offered life-changing surgery.

Two representative publications from supervisors:

Keihaninejad S, Heckemann RA, Gousias IS, Hajnal JV, Duncan JS, Aljabar P, Rueckert D, **Hammers A**. Classification and lateralization of temporal lobe epilepsies with and without hippocampal atrophy based on whole-brain automatic segmentation of MR images. PLoS ONE, 2012; 7(4): e33096. Doi:10.1371/journal.pone.0033096

Boscolo Galazzo I, Mattoli MV, Pizzini FB, **De Vita E**, Barnes A, Duncan JS, Jäger HR, Golay X, Bomanji JB, Koepp M, Groves AM, Fraioli F, Cerebral metabolism and perfusion in MR-negative individuals with refractory focal epilepsy assessed by simultaneous acquisition of (18)F-FDG PET and arterial spin labeling, Neuroimage Clin. 2016;11:648-57. PMID: 27222796

30.2 Investigating localisation and axonal transport of synaptic adhesion molecules and their mRNAs using genome editing technology

Co-Supervisor 1A: Prof. Robert Hindges
Research School/Division or CAG: IoPPN/ Centre for Dev. Neurobiology & MRC Centre for Neurodev. Disorders
E-mail: robert.hindges@kcl.ac.uk
Website: http://tinyurl.com/jgdkxx3

Co-Supervisor 1B: Prof. Uwe Drescher
Research School/Division or CAG: IoPPN/ Centre for Dev. Neurobiology
Email: uwe.drescher@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/uwe.drescher.html

Project Description:

Establishing the correct brain circuitry underlying memory, learning or behaviour requires the **appropriate action of molecules regulating axon pathfinding and synapse formation**. We concentrate on large transmembrane molecules, teneurins, that interact across the synapse and that are believed to shape brain connectivity. Mutations in the human gene family have been **linked to various mental disorders**, including intellectual disabilities, depression, schizophrenia, and bipolar disorder. However, the underlying mechanisms for teneurins in the aetiology of these disorders is unknown.

This project will assess the molecular **mechanisms needed to ensure the correct localisation of these proteins to synaptic sites.** Our preliminary data suggests that the 3' untranslated region of at least one teneurin member targets its mRNA into axons towards synaptic sites, suggesting that protein synthesis does not take place in the cytoplasm, but rather locally at the synapse. Over the course of the project we will investigate the **spatiotemporal distribution of different teneurins using in vitro assays for axon outgrowth and synapse formation.** In addition, we will analyse the role of the highly conserved teneurin 3'UTRs motifs for **mRNA transport and local translation at synapses in vivo using the zebrafish** model system.

Skills training: dissociated neuronal cultures, confocal/light-sheet time-lapse imaging, super-resolution microscopy, CRISPR/Cas9 genome editing, zebrafish model system

Overarching objectives for project:
Rotation/Year 1: Assessment of localisation of Teneurin protein during axon outgrowth and synapse formation in vitro
Year 2: Investigation of Teneurin mRNA localisation determined by 3'UTR motifs
Year 3: Assessment of protein/mRNA localisation in vivo using CRISPR in zebrafish larvae

Two representative publications from supervisors:

Antinucci, P., Suleyman, O., Monfries, C. & Hindges, R. (2016). Neural Mechanisms Generating Orientation Selectivity in the Retina. *Current Biology* 26: 1802-1815.

Suetterlin,P. and Drescher,U. (2014). Target-independent ephrinA/EphA-mediated axon-axon repulsion as a novel element in retino-collicular mapping. *Neuron* 84, 1-13.

33.2 Understanding the impact of psychiatric morbidity on employment and benefit changes: a data linkage project

Co-Supervisor 1A: Professor Matthew Hotopf
Research School/Division or CAG: Academic Psychiatry
E-mail: matthew.hotopf@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/matthew.hotopf.html

Co-Supervisor 1B: Dr Ira Madan
Research School/Division or CAG: Medicine Clinical Academic Group
Email: ira.madan@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/en/persons/ira-madan(310e3b24-3921-4485-be54-647d68ba561b).html

Project description:

The biggest cause of long-term occupational disability is mental disorders. Research suggests that people with a disability (e.g. mental health, musculoskeletal conditions) are 32% less likely to be employed than those without. The student will contribute to accelerating understanding about the dynamics between patients presenting with mental disorders, their occupational status and receipt of welfare benefits. This will be done by analysing data from a unique data linkage between South London Maudsley mental health electronic data (containing details of the largest clinical cohort of adults (n=380,000) referred to UK psychiatric services), with the Department for Work and Pension data. This linkage should be finalised in Spring 2019.
The student will join a wider research team that is also working with this linked dataset. The research questions for the PhD project are "What patient or treatment characteristics are predictive of return to work? How does this vary for different mental health diagnoses?" These questions can be tailored to fit with the student's interest after discussion with the supervisors. The student will be trained in how to apply quantitative data analyses techniques for longitudinal and cross-sectional data in the statistical packages STATA and MPlus. Training will be provided by KCL, but budget will be made available for external courses on a needs basis.

Year one

- Conduct literature review on 'what components of psychiatric morbidity predict occupational outcomes?'
- Write statistical analyses plan
- Data cleaning, preliminary analyses

Year two

- Submit systematic review for publication
- Continue data analyses

Year three:

- Finalise data analyses
- Writing up thesis
- Preparing manuscripts for publication
- Dissemination results on conferences and stakeholder events

Two representative publications from supervisors:

Davis K & **Hotopf M** et al (2018). The validity of selected mental health diagnoses in English Hospital Episode Statistics: Using data linkage to electronic patient records to assess the validity of selected mental health diagnoses in English Hospital Episode Statistics (HES). PLOS One. Online First

Henderson M, **Madan I**, Hotopf M (2014). Work and mental health in the UK. BMJ, 348;7953.

34.2 Understanding Pain and Treatment Response in Neurodegenerative Disease

Co-Supervisor 1A: Dr Matthew Howard
Research School/Division or CAG: Division of Neuroscience, IoPPN
Email: Matthew.Howard@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/matthew.howard.html

Co-Supervisor 1B: Professor Marzia Malcangio
Research School/Division or CAG: Division of Neuroscience, IoPPN
E-mail: Marzia.Malcangio@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/marzia.malcangio.html

Collaborating Clinician: Professor Ray Chauduri
School/Division & CAG: Clinical Neuroscience, IoPPN
Email: ray.chaudhuri@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/en/persons/kallol-ray-chaudhuri(fa1be0c9-c0bb-4f73-903b-07fbbbf13779).html

Project description:

There are currently 35 million people worldwide living with dementia. Estimates suggest that between 30-60% of these individuals live with daily pain, but pain is often overlooked when considering their treatment. Existing pharmacological therapies offer limited efficacy, irrespective of any side effects. Our understanding of how these treatments work remains relatively poor, nor do we fully understand how neurodegenerative diseases perturb how the brain represents pain and responds to treatment. The proposed project, using functional magnetic resonance imaging (fMRI), aims to characterise the experiences of evoked and ongoing pain in patients with two common neurodegenerative disorders, Alzheimer's and Parkinson's disease. We will compare these patients to healthy, pain free individuals. We will also study the analgesic effects of remifentanil, a potent opioid, in these three groups.

The successful candidate will have the opportunity to work at the heart of three vibrant, pioneering KCL research groups, specialising in pain and neuroinflammation (Malcangio), neurodegeneration (Chaudhuri) and neuroimaging (Howard). The student will receive interdisciplinary training in fMRI acquisition, analysis and interpretation, psychometric, psychophysical and clinical investigative techniques. Within the first year, the student will have optimised a multimodal protocol for examining evoked and background pain in patients with neurodegenerative disease. In year two, further investigation of modulation of pain in these patients using remifentanil will be undertaken. In year three, the student will disseminate their findings to their public and their academic peers. The candidate will be expected to present at relevant international conferences (e.g. IASP) and author publications in high impact journals.

Two representative publications from supervisors:

Hodkinson, D. J., Khawaja, N., O'Daly, O., Thacker, M., Zelaya, F. O., Wooldridge, C. L., **Howard, M. A.** (2015). Cerebral analgesic response to non-steroidal anti-inflammatory drug ibuprofen. Pain, 156(7), 1301-1310.

Aman, Y., Pitcher, T., Simeoli, R., Ballard, C. & **Malcangio, M.** (2016) Reduced thermal sensitivity and increased opioidergic tone in the TASTPM mouse model of Alzheimer's disease. Pain. 157, 10, p. 2285-2296

35.2 Is the complement component 4 gene responsible for synaptic pruning and brain volume reduction in schizophrenia?

Co-Supervisor 1A: Dr Matthew Kempton
Research School/Division or CAG: Institute of Psychiatry, Psychology and Neuroscience, Psychosis CAG
E-mail: matthew.kempton@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/matthew.kempton.html

Co-Supervisor 1B: Prof Philip McGuire
Research School/Division or CAG: Institute of Psychiatry, Psychology and Neuroscience, Psychosis CAG
Email: Philip.mcguire@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/philip.mcguire.html

Project description:

Genome wide association studies (GWAS) of patients with schizophrenia show the strongest association[1] with the Major Histocompatibility Complex (MHC) a central component of the immune system. A recent study[2] shows that this association arises in part from the complement component 4 gene (C4). C4 is found in neurons, and animal studies have revealed its importance in synaptic pruning. This is significant as post-mortem studies have shown reduced numbers of synapses in patients with schizophrenia. Synaptic pruning is likely to contribute to the reduction in cerebral grey matter volume observed in MRI studies of patients with schizophrenia. However the pathway between C4 genotype and grey matter loss has not been investigated.

The PhD candidate will use locally-acquired multimodal clinical datasets to investigate this pathway. Rich genetic, proteomic, neuroimaging and clinical data is available. The candidate will have the option to interview patients in studies that are on-going.

Available Datasets (all longitudinal and include genetic, proteomic and MRI data)
-EU-GEI: study completed, 350 at ultra high risk (UHR) of psychosis
-PSYSCAN: study near completion, 300 UHR, 400 first episode psychosis (FEP), 100 controls
-BBC study: On-going n>400 FEP

Population data from the UK-Biobank, will be used to examine the effect of C4 genotype on gray matter volume in n=10,000.

Year-1: Training in neuroimaging, attending relevant courses in genetics and proteomics (Kempton), Analysis of EU-GEI data (Kempton), data collection in BBC study
Year-2: Analysis of PSYSCAN data (McGuire) and UK-Biobank data (Kempton)
Year-3: Analysis of BBC study data (McGuire) and thesis write-up

References
1) Nature 511, p421–427 (2014)
2) Nature 530, p177-183 (2016)

Two representative publications from supervisors:

Kempton MJ, McGuire P (2015) How can neuroimaging facilitate the diagnosis and stratification of patients with psychosis? Eur Neuropsychopharmacol. 2015 May;25(5):725-32.

Pollak TA, Rogers JP, Nagele RG, Peakman M, Stone JM, David AS, **McGuire P** (2018) Antibodies in the Diagnosis, Prognosis, and Prediction of Psychotic Disorders. Schizophr Bull. 2018 Feb 21. doi: 10.1093/schbul/sby021.

36.2 The future is remote: developing remote assessment and monitoring technology for ADHD

Co-Supervisor 1A: Professor Jonna Kuntsi
Research School/Division or CAG: IoPPN
E-mail: jonna.kuntsi@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/jonna.kuntsi.html

Co-Supervisor 1B: Professor Richard Dobson
Research School/Division or CAG: IoPPN
Email: richard.j.dobson@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/richard.j.dobson.html

Collaborating Clinician: Professor Philip Asherson and Professor Chris Hollis
School/Division & CAG: IoPPN (PA); University of Nottingham (CH)
Email: philip.asherson@kcl.ac.uk; Chris.Hollis@nottingham.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/philip.asherson.html;
https://www.nottingham.ac.uk/medicine/people/chris.hollis

Project description:

Remote technology (e.g. smartphones, fitness trackers) provides the opportunity to change the way in which many conditions are managed and treated, with long-term remote assessments enabling the collection of data on a person's condition at a level of detail that was previously impossible.

This project will focus on developing and applying a new remote technology assessment battery, using the RADAR-base platform developed by the supervisory team (RADAR-CNS.org; RADAR-Base.org;), to attention-deficit/hyperactivity disorder (ADHD) in adults. Diagnosis of ADHD signals the need for long-term treatment and monitoring, yet individual needs and long-term outcomes are highly variable. Current clinical practice is not optimally fast or sensitive in responding to changes in the patient's symptoms and treatment needs. Remote technology offers unprecedented opportunities for transforming how ADHD is managed and for obtaining detailed data on predictors and markers of outcomes (persistence/remission). In the future, smartphone-based feedback could also be used to encourage health behaviours, such as physical activity, that may contribute to ADHD remission.

Objectives:

1) To develop and pilot a remote assessment battery for ADHD that incorporates active (questionnaires, cognitive tasks) and passive (activity) monitoring.

2) To apply the remote assessment battery to our sample of adults with ADHD, addressing both clinical and research questions about long-term outcomes.

This project would suit a student with an interest in health informatics related software development and data science. We will work closely with the chosen health informatics SME, and with clinicians (Professors Chris Hollis and Phil Asherson) and patients. Training is provided.

Two representative publications from supervisors:

Cognitive and neurophysiological markers of ADHD persistence and remission.
Cheung CH, Rijsdijk F, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, Kuntsi J.
Br J Psychiatry. 2016 Jun;208(6):548-55. doi: 10.1192/bjp.bp.114.145185. Epub 2015 Aug 6.
PMID: 26250744

RADAR-base: An Open Source mHealth Platform for Collecting, Monitoring and Analyzing data Using Sensors, Wearables, and Mobile Devices
Ranjan Y, Rashid Z, Stewart C, Kerz M, Begale M, Verbeeck D, Boettcher S, The Hyve, Dobson R, Folarin A, RADAR-CNS Consortium
JMIR Preprints. 29/08/2018:11734
DOI: 10.2196/preprints.11734
URL: http://preprints.jmir.org/preprint/11734

37.2 Understanding transdiagnostic mechanisms in cognitive behavioural interventions for patients with Persistent Physical Symptoms

Co-Supervisor 1A: Prof. Sabine Landau
Research School/Division or CAG: IoPPN, Psychology and System Sciences, Dept. Biostatistics and Health Sciences
E-mail: sabine.landau@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/sabine.landau.html

Co-Supervisor 1B: Prof Trudie Chalder
Research School/Division or CAG: Psychological Medicine
Email: Trudie.chalder@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/trudie.chalder.html

Project description:

Persistent Physical Symptoms (PPS) are associated with profound disability and high health care costs. There is a body of evidence demonstrating that cognitive behavioural (CBT) interventions can reduce levels of symptoms and improve functioning in a range of PPS. While it is standard clinical practice to adapt psychological therapies to the patient population it is not clear which components of CBT are transdiagnostic, that is, address responses shared by patients across the PPS spectrum, and which are disorder specific. Identifying such mechanisms can help clinicians target core mechanisms and develop new psychological interventions for other patient groups with PPS.

This PhD project will develop and apply methods for modelling the impact of the symptoms on underlying mechanisms and will provide an opportunity to develop knowledge of psychological theory, interventions and skills in biostatistics. The student will have access to general research skills and advanced statistical methods training provided by the DTP and the Biostatistics & Health Informatics department. In addition, external training will be available if required.

In year one, the student will carry out a systematic review of mechanistic theories in PPS and existing methods for assessing transdiagnostic mechanisms and will prepare individual participant data (IPD) from a number of CBT trials for pooling likely to include the PACE trial (White et al 2011) and the PRINCE Secondary trial. In years 2 and 3 the student will develop modelling techniques (such as structural equation modelling, integrative data analysis) to assess whether mechanisms are shared across disorders or operate differentially.

Two representative publications from supervisors:

Dunn G., Emsley E., Liu H., **Landau S.**, Green J., White I. & Pickles A. (2015) Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health: a methodological research programme. *Health Technology Assessment* **19** (93) http://dx.doi.org/10.3310/hta19930

Chalder T., Goldsmith KA, White PD, Sharpe M, Pickles AR. (2015) Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *Lancet Psychiatry* **2** (2):141-52. doi.org/10.1016/S2215-0366(14)00069-8

38.2 Applying Neuroadaptive Bayesian Optimisation to identify circuit-based stratification biomarkers for Autism Spectrum Disorder

Co-Supervisor 1A: Eva Loth
Research School/Division or CAG: Forensic and Neurodevelopmental Sciences
E-mail: eva.loth@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/eva.loth.html

Co-Supervisor 1B: Prof Robert Leech
Research School/Division or CAG: CNS, Neuroscience, IoPPN
Email: robert.leech@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/robert.leech.html

Project description:

There is great interest in applying precision medicine approaches to autism to guide therapies based on an individual's neurobiological profile. This requires new neuroimaging approaches that shift the focus from group comparisons to individual predictions.

In typical neuroimaging, brain activity is measured while participants perform a pre-determined cognitive task. In this PhD project, we will use a radical new approach that reverses this logic by starting with specific brain circuits and probing how activity in these circuits changes across many cognitive tasks. We propose using Neuroadaptive Bayesian Optimisation (NBO), which employs closed-loop real-time fMRI to find neurofunctional abnormalities across a dozens of tasks much faster than typical fMRI. The approach will generate an individualised neurofunctional fingerprint of the relation between brain function and cognition, with great potential as a stratification biomarker.

PhD plan:
As a proof-of-principle, this PhD project will focus on two well-described brain networks involved in reward processing and emotional reactivity. The first half of the PhD will map out the functioning of each network across a range of cognitive tasks in approximately 20 healthy controls. Subsequently, the approach developed in part 1 will be applied to quantify atypicalities in the functioning of specific circuits in individuals with autism, resulting in individualised neurofunctional fingerprints for 20-40 people with ASD (scanning costs from associated MRC funding).

Over the PhD, the student will learn: core neuroimaging skills and the NBO approach; cognitive paradigm design and testing; FMRI data acquisition with healthy and ASD populations

Two representative publications from supervisors:

Loth, E., Charman, T., Mason, L., Tillmann, J., Jones, E. J., Wooldridge, C., ... & Banaschewski, T. (2017). The EU-AIMS Longitudinal European Autism Project (LEAP): design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. Molecular autism, 8(1), 24.

Lorenz, R., Violante, I. R., Monti, R. P., Montana, G., Hampshire, A., & **Leech, R.** (2018). Dissociating frontoparietal brain networks with neuroadaptive Bayesian optimization. Nature communications, 9(1), 1227.

39.2 What impact do antipsychotic treatments have on self-harm and suicide in psychosis? A pharmaco-epidemiological study.

Co-Supervisor 1A: Dr James H MacCabe
Research School/Division or CAG: IoPPN/ Academic Psychiatry/ Psychosis
E-mail: james.maccabe@kcl.ac.uk
Website: kclpure.kcl.ac.uk/portal/james.maccabe.html

Co-Supervisor 1B: Dr Richard D Hayes
Research School/Division or CAG: IoPPN/ Academic Psychiatry/ Psychological medicine
Email: richard.hayes@kcl.ac.uk
Website: kclpure.kcl.ac.uk/portal/richard.hayes.html

Project description:

Suicide is a major, avoidable contributor to premature death in schizophrenia, with between 5 and 15% of people with schizophrenia completing suicide, and many more attempts. There is increasing evidence that non-adherence to antipsychotic treatment is the largest modifiable risk factor for suicide (OR = 3.75), and that some antipsychotics, particularly clozapine, have the stronger anti-suicidal effects than others.

The student will study the pharmacoepidemiology of suicide and self-harm using the Clinical Research Interactive Search (CRIS), a unique, searchable database of clinical records.

Year 1: the student will identify a cohort of patients with schizophrenia, schizoaffective disorder and other psychotic disorders meeting inclusion criteria for the study, and will document the start and stop dates of antipsychotic treatments in the cohort (the exposure) and identify instances of non-fatal self-harm and completed suicide (the outcome).

Year 2: analysis, which will use cox regression and other time-series analyses to examine associations between treatment and risk for self-harm and suicide.

Year 3: Writing up and presentation at international conferences

Training: the student will undergo training in a number of transferrable skill-sets, including natural language processing, data linkage, data management, data governance, epidemiology (including pharmaco-epidemiology), advanced statistical analysis, presentation skills and academic writing.

The research will have clear translational implications for clinical practice. For example, patients with established risk factors for self-harm and suicide (eg young, male, affective disturbance, previous history of self harm) would preferentially be prescribed drugs which are associated with the greatest protective effects.

Two representative publications from supervisors:

Wimberley T, **MacCabe JH**, Laursen TM, Sørensen HJ, Astrup A, Horsdal HT, Gasse C, Støvring H. Mortality and Self-Harm in Association With Clozapine in Treatment-Resistant Schizophrenia. Am J Psychiatry. 2017; **174**:990-998.

Kadra G, Stewart R, Shetty H, **MacCabe JH**, Chang CK, Taylor D, **Hayes RD**. Long-term antipsychotic polypharmacy prescribing in secondary mental health care and the risk of mortality. Acta Psychiatr Scand. 2018; **138**:123-132

40.2 The biology of vulnerability: Mapping the fetal and neonatal brain at risk of autism and ADHD.

Co-Supervisor 1A: Prof. Grainne McAlonan
Research School/Division or CAG: Behavioural and Developmental Psychiatry, CAG.
E-mail: grainne.mcalonan@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/grainne.mcalonan.html

Co-Supervisor 1B: Dr Jonathan O'Muircheartaigh
Research School/Division or CAG: Imaging and Biomedical Engineering Clinical Academic Group
Email: JonathanOM@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/jonathanom.html

Project description:

Autism Spectrum Disorder (ASD) and related neurodevelopment conditions such as ADHD are highly heterogeneous conditions with diverse outcomes. Genetic and environmental risk factors for this spectrum overlap; and it is increasingly appreciated that compensatory mechanisms and the postnatal environment strongly influence developmental trajectories throughout life. Thus, some individuals at risk may receive a diagnosis in early childhood; others may not be diagnosed until adulthood; some may develop traits only; still others may be unaffected. This means that what is inherited or acquired in these conditions is a 'vulnerability' to adverse neurodevelopmental outcomes. However, the biological basis of this vulnerability is not understood. To reveal this, we need to look at the human brain as early as possible – before post-natal experiences further alter brain maturation. As part of the European Network lead by KCL (holding the world's largest grant for autism research and mental health; https://www.aims-2-trials.eu/), the student will use advanced MRI to identify what subtle alterations in brain structure and function during the perinatal period make children vulnerable to lifelong difficulties.

Skills training: from hands on recruitment and monitoring of data collection to MRI analyses (multiple modalities) and write-up.

Year 1: Training in study protocols, statistical analysis and MRI analysis of existing data (with access to >100 datasets). Contribution to on-going data collection, training in GCP etc. Generating hypotheses.
Year 2: Hypothesis testing – analysis, interpretation and write-up. Generating next phase hypotheses. Continued data collection. International networking.
Year 3: Hypothesis testing – analysis, interpretation and write-up. Attending conferences, career planning. International networking.

Two representative publications from supervisors:

White matter development and early cognition in babies and toddlers
O'Muircheartaigh, J., et al., White matter development and early cognition in babies and toddlers Sep 2014 In : Human Brain Mapping. 35, 9, p. 4475-4487

Andrews, D. S., Marquand, A., Ecker, C. & McAlonan, G. M. Using Pattern Classification to Identify Brain Imaging Markers in Autism Spectrum Disorder
Apr 2018 Current Topics in Behavioral Neuroscience. Springer, p. 1-24

41.2 Physical health, mental health and barriers to employment and other activities

Co-Supervisor 1A: Prof Paul McCrone
Research School/Division or CAG: IoPPN, Psychology and Systems Science
E-mail: paul.mccrone@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/paul.mccrone.html

Co-Supervisor 1B: Dr Barbara Barrett
Research School/Division or CAG: IoPPN, Psychology and Systems Science
Email: Barbara.m.barrett@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/barbara.m.barrett.html

Project description:

Background: Patients with severe mental illness (schizophrenia spectrum and bipolar disorder) experience low levels of employment and a morbidity gap due to physical health problems. The relationship between these two issues isn't clear; are employment difficulties exacerbated by physical health problems? What is the economic impact of this? Severe mental illness and related physical health problems such as diabetes and cardiovascular disease have a considerable cost to the NHS and to both individuals and across society, for example in disability benefits and social and informal care. The individual and combined impact that they have on productivity costs is likely to be substantial.

Aims: To (1) measure the economic consequences of physical health problems in people with SMI, (2) estimate the likelihood of being in employment for those with SMI only, and (3) SMI plus specific physical health problems.

Methods: The project will use survey data including the British Household Panel Survey/ Understanding Society data alongside existing clinical trial data. Key variables on SMI, physical health, and employment will be extracted and analysed.

Skills training: Training will be available in systematic review and the quantitative methods for analysis of longitudinal data.
Objectives: Year 1: Training in and completion of systematic review, setting hypotheses, identification of suitable data sets and permissions for survey and research data. Year 2: Final training and analysis of data. Year 3: Final analysis, write up.

Two representative publications from supervisors:

Pennington M and McCrone P. Does Non-Adherence Increase Treatment Costs in Schizophrenia? PharmacoEconomics 2018; 36: 941-955.

Tyrer, P., Cooper, S., Salkovskis, P., Tyrer, H., Crawford, MJ., Byford, S., Dupont, S., Finnis, S., Green, J., McLaren, E., Murphy, D., Reid, S., Smith, G., Wang, D., Warwick, H., Petkova, H. & Barrett, B. Clinical and cost-effectiveness of cognitive behaviour therapy for health anxiety in medical patients: a multicentre randomised controlled trial. 18 Jan 2014 In : The Lancet. 383, 9913, p. 219-225

42.2 Why does it hurt? Understanding spinal cord neuron function using in vivo imaging and cell-type specific sequencing.

Co-Supervisor 1A: Prof Stephen McMahon
Research School/Division or CAG: IoPPN/ Wolfson CARD
E-mail: stephen.mcmahon@kcl.ac.uk
Website:https://www.kcl.ac.uk/ioppn/depts/wolfson/research/McMahon-Lab/McMahon-Lab.aspx

Co-Supervisor 1B: Dr Franziska Denk
Research School/Division or CAG: IoPPN/ Wolfson CARD
Email: franziska.denk@kcl.ac.uk
Website: franziskadenk.com

Project description:

We all know what it is like to be in pain. The occasional headache, a twinge in our back. It can help us imagine what life must be like for the many unfortunate individuals among us for whom pain has become a daily occurrence. With limited treatment options, most have long resigned and simply suffer in silence.

Science has some understanding as to why we perceive chronic pain. We know spinal cord neurons are majorly involved in amplifying maladaptive neuronal activity coming in from your body and carrying the signal up into your brain. But we still lack detailed knowledge of which populations of neurons are most important and how their activity is altered in different pain conditions.

Your PhD could help shed light on these questions by using two technologies that have recently been developed and are starting to revolutionise neuroscience research in general: in vivo calcium imaging and fluorescence-activated cell sorting (FACS) of specific cell populations using genetically tagged neuronal nuclei. We would train you to use these two techniques to answer the question of how the function of specific spinal cord populations changes in the context of chronic pain.

Your objectives will be:

1) generate imaging data for spinal cord neuron populations to compare their activity in mice that are in a pain state compared to those that are not (year 1+2)
2) isolate these same spinal cord neuron populations for transcriptomic and epigenomic analysis to understand the molecular correlates of any functional change (year 2+3).

Two representative publications from supervisors:

Chisholm KI, Khovanov N, Lopes DM, La Russa F, McMahon SB (2017). Large scale in vivo recording of sensory neuron activity with GCaMP6. bioRxiv 166959; doi: https://doi.org/10.1101/166959

Denk F, McMahon SB, Tracey I (2014). Pain vulnerability: a neurobiological perspective. Nat Neurosci 17(2): 192-200. http://www.nature.com/neuro/journal/v17/n2/abs/nn.3628.html

43.2 Characterising the role of regional GABA and glutamate balance in modulating resting-state functional connectivity in psychosis

Co-Supervisor 1A: Dr Gemma Modinos
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience; Psychosis CAG
E-mail: gemma.modinos@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/gemma.modinos.html

Co-Supervisor 1B: Dr Owen O'Daly
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience; Clinical Neurosciences CAG
Email: o.o'daly@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/o.o%27daly.html

Collaborating Clinician: Prof. Philip McGuire
School/Division & CAG: Institute of Psychiatry, Psychology & Neuroscience; Division of Academic Psychiatry / Psychosis CAG
Email: philip.mcguire@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/philip.mcguire.html

Project description:

Background: About 1 in 100 people will develop a psychotic disorder such as schizophrenia over their lifetime. However, current treatments for schizophrenia do not work for about 40-60% of patients and have no impact on prevention. Post-mortem and preclinical studies strongly implicate abnormal excitatory-inhibitory (E:I) balance (interactions between GABA and glutamate neurotransmission) in the pathophysiology of schizophrenia. This study will use a multimodal neuroimaging approach to investigate the role of local E:I balance in maintaining resting-state functional connectivity patterns within networks linked to the expression of psychosis in healthy controls (HCs), people at ultra-high risk of psychosis (UHR) and patients with a first-episode of psychosis (FEP). This project has enormous translational potential: delineating the impact of E:I balance on resting-state functional connectivity in early psychosis will advance our pathophysiological understanding of the disorder and may facilitate the discovery of biomarkers and new treatments aimed at early intervention and prevention.

Planned research methods and training provided: The student will be trained in participant recruitment (e.g., informed consent, the human tissue act, good clinical practice), assessment, MRI scanning and MRI data analysis.

Objectives / project plan:

- **Year 1**: Data collection: participant recruitment/scanning, maintenance/production of case report forms and databases.
- **Year 2:** Participant recruitment/scanning, preliminary data analysis.
- **Year 3**: Complete participant scanning, finalise data analysis, thesis write-up.
- **Optional, year 4**: This additional time would allow unplanned extensions in case of any delays in participant recruitment and/or offer a period of time following thesis submission for the student to support their transition into the post-doctoral phase.

Two representative publications from supervisors:

Modinos G, Şimşek F, Azis M, et al. (2018) Prefrontal GABA levels, hippocampal resting perfusion and the risk of psychosis. Neuropsychopharmacology. 0:1–8; https://doi.org/10.1038/s41386-017-0004-6

Worker A, Dima D, Combes A, Crum WR, Streffer J, Einstein S, Mehta MA, Barker GJ, C R Williams S, **O'Daly O.** Test-retest reliability and longitudinal analysis of automated hippocampal subregion volumes in healthy ageing and Alzheimer's disease populations. Hum Brain Mapp. 2018 Apr;39(4):1743-1754. doi: 10.1002/hbm.23948. Epub 2018 Jan 16. PubMed PMID: 29341323.

45.2 Identifying brain-behavioral links in toddlers at risk of neuropsychiatric disorder

Co-Supervisor 1A: Dr Chiara Nosarti
Research School/Division or CAG: Psychosis CAG
E-mail: Chiara.nosarti@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/chiara.nosarti.html
Twitter Handle: @PretermResearch

Co-Supervisor 1B: David Edwards
Research School/Division or CAG: Child Health, Imaging and Biomedical Engineering
Email: ad.edwards@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/ad.edwards.html

Project description:

Approximately 25% of children born before 32 weeks (i.e., very preterm) have persisting neuropsychiatric problems. It is a public health priority to increase our understanding of the origins of mental illness by explicating neurodevelopmental mechanisms. Furthermore, there is an urgent need for research that can inform on how to intervene to reduce psychiatric risk.

This study will investigate the antecedents of psychiatric disorder in 2-4 year old children recruited from the Developing Human Connectome Project: 100 children who were born very preterm and 100 typically developing controls. At birth all children received the most sophisticated neuroimaging methods available to date. Multimodal brain imaging information acquired during the neonatal period, together with collateral family, clinical and immune profile information will be used to outline predictors of psychiatric risk by identifying early in life those children who are vulnerable to experiencing behavioural impairments that have been associated with psychiatric disorder (e.g. emotion dysregulation, irritability, socio-emotional impairments). A range of methods including machine learning will be applied to the data, creating measures for the identification of vulnerable children at birth who could benefit from preventive interventions before any psychiatric problem manifests. This information will be used to develop a biologically-informed training programme aimed at enhancing children's resiliency. The successful student will receive training in neurodevelopmental assessment and magnetic resonance imaging methods of the developing brain, including structural and functional connectivity.

Two representative publications from supervisors:

Papini C, White TP, Montagna A, ... **Nosarti C**. Altered resting-state functional connectivity in emotion-processing brain regions in adults who were born very preterm. Psychological Medicine. 2016;46:3025-3039.

Ball G, Aljabar P, Nongena P, ... **Edwards AD**. Multimodal image analysis of clinical influences on preterm brain development. Annals of Neurology. 2017;82:233-246.

46.2 Pre-and post-natal biological and psycho-social risk factors influencing neurodevelopmental outcomes in middle childhood: comparing two longitudinal cohorts in the UK and South Africa

Co-Supervisor 1A: Prof. Carmine M. Pariante
Research School/Division or CAG: Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience
E-mail: carmine.pariante@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/carmine.pariante.html

Co-Supervisor 1B: Prof Daniel Stahl
Research School/Division or CAG: Psychology and System Sciences, IoPPN
Email: daniel.r.stahl@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/daniel.r.stahl.html

Project description:

The in-utero environment is crucial in shaping a child's brain development, and through this, his/ her social, emotional, cognitive and behavioural outcomes. A range of prenatal factors have been shown to impact on these developmental outcomes, including biological factors (e.g., infections) and psycho-social factors (e.g., maternal stress during pregnancy). This PhD project will benefit from a collaboration between two multi-disciplinary, longitudinal cohorts: The UK-based Psychiatry Research and Motherhood-Depression (PRAM-D) project (led by Dr. Pariante) investigates how ante-natal depression modifies stress-reactivity and neurodevelopment in children aged 6-8 years; and the South African Safe Passage Study (in collaboration with Dr Eva Loth) investigates the role of a range of biological and psycho-social perinatal risk factors in developmental outcome in 4,500 mother-child pairs aged 3-12 years. The cohorts include a range of clinical, biological and environmental measures (e.g., mental health, parent-child interaction, cognitive tests/eye-tracking, EEG, cortisol). The aim of this project is to investigate common vs. distinct pathways by which a range of pre- and post-natal risk factors impact neurodevelopmental outcome across two cultures.

In year 1, the student will undertake relevant statistical courses on longitudinal data analyses and prediction modelling, to fit developmental trajectories of symptom development and create subgroupings of peri-natal risk factors. In year 2, he or she will be trained in EEG and eye-tracking analyses to examine cognitive and brain functional differences that may mediate the link between environmental risk and outcome. He or she will also be able to participate in data collection in Stellenbosch, South Africa. Year 3 will focus on comparing and integrating results across the two cohorts.

Two representative publications from supervisors:

Osborne S, Biaggi A, Chua TE, Du Preez A, Hazelgrove K, Nikkheslat N, Previti G, Zunszain PA, Conroy S, Pariante CM. Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: The Psychiatry Research and Motherhood – Depression (PRAM-D) Study. Psychoneuroendocrinology. 2018 Jul 13.

McDonnell, J., Stahl, D., Day, F., McGuire, P., & Valmaggia, L. R. (2018). Interpersonal sensitivity in those at clinical high risk for psychosis mediates the association between childhood bullying victimisation and paranoid ideation: A virtual reality study. DOI: 10.1016/j.schres.2017.04.029

47.2 Psychophysiological mechanisms underlying benign and clinically significant positive psychotic symptoms

Co-Supervisor 1A: Dr Emmanuelle Peters
Research School/Division or CAG: Psychology Department, Psychology & Systems Science Division, previously Psychosis CAG (now Croydon Specialist Psychosis and Neurodevelopmental)
E-mail: Emmanuelle.peters@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/emmanuelle.peters.html

Co-Supervisor 1B: Dr Matteo Cella
Research School/Division or CAG: Psychology Department, Psychology & Systems Science Division
Email: matteo.cella@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/matteo.cella.html

Project description:

Psychotic experiences (PEs), such as hearing voices or having odd beliefs, are not always associated with distress or requiring care. Psychological explanations of psychosis suggest that it is how individuals appraise, and cope with, their PEs, rather than their presence, that leads to distress. Biological explanations suggest that the body's ability to adapt flexibly to stress plays a role in the subjective experience of PEs. Cognitive Behaviour Therapy for psychosis (CBTp) aims to reduce distress by changing how people appraise, and respond to, their PEs. This project seeks to identify the signatures of distress, across both psychological and physiological levels, which can determine whether PEs become clinically significant, and how they reduce through therapy.
Experience Sampling Method (ESM) uses a Smartphone App over a 1-week period, allowing 'in-the-moment' measurement of PEs, thoughts, and emotions within their social and environmental context. Developments in technology also allow for wearable devices to record biological stress indicators, such as heart rate variability (HRV) and electrodermal activity (EDA). We will use HRV, EDA, and ESM concurrently to assess individuals with benign PEs and compare them to patients with distressing PEs pre- and post-CBTp. This will allow us to determine (1) factors that lead to benign or distressing outcomes of PEs (2) how CBTp works. This will improve our understanding of the psychobiology of symptoms, to inform future therapies and contribute to devices that can monitor symptoms and track therapeutic change.

Year 1: Training in ESM, HRV and EDA; ethical permissions; therapy observations; setting up recruitment; draft systematic review
Year 2: Recruitment; training in multi-level modelling statistics; submit review paper; analyse and draft 1st study paper
Year 3: Finish recruitment, analyse study 2, write up thesis

Two representative publications from supervisors:

Peters, E., et al., Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a "need for care". World Psychiatry, 2016. 15(1): p. 41-52.

Cella, M., et al., Using wearable technology to detect the autonomic signature of illness severity in schizophrenia. Schizophrenia Research, 2018. 195:537-542.

48.2 Genetic and environmental causes of mental health and illness in early adulthood

Co-Supervisor 1A: Professor Robert Plomin
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience
E-mail: robert.plomin@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/robert.plomin.html

Co-Supervisor 1B: Dr Tom A. McAdams
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience
Email: tom.mcadams@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/tom.mcadams.html

Project description:

The aim of the project is to investigate the genetic and environmental causes of mental health and illness in early adulthood and their links to earlier development and experiences. A unique feature of the research is that these young adults are members of twin pairs who have been studied longitudinally since infancy, which enables developmental, genetic and environmental investigation of the risk and protective factors responsible for good vs poor outcomes in emerging adulthood. The study is an extension into early adulthood of the Twins Early Development Study (TEDS), the premier twin study of development that has been funded as an MRC programme grant for 25 years.

The project will use both twin and DNA-based methods to analyse these data.

Objective 1: Study associations between environmental experiences and mental health from childhood through early adulthood.
Objective 2: Use twin analysis to investigate genetic and environmental aetiologies of associations between environmental experiences and mental health.
Objective 3: Conduct DNA analyses to predict mental health outcomes in interaction with environmental experiences.

The project will provide high-level skills training in twin and DNA analysis as well as more general statistical skills. TEDS has been central to the PhD (and subsequent) success of more than 30 students and this project is expected to lead to several high-quality publications.

Two representative publications from supervisors:

Plomin, R., von Stumm, S. (2018). The new genetics of intelligence. Nature Reviews Genetics, 19, 148 – 159.

McAdams, T. A., Rijsdijk, F. V., Narusyte, J., Ganiban, J. M., Reiss, D., Spotts, E., ... & Eley, T. C. (2017). Associations between the parent–child relationship and adolescent self-worth: a genetically informed study of twin parents and their adolescent children. *Journal of Child Psychology and Psychiatry*, 58(1), 46-54.

49.2 Investigating synaptic transmission in headache pain using an in vitro microfluidic-based culture platform.

Co-Supervisor 1A: Dr Ramin Raouf
Research School/Division or CAG: Wolfson CARD / IoPPN
E-mail: ramin.raouf@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/ramin.raouf.html

Co-Supervisor 1B: Professor Peter J. Goadsby
Research School/Division or CAG: Basic and Clinical Neuroscience/ IOPPN
Email: peter.goadsby@kcl.ac.uk
Website:https://www.kcl.ac.uk/ioppn/depts/bcn/Our-research/Neurology/goadsby-holland-headache-group/Lab-group-members.aspx

Project description:

Scientific Background:
Migraine headache remains an unmet clinical challenge with significant impact on quality of life for the sufferers. Headache pain is transmitted by the peripheral axons of trigeminal neurons innervating cranial structures and craniofacial blood vessels, while centrally synapsing onto the brainstem nuclei (Goadsby and Hoskin 1997). Several neurotransmitters and neuropeptides such as CGRP and neurokinin-1 are produced in the trigeminal ganglion neurons that modulate pain transmission and the blood vessels but the basic mechanisms of generation of headache pain are largely unknown.
Building upon a novel microfluidic based cell culture platform developed in Raouf lab, the overarching objective of this project is to develop a model the trigeminovascular system in vitro. Using this platform, the aim would be to reconstruct the trigeminovascular system in microfluidic co-culture platform and characterize modulation of synaptic transmission.

Year 1 /2: Techniques: cell culture, microfluidic culture, viral tracing, calcium imaging. The prospective candidate will learn cell culture and cell imaging techniques and begin to characterize the co-cultures.
Year 3/4: Techniques: Pharmacology and patch clamp recording. The objective of the year is to investigate the regulation synaptic transmission by CGRP and other modulators. Stretch goal would be to differentiate neurons that innervate cranial meninges and compare their properties to the neurons innervating the skin.

Translational Significance: Understanding the molecular mechanisms of headache generation will lead to generation of more effective therapeutics. The microfluidic based cell models offer an unprecedented opportunity to investigate the basic mechanisms of headache pain signalling facilitating target selection for therapeutic development.

Two representative publications from supervisors:

Tsantoulas, C., Farmer, C., Machado, P., Baba, K., McMahon, S.B., and Raouf, R. (2013). Probing Functional Properties of Nociceptive Axons Using a Microfluidic Culture System. PLoS One 8(11), e80722.

Ho, T.W., Edvinsson, L., and Goadsby, P.J. (2010). CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol* 6(10), 573-582.

51.2 Development of a cognitive behavioural intervention for young adults with low self-esteem in the context of stigma or discrimination

Co-Supervisor 1A: Dr Katharine Rimes
Research School/Division or CAG: Dept of Psychology, Institute of Psychiatry, Psychology and Neuroscience. Psychological Medicine and Older Adults CAG
E-mail: Katharine.Rimes@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/katharine.rimes.html
https://www.kcl.ac.uk/ioppn/depts/psychology/research/ResearchGroupings/LGBT-Mental-Health.aspx

Co-Supervisor 1B: Dr Patrick Smith
Research School/Division or CAG: Dept of Psychology, Institute of Psychiatry, Psychology and Neuroscience. Child and Adolescent CAG
Email: patrick.smith@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/patrick.smith.html

Project description:

Individuals viewed by others as possessing an attribute associated with less value in their social context (e.g. in relation to sex, race, sexual orientation or mental illness) are more likely to experience negative attitudes, discrimination and lower status in power situations (Corrigan, 2000; Link and Phelan, 2001). These experiences can adversely impact on self-esteem (Mak et al., 2007); low self-esteem is a risk factor for mental health problems (Sowislo & Orth, 2013). Conversely, when one has low self-esteem, it can be more challenging to cope with prejudice and discrimination.

The research team are piloting a cognitive behavioural therapy (CBT) intervention for young adults (16-25 years) who have low self-esteem and feel that stigma, prejudice or discrimination contributes to this. The current format involves face-to-face sessions, which are resource-intensive and not widely accessible. This PhD would involve the development and preliminary evaluation of online video modules containing the same advice. These modules would be provided over a set period (e.g. 8 weeks). They would be accompanied by goal setting for new coping behaviours; a facilitator would monitor these and provide support via email.

Objectives:

Year 1: Developing video modules about effective methods for coping with prejudice or discrimination and improving self-confidence, co-produced with young adults with lived experience of such issues.
Year 2: Case series of new intervention and refinement.
Year 3: Randomised pilot study: intervention versus waiting-list control.

Skills training:

- Research involving people with lived experiences of psychological difficulties.
- Psychological intervention development skills.
- Quantitative and qualitative clinical research methodology.

Two representative publications from supervisors:

Rose, AV, McIntyre, R & Rimes, KA 2018, 'Compassion focused intervention for highly self-critical individuals: Pilot study' *Behavioural and Cognitive Psychotherapy*.
DOI: 10.1017/S135246581800036X

Smith, P, Scott, R, Eshkevari, E, Jatta, F, Leigh, E, Harris, V, Robinson, A, Abeles, P, Proudfoot, J, Verduyn, C & Yule, W 2015, 'Computerised CBT for depressed adolescents: Randomised controlled trial' Behaviour Research and Therapy, vol. 73, pp. 104-110. DOI: 10.1016/j.brat.2015.07.009

52.2 ONCHIP: Optogenetically-controlled Neural Arrays of Circuits in a High-content Imaging Platform

Co-Supervisor 1A: Andrea Serio
Research School/Division or CAG: Tissue Engineering & Biophotonics
E-mail: andrea.serio@kcl.ac.uk
Website: www.seriolab.com

Co-Supervisor 1B: Ian Thompson
Research School/Division or CAG: Tissue Engineering & Biophotonics
Email: i.thompson@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/i.thompson.html

Collaborating Clinician: Dr. Rickie Patani
School/Division & CAG: UCL, Institute of Neurology & The Crick Institute
Email: rickie.patani@ucl.ac.uk

Project description:

This project aims to create a stem cell derived in vitro system to model synaptic communication between neuronal populations in a bioengineered neural-circuit-on-chip platform, controlling neuronal activity with optogenetics.

Using expertise available within our group (in vitro modelling, neural differentiation and neuroengineering, live imaging, micro-fabrication, cell-material interface) and building on already optimised neural tissue engineering platforms, we will create arrays of stem cell derived cortical neurons of different subtypes on bioengineered substrates, which will allow to control interconnectivity between groups of neurons and synapse formation using a combination of topographical cues and surface biofuncionalisation techniques.

Creating a functional circuit with defined connectivity "on-a-chip", will then allow to use high-content live microscopy and automated image analysis to study formation and maturation of synaptic connections. Using surface topography and functionalisation with extracellular matrix proteins we will control the architecture of the circuit and be able to mechanistically study the factors that influence synapse formation/function. We will characterize the network functionality using high-content live fluorescent imaging with advanced molecular imaging tools. The student will have the opportunity to receive a multidisciplinary training spanning: microfabrication, bioengineering, stem cell differentiation, advanced live imaging and molecular cloning, neurobiology and disease modelling. This project will also include translational aspects as, trough established collaborations, we will seek to apply the platform to modelling autism spectrum disorders in vitro, comparing it to existing model platforms.

This platform will recapitulate synapse formation and synaptic transmission "on-a-chip" and serve as a powerful in vitro model for neurodevelopmental disorders.

Two representative publications from supervisors:

Serio, A. et al. "Astrocyte pathology and the absence of non-cell autonomy in an induced pluripotent stem cell model of TDP-43 proteinopathy" *Proc Natl Acad Sci U S A* 110, 4697–4702 (2013)

Hall, C. E. et al. Progressive Motor Neuron Pathology and the Role of Astrocytes in a Human Stem Cell Model of VCP-Related ALS. *Cell Rep* **19**, 1739–1749 (2017).

53.2 Stimulating thought; using brain stimulation and machine learning to improve cognition in health and illness

Co-Supervisor 1A: Prof Sukhi Shergill
Research School/Division or CAG: Institute of Psychiatry, Psychosis CAG
E-mail: sukhi.shergill@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/sukhi.shergill.html

Co-Supervisor 1B: Dr Rosalyn Moran
Research School/Division or CAG: IoPPN, Dept of Neuroimaging
Email: rosalyn.moran@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/rosalyn.moran.html

Project description:

Schizophrenia is often associated with pronounced deficits in executive function, limiting functional outcome. Our recent work indicates that non-invasive trans-cranial direct current stimulation (tDCS) is a promising therapeutic intervention targeting these deficits. Successful clinical translation of tDCS depends on optimal neurostimulation parameters which are currently unknown and vary across individuals. In addition, tDCS is most effective when used with a cognitive task that drives the underlying neural system, facilitating learning; again, the optimal cognitive task is not known.

To address these challenges, the student will optimize tDCS by combining it with recent developments in real-time neuroimaging and machine learning: Neuroadaptive Bayesian Optimisation (NBO). tDCS/NBO will be used to efficiently find, first, the optimal cognitive task and then the optimal stimulation parameters for individual patients, potentially markedly improving the clinical benefit of tDCS.

PhD plan:
i) Analysis of our existing fMRI data in schizophrenia patients across a range of executive tasks, identifying core frontal regions that hypofunctional in schizophrenia; ii) use NBO, in healthy controls, to discover the optimal cognitive task paradigm that can maximise this frontal activity; (iii) once the optimal task has been defined, NBO will be combined with tDCS and used to search out an individual's optimal neurostimulation parameters in both patients and controls; iv) subsequently, once optimal neurostimulation parameters are defined, they will be applied across repeated sessions outside the scanner alongside cognitive testing, to assess improvement in cognitive outcome.
The PhD will involve developing a range of neuroimaging/neurostimulation and analysis skills in a clinical context.

Two representative publications from supervisors:

Stimulating thought: a functional MRI study of transcranial direct current stimulation in schizophrenia.
Orlov, N. D., O'daly, O., Tracy, D. K., Daniju, Y., Hodsoll, J., Valdearenas, L., Rothwell, J. & Shergill, S. S. 24 Jul 2017 In : Brain. 140, 9, p. 2490-2497

Active Inference in OpenAI Gym: A Paradigm for Computational Investigations Into Psychiatric Illness.
Cullen M, Davey B, Friston KJ, Moran RJ.
Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 Sep;3(9):809-818.

54.2 Regulation of neural stem cell quiescence

Co-Supervisor 1A: Dr Rita Sousa-Nunes
Research School/Division or CAG: IoPPN, Centre for Developmental Neurobiology
E-mail: rita.sousa-nunes@kcl.ac.uk
Website:
https://devneuro.org/cdn/groupoverview.php?groupID=88&height=1254&width=2220&ref=group-leaders

Co-Supervisor 1B: Dr Marc-David Ruepp
Research School/Division or CAG: IoPPN, Department of Basic and Clinical Neuroscience
Email: marc-david.ruepp@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/bcn/dri/lab-groups/index.aspx

Project description:

Background. Regulated proliferation of stem cells is required for growth, maintenance and repair of tissues. Many stem cells undergo periods of reversible cell-cycle arrest accompanied by low biosynthetic activity, termed quiescence. Quiescence prevents stem cell exhaustion and proliferation-induced mutations. Neural stem cells (NSCs) are mostly quiescent in the adult mammalian CNS. Their (re)activation also regulates learning, memory and mood. Cancer cells too can undergo quiescence, rendering them refractory to chemo- and radiotherapies. Despite its importance, quiescence remains poorly understood at cellular and molecular levels.

The Sousa-Nunes laboratory has discovered a novel, evolutionarily conserved, post-transcriptional mechanism of controlling NSC quiescence/activation: subcellular compartmentalisation.

Aims. 1. Identification of mRNA species accumulating over time in quiescent NSC subcellular compartments.
2. Determination of the processing status of these mRNA.

Models. Mouse primary adult hippocampal NSC cultures for transcriptomic studies; validation of key findings in vivo in mouse and Drosophila, enquiring into evolutionary conservation.

Training. The student will acquire diverse 'wet' and 'dry' skills (already established among the two laboratories): subcellular fractionation, RNA isolation, RNAseq, small molecule fluorescent in situ hybridisation, molecular biology, lentiviral-mediated gene delivery, immunohistochemistry, confocal microscopy, genetics, and bioinformatics.

Year 1: Total RNAseq on fractions of active and quiescent NSCs

Year 2: Validation of RNAseq results in vitro and then in vivo

Year 3+: Characterization of levels and activity of mRNA export machinery
Deciphering molecular mechanisms of compartmentalisation using validated targets

Two representative publications from supervisors:

Sousa-Nunes R, Lee LL, Gould AP (2011) Fat cells reactivate quiescent neuroblasts via TOR and glial insulin relays in *Drosophila*. *Nature* 471:508-12.

Ruepp MD #, Aringhieri C #, Vivarelli S, Cardinale S, Paro S, Schümperli S, Barabino SML (#equal contribution) (2009) *Mammalian pre-mRNA 3' end processing factor CF Im68 functions in mRNA export. Molecular Biology of the Cell,* 20:5211-5223.

56.2 Establishing the earthworm as a new invertebrate model for regeneration and neurogenesis research

Co-Supervisor 1A: Prof Stephen Sturzenbaum
Research School/Division or CAG: School of Population Health & Environmental Sciences
E-mail: stephen.sturzenbaum@kcl.ac.uk
Website: www.toxicogenomics.info

Co-Supervisor 1B: Dr Darren Williams
Research School/Division or CAG: IOPPN
Email: darren.williams@kcl.ac.uk
Website: http://tinyurl.com/hzbvh8n

Project description:

To understand neural systems, their development and regeneration, we need a versatile macro-invertebrate model that overcomes the many experimental and ethical hurdles encountered in complex vertebrates. An ideal candidate is the earthworm which is characterized by superior regenerative capacities; for example, it is capable of fully regenerating its brain within few weeks of surgically removal. A recent 450 million RNAseq experiment has identified putative molecular genetic drivers, many of which have human homologues. Any knowledge gathered can thus be translated into cell culture, vertebrate models and ultimately the clinic.

The proposed study brings together earthworm molecular genetics (Prof Sturzenbaum) and neuronal growth and in vivo imaging (Dr Darren Williams) which in synergy will enable the generation of the first earthworm neuronal cell line and the first CRISPR-Cas9 mediated gene edited earthworm. These tools will establish the earthworm as a new model within the field of neuronal regeneration.

Year 1: Validate RNAseq targets by qPCR and in situ hybridization. Apply protease/Notch/JNK inhibitors to study downstream effects on regenerative performance.
Year 1 and 2: Develop a neuronal cell line. Apply CRISPR-Cas9 to introduce GFP into key neural genes within the earthworm genome.
Year 3: Apply cell line to conduct neurite outgrowth and axon guidance assays (e.g. collagen gel / co-culture, growth cone turning / collapse and in vitro stripe assays) to characterize drivers of regeneration. Use the gene edited earthworm to visualize cell division and regenerating neurons.

Training: Micro-dissection, molecular genetic, neurobiological and imaging techniques, all of which are theme-overlapping transferable skills.

Two representative publications from supervisors:

Stürzenbaum, S.R., Hoeckner, M., Panneerselvam, A., Levitt, J., Bouillard, J.-S., Taniguchi, S., Dailey, L.-A., Ahmad Khanbeigi, R.A., Thanou, M., Rosca, E.V., Suhling, K., Zayats, A., Green, M. (2013). Biosynthesis of luminescent quantum dots in an earthworm. Nature Nanotechnol. 8(1):57-60.

Constance, W. D, Mukherjee, A., Fisher, Y.E., Pop, S., Blanc, E., Toyama, Y., Williams D.W. (2018). Neurexin and Neuroligin-based adhesion complexes drive axonal arborisation growth independent of synaptic activity. eLife 2018;7:e31659.

57.2 A multi-disciplinary study to understand transporter associated delivery and efflux of antipsychotic drugs prescribed in AD.

Co-Supervisor 1A: Dr Sarah Ann Thomas
Research School/Division or CAG: School of Cancer and Pharmaceutical Sciences
E-mail: sarah.thomas@kcl.ac.uk
Website: https://www.kcl.ac.uk/lsm/research/divisions/ips/about/people/Thomas/index.aspx

Co-Supervisor 1B: Dr Miraz Rahman
Research School/Division or CAG: School of Cancer and Pharmaceutical Sciences
Email: k.miraz.rahman@kcl.ac.uk
Website: https://www.kcl.ac.uk/lsm/research/divisions/ips/about/people/rahman/index.aspx

Collaborating Clinician: Dr Suzanne Reeves
School/Division & CAG: Clinical Senior Lecturer in Old Age Psychiatry, Division of Psychiatry, Faculty of Brain Sciences, University College London
Email: suzanne.reeves@ucl.ac.uk

Project description:

Alzheimer's disease (AD) affects around 35 million people worldwide and with no immediate prospect of disease modification, and numbers set to double in the next 30 years, symptomatic treatment is a priority area. Psychosis in AD, which most commonly presents as delusions, is highly distressing, associated with co-morbid anxiety and agitation, can precipitate aggression towards carers, and reduces a person's ability to live independently. Given the substantial morbidity and mortality associated with antipsychotic drug use and prescribing restrictions, it is important that we fully understand the mechanisms underpinning antipsychotic drug sensitivity in AD and why it differs from older people with other conditions. The proposed multidisciplinary project will explore the phenomenon of transporter associated delivery and efflux of antipsychotic drugs prescribed in AD. The study has the potential to improve the safety of existing antipsychotic drug treatments and, more importantly for the future, guide dose predictions for clinical trials of repurposed and novel drug candidates, based on knowledge of which BBB transporters are most relevant for drug delivery to the CNS. The objectives fall into two categories: transporter function and transporter expression including ultrastructural location.

Years 1-2: Health and Safety training for laboratory work. Training sessions on handling unsealed isotopes. Cell culture training. ***In silico*** **computational study:** To understand the molecular level interactions of antipsychotic drugs with BBB transporters and identify drugs (e.g., risperidone) are substrates for OCT, MATE and PMAT. Functional interaction of selected anti-psychotics with transporters will be assessed using ***in vitro*** BBB models (eg MDCK-MDR, hCMECD3 and bend3).

Year 3: Post-mortem **human brain capillaries from healthy and age matched AD** cases will also be assessed for transporter expression (Western and Quantitative RT-PCR assays).

Year 4: Further analysis of a single transporter will also be carried out on brain AD and healthy human brain samples using **transmission electron microscopy (TEM) immunogold labelling** in collaboration with the CUI.

Two representative publications from supervisors:

Sekhar, G.N., Georgian, A.R., Sanderson, L., Vizcay-Barrena, G., Brown, R.C., Muresan, P. Fleck, R.A. and Thomas, S.A. OCT1 is involved in pentamidine transport at the human and mouse blood-brain barrier (BBB). (2017) PLoS ONE 12(3): e0173474 https://doi.org/10.1371/journal.pone.0173474

Jamshidi, S.; Sutton, J. M.; Rahman, K. M., Mapping the Dynamic Functions and Structural Features of AcrB Efflux Pump Transporter Using Accelerated Molecular Dynamics Simulations. *Scientific Reports* 2018, 8 (1), 10470.

58.2 Characterising abnormal early brain development and links to neurocognitive disorders using diffusion MRI and machine learning

Co-Supervisor 1A: Dr J-Donald Turnier
Research School/Division or CAG: Division of Imaging Sciences & Biomedical Engineering
E-mail: jacques-donald.tournier@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/jacques-donald.tournier.html

Co-Supervisor 1B: Dr Maria Deprez (Murgasova)
Research School/Division or CAG: Division of Imaging Sciences & Biomedical Engineering
Email: maria.murgasova@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/maria.murgasova.html

Collaborating Clinician: Dr Harriet Cullen, NIHR Academic Clinical Lecturer in Clinical Genetics
School/Division & CAG: Division of Imaging Sciences & Biomedical Engineering
Email: harriet.cullen@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/harriet.cullen.html

Project description:

Abnormal early brain development is involved in a range of neuropsychiatric disorders including autism, attention deficit disorders and schizophrenia. Preterm birth in particular has been linked to a 4-fold increase in incidence of serious psychiatric illness.

The developing Human Connectome Project aims to acquire MR images of 1000 preterm and term neonatal and 500 fetal subjects, with over 800 already available. The acquisition includes multi-shell diffusion MRI of unprecedented image quality, suitable for the latest state-of-the art microstructure and connectivity analyses. Additional information includes DNA, clinical information and developmental outcomes at 18 months.

The purpose of this project is to identify neuroimaging markers derived from diffusion MRI that correlate with genetic risk factors for psychiatric diseases, and/or with developmental outcomes at 18 months, using machine learning methods.

Objectives:
Year 1: Understand and apply advanced diffusion analyses to fetal and neonatal subjects, and correlate with clinical factors such as prematurity and sickness at birth.
Year 2: Understand genetic risk factors associated with predisposition to mental illness and poor outcomes following preterm birth, and investigate links with diffusion markers.
Year 3: Devise a machine learning approach to link imaging, genetic and clinical factors to the developmental outcomes at 18 months to discover interaction of these multiple factors and their influence on brain development.

The project would suit a student willing to learn computational approaches for neuroscience. The students will gain extensive experience in diffusion analysis, machine learning and understanding of early brain development.

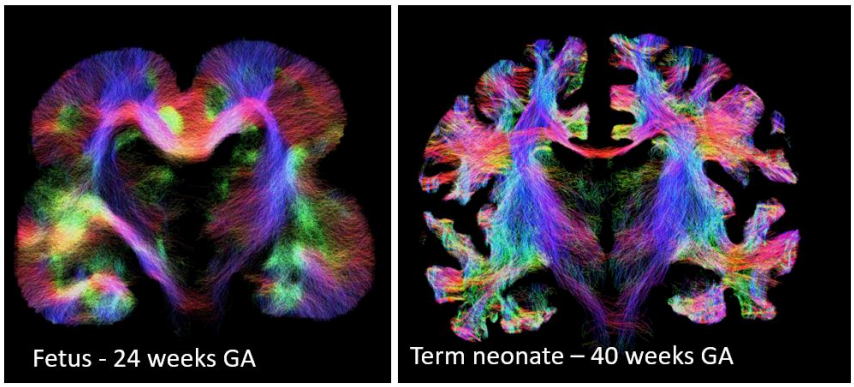

Fig. 1: Developing brain connectivity revealed by diffusion MRI

Two representative publications from supervisors:

Apparent fibre density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. D Raffelt*, JD Tournier*, S Rose, GR Ridgway, R Henderson, S Crozier, Olivier Salvado, Alan Connelly. Neuroimage 59 (4), 3976-3994, 2012.

A dynamic 4D probabilistic atlas of the developing brain. M Kuklisova-Murgasova*, P Aljabar, L Srinivasan, SJ Counsell, V Doria, A Serag, IS Gousias, JP Boardman, MA Rutherford, AD Edwards, JV Hajnal, D Rueckert. NeuroImage 54(4), 2011.

59.2 Identification of associations between oscillatory brain activity and cognitive functioning in young adult twins with autism spectrum disorder

Co-Supervisor 1A: Dr Charlotte Tye
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience
E-mail: charlotte.tye@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/charlotte.tye.html

Co-Supervisor 1B: Dr Grainne McLoughlin
Research School/Division or CAG: Institute of Psychiatry, Psychology & Neuroscience
Email: grainne.mcloughlin@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/grainne.mcloughlin.html

Project description:

Autism spectrum disorder (ASD) is characterised by a diverse range of cognitive and neural atypicalities. Recent work suggests that behavioural performance may reflect underlying differences in oscillatory brain activity. This project aims to investigate these associations within a transitional developmental window, when compensatory mechanisms may be apparent. Data will be analysed from a large-scale twin study of young adults with ASD and typical development (n=400), followed longitudinally as part of the Twins Early Development Study (TEDS). Electroencephalography (EEG) was collected during a battery of tasks indexing attentional processing and social cognition, in addition to measures of cognitive ability, daily functioning, wellbeing and quality of life. This projects aims to address the following objectives:

1) To characterise associations between oscillatory brain activity and attentional processing in adults with ASD compared to typical adults
2) To determine the associations between oscillatory brain activity, daily functioning and well-being in adults with ASD
3) To map developmental predictors of oscillatory brain activity, using existing longitudinal data
4) To chart shared and distinct genetic and environmental influences between oscillatory brain activity and ASD symptoms

To address these objectives, the student will be trained in EEG analytical techniques and twin model fitting analyses. The ultimate aim is to identify more objective brain-based markers of behavioural differences in ASD, in order to target more specific interventions.

Two representative publications from supervisors:

Tye, C., Asherson, P., Ashwood, K., Azadi, B., Bolton, P., & McLoughlin, G. (2014). Attention and inhibition in children with ASD, ADHD and comorbid ASD+ADHD: an event-related potential study. Psychological Medicine, 44(5), 1101-1116.

Tye, C., Johnson, K.A., Kelly, S. Asherson, P., Ashwood, K., Azadi, B., Kuntsi, J., Bolton, P., & McLoughlin, G. (2016). Response time variability under slow and fast-incentive conditions in ASD, ADHD and ASD+ADHD. Journal of Child Psychology and Psychiatry, 57(12), 1414-1423.

60.2 Systems Analysis of Neuroendocrine Circuits that Link Food to Ageing

Co-Supervisor 1A: QueeLim Ch'ng
School/Division or CAG: Developmental Neurobiology, IoPPN
E-mail: queelim@kcl.ac.uk
Website: https://devneuro.org/cdn/group-overview.php?groupID=73

Co-Supervisor 1B: Attila Csikász-Nagy
School/Division or CAG: BMBS/Randall
Email: attila.csikasz-nagy@kcl.ac.uk
Website: http://csikasznagylab.org

Project description:

Ageing is the major risk factor for most diseases, bearing socio-economic implications for many countries with ageing populations . Genetic and diet converge on nutrient-sensing hormonal pathways in the brain to modulate ageing and longevity. These pathways include TGF-beta, serotonin, and catecholamines that are conserved from roundworms to humans, enabling studies in the experimentally tractable roundworm C. elegans to provide new insights into the neural regulation of lifespan. Our project combines experimental and computational approaches to reveal the genetic mechanisms for sensing food to modulate lifespan.

Year 1: Elucidate the impact of food-gene interactions on lifespan by testing mutants in neuroendocrine pathways under different food regimens. Construct transcriptional reporters for the corresponding genes.

Year 2: Perform high-throughput microscopy to quantify expression dynamics of neuroendocrine reporters at single-neuron level using a custom microfluidics system.

Year 3: Model communication in these hormonal circuits to predict food-gene interactions, and validate prediction with experiments.

During this research, the student will discover how hormonal activity in the nervous system links the food to lifespan. These results will help explain how food impact health and longevity.

The student will work closely with both supervisors to design experiments and interpret results. Dr Ch'ng will train the student in molecular genetics, automated microscopy, and lifespan measurements. Dr Csikasz-Nagy will train the student in data handling, data analysis, and modelling. This project provides a unique opportunity to learn systems biology to as a new approach in biomedicine.

Two representative publications from supervisors:

Entchev E. V., Patel D. S., Zhan M., Steele A, Lu H. and **Ch'ng Q**. (2015) A Gene-Expression-Based Neural Code for Food Abundance that Mediates Dietary Effects on Lifespan. *eLife* 4:e06259

Bajpai, A., Feoktistova, A., Chen, J.S., McCollum, D., Sato, M., Carazo-Salas, R.E., Gould, K.L. and **Csikász-Nagy, A.,** (2013) Dynamics of SIN asymmetry establishment. PLoS Computational Biology, 9(7), p.e1003147.

61.2 Role of alternative splicing in mammalian neuronal diversity

Co-Supervisor 1A: Dr Eugene Makeyev
School/Division or CAG: Neuroscience
E-mail: eugene.makeyev@kcl.ac.uk
Website: https://devneuro.org/cdn/people-detail.php?personID=1398

Co-Supervisor 1B: Professor Oscar Marín
School/Division or CAG: Neuroscience
Email: oscar.marin@kcl.ac.uk
Website: http://devneuro.org.uk/marinlab/default.aspx

Project description

Brain function depends on development of multiple types of neurons characterised by distinctive structural, physiological and molecular features. How this diversity is established and maintained remains one of the most fascinating biomedical problems. Many genes can produce more than one RNA species through alternative splicing, a process involving non-uniform use of exons and introns. The nervous system expresses an especially large collection of alternative isoforms, but how this molecular program contributes to the emergence of individual neuronal identities remains poorly understood. The proposed project will address this important question by focusing on GABAergic interneurons, a heterogeneous group containing >20 distinct categories. Briefly, we will analyse single-cell RNA-sequencing data using state-of-the-art bioinformatics tools to detect interneuron type-specific differences in splicing patterns and expression of RNA-binding proteins (RBPs) known/predicted to control splicing decisions (rotation/year 1). RBPs showing the strongest correlation with type-specific splicing patterns will be shortlisted for detailed experimental studies. To elucidate splicing regulation mechanisms, the candidate RBPs will be over-expressed/knocked-down in neural cells in vitro and the effect of these treatments will be assayed using reverse transcription-PCR, single-molecule RNA FISH and immunofluorescence (year 2). Function of the most promising RBP candidate will be examined by modulating its expression in mouse brain using appropriate viral vectors, the CRISP-Cas9 technology or/and classical knockouts followed by morphological, electrophysiological and behavioural analyses (years 3-4). The two supervisors have extensive expertise in bioinformatics, biochemistry, neurobiology and mouse genetics, which will provide an ideal training environment and will ensure successful completion of the PhD studies.

One representative publication from each co-supervisor:

Yap K, Xiao Y, Friedman BA, Je HS, and **Makeyev EV** (2016) Polarizing the neuron through sustained co-expression of alternatively spliced isoforms. *Cell Rep.* 15, 1316-1328.

Mi D, Li Z, Lim L, Li M, Moissidis M, Yang Y, Gao T, Hu TX, Pratt T, Price DJ, Sestan N, and **Marín O** (2018) Early emergence of cortical interneuron diversity in the mouse embryo. *Science* 360, 81-85.