

# **Theme 2**

## **Neurosciences, Psychiatry and Mental Health**



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## Neurosciences, Psychiatry and Mental Health

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

Lead: Professor Francesca Happé and Dr Sandrine Thuret

When choosing a projects from this catalogue in the funding section of the online application form please enter **MRC DTP2018\_Theme2**

**Deadline for application: Sunday 26<sup>th</sup> November 2017**

Shortlisted candidates will be contacted in mid-January.

**Interviews: 31<sup>st</sup> January**

The 2018/19 studentships will commence in September 2018.

For further Information or queries relating to the application process please contact [mrc-dtp@kcl.ac.uk](mailto:mrc-dtp@kcl.ac.uk)

**Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.**

## 1.2 The Effect of Sulforadex on behavioural and molecular processes in genetic mouse models of neurodevelopmental disorders.

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Project description:

Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane) has been shown in a small RCT to have efficacy in core autism features (Singh et al). A stabilised pharmaceutical derivative Sulforadex has potential for therapeutic trials (Evgen). Pre-clinical studies here at St Thomas' Hospital (KCL, KHP) using a novel antibody together with quantitative replicative proteomics, have identified that Sulforadex adducts to SHP-2 (protein phosphatase enzyme) and inhibits its activity, hence providing a potential mechanism of therapeutic action of Sulforadex. Mutations in the PTPN11 gene that codes for Shp2 occur in patients with Noonan syndrome (a RASopathy) and autism traits. The aim of this research is to characterise the effect of Sulforadex on a range of validated tests that assess behaviours of relevance to neurodevelopmental disorders such as autism and schizophrenia. Sulforaphane will be assessed in both control (wild type) and strains with neurodevelopmental phenotypes or mutant mice with mutations in genes identified in the aetiology of neurodevelopmental disorders (specifically Noonan, other RASopathies). In addition to behavioural assessment, the effect of Sulforadex treatment in control versus mutant mice (ex vivo or from cell lines derived from these mice) on molecular processes such as electrophysiology, gene and protein expression will be measured. The molecular targets of Sulforadex in neuronal tissue will also be explored using mass spectrometry methods to define the proteins to which the compound binds or adducts. Biochemical downstream biomarkers which could be used as surrogate markers, or help for stratification will be explored. This information will be used to support an NIHR application to conduct a phase 2 clinical trial.

Two representative publications from supervisors:

Fernandes: Janecka, M., Manduca, A., Servadio, M., Trezza, V., Smith, R., Mill, J., Schalkwyk, L.C., Reichenberg, A., Fernandes, C. (2015). Effects of advanced paternal age on trajectories of social behavior in offspring. *Genes, Brain & Behavior* 14:443-53. doi: 10.1111/gbb.12227.

Eaton: Charles RL, Rudyk O, Prysyazhna O, Kamynina A, Yang J, Morisseau C, Hammock BD, Freeman BA, Eaton P. (2014). Protection from hypertension in mice by the Mediterranean diet is mediated by nitro fatty acid inhibition of soluble epoxide hydrolase. *Proc Natl Acad Sci U S A*. 2014 Jun 3;111(22):8167-72

## 2.2 Putting experience into context: cognitive training for depression

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Project description:

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

The broad project objectives are to (a) develop and test an associative framework for how individual differences in context-dependent memory develop, (b) assess whether cognitive training, based on this framework, can improve context dependent memory and mood.

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

Two representative publications from supervisors:

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

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

### 3.2 Systems Analysis of Food-Sensing Neuroendocrine Circuits that Regulate Fat Metabolism

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Project description:

Obesity affects ~500 million people worldwide, and is the major risk factor for many diseases, including diabetes, heart attacks, and cancer. Genetic and environmental factors converge on hormonal pathways in the brain to affect obesity. These pathways are highly conserved, enabling studies in the experimentally tractable roundworm *C. elegans* to provide new insights into the neural regulation of fat metabolism. 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 fat levels 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 fat metabolism. These results will help explain why different individuals have different fat levels 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 fat measurements. Dr Csikasz-Nagy will train the student in data handling, data analysis, and modelling. This project provides a unique opportunity to learn systems biology to as a new approach in biomedicine.

Two representative publications from supervisors:

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

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

## 4.2: Altering Behaviour in Children (ABC)

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### Project description:

The cost of youth crime in the UK is estimated to be £11 billion per year and is often perpetrated by children/adolescents who have Conduct Problems (CP). The underlying cause(s) for CP is complex but there is compelling evidence that children with CP have differences in brain structure and function. However, no-one has ever analysed whether there are specific brain differences that: a) predict resistance to change; and/or b) are 'reversible'. The successful candidate will be trained to use cutting-edge brain imaging techniques to answer these questions by studying CP children before and after a parent training intervention, which reduces antisocial behaviour in about 1/3<sup>rd</sup> of CP children.

He/she will also have the unique opportunity to work alongside, some the top world leaders in CP and brain imaging including Profs. Stephen Scott, Declan Murphy, Marco Catani, & Steven Williams (IoPPN), Essi Viding (UCL) and James Blair (NIMH (USA)).

**TRANSLATIONAL ASPECT OF THE PROJECT:** It is anticipated that our findings will assist in focusing future research into the molecular basis of CP, and ultimately lead to better treatments.

**SKILLS TRAINING AVAILABLE IN THE PROJECT:** Training in cutting edge, structural and functional brain imaging techniques.

**OVER-ARCHING OBJECTIVES:** YEAR 1: Recruit/scan children (already started for you); Collection of data; Brain image analysis training. YEAR 2: Completion of recruitment and preliminary analysis. YEAR 3: Completion of analysis; Presentation at International meetings; Writing up dissertation/papers.

### Two representative publications from supervisors:

Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. [Sarkar, S., Craig, M. C.], Catani, M., Dell' Acqua, F., Fahy, T., Deeley, Q. & Murphy, D. G. M. Feb 2013 In: Psychological Medicine. 43, 2, p. 401-411.

Punishment and psychopathy: a case-control functional MRI investigation of reinforcement learning in violent antisocial personality disordered men. Blackwood, N. J. 1 Feb 2015 In: The Lancet Psychiatry. 2, 2, p. 153-160.



## 5.2 Neurodevelopmental trajectories and psychotic experiences: a longitudinal MRI study of young adults.

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Project description:

This project will provide the opportunity to participate in a unique study. This is a collaboration between several UK universities, the Avon Longitudinal Study of Parents and Children (ALSPAC) using multimodal brain imaging. Over 250 people from the ALSPAC birth cohort have already undergone structural and functional MRI at age 20 in the Cardiff University Brain Imaging Centre. ALSPAC contains a wealth of data on physical and mental health, cognitive development, DNA, personality and environmental exposures on over 6000 people who have been followed-up intensively since birth. Studies undertaken so far have concentrated on psychotic experiences (PEs) and these show subtle correlations with altered brain connectivity. The study team are planning to re-scan 250 participants to gain information on trajectories of brain development and have already demonstrated feasibility. This project will focus on neuroimaging predictors (imaging biomarkers) of persistence/remission of PEs and development of clinical psychosis, and possible mediating factors which has obvious translational benefits. There will be ample opportunities to develop a PhD project around other symptoms, clinical outcomes, personality factors, genetics or cognition combining multi-modal imaging with these measures. The student will acquire skills in image analysis, longitudinal research, cognitive development and psychiatric disorders and will work with a multidisciplinary team of academics on a truly cutting edge piece of work.

Prof David will supervise all aspects of the study, will facilitate visits to collaborating labs, and guarantee access to data. Dr Dazzan will provide training and supervision in MR imaging and longitudinal data analysis and in interpretation of findings.

Two representative publications from supervisors:

Anthony David: Drake-Smith M, Dutt A, Fonville L, Zammit S, Reichenberg A, Evans CJ, Lewis G, Jones DK, David AS. (2016). Mediation of developmental risk factors for psychosis by white matter microstructure in young adults with psychotic experiences. *JAMA Psychiatry*, 73(4):396-406. doi:10.1001/jamapsychiatry.2015.3375.

Paola Dazzan: Lappin JM, Morgan C, Chalavi S, Morgan KD, Reinders AA, Fearon P, Heslin M, Zanelli J, Jones PB, Murray RM, Dazzan P. Bilateral hippocampal increase following first-episode psychosis is associated with good clinical, functional and cognitive outcomes. *Psychol Med*. 2014 Apr;44(6):1279-91. doi: 10.1017/S0033291713001712. Epub 2013 Jul 18.

## 6.2 Development and testing of novel electronic health interventions to alter drugs, alcohol and tobacco use patterns and trajectories in young people

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### Project description:

Systematic reviews report that opportunistic Screening and Brief Intervention (SBI) is effective and cost effective in changing behaviour (e.g. reducing alcohol consumption). However, these are rarely implemented in clinical practice. Therefore, a cost effective and practical method of implementing SBI both in the NHS and delivered at a whole population level is urgently required.

SBI delivered via electronic media (eSBI) shows promise, with several clinical trials reporting positive outcomes. Recent reviews of the relevant literature (Donoghue et al 2014, Patton et al 2014) further supports the utilisation of eSBI to reduce alcohol consumption and related harms.

This PhD proposal focuses on the development, implementation and evaluation of a purpose designed smartphone intervention app which would focus on a number of health and lifestyle behaviours such as: Alcohol, smoking, drugs use as well as obesity and self-harm. The app will be developed in collaboration with an industry partner (Troo Life Coach Ltd) following proven brief intervention, gamification strategies, and augmented intelligence (ChatScripts) to personalise content, to promote healthier choices, to induce a reduction in quantity and frequency of substance use in adolescents, to provide a wider implementation and uptake of electronic brief interventions to the wider population, with associated health and cost benefits. The app development and evaluation will involve qualitative research with target users through focus groups, interviews and product testing, in order to develop the most user friendly, credible and engaging intervention tool.

### Two representative publications from supervisors:

Deluca P, Coulton S, Alam MF, Cohen D, Donoghue K, Gilvarry E, Kaner E, Maconochie I, McArdle P, McGovern R, Newbury-Birch D, Patton R, Phillips C, Phillips T, Russell I, Strang J & Drummond C. 2015. **Linked randomised controlled trials of face-to-face and electronic brief intervention methods to prevent alcohol related harm in young people aged 14–17 years presenting to Emergency Departments (SIPS junior).** *BMC Public Health*. 15:345. DOI 10.1186/s12889-015-1679-4

Donoghue K, Patton R, Phillips T, Deluca P & Drummond C. 2014. **The effectiveness of electronic Screening and Brief Intervention (eSBI) for reducing levels of alcohol consumption. A Systematic review and meta-analysis.** *Journal of Internet Medical Research*, 16(6):e142. DOI:10.2196/jmir.3193

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

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### Project description:

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

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

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

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

### Two representative publications from supervisors:

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

Denk F, McMahon SB, Tracey I (2014). Pain vulnerability: a neurobiological perspective. *Nat Neurosci* 17(2): 192-200. <http://www.nature.com/neuro/journal/v17/n2/abs/nn.3628.html#8.2>

## 8.2 Identification of neurobehavioural predictors of eating disorders, weight gain and obesity

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Project description:

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

This project will elucidate the neurobiological basis of EDs and identify predictor of EDs, weight gain and obesity in young adulthood. The student will:

Year 1. *(i)* Familiarise themselves with the neurobiological basis of EDs (Prof. Schmidt's area of expertise) and the IMAGEN database (Dr. Desrivières, one of the IMAGEN PIs, will provide access and support); *(ii)* conduct a systematic review (e.g. on neurobiological predictors of EDs/obesity); *(iii)* utilise IMAGEN behavioural and body mass index (BMI) data (age 14 to 21) to identify and characterise distinct trajectories of disordered eating and BMI change.

Year 2. Use age 14 IMAGEN data to identify environmental, biological and psychological factors characterizing the different trajectories.

Year 3. *(i)* Study interactions between these factors to derive bio-behavioural risk/prediction models of EDs, weight gain and obesity, and *(ii)* validate results in a clinical sample of emerging adults with an ED diagnosis.

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

Two representative publications from supervisors:

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

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

## 9.2 Eye-movements in Attention Deficit Hyperactivity Disorder: A potential biomarker and therapeutic route

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Project description:

Background: Research suggests that the superior colliculus, a midbrain multisensory structure, may be critical in the development of Attention Deficit Hyperactivity Disorder (ADHD). This structure is responsible for producing a type of eye movement called a microsaccade (small, fast movements produced 1–2 times per second during fixation). Microsaccades appear to be increased in ADHD and normalised with ADHD medication in a small-scale study. This project will further unpick the changes to microsaccades in ADHD to establish A) whether they are differentially modulated by demand being placed on diverse attentional systems (e.g., non-spatial sustained attention and exogenous and endogenous spatial selective attention) B) whether changes in microsaccades are associated with specific ADHD traits and C) whether microsaccades can be normalised in ADHD with audio-visual training.

Skills training: The student will receive training in programming, data collection and analysis for eye-tracking and advanced statistical methods. They will also be trained in administering the Adult ADHD Self-Report Scale (ASRS). In addition, the student will receive training in data management, academic writing and public engagement.

Yearly objectives:

Year 1: i) Develop understanding of ADHD and microsaccades through literature review; ii) Complete initial eye-tracking and ASRS training; iii) begin data collection for microsaccade task (A+B).

Year 2: i) Complete data collection and receive full analysis training (A+B); ii) Develop and pilot audio-visual training programme (C).

Year 3: i) Evaluate effectiveness of audio-visual training on microsaccades in ADHD (C).

Year 4: i) Complete evaluation of audio-visual training (C); ii) Writing-up period.

Two representative publications from supervisors:

Brace LR, Kraev I, Rostron CL, Stewart MG, Overton PG & Dommatt EJ (2015) Altered visual processing in a rodent model of Attention-Deficit Hyperactivity Disorder. *Neuroscience*, 303, 364-377

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

## 10.2 Targeted drug repurposing to find better treatments for Parkinson's and related dementias.

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Co-Supervisor 1B: Dr Gareth Williams

Research Division/Department or CAG: Wolfson CARD; Division of Neuroscience

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Project description:

Scientific Basis:

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

Yearly Objectives:

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

Skills training:

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

Two representative publications from supervisors:

Sleeman IJ1, Boshoff EL, **Duty S.** (2012). Fibroblast growth factor-20 protects against dopamine neuron loss in vitro and provides functional protection in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. *Neuropharmacology*. 63(7):1268.

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

## 11.2 Inflammation, glutamate and treatment response in schizophrenia.

Co-Supervisor 1A: Dr Alice Egerton

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Co-Supervisor 1B: Dr Valeria Mondelli

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Project description:

Both inflammation and glutamate dysfunction are associated with the pathophysiology of schizophrenia, as well as with the degree to which the symptoms of schizophrenia will respond to antipsychotic treatment. This project explores the novel hypotheses that inflammation and glutamate dysfunction may be mechanistically linked, and that together these processes may underlie poor antipsychotic response. This discovery could lead to new glutamatergic or anti-inflammatory treatments for patients who do not respond to current medication.

The student would join our existing research projects that are separately investigating levels of inflammatory cytokines in blood and brain MRI imaging of glutamate and inflammatory metabolites (myo-inositol and choline) in patients with schizophrenia. The associations between inflammation and glutamate would be determined cross-sectionally (comparing good versus poor responders to antipsychotic treatment), as well as prospectively (to determine whether these biomarkers can predict antipsychotic response).

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

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

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

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

Two representative publications from supervisors:

[Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia.](#)

Egerton A, Brugger S, Raffin M, Barker GJ, Lythgoe DJ, McGuire PK, Stone JM.

Neuropsychopharmacology. 2012 Oct;37(11):2515-21. doi: 10.1038/npp.2012.113. Epub 2012 Jul 4.

[Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis.](#)

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

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

## 13.2 Novelty and Ageing

Co-Supervisor 1A: Prof Karl Peter Giese

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Co-Supervisor 1B: Dr Samuel Frazer Cooke

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Project description:

Deficits in learning and memory emerge during ageing. There is currently an incomplete understanding of how to treat these deficits to improve quality of life and this issue has been a major focus of work in the laboratory of Professor Peter Giese. Novelty is a major factor that is known to enhance synaptic plasticity supporting learning and memory through a process known as novelty priming, where experience of novelty within half an hour prior to learning greatly enhances the longevity of resultant memory. The mechanisms that underlie this novelty effect are not fully understood and they have been a recent focus of research for Dr. Sam Cooke. The proposed PhD project will combine the interests and approaches of the Giese and Cooke laboratories to investigate novelty effects in the ageing nervous systems. In the first year, we will determine if memory and accompanying plasticity is enhanced by novelty priming in the nervous system of aged mice. As ageing is often accompanied by increases in routine that may reduce exposure to novelty, we will determine in the second year whether aged mice exhibit preferences for familiarity over novelty. As a final aim, we will ask whether novelty is harder for aged animals to detect, which may prevent aged individuals from seeking it out. The student will acquire a wide range of skills in this project including behavioural analyses in mice, electrophysiological assessment of plasticity and histological and molecular methods for identifying signatures of ageing that may be affected by novelty priming.

Two representative publications from supervisors:

Tiwari SS, Mizuno K, Gosh A, Aziz W, Troakes C, Daoud J, Golash V, Noble W, Hortobagyi T, Giese KP (2016) Alzheimer-Related Decrease in CYFIP2 Links Amyloid Production to Tau Hyperphosphorylation and Memory Loss. *Brain*. 139(Pt 10): 2751-2765.

Cooke SF, Komorowski RW, Kaplan ES, Gavornik JP, Bear MF (2015) Visual Recognition Memory, Manifest as Long-Term Habituation, Requires Synaptic Plasticity in V1. *Nature Neuroscience*. 18(2): 262-71.



## 14.2 Neural mechanisms for light aversion during migraine

Co-Supervisor 1A: Dr Philip Holland

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Co-Supervisor 1B: Dr Alessio Delogu

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Project Description:

Migraine is the most disabling neurological disorder globally with attacks of intense pain that is often intensified by light. Light-aversion is a defining feature of many attacks highlighting the importance of abnormal light processing. It has been demonstrated that intrinsically-photosensitive retinal ganglion cells that contain pituitary adenylate cyclase activating peptide (PACAP, a known migraine trigger) converge on thalamic networks processing sensory information from the head where they act to enhance signaling.

We have previously identified a sub-population of Sox14-expressing interneurons that provide an inhibitory drive to the visual thalamus and now seek to explore their potential role in photophobia. Our hypothesis is that dysregulation of normal thalamic excitatory/inhibitory drive results in abnormal processing of light and subsequent photophobia in migraines. It further proposes that modulation of this subset of thalamic inhibitory interneurons may represent a novel therapeutic approach.

The project will map the connectivity of Sox14 neurons and head pain networks in-vivo using mouse genetics and viral tracing (12-18 months). Using a combination of optogenetic/chemogenetic approaches with behavioural models of light-aversion and electrophysiology the project will then characterise the functional consequences of their modulation (18-36 months). Key translational aspects will be explored via established clinical collaborations as appropriate.

The study is based on detailed in-vivo approaches and as such would benefit from a 0+3.5 PhD; however, a 1+3 option is also available. The student will develop significant in-vivo skills including surgical, optogenetic/chemogenetic, electrophysiology and behavioural approaches, ensuring they master a number of highly desirable specialist skills above and beyond standard laboratory procedures.

Two representative publications from supervisors:

Akerman S, Romero-Reyes M & Holland PR. (2017). Current and novel insights into the neurophysiology of migraine and its implications for therapeutics. *Pharmacol Ther.* 172; 151-70. DOI: 10.1016/j.pharmthera.2016.12.005.

Jager P, Ye Z & Yu X et al. (2016). Tectal-derived interneurons contribute to phasic and tonic inhibition in the visual thalamus. *Nat Commun.* 7;13579. DOI: 10.1038/ncomms1357

## 15.2 Investigating the protective mechanisms of astrocytes in Alzheimer's disease

Co-Supervisor 1A: Dr Maria Jimenez-Sanchez

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Co-Supervisor 1B: Prof Diane Hanger

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Project description:

In neurodegenerative diseases, compromised protein homeostasis or proteostasis leads to a progressive accumulation of oligomers and aggregated proteins. In Alzheimer's disease (AD), this results in the accumulation of plaques of  $\beta$ -amyloid (A $\beta$ ) and neurofibrillary tangles (NFT) containing tau. Upregulation of proteostasis (autophagy, ubiquitin-proteasome system and chaperones) is currently being investigated as a preventative strategy for neurodegeneration. To date, these mechanisms have been studied in neurons, but it is important to determine the effects of glia on disease progression to enable design of effective therapeutics. This project will investigate how proteostasis mechanisms in astrocytes can protect neurons in AD in a non-cell autonomous manner.

Year 1. Co-culture primary mouse astrocytes and neurons to investigate non-cell autonomous changes on tau pathology in neurons from AD transgenic mice.

Specific proteins involved in proteostasis (autophagy, proteasome and chaperones) will be silenced in astrocytes using small interfering RNA (siRNA) prior to co-culturing with neurons.

Year 2. Organotypic brain slice cultures from AD transgenic mice will be cultured and selected proteins (Year 1) will be silenced using astrocyte-directed viruses.

Year 3. Any non-cell autonomous effects of astrocytes on tau pathology in neurons will be investigated using organotypic cultures from AD mice, in which the amounts of specific proteins can be modulated in astrocytes using viruses.

A range of cell biology and biochemical techniques will be employed: primary neural and glial cultures, brain organotypic slice cultures, western blotting, siRNAs, viral transduction, immunohistochemistry. This project will identify protective targets in AD that may be pursued further as therapeutic strategies.

Two representative publications from supervisors:

Jimenez-Sanchez M, Lam W, Hannus M, Sönnichsen B, Imarisio S, Fleming A, Tarditi A, Menzies F, Ed Dami T, Xu C, Gonzalez-Couto E, Lazzeroni G, Heitz F, Diamanti D, Massai L, Satagopam VP, Marconi G, Caramelli C, Nencini A, Andreini M, Sardone GL, Caradonna NP, Porcari V, Scali C, Schneider R, Pollio G, O'Kane CJ, Caricasole A and Rubinsztein DC. siRNA screen identifies QPCT as a druggable target for Huntington's disease. *Nat Chem Biol*. 2015 May;11(5):347-54. PMID: 25848931

Bondulich, M.K., Guo, T., Meehan, C., Manion, J., Rodriguez Martin, T., Mitchell, J.C., Hortobagyi, T., Yankova, N., Brion, J.-P. Noble, W., and 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. PMID: 27297240.

## 16.2 Impairments of brain function in adolescents born preterm: identifying preterm-birth specific and family-level risk factors

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### Project description:

Preterm birth occurs in 8.6% of births in developed countries. Whilst survival rates of preterm-born children are improving, many negative long-term outcomes have been implicated, including academic difficulties, cognitive-neurophysiological impairments and an increased risk for neurodevelopmental disorders, in particular attention-deficit/hyperactivity disorder (ADHD).

In our recent 'SPIN' (Study of Preterm Inattention) project, we assessed 150 preterm-born adolescents and 150 of their full term-born siblings on cognitive, EEG, skin conductance and interview measures. We first compared the preterm-born adolescents to independent large samples of adolescents with ADHD and controls assessed on identical measures and, second, to their own siblings to control for potential familial confounders. Our first main finding was that even in this sample of well-functioning adolescents recruited from mainstream schools, preterm birth was associated with several impairments of cognition and brain function, as well as with increased ADHD symptoms. Second, we found that most of the impairments were consistent with a possible causal effect of preterm birth, as the preterm-unrelated control differences were replicated in the preterm-sibling analyses. However, executive control processes of inhibition and short-term memory were impaired in both the preterm-born adolescents and their full term –born siblings, compared to unrelated controls, suggesting that these impairments are not causally linked to preterm birth per se but are, instead, linked to family-level risk factors.

The next phase of this research has two main aims. First, we will aim to identify the specific risk factors, both those relating to the preterm birth and family-level risk factors, that link to the outcomes. This will involve going back to the medical records of the siblings and their mothers, as well as telephone interviews with the families where family background details are not available. Second, we will move beyond the standard event-related potential analyses performed so far, to analyse the EEG data with advanced approaches (e.g. brain oscillations and connectivity) in order to obtain maximally informative and sensitive outcome measures of brain function. Training will be provided in all aspects of the project. Overall, the project aims to identify precise targets for future interventions.

Two representative publications from supervisors:

### Association of Preterm Birth With Attention-Deficit/Hyperactivity Disorder-Like and Wider-Ranging Neurophysiological Impairments of Attention and Inhibition.

Rommel AS, James SN, McLoughlin G, Brandeis D, Banaschewski T, Asherson P, Kuntsi J.

J Am Acad Child Adolesc Psychiatry. 2017 Jan;56(1):40-50. doi: 10.1016/j.jaac.2016.10.006. PMID: 27993227

### Six-year follow-up study of combined type ADHD from childhood to young adulthood: Predictors of functional impairment and comorbid symptoms.

Cadman T, Findon J, Eklund H, Hayward H, Howley D, Cheung C, Kuntsi J, Glaser K, Murphy D, Asherson P.

Eur Psychiatry. 2016 May;35:47-54. doi: 10.1016/j.eurpsy.2015.08.007. Epub 2016 Apr 11. PMID: 27077377

## 17.2 Understanding transtherapeutic mechanisms in cognitive behavioral interventions for patients with Persistent Physical Symptoms.

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Project description:

Chronic Fatigue Syndrome (CFS) and Irritable Bowel Syndrome are examples of disorders characterised by Persistent Physical Symptoms (PPS), which are associated with profound disability and high health care costs. There is an accumulating body of evidence demonstrating that cognitive behavioural interventions can reduce levels of symptoms and improve functioning. While it is standard clinical practice to adapt psychological therapies to the patient population it is not clear which components of the cognitive and behavioural intervention are transtherapeutic, that is, address needs shared by patients across the PPS spectrum, and which are disorder specific. Identifying such mechanisms can help clinicians target core mechanisms and develop new psychological interventions for other patient groups with PPS. This PhD project will develop and apply methods for modelling the impact of disorder on underlying mechanisms and will provide an opportunity to develop knowledge of psychological theory and interventions and skills in biostatistics. In year one, the student will carry out a systematic review of mechanistic theories in PPS and existing methods for assessing transtherapeutic mechanisms and will prepare individual participant data (IPD) from a number of CBT trials for pooling; likely to include the PACE and PRINCE Secondary trials in CFS and other PPS populations. A number of putative mediators and effect modifiers have been measured across trials. This project will develop modelling techniques to assess whether mechanisms are shared across disorders or operate differentially. We envisage structural equation modelling and IPD meta-analysis/integrative data analysis techniques to play an important role in this methodological project (years 2 and 3).

Two representative publications from supervisors:

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

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

## 19.2 Post Traumatic Stress Disorder among female offenders: prevalence, correlates and outcomes

Co-Supervisor 1A: Dr Deirdre MacManus

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Co-Supervisor 1B: Dr Hannah Dickson

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### Project Description:

Traumatic events can lead to the development of post-traumatic stress disorder (PTSD) and other mental disorders. Thorough assessment of trauma is fundamental to understanding and managing its effects on an individual's biological, psychological, and social functioning. Timely assessment can lead to interventions to treat trauma-related conditions, such as PTSD, and prevent the development of comorbid conditions and behavioural problems if a trauma history goes undetected and untreated. Trauma related disorders are currently under diagnosed and hence undertreated in offender populations who report high levels of childhood and adulthood traumatic exposures.

The aim of this project is to explore the prevalence of PTSD, including complex PTSD, its association with comorbid mental health problems and impact on behavioural outcomes in a population of female offenders. In year 1, the doctoral researcher will undertake a comprehensive systematic review and meta-analysis of extant literature on the prevalence of PTSD among female offenders, gain ethical approval for the study and gain experience in setting up an interview study within a female prison in London. In years 2 and 3, they will undertake interviews of female offenders to record the type and frequency of life course traumatic exposures, establish diagnoses of PTSD and/or other disorders and follow-up the population using electronic records to establish the longitudinal behavioural outcomes. The researcher will gain training and experience in carrying out standardised clinical interviews and advanced data analysis as well as opportunities for dissemination of findings through publication and presentation at conferences.

Two representative publications from supervisors:

MacManus, D., Rona, R. J., Dickson, H., Somaini, G., Fear, N. T. & Wessely, S. C. Aggressive and violent behaviour among military personnel deployed to Iraq and Afghanistan: prevalence and link with deployment and combat trauma. 2015, *Epidemiologic Reviews*. 37, 1, 196-212

Dickson, H., Cullen, A. E., Reichenberg, A., Hodgins, S., Campbell, D. D., Morris, R. M & Laurens, K.R. (2015). Cognitive impairment among children at-risk for schizophrenia. *Journal of Psychiatric Research*, 50, 92-99.

## 20.2 Perinatal brain maturation in children at risk of developing Autism Spectrum Conditions.

Co-Supervisor 1A: Dr Gráinne McAlonan

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Project description:

The genes and environmental risk factors associated with autism act primarily prenatally or in the first year of life. There is a compelling need to establish who is most likely to benefit from treatment as early as possible; and to identify individual treatment targets within this very diverse population. To do this, powerful MRI techniques and careful behavioural phenotyping will provide the most detailed assessment ever of the growing brain in babies at risk of ASD. We aim to recognise early divergence from typical maturation pathways in children who have a first degree relative with ASD, and so a higher likelihood of developing autistic traits. This will reveal new treatment targets and guide early intervention to children most at risk.

The student will be trained in advanced analyses of multimodal MRI measures. Approximately 800 typically-developing infants have already been scanned using state-of-the-art acquisition methods as part of the developing human connectome project (dHCP) which will provide a reference dataset. A number of foetuses and neonates at risk of ASD will also have been scanned at study outset and this data will be available in year 1 for training/rotational projects and exploration of research questions:

Year 1: Training in recruitment, behavioural and MRI methods.

Year 2: Analyses of existing datasets. Rolling recruitment, scanning and behavioural assessments of infants. Conference (poster) presentations.

Year 3: Analyses. Explore novel multimodal methods (e.g. 'machine learning' techniques) to identify subgroups and predict outcome. Conference oral presentations.

Year 4: Write up.

Two representative publications from supervisors:

Sethna, V., Pote, I. M. D. S. S., Wang, S., Gudbrandsen, C. M., Blasi, A., McCusker, C., ... McAlonan, G. M. (2016). *Mother-infant interactions and regional brain volumes in infancy: an MRI study*. *Brain structure & function*, 1-10. DOI: 10.1007/s00429-016-1347-1

Loth, E., Spooren, W., & Murphy, D. G. (2014). New treatment targets for autism spectrum disorders: EU-AIMS. *The Lancet Psychiatry*, 1(6), 413-415. DOI: 10.1016/S2215-0366(14)00004-2.

## 21.2 Control of body temperature: molecular basis of central sensory mechanisms

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Co-Supervisor 1B: Dr Jon Robbins  
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### Project description:

The aim of the project will be to determine mechanisms that mammals use to sense and to maintain body temperature.

1) How do mammals *sense* their bodily warmth? In previous work (Tan & McNaughton, 2016) we found that TRPM2 is a novel warmth-sensitive mechanism in somatosensory neurons. We will extend this work by determining the critical thermal sensors which detect and defend core body temperature in thermo-regulatory sensory neurons of the hypothalamus.

2) How are thermo-sensitive mechanisms in the brain modulated to cause fever? We will investigate the effect of factors known to cause fever – do these act on the same warmth-sensitive mechanisms as we use to maintain normal body temperature, or are different mechanisms involved? Discovering the molecular mechanisms involved in fever will assist in developing drugs to control pathological fever states.

### Skills training available in the project:

The PhD student will use calcium imaging of isolated hypothalamic neurons to identify those neurons activated by body warmth. The electrical properties of the thermally-activated ion channel will be determined using patch clamp. Thermally-activated neurons will be isolated and their mRNA sequenced to identify uniquely-expressed genes. From this we will identify ion channels involved in sensing and maintaining body temperature.

Year 1: Develop isolation and calcium imaging of thermally-sensitive hypothalamic neurons.

Year 2: Study properties of thermally sensitive ion channels using patch clamp.

Year 3: Implement RNA sequencing to identify the molecular nature of these channels.

Related aspects of this project are funded by a Wellcome Trust Investigator Award to PMcN.

### Two representative publications from supervisors:

Tan CH, McNaughton PA. (2016) The TRPM2 ion channel is required for sensitivity to warmth. *Nature*. 536:460-3.

Robbins J, Passmore GM, Abogadie FC, Reilly JM & Brown DA (2013) Effects of KCNQ2 gene truncation on M-type Kv7 potassium currents. *PLoS ONE* 8(8): e71809.  
doi:10.1371/journal.pone.0071809.

## 22.2 Molecular imaging of corticolimbic GABA-glutamate interactions in early psychosis.

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Co-Supervisor 1B: Prof Federico Turkheimer

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For translational projects:

Collaborating Clinician: Prof. Philip McGuire

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Project description:

Background: Psychosis is the first leading cause of disability in the developed world. However, the treatments that are offered now do not work for about 30-60% of patients, and have little impact on illness prevention. Post-mortem and preclinical studies strongly implicate abnormal interactions between GABA and glutamate neurotransmission within a corticolimbic circuitry involving the medial prefrontal cortex and the hippocampus in the pathophysiology of psychosis. This study will use a multimodal neuroimaging approach to investigate interactions between GABAergic function and glutamate levels in patients with a first-episode of psychosis compared to a group of healthy controls. By using simultaneous PET-MRI scanning, this project has enormous translational potential: delineating the relationship between GABA and glutamate neurotransmission in early psychosis will advance our pathophysiological understanding of psychosis and will facilitate the discovery of biomarkers and new treatments aimed at preventing the development of the disorder.

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

Objectives / project plan:

Year 1: Data collection: participant recruitment/scanning, maintenance/production of case report forms and databases.

Year 2: Participant recruitment/scanning, preliminary data analysis.

Year 3: Complete participant scanning, finalise data analysis, thesis write-up.

Optional, year 4: This additional time would allow unplanned extensions in case of any delays in participant recruitment and/or offer a period of time following thesis submission for the student to support their transition into the post-doctoral phase.

Two representative publications from supervisors:

Modinos G, Allen P, Grace AA, McGuire P. (2015) Translating the MAM model of psychosis to humans. *Trends Neurosci.* 38(3):129-38.

McGinnity CJ, Riaño Barros DA, Rosso L, Veronese M, Rizzo G, Bertoldo A, Hinz R, Turkheimer FE, Koeppe MJ, Hammers A. (2017) Test-retest reproducibility of quantitative binding measures of [11C]Ro15-4513, a PET ligand for GABAA receptors containing alpha5 subunits. *Neuroimage.* 15;152:270-282.



## 25.2 Identifying brain-behavioral links in toddlers at environmental and genetic risk of neuropsychiatric disorder

Co-Supervisor 1A: Dr Chiara Nosarti  
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Co-Supervisor 1B: Prof Carmine M Pariante  
Research School/Division or CAG: Psychological Medicine  
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### Project description:

Approximately 25% of children born before 32 weeks (i.e., very preterm) and 20% of siblings of older children diagnosed with ASD/ADHD have persisting neuropsychiatric problems. It is a public health priority to increase our understanding of the origins of mental illness by explicating neurodevelopmental mechanisms. Furthermore, there is an urgent need for research that can inform on how to intervene to reduce psychiatric risk.

This study will investigate the antecedents of psychiatric disorder in 2-4 year old children recruited from the Developing Human Connectome Project: 50 children who were born very preterm, 50 children with a family history of ASD/ADHD and 50 normal infants. At birth all children received the most sophisticated neuroimaging methods available to date. Multimodal brain imaging information acquired during the neonatal period, together with collateral family, clinical and immune profile information will be used to outline predictors of psychiatric risk by identifying *early in life* those children who are vulnerable to experiencing behavioural impairments that have been associated with psychiatric disorder (e.g. emotion dysregulation, irritability, socio-emotional impairments). A range of methods including machine learning will be applied to the data, creating measures for the identification of vulnerable children at birth who could benefit from preventive interventions before any psychiatric problem manifests. This information will be used to develop a biologically-informed training programme aimed at enhancing children's resiliency. The successful student will receive training in neurodevelopmental assessment and magnetic resonance imaging methods of the developing brain, including structural and functional connectivity

### Two representative publications from supervisors:

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

Cattaneo A, Macchi F, Plazzotta G, ..., Pariante CM. Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. *Front Cell Neurosci*. 2015;Mar 31;9:40.

## 26.2 Elucidating the pathway from benign to pathological positive psychotic symptoms and back again: informing the next wave of psychological therapies.

Co-Supervisor 1A: Dr Emmanuelle Peters

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Co-Supervisor 1B: Dr Lucia Valmaggia

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Project description:

Psychotic experiences (PEs), such as hearing voices or having odd beliefs, are not always associated with distress or requiring care from mental health services. Psychological explanations of psychosis suggest that it is the way individuals make sense of, and cope with, their PEs, rather than their actual presence, that leads to distress. Psychological therapies aim to reduce distress by changing how people think about, and respond to, their PEs, as well as increasing resilience and self-esteem. Experience Sampling Method (ESM) is a structured diary technique, using a Smartphone App over a 1-week period, allowing 'in-the-moment' measurement of PEs, thoughts, and emotions within their social and environmental context as they unfold in daily life. In this project we will use ESM to compare (1) psychosis patients to individuals in the general population who have enduring, but non-distressing, PEs; (2) psychosis patient who do well with therapy with those who do not respond. This will allow us to find out (1) the psychological factors that lead to benign or distressing outcomes of PEs, (2) how successful therapy works. This project will improve our understanding of resilience in people with PEs and inform the next wave of therapies for psychotic disorders.

Year 1: Training in ESM methodology and systematic reviews; ethical permissions; therapy observations; setting up recruitment; draft systematic review

Year 2: Recruitment; training in multi-level modelling statistics for ESM analyses; submit systematic review paper; analyse and draft 1<sup>st</sup> study paper

Year 3: Finish recruitment, analyse study 2 and write up thesis

Two representative publications from supervisors:

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

Reininghaus, U, Gayer-Anderson, CEJ, Valmaggia, LR, Kempton, M, Calem, MDAR, Onyejiaka, A, Hubbard, KMF, ... & Morgan, C. 'Psychological processes underlying the association between childhood trauma and psychosis in daily life: an experience sampling study' (2016) *Psychological Medicine*, pp. 1-15. DOI: 10.1017/S003329171600146X

## 27.2 Multi-modal MR imaging in Familial Parkinson's disease

Co-Supervisor 1A: Prof Marios Politis

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Co-Supervisor 1B: Prof Dag Aarsland

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Project description:

Although Parkinson's disease (PD) is typically a sporadic disorder, recent years have shed light on genetic mutations responsible for multiple familial forms of the disease. Several heritable, monogenic mutations have been identified including SNCA, which is responsible for autosomal-dominant PD forms, as well as Parkin and LRRK2, which are accountable for an autosomal recessive mode of inheritance. Gaining an insight into the pathophysiology of familial forms will provide us with novel insights into neurodegeneration that are broadly relevant to sporadic PD and amenable to therapeutic targeting. The goal of this project is to use neuroimaging and clinical assessments to investigate the pathophysiology of familial PD in asymptomatic and symptomatic PD patients carrying SNCA, Parkin or LRRK2 mutations. This project will provide the student with skills training in the analysis of various Magnetic Resonance Imaging (MRI) sequences, including Arterial Spin Labeling, functional MRI, Neuromelanin-sensitive MR and Diffusion Tensor Imaging. Year one objectives are to understand the principles MR techniques, and gain experience in recruiting and assessing research participants; year 2 objectives include developing expertise in the practical aspects and analysis of neuroimaging; year 3 objectives are to gain expertise in combining the MR techniques to provide a multi-modal approach and analysing clinical data; year 4 objectives are to consolidate skills, present study data and submit dissertation thesis along with high quality publications. This project provides an excellent opportunity to work within a highly talented, multidisciplinary teams directed by Profs. Politis and Aarsland, who are world leaders in neuroimaging and neurodegenerative diseases.

Two representative publications from supervisors:

M. Politis, K. Wu, C. Loane, N.P. Quinn, D.J Brooks, S. Rehncrona, A. Bjorklund, O. Lindvall, P. Piccini, Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci. Trans. Med.* 2, 38ra46 (2010)

Berezcki E, Bogstedt A, Höglund K, Tsitsi P, Brodin L, Ballard C, Svenningsson P, Aarsland D. Synaptic proteins in CSF relate to Parkinson's disease stage markers. *NPJ Parkinsons Dis.* 2017 Feb 8;3:7.

## 28.2 Improving treatment outcomes for sexual minority women with depression or anxiety

Co-Supervisor 1A: Dr Katharine Rimes

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Psychological Medicine and Integrated Care CAG

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Co-Supervisor 1B: Dr Stephani Hatch

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Project description:

Sexual minority women have elevated rates of mental health problems such as depression and anxiety relative to heterosexual women. Furthermore, even adjusting for baseline levels of symptoms severity and other potential confounders, we found that lesbian and bisexual women show a smaller reduction in depression and anxiety after receiving psychological therapy in Improving Access to Psychological Therapy (IAPT) services than heterosexual women (Rimes et al., in press). This PhD will investigate reasons for this inequality in treatment outcomes and will apply these findings to develop a cognitive behavioural therapy intervention specifically for sexual minority women. The primary supervisor has recently developed a group intervention for sexual minority individuals in Southwark IAPT but this group is mainly attended by men. The therapy needs of sexual minority women require specific attention given the evidence that these women (but not sexual minority men) have poorer treatment outcomes in routine clinical care.

Objectives

Year 1: Qualitative study investigating sexual minority women's experiences of IAPT services and their treatment preferences for a new intervention.

Year 2: Quantitative study of IAPT data using the Clinical Record Interactive Search (CRIS) to investigate predictors of therapy outcome in sexual minority women.

Year 3: Applying the findings from the earlier studies, feasibility study of a new psychological intervention for sexual minority women with depression or anxiety in IAPT services

Skills training:

- Qualitative methodology
- Quantitative methodology
- Psychological intervention development skills. If this is a group intervention the student will help deliver the intervention

Two representative publications from supervisors:

Rimes, K. A., Broadbent, M. T. M., Holden, R., Rahman, Q., Hambrook, D., Hatch, S. L., & Wingrove, J. (In press). Comparison of treatment outcomes between lesbian, gay, bisexual and heterosexual individuals receiving a primary care psychological intervention. *Behavioural and Cognitive Psychotherapy*. Available on request ([Katharine.Rimes@kcl.ac.uk](mailto:Katharine.Rimes@kcl.ac.uk))

Woodhead, C., Gazard, B., Hotopf, M., Rahman, Q., Rimes, K. A., & Hatch, S. L. (2016). Mental health among UK inner city non-heterosexuals: the role of risk factors, protective factors and place. *Epidemiology And Psychiatric Sciences*, 25, 450-461. DOI: 10.1017/S2045796015000645

## 29.2 Multi-modal objective measurement of mental health problems in autism.

Co-Supervisor 1A: Prof Emily Simonoff

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Co-Supervisor 1B: Prof Andrew Pickles

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### Project Description:

Three quarters of people with autism have co-existing mental health problems which have a major impact on their outcomes and quality of life. However, they are difficult to detect because of autism-specific problems with communication and lack of 'emotional literacy' – the ability to detect and describe one's own emotions. At present there are no validated objective measures of mental health in people with autism. This project would provide one of the first studies to identify anxiety and ADHD among children with autism through convergent multi-modal measurement, including both traditional and novel methodologies.

This project will start with a literature review and will then focus on data already collected from a community cohort of adolescents with autism (QUEST) who are well-characterized for both autism and additional mental health problems and in whom psychophysiological and facial emotion data are available. You will become familiar with the cohort as well as the experimental constructs and the emotion recognition software Affectiva. You will study a range of statistical techniques for analyzing multi-modal and times-series data in relation to behavioural characteristics. You will have the opportunity to validate the findings from the QUEST study in another cohort of younger children with autism (ASRAR) and to pilot their use in clinical practice, as a potential diagnostic biomarker.

Throughout the project, you will have the opportunity to publish and present at international conferences. For students with a clinical interest, there will be opportunities to learn clinically relevant skills.

Two representative publications from supervisors:

Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2008;47(8):921-9.

Hollocks MJ, Pickles A, Howlin P, Simonoff E. Dual cognitive and biological correlates of anxiety in autism spectrum disorders. *Journal of Autism & Developmental Disorders*. 2016;46(10):3295-007.

### 30.2 Towards personalised medicine for antidepressant drugs: a machine learning approach.

Co-Supervisor 1A: Dr Daniel Stahl

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Co-Supervisor 1B: Dr Raquel Iniesta

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Project description:

Scientific basis: The efficacy of antidepressant drugs varies by individual. Clinicians are unable to predict who will respond to what treatment. Findings suggest that response to antidepressant drugs is a complex trait, driven by multiple components in co-action or interaction. The aim of this project is to develop new Multivariate Machine Learning methods based on Topological Data Analysis and the mapper algorithm that will combine genetic with demographic and clinical variables to improve prediction of antidepressant outcome at the individual level. Algorithms will be applied to 3899 subjects from different international datasets. This project combines (a) the development of cutting-edge methods for treatment personalization, using TDA as a novelty, plus (b) the practical application of the developed methods to a very relevant area, with a real potential to improve patients' health.

Objectives by year: Year 1: Develop and implement free standing code of a method for predictors' selection based on the mapper TDA algorithm. Year 2: Develop and implement free standing code of a predictive algorithm based on the combination of a TDA method for predictors' selection and a machine learning classifier. Year 3: Validate the predictive algorithm internally and externally, in existing datasets. Year 4: Apply the developed algorithms to assess the role that clinical and genetic variation plays in response to antidepressant treatment in existing studies.

Training: This PhD studentship will include an individualised training plan in methodology required for personalised medicine, including: statistical genetics, machine learning, longitudinal analysis of multivariate phenotypes and predictive modelling.

Two representative publications from supervisors:

Machine learning, statistical learning and the future of biological research in psychiatry. Iniesta R, Stahl D, McGuffin P. In: *Psychol Med*. 2016 Sep;46(12):2455-65. doi: 10.1017/S0033291716001367. Epub 2016 Jul 13.

Combining clinical variables to optimize prediction of antidepressant treatment outcomes. Iniesta R, Malki K, Maier W, Rietschel A, Mors N, Hauser M, Henigsberg B, Dernovsek M, Souery D, Stahl D, Dobson R, Aitchison KJ, Farmer A, Lewis CM, McGuffin P, Uher R. J In: *Psychiatr Res*. 2016 Jul;244:94-102. doi: 10.1016/j.jpsychires.2016.03.016. Epub 2016 Apr 1.

### 31.2 Investigating the potential of 5HT<sub>7</sub> antagonists for the treatment for cognitive impairment in bipolar disorder: a proof of principle neuroimaging project.

Co-Supervisor 1A: Prof Allan Young

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Co-Supervisor 1B: Dr Paul Stokes

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#### Project description:

**Scientific basis:** Bipolar disorder is a serious mental health problem which affects 1.2 million people in the UK. Around 60% of people with bipolar disorder experience cognitive impairment which greatly impacts on work and relationships. Currently there are no effective treatments for cognitive impairment in bipolar disorder, however 5HT<sub>7</sub> receptor antagonism is a promising new treatment mechanism.

**Translational relevance:** This innovative MRC funded study, in collaboration with Janssen Pharmaceuticals, will advance our understanding of the potential of 5HT<sub>7</sub> antagonists for the treatment of cognitive impairment in bipolar disorder by investigating the effect of 5HT<sub>7</sub> antagonism on brain activity and cognitive performance.

**Research methods:** This project will provide excellent skills in the use of pharmacological functional MRI (fMRI) to examine the effects of the 5HT<sub>7</sub> receptor antagonist, JNJ-18038683, and placebo on brain activity and cognitive performance in people with bipolar disorder and healthy controls. Drug related effects on brain function will be assessed using state of the art neuroimaging analysis infrastructure available at the Centre for Neuroimaging Sciences.

**Training:** Training will be provided in pharmacological neuroimaging, participant recruitment, cognitive and mood assessment, fMRI imaging and analysis.

#### Project objectives:

**Year 1:** Understand fMRI methodology, systematically review previous neuroimaging studies, and gain expertise in recruiting and assessing participants.

**Year 2:** Develop expertise in MRI imaging, working with industry partners, and experience in the analysis of neuroimaging and behavioural data.

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

Two representative publications from supervisors:

Thompson JM, Gallagher P, Hughes JH, Watson S, Gray JM, Ferrier IN, Young AH. Neurocognitive impairment in euthymic patients with bipolar affective disorder. *British Journal of Psychiatry*. 2005 Jan;186:32-40.

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

### 33.2 A randomized controlled trial of RESIST a computerized training intervention for binge eating: testing the food addiction model.

Co-Supervisor 1A: Dr Grainne McLoughlin

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Co-Supervisor 1B: Prof Janet Treasure

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#### Project description:

Weight and eating disorders are major problems of public health. Current treatments are disappointing with a recovery rate of only 40%. We have updated the theoretical model explaining binge eating with the new conceptualisation of food addiction. Proof of concept studies using computerised training (RESponse Inhibition Training to food, RESIST) to inhibit bingeing have been positive. The latest iteration of RESIST is personalized with an app for easy delivery.

This project will use a double blind randomised trial to examine efficacy, moderators and mediators, of RESIST in people with BN and BED. We will examine the neuroplasticity of food addiction with EEG. EEG has excellent temporal resolution and can examine fast-occurring changes in the brain without a behavioural response (during inhibition trials). Training will be provided in: 1) Skills of systematic review and meta-analysis; 2) Design, delivery and analysis of randomised controlled clinical trials; 3) Skills in neurocognitive assessments and analysis (including EEG); 4) Skills in data analysis using MATLAB and R 5) The synthesis of the above in order to optimise and personalise treatment interventions.

#### Objectives:

Year 1: Systematic review of food addiction in BN, BED. Updated theoretical model of BN and BED. Completion of governance issues for RCT. (Ethics for intervention completed, predictors to be added). Training in assessment of predictors using EEG.

Year 2: Completion of recruitment by 18 m. Completion of follow-up: 24m

Year 3: Data cleaning and analysis. Preparation of reports.

Year 4: Submission of papers and PhD thesis. Preparation of post-doctoral fellowship.

#### Two representative publications from supervisors:

Turton, R., Chami, R. & Treasure, J. (2017). Emotional Eating, Binge Eating and Animal Models of Binge-Type Eating Disorders. *Curr Obes Rep*, doi:10.1007/s13679-017-0265-8.

McLoughlin,GM, Makeig,S, Tsuang, M (2014).American Journal Medical Genetics B Neuropsychiatric Genetics.



### 34.2 Dissecting the role of neuronal local protein synthesis and synapse formation as mechanisms for the antidepressant effect of ketamine.

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Co-Supervisor 1B: Dr Deepak Srivastava  
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#### Project description:

Ketamine is an N-methyl-d-aspartate receptor antagonist that rapidly improves symptoms in treatment-resistant depression. However, the neural mechanism is unknown - hence no translational biomarkers exist to quantify its action. Converging lines of evidence suggest depression is associated with deficits in dendritic spines and synapse loss in stress-sensitive brain regions, including the prefrontal cortex, hippocampus and amygdala. This is paralleled by a decrease in local protein synthesis, which is an essential cellular mechanism in the formation of dendritic spines and ultimately synapses synaptic plasticity. We hypothesise therefore that ketamine, downstream of spontaneous increases in glutamate transmission, increases neuronal local protein synthesis, leading to recovery of dendritic spines and synapses and ultimately remission of depressive-like behaviours and symptoms. This project will address this knowledge gap by combining complementary *in vitro* and *in vivo* approaches. Specifically, the student will investigate whether a single dose of ketamine, but not fluoxetine (a slow acting antidepressant) increases (i) glutamate signalling, (ii) local protein synthesis measured by puromycin incorporation (SuNSET), (iii) relevant biochemical signalling pathways (mTOR, ERK) and (iv) synapse formation, using primary rat cortical neurons. We will then extend these *in vitro* observations into a relevant *in vivo* rodent model (chronic social defeat stress in mice) to link changes in protein synthesis and synapse number to behavioural read-outs relevant to depression. Importantly, protein synthesis and synapse density may be quantified *in vivo* using  $^{11}\text{C}$ -leucine and  $^{11}\text{C}$ -SV2A positron emission tomography (PET). This offers the potential to ultimately investigate our proposed mechanism for ketamine's antidepressant effects in humans.

#### Two representative publications from supervisors:

Richetto J, Chesters R, Cattaneo A, Labouesse MA, Gutierrez AMC, Wood TC, Luoni A, Meyer U, Riva MA, Vernon AC. Genome-Wide Transcriptional Profiling and Structural Magnetic Resonance Imaging in the Maternal Immune Activation Model of Neurodevelopmental Disorders. *Cereb Cortex*. 2017. doi: 10.1093/cercor/bhw320.

Deans, PJM, Raval, P, Sellers, KJ, Gatford, NJF, Halai, S, Duarte, RRR, Shum, C, Warre-Cornish, K, Kaplun, VE, Cocks, G, Hill, M, Bray, NJ, Price, J & Srivastava, DP "Psychosis risk candidate ZNF804A localizes to synapses and regulates neurite formation and dendritic spine structure" *Biological Psychiatry* 2017 July, 82(1):49-61.

## 36.2 Bioengineered Cortical Neuronal Network (BioCoNNet): a stem-cell derived bioengineered platform to recreate the human cerebral cortex in vitro

Co-Supervisor 1A: Prof Lucy Di Silvio

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Co-Supervisor 1B: Dr Andrea Serio

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Co-Supervisor 1B: Dr Ciro Chiappini

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For translational projects:

Collaborating Clinician: Dr. Rickie Patani

Research School/Division or CAG: Francis Crick Institute – Institute of Neurology (UCL)

Project description:

**BioCoNNet** is a new bioengineered platform that recreates the complexity of human cortical circuits in vitro using stem cell derived neurons. It uses this neuronal network to understand how connections in cortex are established and maintained, and how they are lost in Dementias. Using the expertise of the Serio (stem cell modelling, neuroengineering, imaging) and Chiappini Lab (nanotechnology, microfabrication, cell-material interface) we will create a complex array of human cortical neurons of different subtypes. This array will form a functional circuit with defined architecture, inspired by evolution's design in the human cortex, which is the centre of human higher cognitive functions and the target of devastating diseases.

This platform advances *in vitro* neuroscience by modelling neurodevelopment and neurodegeneration for first time not just on cells with the right identity, but on a functional network with the right architecture.

We will combine microfabrication (soft-lithography, micro-contact printing, photopatterning) and stem cells (directed differentiation, neurodevelopment-in-a-dish) to build a complex-yet-controlled neuronal network. We will then characterize the network functionality using high-content live fluorescent imaging with advanced molecular imaging tools (passive and active optogenetic tools, stochastic multi-coloured fluorescent labelling and optical pulse chase labelling tools).

Project outline: microfabrication, functionalization and assembly of the platform, and optimisation of culture/plating (Year1), functional characterisation of BioCoNNet arrays using live imaging, validation of imaging tools (Year2), disease modelling using patient derived neurons (Year3).

This platform will recapitulate human cortical networks in a dish and establish new functional models of cortical connectivity for the study of neurodegeneration and neurodevelopmental disorders.

Two representative publications from supervisors:

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

Chiappini C. *et al.* "Biodegradable silicon nanoneedles delivering nucleic acids intracellularly induce localized in vivo neovascularization" *Nat. Materials* (2015)

## 38.2 Role of long noncoding RNAs in neural differentiation

Co-supervisor 1: Eugene Makeyev

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Co-Supervisor 2: Professor Benedikt Berninger

School/Division or CAG: Psychology & Neuroscience

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### Project Description:

Cell differentiation relies on extensive changes in gene expression affecting virtually all categories of transcripts. Mammalian genomes encode thousands of so-called long noncoding RNAs (lncRNAs) that lack functional open reading frames. Although lncRNAs have attracted considerable interest the last few years, their roles in acquisition and maintenance of distinct cellular identities remains poorly understood. We have recently identified a new class lncRNAs enriched in short tandem repeats (STRs), multiple iterations of 2-12 nucleotide-long “words”. Student joining our team will elucidate functional significance of STR-lncRNAs in cell differentiation by addressing the following questions.

Rotation-Year 1: What STR-lncRNAs are expressed in stem cells and how their expression changes during neural differentiation? The student will analyse corresponding next-generation RNA-sequencing (RNA-seq) datasets using an established computational pipeline and will validate the most promising predictions using RT-qPCR and fluorescence in situ hybridization.

Year 2: How do newly identified STR-lncRNAs contribute to neural differentiation? STR-lncRNAs will be over-expressed or knocked down/out and the effects of these treatments on neuronal and glial differentiation will be assessed using appropriate in vitro and in vivo assays.

Year 3: What molecular mechanisms regulate differentiation-specific changes of STR-lncRNAs? This will involve bioinformatics identification of possible transcriptional and post-transcriptional regulators of STR-lncRNA abundance and validation of the predicted candidates using transgenic and CRISP-Cas9 genome editing approaches.

Taken together, this program will allow the student to acquire multidisciplinary skills in bioinformatics, gene expression analysis, high-end microscopy, work with stem cells, and various cell differentiation and trans-differentiation techniques.

### One representative publication from each co-supervisor:

Yap, K., Mukhina, S., Zhang, G., Tan, J. S. C., Ong, H. S., and Makeyev, E.V. A short tandem repeat-enriched RNA assembles a nuclear compartment to control alternative splicing and promote cell survival. 11 Oct 2018, *Mol. Cell*.

Tiwari, N., Pataskar, A., Peron, S., Thakurela, S., Sahu, S. K., Figueres-Onate, M., Marichal, N., Lopez-Mascaraque, L., Tiwari, V. K., and Berninger, B. Stage-specific transcription factors drive astroglialogenesis by remodeling gene regulatory landscapes. 4 Oct 2018, *Cell Stem Cell*.