Theme 2
Neurosciences, Psychiatry and Mental Health

Neurosciences, Psychiatry and Mental Health

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

Lead: Prof Francesca Happé and Dr Sandrine Thuret

When choosing a project from this catalogue in the funding section of the online application form please enter **MRCDTP2021_Theme2**

Deadline for application: Sunday 29th November, 23:59
Shortlisted candidates will be contacted in mid-January.

Interviews: Thursday 28th January
The 2021/22 studentships will commence in September 2021.

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

1.2 Unravelling the cause of inflammatory bowel syndrome (IBS)

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Project Description:

Fibromyalgia is an incurable condition characterized by chronic widespread pain, fatigue, and emotional distress. Despite that >2% (mostly women) of the population live with fibromyalgia, there are no effective therapies available. The mechanisms responsible remained unknown until our recent, transformational discovery that fibromyalgia is caused by autoantibodies, and that patient symptoms can be transferred to mice by administration of patient antibodies. A third of fibromyalgia patients also suffer from the unexplained condition inflammatory bowel syndrome (IBS). IBS is very common, with a prevalence >10%, and has a severe impact on quality of life. This studentship offers an opportunity to examine whether IBS, like fibromyalgia, can be explained by autoantibodies.

This project is based on “passive transfer” of IBS, where patient samples transfers symptoms from patients to mice, thereby ensuring that results are directly relevant to the clinical condition.

During the first 12-18 months, behavioural assays of locomotor activity, abdominal pain-sensitivity, and gastrointestinal function will determine which types of symptoms that can be transferred from fibromyalgia patients with IBS to mice. In parallel, immunohistochemistry, immunoprecipitation and transcriptomic analysis will identify cells and molecules targeted by patient antibodies.

During the remainder of years 2-3, electrophysiological studies of tissue preparations from mice will identify which neurons are responsible for pain and discomfort in IBS.

Year 4 will be spent completing experiments, writing manuscripts, thesis, and fellowship applications. The student will be encouraged to present findings at national and international meeting and will have opportunities to discuss IBS and the project with patients.

One representative publication from each co-supervisor:

Andersson DA, Gentry C, Alenmyr L, Killander D, Lewis SE, Andersson A, Bucher B, Galzi JL, Sterner O, Bevan S, Hogestatt ED, Zygmunt PM (2011) TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid Delta(9)-tetrahydrocannabiorcol. **Nat Commun** 2:551.
(This paper describes the discovery of the analgesic mechanism of action of paracetamol.)

Quallo T, Vastani N, Horridge E, Gentry C, Parra A, Moss S, Viana F, Belmonte C, Andersson DA, **Bevan S** (2015) TRPM8 is a neuronal osmosensor that regulates eye blinking in mice. **Nat Commun** 6:7150.
(Discovery of TRPM8 is an exquisitely sensitive sensor of osmolality that controls the rate of eye blinking.)

2.2 Course of ADHD from childhood to adulthood and physical health outcomes: a multi cohort epidemiological study

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Project Description:

ADHD is associated with poor mental and physical outcomes (Agnew-Blais et al., 2019; Agnew-Blais, 2018; Chen et al., 2018). However, much of the current research in this area is limited to cross-sectional studies and often relies on clinical populations. We propose to investigate, across several population-based cohorts, the longitudinal association between ADHD and physical outcomes, including obesity, asthma and inflammation. Four separate but related studies focus on: (1) the epidemiology of the longitudinal association between ADHD and obesity; (2) the developmental association between ADHD with inflammation and asthma from childhood to mid-life (possibly mediated by cigarette smoking); (3) the genetic link between ADHD and obesity using ADHD polygenic risk scores (PRS), possibly modified by gender; and (4) the role of inflammation in the link between ADHD and poor health. We aim to replicate findings and harmonise measures across cohorts.

This project will capitalise on existing data collected as part of international longitudinal cohort studies including the UK National Child Development Study (NCDS), the Environmental Risk Longitudinal Twin Study in the UK, Generation R in the Netherlands, 1993 Pelotas cohort in Brazil, and ELEDEQ from Canada. The student will gain statistical skills on longitudinal and genetically-sensitive analyses (e.g., PRS, twin design) and experience disseminating findings.

Timeline
Objectives
Year 1: Get familiarised with literature on ADHD and physical health; consolidate statistical knowledge and skills
Year 2: Appreciate the value of cross cohort approaches and learn scientific writing
Year 3: Practice communication skills and learn genetic analyses
Year 4: Grants(wo)manship and public engagement

One representative publication from each co-supervisor:

Asherson, P., Agnew-Blais, J. (2019). Annual Research Review: Does late-onset attention-deficit/hyperactivity disorder exist? Journal of Child Psychology and Psychiatry, 60, 333-352. (doi: 10.1111/jcpp.13020).

Agnew-Blais, J.C, Polanczyk, G., Danese, A., Wertz, J., Moffitt, T.E., & Arseneault L. (2016). Persistence, remission and emergence of ADHD in young adulthood: Results from a longitudinal, prospective population-based cohort. JAMA Psychiatry, 73, 713-720. (doi:10.1001/jamapsychiatry.2016.0465).

3.2 Mental Health consequences of AIR pollution over the LIFE course

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Project Description:

The World Health Organization (WHO) recently estimated that ambient air pollution causes 482,000 premature deaths within the WHO European Region with an estimated economic cost of 1.575 trillion US$ including morbidity costs. However, the significant potential health and societal costs of poor mental health in relation to air quality are not represented in the WHO report due to limited evidence and gaps and uncertainties in our knowledge of the underlying pathophysiologic mechanisms that drive the reported associations. Benefiting from collaborations within King's College London, Imperial College London, University of Leicester and University College London in providing access to data on air pollution (e.g. CMAQurban), genetics and mental health (e.g. 1946, 1958, 1970 birth cohorts, E-Risk, Clinical Record Interactive Search (CRIS)), this project aims to systematically explore associations between air pollution and mental function over the life course. Throughout the project, the PhD candidate will use a range of advanced Geographical Information Systems (GIS) and state of the art statistical techniques and epidemiological designs (under main supervision of IB) to gain a deep understanding of how air pollution stressors could affect mental health and the potential mechanisms and moderators (under main supervision of HF).

Yr1: A systematic review of the associations between air pollution and a range of mental health outcomes
Yr2: Augment the linkages of existing air pollution databases with E-Risk, CRIS, and 1946 birth cohort.
Yr3: Conduct epidemiological cross-cohort analyses
Yr4: Synthesise findings and draft a list of recommendations for tackling air pollution levels and identifying vulnerable populations.

One representative publication from each co-supervisor:

Bakolis, I, Hammoud, R, Smythe, M, Gibbons, J, Davidson, N, Tognin, S & Mechelli, A 2018, 'Urban Mind: Using Smartphone Technologies to Investigate the Impact of Nature on Mental Well-Being in Real Time', *BioScience*, vol. 68, no. 2, pp. 134-145. https://doi.org/10.1093/biosci/bix149

Newbury, JB, Arseneault, L, Beevers, S, Kitwiroon, N, Roberts, S, Pariante, CM, Kelly, FJ & **Fisher, HL** 2019, 'Association of Air Pollution Exposure with Psychotic Experiences during Adolescence', *JAMA Psychiatry*, vol. 76, no. 6, pp. 614-623. https://doi.org/10.1001/jamapsychiatry.2019.0056

4.2 Epigenetic regulation of learning and memory

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Project Description:

The ability to learn and remember is essential for survival of all animal species. Fundamental questions remain about how memories are encoded and stored in the brain. The formation of long-term memories (memory consolidation), requires new gene transcription. As long-term memory is established or modified through gene expression changes, epigenetic mechanisms that regulate gene transcription are likely to have key roles in memory consolidation. Indeed, mutation of genes encoding chromatin remodelling factors have been linked to intellectual disability and specific learning deficits in the human population. Deficits in memory consolidation are thought to be the primary cause of age-related learning deficits. Thus, manipulating the epigenome may help prevent or even treat memory deficits in intellectual disability, old age and neurodegenerative conditions.

In this project, the student will investigate the epigenetic basis whereby mutations in chromatin modifying and remodelling factors affect memory and learning in mouse models. Mouse genetics, targeted delivery of substances in the brain, and quantitative (PCR, Western blot), semi-quantitative (immunostaining) and genome-wide next-generation sequencing methods (RNA-seq, ChIP-seq, ATAC-seq) will be employed.

Specific aims:
1) To identify transcriptomic changes that characterise specific memory phenotypes in mutant mice during learning (Year 1),
2) To identify alterations in chromatin structure and dynamics that underlie these transcriptional changes (Year 2),
3) To validate functionally relevant chromatin and gene expression changes in vivo (Year 3-4).

Together, this work will reveal how altered chromatin dynamics impact memory and learning and identify novel therapeutic avenues to treat cognitive disorders.

One representative publication from each co-supervisor:

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

Vigil FA, Mizuno K, Lucchesi W, Comamala VV, **Giese KP** (2017). Prevention of long-term memory loss after retrieval by an endogenous CaMKII inhibitor. ***Sci Rep*** 7, 4040.

5.2 Investigating how mitochondrial DNA dynamics contribute to ageing and neurodegeneration

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Project Description:

Mitochondrial DNA (mtDNA) encodes vital components of the mitochondrial respiratory machinery. Loss of, and mutations in, mtDNA occur during ageing in the brain and contribute to neurodegenerative diseases such as Alzheimer's and Parkinson's disease. mtDNA is packaged in nucleoprotein complexes called 'nucleoids'. In neurons, efficient transport and distribution of nucleoids in axons and dendrites is essential but this process is poorly understood. The aim of this project is to investigate nucleoid dynamics using cutting edge imaging techniques in Drosophila and mammalian neurons during ageing and neurodegeneration. Overall, this project will reveal important new insight into the contribution of mtDNA to ageing and neurodegeneration.

Over-arching objectives:
Year 1 (or rotation project): Super resolution imaging and quantification of nucleoids in Drosophila neurodegenerative disease models (Parkinson's, Leigh syndrome) and during ageing.
Year 2: Live imaging and analysis of nucleoid dynamics in Drosophila neurodegenerative disease models and mammalian neurons.
Year 3: Testing manipulation of nucleoid dynamics as a therapeutic strategy for neurodegenerative disease in Drosophila and mammalian models.
Year 4: Completion of experiments, writing manuscripts and thesis.

The student will use state-of-the-art fluorescence and super resolution imaging to visualise nucleoids in mammalian and Drosophila neurons in neurodegeneration models and during ageing. They will be trained in the practical and theoretical aspects of Drosophila genetics; behavioural analyses; mammalian cell culture; quantitative image analysis.

The supervisors have different backgrounds but complementary interests, providing an ideal supervisory team for the project. Dr Bateman is interested in the role of mitochondria in neurological disease and has developed Drosophila genetic models to investigate the role of mitochondrial signalling in neuronal function. Dr Vagnoni is an expert in neuronal transport mechanisms and has pioneered methods to study mitochondrial transport during ageing.

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.

A. Vagnoni, S.L. Bullock (2018). A cAMP/PKA/Kinesin-1 Axis Promotes the Axonal Transport of Mitochondria in Aging Drosophila Neurons. *Curr Biol.* 28:1265-1272.e4

6.2 Cannabidiol for psychosis in neurodegenerative disorders

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Project Description:

Symptoms of psychosis in Alzheimer's disease (ADP) or Parkinson's disease (PDP) can be very distressing, cause considerable suffering to patients and caregivers and there are currently no approved treatments available. While cannabidiol is a promising candidate treatment, it's unclear if it will work for ADP or PDP. The next stage of clinical development for cannabidiol as a treatment for ADP or PDP involves the conduct of fully powered pivotal clinical trials. Such studies are expensive. Therefore, go/no-go decisions regarding further clinical development need to be informed by supportive mechanistic evidence in these patient groups to complement preliminary efficacy signals. However, no such evidence exists at this point of time. The proposed PhD will be nested within Randomized Controls Trials (RCT) using cannabidiol (CBD) in ADP and PDP. The proposed PhD project will generate such mechanistic evidence if it can demonstrate an effect of cannabidiol on some of the brain substrates implicated in psychosis in neurodegenerative disorders.

Planned research methods and training provided:
· Acquisition & analysis of neuroimaging and cognitive data.
· Evaluation of novel treatments; clinical research in neurodegenerative disorders; industrial collaboration

Year 1: Liaison with RCT team; subject enrolment; cognitive data acquisition, neuroimaging data (verbal learning and resting state fMRI) will be acquired on a 3T MRI scanner using established protocols.

Year 2: Data collection; Industrial secondment with the supplier of study drug.

Year 3: Investigate the effect of CBD treatment on the fMRI BOLD signal and analysis of neuroimaging data using established software; Dissemination; Submission of PhD

One representative publication from each co-supervisor:

Bhattacharyya S, Wilson R, Appiah-Kusi E, et al. Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. *JAMA Psychiatry.* 2018;75(11):1107-1117.

Velayudhan L, Van Diepen E, Marudkar M, Hands O, Suribhatla S, Prettyman R,Murray J, Baillon S, Bhattacharyya S. Therapeutic Potential of Cannabinoids in Neurodegenerative Disorders: A Selective Review. *Curr Pharm Des*. 2014;20(13):2218-30.

7.2 A neuroimaging assessment of brain metastability changes in Epilepsy

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Collaborating Clinician: Mark Richardson
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Project Description:

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

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

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

One representative publication from each co-supervisor:

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

Brain. 2018 Aug 28.

Cascades and Cognitive State: Focused Attention Incurs Subcritical Dynamics
Erik D. Fagerholm, Romy Lorenz, Gregory Scott, Martin Dinov, Peter J. Hellyer, Nazanin Mirzaei, Clare Leeson, David W. Carmichael, David J. Sharp, Woodrow L. Shew and Robert Leech
Journal of Neuroscience 18 March 2015

8.2 Identifying common and distinct neurodevelopmental risk and resilience factors in infants at elevated familial likelihood of ASD and ADHD

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Co-Supervisor 1B: Prof. Andrew Pickles
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Project Description:

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) are neurodevelopmental disorders with high heritability and rates of co-occurrence. The prospective study of infants at elevated familial likelihood of ASD and ADHD (a first degree relative with a diagnosis) enables identification of neurocognitive and behavioural profiles that may help to identify common and distinct mechanisms that lead to the two clinical disorders. However, to date most work has focused on single antecedent markers and not combined these to model the interplay between risk and resilience factors over time. Variability in aetiology and presentation of these disorders suggests that different neurodevelopment risk factors will act in combination, and further that these combinations will differ between individuals. As part of the MRC-funded BASIS network (http://www.basisnetwork.org/) we study ~450 children at familial risk of ASD and ADHD using multiple methods (EEG, eye-tracking, behavioural experiments, clinical measures, genetics) at multiple timepoints from 6 months to 10 years of age.

The student will develop expertise in innovative developmental theory and statistical modeling approaches (e.g. SEM, LCA, MIMIC) to test whether combinations of risk and resilience biomarkers better predict developmental trajectories and clinical outcomes than single markers alone. Identifying the mechanisms and timing underlying atypical development will inform translational approaches to early intervention.

Skills: Training in EEG, eye-tracking and electrophysiological data collection and analysis. Clinical assessments of infants and children. Complex statistical modelling.

Year 1: Training on assessments. *Year 2:* Training in statistical modelling *Year 3:* Analysis and paper writing. *Year 4 (6 months):* Complete thesis.

One representative publication from each co-supervisor:

Shephard, E., Bedford, R., Milosavljevic, B., Gliga, T., Jones, E. J. H., **Pickles, A.**, Johnson, M. H., **Charman, T.**, & The BASIS Team. (2019). Early developmental pathways to childhood symptoms of attention-deficit hyperactivity disorder (ADHD), anxiety, and autism spectrum disorder (ASD). *Journal of Child Psychology & Psychiatry, 60,* 963-974.

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

9.2 Systems Analysis of Food-Sensing Neuroendocrine Networks that Regulate Ageing

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Co-Supervisor 1B: Attila Csikász-Nagy
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Project Description:

Age is the major risk factor for many diseases, including diabetes, heart attacks, and cancer. Ageing populations are also a major challenge for developed countries globally. 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 neural regulation of ageing. Our project combines experimental and computational approaches to delineate the neuroendocrine circuitry 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.

During this work, the student will discover how hormonal activity in the nervous system can modulate the effects of food on lifespan. These results will help explain why different individuals show different lifespans despite eating the same amount of food.

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

One representative publication from each co-supervisor:

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

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

10.2 "How do I even begin to say 'Thank you'": understanding perceptual barriers to living kidney donation from the recipient's perspective

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Project Description:

Living kidney donation (LKD) is the gold standard treatment for end-stage renal disease. In the UK there are two pathways: specified donation to a recipient known to the donor, and unspecified kidney donation (UKD) to an anonymous recipient. UKD is controversial and still illegal in many countries, however where practiced, facilitates significant numbers of transplants. Research suggests that living kidney donors largely experience no long-term physical or psychological harm. However, there is a lack of research on the psychological dimensions for recipients, or the effects of time spent on transplant waitlists. For specified donations, little is known about the accompanying family dynamics or possible psychological burden. For unspecified recipients, scant research indicates that accepting UKD can be a difficult choice; reactions range from gratitude to guilt to feelings of unworthiness.

This mixed methods study will explore the attitudes of specified and unspecified recipients toward LKD, along with the psychological impact of time spent on the transplant waitlist. By identifying and addressing perceptual barriers to acceptance, this research aims to ensure that both donors and recipients derive maximum benefit from LKD, and that NHS resources are utilised in the most efficient and cost-effective manner.

Year 1: Systematic review of existing research; design, conduct and analyse qualitative interviews exploring recipients' attitudes towards LKD.

Year 2: Cross sectional-observational study: develop questionnaire probing barriers to acceptance, disseminate through UK (and possibly Canadian) transplant centres; analyse this larger set of quantitative data.

Year 3/4: Analyse and disseminate aggregate results; propose clinical applications for transplant community.

One representative publication from each co-supervisor:

Maple, H., Draper, H., Gogalniceanu, P., Burnapp, L., **Chilcot, J.**, & **Mamode, N.** (2020). Donating a Kidney to a Stranger: A Review of the Benefits and Controversies of Unspecified Kidney Donation. *Annals of surgery, 272*(1), 45-47.

Maple, H., **Chilcot, J.**, Weinman, J., & **Mamode, N.** (2017). Psychosocial wellbeing after living kidney donation - a longitudinal, prospective study. *Transpl Int*, *30*(10), 987-1001.

11.2 Pathophysiological role of the RNA-binding protein TDP-43 in Dementia

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Project Description:

Dementia is a progressive memory impairment. The most commom pathology involves the weakening of synaptic connections and ultimately their elimination, which is thought to correlate with the severity of symptoms. The aberrant aggregation of the RNA-binding protein TDP43 causes neurotoxicity, hippocampal sclerosis and is involved in dementia. However, it is not well known how aggregated TDP-43 underlies synapse dysfuction. Preliminary in vitro work in Pastore's group has indicated that RNA aptamers are able to abolish TDP-43 aggregation. The focus of this programme is to explore the consequence of the aberrant aggregation of TDP-43 in synaptic dysfunction and subsequent epigenetic alterations in the CA1 and CA3 hippocampal neurons, and the potential opportunity for therapy in dementia.

(Year 1) The consequences of TDP-43 aggregation in hippocampal neurons (Cho-Lab).

We will test whether TDP-43 regulates dendritic spine activity, synapse structure and synaptic plasticity in conjunction with proximal and distal segmentation of dendritic spines in hippocampal neurons. **Method**: Multi-photon imaging; glutamate-uncaging; whole-cell patch clamp electrophysiology.

(Year 2) The role of dendritic activity in TDP-43 mediated pathophysiology (Cho/Pastore-Lab).

We will examine whether local dendritic activity and TDP-43 aggregates alter the epigenetic (methylation) status of key TDP-43 associated synaptic genes that ultimately results in synapse dysfunction. **Method**: Optogenetics; single-cell PCR; Multi-photon imaging.

(Year 3 – 4) Determine the consequences of interfering with TDP-43 aggregation in synapse dysfunction (Pastore/Cho-Lab).

We will test whether already developed high affinity RNA aptamers, which interfere with TDP-43 aggregates in vitro, rescue TDP-43 aggregation and synapse dysfunction. **Method**: Structural biology; super-resolution imaging; glutamate-uncaging; single-cell PCR.

One representative publication from each co-supervisor:

Cho: Jo J. et al. (2011) $A\beta_{1-42}$ inhibition of LTP is prevented by manipulation of a signalling pathway involving caspase-3, Akt and GSK-3β. Nat Neurosci 14, 545-.

Pastore: Zacco, E. et al. (2019) RNA as a key factor in driving or preventing self-assembly of the TAR DNA-binding protein 43. J. Mol. Biol. 431, 1671-1688.

12.2 Mapping the pharmacology of Autism using multi-modal brain imaging data from drug shiftability studies.

Co-Supervisor 1A: Dr Eileen Daly
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Co-Supervisor 1B: Professor Declan Murphy
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Project Description:

At present, there are no medications for the treatment of Autism core or co-occurring symptoms. There is evidence that the neurobiological underpinnings of ASD include aberrations in brain growth, neuronal patterning and cortical connectivity. Altered molecular pathways implicated include serotonin system and excitation/inhibition neurotransmitter systems. The PhD will investigate if modulation of these abnormalities from multiple perspectives (brain function, structure and pharmaco-challenge) can lead to a medication stratification biomarker for translation to clinical trials. Our laboratory has been performing randomised, double blind, placebo-controlled biomarker shiftability studies comparing brain functional resonse in adults with and without. Specifically, we have tested the impact of acute doses of several medications, using multimodal imaging techniques, on resting and active brain functional connectivity, structure and chemistry. While each brain imaging modality reveals different aspect of the brain, this PhD will develop multivariate methods which use higher order statistics to combine diverse information to identify correspondence among data types. The PhD candidate will utilise our completed and ongoing multimodal pharmoco-challenge datasets to investigate this mapping.

Pharmacological Agents - GABA & glutamate – Arbaclofen, Riluzole & AZD7325, Serotonin – Citralopram & Tianeptine, Cannabanoid – Cannabadiol & Cannabidvarin

Imaging - Anatomical Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), Resting state functional Magnetic Resonance Imaging (rsfMRI), Task based functional Magnetic Resonance Imaging (fMRI)
Magnetic Resonance Sprectroscopy (MRS), Electroenchephalogram (EEG)

Potential schedule
Year-1: Training in all neuroimaging paradigms and analysis. Participate in data collection of ongoing studies
Year-2: Neuroimaging data Analysis. Training in Multimodal Data analysis.
Year-3: Data analysis. Thesis write-up.

One representative publication from each co-supervisor:

Wong, N. M. L., Findon, J., Wichers, R., Giampietro, V., Stoencheva, V., Murphy, C., Blainey, S., Ecker, C., **Murphy, D., McAlonan, G. & Daly, E**. Serotonin differentially modulates the temporal dynamics of the limbic response to facial emotions in male adults with and without autism spectrum disorder (ASD): a randomised placebo-controlled single-dose cross-over trial. *Neuropsychopharmacology*, 2020.

Pretzsch, Freyberg, Voinescu, Lythgoe, Horder, Mendez, Wichers, Ajram, Ivin, Heasman, Edden, Williams, **Murphy DGM, McAlonan, Daly, E**. Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder. *Neuropsychopharmacology*, 2019 (44:8).

13.2 Predictors of psychosis and outcomes: Using large-scale linked health records to unlock the role of the environment on the developing brain

Co-Supervisor 1A: Dr Jayati Das-Munshi
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Co-Supervisor 1B: Dr Peter Schofield
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Project Description:

Psychosis (schizophrenia and related disorders, bipolar disorder, depressive psychosis) are chronic conditions with substantial impacts on individuals across the life-course. Outcomes show high individual variability, ranging from discrete episodes followed by prolonged recovery in some people, to a chronic and highly disabling course in others. Little is known about environmental predictors of prognosis following the onset of disorder. In this project we will use linked data from the electronic health records of 20,000+ individuals with clinically defined psychoses linked to individual-level UK census data, which will bring in rich detail relating to social and environmental characteristics. Using this linked longitudinal dataset, the student will undertake analyses focusing on modifiable social/ environmental predictors of prognosis (employment, mortality and admissions) in psychoses.

The project would suit a student with a good MSc or equivalent qualification in epidemiology, statistics, or other data sciences with experience in working with STATA, MPLUS, R or equivalent. An understanding of mental illness and psychiatry is desirable and enthusiasm for the topic essential. The student will undertake ONS approved researcher training and encouraged to attend interdisciplinary training (e.g. provided through ESRC Centre for Society & Mental Health, for which the lead supervisor is a core member). Indicative timeline: Year 1- Undertake training, gain necessary approvals, complete systematic reviews. Data analysis. PhD Upgrade. Year 2- Undertake/ complete main analyses relating to predictors of employment, admissions and/ or mortality in psychoses. Year 3- Advanced analyses (e.g. SEMs), finalise analyses and complete PhD write up. Submit papers for publication. PhD viva/completion.

One representative publication from each co-supervisor:

Das-Munshi, Jayati; Schofield, Peter; Bhavsar, Vishal et al. Ethnic density and other neighbourhood associations for mortality in severe mental illness: Retrospective cohort study with multi-level analysis from an urbanised and ethnically diverse location in the UK. *The Lancet Psychiatry*, Vol. 6, No. 6, 01.06.2019, p. 506-517.

Heslin M, Khondoker M, Shetty H, Pritchard M, Jones PB, Osborn D, Kirkbride JB, Roberts A, Stewart R. Inpatient use and area-level socio-environmental factors in people with psychosis. *Social psychiatry and psychiatric epidemiology*. 2018 Oct 1;53(10):1133-40.

14.2 Investigating cultural modulation of cognition and brain function with virtual reality and EEG

Co-Supervisor 1A: Dr Quinton Deeley
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Co-Supervisor 1B: Professor Hugh Bowden
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Project Description:

This AHRC funded interdisciplinary project combines cognitive neuroscience, ancient history, human-computer interaction, and psychology to create a virtual reality experience of the ancient Greek oracle at Dodona in NW Greece: the Virtual Reality Oracle (VRO). An oracle was a site where ancient Greeks asked the gods to answer questions about the past, present and future. Divinatory practices of this kind are widespread and undertaken to guide action and reduce anxiety under conditions of salient uncertainty. User responses to the VRO will be researched qualitatively and experimentally. Experiments in healthy participants will manipulate a) cognitive context (information given to participants); b) sensory components, c) action sequences during the VRO whilst measuring brain activity (EEG). Neurocognitive hypotheses relate to the interaction of narrative and sensory information to elicit experiences of intentional agents (gods); and the effects of trait anxiety and prior beliefs on the modulation of emotion by the VRO. The student will also develop novel experiments in a subgroup of participants with high trait anxiety to inform VR treatment of anxiety disorders. The research has broader relevance to mechanisms and applications of VR; reconstruction of ancient cognition with VR; and social and cultural neuroscience.

Teaching and training: regular group meetings, seminars, and primers for qualitative / phenomenology and EEG methods, amongst other opportunities. Supervision on cultural and historical aspects of the VRO will be provided.

Year 1: Develop study protocols, obtain ethics, attend interdisciplinary meetings and review literature.

Year 2: conduct experimental studies.

Year 3: complete experiments, analyses, and write up.

One representative publication from each co-supervisor:

Deeley Q, Oakley DA, Walsh E, Bell V, Mehta MA, Halligan PW. Modelling psychiatric and cultural possession phenomena with suggestion and fMRI. Cortex. 2014 Apr;53:107-19. doi: 10.1016/j.cortex.2014.01.004.

Bowden, H 2018, 'Believing in Oracles', *Method & Theory in the Study of Religion*, vol. Supplement 13, pp. 435-446. https://doi.org/10.1163/9789004385375_030

15.2 Stratification of people at risk of psychosis using automated measures of thought disorder

Co-Supervisor 1A: Dr Kelly Diederen
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Co-Supervisor 1B: Dr Tom Spencer
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Project Description:

Formal thought disorder, a marked disturbance in the organisation of thought expressed in patients' speech, is a cardinal feature of psychosis and is predictive of poor clinical and socio-occupational outcomes (Yalincetin et al., 2017; Demjaha et al., 2017). Recently, automated methods such as semantic, syntactic and graph analysis have been developed to rapidly assess formal thought disorder based on brief speech fragments (Corcoran et al., 2018 , Mota et al., 2017). Using these novel methods, we found preliminary evidence that people with psychosis have disconnected speech, suggesting that disturbed speech might be a promising biomarker of psychosis. Recent developments in online testing allow large-scale collection of speech samples with limited costs and effort.

This PhD project will combine online assessment of speech (Gorilla.sc), using the Thematic Apperception Test (Murray,1943) in 500 individuals at clinical high-risk for psychosis and 500 individuals experiencing their first episode psychosis with novel automated speech methods, to determine whether speech can predict clinical outcomes. This may improve clinicians' ability to target treatment to those who are most vulnerable.

Year-1: Data collection and training in speech analysis (supervisors). Training in Python and predictive modelling (IoPPN Biostats courses).

Year-2: Data collection of follow-up data, analysis of baseline speech and clinical data, preparation for 1-2 manuscripts, and abstract for conference presentation.

Year-3: Analysis of follow-up data, preparation for 1-2 manuscripts, abstract for conference presentation, thesis-write-up.

Additional training including communication, writing academic papers, time management and career planning will be available via the Centre for Doctoral Studies at KCL.

One representative publication from each co-supervisor:

Spencer TJ, Thompson B, Oliver D, Diederen K, Demjaha A, Weinstein S, Morgan S, Day D, Valmaggia L, Rutigliano G, De Micheli A, Mota N, Fusar-Poli P, McGuire P. Lower speech connectedness linked to incidence of psychosis in people at clinical high risk. *Schizophrenia Research*, in press.

Haarsma J, Fletcher PC, Griffin JD, Taverne HJ, Ziauddeen H, Spencer TJ, Miller C, Katthagen T, Goodyer I, Diederen KMJ*, Murray GK*. Precision weighting of cortical unsigned prediction error signals benefits learning, is mediated by dopamine, and is impaired in psychosis. *Mol Psychiatry*. 2020;10.1038/s41380-020-0803-8.

*These authors contributed equally

16.2 Brain mechanisms underlying response to clozapine in treatment resistant schizophrenia

Co-Supervisor 1A: Dr Alice Egerton
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Co-Supervisor 1B: Dr Gemma Modinos
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Collaborating Clinician: Prof James MacCabe
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Project Description:

Although the symptoms of schizophrenia can be reduced by antipsychotic medication, antipsychotics are not effective for everyone. This can be termed Treatment Resistant Schizophrenia (TRS), for which there are very few treatment options. Clozapine appears more effective than other antipsychotics in treating TRS, but it is unknown why this is, and is also not possible to predict the likelihood of a good response to clozapine in advance. Better understanding of these mechanisms may ultimately lead to improved clinical care for those with schizophrenia.

In this project, we will apply neuroimaging methodologies to better understand the brain mechanisms underlying clozapine response in TRS. The PhD candidate will compare the patterns of brain network activity (using resting state functional MRI) in patients with TRS before and 12 weeks after switching to clozapine treatment and determine how these changes relate to symptomatic improvement (Year 1). Depending on the student's interests, in Years 2 and 3 these data can be combined with information on regional cerebral blood flow, brain glutamate levels, brain structure or proteomic data collected in the same participants, to provide deeper understanding using state-of-the-art multimodal analyses.

The student will be hosted in the groups of Dr Egerton and Dr Modinos, within the world-leading research community of the Dept. Psychosis Studies. They will be provided with training in neuroimaging analyses, by the supervisors and their collaborators within the Dept. Neuroimaging. Understanding of the clinical aspects and

translational potential will be developed through collaboration with Prof MacCabe.

One representative publication from each co-supervisor:

Egerton A, et al. Response to initial antipsychotic treatment in first episode psychosis is related to anterior cingulate glutamate levels: a multicentre $_1$H-MRS study (OPTiMiSE). Mol Psychiatry. 2018 Nov;23(11):2145-2155.

Modinos G, et al. Prefrontal GABA levels, hippocampal resting perfusion and the risk of psychosis. Neuropsychopharmacology. 2018 Dec;43(13):2652-2659.

17.2 Exploring the genetics of common mental health conditions in BAME populations

Co-Supervisor 1A: Prof Thalia Eley
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Co-Supervisor 1B: Prof Gerome Breen
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Project Description:

This project will expand our understanding of the genetics of depression and anxiety in African ancestry populations. The student would learn advanced psychiatric and population genetic methods and work with UK and Africa based collaborators within a network of studies. There have been rapid advances psychiatric genetic findings within European ancestries over the last 5 years, leading to more accurate risk stratification and stronger causal inferences. However, there is a lack of generalisability to individuals of non-European ancestries and those residing in low- and middle-income countries (LMIC). The work within this studentship would help address the growing health disparities between high and LMIC countries. It would allow the student to triangulate findings from EA populations with African samples in different genetic, economic and social contexts and for stronger causal inferences to be made.

Training will be provided in genetics, psychiatric epidemiology and statistics through a mixture of short courses, online courses and peer support. The student will have access to large datasets from different populations and work remotely, and eventually visit with collaborators.

This project is also available as a rotation for students wishing to undertake the 1+3 route.

Year 1 aims: Learn genetic analysis methods with and across ancestries, as well how common mental disorders and their epidemiological risk factors vary and are assessed in different populations and cultures.

Year 2 aims: Undertake pilot genome-wide association analyses of depression and anxiety within available African ancestry cohorts.

Year 3 aims: Compare genetic architecture of depression and anxiety within and across African countries with that found in European and East Asian ancestry samples.

One representative publication from each co-supervisor:

Purves, K., Coleman, J., Meier, S., Rayner, C., Davis, K., Cheesman, R., Bækvad-Hansen, M., Børglum, A., Wan Cho, S., Deckert, J., Gaspar, H., Bybjerg-Grauholm, J., Hettema, J., Hotopf, M., Hougaard, D., Hübel, C., Kan, C., McIntosh, M., Mors, O., Mortensen, P., Nordentoft, M., Werge, T., Nicodemus, K., Mattheisen, M., Breen., G.*, & **Eley, T.C.*** (2019) A major role for common genetic variation in anxiety disorders. *Molecular Psychiatry*. doi: 10.1038/s41380-019-0559-1

Coleman, J., Peyrot, W.J. Purves, K.L., Davis, K. A. S., Rayner, C., Choi, S.W., Hübel, C., Gaspar, H. A., Kan, C., Auwera, S. V. D., Adams, M. J., Lyall, D. M., Choi, K. W., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium., Dunn, E. C., Vassos, E., Danese, A., Maughan, B., Grabe, H. J., Lewis, C. M., O'Reilly, P. F., McIntosh, A. M., Smith, D. J., Wray, N, R., Hotopf, M., **Eley, T. C***., & Breen*, G. (2020) Genome-wide gene-environment analyses of depression and reported lifetime traumatic experiences in UK Biobank. *Molecular Psychiatry. doi:10.1038/s41380-019-0546-6*

18.2 Adult neurogenesis in the olfactory bulb: unlocking the secrets of newborn neuron function

Co-Supervisor 1A: Matthew Grubb
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Co-Supervisor 1B: Laura Andreae
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KCL/KHP Website: https://devneuro.org/cdn/group-overview.php?groupID=84

Project Description:

Naturally-occurring regeneration is rare in the adult mammalian brain, where most circuits operate for lifetimes with the same neurons that were present at birth. An exception is the olfactory bulb, whose neurons can be born throughout adulthood. Understanding how these adult-born neurons function and integrate into existing circuits could be critical to developing regenerative therapies for neurological disorders.

Adult-born olfactory bulb neurons include a subpopulation that release dopamine. These cells also completely lack an axon, so must receive and send synaptic information exclusively from their dendrites. But are their dendritic release sites just like those normally found at axon terminals, or are they molecularly specialised? And how do these processes change as newborn neurons mature and integrate into their host circuits? We will use genetic, imaging and electrophysiological approaches to answer these questions in a truly collaborative project.

Techniques include coupling conditional transgenic mouse lines with viral expression targeted to newborn neurons, to selectively label these cells and delete key synaptic proteins. Immunological labelling of neurons, including optical clearing and lightsheet microscopy, will characterise the morphology and molecular signature of these neurons and their synapses. Finally, patch clamp electrophysiology and/or functional imaging will be used to understand how the synapses function.

Year 1: Establish transgenic colonies, target cells with viral injections, imaging of neurons and synaptic labelling
Year 2: Examine impact of deleting synaptic proteins on development of newborn neuron synapses
Year 3: Functional characterisation using electrophysiology and imaging.

One representative publication from each co-supervisor:

Galliano E, Franzoni E, Breton M, Chand AN, Byrne DJ, Murthy VN, Grubb MS (2018) Embryonic and postnatal neurogenesis produce functionally distinct subclasses of dopaminergic neuron. eLife, 7:e32373. https://doi.org/10.7554/eLife.32373

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

19.2 Defective nucleocytoplasmic transport as a potential molecular mechanism underlying the development of Alzheimer's disease

Co-Supervisor 1A: Professor Diane Hanger
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Co-Supervisor 1B: Dr Sarah Mizielinska
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Project Description:

The molecular processes that underlie Alzheimer's disease and dementia are unknown and no disease-modifying treatments are available. The key neuropathological features of Alzheimer's disease are amyloid plaque and neurofibrillary tangles, comprised of aggregated tau protein. Recently, dysfunctional nuclear-cytoplasmic trafficking of macromolecules has been suggested to be involved in dementia. For example, the nuclear pore protein, Nup98 promotes tau aggregation. The aim of this project is to determine whether and how nucleoporin proteins that regulate nuclear import/export interact with tau, resulting in the development of dementia.
Skills training will encompass a wide range of cell and molecular biological techniques including cell culture, transfection, immunofluorescence, super-resolution microscopy and image analysis. Training will also be provided in protein biochemical techniques including polyacrylamide gel electrophoresis and western blots.

Objectives:

Year 1: Determine the effects of normal and disease-associated tau on the structure and composition of the nuclear pore using a cell model of dementia previously characterised in the host lab. Identify specific nuclear-associated proteins that are influenced by tau. Examine the effects of tau on nuclear translocation and potentially aggregation of other key proteins.

Year 2: Determine whether and how nucleoporins and tau interact in vitro, in isolated nuclei, and in cells. Use fluorescent reporters to investigate whether and how nucleocytoplasmic transport function in cells is modulated by

tau.

Year 3: Validate the nuclear-associated proteins identified as being affected by abnormal tau in human tissue from Alzheimer's disease and other dementias. This will include determining the localisation of nuclear pore proteins relative to disease pathology.

One representative publication from each co-supervisor:

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.

Mizielinska, S., Ridler, C. E., Balendra, R., Thoeng, A., Woodling, N. S., Grässer, F. A., Plagnol, V., Lashley, T., Partridge, L. & Isaacs, A. M. (2017) Bidirectional nucleolar dysfunction in C9orf72 frontotemporal lobar degeneration. Acta Neuropathologica Communications. 5, 29.

20.2 Exploring trauma and post-traumatic stress symptoms in autistic children and those with high autistic traits

Co-Supervisor 1A: Professor Francesca Happé
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Co-Supervisor 1B: Professor Andrea Danese
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Project Description:
Autistic children and adults are at greater risk of exposure to negative life events, including bullying and trauma. Recently, we have suggested that features of cognitive style (e.g., detail focus) in autism may predispose to the development of post traumatic stress disorder/symptoms. Autistic people may also be traumatised by experiences not traditionally recognised as traumas, and not qualifying for PTSD diagnosis in DSM-5. However, there is scarcely any research on how autistic traits relate to PTSD, and none in children. This PhD project will explore how autism/autistic traits relate to PTSD symptoms following trauma (broadly defined). The student will gain qualitative and quantitative skills, work directly with children and young people, as well as designing online surveys and semi-structured interviews.

Year1

- Complete literature review (for publication) on autism and trauma/PTSD.
- Plan studies and obtain ethical permission.
- Join clinical team at the Maudsley NHS National & Specialist CAMHS Trauma, Depression, and Anxiety clinic, to receive training in administering appropriate assessments.
- Possible case studies of children in trauma service with un/diagnosed autism re treatment response.
- Training in qualitative research methods.

Year2

- In-depth interviews with autistic children to explore the association between autistic traits and cognitive styles, trauma types, and PTSD symptoms. Quantitative and qualitative (e.g. thematic) analyses, and write up.
- Analyse relevant data on autistic traits/diagnosis and trauma in existing large datasets (e.g., TEDS, E-Risk).

Year3

- Online study of adults' retrospective recall of childhood trauma, autistic traits, sensory sensitivities, cognitive style and PTSD symptoms. Write up for publication.
- Design parent and teacher psychoeducational materials on autism and PTSD informed by survey and empirical work.
- Write up and submit thesis.

One representative publication from each co-supervisor:

Rumball, F., Happé, F. and Grey, N., (2020). Experience of Trauma and PTSD Symptoms in Autistic Adults: Risk of PTSD Development Following DSM-5 and Non-DSM-5 Traumatic Life Events. *Autism Research*. https://doi.org/10.1002/aur.2306

Lewis, S.J., Arseneault, L., Caspi, A., Fisher, H.L., Matthews, T., Moffitt, T.E., Odgers, C.L., Stahl, D., Teng, J.Y., **Danese, A**. (2019) The Epidemiology of Trauma and Post-Traumatic Stress Disorder in a Representative Cohort of Young People. Lancet Psychiatry, 6(3):247-256. doi:10.1016/S2215-0366(19)30031-8

21.2 Role of Tenm4, a synaptic adhesion molecule linked to bipolar disorder, during synapse formation

Co-Supervisor 1A: Prof. Robert Hindges
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Co-Supervisor 1B: Juan Burrone
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Project Description:

Establishing the correct brain circuitry underlying memory, learning and behaviour requires **appropriate action of molecules regulating axon pathfinding and synapse formation**. We concentrate on transmembrane molecules, teneurins, that interact across the synapse and are believed to shape brain connectivity. Mutations in the human gene family have been **linked to various mental disorders**, including depression, schizophrenia, and bipolar disorder. However, the underlying mechanisms for teneurins in the disorder aetiology is unknown. Our recent results have shown a strong **aberrant organisation of synapses in teneurin 4 mutants**.

This project will investigate the **role of Tenm4 in synapse formation and function**. Our results show defects in the presynaptic structure, but the consequences for postsynaptic structures are still unclear. Over the course of the project, we will **assess the molecular integrity of pre- and postsynaptic structures using state-of-the-art super-resolution and electron microscopy**. Furthermore, we will investigate the **consequences of Tenm4 deletions for circuit functionality and animal behaviour**. Finally, using CRISPR-based approaches, we will identify **crucial tenm4 domains for correct synapse formation**. The project will use a combination of dissociated neuronal cultures and the zebrafish model.

Skills training: zebrafish system, neuronal cultures, confocal/light-sheet imaging, super-resolution microscopy, CRISPR/Cas9 genome editing, molecular cloning.

Overarching objectives for project

Rotation/Year 1: Assessment of localisation of Teneurin protein during synapse formation in vivo. Behavioural assessment of tenm4 mutant fish.

Year 2: Super-resolution and electron microscopy analysis of aberrant synapses in tenm4 mutant fish. Creation of CRISPR deletion mutants.

Year 3/4: Identification of Tenm4 domains and interactors linked to synapse organisation

One representative publication from each co-supervisor:

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

Grillo, F, Neves G, Walker, A, Vizcay G, Fleck R, Branco T, Burrone J. (2018). A distance-dependent distribution in presynaptic structure and function tunes frequency-dependent dendritic integration. Neuron, 99: 275-282.

22.2 Analysing Gaucher disease phenotypes in patients diagnosed with Dementia with Lewy Bodies and GBA (Lysosomal Glucocerebrosidase) risk variants

Co-Supervisor 1A: Dr. Angela Hodges
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Co-Supervisor 1B: Prof. Dag Aarsland
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KCL/KHP Website: https://kclpure.kcl.ac.uk/portal/en/persons/dag-aarsland(2e4e0a4f-7d95-42e1-aede-50e5d7a54343).html

Project Description:

Subclinical Gaucher disease (GD) pathology in brain or periphery has not previously been evaluated in Dementia with Lewy Body (DLB) patients, despite both diseases being genetically linked (~3-25% DLB have GBA – glucocerebrosidase risk variants). This could be clinically relevant. High fall and fracture rates in DLB may be falsely attributed to dementia and motor symptoms, when in fact they may be caused by typical GD macrophage pathophysiology and able to be treated. GBA is a crucial catabolising enzyme for membrane-associated glycosphingolipids (GSLs). Hypomorphic GBA variants in GD lead to dysfunctional lysosomal GSL acumulation in macrophages, bone pain, fractures and disease and in some cases dementia. We hypothesise that dysfunctional macrophage lipid catabolism (microglia in brain and osteoclasts in bone) may underlie DLB aetiology.

This project will evaluate bone symptoms in DLB patients and neuronal and microglia function in donor samples and cells with/without GBA variants by:

1) Analysing co-morbid bone symptoms (pain, fractures, osteoporosis) and prescribing history for bone disease (Bisphosphonates) in GBA+/- DLB patients compared to controls **(Yr 1, Data Analysis)**

2) Evaluating GSL accumulation (GluCer/GalCer, LacCer, sulfatide, and gangliosides) in blood-derived macrophages from GBA+/- DLB patients compared to controls with/without exogenous ganglioside treatment **(Yr 2, Lipid Analysis, Mass Spectrometry)**

3) Evalating regional inflammation, altered autophagy/degradation correlating with GSL accumulation in GBA+/- DLB donor brain compared to controls **(Yr 3, Immunohistochemistry)**
4) Conducting cellular analyses (neuronal neurite outgrowth/microglia inflammation, autophagy, and lipid degradation in iPSC-derived neuronal/microglia with/without GBA KO exposed to exogenous gangliosides **(Yr 2-3, iPSCs, Functional Assays)**

One representative publication from each co-supervisor:

Hodges, A., Piers, T., Collier, D., Cousins, O. & Pocock, J. Mechanisms linking Alzheimer's Disease risk genes expressed highly in microglia. *Neuroimmunology and Neuroinflammation* (2020, submitted).

Rongve, A. *et al.* GBA and APOE epsilon 4 associate with sporadic dementia with Lewy bodies in European genome wide association study (vol 9, 7013, 2019). *Scientific Reports* **9**, 2, doi:10.1038/s41598-019-51827-0 (2019).

23.2 Assessing parent-child interactions in cross-cultural contexts: validating an outcome measure for use in a large international trial in Ethiopia and Kenya

Co-Supervisor 1A: Dr Rosa A. Hoekstra
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Co-Supervisor 1B: Dr Charlotte Hanlon
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Project Description:

Ethiopian and Kenyan children with developmental disorders (including intellectual disability and autism) and their caregivers experience severe challenges; most families receive no formal support. 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 includes a large randomised controlled trial of a new intervention developed by the World Health Organization, the Caregiver Skills Training. SPARK will constitute one of the largest trials conducted in developmental disorder research.

Evaluations of caregiver-mediated interventions usually include assessments of parent-child interactions, typically based on video-recorded play sessions in a lab. SPARK however is community-based, often conducted in poorly lit small dwellings, and play between parents and children is less common in Ethiopia and Kenya than in Western contexts. Nevertheless, a pilot in Ethiopia showed video-recorded play sessions are feasible and acceptable to families.

This PhD project focuses on developing and validating a coding scheme to rate parent-child interactions in Ethiopia and Kenya, to be used as outcome measure in the SPARK trial. 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: Assessments of young children; statistical modelling; cross-cultural validation. *Year 1:* Training on assessments; fieldwork in Ethiopia and Kenya. *Year 2:* Training in statistical modelling; fieldwork. *Year 3:* Analysis and paper writing. *Year 4:* Completion of thesis.

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.

Tilahun, D., Fekadu, A., Tekola, B., Araya, M., Roth, I., Davey, B., **Hanlon, C., Hoekstra, R.A.**, 2019. Ethiopian community health workers' beliefs and attitudes towards children with autism: impact of a brief training intervention. *Autism*, 23 (1), pp. 39-49. DOI 10.1177/1362361317730298

24.2 Identification of subtypes of depression using remote measurement technologies

Co-Supervisor 1A: Professor Matthew Hotopf
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Co-Supervisor 1B: Dr Nicholas Cummins
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Project Description:

Despite its heterogenous nature, it has proved difficult to identify sub-types of major depressive disorder (MDD), which has limited the development of novel therapeutics. Using remote measurement technologies (RMT) data from smartphones and wearable devices can be streamed in real time, providing a 360 degree picture of the individual's day-to-day life, including sleep, activity, heart rate, location, cognition, speech and mood/stressors. RMT therefore provides a read-out of many of the higher functions of the CNS. Our aim is to identify behavioural/physiological subtypes which are associated with different trajectories of depression.
This proposal will use data from the RADAR-CNS consortium (https://www.radar-cns.org/) – 625 people with MDD followed over 2 years, during which time they wore Fitbits and donated data from smartphones and completed repeated, detailed clinical assessments.
Skills training – the student be part of two vibrant infrastructures – (1) RADAR-CNS, which includes data scientists, clinicians and PPI groups and (2) Centre for Translational Informatics within Maudsley BRC, where the project will be based. They will be supported to attend courses on statistics and data science within IoPPN and beyond.
First year: Set up: orientation, development of analytic plan, identification and plan of training needs, start systematic review on stratification of MDD, preliminary analyses
Second year: Complete systematic review. Identify symptomatic clusters from data. Familiarisation with RMT data. Complete paper on trajectories of depression
Third year: Complete analyses. Identify additional complementary datasets for potential replication study.
Last six months: Write up and submission.

One representative publication from each co-supervisor:

Holmes, E.A*. O'Connor, R.C*. Perry, H. Tracey, I. Wessely, S. Arseneault, L. Ballard, C. Christensen, H, Cohen Silver, R. Everall, I. Ford, T. John, A. Kabir, T. King, K. Madan, I. Michie, S. Przybylski, A.K. Shafran, R. Sweeney, A. Worthman, C. Yardley, L. Cowan, K. Cope, C. **Hotopf*, M.** Bullmore, E*. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science *Lancet Psychiatry (2020)* https://doi.org/10.1016/S2215-0366(20)30168-1 *equal contribution

Cummins, N. F. Matcham, F., J. Klapper, J. Schuller, B. Artificial Intelligence to aid the early detection of Mental Illness *Artificial Intelligence in Precision Health* (D. Barh, ed.), ch. 10, pp. 231–256, London, U.K.: Elsevier Academic Press, 1st ed.,2020 https://doi.org/10.1016/B978-0-12-817133-2.00010-0

25.2 The neuroinflammatory basis of depression following traumatic brain injury

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Co-Supervisor 1B: Dr Claire Troakes
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Project Description:

Background
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 markers of neuroinflammation are associated with higher levels of depressive symptoms following TBI. This project is part of a large randomised controlled trial testing the effectiveness of a selective serotonin reuptake inhibitor (sertraline) on preventing depression following TBI. It is set in the 4 London Major Trauma Centres. The findings will be translated into evidence-based mental health provision in trauma pathways.

Year 1 Objective: to i) conduct a systematic review and meta-analysis of observational studies of the association between markers of neuroinflammation (neuroimaging, spinal fluid, peripheral markers) with a) depressive symptoms and b) cognitive functioning and ii) develop the protocol for an observational study to test in people with TBI of the association between depressive symptoms and neuroinflammation and the course of depressive symptoms over 12 months.

Year 2 Objective: to conduct the observational study of the effect of neuroinflammation on depression outcomes in people with TBI.

Year 3 Objective: to conduct a mechanistic study to test whether sertraline is associated with a reduction in neuro-inflammation and in depressive symptoms in people with TBI.

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 in medicinal products

One representative publication from each co-supervisor:

Moulton, C, Pickup, JC, Rokakis, AS, Amiel, SA, **Ismail, K** & Stahl, D 2019, 'The Prospective Association Between Inflammation and Depressive Symptoms in Type 2 Diabetes Stratified by Sex', Diabetes Care, vol. 42, no. 10, pp. 1865-1872. https://doi.org/10.2337/dc19-0813

Al-Diwani, A., Handel, A., Townsend, L., Pollak, T., Leite, M.I., Harrison, P.J., Lennox, B.R., **Okai, D.**, Manohar, S.G. and Irani, S.R. (2019). The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. *The Lancet Psychiatry.* 6(3); 235-246

26.2 Non-cell autonomous regulation of autophagy by glial cells

Co-Supervisor 1A: Maria Jimenez-Sanchez
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Co-Supervisor 1B: Wendy Noble
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Project Description:

Autophagy is a self-degradation pathway necessary to clear aggregate prone proteins that accumulate in neurodegenerative diseases such as in Alzheimer's disease (AD). For this reason, investigating mechanisms that regulate neuronal autophagy are explored as potential therapeutic targets.

The study of autophagy in neurodegenerative diseases has mostly focused on neurons. However, to understand how neuronal autophagy can be regulated in the context of other brain cells in AD is crucial to recognize the mechanisms modulating autophagy in disease and to identify new pharmacologic strategies. Microglia and astrocytes become active in AD and secrete a number of pro-inflammatory factors that contribute to neuronal toxicity. We hypothesize that some of these secreted factors may modulate autophagy in neurons.

The aim of this PhD project is to investigate how microglia and astrocytes modulate neuronal autophagy in conditions mimicking AD.

In year 1, we will investigate the impact that resting and activated glial cells have on neuronal autophagy, using primary mouse cultures and a range of assays to monitor autophagy function and dynamics.

Through proteomics and bioinformatic approaches, in year 2, we will identify and validate potential factors secreted by glial cells that could constitute autophagy modulators.

In year 3, we will use organotypic brain slice cultures from a mouse model of AD, to further investigate the non-cell autonomous role of glia on neuronal autophagy and to explore its therapeutic relevance.

This project will combine the expertise of Maria Jimenez-Sanchez on autophagy with Wendy Noble lab's expertise on AD. Both groups are interested on the contribution of glial cells to disease pathology.

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)

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.

27.2 Large scale neuroimaging analysis of at-risk adolescents and individuals with first episode psychosis and established schizophrenia.

Co-Supervisor 1A: Dr Matthew Kempton
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Co-Supervisor 1B: Professor Paola Dazzan
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Project Description:

What is the pathway from healthy adolescence, to developing first episode psychosis and then established schizophrenia? What is happening in the brain to explain such radical changes in behaviour? This project will give the applicant a unique chance to delineate this trajectory using four distinct neuroimaging datasets. The student will start by investigating the brain in adolescence, joining Professor Dazzan's research team, collecting new neuroimaging data for the e-BRAIN study which is determining the impact of early adversity on brain maturation. The student will then investigate the brain in patients with first episode psychosis, accessing MRI data from the completed IoPPN 'GAP study'. Dr Kempton has recently developed the ENIGMA-VBM tool a novel technique of analysing structural MRI scans from multiple sites. Joining the ENIGMA consortium, the student will apply this tool to neuroimaging data from over 50 international sites encompassing 5000 patients with schizophrenia. Finally, to clarify how risk factors such as early adversity affect brain structure in the wider population, the student will analyse data from the UK-Biobank a resource of over 40,000 MRI scans.

Year-1: Training in neuroimaging and the VBM-tool, contacting ENIGMA sites, applying to UKBiobank (Kempton). Data collection in e-BRAIN study and access to GAP sample (Dazzan).
Year-2: Analysis of ENIGMA data, processing UK-Biobank data (Kempton), e-BRAIN data collection, GAP data analysis (Dazzan).
Year-3: Completing data analysis, thesis write-up and publications (Kempton-Dazzan).

Additional training in PhD skills including communication and writing academic papers via the supervisors' lab meetings and the Centre for Doctoral Studies.

One representative publication from each co-supervisor:

Modinos G, **Kempton MJ**, Tognin S, Calem M ... Valmaggia LR, McGuire P, EU-GEI High Risk Study Group (2019) Association of Adverse Outcomes With Emotion Processing and Its Neural Substrate in Individuals at Clinical High Risk for Psychosis, JAMA Psychiatry 77(2) 190-200

Nieuwenhuis M, Schnack HG, van Haren NE... Mourao-Miranda J, **Dazzan P** (2017) Multi-center MRI prediction models: Predicting sex and illness course in first episode psychosis patients. Neuroimage. 2017 Jan 15;145(Pt B):246-253.

28.2 Investigating the role of α-synuclein in β-amyloid-driven synaptotoxicity

Co-Supervisor 1A: Richard Killick
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Co-Supervisor 1B: Gareth Williams
School/Division & CAG: Wolfson CARD
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Project Description:

Alzheimer's disease (AD), driven by β-amyloid (Aβ), and Parkinson's disease (PD), driven by α-synuclein (α-syn), share many common features, not least both feature major synapse lose. We have uncovered the signalling pathway through which Aβ acts on synapses, the non-canonical arm of Wnt. How α-syn acts on synapses remains unclear.

Adopting state-of-the-art, super resolution, live-cell imaging the group observe previously unrecognised processes, giving novel insight into how Aβ acts. The Wnt component Dickkopf-1 (Dkk1), which Aβ induces, mimics these effects albeit more rapidly. Silencing Dkk1 renders Aβ harmless. We observe α-syn also exerting the same effects as Aβ/Dkk1, more immediately, and they are not impacted by Dkk1 knockdown. Our **working hypothesis** is that Aβ sits upstream, and α-syn downstream, of Dkk1 in a common pathway, i.e., α-syn is a downstream effector Aβ and component of the Aβ-driven synaptotoxic pathway.

The project aims to deconvolute the pathway further using advanced live imaging along with neuronal gene expression and gene silencing technologies.

Objectives. Y1: to establish the position of α-syn in this pathway.

Y2: identify which, and how, α-syn acts on downstream elements.

Y3: determine if drugs (which are now entering clinical trials for AD) protect synapses against α-syn.

Achieving these objectives would constitute a major advance in our understanding of the relationship between Aβ and α-syn and between AD and PD (and other Lewy body dementias), which account for ~90% of all cases of dementia. Translationally, drugs which target this pathway may also be of therapeutic benefit for PD.

29.2 Bridging the gap between trials of health interventions and impact on patients: generalizing trial findings using electronic case records systems

Co-Supervisor 1A: Prof. Sabine Landau
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Co-Supervisor 1B: Dr Johnny Downs
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Project Description:

Childhood conduct problems are a costly public health problem. Parenting programmes such as the Incredible Years programme for reducing conduct problems have been shown to effective in many

trials. However, policy makers have long been concerned that trial results may not be generalizable to those who would be offered the intervention. We recently pooled trials in a pan-European study, which detected child characteristics that impact how much child behaviour improves with parent training. The existence of such moderating factors raises the possibility of a different treatment effect in the population who would be offered the programme.

The *aim of this project* is to explore whether information provided by routinely collected data can be used to project trial findings onto real-world populations using parenting trials as an exemplar. The South London and Maudsley NHS Foundation Trust (SLaM) collects data in an electronic medical records system (EMR) that can be searched using the Clinical Record Interactive Search (CRIS). We have already ascertained that CRIS can obtain records of at least N=3738 children diagnosed with conduct disorder or oppositional defiant disorder.

Project plan: Year 1: Use of the CRIS interactive system to retrieve information, establishment of an updated parenting trials data set, familiarisation with literature on estimating intervention effects in a target population. Year 2: Set up of programs that can be run behind the firewall of an EMR. Year 3: Application of these methodologies to investigate the benefit of making the Incredible Years intervention available to all those presenting at SLaM.

One representative publication from each co-supervisor:

Gardner F., …, Scott S., **Landau S.** (2019) Equity effects of parenting interventions for child conduct problems: a pan-European individual participant data meta-analysis, *Lancet Psychiatry* 6 (6): 518-527 DOI: http://dx.doi.org/10.1016/S2215-0366(19)30162-2

O'Connor, C., **Downs, J. M** *et al.* (2019) Diagnostic trajectories in child and adolescent mental health services: Exploring the prevalence and patterns of diagnostic transitions in an electronic mental health case register. *European Child and Adolescent Psychiatry* 29: 1111–112 DOI: https://doi.org/10.1007/s00787-019-01428-z

30.2 Understanding neuronal migration disorders using human tissue models.

Co-Supervisor 1A: Katie Long
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Co-Supervisor 1B: Benedikt Berninger
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KCL/KHP Website: https://www.kcl.ac.uk/ioppn/depts/devneuro/index.aspx

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.

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

Co-Supervisor 1A: Prof James MacCabe
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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

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

32.2 Role of alternative splicing in diversity of mammalian neurons

Co-Supervisor 1A: Eugene Makeyev
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Co-Supervisor 1B: Oscar Marín
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Project Description:

Brain function depends on development of multiple types of neurons characterised by distinctive structural, physiological and molecular features. How this diversity emerges from a smaller number of progenitor states is a fascinating biological problem. Many genes can generate more than one RNA product through alternative splicing, a process involving non-uniform use of exons and introns. The nervous system expresses an especially large collection of alternative isoforms, but how this molecular program contributes to the emergence of individual neuronal identities remains poorly understood. The proposed project will address this important question by focusing on GABAergic interneurons, a heterogeneous group containing >20 distinct categories. Briefly, we will analyse single-cell RNA-sequencing data using state-of-the-art bioinformatics tools to detect interneuron type-specific differences

in splicing patterns and expression of RNA-binding proteins (RBPs) known/predicted to control splicing decisions (rotation/year 1). RBPs showing the strongest correlation with type-specific splicing patterns will be shortlisted for detailed experimental studies. To elucidate splicing regulation mechanisms, the candidate RBPs will be over-expressed/knocked-down in neural cells in vitro and the effect of these treatments will be assayed using reverse transcription-PCR, single-molecule RNA FISH and immunofluorescence (year 2). Function of the most promising RBP candidate will be examined by modulating its expression in mouse brain using appropriate viral vectors, the CRISPR-Cas9 technology or/and classical knockouts followed by morphological, electrophysiological and behavioural analyses (years 3-4). The two supervisors have extensive expertise in bioinformatics, biochemistry, neurobiology and mouse genetics, which will provide an ideal training environment and will ensure successful completion of the PhD studies.

One representative publication from each co-supervisor:

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

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

33.2 Exploring the acute interactions of THC and CBD in heavy cannabis users

Co-Supervisor 1A: John Marsden
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Co-Supervisor 1B: 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:

Englund A, Freeman T, Murray R, McGuire P (2017). Can we make cannabis safer? The Lancet Psychiatry. https://pubmed.ncbi.nlm.nih.gov/28259650/

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.

34.2 Transition to Adulthood: How Genetic and Environmental Risk Factors Influence the Mental Health Response to Major Life Changes

Co-Supervisor 1A: Dr Tom McAdams
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Co-Supervisor 1B: Dr Helena Zavos
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Project Description:

Early adulthood comprises many major life transitions including leaving home, starting university, starting work, and parenthood. The successful negotiation of these transitions is a crucial developmental steppingstone and can play a role in determining future success and wellbeing. Many individuals negotiate these transitions successfully, but for some they associate with the onset of mental health conditions. This differential response is likely influenced by

genetic risk factors, previous life experiences, and the interaction between genetic and environmental risk. Using behavioural genetic approaches (e.g. twin and family designs) you will explore interactions between genetic risk factors and life experiences in predicting differential responses to life transitions in early adulthood.

You will have access to excellent large-scale genetically sensitive datasets spanning childhood to adulthood. These will include the Twins Early Development Study (TEDS), children-of-TEDS project, Scandinavian population registries, and Norwegian Mother, Father and Child Cohort Study (MoBa). You will be able to develop hypotheses in line with your own interests.

Skills Training

Data management and appropriate statistical and methodological training will be provided throughout. (e.g. structural equation modelling in R, causal inference methodology, quantitative genetics). Formal training courses will likely include the Workshop on Statistical Genetic Methods for Complex Traits in Boulder, Colorado.

Objectives

Year 1-2: Conduct literature reviews and develop hypotheses in collaboration with supervisors. Learn theory and concepts of behavioural genetics and structural equation modelling.

Year 3-4: Analysis and write up of findings. Become adept at database management. Publish papers.

One representative publication from each co-supervisor:

Hannigan, L. J., Eilertsen, E. M., Gjerde, L., Eley, T. C., Rijsdijk, F. V., Ystrom, E., McAdams, T. A. (2018). Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: genetic analyses in the Norwegian Mother and Child Birth Cohort Study. *Lancet Psychiatry.* https://doi.org/10.1016/S2215-0366(18)30225-6

Zavos, H,M,S et al. (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, 237-249.

35.2 Improving Memory in Schizophrenia with PDE4 inhibitors

Co-Supervisor 1A: Prof. Mitul Mehta
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Co-Supervisor 1B: Dr F Zelaya
School/Division & CAG: IoPPN/Neuroscience
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KCL/KHP Website: https://kclpure.kcl.ac.uk/portal/sukhi.shergill.html

Project Description:

Persistent memory deficits are present in patients with schizophrenia, and these are not treated by existing drugs. This impairment is large (>1 SD) and is associated with everyday functioning to a greater extent than the positive symptoms of the illness. PDE inhibitors enhance neuronal function through increasing signalling via second messenger systems and studies in animals and healthy volunteers support pro-cognitive effects of these drugs. We have shown a repurposed PDE4 inhibitor can improve memory in 13 patients. This PhD will provide a replication study with more patients using a more complete assessment of memory and analyses of the potential brain systems associated with

the aspects of memory most affected. The skills to be developed include patient recruitment, neuropsychological assessment, psychopharmacological study conduct. Memory will be tested on a range of measures including source memory, verbal episodic memory and learning as well as working memory and tests of everyday memory function. Existing neuroimaging data with roflumilast will be supplemented with newly collected data to test hypotheses resulting from the behavioural studies. Overall, these studies will provide an evidence base for the mechanisms through which PDE4 inhibition can improve memory and pave the way to clinical trials.

Year 1: Set-up neuropsychological study including pre-registration of hypotheses, recruitment sources, conduct study, training in neuroimaging analysis, review literature
Year 2: Complete neuropsychological study, analysis formulate and pre-register imaging hypotheses, design imaging analysis, apply for neuroimaging ethics, conduct study, prepare neuropsychology publication(s)
Year 3: Combine prior and new neuroimaging data, analyse data, prepare manuscripts, write-up thesis

One representative publication from each co-supervisor:

Gilleen J, Farah Y, Davison C, et al. An experimental medicine study of the phosphodiesterase-4 inhibitor, roflumilast, on working memory-related brain activity and episodic memory in schizophrenia patients. Psychopharmacology (Berl). 2018;10.1007/s00213-018-5134-y. doi:10.1007/s00213-018-5134-y

Increased resting hippocampal and basal ganglia perfusion in people at ultra high risk for psychosis: replication in a second cohort.
Paul Allen, Matilda Azis, Gemma Modinos, Mathijs Bossong, Ilaria Bonoldi, Carly Samson, James Stone, Matthew Kempton, Maria Calem, Jesus Perez, Matthew Broome, Anthony Grace, Oliver Howes, Fernando Zelaya and Phil McGuire,. *Schizophrenia Bulletin*, accepted Nov 09, 2017. 2017 Dec 27. doi: 10.1093/schbul/sbx169

36.2 In vivo studies of endoplasmic reticulum (ER)-mitochondria signaling in neurological function

Co-Supervisor 1A: Dr Jacqueline Mitchell
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Co-Supervisor 1B: Professor Chris Miller
School/Division & CAG: IoPPN, Neuroscience and Department of Basic and Clinical Neuroscience
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Project Description:

ER-mitochondria signaling is now known to regulate a number of fundamental physiological functions including calcium homeostasis, lipid metabolism, bioenergetics, organelle trafficking, autophagy and inflammation. Moreover, damage to ER-mitochondria signaling is strongly implicated in Alzheimer's, Parkinson's and motor neuron diseases. As such, ER-mitochondria signaling is a highly topical research area. ER-mitochondria signaling requires close physical contacts between the two organelles that are mediated by "tethering proteins" which function to recruit regions of ER to the mitochondrial surface. An interaction between the ER protein VAPB and the mitochondrial protein PTPIP51

represents one such tether. We have created novel knockout mice for PTPIP51 and this project is to utilise these animals to study the neuronal roles of ER-mitochondria signaling in vivo. The hypothesis is that loss of PTPIP51 will disrupt learning, memory and motor functions, and that this will involve synaptic damage.

The student will learn skills involved in the management of transgenic mice colonies, behavioural and neurological testing of transgenic mice (e.g. Morris Water maze, rotarod) and morphological studies involving advanced microscopy. The aim is to correlate behavioural changes with alterations to synaptic morphology. Training in all of these techniques is available within the supervisor's research groups and in the Nikon centre for advance microscopy.

The objectives for each year are:

Year 1. Obtain Home Office licence and establish cohorts of wild-type, heterozygous and homozygous knockout PTPIP51 mice for study. Commence behavioural/neurological testing to monitor age-related changes (analyses from 3 to 18 months age).

Year 2. Continue analyses of ageing mice and commence studies of synaptic morphology using advance microscopy.

Year 3 and 4. Finalise behavioural/neurological and synaptic morphology studies. Perform full analyses of the data and commence write-up of PhD thesis and publication of data.

One representative publication from each co-supervisor:

Mitchell, J.C., R. Constable, E. So, C. Vance, E. Scotter, L. Glover, T. Hortobagyi, E.S. Arnold, S.C. Ling, M. McAlonis, S. Da Cruz, M. Polymenidou, L. Tessarolo, D.W. Cleveland, and C.E. Shaw. 2015. Wild type human TDP-43 potentiates ALS-linked mutant TDP-43 driven progressive motor and cortical neuron degeneration with pathological features of ALS. *Acta Neuropathol. Commun.* 3:36.

Gomez-Suaga, P., B.G. Perez-Nievas, E.B. Glennon, D.H.W. Lau, S. Paillusson, G.M. Morotz, T. Cali, P. Pizzo, W. Noble, and C.C.J. Miller. 2019. The VAPB-PTPIP51 endoplasmic reticulum-mitochondria tethering proteins are present in neuronal synapses and regulate synaptic activity. *Acta Neuropathol. Commun.* 7:35.

37.2 Unravelling Disruptions in Cortical Hierarchies in Psychosis: A Computational Psychiatry approach using fMRI and Artificial Intelligence methods

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Co-Supervisor 1B: Sukhi Shergill
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Project Description:

A now well-developed theory of brain function and behaviour known as *the free energy principle* has provided an explanation of the brain-environment nexus in the context of several psychiatric conditions. Crucially it has constructed an artificial intelligence to mirror patient-environment interactions.

This proposal aims to advance the treatment of psychosis by developing this framework and utilizing fMRI and computational modeling to probe, challenge and potentially adapt to a patient's cognitive and behavioural state.

We are interested in developing novel paradigms, methods and models that reveal specific treatment plans for patients with schizophrenia – in particular for those who remain refractory to current medications.

Using decision based and gaming paradigms in the scanner, this personalized medicine platform will be built to 1) provide insights into the neurobiological processes that lose/gain function during distinct times in the disease and 2) provide a template for the development of AI applications more generally that consider, support and buttress a healthy human state.

Translational Aspects, Skills and Training

Data Analysis, Computational Modelling & Machine Learning:

A machine learning skill set will be developed in order to deploy personalised models onto brain imaging and behavioural data.

Brain imaging techniques, statistical approaches, brain connectivity analysis, models of behaviour and python or matlab-based coding will be developed by the candidate.

Objectives by Year

1: Paradigm Development, Coding & Model Development; 2: Data Acquisition fMRI; 3: AI based phenotyping; 4: Combined Behavioural and Brain Imaging Models

One representative publication from each co-supervisor:

Cullen, Maell, Ben Davey, Karl J. Friston, and Rosalyn J. Moran. "Active inference in OpenAI gym: a paradigm for computational investigations into psychiatric illness." Biological psychiatry: cognitive neuroscience and neuroimaging 3, no. 9 (2018): 809-818.

In the eye of the beholder? Oxytocin effects on eye movements in schizophrenia. Porffy, L. A., Bell, V., Coutrot, A., Wigton, R., D'Oliveira, T., Mareschal, I. & Shergill, S. S., 10 Dec 2019, In : Schizophrenia Research.

38.2 Exploring the relationship between stress/distress reduction, inflammatory markers and relapse in relapsing remitting Multiple Sclerosis (MS).

Co-Supervisor 1A: Prof Rona Moss-Morris (Clinician scientist)
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Co-Supervisor 1B: Dr Valeria Mondelli
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Project Description:

Multiple Sclerosis (MS) is a chronic, autoimmune, inflammatory condition, with disease activity related to multifactorial inflammatory mechanisms. Separate studies have shown that hypothalamic-pituitary-adrenal (HPA) axis activity, inflammatory markers and psychological attributes are correlated with severity and progression of MS. However, the causal links between psychological factors, inflammation and disease outcomes remain under-researched. This study will be the first to investigate whether changes in distress can drive changes in inflammatory biomarkers pre- and post an online intervention designed to reduce distress in MS. A second aim is to explore the relationship between change in inflammation and relapse.

Year 1: Systematic review of stress in MS and disease-related outcomes and markers, including inflammation and HPA axis activity, to determine the best candidate biomarkers relevant to stress and disease outcomes for phase 2 of the project. The number of disease markers investigated will depend on review findings and available funding.

Year 2: 250 clinically distressed patients with relapsing-remitting MS will be recruited via the national MS registry to receive COMPASS, an online CBT program to treat illness-related distress in the people with long-term conditions. COMPASS was designed by the first supervisor and team.

Psychosocial, clinical and inflammatory biomarker measures will be collected at baseline, post-intervention (3 months) 1-year follow up and number of relapses during follow-up. Cross-sectional analysis will investigate the relationships between these factors at baseline.

Year 3 – 3.5: Longitudinal analysis to investigate sustained effects of the intervention and the relationship between reductions in distress and inflammatory /HPA markers and relapse frequency.

One representative publication from each co-supervisor:

Moss-Morris, R., Dennison, L., Landau, S., Yardley, L., Silber, E., & Chalder, T. (2013). A randomized controlled trial of cognitive behavioral therapy (CBT) for adjusting to multiple sclerosis (the saMS trial): does CBT work and for whom does it work?. Journal of Consulting and Clinical Psychology, 81(2), 251.

mrc-dtp@kcl.ac.uk., Ciufolini, S., Belvederi Murri, M., Bonaccorso, S., Di Forti, M., Giordano, A., ... & Pariante, C. M. (2015). Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. Schizophrenia bulletin, 41(5), 1162-1170.

39.2 Development and validation of patient reported outcomes for intensive monitoring of treatment response in people with musculoskeletal conditions

Co-Supervisor 1A: Sam Norton
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Co-Supervisor 1B: James Galloway
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Project Description:

The Covid-19 pandemic necessitated a dramatic shift of healthcare to remote clinics and outcome assessments. For example, as of September 2020, over 70% of rheumatology appointments at King's College Hospital are now conducted remotely, compared to <5% before March 2020. One of the key opportunities is the potential for remote assessment of symptoms using electronic patient reported outcomes (PROs) to provide near real-time information about treatment response, with symptom reports daily or even multiple times per day. However, PROs are typically designed to be completed infrequently (e.g. PHQ9, GAD7, MSKHQ use two-week response frames). While daily assessments are increasingly used there is a paucity of data regarding reliability and validity, particularly in those with long-term physical conditions.

This studentship will develop and validate a PRO that allow for daily (or more frequent) assessments of physical and mental health in people with musculoskeletal conditions.

Study 1 (0 to 12 months): Systematic review of outcome measurement instruments for assessing physical and mental symptoms daily or more frequently in people with long-term physical conditions

Study 2&3 (0 to 18 months): Mixed-methods study to develop a 'core-outcome set' for daily (or more frequent) assessment of physical and mental symptoms in people with musculoskeletal conditions

Studies 4 (18 to 36 months): Observational study validating new PRO for monitoring treatment response to i) pharmacological (e.g. biologic treatment) and ii) non-pharmacological (e.g. mood psychoeducational intervention) in people with musculoskeletal conditions

Training will be undertaken in quantitative techniques, focusing on longitudinal psychometric methods from a dynamic systems perspective.

One representative publication from each co-supervisor:

Tung, H., **Galloway, J.,** Matcham, F., Hotopf, M., & **Norton, S.** (2020). High-frequency follow up studies in musculoskeletal disorders: a scoping review. Rheumatology, *in press*

Matcham, F., **Galloway, J.,** Hotopf, M., Roberts, E., Scott, I. C., Steer, S., & **Norton, S.** (2018). The impact of targeted Rheumatoid Arthritis pharmacological treatment on mental health: A systematic review and network meta-analysis. Arthritis and Rheumatology, 70(9), 1377-1391. https://doi.org/10.1002/art.40565

40.2 Identifying brain-behavioral links in typically and atypically developing toddlers

Co-Supervisor 1A: Chiara Nosarti
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Co-Supervisor 1B: David Edwards
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Project Description:

Most mental health issues begin early in life: half of all lifetime cases of psychiatric disorder initiate by age 14. However, overt symptoms emerge long after the contributing processes leading to psychiatric disorder have begun.

This study will increase our understanding of the origins of mental illness by explicating neurodevelopmental mechanisms associated with the earliest signs/precursors of mental disorders. The study will be carried out in the most comprehensively phenotyped sample of children that has been studied from birth to age 18 months as part of the Developing Human Connectome Project (n=650). At birth children received the most sophisticated neuroimaging methods available to date. Imaging data, together with collateral environmental and clinical information will be used to outline predictors of psychiatric risk by identifying early in life those children who are vulnerable to experiencing behavioural features that have been associated with psychiatric disorder (e.g. emotion dysregulation, irritability). Several methods including machine learning and similarity network fusion will be applied to the data, creating measures for the identification of vulnerable children who could benefit from preventive interventions aimed at strengthening their resilience.

The successful student will work within a multidisciplinary team with unparalleled expertise in neuropsychology, psychiatry, paediatrics, biostatistics, advanced MRI methods.

Objectives: Y1: Understand the principles of structural and functional MRI. Become familiar with operating environments and innovative image analysis software. Y2: Study connectivity pathways involved in atypical development and psychopathology. Assess associations between measures of psychiatric risk and connectivity. Y3: Assess associations between multimodal MRI and toddlers' neurodevelopmental outcomes.

One representative publication from each co-supervisor:

Papini C, White TP, Montagna A, Brittain PJ, Froudist-Walsh S, Kroll J, Karolis V, Simonelli A, Williams SC, Murray RM, **Nosarti C**. Altered resting-state functional connectivity in emotion-processing brain regions in adults who were born very preterm. Psychol Med. 2016 Oct;46(14):3025-3039. doi: 10.1017/S0033291716001604.

Ball G, Aljabar P, Nongena P, Kennea N, Gonzalez-Cinca N, Falconer S, Chew ATM, Harper N, Wurie J, Rutherford MA, Counsell SJ, **Edwards AD**. Multimodal image analysis of clinical influences on preterm brain development. Ann Neurol. 2017 Aug;82(2):233-246. doi: 10.1002/ana.24995.

41.2 Neural circuits underlying trauma memory in patients with co-morbid PTSD and psychosis prior to psychological therapy: fMRI and smartphone-based ecological momentary assessment

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Co-Supervisor 1B: Steve Williams
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Project Description:

Traumatic events play a key, and likely causal, role in psychosis. Trauma-Focused Cognitive Behaviour Therapy for psychosis (TF-CBTp) is a promising psychological therapy for both post-traumatic stress disorder (PTSD) and psychotic symptoms. Alongside a large NIHR-funded randomised controlled trial evaluating TF-CBTp effectiveness, this project examines the neural mechanisms underlying re-experiencing symptoms ("flashbacks") and hyper-vigilance for social threat.

Prevailing PTSD accounts contend that distressing "flashbacks" occur when the trauma memory is incompletely processed; specifically, the memory content is poorly integrated with contextual features of the traumatic event. This project tests whether, prior to TF-CBTp:
1) PTSD symptoms, especially re-experiencing symptoms, are predicted by a bias towards affective representation of the trauma memory (excessive amygdala activation) with poorer integration of the spatial and temporal features (hippocampus hypoactivation) when recalling trauma memories.
2) Psychotic symptoms, especially paranoia, are predicted by a poorer ability to reappraise potential social threat, testing a mechanism of reduced prefronto-limbic connectivity[1,2].
3) The above neural circuits predict momentary symptoms in daily life, measured by smartphone.

Depending on trial progress, it may be possible to examine mechanisms of change following TF-CBTp (final clinical assessments are predicted to be completed in 2024).

The student will gain experience in clinical assessments, ESM and fMRI in both clinical and healthy samples.
Year one: Data collection alongside a world-leading trial team.
Year two: Analysis of fMRI tasks probing trauma memory and social threat processing.
Year three: opportunity to develop more nuanced analyses (e.g. Dynamic Causal Modelling) and relate to smartphone-based momentary assessments of symptoms.

One representative publication from each co-supervisor:

Tolmeijer, E., Kumari, V., **Peters, E**., **Williams, S**. C. R., & Mason, L. (2018). Using fMRI and machine learning to predict symptom improvement following cognitive behavioural therapy for psychosis. NeuroImage: Clinical, 20, 1053-1061. doi:10.1016/j.nicl.2018.10.011

Mason, L., **Peters, E**., **Williams, S**. C., & Kumari, V. (2017). Brain connectivity changes occurring following cognitive behavioural therapy for psychosis predict long-term recovery. Translational Psychiatry, 7 (1), e1001. doi:10.1038/tp.2016.263

42.2 Building the brain - Making and breaking synapses with cholesterol

Co-Supervisor 1A: Dr Marija Petrinovic
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Co-Supervisor 1B: Dr Eva Loth
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Project Description:

The brain is made of billions of neurons which communicate with each other via synapses. Synapse formation (synaptogenesis), function, plasticity and maintenance – processes crucial for normal brain development and function – are all controlled by cholesterol. Forming up to 25% of the body's cholesterol, dysregulation of the brain cholesterol metabolism is associated with neurodegenerative (e.g. Alzheimer's disease) and neurodevelopmental disorders, such as autism. Atypical levels of cholesterol were reported in some individuals with autism (and their parents). Similarly, our group found cholesterol disturbances in several genetic and environmental rodent models of autism that also show synaptic deficits, aberrant brain function and behavioural deficits. However, it is still not known: i) how cholesterol regulates synapses in the healthy brain, ii) how that process is affected in individuals with autism (and if we put cholesterol levels within normal ranges can we impact behaviour), iii) which autism-linked genetic mutations and stress-related experiences result in dysregulated cholesterol metabolism.
These questions will be addressed in this translational PhD project by using mouse models. Furthermore, through our collaboration with the largest autism consortium, AIMS2-TRIALS, we will address the third question by testing cholesterol levels in the blood of autistic individuals and linking that to their genotype, environmental factors and clinical features. This approach has the potential to develop a new biomarker for patient stratification and pave the way for development of specific and targeted (personalized) treatments.

Overarching objectives:
Year1: in vitro examination of the role of cholesterol in synapse formation and function
Year2: examining the role of autism-related mutations on cholesterol-dependent synapse formation and function
Year3: continuing the Year 2 experiments and testing human blood samples (autism and controls) for cholesterol levels and linking them with patients' genotypes

Skills training:
Cell culture, electrophysiology, optogenetics, animal behaviour, pharmacological treatments, immunohistochemistry, clinical assessments, normative modelling and multivariate approaches (e.g. clustering techniques) for patient stratification

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

K Warre-Cornish, L Perfect, R Nagy, RR Duarte, MJ Reid, P Raval, A Mueller, AL Evans, A Couch, C Ghevaert, G McAlonan, E Loth, D Murphy, TR Powell, AC Vernon, DP Srivastava, J Price. "Interferon-γ signaling in human iPSC-derived neurons recapitulates neurodevelopmental disorder phenotypes". Science Advances, 2020. doi: 10.1126/sciadv.aay9506.

43.2 Excitation/inhibition balance in Autism across the lifespan

Co-Supervisor 1A: Nicolaas Puts
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Co-Supervisor 1B: Enrico De Vita
School/Division & CAG: School of biomedical engineering and imaging sciences
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KCL/KHP Website: https://kclpure.kcl.ac.uk/portal/enrico.devita.html

Collaborating Clinician: Grainne McAlonan
School/Division & CAG: Department of Forensic and Neurodevelopmental Sciences, IOPPN
Email: grainne.mcalonan@kcl.ac.uk

Project Description:

Autism (ASD) is defined by impairments in social communicative interactions. However, the underlying neurophysiology of ASD is not well known and diagnosis and treatment are ill-defined. One theory focuses on excitatory and inhibitory neurotransmitter imbalance. However, available human evidence is limited; small samples and inconsistencies between children and adults only allow evaluation of mean group differences. In AIMS-2-TRIALS, the largest autism consortium and based at KCL, we are focusing on stratification of ASD to develop biomarkers for diagnosis and treatment. We will use Magnetic Resonance Spectroscopy to directly quantify GABA and Glutamate (the main inhibitory and excitatory neurotransmitters) in humans across the lifespan (ages 3-35). This enables examination of subgroups and lifespan trajectories within heterogeneous ASD populations with impact on & relevance to clinical manifestations of ASD. Through AIMS-2-TRIALS, a wealth of multi-centre clinical, cognitive, and imaging data will be available. This project has unprecedented opportunity to make a direct impact on the diagnosis and treatment of ASD.

Skills:

- Multi-site acquisition and analysis of novel edited MRS using new approaches.
- Novel statistical approaches (normative modelling and canonical correlations) to assess alterations in the lifespan trajectory and associations between neurochemistry and ASD.

Objectives:
Year 1. Training on advanced MR spectroscopy with a unique emphasis on application in clinical pediatric populations. Strong emphasis on interpreting the neurochemistry and pathology of ASD. Data acquisition commences.
Year 2. Develop novel analyses and quality assurance approaches for MRS
Year 3. Use novel statistical approaches to stratify ASD based on neurochemistry and develop new biomarkers. Write-up.

One representative publication from each co-supervisor:
Puts N.A.J., Wodka, E.L., Harris, A.D., Crocetti, D., Tommerdahl, M., Mostofsky, S.H., Edden, R.A.E., (2016) *Reduced GABA and altered somatosensory function in children with autism spectrum disorder*, Autism Research, 10 (4), 608-619. 10.1002/aur.1691

De Vita, A. Bainbridge, J.L.Y Cheong, P. Kinchesh, A. Huertas-Ceballos, R.J. Ordidge, N.J. Robertson, E.B. Cady, (2005). *Localised 4.7 Tesla proton magnetic resonance spectroscopy in neonatal encephalopathy: implementation, safety, and preliminary interpretation of results.* Imaging Decisions 9(4):31-41

44.2 Sex differences in mental health problems: Investigation of contributory factors

Co-Supervisor 1A: Dr Katharine Rimes
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Co-Supervisor 1B: Dr Edward Barker
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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

45.2 Investigating CGRP-mediated modulation of the first central synapse in headache pain

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Co-Supervisor 1B: Professor 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 and headache pain remain unmet clinical challenges with significant impact on the quality of life for the sufferers. Several neurotransmitters and neuropeptides such as CGRP released during a migraine headache can modulate pain transmission but the exact mechanisms of this modulation are largely unknown.

Building upon a novel microfluidic based cell culture platform developed in Raouf lab, the first objective of this project is to develop a microfluidic model that recapitulates the nociceptive neuronal circuit of headache pain, i.e., a cell culture "model" of headache. The second objecetive is to use this microfluidic co-culture platform to investigate the molecular mechanisms of sensitisation 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: You will become proficient in cell culture, microfluidic culture, viral tracing, and calcium imaging techniques.

Year 3/4: Techniques: Optogenetics and cell biology. The objective of the year is to investigate the regulation synaptic transmission by CGRP and other modulators.

Translational Significance: Understanding the molecular mechanisms that are involved in headache pain will lead to the development of more effective therapeutics. The microfluidic cell model offers a novel approach to investigate the basic mechanisms of headache pain signalling that can be used for drug discovery.

One representative publication from each co-supervisor:

Vysokov, N., McMahon, S.B. & Raouf, R. The role of Na_V 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**

46.2 Dreaming Rapid Eye Movement (REM) Sleep

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Co-Supervisor 1B: Dr Antonio Valentin
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Project Description:

Dreams are experiences that occur during sleep, while we are disconnected from the environment. Rapid eye movement (REM) sleep, during which most of dreaming occurs, is a peculiar and enigmatic neural state. In the 21st century we still know very little about REM sleep, although it appears to play critical role in a variety of functions spanning from basic physiological mechanisms to complex cognitive processes. Dreaming is reflected in physiological signals, behaviours and brain activity patterns. Thanks to recent progress in optogenetic techniques, it is now becoming possible to relate specific sleep features to specific patterns of brain activity.

The aim of this exciting PhD project is to utilise new optogenetic, EEG and imaging techniques to explore in animal models the fine microstructure of REM sleep, especially its phasic and tonic constituents, with a major goal to provide a pioneering framework that targets the basic mechanisms and putative functions of REM (dreaming) sleep.

PhD-project milestones
Year1: development of the optimal optogenetic and electrophysiologic set up;
Year2: creating and testing the platform to connect and integrate EEG and fMRI; main experimental sleep data collection.
Year3: test the methodology and collect further data in several relevant animal models of disturbed REM sleep (e.g. GBA mice). Final analyses/write up.

Methods: the student will utilise and learn optogenetic, neurophysiologic (EEG), polysomnography and imaging skills, they will learn to programme in Matlab, Python and R scripting, image analysis tools, as well as gain practical training in MRI, EEG and optogenetic data acquisition.

One representative publication from each co-supervisor:

Polsek D, Cash D, Veronese M, Ilic K, Wood TC, Milosevic M, Kalanj-Bognar S, Morrell MJ, Williams SCR, Gajovic S, Leschziner GD, Mitrecic D, **Rosenzweig I** (2020) The innate immune toll-like-receptor-2 modulates the depressogenic and anorexiolytic neuroinflammatory response in obstructive sleep apnoea. Sci Rep 10:404–13. doi: 10.1038/s41598-020-68299-2

Occipital cortex and cerebellum grey matter changes in visual snow syndrome.
Puledda F, Bruchhage M, O'Daly O, Ffytche D, Williams SCR, **Goadsby PJ.**
Neurology. 2020 Aug 5:10.1212/WNL.0000000000010530. doi: 10.1212/WNL.0000000000010530.

47.2 Comparison of the effects of Guanfacine and Lisdexamfetamines on fMRI brain function in ADHD adolescents

Co-Supervisor 1A: Prof Katya Rubia
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Co-Supervisor 1B: Prof Jonna Kuntsi
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Collaborating Clinician: Prof Paramala Santosh
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Project Description:

The stimulant Methylphenidate and the non-stimulant Atomoxetine have shared and differential mechanisms of action on ADHD brain function. The more recently licensed drugs, the stimulant Lisdexamfetamine and non-stimulant Guanfacine, have shown to be more efficacious in reducing ADHD symptoms than older drugs with fewer side effects. However, their mechanisms of action on the ADHD brain function are unknown.

Primary aim - To investigate shared and drug-specific effects of single doses of Guanfacine, Lisdexamfetamine and placebo on brain function and connectivity in 20 ADHD adolescents using fMRI in a randomised, double-blind, within-group, placebo-controlled design. The fMRI data will also be compared to healthy age and IQ matched adolescents to assess (differential) normalization effects of each drug.

Translational Aspect - The project investigates the neurofunctional correlates of novel ADHD drugs which will help the understanding of the underlying neurotransmitter abnormalities in ADHD; the development of more personalized drug treatment; lead to the development of novel drugs that target the same underlying dysfunctional mechanisms.

Planned research methods and training provided - Training in 1) the neurobiology of ADHD 2) cognitive neuroscience 3) pharmacological fMRI 4) fMRI analyses using FSL 5) clinical and neurocognitive assessments 6) Statistical analysis 8) Publications.

Supervision by an interdisciplinary team (Prof Katya Rubia; Cognitive Neuroscience; Prof Jonna Kuntsi: Developmental Psychologist; Prof Mitul Mehta; Psychopharmacologist; Prof Santosh Child Psychiatrist, Dr Valeria Parlatini: Child Psychiatrist)

Objectives / plan - Year 1: Training in above mentioned skills; patient recruitment & scanning, **Year 2:** Recruitment & scanning, data analysis, **Year 3:** Data analysis and write-up

One representative publication from each co-supervisor:

Smith A, Cubillo A, Barrett N, Giampietro V, Simmons A, Brammer M, **Rubia K.** (2013) Neurofunctional effects of methylphenidate and atomoxetine in boys with attention-deficit/hyperactivity disorder during time discrimination. Biol Psychiatry 15;74(8):615-22.

Yannis Paloyelis, Mitul A Mehta, Stephen V Faraone, Philip Asherson, **Jonna Kuntsi** (2012) Striatal sensitivity during reward processing in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 51(7):722-732.

48.2 Investigating the molecular basis for selective vulnerability in FET-linked Amyotrophic Lateral Sclerosis (ALS) and Fronto-temporal dementia (FTD).

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Co-Supervisor 1B: Caroline Vance
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Project Description:

FUS-ALS and FET-FTD are two neurodegenerative diseases linked by the FET proteins FUS, EWS, and TAF-15. FUS-linked ALS is caused by mutations in FUS, leading to aggregation in the cytoplasm of neurons and glial cells causing selective motor neuron death. FET-FTD in contrast is not caused by mutations, but all three FET proteins form pathologic inclusions. We have recently shown that FUS' autoregulation is disturbed in FUS-ALS, leading to increased FUS levels (Humphrey et al, 2020). However, little is known about the FET expression pattern in the central nervous system (CNS) and especially in FTD-vulnerable cells throughout ageing - a critical factor for dementia. This project will map RNA and protein expression patterns of the FET proteins at single cell resolution throughout the mouse CNS and ageing, followed by a comparison with healthy and FUS-ALS and FET-FTD tissue to uncover the contribution of dysfunctional protein homeostasis in disease.

Yearly objectives:

- Year 1: Temporospatial analysis of FET protein expression throughout the brain and spinal cord of young and aged mice using super-resolution microscopy.
- Year 2: Temporospatial analysis of FET gene expression throughout the brain and spinal cord of young and aged mice using RT-qPCR
- Year 3-4: Comparative analysis of FET protein expression in human control and ALS/FTD vulnerable and resistant patient tissue.

Skills training: This project will train the student in animal handling and a large breadth of techniques including cloning, site directed mutagenesis, PCR, cellular fractionations, western blotting, proximity ligation assays, RNA isolation, reverse transcription, real-time qRT-PCR and super-resolution microscopy.

One representative publication from each co-supervisor:

Marc-David Ruepp: Reber S, Stettler J, Filosa G, Colombo M, Jutzi D, Lenzken SC, Schweingruber C, Bruggmann R, Bachi A, Barabino SM, Mühlemann O, Ruepp MD. Minor intron splicing is regulated by FUS and affected by ALSassociated FUS mutants. EMBO J. 2016 Jul 15;35(14):1504-21. doi: 10.15252/embj.201593791.

Caroline Vance: So E, Mitchell, JC, Memmi C, Chennell G, Vizcay-Barrena G, Allison L, Shaw C, Vance C. Mitochondrial abnormalities and disruption of the neuromuscular junction precede the clinical phenotype and motor neuron loss in hFUSWT transgenic mice. Hum Mol Genet. 2018 Feb 1;27(3):463-474. Doi: 10.1093/hmg/ddx415

49.2 Healthy ageing, memory and cognitive decline: How important is remembering through our own eyes?

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Co-Supervisor 1B: Dr Caroline Catmur
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Collaborating Clinician: Dr Paresh Malhotra
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Website: https://www.imperial.ac.uk/people/p.malhotra

Project Description:

Episodic memory, our memory for personally experienced events, is central to our identity and sense of self. This complex cognitive process is among the first to show age-related decline. Decline in this longterm memory system is linked to poorer quality of life, an increased risk of dementia and functional decline in daily activities. These impacts make it crucial to understand how episodic memory changes with age and which changes are associated with a diagnosis of Mild Cognitive Impairment (MCI). This is important as MCI increases the risk of developing dementia. Our recent work has shown that there is a specific decline in remembering from one's own perspective as we age (Russell et al, 2019). Here we are interested in investigating both the extent and the implications of this deterioration of self-perspective in episodic memory. We then will examine whether targeting this skill with transcranial direct current stimulation (tDCS) will lead to improvements in our tasks and in memory. Skills training will be provided in both neuropsychological testing and neurostimulation.

Objectives:

Year 1: Development, running and analysis of two behavioural studies with healthy ageing participants. Commence patient recruitment.

Year 2: Based on data from Year 1, develop, run and analyse behavioural study comparing MCI patient and control participants. Commence neurostimulation interventions with both patients and healthy groups.

Year 3: Complete and analyse neurostimulation interventions. Write-up thesis.

One representative publication from each co-supervisor:

Russell C., Davies S., Li K., Musil A.S., Malhotra P.A., Williams A.L. (2019) Self-perspective in episodic memory after parietal damage and in healthy ageing. Neuropsychologia.;124:171-181.

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

50.2 Developing a novel psychologically-informed pain management treatment for people with severe mental illness and their carers: A mixed-methods project

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Co-Supervisor 1B: Dr Juliana Onwumere
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Project Description:

Chronic pain is debilitating and elevated in people with severe mental illness (SMI) and their family carers, compared to the general population. Limited research, however, has investigated how pain is experienced and managed in people with SMI and their carers. Such data is needed to provide evidence-based psychologically-informed pain management. This PhD will use mixed-methods to develop and evaluate a novel psychological treatment at the interface of physical and mental health.

PhD year 1 objectives: Engage stakeholders and systematically review existing evidence

1) Undertake patient and public involvement (PPI) to feed into study design and dissemination plans.
2) Systematically-review the experience and impact of pain in carers of people with SMI.

Skills training: PPI and systematic review methods

Year 2: Identify stakeholders' needs to inform treatment design

3) Qualitative interview study with SMI participants and carers to understand their pain experiences, coping strategies, and acceptability of psychologically-informed pain management. Health professionals (e.g GPs, pain specialists) will also be interviewed to inform treatment/implementation.

4) Incorporate data from earlier stages to develop a psychological pain management treatment manual for people with SMI and their carers.

Training: qualitative interviewing/analysis; complex intervention development; clinical attachments with supervisors in psychosis & pain NHS services

Year 3 objectives: evaluation of the novel treatment

5) Evaluate the novel treatment in replicated single-case designs with people with SMI and their carers (15-20 total participants). Intensive longitudinal data will be collected to evaluate with-person effects.

Training: single-case methodology; analysis of longitudinal singe-case data.

One representative publication from each co-supervisor:

Scott W, Chilcot J, Guildford B, Daly-Eichenhardt A, & McCracken LM. (2018). Feasibility randomized-controlled trial of online Acceptance and Commitment Therapy for patients with complex chronic pain in the United Kingdom. *European Journal of Pain*, *22,* 1473-1484.

Onwumere, J., Bonetto C., Lasalvia A., Miglietta E., Veronese A., Bellini F., Imbesi M., Bebbington, P., Kuipers, E, Ruggeri M. & The GET UP Group (2020). Predictors and moderators of burden of care and emotional distress in caregivers. Results from the GET UP pragmatic cluster randomized controlled trial. *Epidemiological and Psychiatric Sciences,* 29, e27, 1-112 https://doi.org/10.1017/S2045796019000155

51.2 Understanding the impact of the Covid-19 pandemic on the mental health of children and young people with pre-existing mental health conditions.

Co-Supervisor 1A: Prof. Emily Simonoff (Head of department)
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Co-Supervisor 1B: Dr Valeria Parlatini (Clinical Lecturer in Child and Adolescent Psychiatry)
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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.

Year 1) Undertake a systematic review for publication, reviewing the limited literature on the impact of Covid on children and young people's mental health from different Countries. This will focus of relationship between different risk factors and CYP mental health outcomes. The student will also take statistical courses in epidemiological methods and time-series analysis.

Year 2) The student will focus on data extraction and analysis including structured and unstructured data from clinical records to generate a rich and comprehensive dataset. The student will then explore the effect of time-dependent factors, such as changes in restrictions and education as the pandemic evolves, by analysing longitudinal data. One publication on risk/protective factors in relation to initial impact of social restrictions.

Year 3) The student will implement their knowledge of time-series analyses to explore the interplay between underpinning risk/protective factors and initial mental health symptoms to model how these influence longer-term effects on mental health, including the role of any further restrictions and family impacts. This will lead to a further peer-reviewed publication. The student will also 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.

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).

Parlatini V, Radua J, Dell'Acqua F, et al. Functional segregation and integration within fronto-parietal networks. *Neuroimage*. 2017;146:367-375. doi:10.1016/j.neuroimage.2016.08.031

52.2 Interrogating Novel Neuroglial Iron and Lipid Interactions in Alzheimer's Disease Pathogenesis – a Toxic Duet

Co-Supervisor 1A: Dr Po-Wah So
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Co-Supervisor 1B: Dr Mads Sylvest Bergholt
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Project Description:

Background - Iron dyshomeostasis has been observed in Alzheimer's disease (AD)[1], indeed, we have recently published evidence of ferroptosis, a newly discovered form of iron-induced cell death in AD[2]. Ferroptosis is characterised by iron accumulation or functional iron overload; lipid peroxidation and impaired glutathione antioxidation[2]. Although iron accumulation has been observed by some, we and others have not observed this in AD[2,3]. We hypothesize iron dyshomeostasis arises in microglia and astroglia in AD, to induce abnormal iron distribution between cell types including neurons, ultimately resulting in neuroglial cell death by ferroptosis.
Aim - To determine iron levels and dyshomeostasis in individual neuroglial cell types, and iron dynamics between cell types, concomitant with oxidation of ferroptosis-susceptible lipids to induce neuroglial cell death in AD.

Techniques and skills

- Culturing of mono and co-cultures of neuroglia.
- Bulk and state-of-the-art high-resolution metal mapping, e.g., by synchrotron radiation X-ray fluorescence, of cellular distributions of iron of neuroglial mono- and co-cultures.
- Bulk and state-of-the-art high-resolution mapping of lipids involved in ferroptosis, e.g., using mass spectrometry and/or Raman imaging.
- Metabolic/dynamic cell assays e.g., for lipid peroxidation and use of novel iron optical probes to decipher cellular iron dynamics.
- Immunohistochemistry and microscopy

Objectives
Year 1: Implementation of mouse neuroglia mono- and co-cultures, and development/implementation of correlative iron and lipid mapping methods.
Year 2: Assessment of iron-lipid metabolism in normal and AD neuroglia monocultures.
Year 3: Assessment iron-lipid dynamics between neuroglia cell types in health and AD.

One representative publication from each co-supervisor:

A Ashraf, J Jeandriens, HG Parkes, **P-W So** (2020). Iron dyshomeostasis, lipid peroxidation and perturbed expression of cystine/glutamate antiporter in Alzheimer's disease: evidence of ferroptosis. Redox Biol 32: 101494.

MS Bergholt, A Serio, JS McKenzie, A Boyd, RG Soares, J Tillner, C Chiappini, V Wu, A Dannhorn, Z. Thakats, A Williams, MM Stevens (2018). Correlated heterospectral lipidomics for biomolecular profiling of remyelination in multiple sclerosis. ACS Central Science 4: 39.

53.2 Inflaming the brain: Understanding the relationship between inflammation, SARSs-CoV-2 and neuropsychiatric disorders

Co-Supervisor 1A: Deepak P. Srivastava
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Co-Supervisor 1B: Anthony C Vernon
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Project Description:

During pandemics of respiratory pathogens, including the novel coronavirus SARS-CoV-2, large numbers of patients present with neurological and psychiatric complications. Whether these reflect a direct viral cytopathy or are an indirect consequence of the so-called “cytokine storm” following immune response to infection is however, unclear. Whilst SARS-CoV-2 shows neuroinvasive potential this effect is relatively weak. By contrast, SARS-CoV-2 disease severity positively correlates with levels of IL-17 and other T helper 17 (TH17) cell-related pro-inflammatory cytokines, such as IL-1, IL-6, IL-15, TNF and IFNγ. How human neurons respond this cocktail of cytokines is as yet unknown and may offer an insight into aforementioned neurological and psychiatric complications of SARS-CoV-2. Supporting this view, we previously demonstrated using human induced pluripotent stem cells (hiPSCs) to generate human neurons, that IFNγ induces long-lasting changes on neuronal morphology and transcriptomic profile, which overlaps that seen in psychiatric disorders (Warre-Cornish et al., 2020). The aim of this PhD project is to use this approach to model the impact of the aforementioned cytokines induced by SARS-CoV-2 infection, alone and/or in combination on human neuronal function using 3D brain organoids generated from hiPSCs as our model system.

The overarching objectives are:
Year 1: To determine how cytokines impact on neuronal morphology and connectivity
Year 2: To characterise the transcriptomic response to this cytokine exposure and test for overlap to the genetic profile reported in neurological and psychiatric disorders.
Year 3: To elucidate whether distinct brain regions have different responses to the ‘cytokine STORM’

One representative publication from each co-supervisor:

Warre-Cornish K, Perfect L, Nagy R, et al. Interferon-γ signaling in human iPSC-derived neurons recapitulates neurodevelopmental disorder phenotypes. *Science Advances*. 2020; 6(34): eaay9506. Published 2020 Aug 19. doi: 10.1126/sciadv.aay9506

Kępińska AP, Iyegbe CO, Vernon AC et al. Schizophrenia and Influenza at the Centenary of the 1918-1919 Spanish Influenza Pandemic: Mechanisms of Psychosis Risk. Front Psychiatry. 2020 Feb 26;11:72. doi: 10.3389/fpsyt.2020.00072.

54.2 Of mice and man: A translational approach to aggression and irritability in Neurodevelopmental Disorders

Co-Supervisor 1A: Prof. Andre Strydom
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Co-Supervisor 1B: Dr Hannah Dickson
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Project Description:

Aggression is a common form of challenging behaviour among some individuals with neurodevelopmental disorders (NDDs), including autism, intellectual disability and schizophrenia. Aggressive behaviours have a serious negative impact on both affected individuals and their families, and society (e.g. school exclusion, costly care, and criminal justice system involvement) - yet we lack effective treatments. Given the increase in the incidence of NDDs, development of better interventions is urgently needed, but our poor understanding of causal mechanisms hampers this.

In this project, we will combine human and rodent studies to examine neurobiological underpinnings of NDD-associated aggression and irritability. Using mutation in the *NRXN1* gene as exemplar, the student will work with both humans and rodents to examine the brain biology of aggression in NDDs. Mutations in this gene are associated with intellectual impairment, autism and schizophrenia in humans. The student will use EEG and MRI/MRS as translational tools to examine brain structure, function and biochemistry in-vivo. Thus, we aim to define the brain systems potentially involved in aggression and irritability in NDDs in patients and then establish whether these signatures can be recapitulated in mice carrying the same genetic mutation. This back-translation into animal models coupled with cutting-edge methods (e.g. 3D imaging in transparent brains (CLARITY), optogenetics, electrophysiology) will help to identify underlying mechanisms and generate treatment targets.

Skills Training: ethics, patient assessment, human/rodent MRI, EEG and behavioural tests, immunohistochemistry, microscopy, optogenetics, electrophysiology

Overarching objectives for the project

Rotation/Year 1: Patient recruitment/assessment; behavioural tests for social interaction/aggression in a mouse model. **Year 2:** Structural/functional assessment of patients/ mouse model. **Year 3:** Data analysis; leading to planning pharmacological intervention in a mouse model with subsequent structural/behavioural evaluation.

One representative publication from each co-supervisor:

Thygesen, J., Wolfe, K., McQuillin, A., Viñas-Jornet, M., Baena, N., Brison, N., . . . , **Strydom, A**., Vogels, A. (2018). Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders. *British Journal of Psychiatry, 212*(5), 287-294. doi:10.1192/bjp.2017.65

J Horder, M Andersson, MA Mendez, N Singh, A Tangen, J Lundberg, A Gee, C Halldin, M Veronese, S Bölte, L Farde, T Sementa, D Cash, K Higgins, D Spain, F Turkheimer, I Mick, S Selvaraj, DJ Nutt, A Lingford-Hughes, Oliver Howes, DG Murphy, J Borg. "GABA A receptor availability is not altered in adults with autism spectrum disorder or in mouse models". Science Translational Medicine, 2018. doi: 10.1126/scitranslmed.aam8434.

55.2 Investigating memory impairment and hippocampal neurogenesis in Parkinson's disease

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Background: Cognition is one of the biggest unmet needs in relation to treatment and prognosis in Parkinson's disease (PD)[1]. Early PD patients with normal cognition on objective-testing may complain of Subjective Memory Decline (SMD), which may develop later in Objective Memory Decline (OMD). As such, SMD-PD patients might already be affected early on by heterogeneous pathophysiological changes of prodromal PD.

Hypothesis: SMD-PD patients will show hippocampal dysfunction potentially arising from impaired adult hippocampal neurogenesis (HP), which serves to regulate the production of new hippocampal neurons important for cognition/memory maintenance.

Rational: Cognitive impairment in PD is a risk factor for the development of PD-associated dementia. Thus, an early biomarker could help confirm the deficit and allow prognostic management strategies and new drug discovery targets.

Project Aim: Investigate how memory impairment in PD patients is linked with HP and its associated cellular/molecular mechanisms in order to validate HP as a biomarker/target to prevent/slowdown cognitive/memory decline in PD patients.

Objectives(O)/ Methods/Timeline:

- **O1- Recruit/Clinically-assess** PD patients with (i)SMD, (ii)OMD, (iii)neither-SMD-nor-OMD from KCL/KCH Parkinson's Centre of Excellence. *Year1-w/Chaudhuri/Batzu*
- **O2- Investigate** differential effects of the systemic milieu of O1-PD patients on HP according to patients' cognitive status employing a novel in vitro assay[2] using a human hippocampal stem cell line in contact with patients' blood samples and cellular/morphological phenotyping. *Year1+2-w/Thuret*
- **O3- Identify** correlations between cellular and clinical data. *Year-2+3w/-Chaudhuri/Batzu/Thuret*
- **O4- Identify** molecular pathways by which the systemic milieu of PD patients modulates hippocampal stem cell fate according to patients' cognitive status using gene expression/transcriptomic characterization. *Year3-w/Thuret*

One representative publication from each co-supervisor:

[1] Schapira AHV, **Ray Chaudhuri K**, Jenner P. Non-motor features of Parkinson disease. Nature Reviews Neuroscience. 2017 Aug;18(8):509. doi: 10.1038/nrn.2017.91

[2] Borsini A, Pariante CM, Zunszain PA, Hepgul N, Russell A, Zajkowska Z, Mondelli V, **Thuret S**. The role of circulatory systemic environment in predicting interferon-alpha-induced depression: The neurogenic process as a potential mechanism. Brain Behav Immun. 2019 Oct;81:220-227. doi: 10.1016/j.bbi.2019.06.018.

56.2 Neural predictors of emerging autism in infants with epilepsy

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Project Description:

Up to 40% of autistic individuals have epilepsy. The combination of autism and epilepsy significantly impacts upon quality of life as well as physical and mental health. The majority of studies to date have been retrospective investigations after a diagnosis of autism has been established. This project will use cutting-edge EEG technology to measure brain development in infants with epilepsy in the family home, at several time-points over the first two years of life. By studying brain development prior to the emergence of autistic traits, it will be possible to identify objective features that predict later outcome, during a developmental period in which autistic behaviours cannot be reliably measured. Large existing datasets of infants with high familial likelihood for later autism diagnosis and typically developing infants, collected using the same behavioural, cognitive and EEG protocols, will enable a test of convergent neural pathways. The findings from this research will pave the way for stratifying infants with epilepsy according to behavioural outcome and for informing and testing early intervention delivery.

Project plan
Year 1: Training (see below) and data collection with infants with epilepsy.
Year 2: Complete data collection; ongoing analysis of behavioural and neurocognitive data.
Year 3: Dataset merging; longitudinal analysis; publication and thesis preparation.
The student will be trained in epilepsy, behavioural, clinical and neurocognitive measurement with young children (including home-based EEG), and longitudinal data analysis, to provide a unique interdisciplinary skillset.

One representative publication from each co-supervisor:

Tye, C., Farroni, T., Volein, A., Mercure, E., Tucker, L., Johnson, M.H., & Bolton, P.F. (2015). Autism diagnosis alters neurophysiological responses to faces in adults with tuberous sclerosis complex. Journal of Neurodevelopmental Disorders, 7, 33.

Tang S, Addis L, Smith A, Topp SD, Pendziwiat M, Mei D, Parker A, Agrawal S, Hughes E, Lascelles K, Williams RE, Fallon P, Robinson R, Cross HJ, Hedderly T, Eltze C, Kerr T, Desurkar A, Hussain N, Kinali M, Bagnasco I, Vassallo G, Whitehouse W, Goyal S, **Absoud M**; EuroEPINOMICS-RES Consortium, et al. Phenotypic and genetic spectrum of epilepsy with myoclonic atonic seizures. Epilepsia 2020 May;61(5):995-1007.

57.2 'Food of the Mind': Promoting Mental Wellbeing and Higher Academic Achievement through a Balanced Academic 'Diet'

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Project Description:

Education research shows that learning protects against illness, and improves cognitive performance and economic prospects. However, the positive impact that learning *should* have on students' well-being contrasts starkly to the actual greater levels of stress, anxiety and depression observed. In this Age of Information, students are bombarded with an endless stream of content on-demand.

Building on our existing work (e.g. Time to Flourish; Dias, Foster & Zunszain, 2019), this PhD will develop an objective tool to measure Student 'consumption' of learning content, while proposing a "balanced informational diet", drawing parallels to the successful "5 A Day" campaign which encourages the healthy daily consumption of recommended portions of fruit and vegetables.
Specifically, this PhD aims to:
- develop a tool to measure and later recommend a healthy 'consumption' of learning material i.e. a '5 a day' digital equivalent
- infuse wellbeing throughout curriculum content to help students healthily achieve their personal best
- illustrate approaches for implementation across University programmes

The student will attend regular group meetings, departmental seminars, and primers for research methodology, and will be able to support MSc students if they so wish, amongst other training opportunities. The student will learn mixed-methods approaches including survey design**,** data collection and analysis, IT coding, and quantitative and qualitative analysis.

Year 1: Review literature, develop study protocols, obtain ethics, run survey and pilot study
Year 2: Conduct studies in student cohorts to develop tool. Plan, run and evaluate use-of-tool study
Year 3 Complete use-of-tool study, all analyses, write up

One representative publication from each co-supervisor:

Moretto, G., Walsh, E., & Haggard, P. (2011). Experience of agency and sense of responsibility. Consciousness and cognition, 20(4), 1847-1854.

Dias GP, Foster JLH & Zunszain PA (2019). Time to Flourish: designing a coaching psychology programme to promote resilience and wellbeing in postgraduate students. *European Journal of Applied Positive Psychology,* 3 (7), 1-12.

58.2 Lithium response and cognition in Bipolar Disorder

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Co-Supervisor 1B: Dr Mario F. P. Juruena
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Project Description:

Lithium is the gold standard of treatment in Bipolar Disorder (BD), but some individuals discontinue treatment because of cognitive dysfunction (Burdick et al., 2020). However, the effect of lithium on most cognitive domains are inconclusive and there are even preliminary indications of lithium having a pro-cognitive effect (Wingo et al., 2009). An explanation for this could be variations of lithium response on clinical symptoms, with excellent lithium responders appearing to perform similarly to healthy controls on cognitive tests and significantly better than partial lithium responders (Burdick et al., 2020; Rybakowski and Suwalska, 2010).

This PhD comprises three studies to establish the relationship between response to lithium and cognitive function. The project will facilitate skill development in systematic reviews and meta-analysis, and predictive modelling and conducting primary clinical research.

Study 1: systematic review of cognitive performance in those with BD before and after lithium treatment.

Study 2: a secondary analysis from an extensive naturalistic cohort of individuals with BD. The study will examine complex relationships between cognitive and clinical functioning in individuals treated with lithium compared to other interventions.

Study 3: primary cross-sectional study of 150 participants with BD aiming to validate and extend the findings from study 2.

The first year will focus on study 1 as well as setting up study 3. Study 2 will be completed in the second year alongside recruitment for study 3. The final year will focus on data analysis and completion of study 3 and writing up the PhD thesis.

One representative publication from each co-supervisor:

Angst J, Azorin J-M, Bowden CL, Perugi G, Vieta E, Gamma A, **Young AH**. et al. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. Arch Gen Psychiatry. 2011 Aug;68(8):791–8.

Jauhar S, Nour MM, Veronese M, Rogdaki M, Bonoldi I, Azis M, et al. A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. JAMA Psychiatry. 2017 Oct 11;74(12):1206–13.

59.2 The neurophysiology of recurrence risk in depression

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Project Description:

To develop novel prophylactic treatments and decision support systems, there is an urgent need to understand the pathophysiology and predict risk of recurrence in major depressive disorder (MDD). Using fMRI, we have previously found that balanced connectivity across fronto-temporo-subcortical networks guards against overgeneralised self-blame and recurrence in MDD. fMRI, however, due to its slower timescale, is poorly suited to measure temporal binding in neural networks which has been shown to be of major importance to conscious experience. Electroencephalography (EEG) is an affordable method with higher temporal resolution and therefore ideally suited to investigate temporal dynamics and binding. The proposed PhD project will investigate this intriguing question. During year 1, the student will re-analyse an existing EEG dataset (71 MDD and 48 controls). Recruitment of remitted MDD patients as part of a large ongoing MRC-funded study will complete in year 2 (n=80 MDD, n=40 controls). The student will learn how to assess patients and carry out 64-channel mobile EEG recordings at baseline. We expect about 50% of patients to develop a recurrent episode over 14 months of clinical follow-up. This will allow us to compare baseline EEGs of those with and without subsequent recurrence. The last half of year 3 and the beginning of year 4 will be devoted to completing analyses and thesis/journal submissions investigating 1) whether self-blame-evoked shifts in theta- and alpha-power networks can be replicated as characteristic of MDD and 2) whether self-blame-induced resting state EEG power distribution maps are useful for risk prediction models using machine learning.

One representative publication from each co-supervisor:

Lythe K.E., Moll J., Gethin J.A., Workman C.I., Green S., Lambon Ralph M.A., Deakin J.F., Zahn R. Self-blame-selective hyperconnectivity between anterior temporal and subgenual cortices and prediction of recurrent depressive episodes. JAMA Psychiatry (2015) doi:10.1001/jamapsychiatry.2015.1813.

McLoughlin, G, Makeig, S & Tsuang, MT 2014, 'In Search of Biomarkers in Psychiatry: EEG-Based Measures of Brain Function', American Journal of Medical Genetics. Part B: Neuropsychiatric Genetics, vol. 165, no. 2, pp. 111-121. https://doi.org/10.1002/ajmg.b.32208

60.2 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.

Two representative publications from supervisors:

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.