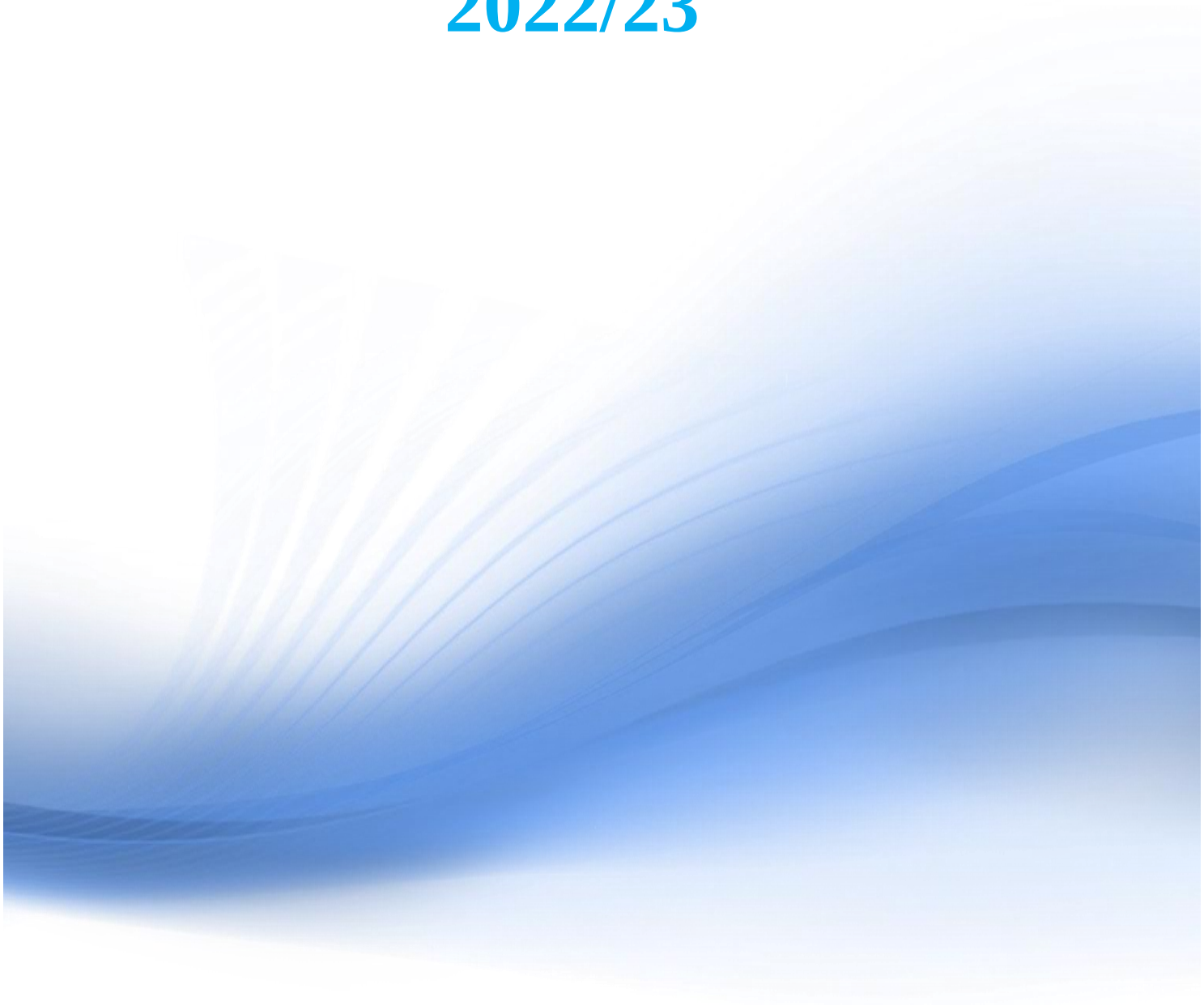
NS-MH

Neurosciences, Psychiatry and Mental Health

2022/23



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 **MRCDTP2022_NS-MH**

Deadline for application: Thursday 18th November, 23:59
Shortlisted candidates will be contacted in mid-January.

Interviews: Wednesday 26th & Thursday 27th January
The 2022/23 studentships will commence in September 2022.

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.

Contents

NS-MH 20221 Recruiting endogenous stem cells for repair following Traumatic Brain Injury

Co-Supervisor 1A: Dr Aminul Ahmed
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Co-Supervisor 1B: Prof. Marzia Malcangio
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Project Description:

Traumatic Brain Injury (TBI) is the largest cause of disability and death in the under 40s. No drug treatments are available, so interest has turned to neural stem cells (NSCs) as alternative strategies for treatment. Endogenous NSCs can be activated following injury to provide local trophic support. The key hypothesis is that injury-activated endogenous NSCs can be harnessed for recovery using pharmacological agonists to Sonic Hedgehog (Shh) signalling, a key NSC regulatory pathway.

The candidate will use both human tissue (resected following Neurosurgery) and rodent models to investigate this injury-induced process in the cerebral cortex. They will investigate potential small-molecule therapies to exploit this effect.

Key aims:

1. Define fate and proliferation characteristics of injury-induced cortical NSCs using rodent models (**Year 1 and 2**).
2. Determine the most effective candidate small molecule modulator of Shh signalling that alters NSCs (**Year 2 and 4**). Techniques include in vivo surgery, immunohistochemistry, fluorescence-activated cell sorting, cell culture in vitro proliferation assays and confocal microscopy.
3. Determine the response of human neurosurgical tissue-derived cortical NSCs to candidate molecules (**Years 2 to 4**).

A novel technique is culture of primary human NSCs, using tissue resected from neurosurgical cases.

We are using a systematic approach to determine which cells could be targeted and determine the most effective pharmacological compounds that alter the characteristics of endogenous injury-induced NSCs. By testing the pharmacological agents on primary human tissue, we can begin to predict whether a potential treatment would be effective in patients.

One representative publication from each co-supervisor:

Pringle AK, Solomon E, Coles BJ, Desouza BR, Shtaya A, Gajavelli S, Dabab N, Zaben MJ, Bulters DO, Bullock MR, Ahmed AI (2021). Sonic Hedgehog signalling promotes perilesion cell proliferation and functional improvement following Cortical Contusion Injury. Neurotrauma Reports 2: 27-38.

Simeoli R, Montague K, Jones HR, Castaldi L, Chambers D, Kelleher JH, Vacca V, Pitcher T, Grist J, Al-Ahdal H, Wong LF, Perretti M, Lai J, Mouritzen P, Heppenstall P, Malcangio M. Exosomal cargo including microRNA regulates sensory neuron to macrophage communication after nerve trauma. Nat Commun. 8:1778, 2017

NS-MH 20222 Mapping the complexity of the descending pain modulatory system in the transition from acute to chronic pain

Co-Supervisor 1A: Dr Kirsty Bannister
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Co-Supervisor 1B: Prof. Stephen McMahon
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Project Description:

The unique experience of pain is driven in part by the descending pain modulatory system (DPMS). Activity in DPMS-encompassed descending inhibitory and facilitatory pathways is altered in some chronic pain states. This PhD proposal is concerned with mapping the mechanisms that underlie DPMS functionality in the transition from health to disease.

To study modulatory pathways in rodents the student will be trained in a range of cutting-edge skills including behavioural tests (e.g. home cage analyser, conditioned place preference), surgical techniques (e.g. spinal nerve ligation), in vivo and ex vivo electrophysiology, optogenetic techniques and immunohistochemistry.

Specifically, the student will study how noradrenergic transmission from discrete brainstem nuclei (A5-A7) governs pain-like responses (behavioural and neuronal read outs) in health and disease by:

Year 1 - Validating that manipulation of purported descending inhibitory mechanisms from brainstem noradrenergic nuclei impacts pain-like behaviours/neuronal activity in wakeful/anaesthetised rodents
Year 2 - Determining whether the relative contribution of spinally projecting brainstem noradrenergic nuclei (A5-A7) activity differentially impacts behavioural manifestations of pain and spinal neuronal activity in health and disease.
Year 3 - Determining whether changes in the influence of A-nuclei activity on behavioural and neuronal read outs in the transition from health to disease is linked to dysfunctional reciprocity between brainstem noradrenergic (A nuclei). Depending on the progress the student will also have the opportunity to investigate brainstem serotonergic pathways and their reciprocity with noradrenergic transmission mechanisms.

The Bannister and McMahon labs have a great track record in generating high impact results and publications and in training, supervising, and supporting PhD students.

One representative publication from each co-supervisor:

Dickenson AH, Navratilova E, Patel R, Porreca F, Bannister K. Supraspinal opioid circuits differentially modulate spinal neuronal responses in neuropathic rats. Anesthesiology, 2020 132(4):881-894

Kucharczyk MW, Chisholm KI, Denk F, Dickenson AH, Bannister K, McMahon SB
The impact of bone cancer on the peripheral encoding of mechanical pressure stimuli. Pain, 2020 161(8):1894-1905

NS-MH 20223 Epigenetic and circuit abnormalities in neurodevelopmental disorders

Co-Supervisor 1A: Prof. M. Albert Basson
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Co-Supervisor 1B: Dr Laura Andreae
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KCL/KHP Website: https://devneuro.org/cdn/group-overview.php?groupID=80

Project Description:

Mutations in epigenetic regulators have emerged as a significant risk factor for a diverse group of neurodevelopmental disorders, with most characterised by autism and intellectual disability. The over-arching aim of this project is to identify the molecular, epigenetic, cellular and circuit abnormalities that underlie these conditions, with the ultimate objective of eventually being able to use this information to treat these conditions.
We have generated mouse models for conditions with mutations in high-risk genes that encode epigenetic regulators. The goal of this project is to use these models to identify cell type specific molecular, epigenetic and circuit abnormalities that underlie the behavioural phenotypes associated with these neurodevelopmental disorders. Techniques and skills include conditional, targeted gene deletion, behavioural assays, patch clamp electrophysiology, optogenetics, next generation sequencing and a range of molecular approaches including qRT-PCR, ChIP, Western blot, immunostaining, immunoprecipitation and advanced microscopy, tailored to suit student preferences and priorities.

Year 1: To use patch clamp electrophysiology and synaptic imaging to comprehensively characterise synaptic and plasticity abnormalities in the prefrontal cortex.
Year 2: To use a combination of cell type specific conditional gene deletion, patch clamp electrophysiology and optogenetics to comprehensively characterise cell-type-specific synaptic phenotypes.
Year 3-4: To use next generation sequencing, molecular and imaging techniques and behavioural assays to identify cell type specific mechanisms that underpin specific behavioural abnormalities.

Together, this project will link epigenetic perturbations in specific neuronal cell types to circuit and synaptic abnormalities responsible for behavioural and cognitive phenotypes associated with specific neurodevelopmental conditions.

One representative publication from each co-supervisor:

Hurley, S., Mohan, C., Suetterlin, P., Ellingford, R., Riegman, K.L.H., Ellegood, J., Caruso, A. , Michetti, C., Brock, O., Evans, R., Rudari, F., Delogu, A., Scattoni, M.L., Lerch, J.P., Fernandes, C. & Basson, M.A. (2021) Distinct, dosage-sensitive requirements for the autism-associated factor CHD8 during cortical development. Mol. Autism 12:16.

Ellingford, R.A., Panasiuk, M.J., Rabeshala De Meritens, E., Shaunak, R., Naybour, L., Browne, L., Basson, M.A.*, Andreae, L.C.* (2021) Cell-type-specific synaptic imbalance and disrupted homeostatic plasticity in cortical circuits of ASD-associated Chd8 haploinsufficient mice. Mol. Psych. doi: 10.1038/s41380-021-01070-9 *Joint corresponding authors https://doi.org/10.1101/2020.05.14.093187

NS-MH 20224 Investigating the synergy between tau and mitochondria in neurodegenerative disease

Co-Supervisor 1A: Dr Joseph Bateman

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Co-Supervisor 1B: Prof. Diane Hanger
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Project Description:

The Hanger lab have identified a tau protein fragment (Tau35), which is involved in the development of human tauopathies, including Alzheimer's disease (AD) and frontotemporal dementia. Tau35 mice exhibit deposits of highly phosphorylated tau in the brain, accompanied by age-related and progressive impairments in cognitive and motor function, and reduced survival, modelling human tauopathy. Together with amyloid plaques and tau aggregates, mitochondrial dysfunction is now considered a hallmark pathological feature of AD. Observations in patients suggest that defects in mitochondria are among the earliest manifestations of the disease. However, the relationship between Tau35 and mitochondria and their contribution to neurodegenerative disease are unknown. In this project the student will use newly developed Drosophila and mouse models expressing Tau35 to investigate the crosstalk between Tau35 and mitochondria and the underlying mechanisms contributing to disease. The overarching objectives are:

Year 1 (or rotation): Characterise the cellular and behavioural phenotypes of flies expressing intact tau and Tau35; analyse mitochondrial phenotypes in flies and mice expressing Tau35.

Year 2: Analyse the crosstalk between Tau35 and mitochondrial function in Drosophila; perform a genetic screen in flies expressing Tau35 to identify novel genes contributing to tau-induced neuropathology.

Year 3: Validate selected hits from the genetic screen in Tau35-expressing mice; test the effects of modifying mitochondrial function in Tau35-expressing mice as a potential therapeutic strategy for dementia.

The student will be trained in cutting edge Drosophila genetics and behavioural analysis techniques, mouse genetics, molecular techniques and confocal imaging by experienced members of the Bateman and Hanger labs.

One representative publication from each co-supervisor:

R.J. Hunt, L. Granat, G.S. McElroy, R. Ranganathan, N.S. Chandel, J.M. Bateman (2019). Mitochondrial stress causes neuronal dysfunction via an ATF4-dependent increase in L-2-hydroxyglutarate. J. Cell Biol. 218: 4007-4016.

Bondulich, M.K., Guo, T., Meehan, C., Manion, J., Rodriguez Martin, T., Mitchell, J.C., Hortobagyi, T., Yankova, N., Stygelbout, V., Brion, J.-P., Noble, W., & Hanger, D.P. (2016). Tauopathy induced by low level expression of a human brain-derived tau fragment in mice is rescued by phenylbutyrate. Brain. 139: 2290-2306.

NS-MH 20225 Understanding neural and cognitive mechanisms of action underpinning neuromodulation treatment in young people with persistent anorexia nervosa

Co-Supervisor 1A: Prof. Iain Campbell
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Co-Supervisor 1B: Dr Owen O'Daly
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Collaborating Clinician: Ulrike Schmidt
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Project Description:

Anorexia nervosa (AN) is a deadly and disabling neuro-circuit disorder with a typical onset in adolescence. Approximately 30% do not respond to psychotherapies, resulting in a persistent unremitting illness, with the potential to disrupt their development. We have pioneered brain stimulation treatments in adults with AN. We now have funding for a sham-controlled double-blind feasibility RCT of 20 sessions of intermittent theta-burst stimulation (iTBS) to the dorsolateral prefrontal cortex (DLPFC) in young people with persistent AN. iTBS is used in depression and is safe. We will include neuroimaging and neurocognitive tasks before and after iTBS treatment. We propose that iTBS promotes neuroplasticity and changes the relationship between the DLPFC and amygdala.
The student will learn about eating disorders, assessment of clinical/neurocognitive outcomes, neuromodulation and neuroimaging. A training needs analysis will be conducted with the student. They will be part of the vibrant eating disorders group where they will be taught project specific skills as needed (e.g. how to assess eating disorder symptoms, deliver iTBS, analyse clinical and neurocognitive tasks, utilise neuroimaging and analyse different types of neuro-imaging data. In addition, the student will be expected to attend transferrable skills training as required by their project.

Objectives: **Year 1** - The student will familiarise themselves with the elements of the project and will write a systematic review e.g. on neuro-imaging outcomes in neuromodulation in eating disorders. **Year 2** - The student will participate in data acquisition related to the ongoing RCT. **Year 3** - The student will analyse and write up their data.

One representative publication from each co-supervisor:

Dalton B, Maloney E, Rennalls SJ, Bartholdy S, Kekic M, McClelland J, Campbell IC, Schmidt U, O'Daly OG. A pilot study exploring the effect of repetitive transcranial magnetic stimulation (rTMS) treatment on cerebral blood flow and its relation to clinical outcomes in severe enduring anorexia nervosa. J Eat Disord. 2021 Jul 9;9(1):84.

Dalton B, Bartholdy S, McClelland J, Kekic M, Rennalls SJ, Werthmann J, Carter B, O'Daly OG, Campbell IC, David AS, Glennon D, Kern N, Schmidt U. Randomised controlled feasibility trial of real versus sham repetitive transcranial magnetic stimulation treatment in adults with severe and enduring anorexia nervosa: the TIARA study. BMJ Open. 2018 Jul 16;8(7):e021531.

NS-MH 20226 Laminar specific simultaneous Electroencephalography and Functional Magnetic Resonance Imaging in Epilepsy

Co-Supervisor 1A: Dr David Carmichael
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Co-Supervisor 1B: Dr Joel Winston
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Project Description:

We have been engaged in understanding epilepsy as a disease where the brain is considered to be a complex network with regions and/or networks where the normal E/I balance is perturbed with a resulting repertoire of dynamics that includes seizures. Neuroimaging methods such as EEG and fMRI can provide a window onto these networks, however, they are only able to measure large-scale (brain regions) whereas alterations in connectivity and structure often occur at a smaller scale.

Recent advances in MRI technology have allowed for cortical layer-dependent high (sub-millimetre) spatial resolution fMRI which has been used to address questions regarding the functioning of cortical circuits. However, this technology has not been used to study patients and is ideally placed to answer questions regarding alterations Our unique position at St Thomas provides access to large epilepsy patient groups, and an ultra-high field MRI system capable of imaging at the level of cortical layers in patients.

We hypothesise that layer specific fMRI can characterise epileptic networks by providing an assessment of E/I balance and inter and intra columnar connectivity. By measuring EEG at the same time these alterations will be related to frequency specific EEG features.

Year 1: Training in neuroimaging and associated analysis methods.
Year 2-3: Obtain simultaneous measurements of layer specific fMRI and EEG in patients with epilepsy. Measure differences associated with epileptic discharges and their frequency specific components.
Year 4: The main objective will be to complete and write up scientific papers and thesis.

One representative publication from each co-supervisor:

RD Sanders*, JS Winston*, GR Barnes, G Rees Magnetoencephalographic correlates of perceptual state during auditory bistability. Scientific reports, 2018, 8:976

M. Centeno et al.. DW Carmichael, “Combined electroencephalography-functional magnetic resonance imaging and electrical source imaging improves localization of pediatric focal epilepsy,” Ann. Neurol., vol. 82, no. 2, pp. 278–287, Aug. 2017, doi: 10.1002/ana.25003.

NS-MH 20227 Unravelling brain activity and sleep disturbances in prodromal Parkinson’s Disease

Co-Supervisor 1A: Dr Diana Cash
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Project Description:

Abnormalities of the lysosomal degradation system including glucocerebrosidase enzyme (encoded by GBA1) are amongst the most common genetic factors that increase the risk of developing Parkinson's Disease (PD). In particular, they are thought to underlie the early, non-motor symptoms of PD characterised by disturbances in brain-activity and sleep (named Rapid-Eye-Movement-Sleep-Behavioural-Disorder (RBD)). Using clinically-translational imaging and EEG methods, this project will first characterise abnormal brain-activity during wakefulness and sleep in the GBA1 mutant-mice, during ageing (**Phase-1**). The findings will contribute toward further modelling of the pathological neural-circuitry, using precise targeting of brain regions and cellular subpopulations by chemo- and opto-genetic methodology, in conjunction with functional-MRI (fMR; **Phase-2**).
The final, clinical phase (**Phase-3**), will build on this, whilst focusing on RBD, as an important non-motor symptom of PD. Indeed, RBD is sometimes the first and only sign of an ongoing underlying neurodegeneration that provides an unparalleled opportunity for therapeutic intervention. Unfortunately, very little is still understood about the neural-circuitries that underlie it. Intriguingly, our recent work suggests involvement of a novel cortical somatosensory-spatial-navigation-system in violent-nocturnal-body-movements that define RBD, and that can lead to serious sleep-related injuries. Here, neurostimulation/high-density-fMR-EEG imaging will be used to explore and define its role in memory and sleep deficits in RBD.

Techniques & skills: Animal models, MRI, EEG, optogenetics, chemogenetics

Objectives:

1. Characterise brain activity during wakefulness and sleep in GBA1-vs-normal mice
2. Develop hypothesis-driven-model of affected neural-circuits and target these using opto and chemogenetic tools
3. Characterise and/or manipulate an extra-hippocampal sensory-navigational-system that leads to abnormal sleep-movements in RBD-patients

One representative publication from each co-supervisor:

Westphal R, Simmons C, Mesquita BM, Wood TC, Williams SCR, Vernon AC, Cash D (2017) Characterization of the resting-state brain network topology in the 6-hydroxydopamine rat model of Parkinson's disease. PLOS One (12:e0172394–18)

Gelegen C, Cash D, Rosenzweig I (2021) Dispersed Sleep Microstates and Associated Structural Changes in GBA1 Mouse: Relevance to Rapid Eye Movement Behavior Disorder. Biorxiv doi: https://doi.org/10.1101/2021.05.26.445845

NS-MH 20228 Systems Analysis of Food-Sensing Neuroendocrine Networks that Regulate Ageing

Co-Supervisor 1A: Dr QueeLim Ch'ng
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Co-Supervisor 1B: Dr Attila Csikász-Nagy
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Project Description:

Age is the major risk factor for many diseases, including diabetes, heart attack, cancer, and neurodegeneration. Globally, ageing populations pose a major socio-economic challenge. Genetic and environmental factors converge on hormonal pathways in the brain to affect the ageing process. These pathways are highly conserved, enabling studies in the experimentally tractable roundworm C. elegans to provide new insights into the neuroendocrine regulation of ageing. Our project combines experimental and computational approaches to delineate the neuroendocrine network involving TGF-beta, serotonin, and catecholamines that are conserved from roundworms to humans.

Year 1: Investigate the effects of food-gene interactions on lifespan by testing mutants in neuroendocrine pathways under different food levels. Construct transcriptional reporters for the corresponding genes.
Year 2: Perform high-throughput microscopy to quantify single-cell expression of neuroendocrine reporter genes using a unique microfluidics system to automate experiments.
Year 3: Model communication in these hormonal circuits to predict food-gene interactions and validate prediction with experiments.

The student will discover how cross-regulation among hormones in the nervous system modulates the effects of food on lifespan. These results will help explain how nutrient information is processed by the brain and communicated to the body.

The student will work closely with both supervisors to design experiments and interpret results. Dr Ch'ng will train the student in molecular genetics, 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.

One representative publication from each co-supervisor:

Patel D.S., Diana G., Entchev E.V., Zhan M., Lu H., and Ch'ng Q. (2019) A Multicellular Network Mechanism for Temperature-Robust Food Sensing. Cell Reports 33:108521 https://doi.org/10.1016/j.celrep.2020.108521

Howell, R. S., Klemm, C., Thorpe, P. H., & Csikász-Nagy, A. (2020). Unifying the mechanism of mitotic exit control in a spatiotemporal logical model. PLoS Biology, 18(11), e3000917.

NS-MH 20229 Genetic and environmental influences on post-traumatic stress disorder

Co-Supervisor 1A: Dr Jonathan Coleman
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Co-Supervisor 1B: Prof. Thalia Eley
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Project Description:

Post-traumatic stress disorder (PTSD) is characterised by prolonged distress after experiencing a traumatic event. Many people experience trauma, but most do not develop PTSD. These individual differences in developing PTSD partly reflect genetic differences. Studies of psychiatric disorders like PTSD show that they are *complex* (affected by multiple genetic and environmental factors), and *polygenic* (genetic influences result from many genetic variants, each of very small individual effect). Recent studies have begun to identify genetic variants associated with PTSD.

In this project, the student will investigate separate and combined effects of genetic and environmental factors on PTSD, using data from cohorts including the Genetic Links to Anxiety and Depression study and the Twins Early Development Study. The student will learn to manage and analyse large-scale data, including genome-wide genotypes and detailed phenotype data, and will be based at the Social, Genetic and Developmental Psychiatry Centre, a supportive and internationally renowned centre of excellence for gene-environmental research. During the PhD, the student will:

- Examine associations between specific traumas and PTSD, and how genetic influences on trauma and PTSD affect these associations (**year 1**)
- Replicate published associations between common genetic variants and PTSD, and examine how these change in the context of social factors and psychiatric comorbidities (**year 2**)
- Use hospital records data to identify healthcare concerns that are more common in people at high genetic risk for developing PTSD (**year 3**)
- Combine genetic and environmental data to predict PTSD diagnoses, and compare prediction performance between individuals from different genetic ancestries (**year 4**)

One representative publication from each co-supervisor:

Mundy, J., Hübel, C., Gelernter, J., Levey, D., Murray, R., Skelton, M., … Coleman, J.R.I. (2021). Psychological trauma and the genetic overlap between posttraumatic stress disorder and major depressive disorder. Psychological Medicine, 1-10. https://doi.org/10.1017/S0033291721000830

Peel, A. J., Purves, K. L., Baldwin, J. R., Breen, G., Coleman, J. R. I., Pingault, J.-B., … Eley, T. C. (2021). Genetic and early environmental predictors of adulthood self-reports of trauma. MedRxiv. https://doi.org/10.1101/2021.06.09.21258603

NS-MH 202210 Bipolar Disorder and the Menstrual Cycle

Co-Supervisor 1A: Prof. Michael C. Craig
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Co-Supervisor 1B: Prof. Paola Dazzan
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Project Description:

The aim of this PhD project is to explore the relationship between mood and cognition across the menstrual cycle in women with bipolar disorder (BD). This is important because previous studies suggest that a subgroup of women with BD are more likely to experience manic and/or depressive symptoms during the late luteal phase of the menstrual cycle (Teatero et al., 2013). The biological basis of this is still poorly understood but may include direct hormonal changes or alteration of mood stabilising medication.

For example, some studies report a decrease in lithium and valproate concentration during the luteal phase (Carmassi et al., 2019). Also, brain imaging studies suggest that sex hormones modulate brain function in regions directly involved in mood and cognition (Craig et al., 2008) and these effects may be different in 'at risk' women (O'Brien et al., 2021).

Furthering our understanding of these relationships may have significant implications for treatment approaches. The project will also provide a unique opportunity to develop the requisite research skills needed to (a) carry out systematic review and meta-analysis, and (b) analyse in vivo brain imaging and behavioural data within a clinical sample.
Part 1, **year 1**: Systematic review of available literature regarding the menstrual cycle's influence on BD symptoms and cognitive changes.

Part 2, **year 2-4**: Recruitment of normally menstruating bipolar and matched control women, followed by analysis of cognitive, behavioural and in vivo brain imaging changes across the follicular and luteal phases cycle with post hoc analysis of secondary modifiers (e.g. medication).

One representative publication from each co-supervisor:

O'Brien S, Sethi A, Gudbrandsen M, Lennuyeux-Comnene L, Murphy DGM & Craig, MC. Is postnatal depression a distinct subtype of major depressive disorder? An exploratory study Arch Womens Ment Health. 2021 Apr;24(2):329-333. doi: 10.1007/s00737-020-01051-x

Hazelgrove K, Biaggi A, Waites F, Fuste M, Osborne S, Conroy S, Howard LM, Mehta MA, Miele M, Nikkheslat N, Seneviratne G, Zunszain PA, Pawlby S, Pariante CM, Dazzan P. Risk factors for postpartum relapse in women at risk of postpartum psychosis: The role of psychosocial stress and the biological stress system. Psychoneuroendocrinology. 2021 Jun;128:105218. doi: 10.1016/j.psyneuen.2021.105218. Epub 2021 Apr 3. PMID: 33892376.

NS-MH 202211 "Voices of God": understanding altered self-experience in religion and psychopathology through Social Sciences, Humanities, Psychiatry and Neuroscience

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Project Description:

Many people with psychosis, and psychologically healthy religious practitioners, report experiences of interaction with supernatural agents, such as hearing the voice of God or divinely controlled thought or movement. This project aims to improve understanding of similarities, and differences, in altered self-experience in religious experience and psychopathology. You will join a mixed methods interdisciplinary research group linking KCL, UCL and Stanford University. Phase 1 combines interviews in 40 spiritualist mediums with EEG and fMRI acquisition during reported spirit communication. You will apply natural language processing techniques using machine learning to test for semantic similarity between accounts of experiences with normative accounts from co-religionists. In Phase 2 you will interview psychosis individuals with experiences of supernatural agents, and healthy co-religionists (Pentecostal or Evangelical Christians), also acquiring EEG and fMRI. A computational measure of 'degree of cultural normativity' for reported experiences will be correlated with neurobiological measures. This will help determine shared and distinct brain processes motivating religiously interpreted alterations in self-experience in psychosis and spiritualist mediumship respectively, and what contributes to the distress and disability in mental illness compared to normative religious experience. This is relevant to improving understanding and treatment for people with psychosis.

Year 1: Develop study protocols, obtain ethics, qualitative interviewing training, computational analysis of free text and interviews with spiritualist mediums, EEG and fMRI. Review literature. Begin recruitment for Phase 2.

Year 2: Interviews with psychosis and religious groups. Computational analyses. Acquire EEG and fMRI. Exploratory analyses with brain measurement data.

Year 3: complete study, analyses, write-up.

One representative publication from each co-supervisor:

Peters E., Ward T., Jackson M., Morgan C., Charalambides M., McGuire P., Woodruff P., Jacobsen P., Chadwick P., Garety P. (2016) Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a 'need-for-care'. World Psychiatry, 15(1), 41-52. https://doi.org/10.1002/wps.20301

Deeley, Q. (2019). Revelatory experiences: meanings, motives, and causes. Religion, Brain & Behavior, 9(3), 284-291.

NS-MH 202212 Characterising the function of a novel microglial ASD biomarker using human iPSC neuron/microglia co-cultures

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https://devneuro.org/cdn/group-overview.php?groupID=30

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Collaborating Clinician: Prof. Grainne McAlonan
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Project Description:

Autism predominantly affects males, but the precise pathophysiology is unclear. Microglia, which regulate synapse formation and refinement during neurodevelopment, have been implicated here, but their precise role in disrupting neural connectivity in the brain of (male) autistic individuals is unknown.
Our own work on microglia using mouse ASD models and data mining of transcriptomes of human ASD patients led us to identify a microglia-specific cytokine, which is up-regulated only in cortical tissue of male - but not female - individuals with autism, relative to controls. Critically, whilst this cytokine has not been previously associated with autism, it is known to be involved in aberrant neuron-microglia interactions in the context of neurodegenerative diseases.

Hence, the overall aim of this project is to characterise the function of this cytokine using human in vitro cell culture systems relevant to the study of ASD. In **Year 1**, the student will establish human iPSC neuron/microglia co-cultures and determine the cell type specific expression and regulation of the cytokine using molecular and biochemical methods, also comparing cell lines donated by controls and individuals with autism. In **Years 2 and 3**, the student will investigate the functional role of the cytokine on neuron-microglia interactions, using CRISPR-mediated knockouts and overexpression of this protein. A key focus of these experiments will be the analysis of the formation, elimination and function of excitatory and inhibitory synapses using high resolution time lapse and/or Ca2+ imaging. This project will lead to a better understanding of the putative role of microglia in autism.

One representative publication from each co-supervisor:

The GTPase Arl8B Plays a Principle Role in the Positioning of Interstitial Axon Branches by Spatially Controlling Autophagosome and Lysosome Location. Adnan, G., Rubikaite, A., Khan, M., Reber, M., Suetterlin, P., Hindges, R. & Drescher, U. (2020) J. Neuroscience 40, p. 8103-8118

Interferon-γ signaling in human iPSC-derived neurons recapitulates neurodevelopmental disorder phenotypes. Warre-Cornish, K., Perfect, L., Nagy, R., Duarte, R. R. R., Reid, M. J., Raval, P., Mueller, A., Evans, A. L., Couch, A., Ghevaert, C., McAlonan, G., Loth, E., Murphy, D., Powell, T. R., Vernon, A. C., Srivastava, D. P. & Price, J. (2020): Science Advances 6, 34, eaay9506.

NS-MH 202213 Retinoid receptor modulators as novel disease-modifying therapeutics for Parkinson's disease

Co-Supervisor 1A: Prof. Susan Duty
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Project Description:

Parkinson's disease (PD) is a complex disease with multiple processes driving progressive neurodegeneration that results in motor and non-motor clinical signs. There are currently no treatments that slow down or repair existing damage in the brain of PD patients. This project will investigate the potential of a new therapeutic strategy we believe could fill this void.

Nevrargenics Ltd. have developed a new and exciting class of drugs, retinoic acid receptor modulators (RAR-Ms). These mimic the actions of endogenous retinoids to regulate multiple protective genes, supporting neuronal survival. Retinoic acid itself is effective at providing neuroprotection in animal models of PD but is not useful clinically due to activation of both the beneficial RAR targets and RXRs which trigger adverse effects. Nevrargenics' modulators are RAR-selective thus hold significant potential. In pilot studies, we showed one RAR-M, NVG0645, provided neuroprotection in a rat model of PD. This project will employ cell-based and rodent models to gather evidence supporting the beneficial effects of the RAR-Ms in PD and study human tissue to investigate whether RAR dysfunction contributes to PD.

Over-arching objectives are:
Year 1: Establish in-vivo dosing regimen and mechanistic profile of RAR modulators
Year 2: Examine neuroprotective efficacy of RAR-Ms in rodent models of PD.
Year 3: Conduct studies in human PD tissue to examine retinoid dysfunction in PD; commence examination of neurorepair efficacy in PD rodent models
Year 4: Complete neurorepair studies in rodent models with full mechanistic examination.

One representative publication from each co-supervisor:

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. DOI: 10.1016/j.neuropharm.2018.04.017.

Trigo D, Goncalves MB, Corcoran JPT. (2019). The regulation of mitochondrial dynamics in neurite outgrowth by retinoic acid receptor β signaling. FASEB J. 33(6):7225-7235. doi: 10.1096/fj.201802097R.

NS-MH 202214 Investigating the relationships between risk factors and brain glutamate in schizophrenia

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Project Description:

Several environmental and genetic risk factors have been associated with the development of psychosis and with more severe forms of schizophrenia. The biological mechanisms which link these risk factors to the onset and persistence of symptoms are unclear. One of the leading biological hypotheses of schizophrenia involves dysfunction of glutamate neurotransmission in the brain. Research using brain MRI scans in schizophrenia has found that higher levels of glutamate, particularly in the anterior cingulate cortex (ACC), are associated with more severe symptoms and poorer clinical outcomes. The overall aim of this PhD is therefore to investigate whether the presence of risk factors, including family history, early age of onset, childhood trauma and adolescent cannabis use, are associated with elevations in brain glutamate in patients with schizophrenia. Data for the PhD will be collected as part of a large international study, including up to 500 patients. Skills training includes acquisition, analysis and reporting of glutamate neuroimaging data and clinical interview of people with schizophrenia.

Years 1 and 2: Recruit, clinically assess and acquire MRI at KCL site; collate data from all participating sites; training in neuroimaging analysis, review literature.

Year 3: Complete data analyses, prepare publications, write-up thesis.

One representative publication from each co-supervisor:

Merritt K, McGuire PK, Egerton A: Association of Age, Antipsychotic Medication, and Symptom Severity in Schizophrenia With Proton Magnetic Resonance Spectroscopy Brain Glutamate Level: A Mega-analysis of Individual Participant-Level Data. JAMA Psychiatry 2021 78(6):667-681

Paetzold, I, Kempton M et al., Stress reactivity as a putative mechanism linking childhood trauma with clinical outcomes in individuals at ultra-high-risk for psychosis: Findings from the EU-GEI High Risk Study. Epidemiol Psychiatr Sci 2021 May 28;30:e40. doi: 10.1017/S2045796021000251.

NS-MH 202215 Mechanisms of cannabis-based medicines in treating tumour-associated seizures

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Project Description:

People with brain tumours frequently experience tumour-associated seizures, which respond poorly to antiseizure medication. Cannabis-based treatments have the potential to fill this therapeutic gap. The medicinal use of cannabis extracts is, however, controversial. One key issue for cannabis-based treatments of seizures is that their mechanism of action is unclear.

Hence, we propose a project to investigate the anti-seizure mechanisms of two common phytocannabiniods, Δ9-tetrahydrocannabidiol (THC) and Cannabidiol (CBD) using ex vivo living human brain tissue, donated by individuals who are undergoing brain tumour surgery. The live human brain tissue generates spontaneous seizure-like discharges.

Year 1: Local field potential recordings to identify spontaneous epileptic discharges in peritumoural cortex. Wash on Cannabidiol and THC separately and together to determine dose-response curves for their effects on seizure discharges.
Year 2: Investigate the mechanisms of the anticonvulsant effects of CBD and THC, focusing on excitatory circuitry. The student will use patch-clamp recording of visualised pyramidal neurons to study changes in neuronal excitability and excitatory neural circuitry and whether CBD and THC block the proconvulsant effects of glutamate release by glioma cells.
Year 3: Evidence suggests that Inhibition in the peritumoural cortex is reduced, which contributes to tumour-associated seizures. The student will therefore assess whether CBD and THC boost inhibition to suppress seizure discharges.

Recorded neurons will be filled with a fluorescent dye and biocytin for imaging after recording has finished. The extent of tumour infiltration in recorded human brain tissue will be assessed by labelling the tumour cells and the excitatory and inhibitory neurons.

One representative publication from each co-supervisor:

Kirby AJ, Lavrador JP, Bodi I, Vergani F, Bhangoo R, Ashkan K, Finnerty GT. (2021) Multicellular 'hotspots' harbour high-grade potential in adult lower-grade gliomas. Neurooncol Adv, 3(1):vdab026.

Stephanie Oates, Michael Absoud, Sushma Goyal, Sophie Bayley, Jennifer Baulcomb, Annemarie Sims, Amy Riddett, Katrina Allis, Charlotte Brasch Andersen, Meena Balasubramanian, Renkui Bai, Bert Callewaert, Diana LeDuc, Maximilian Radtke, Christian Korff, Joanna Kennedy, Karen Low, Bernt Popp, Lina Quteineh, Amelle Shillington, Pernille M Toerring, T Michael Yates, Christiane Zweier, Richard Rosch, M. Albert Basson, Deb K. Pal. (2021) ZMYND11 variants are a novel cause of centrotemporal and generalised epilepsies with neurodevelopmental disorder. Clinical Genetics, 100(4):412-429.

NS-MH 202216 Charting structural brain development between childhood and adulthood

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Project Description:

Characterizing brain development is a fundamental task in neuroscience. Yet, most developmental neuroimaging studies to-date have relied on cross-sectional data, which precludes investigation of developmental changes and has hampered progress in understanding the mind-brain relationship during development. In collaboration with the Danish Centre for Magnetic Resonance (DCMR), the PhD project will close this gap in our understanding of brain development. Leveraging longitudinal modelling techniques and emerging cohorts like HUBU (N = 90, 12-waves, ages 7 -21) and ABCD (N = 11,000, currently 3 waves, ages 9 -14), the PhD student will develop analysis methods for capturing longitudinal changes in brain structure and link these to biological (e.g., puberty) and behavioral predictors (e.g., alcohol usage). They will provide normative data of brain development and produce a new understanding of how the environment shapes brain development. Project 1, for instance, will use nonlinear mixed models to investigate whether alcohol usage in HUBU predicts changes in cortical thickness and whether the age of alcohol exposure moderates these effects, providing insights into sensitive periods. This PhD is expected to drive theory and methods development in the field and inform prevention and intervention work.

Skills training:
- Reproducible longitudinal modelling in R
- Behavioral genetics approaches
- Developing neuroimaging pipelines
- Science communication

Objectives:
Year 1: Skills training; literature review; preregistration & data analysis for Project 1
Year 2: Writing up Project 1; completing Project 2
Year 3: Secondment to DRCMR (www.drcmr.dk) to acquire imaging analysis skills; completion Project 3
Year 4: Completion Project 4 and writing up PhD.

One representative publication from each co-supervisor:

Fuhrmann, D., van Harmelen, A., & Kievit, R. (in press). Wellbeing and cognition are coupled during development: A preregistered longitudinal study of 1136 children and adolescents. Clinical Psychological Science, doi: https://doi.org/10.1177/21677026211030211

Zavos, H.M.S., Dalton, B., Jayaweera, K., Harber-Aschan, L., Pannala, G., Adikari, A., Hatch, S.L., Siribaddana, S., Sumathipala, A., Hotopf, M., Rijsdijk, F.V. (2020) The relationship between independent and dependent life events and depression symptoms in Sri Lanka: a twin and singleton study. Social Psychiatry and Psychiatric Epidemiology, 55 (2), pp. 237-249. DOI: 10.1007/s00127-019-01765-z

NS-MH 202217 Biomarker stratification and response to cannabidiol intervention in early stages of psychosis

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Project Description:

Prevention during a clinical high risk state for psychosis (CHR) and early intervention during a First Episode of Psychosis (FEP) are mainstream strategies to improve clinical outcomes in young people. Nonetheless, existing interventions are not personalised to individual pathophysiology, clinical needs and patterns of response/outcomes. This PhD will leverage a recently funded, large-scale, international RCT of cannabidiol in early psychosis (Stratification and Treatment in Early Psychosis, STEP), to develop the first personalised risk stratification model which can predict clinical outcomes/response to cannabinoid interventions in CHR/FEP individuals.

During **Year 1**, the candidate will learn how to analyse multimodal and multivariable prognostic models employing advanced artificial intelligence methods. During **Year 2**, they will learn how to collect, combine an and analyse core biomarkers. During **Year 3**, they will complete the analyses and develop the clinical prediction model. During **Year 4**, the candidate will learn how to validate and implement it in clinical practice. The candidate will have the opportunity to train on clinical prediction modelling methods involving artificial intelligence, big data (e.g. Electronic Health Records, digital health data, structural/functional neuroimaging and deep phenotyping measures), in combination with experimental therapeutics/psychopharmacology and preventive/early intervention strategies in one of the largest and most productive research groups on early psychosis. The candidate will additionally have the opportunity to access international clinical research networks (e.g. STEP, ECNP, PRONET), high-quality teaching and NHS clinical services (e.g. OASIS). This PhD will deliver the first-ever, individualised risk stratification model for guiding the clinical prevention/early intervention of psychosis, with extraordinary, real-world, global translational impact.

One representative publication from each co-supervisor:

Development and Validation of a Clinically Based Risk Calculator for the Transdiagnostic Prediction of Psychosis. Fusar-Poli P, Rutigliano G, Stahl D, Davies C, Bonoldi I, Reilly T, McGuire P.JAMA Psychiatry. 2017 May 1;74(5):493-500. doi: 10.1001/jamapsychiatry.2017.0284.PMID: 28355424

Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. Bhattacharyya S, Wilson R, Appiah-Kusi E, O'Neill A, Brammer M, Perez J, Murray R, Allen P, Bossong MG, McGuire P.JAMA Psychiatry. 2018 Nov 1;75(11):1107-1117. doi: 10.1001/jamapsychiatry.2018.2309.PMID: 30167644

NS-MH 202218 How does presynaptic inhibition influence axonal regeneration?

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Co-Supervisor 1B: Prof. Elizabeth Bradbury
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Project Description:

A major goal in translational neuroscience is to enhance the ability of the nervous system to repair itself after injury. This project will learn lessons in effective regeneration from part of the nervous system which can repair itself successfully – the olfactory nerve (Grubb lab) – and apply them to part of the nervous system which cannot regenerate – the spinal cord (Bradbury lab). We will focus on presynaptic inhibition, a feedback mechanism used by neuronal circuits to regulate neurotransmitter release from incoming axonal inputs. Ongoing work in the Grubb lab has shown that presynaptic inhibition is strong in olfactory nerve axons that are in the early stages of re-connecting with their target circuits, and that altering the strength of this presynaptic inhibition can affect naturally-occurring axonal regeneration in this system. But are alterations in presynaptic inhibition crucial for successful brain repair in the olfactory system, and can similar mechanisms be co-opted to promote functional recovery from spinal cord injury? This project will ask precisely these questions, using a combination of slice electrophysiology, in vivo functional imaging, ex vivo histology, and behavioural analysis, all accompanied by quantitative numerical analysis. **Year 1** will involve training in slice electrophysiology, and assessments of presynaptic inhibition in a spinal cord preparation. **Year 2** will see manipulations of presynaptic inhibition assayed with anatomical assessments of neuronal regeneration in both systems. Finally, **Year 3** will involve behavioural analyses, studying functional recovery after manipulations of presynaptic inhibition in regenerating olfactory nerve and spinal cord projections.

One representative publication from each co-supervisor:

Grubb lab work on natural regeneration in the olfactory system has been proceeding for the past few years but is still unpublished. See Dr Grubb old post-doc paper below for some of the slice physiology techniques they use to study functional features of re-connecting axons:

Grubb MS, Nissant A, Murray K, Lledo PM (2008) Functional maturation of the first synapse in olfaction: development and adult neurogenesis. J Neurosci, 28:2919-32. https://doi.org/10.1523/JNEUROSCI.5550-07.2008

Burnside et al (2018) Immune-evasive gene switch enables regulated delivery of chondroitinase after spinal cord injury Brain 141:2362-2381 https://doi.org/10.1093/brain/awy158

NS-MH 202219 What is the chronology of white matter damage in acute and chronic ischaemia, and how can it be prevented?

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Project Description:

White matter damage (WMD), correlates with cognitive impairment1 and is associated with an increased risk of Alzheimer's disease and stroke2,3, and is likely a consequence of cerebral hypoperfusion and hypoxia. Prevention of WMD due to hypoperfusion is likely, therefore, to have significant clinical benefits, making it critical to understand the processes that lead to WMD.
This project will test how hypoperfusion leads to WMD by investigating the time course of cell damage using electrophysiological recordings, immunohistochemistry, electron microscopy and, tissue taken from an in vivo model of chronic hypoxia (bilateral common carotid artery stenosis, BCCAS).

Year 1:
(1) Develop expertise in making coronal mouse brain slices kept for hours or weeks.
(2) Simulate acute ischaemia with oxygen and glucose deprivation (OGD) in acutely isolated brain slices.
   a. Test how OGD affects oligodendrocyte membrane currents and ion concentrations (with patch-clamping and imaging of ion-selective probes; Hamilton et al. Nature, 2016) in the initial stages of ischaemia.
   b. Investigate OGD-evoked morphological changes in oligodendrocytes, astrocytes, microglia, myelin and axons with immunohistochemistry.
   c. Compare these changes in WT and conditional TRPA1 knockouts.

Year 2:
(3) Using organotypic brain slices, simulate chronic ischaemia and repeat the experiments in (2).
(4) Investigate the possible benefits of blocking candidate receptors by measuring morphological and ultrastructural changes with electron microscopy that occur over the time course of pathology observed in tasks 1 and 2 above.

Year 3:
(5) Using the knowledge gained, investigate whether the same changes occur in BCCAS tissue obtained from collaborators.

One representative publication from each co-supervisor:

Hamilton, N., Kolodziejczyk, K., Kougioumtzidou, E. et al. Proton-gated Ca2+-permeable TRP channels damage myelin in conditions mimicking ischaemia. Nature 529, 523–527 (2016).

Manso Y, Holland PR, Kitamura A. et al. Minocycline reduces microgliosis and improves subcortical white matter function in a model of cerebral vascular disease. Glia 66(1), 34-46 (2018).

NS-MH 202220 Cross-cultural evaluation of multisectoral care models for children with developmental disorders in Ethiopia and Kenya

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Project Description:

Ethiopian and Kenyan children with developmental disorders and their caregivers experience severe challenges; most families receive no formal help. The NIHR-funded SPARK project ('SuPporting AfRican communities to improve mental health in Kids with developmental disorders') aims to improve support for these children and their caregivers. SPARK will include one of the largest trials conducted in developmental disorder research, evaluating a new intervention developed by the World Health Organization, the Caregiver Skills Training. Moreover, SPARK aims to improve early identification of children with developmental disorders in the community and promote inclusion. To that end, multi-sectoral care models will be developed for each of the SPARK trial sites (located in rural and urban Ethiopia and Kenya), to promote referral pathways and increase access to healthcare and education services.

This PhD project will focus on the evaluation of the multisectoral care models, including a process evaluation of actual service access and qualitative interviews with caregivers and service providers. Findings will be compared across urban and rural settings and across countries. The results of this PhD can inform service development across sub-Saharan Africa. The supervisory team comprises Dr Hoekstra (expert in developmental disorders and SPARK co-PI) and Dr Hanlon (global mental health expert), with additional supervision from Prof Amina Abubakar (Kenya-based cross-cultural psychologist and SPARK co-PI).

Skills development during the PhD: Mixed methods analysis; qualitative analysis; service development research.

Year 1: acquire essential skills in qualitative and quantitative research methodology **Year 2**: Fieldwork in Ethiopia and Kenya **Year 3**: Analysis and paper writing. **Year 4**: Thesis completion.

One representative publication from each co-supervisor:

Tekola, B., Girma, F., Kinfe, M., Abdurahman, R., Tesfaye, M., Yenus, Z., WHO CST Team, Salomone, E., Pacione, L., Fekadu, A., Servili, C., Hanlon, C., Hoekstra, R. A., 2020. Adapting and pre-testing the World Health Organization's Caregiver Skills Training programme for autism and other developmental disorders in a very low-resource setting: Findings from Ethiopia. Autism, 24 (1) pp. 51-63. DOI 10.1177/1362361319848532.

Hanlon, C., Medhin, G., Selamu, M., Birhane, R., Dewey, M., Tirfessa, K., Garman, E., Asher, L., Thornicroft, G., Patel, V., Lund, C., Prince, M., Fekadu, A. Impact of integrated district level mental health care on clinical and social outcomes of people with severe mental illness in rural Ethiopia: an intervention cohort study. Epidemiology and Psychiatric Sciences (2019). https://doi.org/10.1017/S2045796019000398

NS-MH 202221 The neuroinflammatory basis of depression following traumatic brain injury

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Collaborating Clinician: Dr David Okai
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Project Description:

Depression following traumatic brain injury (TBI) is very common. The mechanisms may involve complex interactions between the psychological experience of the TBI and the pathophysiology of injured neurones. The main hypothesis is that peripheral biomarkers of neuroinflammation are associated with higher levels of depressive symptoms following TBI. This project is nested within a randomised controlled trial (RCT) testing the effectiveness of a selective serotonin reuptake inhibitor (sertraline) on preventing depression following TBI.
Year 1 - Objective: to i) conduct a systematic review and meta-analysis of observational studies of the association between proxy markers of neuroinflammation (neuroimaging, spinal fluid, peripheral biomarkers such as neurofilament light chains and neuronal exosomes) with a) depressive symptoms and b) cognitive functioning and ii) use the findings to inform an observational study to test whether the course of depressive symptoms is associated with biomarkers of neuroinflammation over 12 months. **Year 2 -** Objective: to conduct the observational study of the association between proxy biomarkers of neuroinflammation and the course of depression following TBI. **Year 3 -** Objective: to conduct a mechanistic study nested with the RCT to test whether sertraline is associated with a reduction in neuro-inflammation and in depressive symptoms in people with TBI, and whether this modified by cytochrome P450 (CYP) gene variants (1A2, 2D6, 3A4, 2C9/19)

Skills: 1. systematic review and meta-analysis methods; 2. epidemiology
3. inflammation and neuroimaging; 4. fieldwork including communication skills with patients and clinicians; 5. data management; 6. complex statistical methods; 7. presentation skills; 8. clinical trials investigating medicinal products

One representative publication from each co-supervisor:

Moulton, C, Pickup, JC, Rokakis, AS, Amiel, SA, Ismail, K & Stahl, D. The Prospective Association Between Inflammation and Depressive Symptoms in Type 2 Diabetes Stratified by Sex. Diabetes Care, 2019; 42:1865-1872. https://doi.org/10.2337/dc19-0813

Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran VH, Nutt DJ 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3:619-27. doi: 10.1016/S2215-0366(16)30065-7

NS-MH 202222 Autophagy and inflammation in astrocyte reactivity and neuronal response

Co-Supervisor 1A: Dr Maria Jimenez-Sanchez
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Co-Supervisor 1B: Dr Manolis Fanto
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Project Description:

Autophagy is a self-degradation pathway necessary to clear aggregate prone proteins that accumulate in neurodegenerative diseases. The study of autophagy in neurodegeneration has mostly focused on neurons. However, less is known about the implications of modulating autophagy in glial cells. In neurodegeneration, astrocytes become reactive and secrete a number of pro-inflammatory factors. While autophagy modulates inflammation, the interplay between autophagy and inflammation in astrocytes has not been explored. In addition, the impact that astrocytes secreted factors have on neuronal autophagy remains to be elucidated.

We hypothesize that autophagy can modulate the inflammatory response in glial cells. This may lead to changes in the glial secretome, which could potentially modulate autophagy in neurons. The aims of this PhD project are: 1) to explore the link between autophagy and inflammation in astrocytes and 2) to investigate how astrocytes modulate neuronal autophagy in neurodegenerative diseases.

In **year 1**, using primary mouse cultures and a range of assays to monitor autophagy function and dynamics, we will investigate how modulating autophagy may impact astrocyte reactivity.

In **year 2**, we will explore whether changes in astrocyte inflammatory response may also have an impact on neuronal autophagy. Next, we will identify and validate potential factors secreted by glial cells that could constitute autophagy modulators.

Using Drosophila models of human disease, including flies expressing polyQ and C9ORF72 repeat expansions, we will validate in **year 3** the relevance of our findings and explore its therapeutic relevance.

The groups of Maria Jimenez-Sanchez and Manolis Fanto are both interested on the study of autophagy in neurodegeneration. This project will combine the expertise of Jimenez-Sanchez lab, investigating the role astrocytes in neurodegeneration, and Fanto's lab, with expertise in a number of disease models in flies

One representative publication from each co-supervisor:

Sung K and Jimenez-Sanchez M. Autophagy in astrocytes and its implications in neurodegeneration. J Mol Biol. 2020 Apr 3;432(8)

O.Baron, A.Boudi, C.Dias, M.Schilling, A.Nölle, G.Viczcay-Barrena, I.Rattray, H.Jungbluth, W.Scheper, R.Fleck, G.P.Bates and M.Fanto (2017). Stall in canonical autophagy-lysosome pathways prompts nucleophagy-based nuclear breakdown in neurodegeneration. Curr. Biol. 27;3626-3642.

NS-MH 202223 Understanding neuronal migration disorders using human tissue models

Co-Supervisor 1A: Dr Katie Long
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Project Description:

The cerebral cortex is the seat of many of the higher cognitive functions that make us human, such as our advanced learning and speech. We know that the correct organisation of the cortex is vital for these functions, but how this is achieved during development remains elusive. Evidence from studies on neurodevelopmental disorders has indicated that neuronal migration is crucial to ensure that the right number of neurons end up in the right place at the right time. A key example of such a disorder is lissencephaly, where the folding of the cortex (the wrinkles on the outer surface) is greatly reduced. This lack of folding is associated with cognitive defects and has been suggested to be due to an over-migration of neurons.

This project will use cutting-edge human cell and tissue culture systems to investigate how neuronal migration is dysregulated in neurodevelopmental disorders. It will take advantage of both laboratories' expertise, combining the Long lab's experience in human fetal neocortex development and explant models with the Berninger lab's experience in human induced pluripotent stem cells (iPSC) and organoid models. We will use a multidisciplinary approach, including live-imaging, transcriptome analysis, confocal-imaging and cell biology.

The student will investigate:
Year 1 – Neuronal migration in human fetal neocortex explant models of lissencephaly; establishment of human cerebral organoids from iPSCs
Year 2 – Neuronal migration in iPSC/organoid models and effect of tissue/substrate stiffness
Year 3 – Identification of mechanisms underlying defects in neuronal migration; rescue of these defects in iPSC/organoid and human fetal neocortex models

One representative publication from each co-supervisor:

Long KR, Newland B, Florio M, et al. Extracellular Matrix Components HAPLN1, Lumican, and Collagen I Cause Hyaluronic Acid-Dependent Folding of the Developing Human Neocortex. Neuron. July 2018. doi:10.1016/j.neuron.2018.07.013

Karow M, Camp JG, Falk S, et al., Berninger B. Direct pericyte-to-neuron reprogramming via unfolding of a neural stem cell-like program. Nat Neurosci. July 2018. doi: 10.1038/s41593-018-0168-3.

NS-MH 202224 When should antipsychotics be discontinued? Predicting relapse risk in psychotic disorders following antipsychotic discontinuation using electronic health record data analytics

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Co-Supervisor 1B: Dr Rashmi Patel
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Project Description:

Psychotic disorders have a substantial impact on functioning and quality of life. Antipsychotics block dopaminergic receptors to reduce psychotic symptoms, and discontinuation of antipsychotics is associated with increased risk of relapse. However, long-term antipsychotic treatment may lead to supersensitivity of dopamine receptors which could further increase the risk of relapse if discontinued following long-term treatment. This presents a clinical dilemma: how long should antipsychotic treatment be continued and when is it safe to stop?

We invite a PhD student to investigate whether people exposed to long durations of antipsychotic treatment are at higher risk of relapse following discontinuation using the Clinical Record Interactive Search tool (CRIS), a state-of-the-art electronic health record (EHR) data analytic platform and to develop a clinical prediction tool to identify people who may be at lower risk of relapse following discontinuation.

Year 1: Data assembly of psychosis cohort using the SQL CRIS tool
Year 2: Data cleaning and ascertainment of antipsychotic exposure using R
Year 3: Development and pilot of clinical prediction tool for relapse

Training in the extraction and analysis of EHR data using SQL and R will be provided within the Centre for Translational Informatics (https://ctiuk.org/) and data analysis conducted at the Maudsley BRC (https://www.maudsleybrc.nihr.ac.uk/facilities/clinical-record-interactive-search-cris/) which has supported over 180 research projects in mental health clinical informatics.

One representative publication from each co-supervisor:

Risha Govind, Daniela Fonesca de Freitas, Megan Prtichard, Richard Hayes, James H MacCabe. Clozapine treatment and risk of COVID-19 infection: retrospective cohort study. Open access BJPsych July 2020 https://doi.org/10.1192/bjp.2020.151

Rashmi Patel, Edward Chesney, Matthew Taylor, David Taylor and Philip McGuire, Is paliperidone palmitate more effective than other long-acting injectable antipsychotics? Psychological Medicine, Jul 2018; 48 (10): 1616-1623. doi: 10.1017/S0033291717003051.

NS-MH 202225 A new perspective on complexity in Neurodevelopmental Psychiatric Conditions: A Network Analysis Approach to the Structure of Psychopathology

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Co-Supervisor 1B: Prof. Federico Turkheimer
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Project Description:

Traditional psychopathology identities categorical disorders on the assumption that symptoms are manifestations of some underlying diagnostic factor, the condition itself (e.g major depression, bipolar depression, schizophrenic disorder, autism etc.). However, it's not so simple. Neurodevelopmental conditions (like autism and ADHD) and psychiatric conditions have overlapping and ever shifting symptoms which likely reflect common (genetic and environmental) causes and consequently their shared biological, psychological and societal mechanisms. i.e. Psychiatric neurodevelopmental conditions = Symptom networks.

We plan a redefinition of psychiatric neurodevelopmental conditions through a data driven analyses of how symptoms are organised in dynamic networks. We move away from categorical diagnoses, and towards transdiagnostic efforts which reflect the reality of complex neurodevelopmental psychiatric conditions.

The student will use Dynamic network approaches to map the symptoms space and its changes across time in our patients. The project will utilise data from existing large multimodal patient datasets held by our teams at KCL (e.g. our AIMS-2-TRIALS European Autism project; https://www.aims-2-trials.eu/) and/or the South London and Maudsley NHS Foundation Trust (e.g. our electronic patient record https://www.slam.nhs.uk/quality-and-research/clinical-record-interactive-search-cris/).

By better defining dynamic symptom networks, we can begin to understand their emergence, persistence, response to intervention and resolution. We can then examine their neurobiological bases (for example, through linked neuroimaging and/or genomics datasets).
Year 1: Training dynamic network analysis and statistics. Training in transdiagnostics.
Year 2: Characterization symptom networks in patient cohorts identified in year 1.
Year 3: Writing up analyses for publication. Explore novel multimodal methods to identify neurobiological mechanisms underpinning symptom networks.

One representative publication from each co-supervisor:

Ciarrusta, J., Dimitrova, R. & McAlonan, G., 2020, Progress in Brain Research. Hunnius, S. & Meyer, M. (eds.). Vol. 254. p. 49-70 (Progress in Brain Research).

Turkheimer, F. E., Rosas, F. E., Dipasquale, O., Martins, D., Fagerholm, E. D., Expert, P., Váša, F., Lord, L-D. & Leech, R., A Complex Systems Perspective on Neuroimaging Studies of Behavior and Its Disorders. 16 Feb 2021, In: Neuroscientist. p. 1073858421994784

NS-MH 202226 Dissecting TDP-43 toxicity with novel FTD/ALS iPSC models

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Co-Supervisor 1B: Dr Marc-David Ruepp
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Project Description:

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two clinically different neurodegenerative diseases that lie on a pathogenic spectrum. The most common pathology present in ALS and FTD cases is cytoplasmic mislocalisation and aggregation of the RNA-binding protein TDP-43.

This PhD aims to dissect the contributions of RNA-binding and liquid-liquid phase separation to TDP-43 toxicity using novel iPSC models of ALS/FTD. This includes rational design of mutations in the TDP-43 gene that disrupt RNA binding while conserving the domain structures, as well as the generation of phase separation deficient mutants. The generated mutants will then be knocked into human induced pluripotent stem cell (iPSC) lines using CRISPR/Cas9. Resultant iPSCs will be differentiated into neurons and the effect on neuronal health (longitudinal dendritic branching and survival) and TDP-43 functionality (nucleocytoplasmic transport, phase separation, stress granule association and RNA metabolism) assessed. This will give insights into the molecular basis of TDP-43 toxicity, inform on the initiating factors in disease pathogenesis, and provide potential targets for therapeutic intervention.

This project combines the TDP-43 and microscopy (including super-resolution) expertise of the Mizielinska group with the RNA, genome editing and iPSC expertise of the Ruepp group. This will provide the student with a wealth of skills in stem cell culture, genome editing, molecular biology, biochemistry, and microscopy.

Year 1: Design and generation of TDP-43 mutants and characterisation in vitro

Year 2: Genome editing of iPSCs, neuronal differentiation and characterisation of generated lines

Year 3+: Study of toxicity and TDP-43 biology-based phenotypes in mutant neurons

One representative publication from each co-supervisor:

Solomon, D.A., Smikle, R., Reid M.J., Mizielinska, S. (2021). Altered phase separation and cellular impact in C9orf72-linked frontotemporal dementia and amyotrophic lateral sclerosis. Frontiers in Cellular Neuroscience, 15, 121.

Reber, S., Jutzi, D., Lindsay, H., Devoy, A., Mechtersheimer, J., Levone, B.R., Domanski, M., Bentmann, E., Dormann, D., Mühlemann, O., Barabino, S.M.L., Ruepp, M.-D. (2021). The phase separation-dependent FUS interactome reveals nuclear and cytoplasmic function of liquid–liquid phase separation, Nucleic Acids Research, Volume 49, Issue 13, Pages 7713–7731

NS-MH 202227 Amyloid-induced pre-synaptic degeneration in Alzheimer's disease

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Co-Supervisor 1B: Prof. Peter Giese
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Project Description:

The pre-synaptic co-chaperone protein, cysteine string protein (CSP) alpha, is involved in the maintenance of protein folding, neurotransmitter release and synaptic stability. We identified alterations in CSPalpha in association with A plaques in Alzheimer's disease (AD) brain. This includes the accumulation of amorphous protein aggregates that mark early presynaptic degeneration in AD. In addition, these CSPalpha accumulations may be indicative of the secretion of CSPalpha in association with tau, a process linked with the neuronal activity-dependent "prion-like" trans-synaptic spread of modified tau in AD brain.

This project is to investigate the importance of CSPalpha for tau release from neurons in response to Aand to gain mechanistic insights into the contribution of CSPalpha to pre-synaptic degeneration in AD.

1. To determine the effects of exposing neurons to physiological forms of human A on pre-synapse numbers and pre-synaptic molecules including CSPalpha (**Year 1**)
2. To determine if CSPalpha is released in association with tau when neurons are stimulated with A (**Year 2**)
3. To determine effects on pre-synapse health and tau release upon knockdown of CSPalpha in neurons (**Year 2,3**)
4. To determine effects on pre-synapse health and tau release upon overexpression of CSPalpha in neurons (**Year 3**)

The project will involve training in molecular/cellular neurosciences including preparation of rodent primary neural cell cultures, isolation of synaptoneurosomes and pre-synaptic compartments, and advanced imaging techniques.

One representative publication from each co-supervisor:

Glennon EB, Lau DH-W, Gabriele RMC, Taylor MF, Troakes C, Opie-Martin-Sarah, Elliott C, Killick R, Hanger DP, Perez-Nievas BG, Noble W. BIN1 protein loss in Alzheimer's disease promotes synaptic tau accumulation and disrupts tau release. Brain Comms. 2020 2(1): fcaa011.

Ghosh A, Mizuno K, Tiwari SS, Proitsi P, Perez-Nievas BG, Glennon E, Matrinez Nunez RT, Giese KP. Alzheimer's disease-related dysregulation of mRNA translation causes pathological features with ageing. Transl. Psychiatry 2020 10(1):192.

NS-MH 202228 The amygdala, a key upstream regulator of the hypothalamic GnRH pulse generator

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Co-Supervisor 1B: Prof. Helen Cox
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Project Description:

The amygdala, a key limbic brain structure commonly known for its role in higher-order emotional processing, is implicated in stress-induced suppression of gonadotrophin-releasing hormone (GnRH) pulse generator frequency, to cause infertility. Our pioneering discovery that kisspeptin signalling in the medial amygdala robustly regulates hypothalamic GnRH pulse generator frequency, provides new insight into how the amygdala controls reproduction. The medial amygdala comprises primarily GABAergic neurones with a predominantly (60%) inhibitory GABA output to the hypothalamus. The medial amygdala is also rich in the stress neuropeptide urocortin-3, which is activated by psychological stress. We hypothesise that the urocortin system regulates kisspeptin-GABAergic signalling intrinsic to the medial amygdala to mediate the effects of psychological stress on fertility in the female mouse.

Objectives:

1. To establish the functional dynamic relationship between the kisspeptin and GABA neurocircuitry in the medial amygdala that underlie the upstream regulation of the hypothalamic GnRH pulse generator frequency using in-vivo optogenetics and deep-brain GCaMP6 GRIN lens microendoscopic calcium imaging.
2. To determine how the GABAergic projections from the medial amygdala modulate the frequency of the hypothalamic GnRH pulse generator.
3. To determine how stress activated urocortin-3 neurones regulate kisspeptin-GABA neurocircuitry in the medial amygdala to suppress GnRH pulse generator frequency.

Professors O'Byrne and Cox have worked together for many years, with vast experience in complex in-vivo experimentation. This project will use the latest cutting-edge technologies of combined targeted optogenetic manipulations with in-vivo gradient-index (GRIN) lens microendoscopic systems to monitor in real time neurone calcium dynamics, a proxy for neuronal activity, of selective GCaMP-expressing neurones.

One representative publication from each co-supervisor:

Voliotis M, Feng Li X, De Burgh R, Lass G, Lightman SL, O'Byrne KT, Tsaneva-Atanasova K. The origin of GnRH pulse generation: An integrative mathematical-experimental approach. J Neurosci. 2019, 9:9738-9747. doi: 10.1523/JNEUROSCI.0828-19.2019.

M Ghamari-Langroudi, GJ Digby, JA Sebag, GL Millhauser, R Palomino, R Matthews, T Gillyard, IR Tough, HM Cox, JS Denton & RD Cone. G-protein-independent coupling of MC4R to Kir7.1 in hypothalamic neurons. Nature 2015, 520:94-98 doi: 10.1038/nature14051

NS-MH 202229 Muller glial-mediated regeneration in human stem cell-derived retinal organoids

Co-Supervisor 1A: Prof. Rachael Pearson
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Project Description:

Photoreceptors are highly-specialized, light-sensing neurons located in the retina. They are prone to damage and once lost are not replaced, leading to blindness. An attractive but unproven therapeutic strategy is to induce the retina to repair itself. Unfortunately, the mammalian (including human) retina does this very poorly, but studies of fish and frogs, which undergo efficient retinal repair, have found that Müller glia (MG), a type of support cell in the retina, retain stem cell-like properties that allow them to produce new functional neurons, including photoreceptors. Key signaling pathways have been identified in this process, including Ascl1/Lin28/Let7 and □-catenin, amongst others, as well as the methylation state of these genes. Intriguingly, we have found that MG in mice undergoing retinal degeneration show better regenerative responses following over-expression of Ascl1, compared to uninjured MG and those undergoing acute injury (unpublished data). This project will compare the regenerative capacity of MG from diseased, versus normal, human pluripotent stem cell (hPSC)-derived retinal organoids engineered to contain "lineage tracers" to follow the fate of MG-derived progeny.

Year 1: Establish retinal organoids from hPSC mTmGfloxed reporter line. Determine effect of manipulating Ascl1/Lin28/Let7 and □-catenin expression in human MG and perform lineage tracing.
Year 2: Examine role of methylation state with respect to above pathways; Generate retinal degeneration (rd) hPSC mTmGfloxed lineage reporter line using CRISPR.
Year 3: Determine effect of manipulating Ascl1/Lin28/Let7 and □-catenin expression and methylation states in (rd)hPSC Cre-loxP line and perform lineage tracing.

Skills: human stem cell culture; viral vector design/manufacture; CRISPR; microscopy (confocal, lightsheet)

One representative publication from each co-supervisor:

Pearson RA, Barber AC, Hippert C, …Ali RR (2012) Functional and behavioural rescue of vision by rod photoreceptor transplantation. Nature, 485(7396):99-103.

Ribeiro J, Procyk C, O'Hara-Wright M, …Gonzalez-Cordero A*, Pearson RA*, Ali RR (2021). Rescue of advanced retinal degeneration following transplantation of pure population of hESC-derived cone photoreceptors. Cell Reports. 35, 109022.

NS-MH 202230 From zebrafish to patients: Using zebrafish to uncover the genetic and neural basis of aggression in neurodevelopmental disorders

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Project Description:

Autism is a pervasive neurodevelopmental condition characterized by repetitive behaviours and difficulties in social interaction. In addition, 2-out-of-3 autistic individuals also show increased aggression, having detrimental effects on life quality of both affected individuals and their families. Yet, despite the worldwide incidence increase of autism, we lack effective treatments for both core symptoms and aggression. This is because of our poor understanding of underlying mechanisms. While hundreds of autism-related genetic mutations have been identified, the mechanisms by which they perturb developmental trajectories and wiring of the brain remain largely unknown. Zebrafish is an ideal model organism for answering those questions, due to their transparency at larval stages providing a real-time window into the development of neural circuits, their structure and function.
Individuals with autism and mouse models carrying mutations in two high-confidence risk genes for autism, Neuroligin3 (Nlgn3) and Neurexin 1α (Nrxn1α), show increased levels of aggression. Some Neurexin/Neuroligin mutants have been established in the lab. Our overarching aim is to understand the mechanisms by which aberrant functioning of the neuroligin-neurexin signalling cascade leads to an increase in autism-associated aggression.

Overarching objectives:
Year1: Behavioural assessments of existing mutants. Establishment of additional Nlgn3 and Nrxn1α mutants.
Year2: Examining brain connectivity in Nlgn3/Nrxn1α mutants during development through in vivo structural and functional imaging. Correlation with behavioural assessment.
Year3: continuing the Year2 experiments and drug screening to reduce aggression (continuing into year 4 of 0+4 pathway)

Skills training:
Zebrafish husbandry, embryo injections, genome editing, CRISPR, optogenetics, animal behaviour, pharmacological treatments, immunohistochemistry, structural/functional imaging

One representative publication from each co-supervisor:

MM Petrinovic, R Hourez, EM Aloy, G Dewarrat, D Gall, O Weinmann, J Gaudias, LC Bachmann, SN Schiffmann, KE Vogt, ME Schwab. “Neuronal Nogo-A negatively regulates dendritic morphology and synaptic transmission in the cerebellum”. PNAS, 2013. doi: 10.1073/pnas.1214255110

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

NS-MH 202231 The neurobiology of sensory difficulties in preschool children with neurodevelopmental conditions

Co-Supervisor 1A: Dr Nicolaas Puts
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Collaborating Clinician: Tony Charman
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Project Description:
Sensory difficulties are common in neurodevelopmental conditions such as Autism Spectrum Disorder (ASD) (70-90%) and ADHD (~40%). There remains substantial lack of understanding of the biology underlying ASD and ADHD. Increasing evidence suggests that sensory difficulties contribute to the emergence of core symptoms of ASD and ADHD. Understanding the biology, and impact, of sensory differences early in development may form a mechanistic basis improving stratification, diagnosis, and treatment of these debilitating conditions. The Preschool Brain Imaging and Behaviour Project (PIP) is the first Europe-wide study of preschool children with and without autism, ADHD, developmental delay and epilepsy, and is part of AIMS-2-TRIALS and Horizon 2020 CANDY Consortia. One component of PIP is a multi-modal approach for understanding the profile and neurobiology of sensory difficulties in neurodevelopment.
Skills: To examine the neurobiology of sensory differences in preschool children with neurodevelopmental conditions, the project integrates information about the behavioural profile of sensory processing difficulties, as well as underpinning neurofunctional and neurochemical atypicalities by using: 1) Novel tablet-tasks to test low-level perception; 2) Sensory EEG experiments to examine the electrophysiology of sensory perception; 3) Magnetic Resonance Spectroscopy to quantify brain GABA and Glutamate; 4) Advanced statistical modelling approaches (e.g. cluster-based approaches; canonical correlations) to examine the heterogeneity of sensory difficulties and their impact.
Objectives: **Year 1**. Emphasis on data acquisition in preschoolers. Support interpreting the neurophysiology of ASD. Focus on EEG analysis. Data acquisition commences. **Year 2**. Focus on MRS acquisition/analysis. Advanced analytical and statistical approaches to stratify developmental conditions. **Year 3**. Continue analyses. Communicate data. Write-up.

One representative publication from each co-supervisor:
He JL, Wodka E, Tommerdahl M, Edden RAE, Mikkelsen M, Mostofsky SH, Puts NAJ. Disorder-specific alterations of tactile sensitivity in neurodevelopmental disorders. Commun Biol. 2021 Jan 22;4(1):97. doi.org/10.1038/s42003-020-01592-y. PMID: 33483581; PMCID: PMC7822903.

Loth E, Spooren W, Ham LM, Isaac MB, Auriche-Benichou C, Banaschewski T, Baron-Cohen S, Broich K, Bölte S, Bourgeron T, Charman T, Collier D, de Andres-Trelles F, Durston S, Ecker C, Elferink A, Haberkamp M, Hemmings R, Johnson MH, Jones EJ, Khwaja OS, Lenton S, Mason L, Mantua V, Meyer-Lindenberg A, Lombardo MV, O'Dwyer L, Okamoto K, Pandina GJ, Pani L, Persico AM, Simonoff E, Tauscher-Wisniewski S, Llinares-Garcia J, Vamvakas S, Williams S, Buitelaar JK, Murphy DG. Identification and validation of biomarkers for autism spectrum disorders. Nat Rev Drug Discov. 2016 Jan;15(1):70-3. doi: 10.1038/nrd.2015.7.

NS-MH 202232 The molecular and cellular basis of CGRP-mediated modulation of trigeminal synaptic transmission.

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Co-Supervisor 1B: Prof. Peter Goadsby
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Project Description:

In this project you will use a combination of cell culture, molecular biology, optogenetics and cell biology to study the modulation of the first pain synapse in the headache pain pathway. Migraine headache remains an unmet clinical challenge with significant impact on quality of life for the sufferers. Headache pain is mediated by the peripheral axons of trigeminal neurons innervating cranial structures and craniofacial blood vessels, while centrally synapsing onto the brainstem nuclei. Several neurotransmitters and neuropeptides such as CGRP and neurokinin-1 that are released during migraine headache, regulate 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 objective of this project is to develop a microfluidic model that recapitulates the nociceptive neuronal circuit headache pain, i.e., an in vitro model of headache. Using this microfluidic co-culture platform, the candidate will investigate sensitization of trigeminal neurons and modulation of synaptic transmission between the trigeminal and brain stem neurons. The project will be based at the Wolfson Centre for Age-Related Diseases, Guy's Campus.

Year 1 /2: Techniques: cell culture, microfluidic culture, viral tracing, calcium imaging. The prospective candidate will learn cell culture and cell imaging techniques and 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.

One representative publication from each co-supervisor:

Vysokov, N., McMahon, S.B. & Raouf, R. The role of NaV channels in synaptic transmission after axotomy in a microfluidic culture platform. Sci Rep 9, 12915 (2019). https://doi.org/10.1038/s41598-019-49214-w

Ho, T., Edvinsson, L. & Goadsby, P. CGRP and its receptors provide new insights into migraine pathophysiology. Nat Rev Neurol 6, 573–582 (2010). https://doi.org/10.1038/nrneurol.2010.127

NS-MH 202233 The synaptic basis of learning

Co-Supervisor 1A: Prof. Beatriz Rico
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Co-Supervisor 1B: Dr Adil Khan
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Project Description:

Animals are remarkably adept at learning new associations between objects, places, and events, and this ability is essential for survival in an ever-changing environment. During learning neurons change their response properties, sharpening their responses to relevant features of the environment. This plasticity depends on changes in the tens of thousands of excitatory synapses and several thousand inhibitory synapses present on each neuron.

Changes in individual synapses during learning are challenging to study. Even when average changes in synaptic properties are known, it is not straightforward to relate then to the changes in the properties of individual neurons as they function in a network. Thus, it remains poorly understood whether learning leads to changes in a small number of strong synapses, or more widely distributed changes across a large number of synapses. Are synaptic changes clustered, to drive non-linear dendritic events? Are most synaptic changes during learning top-down (in apical dendrites) or bottom up (in basal dendrites), or is there transfer across these domains over days?

This project will address these questions by measuring activity in individual synaptic spines using multi-day in-vivo two-photon calcium imaging as mice learn a visual discrimination task. We will use a multidisciplinary approach, including optogenetics, imaging GCaMP7f fused with PSD-95 Fingrs, and quantitative mouse behaviour. The activity of individual spines will be related the activity of the soma of the same neurons and the mouse behaviour. Finally, we will investigate how genetic mouse models with altered inhibitory circuits accomplish learning, using loss of function experiments (cre-loxP, shRNA, CRISPR-Cas9).

Over-arching objectives
Year 1: Learn experimental techniques, including synaptic imaging and mouse behaviour. Acquire pilot data for candidate genes.
Year 2: Acquire synaptic data from behaving mice.
Year 3: Perform in-vivo imaging with genetic disruptions.

One representative publication from each co-supervisor:

Favuzzi E*, Deogracias R*, Marques-Smith A, Maeso P, Exposito-Alonso D, Kroon T., Baglia M., Fernandez- Maraver E, Rico B. Distinct molecular programs regulate synapse specificity in cortical inhibitory circuits, Science, 263:413 (2019).

Khan, A.G., Poort, J., Blot, A., Chadwick A., Sahani, M., Mrsic-Flogel, T.D., Hofer, S.B. (2018). Distinct learning-induced changes in stimulus selectivity and interactions of GABAergic interneuron classes in visual cortex. Nature Neuroscience 21(6):851-859

NS-MH 202234 Sex differences in mental health problems: Investigation of contributory factors

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Project Description:

Females have increased risk for many mental health problems including depression, anxiety, eating disorders and PTSD, compared to males, after puberty. Proposed social processes include their lower social status/power and greater body objectification. Such factors may contribute to more frequent experiences of child sexual abuse, relational bullying, lifetime sexual victimisation and intimate partner violence. Victimisation experiences may contribute to mental illness via physiological stress responses and indirectly, e.g. by causing the individual to develop more negative beliefs about the self and one's body. Such beliefs are risk factors for the development of mental illness. There has been little longitudinal research into whether factors such as victimisation experiences and negative self-beliefs contribute to the increased risk for psychological problems in females. Improved understanding would inform prevention and early intervention approaches.

This project will include a systematic review of psychological mediators of sex differences in mental illness, then focus on secondary analyses of longitudinal birth cohort data. It will investigate whether sex differences in problems such as depression, anxiety, PTSD and eating disorders are mediated by victimisation experiences and negative self-beliefs. Complex moderated mediational pathways will be tested involving interactions between victimisation experiences and self-beliefs.

Training will include advanced statistical analysis of longitudinal data; moderated mediation analysis; structural equation models; at least one statistical programme (e.g. R).

Year 1: Systematic review about psychological mediators of sex differences in mental illness. Training in longitudinal data preparation and analysis. Begin first longitudinal study.
Year 2: Complete first longitudinal study; undertake second; start final study.
Year 3: Complete final study. Write up and publications; disseminate results.

One representative publication from each co-supervisor:

Argyriou, A, Goldsmith, KA, Tsokos, A & Rimes, KA 2020, 'Psychosocial mediators of the relations between sexual orientation and depressive symptoms in a longitudinal sample of young people', Psychology of Sexual Orientation and Gender Diversity, vol. 7, no. 2, pp. 142-153. https://doi.org/10.1037/sgd0000369

Kretschmer, T., Barker, E. D., Dijkstra, J. K., Oldehinkel, A. J., & Veenstra, R. (2015). Multifinality of peer victimization: maladjustment patterns and transitions from early to mid-adolescence. European Child and Adolescent Psychiatry, 24(10), 1169-1179. https://doi.org/10.1007/s00787-014-0667-z

NS-MH 202235 Using remote measurement technology to understand recovery processes in eating disorders

Co-Supervisor 1A: Prof. Ulrike Schmidt
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Co-Supervisor 1B: Dr Amos Folarin
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Project Description:

Eating disorders (EDs) are common and disabling mental disorders. Processes that help or hinder recovery are poorly understood. Remote Measurement Technology (RMT) uses inbuilt sensors in smartphones and/or wearables to: (a) unobtrusively measure human behaviour and physiology (passive RMT) or (b) actively measure daily experiences via smartphone apps (active RMT). RMT provides real time information about patients' clinical state and can predict remission/recovery or relapse. It hasn't been used in EDs.

This project is embedded in a longitudinal study, using biological and psychological RMT measures to (1) compare young people with a 1st episode of an ED with healthy controls; (2) assess differences in recovery trajectories within/across ED groups and (3) identify early RMT predictors of recovery at 12 months. [See https://radar-cns.org (as an exemplar) and https://radar-base.org (for reference to the platform)].

The student will learn about EDs, design and conduct of RMT studies, and analysis of features obtained from biosensors, smartphones, cognitive/speech tests and experience sampling methodology. A training needs analysis will be conducted. They will be working across the vibrant eating disorders and bioinformatics groups, where they will be taught project specific skills. In addition, the student will be expected to attend transferrable skills training as required by their project.

Objectives
Year 1: The student will familiarise themselves with the project and will write a systematic review e.g. on RMT in psychiatric disorders.
Year 2: The student will participate in recruitment and data acquisition in the ongoing cohort study.
Year 3: Data analysis and write up.

One representative publication from each co-supervisor:

Austin A, Flynn M, Shearer J, Long M, Allen K, Mountford VA, Glennon D, Grant N, Brown A, Franklin-Smith M, Schelhase M, Jones WR, Brady G, Nunes N, Connan F, Mahony K, Serpell L, Schmidt U. The First Episode Rapid Early Intervention for Eating Disorders - Upscaled study: Clinical outcomes. Early Interv Psychiatry. 2021 Mar 29. doi: 10.1111/eip.13139.

Zhang Y, Folarin AA, Sun S, Cummins N, Ranjan Y, Rashid Z, Conde P, Stewart C, Laiou P, Matcham F, Oetzmann C, Lamers F, Siddi S, Simblett S, Rintala A, Mohr DC, Myin-Germeys I, Wykes T, Haro JM, Penninx BWJH, Narayan VA, Annas P, Hotopf M, Dobson RJB. Predicting Depressive Symptom Severity Through Individuals' Nearby Bluetooth Device Count Data Collected by Mobile Phones: Preliminary Longitudinal Study. JMIR Mhealth Uhealth. 2021 Jul 30;9(7):e29840. doi: 10.2196/29840. PMID: 34328441; PMCID: PMC8367113.

NS-MH 202236 Using virtual reality to investigate sense of body ownership and agency in patients with functional neurological disorder

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Project Description:

Functional Neurological Disorder (FND) is the second commonest diagnosis in neurology clinics and causes significant disability (Carson & Stone, 2015). Motor FND symptoms are subjectively reported by patients as involuntary (Edwards, 2012). This may be mediated by altered sense of body ownership and agency, also found in schizophrenia (Shergill 2014).

Previous studies of these constructs, using experimental paradigms such as the rubber hand illusion, have led to conflicting results. In this project, novel VR environments will be used. We anticipate that their immersive nature plus the ease of manipulation to change experimental conditions will allow more valid investigation.

The hypotheses are that, compared to controls, patients with FND and schizophrenia will; 1. be more susceptible to manipulation of sense of body ownership. 2. show reduced agency over the movements of an avatar.
25 individuals diagnosed with FND, 25 with schizophrenia and 25 healthy controls recruited. Body ownership and agency assessed in two VR environments; a 'virtual mirror' avatar (participants see an avatar in front of them that follows their movements), and a 'virtual body illusion' (participants see a projected true image of their body from the back).

Skills Training: 1. assessment of FND/schizophrenia patients 2. VR design 3. all aspects of relevant research methods and data analysis.

Objectives:
Year 1: Systematic review of agency / body ownership in FND and other clinical populations. Finalise design and VR environments, prepare final protocol, regulatory approval, start recruitment.
Year 2: Run and complete study, secondment with Mesmerise
Year 3: Write up thesis and publications, disseminate results.

One representative publication from each co-supervisor:

Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study. McCormack R, Moriarty J, Mellers JD, Shotbolt P, Pastena R, Landes N, Goldstein L, Fleminger S, David AS. J Neurol Neurosurg Psychiatry. 2014 Aug;85(8):895-900

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

NS-MH 202237 Understanding the impact of the Covid-19 pandemic on the mental health of children and young people with pre-existing mental health conditions

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Project Description:

Understanding the impact of the Covid-19 pandemic on the mental health of children and young people (CYP) with pre-existing psychiatric conditions is crucial to provide preventive and early interventions, plan mental health services, and influence policy makers.

The candidate will receive training in epidemiology and health informatics and will closely collaborate with clinicians and informaticians within the Department of Child and Adolescent Psychiatry (IoPPN) and the Maudsley Hospital, which are world-renowned for their research and clinical portfolio. Supervision will cover all aspects of the project, from study design/planning (1st co-supervisor) to data analysis/writing up (2nd co-supervisor).

The candidate will learn how to combine survey data on how children and families are coping with the pandemic with clinical and service information as extracted from electronic health records.

Initially, they will investigate how the different aspects of the pandemic, from social distancing to financial strain, interplay with pre-Covid individual and socio-demographic characteristics to differentially impact on the mental health of CYP attending mental health services.

They will then explore the effect of time-dependent factors, such as changes in restrictions and education as the pandemic evolves, by analysing longitudinal data.

Finally, they will support an innovative way to bring information technology into clinical practice by feeding survey results into care records, to enable timely clinical follow-up; and by measuring how survey responses impact on care provision.

Overall, the data gathered with this study are pivotal to effectively respond to the current pandemic and to plan for any future scenarios.

One representative publication from each co-supervisor:

Developing an E-Platform for Monitoring Wellbeing in London Schools: Involving Young People in a Co-Design Process. / Grant, Claire; Widnall, Emily; Cross, Lauren; Stewart, Robert; Simonoff, Emily; Downs, Johnny. Research involvement and engagement (2/7/20).

'The longitudinal association between early childhood onset epilepsy and Attention-Deficit Hyperactivity Disorder in 3237 children and adolescents with Autism Spectrum Disorders: a historical cohort data linkage study'. Carson L., Parlatini V., Safa T., Baig B., Shetty H., Philips-Owen J., Prasad V*., Downs J*, under review.

NS-MH 202238 Face-to-face or remote consultations for people with severe mental illness? A Mixed methods evaluation

Co-Supervisor 1A: Prof. Robert Stewart

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Project Description:

Tele-health is a core component of the UK mental health care in the NHS 5-year plan. Whilst the implementation was rapidly accelerated during the pandemic, it relies on the technological resources available in the mental health care services and on patients' ability to use digital devices.

This PhD project will investigate differences in the two emerging consultation models (face-to-face and remote) including the changing patterns of their use (frequency, duration, timing) pre- and post-pandemic, and their personal and service impact (satisfaction, health outcomes).

This mixed methods project will provide a broad range of training opportunities in the following: i) conduct of systematic reviews; ii) management of big data, statistical skills and data analysis; iii) recruitment of study participants and qualitative skills of conducting in-depth interviews and thematic analysis. Additional training in general PhD skills such as communication and writing academic papers will be available through the Centre for Doctoral Studies at KCL.

Year 1: Systematic review on the two models of care (face-to-face and remote)

Years 1 and 2: A series of analyses of CRIS data comparing face-to-face and remote consultations

Year 3: Interviews with patients and mental health professionals on their views and experiences with face-to-face and remote consultations

The student will work closely with both supervisors to design the studies and interpret the results. Throughout the PhD project the student will be supported by both supervisors in disseminating their work and publishing it in high impact scientific journals and in national and international meetings.

One representative publication from each co-supervisor:

Perera G, Broadbent M, Callard F, Chang C-K, Downs J, Dutta R, Fernandes A, Hayes RD, Henderson M, Jackson R, Jewell A, Kadra G, Little R, Pritchard M, Shetty H, Tulloch A, Stewart R. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an Electronic Mental Health Record derived data resource. BMJ Open 2016; 6: e008721.

Greig, F, Perera, G, Tsamakis, K, Stewart, R, Velayudhan, L & Mueller, C 2021, 'Loneliness in older adult mental health services during the COVID-19 pandemic and before: Associations with disability, functioning and pharmacotherapy', International Journal of Geriatric Psychiatry.

NS-MH 202239 Reward and stress: Developing neuroimaging biomarkers for bipolar depression

Co-Supervisor 1A: Dr Paul Stokes
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Project Description:

Overview: Depressive symptoms experienced by people with bipolar disorder are distressing and increase self-harm risks. People with bipolar depression often don't enjoy their lives, experience difficulties with reward and motivation, and show abnormal stress hormone responses measured by the Dex/CRH test. Although bipolar depression is an important challenge for which we have few treatments, little is known about how abnormal brain signalling causes symptoms and how these are linked to stress hormone responses.

This project will use state-of-the-art functional neuroimaging (fMRI) to examine reward, motivation, and emotional processing brain activity in people with bipolar depression, unipolar depression and healthy people. We will investigate whether abnormal fMRI brain activity patterns may be linked to stress hormone responses. The project aims to develop a neuroimaging biomarker for bipolar depression which may be used to examine the effect of new treatments.

Training: This project, supervised by two leading experts in mood disorders and neuroimaging, provides a fantastic range of training opportunities. The student will receive training in the clinical assessment of people with mood disorders, fMRI neuroimaging, and measuring stress hormone responses. The project provides great opportunities to learn the practicalities of participant recruitment and fMRI imaging in mood disorders.

Objectives:

Year 1: Understand fMRI methodology and the Dex/CRH test. Gain expertise in recruiting and imaging participants.

Year 2: Develop expertise in fMRI neuroimaging and measuring stress hormone responses.

Year 3 /4: Consolidate skills, complete imaging and data analysis, present results at an international conference, submission of thesis and study publications.

One representative publication from each co-supervisor:

Yalin N, Kempton MJ, Mazibuko N, Mehta MA, Young AH & Stokes PRA Mifepristone enhances the neural efficiency of human visuospatial memory encoding and recall. Psychoneuroendocrinology 125, March 2021, 105116

Markopoulou K, Fischer S, Papadopoulos A, Poon L, Rane L, Fekadu A, Cleare AJ (2021). Contrasting HPA activity in treatment resistant unipolar and bipolar depression. Translational Psychiatry, 11, 244. https://doi.org/10.1038/s41398-021-01343-5

NS-MH 202240 Exploring the acute interactions of THC and CBD in heavy cannabis users

Co-Supervisor 1A: Prof. John Strang
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Project Description:

Laws regulating cannabis are rapidly changing globally, with Uruguay, Canada, and several US states now permitting recreational use. Concurrently, cannabis potency (of Δ9-tetrahydrocannabinol, THC) has increased in most parts of the world, and research suggests high-potency cannabis has a stronger association with risks of psychosis, cognitive impairment and cannabis addiction. However, recent evidence shows the second most prevalent compound in the cannabis plant, cannabidiol (CBD), has anti-psychotic and cognitively protective effects, and may help prevent or treat cannabis addiction.

This project explores the effects of CBD on THC-elicited negative effects in people with heavy problematic cannabis use.

The project will utilise multiple study designs:

- An online survey of regular cannabis users, who will complete a series of cognitive assessments while using their own cannabis at home (**Year 1**).
- A highly novel remote experimental study, where pharmacy-prepared cannabis with different doses of THC are delivered to participants along with a randomly-assigned blinded oral dose of CBD or placebo. Participants will self-administer study drugs and will complete cognitive tasks and clinical assessments via an online platform and videoconference (**Year 2**).
- An experimental psychopharmacology study in heavy users in a controlled setting who will, over separate visits, be administered different doses of THC with or without a CBD pre-treatment (**Year 2-3**).

The successful candidate will join a world-leading experimental psychopharmacology unit. They will gain skills administering cognitive and psychological symptom assessments, experience designing and conducting experimental research with scheduled drugs, and will contribute to a rapidly emerging field of high policy relevance internationally.

One representative publication from each co-supervisor:

Marsden J, et al. Medicines associated with dependence or withdrawal: a mixed-methods public health review and national database study in England. Lancet Psychiatry. 2019. PMID: 31588045

Hines LA, Morley KI, Strang J, Agrawal A, Nelson EC, Statham D, Martin NG, Lynskey MT. (2016). Onset of opportunity to use cannabis and progression from opportunity to dependence: Are influences consistent across transitions? Drug & Alcohol Dependence, 2016; 160: 57-64. doi: 10.1016/j.drugalcdep.2015.12.032.Epub 2016 Jan 6.

NS-MH 202241 Disease modifying effects of nutrition in ALS models

Co-Supervisor 1A: Dr Caroline Vance
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Project Description:

ALS is a complex neurodegenerative disorder involving genetic and environmental factors. Whilst much focus has been on understanding the genetic forms of the disease, the contribution of environmental factors is increasingly being recognised as crucial to the disease process. One such factor is nutrition, with evidence from multiple studies suggesting that the nutritional/dietary status of patients may impact on both disease onset and progression.
This study will build on pilot data demonstrating that modifying the nutrition of an aggressive ALS mouse model improved phenotypic and lifespan outcomes. It will assess the impact of nutritional supplements associated with altered mitochondrial and energy metabolism across different well-established mouse models of ALS, to investigate how diet can affect the progression of disease and explore the mechanisms that underpin this.

Behavioural assessment of mice on different nutritional supplements will be performed, and tissue taken from these animals will be used to explore molecular changes. Changes in microglial, lysosomal and mitochondrial function will be studied to identify key pathways involved in the disease process. This will provide new targets for the future development of nutrition and/or drug therapies for patients.

Techniques and Skills

In vivo handling skills, mouse behavioural and disease phenotyping, molecular analysis including western blotting, immunohistochemistry, cell culture and super-resolution microscopy.

Year 1: In vivo assessment of TDP-43 and FUS mouse models on different nutritional supplements

Year 2: Molecular analysis of mouse tissue to determine cellular changes behind the improved phenotypes

Year 3: Cellular modelling of nutritional changes to develop enhanced therapeutic diets

One representative publication from each co-supervisor:

Salam, S., Tacconelli, S., Smith, B.N. Mitchell JC, Glennon E, Nikolaou N, Houart C, Vance C Identification of a novel interaction of FUS and syntaphilin may explain synaptic and mitochondrial abnormalities caused by ALS mutations. Sci Rep 11, 13613 (2021). https://doi.org/10.1038/s41598-021-93189-6

Mitchell JC, Constable R, So E, Vance C, Scotter EL, Glover L, Hortabagyi T, Arnold ES, Ling SC, McAlonis M, Da Cruz S, Polymenidou M, Tessarolo L, Lagier-Tourenne C, Cleveland DW, Shaw CE.
"Wild type human TDP-43 potentiates ALS and FTLD-linked mutant TDP-43 driven progressive motor and cortical neuron degeneration with pathological features of ALS and FTLD." Acta Neuropath Comm. 2015; 3(1):36

NS-MH 202242 Pharmacogenetics and antidepressant response

Co-Supervisor 1A: Prof. Allan Young
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Project Description:

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are

important major depressive disorder (MDD) treatments in primary care, but only 1/3rd of antidepressant-treated patients achieve remission. Adverse effects are also common, often inducing non-compliance. Pharmacogenetic markers that distinguish between good and failed responders would enable precision prescribing, thereby improving outcomes and indicating cost-effective NHS treatments.

Heterogeneity in the efficacy and tolerability of SSRIs/SNRIs in MDD is mediated by numerous factors, including pharmacogenetic (i.e., enzyme metabolism and gene expression), as well as epigenetic changes resulting from adverse life events.

In the **first year**, 'treatment failure' data will be obtained using UK biobank-linked primary care records, defined as starting a new antidepressant medication within 6 months of having been prescribed an SSRI or SNRI. In the **subsequent years**, the project will analyse biobank genetic data to compare the presence of S or L(G) alleles of the SLC64A, HTR1A, HTR2A, TPH1, BDNF, CYP2C19 and CYP2D genes between good responders and failed responders to SSRIs/SNRIs. Additionally, biobank data will be interrogated to determine if experiencing childhood trauma is associated with alterations in the pharmacogenetic factors outlined above, thereby mediating antidepressant treatment response. In **the final year**, the value of predictive modelling utilising these findings will be evaluated prospectively alongside the ongoing 'A New Intervention for Implementation of Pharmacogenetics in Psychiatry' project.

The prospective student will develop statistical analysis skills in machine learning approaches to predictive modelling and analysing 'big data' sets, as well as relevant programming languages such as 'R'.

One representative publication from each co-supervisor:

Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., & Cowen, P. et al. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal Of Psychopharmacology, 29(5), 459-525. https://doi.org/10.1177/0269881115581093

Juruena, M. F., Gadelrab, R., Cleare, A. J., & Young, A. H. (2020). Epigenetics: A missing link between early life stress and depression. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 109, 110231. https://doi.org/10.1016/j.pnpbp.2020.110231

NS-MH 202243 Virtual reality-assisted interventions to tackle self-blame in major depressive disorder

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Project Description:

Many people with major depressive disorder (MDD) are ambivalent about medication or therapeutic relationships. Self-guided virtual-reality (VR)-assisted therapy is a promising approach to meet their needs. In this project, based on our previous VR-based self-assessment study of self-blame-related action tendencies, such as feeling like punishing oneself and hiding in MDD, we propose to develop such a novel intervention and probe its feasibility. After developing a VR-based version of a previously developed self-guided self-blaming bias intervention where people were given strategies to tackle self-blame-related memories and thoughts, we propose to randomise MDD patients who have not responded to standard treatment to 1) Treatment-as-usual vs. 2) 4 weekly sessions of our novel VR-assisted intervention. This will make an indispensable contribution towards the long-term goal of delivering novel neurocognitive treatments for MDD.

During year 1, the student will co-design the VR-intervention, learn how to assess patients, and how to deliver VR-interventions. Recruitment will start after 6 months and complete after the first half of year 3 (n=86, 3.6/month, n=70 completers over 24 months, allowing robust effect size estimates) . The last half of year 3 and the beginning of year 4 will be devoted to completing analyses and thesis/first-authored journal submissions describing baseline and trial results, as well as neurocognitive mechanisms in three papers. The PhD student will acquire psychotherapeutic, as well as diagnostic and skills in intervention design and clinical trials.

One representative publication from each co-supervisor:

Neurocognitive measures of self-blame and risk prediction models of recurrence in major depressive disorder. Lawrence, A. J., Stahl, D., Duan, S., Fennema, D., Jaeckle, T., Young, A. H., Dazzan, P., Moll, J. & Zahn, R. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging (2021): https://doi.org/10.1016/j.bpsc.2021.06.010

Virtual reality-based assessment and treatment of social functioning impairments in psychosis: a systematic review. Riches, S., Pisani, S., Bird, L., Rus-Calafell, M., Garety, P. & Valmaggia, L., 14 Jun 2021, In: International Review of Psychiatry. 33, 3, p. 337-362. https://doi.org/10.1080/09540261.2021.1918648