UCL MRC DTP BIRKBECK

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Neuroscience and Mental Health

Project Booklet 2024-25

Professor Rick Adams

Position: Future Leaders Fellow
Department: Institute of Cognitive Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/30181-rick-adams
Email contact: rick.adams@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

I am a psychiatrist and neuroscientist interested in using computational methods to understand the pathological processes underlying brain imaging and/or behavioural changes in people suffering from psychosis (schizophrenia, bipolar disorder, etc). To do this I use biophysical models of how pyramidal cells and interneurons generate imaging data, or cognitive models of how the brain solves various tasks.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Rotation project: The student will analyse a large resting state fMRI dataset consisting of people with psychosis and controls. All preprocessing is completed and analysis code written, so analysis can start immediately. The student will use dynamic causal modelling (DCM) to look at novel neurobiologically-defined subgroups ('biotypes' see Clementz et al, 2016, Am J Psych) within the psychosis group, in terms of cortical excitability and connectivity. Familiarity with Matlab would help but strong computational skills aren't essential. PhD project: The student will develop a cognitive task that will explore some key cognitive computational domains of schizophrenia. Possible questions include i) whether people with a diagnosis of schizophrenia (PScz) show abnormalities of causal inference, ii) whether PScz demonstrate effects of poor access to a 'world-model' in inference, such as impaired likelihood normalisation during Bayesian belief updating, and overreliance on 'egocentric' maps, e.g. during navigation. For the PhD project, we would first seek to demonstrate the behavioural effects of interest in controls, then establish behavioural differences in PScz, model these using computational models, and finally (funding and time-permitting) conduct model-based imaging using MEG or fMRI to establish the brain correlates of the computational deficits.

Relevant publications 1

https://pubmed.ncbi.nlm.nih.gov/26651391/

Relevant publications 2

https://pubmed.ncbi.nlm.nih.gov/34598786/

Dr Athena Akrami

Position: Senior Research Fellow
Department: Sainsbury Wellcome Centre
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/66938-athena-akrami
Email contact: athena.akrami@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

In our lab, we employ a synergistic combination of theory and experiment to study the fundamental principles by which the nervous system computes, represents and integrates various forms of sensory memories and priors in the process of learning and inferring meaningful statistical patterns and abstract relations in the environment. We use high-throughput training to combine sophisticated, well-controlled and quantifiable behavioural paradigms with powerful tools to monitor and manipulate neural circuits

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We have two well-established cross-species paradigms to study statistical learning in feedback-based and non-feedback-based settings. You can choose one of the following 3 rotation projects: 1. Chronic recording from mPFC in head-fixed mice, trained on an auditory task, while tracking their pupil responses as sound statistics are implicitly manipulated. We have shown the causal involvement of hippocampus in fast learning of abstract sound sequences. You will investigate the role of prefrontal cortex by performing recordings (and perturbations) in mPFC. 2. Chronic recordings in a novel working memory paradigm in head-fixed mice, where the goal is to investigate the dynamics during the working memory, when sound to category abstraction and integration with the prior happens. We are currently collecting large-scale optogenetic recording (using fast galvo-scanning over the dorsal surface). 3. Statistical learning in young vs adult mice. You'll adapt the same behavioural paradigms in adult head-fixed mice to p30 mice, and compare the learning curve and capacities. This is a project in collaboration with Linda Wilbrecht at UC Berkley, as she studies learning in adolescents. Eventually we'd like to probe the role of Anterior Cingulate Cortex and Hippocampus in statistical learning across different ages. Depending on whether you already have your PIL or not, you can do relevant surgeries, or work with already implanted animals.

Relevant publications 1

Akrami, Athena, Charles D. Kopec, Mathew E. Diamond, and Carlos D. Brody. "Posterior parietal cortex represents sensory history and mediates its effects on behaviour." Nature 554, no. 7692 (2018): 368-372.

Relevant publications 2

Pedrosa, Victor, Elena Menichini, Quentin Pajot-Moric, Peter Vincent, Liang Zhou, Lillianne Teachen, Peter Latham, and Athena Akrami. "Humans, rats and mice show species-specific adaptations to sensory statistics in categorisation behaviour." bioRxiv (2023): 2023-01.

Dr Andre Altmann

Position: Associate Professor
Department: Medical Physics and Biomedical Engineering
University UCL
Faculty: Engineering Sciences
Profile: https://profiles.ucl.ac.uk/52653-andre-altmann
Email contact: a.altmann@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Normative modeling is a machine learning approach that describes how a measurement or biomarker behaves in a healthy group of people. For instance, in dementia research normative models describe the volume of the hippocampus across age, which can then be used to detect abnormal shrinkage of the hippocampus.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Recently, using data from the UK Biobank, our team developed normative models for hippocampal volume that also include the person's genetic information to gain extra precision (see Reference 1). In follow-up work we have shown that this translates to better forecasting of disease progression and disease related symptoms in Alzheimer's disease in the ADNI database. During the rotation project you will gain hands-on experience on using machine learning to build normative models for a different brain region, e.g., the amygdala, and test whether similar gains of genetically informed models can be achieved for disease progression prediction in Alzheimer's disease. With the focus on the hippocampus, the current approach is limited to improving the detection of Alzheimer's dementia. Further extension during the PhD are (i) to build genetically-enhanced normative models for subcortical structures and cortical regions, (ii) to integrate genetic information into multi-modal normative models based on deep-learning (such as our variational autoencoder approach; Reference 2) and (iii) to integrate these genetically personalized abnormality scores into disease progression models and disease subtyping models, such as SuStaIn (https://doi.org/10.1038/s41467-018-05892-0). Finally, clinical improvement will be assessed on a range of external datasets featuring participants at different disease stages: ADNI (Alzheimer's disease spectrum), EPAD (people at risk of developing Alzheimer's disease) or Insight46 (people participating in a population cohort). Furthermore, extension to other diseases such as Parkinson's disease or Multiple sclerosis will be explored.

Relevant publications 1

Janahi, Mohammed, et al. "Nomograms of human hippocampal volume shifted by polygenic scores." Elife 11 (2022): e78232.

Relevant publications 2

Lawry Aguila, Ana, James Chapman, and Andre Altmann. "Multi-modal variational autoencoders for normative modelling across multiple imaging modalities." International Conference on Medical Image Computing and Computer-Assisted Intervention. Cham: Springer Nature Switzerland, 2023.

Dr Kirill Aristovich

Position: Associate Professor
Department: Medical Physics and Biomedical Engineering
University UCL
Faculty: Engineering Sciences
Profile: https://profiles.ucl.ac.uk/35960-kirill-aristovich
Email contact: k.aristovich@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

The work of our group at UCL has been to pioneer EIT for imaging brain function. It could be used to image in acute stroke or epileptic seizures, when its portability and low cost would give it unique practical advantages over existing methods such as fMRI.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Epilepsy affects approximately 400,000 people in the UK, and 30% of these cases are refractory to anticonvulsant medication. Many individuals with refractory epilepsies can benefit from surgical resection of epileptogenic tissue. However, difficulties in the precise localisation of seizure foci have limited the number of patients eligible for surgery and lowered its effectiveness, evidenced by seizure recurrence in over half of these individuals. The project aims to improve the localisation accuracy of seizure foci during presurgical monitoring in humans by imaging impedance changes in cerebral tissue during seizures using Electrical Impedance Tomography (EIT). This method involves injecting safe, insensible currents into the brain through intracranial depth electrodes previously implanted for conventional EEG recordings and reconstructing the tissue impedance from the measured voltages. This allows imaging of neuronal depolarisation and cell swelling during seizures, which can be used to precisely map the seizure onset and progression. There is no interference with standard EEG monitoring equipment, which can proceed in parallel. As such, EIT can provide additional diagnostic data using pre-implanted electrodes and without altering clinical workflows. This has the potential to increase localisation accuracy of the epileptogenic zone and ultimately improve surgical outcome. The project will focus on the initial assessment of the accuracy of EIT data, and will be developed into a full PhD project where the improved method of EIT-driven deep brain stimulation will be employed as a therapy.

Relevant publications 1

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8204270/

Relevant publications 2

https://pubmed.ncbi.nlm.nih.gov/29499314/

Professor Folkert Asselbergs

Position: Professorial Research Associate
Department: Institute of Health Informatics
University UCL
Faculty: Population and Health Sciences
Profile: https://profiles.ucl.ac.uk/36355-folkert-asselbergs
Email contact: f.asselbergs@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

The translational Health Data Science (THDS) group from the Institute of Health Informatics in collaboration with Institute of Cardiovascular Science use existing routine electronic healthcare data enriched with omics and imaging data to unravel underlying disease mechanisms for drug target validation and to improve early risk stratification.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Traditional cardiovascular risk factors such as hypertension, hypercholesterolemia, diabetes, and physical inactivity also associate with early cognitive decline and dementias. It follows that people with established cardiovascular disease, such as coronary heart disease or atrial fibrillation are disproportionately affected by neurodegenerative diseases such as Alzheimer's disease. To further our understanding of this "heart-brain" axis, the rotational project will focus on the analysis of 70K+ participants imaging data of both brain and heart. Specifically, the student will leverage modern artificial intelligence tools, to develop a conditional variational autoencoder (VAE) to derive shared embeddings representing heart-brain imaging biomarkers. The VAE will account (i.e., through conditioning) on difference in sex, age, self-reported ethnicity, genetic ancestry, as well as on APOE status (the canonical Alzheimer's disease genetic mutation). These heart-brain imaging biomarkers will be used to identify and externally validate participants clusters. The clusters will be empirically validated by identifying associations with time to the development of CVD, early cognitive decline and dementia. This project will form the basis for a possible PhD where the student will develop their expertise in machine learning, genome-wide association studies, and causal inference methods to 1) identify people at risk of both heart and brain disease, 2) identify people with an established genomic risk profile, in need of early preventative intervention, and 3) identify potential novel interventional targets, informing wet-lab experimentation.

Relevant publications 1

Schmidt AF, Bourfiss M, Alasiri A, Puyol-Anton E, Chopade S, van Vugt M, van der Laan SW, Gross C, Clarkson C, Henry A, Lumbers TR, van der Harst P, Franceschini N, Bis JC, Velthuis BK, Te Riele ASJM, Hingorani AD, Ruijsink B, Asselbergs FW, van Setten J, Finan C. Druggable proteins influencing cardiac structure and function: Implications for heart failure therapies and cancer cardiotoxicity. Sci Adv. 2023 Apr 28;9(17):eadd4984. doi: 10.1126/sciadv.add4984. Epub 2023 Apr 26. PMID: 37126556; PMCID: PMC10132758.

Relevant publications 2

Dziopa K, Chaturvedi N, Asselbergs FW, Schmidt AF. Identifying and ranking novel independent features for cardiovascular disease prediction in people with type 2 diabetes. medRxiv [Preprint]. 2023 Oct 24:2023.10.23.23297398. doi: 10.1101/2023.10.23.23297398. PMID: 37961704; PMCID: PMC10635178.

Professor David Attwell

Position: Jodrell Professor of Physiology
Department: Neuroscience, Physiology & Pharmacology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/4656-david-attwell
Email contact: d.attwell@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We are interested in how the properties of glial cells and blood vessels contribute to the development of dementia, for example in Alzheimer's disease (AD). We study this using 2-photon imaging and patch-clamping techniques.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Rotation project option 1: We have shown that pericyte-mediated capillary constriction reduces blood flow early in AD. We are now developing means to prevent this, including by preventing [Ca2+] rises in pericytes. You will learn 2-photon imaging in vivo and in brain slices, and apply it to test whether capillary constriction is prevented by pharmacological manipulations in transgenic mice. Extension to full PhD You will define the mechanisms by which capillary constriction occurs early in AD, and how the pharmacological manipulations that block it work. Rotation project option 2: We have previously shown that ion channels in microglia play a key tole in regulating their surveillance and immune cell properties. Our preliminary data also suggest they regulate brain blood flow. You will characterise how microglia interact with blood vessels in brain slices and in vivo. Extension to full PhD Using mice with microglia lacking particular ion channels or other molecules, you will use patch-clamping and imaging to define how they control brain blood flow.

Relevant publications 1

Korte, N....Attwell, D. Tammaro, P. (2022) The Ca2+-gated channel TMEM16A amplifies capillary pericyte contraction and reduces cerebral blood flow after ischemia. J. Clin. Invest. 132, e154118.

Relevant publications 2

Nortley, R., ... Attwell, D. (2019) Amyloid b oligomers constrict human capillaries in Alzheimer's disease via signaling to pericytes. Science 365, eaav9518.

Professor Giovanni Baranello

Position: Professor of Paediatric Neuromuscular Disorders
Department: Institute of Child Health
University UCL
Faculty: Population and Health Sciences
Profile: https://profiles.ucl.ac.uk/70972-giovanni-baranello
Email contact: g.baranello@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

This project aims to investigate the development expression of the SMN protein, primarily in the brain of two mouse models of Spinal muscular atrophy (SMA), a rare genetic neuromuscular disorder. We are investigating how two different treatments (administrated prenatally and/or postnatally) can rescue the phenotype seen in untreated diseased mice.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

SMA type 1 (SMA1) is the most common and severe form of SMA with symptoms onset within the first months of life which include breathing difficulties and movement problems. The extended survival of treated SMA1 children is enabling us to appreciate neurodevelopmental phenotypes that were not seen before, as untreated patients did not generally survive beyond the age of two. We are now observing that a high proportion of treated SMA1 patients exhibit developmental delay and speech-communication difficulties. In our lab we have two SMA transgenic mouse models which we treat with two of the available therapies (a small molecule and an antisense drug). Our aim is to investigate the expression of SMN transcripts and protein levels in brain tissue before and after treatment, comparing wildtype and SMA mice, as well as investigating how these levels change with age. The project involves several different techniques such as mouse genotyping using PCR and gel electrophoresis, mouse tissue dissections (brain, spinal cord, muscle) from treated and untreated mice at different ages and protein and RNA extraction from these tissues. It also involves western blots and RTqPCR to measure protein and transcript levels, as well as immunohistochemistry to study markers of neuronal growth in brain tissue. Taking this further into a PhD, behavioural studies will be carried out to investigate social interactions of untreated versus treated mice as well as investigating the deletion of SMN gene in specific cell types using a Cre-Lox system in mice.

Relevant publications 1

Ramos DM, d'Ydewalle C, Gabbeta V, Dakka A, Klein SK, Norris DA, Matson J, Taylor SJ, Zaworski PG, Prior TW, Snyder PJ, Valdivia D, Hatem CL, Waters I, Gupte N, Swoboda KJ, Rigo F, Bennett CF, Naryshkin N, Paushkin S, Crawford TO, Sumner CJ. Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. J Clin Invest. 2019 Nov 1;129(11):4817-4831. doi: 10.1172/JCI124120. PMID: 31589162; PMCID: PMC6819103.

Relevant publications 2

Wishart TM, Huang JP, Murray LM, Lamont DJ, Mutsaers CA, Ross J, Geldsetzer P, Ansorge O, Talbot K, Parson SH, Gillingwater TH. SMN deficiency disrupts brain development in a mouse model of severe spinal muscular atrophy. Hum Mol Genet. 2010 Nov 1;19(21):4216-28. doi: 10.1093/hmg/ddq340. Epub 2010 Aug 12. PMID: 20705736; PMCID: PMC2951867.

Dr Julien Baruteau

Position: Principal Clinical Research Fellow
Department: Great Ormond Street Institute of Child Health
University UCL
Faculty: Population and Health Sciences
Profile: https://profiles.ucl.ac.uk/42299-julien-baruteau
Email contact: j.baruteau@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

In the lab, we use rare monogenic diseases to decipher the pathophysiology of common diseases. We have expertise in arginine/nitric oxide metabolism, their role in neurotransmitter imbalance and consequences on mental health and depression. We aim to study this on 3D-iPSC-derived assembloids and design messenger RNA therapy as a cure.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Major depression and anxiety disorders (MDAD) are leading public health burden with limited therapies and reliable preclinical models. Arginine metabolites (nitric oxide, polyamines) play key-role in neurotransmission and brain energy homeostasis. Why dysregulated arginine metabolism is observed in mental health diseases is unclear. Here, we will use the inherited deficiency of argininosuccinate lyase, the only enzyme synthesising arginine, as a model to interrogate the effect of arginine deprivation on chronic stress and synaptic plasticity. Patients with inherited argininosuccinate lyase deficiency (ASLD) present with psychiatric symptoms (AD, apathy mimicking depression, schizophrenia). ASLD mouse models show deficient cerebral GABA, the main inhibitory neurotransmitter and MDAD feature. GABA is both neuro- and glio-transmitter. This project investigates the hypothesis that psychiatric symptoms in ASLD are caused by deficient astrocytic arginine-GABA pathway altering neuron-astrocyte coupling. Modelling a rare inherited disease will help unravel MDAD pathophysiology. Rotation project: Using argininosuccinate lyase deficient (ASLD) induced pluripotent stem cell (iPSC)-derived astrocytes, you will study the alteration of gamma-aminobutyric acid (GABA) metabolism on both arginine- and glutamate-GABA production pathways respectively with metabolomics, transcriptomics and metabolic fluxes via stable isotopes. Extension to full PhD: You will assess astrocytic GABA metabolism with a novel and specific radiotracer by positron emission tomography, neuronal function and synaptic transmission in assembloid slices with patch clamping and determine response to messenger RNA therapy.

Relevant publications 1

Gurung S, Timmermand OV, Perocheau D, Gil-Martinez AL, Minnion M, Touramanidou L, Fang S, Messina M, Khalil Y, Spiewak J, Barber AR, Edwards RS, Pinto PL, Finn PF, Cavedon A, Siddiqui S, Rice L, Martini PGV, Ridout D, Heywood W, Hargreaves I, Heales S, Mills PB, Waddington SN, Gissen P, Eaton S, Ryten M, Feelisch M, Frassetto A, Witney TH, Baruteau J. mRNA therapy corrects defective glutathione metabolism and restores ureagenesis in preclinical argininosuccinic aciduria. Sci Transl Med. 2024;16(729):eadh1334. PMID: 38198573

Relevant publications 2

Qiu Y, O'Neill N, Maffei B, Zourray C, Almacellas-Barbanoj A, Carpenter JC, Jones SP, Leite M, Turner TJ, Moreira FC, Snowball A, Shekh-Ahmad T, Magloire V, Barral S, Kurian MA, Walker MC, Schorge S, Kullmann DM, Lignani G. On-demand cell-autonomous gene therapy for brain circuit disorders. Science. 2022;378(6619):523-532. PMID: 36378958

Professor Daniel Bendor

Position: Professor of Behavioural Neuroscience
Department: Experimental Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/40594-daniel-bendor
Email contact: d.bendor@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

During sleep, memories are reactivated by the brain to aid in their consolidation and long-term storage. Over the last decade, a method of selectively enhancing memories by directed reactivation (targeted memory reactivation or TMR), has been developed and used successfully in humans to improve learning. While simple in its design (pairing a sensory cue with a task, and re-presenting this cue during sleep), we do not understand how it is able to selectively enhance memories. We will develop a TMR task in rodents, and causally interrogate the neural pathways hypothesized to be required for the phenomenon.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The goal of the PhD project is to trace how the olfactory cue during sleep travels from the olfactory bulb to the hippocampus, and leads to more reactivation of a memory. First, we will use neuropixel 2.0 probes to chronically record hippocampal reactivations (replay) during the task, the measure the hypothesized enhancement in memory reactivation related to the presented odour (associated with that memory). Next, we will use a unique transgenic, circuit-tracing approach: optogenetically inducing Targeted Memory reactivation in a transgenic mouse line (expressing ChR2 in a single olfactory receptor), while using an inhibitory opsin (JAWS) to selectively suppress direct olfactory projections to memory circuits. Using this approach we can precisely test each possible neural circuit hypothesized to be responsible for driving memory selection for reactivation. This project will involve electrophysiology, optogenetics, behaviour, and computational methods.

Relevant publications 1

Lewis, P. A., & Bendor, D. (2019). How targeted memory reactivation promotes the selective strengthening of memories in sleep. Current Biology, 29(18), R906-R912.

Relevant publications 2

Huelin Gorriz, M., Takigawa, M., & Bendor, D. (2023). The role of experience in prioritizing hippocampal replay. Nature Communications, 14(1), 8157.

Professor Sven Bestmann

Position: Professor Clinical and Movement Neurosciences
Department: Clinical and Movement Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/11657-sven-bestmann
Email contact: s.bestmann@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We don't know well how the spinal cord and brain interact in humans to produce healthy and pathological movement. The project will leverage recent advances in neuroimaging and neurophysiology to study corticospinal interactions and the neural dynamics of brain and spinal circuits during movement, in health and movement disorders.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The spinal cord and its interactions with the brain are difficult structures of the central nervous system (CNS) to study in humans. Consequently, much of our knowledge about the neurophysiology of the spinal cord comes from animal models. Because the brain and spinal cord interact heavily, damage to one affects the other, but it has been very difficult to study these effects in humans. At UCL, we have recently developed a novel technology for neuroimaging that can be worn during natural movement (Boto, Nature 2018). The Optically Pumped Magnetoencephalography (OPMEG) brain scanner uses sensors that can be placed within a few millimetres of the skin surface. Doing so provides customizable sensor arrays that can be positioned over the entire head and spinal cord. This enables neurophysiological recordings of these structures at the same time (Mardell, 2024; Spedden, 2024). Advances in high-density electromyography (hdEMG) provide a complementary approach by identifying the dynamics of individual motoneurons in the spinal cord during behaviour. In combination, we're now in an unprecedented position for studying spinal cord neurophysiology in health and disease. Students will be trained in the recording and analysis of OPMEG/hdEMG, with experience in signal processing desirable. They will then conduct an experiment to quantify to cortico-spinal dynamics during learning (5 days) of motor tasks using the upper limb. This will provide the basis for a PhD project that will quantify the reorganization at cortico-spinal levels during learning and recovery from injury after stroke and spinal cord injury.

Relevant publications 1

[10] Mardell L, O'Neill G, Tierney T, Lim M, Barnes G, Bestmann S. (2024) Concurrent spinal and brain imaging with optically pumped magnetometers. J Neurosci Methods. 2024 Jun;406:110131.

Relevant publications 2

[53] Boto E, Holmes N, Leggett J, Roberts G, Shah V, Meyer S, Muñoz LD, Mullinger KJ, Tierney TM, Bestmann S, Barnes GR, Bowtell R, Brookes MJ (2018) Moving magnetoencephalography towards real-world applications with a wearable system. Nature 555:657-66 doi: 10.1038/nature26147

Professor Isaac Bianco

Position: Professorial Research Fellow
Department: Neuroscience, Physiology & Pharmacology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/7550-isaac-bianco
Email contact: i.bianco@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We want to understand fundamental principles underlying the organisation and operation of brain-wide circuits and we use larval zebrafish which have a tiny, optically transparent brain. We're particularly interested in how neural networks integrate sensory information in the context of internal brain states to flexibly select and control behavioural programmes.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The themes of two possible rotation projects are outlined below. However, interested students are encouraged to visit the lab to design a project tailored to their interests. Techniques we specialise in include 2-photon calcium imaging, optogenetics, behavioural analyses and computational modelling. 1. From pretectal command signals to goal-directed actions Recently my lab has discovered a small population of pretectal neurons that operate as a command system controlling complete hunting sequences. We now want to explore how these forebrain command neurons interface with downstream (pre)-motor circuits to select and coordinate individual motor actions to assemble a target-directed hunting sequence. The project will involve a combination of circuit tracing (using photoactivatable proteins and EM datasets), 2-photon holographic optogenetics, calcium imaging and behavioural assays. 2. Predicting internal brain states from low dimensional whole-brain population dynamics Animal behaviour is highly flexible and is modulated by factors including recent experience and physiological state. In this project, you will use light-sheet microscopy and deep learning approaches to (1) monitor calcium activity at cellular resolution throughout the entire brain and (2) explore whether latent features of brain-wide population dynamics can predict future behavioural responses. We hypothesise this will lead to identification of the neural correlates of internal brain states that encode experience and influence the coupling of sensory inputs to behavioural outputs.

Relevant publications 1

Antinucci P, Folgueira M, Bianco IH. Pretectal neurons control hunting behaviour. eLife (2019) 8 doi.org/10.7554/eLife.48114

Relevant publications 2

Zylertal A, Bianco IH. A recurrent network architecture explains tectal activity dynamics and experience-dependent behaviour. eLife (2023). doi.org/10.7554/eLife.78381

Professor Geoff Bird

Position: Associate Professor in Autism Research
Department: Centre for Research in Autism and Education
University UCL
Faculty: Institute of Education
Profile: https://profiles.ucl.ac.uk/16150-geoff-bird
Email contact: geoff.bird@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

I am interested in those cognitive factors that contribute to poor mental health across diagnostic categories, although I have a particular interest in autism and Feeding and Eating Disorders. I focus on social skills, and the ability to understand one's own emotions and bodily signals.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Rethinking Theory of Mind as a Transdiagnostic Mental Health Symptom Theory of Mind refers to our ability to represent the mental states of other people. It has long been thought that theory of mind impairments are a symptom of clinical conditions, notably Autism, but also schizophrenia, Feeding and Eating Disorders, Substance Use Disorder among others. Some theorists have recently suggested that Theory of Mind is not 'broken' in these conditions – rather it is just different – and that neurotypical and neurodivergent people just don't understand each other. Unfortunately, it has not been explained what these differences are, how they impact theory of mind, and no evidence in favour of this suggestion has been put forward. This project attempts to test a novel account of theory of mind and how it is impacted by neurodivergence, and finally provide some evidence to test the rival accounts of how theory of mind is impacted in clinical conditions. You will work with myself and another member of my team conducting research with clinical populations with existing materials for a study with existing ethics. Although a lot of the (very boring) groundwork to the project has been done, this project will be yours to shape as you see fit. It will involve a mixture of in-person and online testing, although it could probably be entirely online if preferred. We expect the project to lead to publications and easily expands into a full PhD project.

Relevant publications 1

Conway, J., Catmur, C. & Bird, G. (2019). Understanding Individual Differences in Theory of Mind via Representation of Minds, Not Mental States. Psychonomic Bulletin & Review, 26(3), 798-812.

Relevant publications 2

Long, M., Cuve, H.C., Conway, J.R., Catmur, C., & Bird, G. (2022). The Interview Task: Novel Theory of Mind Task Demonstrates Representation of Minds in Mental State Inference. Scientific Reports, Sci Rep 12, 21133.

Dr James Bisby

Position: Associate Professor Epidemiology & Applied Clinical Research
Department: Division of Psychiatry
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/27399-james-bisby
Email contact: j.bisby@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My research interest is on the psychological and neural mechanisms of human memory and how alterations in these systems underpin memory disturbances that are a common feature in psychological disorders such as posttraumatic stress disorder.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Following the recent addition of complex posttraumatic stress disorder (cPTSD) to the International Classification of Disorders 11 (ICD-11), research has attempted to understand its distinct characteristics that set it apart from PTSD and other trauma-related disorders (Brewin et al., 2017). To further our understanding of cPTSD, there is a need to define the way in which the neural circuitry relates to specific symptom clusters and how these are similar or dissimilar from those often seen in PTSD. PTSD is associated with a range of neural alterations in brain areas that underpin memory re-experiencing symptoms, such as the hippocampus, amygdala and mPFC. However, little is known about the brain areas involved in symptoms specific to cPTSD such as emotional dysregulation and disturbances in self-concept. Childhood and adolescence are vulnerable periods in which areas involved in emotion regulation and self-concept develop, including medial and lateral PFC and anterior cingulate cortex (ACC), highlighting potential mechanisms that might support cPTSD symptomatology. This project will utilise an fMRI resting state data set of North Korean defectors who have experienced prolonged exposure to multiple and repeated traumas, orthogonalized for PTSD (n=21), cPTSD (n=23) and asymptomatic controls (n=29). We aim to explore neural activity changes relating to CPTSD specific symptoms in emotional regulation and disturbances in self-concept. The project will provide important insights in cPTSD and could be developed into a more extensive PhD on the neural mechanisms involved in cPTSD, collaborating with the wider research team (Yongsie University, Stirling University, Ulster University).

Relevant publications 1

Kim et al., (2024). North Korean defectors with PTSD and complex PTSD show alterations in default mode network resting-state functional connectivity. BJPsych Open. 2024;10(1):e25.

Relevant publications 2

Bisby et al. (2020). Reduced memory coherence for negative events and its relationship to posttraumatic stress disorder. Current Directions in Psychological Sciences 29: 267-272.

Professor Jennifer Bizley

Position: Professor of Auditory Neuroscience
Department: Ear Institute
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/31788-jennifer-bizley
Email contact: j.bizley@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We seek to understand the neural basis of listening, by linking the activity of neurons to perception, in animals engaged in auditory tasks. Research projects span spatial hearing, auditory attention, auditory scene analysis and audiovisual integration and is complemented by behavioural studies in humans, and computational and machine learning approaches.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Auditory space must be computed from a comparison of the sounds arriving to each ear. Moving sounds and moving listeners can generate identical changes in localisation cues, yet listeners have no difficulty differentiating self and source motion. The brain may solve this problem by forming listener-independent representations of a sound's position in the environment. Indeed, by recording spatial responses in freely-moving animals, we were able to demonstrate that such 'world-centred' representations exist in a minority of neurons in auditory cortex. We have built a large arena under which 10s of speakers are located, and trained ferrets to 'hunt' sounds. We will track head and eye movements in high resolution to understand how active sensation supports the construction of auditory spatial representations. A rotation project could involve participation in these experiments and analysis of the resulting, highly novel, behavioural data. Animals will be implanted with Neuropixels 2.0 probes that target auditory cortex and hippocampus. Viral tracing injections in the lab demonstrate direct projections from hippocampus to higher auditory cortex, but surprisingly little is known about how sound contributes to the formation of hippocampal spatial representations or how hippocampal signals contribute to auditory processing. Investigating these links through neural recordings and computational analysis could form the basis of a PhD project. Given the links between hearing loss and dementia, understanding how the hippocampus participates in auditory processing is of great interest and potential clinical relevance. Projects are additionally available on any of the topics listed in the research overview.

Relevant publications 1

Town, Brimijoin and Bizley "Egocentric and allocentric representations in auditory cortex", Plos Biology, 2017. https://doi.org/10.1371/journal.pbio.2001878

Relevant publications 2

Dunn,Town, Bizley and Bendor "Behaviourally modulated hippocampal theta oscillations in the ferret persist during both locomotion and immobility", Nature Communications 2022 https://doi.org/10.1038/s41467-022-33507-2

Professor Elvira Bramon

Position: Professor of Mental Health
Department: Mental Health Neuroscience Research Department
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/36030-elvira-bramon
Email contact: e.bramon@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We investigate neurophysiology, cognitive and clinical biomarkers to understand how genetic variation leads to the onset of psychosis. We study genetic tests that can help us tailor antipsychotic and antidepressant treatment to reduce side effects and improve recovery.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Genetics, Environment and Mechanisms in Schizophrenia (GEMS): There has been major progress in the understanding of the genetics of psychotic disorders. Over 270 loci harbouring common variants are involved in psychosis and Polygenic Risk Scores have been developed. Rare Copy number variants (CNVs), where segments of DNA sequence are deleted or duplicated, as well as single gene mutations (SNVs) are also important. Many CNVs/SNVs are benign and contribute to natural human variation. However, some increase the risk for schizophrenia, autism, and other neurodevelopmental disorders. Genetic factors influence the likelihood of responding to medications and of developing side effects. Aims: To investigate the influence of genetic variants on brain function & structure in psychosis. To use genetics to optimise treatment with antipsychotic and other psychotropic medications. Methods: You will investigate CNV/SNV effects on brain connectivity and cognition by integrating EEG and cognitive biomarkers into a genetic association study. We have extensive microarray, gene panels and whole genome/exome sequencing data. Samples available include: • The Psychosis Endophenotypes International Consortium. A study of 5,000 people with psychosis, and their families. • The UK Biobank with 500,000 general population participants. • We are leading one of the first UK studies offering pharmacogenetic testing for mental health with over 350 patients already enrolled. With students in the team, we publish papers in high quality journals. This is an outstanding opportunity to work with the latest “big data” including genetics and electronic health records. We are applying advancements in genomics to improve the treatment of people with psychosis.

Relevant publications 1

Thygesen et al. (2020). Mol Psychiatry 26(9):5307-5319.

Relevant publications 2

Saadullah Khani et al Nature Mental Health 2024;2(5):616-626

Professor Matteo Carandini

Position: Professor of Visual Neuroscience
Department: UCL Institute of Ophthalmology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/6424-matteo-carandini
Email contact: m.carandini@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Our lab (https://www.ucl.ac.uk/cortexlab) focuses on the computations performed by populations of neurons, the underlying circuits, and the resulting behaviors. We study this in mice that perform spontaneous actions or trained tasks that require integrating multiple sensory and nonsensory factors. We also help advance neuroscience techniques such as Neuropixels probes (https://www.ucl.ac.uk/neuropixels)

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The brain has a vast but finite number of neurons so it must use the same neurons in different situations. For instance, neurons in some regions may change their activity profiles dynamically to favor sensory inputs that are associated with actions. Using 2-photon imaging we have examined this process in the parietal cortex, where to our surprise we found that different neurons are active in different tasks [1]. We don't know, however, what happens elsewhere in cortex, in the rest of the brain, and in a wider variety of tasks and behavioral conditions. Studying this has now become possible: thanks to Neuropixels probes and advanced algorithms, we can record from the same neurons chronically for weeks or months throughout the brain [2]. We propose to exploit this new ability in mice that perform trained tasks and that exhibit natural behavior including sleep. We will thus be able for the first time to see how the brain reallocates its neurons depending on contextual demands and while learning a task. An added bonus is that we will be able to relate what neurons do during wakefulness to what they do during sleep, potentially helping to reveal fundamental features of sleep. A rotation student could jump right in: we have mice implanted with chronic Neuropixels probes and it would be great to record from them in a variety of behavioral situations, and relate neural activity to behavior. This could then be a good introduction to the longer project.

Relevant publications 1

Lee, J.J., Krumin, M., Harris, K.D., and Carandini, M. (2022). Task specificity in mouse parietal cortex. Neuron. https://doi.org/10.1016/j.neuron.2022.07.017

Relevant publications 2

van Beest, E.H., Bimbard, C., Fabre, J.M.J., Takács, F., Coen, P.H., Lebedeva, A., Harris, K.D., and Carandini, M. (2024). Tracking neurons across days with high-density probes. Nature Methods (in press), available at https://doi.org/10.1101/2023.10.12.562040

Dr Lorena Arancibia Cárcamo

Position: Principal Research Fellow
Department: UKDRI / Institute of Neurology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/6752-lorena-arancibia-carcamo
Email contact: l.carcamo@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Our lab aims to understand the cellular responses to amyloid accumulation in Alzheimer's disease, specifically those of microglia and astrocytes. The group uses state-of-the-art technology to analyse individual cells from genes to function as well as cell-cell interactions to further our understanding of the pathways leading to neurodegeneration.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Alzheimer disease (AD) is a major health problem worldwide and yet there are currently no successful therapies to treat the disease. Microglia dysfunction has been implicated in several pathologies including Alzheimer's disease (AD). For example, microglia have been shown to play a role in the inflammation frequently associated with AD, remove synapses in response to Aβ peptide and have been shown to contribute to the formation of amyloid plaques. It is well established now that microglia change their gene expression patterns throughout disease development but how these changes correlate with microglia function is still unknown. More recently, astrocytes have been identified as one of the earliest responders in the development of AD. Our data suggests that astrocytes and microglia respond together to increasing levels of Aβ. However, the exact role of this response in the development of the disease remains unknown. The aim of the rotation project will be to assess microglia-astrocyte signalling pathways around and away from plaques during plaque formation in a mouse model of Alzheimer's disease. The rotation can form the basis of a more substantive PhD project that would involve studying microglia function in vivo in AD. Techniques learnt during the rotation project will include: animal handling, immunohistochemistry, confocal microscopy and STED microscopy, image processing and analysis.

Relevant publications 1

Mallach et al., 2024. Microglia-astrocyte crosstalk in the amyloid plaque niche of an Alzheimer's disease mouse model, as revealed by spatial transcriptomics. Cell Reports. (DOI: 10.1016/j.celrep.2024.114216)

Relevant publications 2

Lezmy et al., 2021. Astrocyte Ca2+-evoked ATP release regulates myelinated axon excitability and conduction speed. Science. DOI: 10.1126/science.abh2858

Associate Professor Velia Cardin

Position: Associate Professor
Department: Experimental Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/28186-velia-cardin
Email contact: velia.cardin@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We study multisensory integration and crossmodal plasticity. We use neuroimaging and behavioural techniques, and focus on how sensory experience impacts the organisation of sensory and cognitive brain networks in deaf, hearing and hard of hearing individuals.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The extraordinary capacity of the brain for functional and structural reorganisation is known as neural plasticity. Understanding this phenomenon not only provides insights into brain function, but also into its potential for change and enhancement, with applications for sensorimotor substitution, artificial intelligence, policy, and education. The student will take part in an fMRI project studying the reorganisation of auditory areas in older adults with hearing loss. More than 50% of the individuals over 70 years of age have hearing loss. Furthermore, hearing loss is one of the most important preventable contributors to dementia. Therefore, this project has important implications both, for interventions, and for our understanding of brain function. We hypothesise reorganisation of auditory areas due to acquired hearing loss. The rotation project can develop into a PhD project where the student explores the relationship between crossmodal plasticity and cognitive decline in older adults.

Relevant publications 1

Manini B*, Vinogradova V*, Woll B, Cameron D, Eimer M, Cardin V. (2022). Sensory experience modulates the reorganisation of temporal auditory regions for executive processing. Brain, Volume 145: 3698–3710.

Relevant publications 2

Cardin V, Grin K, Vinogradova V, Manini B. (2020). Crossmodal reorganisation in deafness: mechanisms for functional preservation and functional change. Neuroscience & Biobehavioral Reviews. 113: 227-237.

Dr Christina Carlisi

Position: Associate Professor
Department: CEHP
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/62628-christina-carlisi
Email contact: c.carlisi@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My research combines methods in clinical psychology, cognitive neuroscience and epidemiology to understand how mental illness develops and persists across childhood and adolescence. I study brain-behaviour relationships using neuroimaging (functional/structural MRI), cognitive tasks and computational approaches, with a key focus on emotion processing and affective neuroscience.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Adolescence can be a difficult period. It is a time when emotions are especially important as young people forge new social relationships and become more independent. Adolescence is also when 75% of common mental health difficulties emerge. This project investigates the neurocognitive and neurobiological factors that influence the development and persistence of anxiety and depression, and how these factors interact with one's environment to shape behaviour. Specifically, fMRI data (new 'movie fMRI data' and/or existing cohort data, e.g., ABCD) will be analysed alongside sociodemographic and mental health measures. The student would investigate the interaction between the neurocognitive processing of emotional information and the onset of mental health problems (e.g., anxiety, conduct problems) across adolescence, with the hypothesis that aberrant patterns of activation in affective brain networks, and biases in cognitive processing of emotional information are linked to increased vulnerability for mental health problems and poor treatment outcomes. Practical skills learned would include fMRI analysis, with the possibility of collecting new fMRI data and/or incorporating computational modelling. Moreover, if students have a valid DBS check, there is scope for collecting cognitive task and behavioural data from adolescents in school-based settings. All aspects of data collection and analysis could develop into a full PhD project.

Relevant publications 1

Carlisi CO, Moffitt TE, Knodt AR, Harrington H, Ireland D, Melzer, TR, Poulton R, Ramrakha S, Caspi A, Hariri AR, Viding E (2020): Associations between life-course-persistent antisocial behaviour and brain structure in a population representative longitudinal birth cohort. The Lancet Psychiatry. 7(3): 245-253

Relevant publications 2

Carlisi CO, Reed K, Helmink FGL, Lachlan R, Cosker DP, Viding E, Mareschal I (2021). Using Genetic Algorithms to uncover individual differences in how humans represent facial emotion. Royal Society Open Science 8(10).

Professor Tom Carlson

Position: Professor of Assistive Robotics
Department: Research Department of Orthopaedics and Musculoskeletal Science
University UCL
Faculty: Medical Sciences
Profile: https://profiles.ucl.ac.uk/41842-tom-carlson
Email contact: t.carlson@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We are developing non-invasive Brain-Computer Interfaces (BCI), based on EEG/fNIRS, that support people with severe motor impairments (e.g. due to SCI, MND etc.) to turn their thoughts into actions in the real-world. We work extensively with motor imagery protocols, as well as speech imagery and cognitive state estimation.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

To Err is human! AI machines also make mistakes when decoding human intention through brain-machine interfaces. However, it is possible to detect error-related potentials (ErrPs) in EEG when a human notices that a mistake has been made. For binary-classifier situations, these have been used to correct BCI decoding errors. However, such experiments tend to use simple, discrete visual stimuli. Instead, we investigate the extrapolation of these early results to use in real-world BCI scenarios, with asynchronous decoding or errors from more natural, multi-class stimuli. Then, instead of simply correcting errors, we anticipate using this data to additionally support the re-training of a BCI classifier, thus accounting for the non-stationarity of brain signals, and supporting long-term BCI use. In this rotation project, you will build upon previous work to design and run an experiment using PsychoPy to elicit (and classify) ErrPs from more complex stimuli (multimodal, non-discrete). Healthy, able-bodied participants will be recruited for this study. In collaboration with other members of our team, the ErrPs will then be used to support classifier re-training. The full PhD project will then translate these findings into a closed loop virtual reality setting using OpenVibe and our Unity3D framework, with possible extension to real-world assistive robotics application (e.g. a smart wheelchair). You will investigate using ErrPs to modulate task difficulty and adjust the level of AI assistance provided. It is anticipated that the studies during the main PhD will include participants with motor impairments recruited through our charity partners.

Relevant publications 1

Chavarriaga, R., Sobolewski, A. and Millán, J.D.R., 2014. Errare machinale est: the use of error-related potentials in brain-machine interfaces. Frontiers in neuroscience, 8, p.208.

Relevant publications 2

Thomas, A., Chen, J., Heller-Szabo, A., Kelly, M. and Carlson, T., 2024, High stimuli virtual reality training for a brain controlled robotic wheelchair. IEEE International Conference on Robotics and Automation. May 2024

Professor Dennis Chan

Position: Clinician Scientist
Department: Institute of Cognitive Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/72680-dennis-c-f-chan
Email contact: dennis.chan@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

The focus of my group is the early detection of Alzheimer's disease (AD), using VR and AR tests of spatial navigation combined with 7T MRI to probe the function of the entorhinal cortex, the first brain region affected in AD.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Early detection of Alzheimer's disease (AD), prior to symptom onset, is key to prompt diagnosis and treatment initiation to reduce risk of progression to dementia. This project will build on our previous work showing that path integration, a form of spatial navigation dependent on entorhinal cortex (EC) function, is impaired in people at risk of AD, in advance of memory impairment. Middle-aged people at risk of AD will be tested on VR and AR navigation tasks, with spatial performance compared with genetic and lifestyle risk factors as well as amyloid and tau biomarkers of AD. Ultra high resolution 7T MRI scanning of the EC will yield structural and functional imaging outcomes to correlate with the spatial behavioural data while future planned work with optically pumped MEG (magneto-encephalography) aims to deliver a neurophysiological measure of disease onset. The prospective student will learn about AD, its impact on individuals and health services, and the challenges of early diagnosis and treatment. On a skills acquisition level, they will gain experience in various cutting edge technologies such as VR, AR and high field MRI as well as in analysis of behavioural and MRI data. The contact with human participants will aid those interested in a future career in clinical practice, while those inclined towards translational research will benefit from the collaboration with UCL molecular and cellular neuroscientists collectively aiming to understand how disease at the neuronal level leads to the occurrence of the clinical disorder.

Relevant publications 1

Newton C, Pope M, Rua C, Henson R, Ji Z, Burgess N, C, Stangl M, Dounavi M-E, Castegnaro A, Koychev I, Malhotra P, Wolbers T, Ritchie K, Ritchie C, O'Brien J, Su L, Chan D (2024) Entorhinal-based path integration selectively predicts midlife risk of Alzheimer's disease. Alzheimer's and Dementia 20, 2779-2793

Relevant publications 2

Howett D, Andrea Castegnaro A, Krzywicka K, Hagman J, Marchment D, Henson R, Rio M, King J, Burgess N, Chan D (2019) Differentiation of mild cognitive impairment using an entorhinal cortex-based test of VR navigation. Brain 142, 1751-1766

Dr Jon Clayden

Position: Associate Professor
Department: UCL GOS Institute of Child Health
University UCL
Faculty: Population and Health Sciences
Profile: https://profiles.ucl.ac.uk/3862-jon-clayden
Email contact: j.clayden@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My interests are in using neuroimaging to further understanding of connectivity and information processing in the brain, and the mechanisms by which these change due to normal development and disease. My group works on methodology and a range of applications in paediatric neurology, neurosurgery and psychology.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Magnetic resonance imaging (MRI) produces images of three and four dimensions, which often require significant computational post-processing to be maximally useful in medicine and neuroscience. However, the field has been historically dominated by "black-box" processing pipelines whose overall success or failure on a given image are hard to interrogate or understand, and the contemporary pivot towards deep learning methods largely does not help in this regard. While successful in a research context, these methods' complexity and the level of expertise required to use them with confidence limits clinical adoption. In the wider field of data science, the iterative cycle of "data understanding" has become an influential paradigm (see, for example, Wickham et al., 2023), but while pipelines of elemental image processing operations can be straightforwardly applied (Rorden et al., 2024) these cannot yet match the sophistication of the black boxes. The aim of this rotation project will be to review the literature, work with MRI scans and develop a framework to think about understanding-driven data science for neuroimaging. A follow-on PhD project could then continue to move this framework towards practical usefulness and availability for future analysis.

Relevant publications 1

H. Wickham, M. Çetinkaya-Rundel & G. Grolemund (2023). R for Data Science, 2nd edition. O'Reilly. ISBN 978-1492097402. https://r4ds.hadley.nz

Relevant publications 2

C. Rorden, M. Webster, C. Drake, M. Jenkinson, J.D. Clayden, N. Li & T. Hanayik (2024). niimath and fslmaths: Replication as a method to enhance popular neuroimaging tools. Aperture Neuro 4. https://doi.org/10.52294/001c.94384

Professor Anthony David

Position: Professor of Mental Health and Director, UCL Institute of Mental Health
Department: Neuroscience and Psychiatry
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/70058-anthony-david
Email contact: anthony.s.david@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

The research makes use of large-scale longitudinal data from a population birth cohort to look at predictors (eg immune markers; polygenic risk scores; social adversity) of later mental disorder (eg psychosis and depression) and brain development (MRI scans of grey/white matter volumes; cortical thickness).

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The association between inflammatory markers and brain structure in psychosis and depression Project overview: Recent research suggests that inflammation and immunity may play a role in the aetiology of depression and psychotic disorders. There is a need for longitudinal studies to assess whether inflammation is a cause or consequence of illness, and the mechanisms that underlie the association between inflammation and mental disorders. This project will use longitudinal neuroimaging and inflammation data from the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC is the largest UK birth cohort (n~10,000) dedicated to examining mental health. This rotation project will investigate the association between longitudinal trajectories of inflammatory markers measured at difference ages and their impact on brain structure in individuals with depression or psychotic experiences, or in those with high and low polygenic risk scores for schizophrenia. During this project the student will work with teams across Bristol and Cardiff Universities and UCL and will learn about indices of immune activation applicable in population studies. They will acquire skills in neuroimaging (MRI – Grey matter volume alterations will either be assessed using Freesurfer outputs or SPM), and there will be an opportunity to use advanced statistical methods to categorise inflammation trajectories applicable to longitudinal analysis, and to examine aspects of gene-environment interactions.

Relevant publications 1

Perry, B. I., Zammit, S., Jones, P. B., & Khandaker, G. M. (2021). Childhood inflammatory markers and risks for psychosis and depression at age 24: examination of temporality and specificity of association in a population-based prospective birth cohort. Schizophrenia Research, 230, 69-76.

Relevant publications 2

Merritt, K., Luque Laguna, P., Sethi, A. et al. The impact of cumulative obstetric complications and childhood trauma on brain volume in young people with psychotic experiences. Mol Psychiatry 28, 3688–3697 (2023). https://doi.org/10.1038/s41380-023-02295-6

Dr Michael Devine

Position: Group Leader Clinical and Movement Neurosciences
Department: Department of Clinical and Movement Neurosciences
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/7748-michael-devine
Email contact: michael.devine@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Neuronal synaptic activity is a highly energy dependent process that is precisely regulated by mitochondria via ATP production and Ca2+ buffering (Devine et al. 2018). We are working out how synapses are regulated by mitochondria, and how this regulation goes wrong in diseases that affect the brain.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Mitochondria form dynamic contact sites with other intracellular organelles. These specialised sites act as signalling hubs which regulate metabolism, calcium handling and lipid synthesis. We are interested in minimally explored contact sites between mitochondria and the plasma membrane in neurons. The lab has identified a novel 'contactome' of candidate proteins at mito-plasma membrane contact sites using proximity labelling and mass spectrometry. The project focuses on confirming these candidates in cells and identifying their role in the formation and maintenance of these contact sites. Using the state-of-the-art microscopy facilities at the Crick, initial experiments will involve manipulating levels of these key proteins and quantifying numbers of contact sites using fixed imaging and image analysis methods. Hits from these experiments will be further explored with respect to their contribution to neuronal signalling and synaptic activity. Approaches here would include live microscopy for calcium imaging with GCaMPs, vesicle release imaging with pHluorins and multielectrode array recordings. This 'contactome' dataset is a strong resource for designing independent research projects. The project could be extended to a more complete and independent investigation of one or more candidate proteins to mito-plasma membrane contact sites and neuronal physiology. Another potential avenue would be to conduct an unbiased assessment of the list of candidates via a high throughput screen. Alternatively, the techniques learned here could be adapted to study other contact sites between other organelles in neurons and/or how these contact sites are disrupted in neurological disease. Techniques: Neuron cultures, Immunocytochemistry, Light microscopy, Live imaging, Image analysis, Biochemistry

Relevant publications 1

Devine MJ, Kittler JT. Mitochondria at the neuronal presynapse in health and disease. Nat Rev Neurosci. 2018 Jan 19;19(2):63-80. doi: 10.1038/nrn.2017.170. PMID: 29348666

Relevant publications 2

Cho KF, Branon TC, Rajeev S, Svinkina T, Udeshi ND, Thoudam T, Kwak C, Rhee HW, Lee IK, Carr SA, Ting AY. Split-TurboID enables contact-dependent proximity labeling in cells. Proc Natl Acad Sci U S A. 2020 Jun 2;117(22):12143-12154. doi: 10.1073/pnas.1919528117. Epub 2020 May 18. PMID: 32424107; PMCID: PMC7275672

Professor Beate Diehl

Position: Professor of Neurophysiology
Department: Department of Clinical and Experimental Epilepsy
University UCL
Faculty: Medical Sciences
Profile: https://profiles.ucl.ac.uk/23004-beate-diehl
Email contact: b.diehl@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Epilepsy affects 600,000 people in the UK, leading to dangerous, sometimes unending seizures and tripling the risk of death. Annually, epilepsy is linked to 1,200 deaths, with half being sudden and unexplained (SUDEP). Research is urgently needed to understand these fatalities better, as heart problems during seizures increase the risk.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

For some patients, electrodes are placed in the brain to locate seizure origins for potential surgery, often in areas controlling heartbeat. We have amassed a large dataset of heart activity (ECG) during brain stimulation via these electrodes, recorded simultaneously with video electroencephalography (brainwave signals). We will apply advanced signal processing methods to detect stimulation-induced heart rhythm abnormalities. We will then map the stimulation sites involved and use cutting-edge methods of brain connectivity analysis to elucidate the networks associated with heart irregularities. This research will facilitate tailored interventions and personalised risk assessments for SUDEP. The rotation project will involve a structured literature review to identify fMRI studies which reveal brain areas involved in the control of the autonomic function, particularly heart activity and breathing. The student will then perform a meta-analysis using https://compose.neurosynth.org/ in combination with normative connectomics implemented in the Lead-DBS toolbox (https://www.lead-dbs.org/). This analysis will identify brain areas and fibre tracts whose stimulation could potentially affect these functions. We will compare these areas and tracts with the electrode implantation sites our dataset to identify candidate patients in whom we could search for stimulation-induced changes in ECG. If the time permits, pilot analyses of data from several such patients can be performed to test the connectomics-based predictions. In the future, such sites may allow for powerful interventions to explore and potentially stabilse autonomic functions in people with epilepsy and reduce SUDEP risk.

Relevant publications 1

Zeicu, C., Legouhy, A., Scott, C. A., Oliveira, J. F. A., Winston, G. P., Duncan, J. S., . . . Diehl, B. (2023). Altered Amygdala Volumes and Microstructure in Focal Epilepsy Patients with Tonic-Clonic Seizures, Ictal and Post-convulsive central apnea.. Epilepsia. doi:10.1111/epi.17804

Relevant publications 2

Kassinopoulos, M., Rolandi, N., Alphan, L., Harper, R., Oliveira, J., Scott, C., . . . Diehl, B. (2023). Brain Connectivity Correlates of Breathing and Cardiac Irregularities in SUDEP: A Resting-State fMRI Study. doi:10.1101/2023.05.19.541412

Dr Karolina Dziemidowicz

Position: Lecturer in Pharmaceutics
Department: School of Pharmacy
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/58083-karolina-dziemidowicz
Email contact: k.dziemidowicz@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

The overarching theme of my group is polymer-based drug delivery to the nervous system and malignancies, with particular interest in cancer immunotherapy and protein drug delivery. We are a multidisciplinary group working at the intersection of materials science, engineering, chemistry and biology.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Convection Enhanced Delivery (CED) is a targeted drug delivery technique used primarily in the brain to treat neurological disorders and malignancies. By using a pressure gradient, CED allows therapeutic agents to bypass the blood-brain barrier, achieving high local concentrations directly at the treatment site, enhancing efficacy, and minimising systemic side effects. While promising, CED faces several limitations, including difficulty in precisely controlling drug distribution and concentration as well limited duration of therapeutic effect due to drug dispersing into brain tissue. One way to overcome these challenges is to formulate CED infusates into long-acting micro-and nanoparticles capable of targeting and attacking affected cells, while minimising impact on the surrounding healthy tissue. This project will therefore explore the feasibility of using advanced formulation technologies to enhance outcomes in CED. For the initial proof-of-concept work, we will focus on targeting diffuse intrinsic pontine glioma, an aggressive form of paediatric brain cancer. The student will fabricate polymeric microparticles loaded with MEK inhibitors and characterise them using physicochemical methods (SEM, TEM, XRD, DSC, TGA) before testing their drug release kinetics in a brain tissue phantom of the CED procedure. If successful, further tests will be performed on ex vivo sheep brains. This study can further develop into a PhD project where formulated infusates can be explored for either neurodegenerative disorder or brain cancer. It would involve a combination of artificial intelligence, materials science, engineering, chemistry and biology, closely working with clinicians from Great Ormond Street Hospital to accelerate progression into the clinic.

Relevant publications 1

https://doi.org/10.1002/wnan.1965

Relevant publications 2

https://www.mdpi.com/1999-4923/13/4/561

Professor Antonia Hamilton

Position: Professor of Social Neuroscience
Department: Institute of Cognitive Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/26902-antonia-hamilton
Email contact: a.hamilton@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Loneliness is a major risk factor for poor mental health. This research uses wearable sensors and questionnaires to track people's social connections and social synchrony in relation to personality traits. It will reveal risk factors for loneliness and what can help in real-world data

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The way people move about in the real world can tell us a lot about their mental states and their social interactions. New methods using wearable sensors are now allowing us to capture meaningful patterns of behaviour in the context of classrooms, theatres and social spaces. We have several large datasets from adults, children and autistic children who wore accelerometers during group activies. This project will implement additional analyses on these data with the aim of writing a paper on how interpersonal movement coherence can reveal the structure of real-world social networks. The student involved in this project will learn advanced data analysis skills as well as presentation and writing skills. You will be part of a cross-disciplinary team with researchers in psychology, neuroscience and engineering.

Relevant publications 1

Sun, Greaves, Orgs, Hamilton, Day & Ward (2023) Using wearable sensors to mesure interpersonal synchrony in actors and audience members during a live theatre performance Proc ACM IMWUT

Relevant publications 2

Ward, Richardson, Orgs, Hunter & Hamilton (2018) Sensing interpersonal synchrony between actors and autistic children using wrist-worn accelerometers International Symposium on Wearable Computers

Professor Quentin Huys

Position: Professor of Computational Psychiatry
Department: Division of Psychiatry and Institute of Neurology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/23412-quentin-huys
Email contact: q.huys@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

The Applied Computational Psychiatry Lab works at the interface of computational neuroscience and psychiatry. We use computational methods to improve our understanding of how treatments in psychiatry work and can be made more efficient. We currently work on psychotherapy and psychopharmacology. A substantial component is also to understand the basic underlying mechanisms, e.g. of emotions, self-report, decision-making and learning, and in principle projects across these domains are available, based on preferences, interest and existing expertise and skill. The methods we use are quite wide-ranging, from computational modelling to neuroimaging, online behavioural task and psychotherapy interventions all the way to large-scale multisite clinical trials.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Project 1: Neurocognitive predictors of depression relapse after antidepressant discontinuation Depression can sometimes remit with antidepressant medication. However, relapse rates after discontinuation are very high. What is missing are predictors which can identify patients who are safe, and those who are at risk of relapse after discontinuation. The AIDA study examined patients who remitted on antidepressants and wanted to discontinue. Patients were tested both before and after discontinuation using a range of neurobiological probes including EEG, fMRI, behaviour, self-report and biological assays. In this project, existing data from the study will be analysed. There are opportunities to analyse EEG, fMRI or behavioural data depending on the student's preference and skills. Project 2: Computational mechanisms of psychotherapeutic interventions Psychotherapy is one of the key cornerstones for the treatment of mental illness. However, we still don't properly understand how different psychotherapy interventions work, why, and for whom. This project will combine computational cognitive neuroscience with psychotherapy. You will read psychotherapy manuals, extract key interventions, and then build cognitive-computational tasks and models to selectively capture the specific effects of the interventions. This will give you a broad array of skills, from modelling to online tasks and trial delivery, and contribute to a broader project of identifying mechanistically interpretable biomarkers for specific treatments in psychotherapy. Project 3: Neural semantics of emotional self-report Mental illness depends on self-report. However, there is little understanding of exactly how self-report works. This has been a major issue in that it has been difficult to relate neurobiological mechanisms to self-reported symptoms. This project will examine these mechanisms. It will involve neuroimaging, work with large language models, and highly controlled tasks to induce variation in self-reported feelings. The project will examine whether semantic maps can be used to shed light on the mechanisms linking computational processes to self-report.

Relevant publications 1

https://doi.org/10.1126/sciadv.adk3222

Relevant publications 2

https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2761562

Professor Parmjit Jat

Position: Professor of Molecular Cell Biology
Department: UCL Institute of Prion Diseases / MRC Prion Unit at UCL
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/9783-dan-jagger
Email contact: p.jat@prion.ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Prions are infectious proteins that cause fatal brain diseases. A kinetic model of prion propagation predicts that accumulation of neurotoxic form (PrPL) begins after the infection is fully established. To characterise PrPL toxicity we aim to develop a functional assay based on electrical activity of neurons grown on multielectrode arrays.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The rotation project will provide a flavour of the PhD work, while working within a narrower remit to enable significant progress to be made in a short time period. Primary mouse embryonic neurons will be used to set up neuron-on-chip assay on MED64 platform to test prion-infected mouse brains harvested at different stages of the disease to figure out when the prion-induced toxicity is the highest. During the rotation the student will learn how to culture primary embryonic neurons followed by live cell imaging and neurite retraction assay on the IncuCyte S3 platform as well as high-content imaging on Opera-Phenix using previously developed prion-induced toxicity assay protocols. In parallel to imaging, the student will be trained in growing neurons on 4- and 8-well substrates for cell activity recordings on MED64 platform and in the analysis of electrophysiological data. The student will optimize the assay parameters and set up data analysis scripts to determine key parameters of prion-induced synaptotoxicity. Furthermore, using Prnp-null mouse strains the student will be able to look into the role of cellular prion protein as a survival factor. The rotation will provide experience of the key practical skills to be used in the PhD project (primary neuronal culture, handling of mouse prions, prion-induced toxicity assay, data analysis and scripting). Both PJ and IB are funded by a core grant to the MRC Prion Unit which is renewable every 5 years. The current grant runs from April 2023 until March 2028.

Relevant publications 1

Sandberg MK, Al-Doujaily H, Sharps B, Clarke AR, Collinge J (2011) Prion propagation and toxicity in vivo occur in two distinct mechanistic phases. Nature 470(7335), 540.

Relevant publications 2

Benilova I,* Reilly M*, Terry C, Wenborn A, Schmidt C, Marinho A, Risse E, Al-Doujaily H, Wiggins De Oliveira M, Sandberg M, Wadsworth J, Jat P, Collinge J (2020) Highly infectious prions are not directly neurotoxic. PNAS 117 (38), 23815. *Denotes equal contribution

Professor Sunjeev Kamboj

Position: Professor of Translational Clinical Psychology
Department: Research Dept Clinical, Educational and Health Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/5848-sunjeev-kamboj
Email contact: sunjeev.kamboj@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Title: Testing a novel 'memory-therapeutic' approach to treating post-traumatic re-experiencing symptoms using nitrous oxide in a human model of PTSD. This is part of our wider programme of research on novel approaches for treating addiction and PTSD (i.e., disorders of 'maladaptive memory').

Rotation project **(including a brief outline of how this will develop into a PHD project)**

This project looks at whether reactivated 'traumatic' memories can be weakened during reconsolidation using the NMDA receptor antagonist and dissociative anaesthetic drug nitrous oxide (50%-N2O). We have previously shown that N2O speeds up recovery from 're-experiencing symptoms' in a human model of PTSD (the 'trauma film' paradigm). The proposed project extends this previous work by testing a new translation approach for reactivating trauma-like memories. Our collaborator, Jonathon Lee (Birmingham), has shown that fear memories in rodents can reliably be reactivated using bilateral whisker stimulation and then over-written using amnestic drugs. The equivalent in humans is bilateral visual stimulation. In the current study, we will therefore examine the effects of eye-movements (resembling Eye-Movement Desensitization-Reprocessing - 'EMDR' - a psychological treatment for PTSD) as a method for reactivating traumatic-stress-like memories, followed by treatment with N2O to overwrite or weaken these memories. We will monitor the effects of this treatment using standard diary methods to assess intrusive memories. We predict that relative to control groups, participants who undergo the eye-movement memory reactivation followed by N2O treatment will have fewer, less vivid and less distressing involuntary traumatic-stress-like memories. The rotation project would involve developing/refining the experimental procedure, including EEG and eye-tracking methods. A significant part of your PhD would involve testing this novel experimental treatment in healthy volunteers using the trauma-film model. Depending on your interests, this project could be a prelude to your involvement in a clinical trial testing the effects of N2O in patients with PTSD.

Relevant publications 1

Das et al (2016) Nitrous oxide speeds the reduction of distressing intrusive memories in an experimental model of psychological trauma. Psychological Medicine 46, 1749–1759.

Relevant publications 2

Kamboj et al (2021) Rewarding Subjective Effects of the NMDAR Antagonist Nitrous Oxide (Laughing Gas) Are Moderated by Impulsivity and Depressive Symptoms in Healthy Volunteers. International Journal of Neuropsychopharmacology 24(7): 551–561

Dr Stephanie Koch

Position: Senior Research Fellow
Department: Neuroscience, Physiology and Pharmacology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/26387-stephanie-koch
Email contact: s.koch@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We study the mechanisms by which we learn to respond to our environment and how this learning can lead to long-term consequences. How are our behaviours shaped by our experiences? To answer these questions, we use a combination of genetic intersections, 3D kinematic behavioural analysis, molecular biology, modelling and electrophysiology.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Working with Dr Lorenzo Fabrizi: Pain perception is associated with the activation of a widespread network of brain regions, called the pain connectome. Flexible routing of information between each of the areas within this framework is thought to be encoded in the modulation of amplitude and phase of action and local field potentials at specific frequency bands. For example, the sending of feedforward information is associated with gamma oscillations and synchrony across brain areas, while feedback is associated with alpha/beta oscillations. In this experiment, we will focus on the maturation of the first (even if not sufficient) of these connections, that is between the thalamus and the primary somatosensory cortex (SI). To do this, we will perform in-vivo multisite, multiunit and local field potential recording using a single Neuropixels probe in mice pups of different ages. We will then be able to simultaneously measure thalamic and cortical activity following mechanical innocuous and noxious stimulation. To measure the direction of cortical transmission within different frequency bands and the relationship between neuronal firing and local field potential phase, I will assess the delay between band-passed filtered signals recorded in SI and thalamus and their spike-field coherence. The results of this experiment will map the development of the first cortical communication network necessary for pain perception. If the student already has an animal license, they will be able to perform these experiments first hand while supervised, otherwise they will be able to shadow a postdoctoral research fellow during recordings and conduct data analysis.

Relevant publications 1

Ploner, M., Sorg, C. & Gross, J. Brain Rhythms of Pain. Trends Cogn. Sci. 21, 100–110 (2017).

Relevant publications 2

Chang, P., Fabrizi, L., Olhede, S. & Fitzgerald, M. The Development of Nociceptive Network Activity in the Somatosensory Cortex of Freely Moving Rat Pups. Cereb. Cortex 26, 4513–4523 (2016).

Professor Matthias Koepp

Position: Professor of Neurology
Department: UCL Queen Square Institute of Neurology, Department of Clinical and Experimental Epilepsy
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/11619-matthias-koepp
Email contact: m.koepp@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Cognitive dysfunctions in epilepsy and Alzheimer's Disease are associated with the presence of neocortical tau-pathology. Understanding the relationship between tau-pathology, seizures and cognitive comorbidities is critical to identify early those at risk of cognitive decline in epilepsy and to define drivers of disease progression and cognitive decline.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Cognitive deficits in epilepsy occur across all domains in ~1/3 of patients with epilepsy, and medically-refractory epilepsy can lead to cognitive dysfunction similar to incipient states of AD. Recently developed plasma phosphorylated tau 217 (p-tau217) is a highly accurate blood-based biomarker to clinically assess tau-pathology in AD. Prolonged epilepsy, especially status epilepticus (SE), is considered to lead to dementia-related pathology and increase the risk of dementia. We aim to utilise novel blood tests in combination with recent imaging developments to identify biomarkers targeting development and progression of cognitive decline in epilepsy. Rotational project: Targeting epilepsy patients who underwent surgery and showed cognitive decline, we will include 40 individuals for whom we have collected blood and CSF-samples for p-tau217 peri-operatively. Tau-pathology, neuronal loss, white matter abnormalities, and vascular disease in historical surgical specimens will be compared with current tau-PET, MRI, genetic, and cognitive studies. The retrospective analysis of existing data in the rotational project study will inform the prospective data acquisition during the PhD project, which will be focusing on two cohorts: in people with late-Onset Epilepsy over 50 years old who have higher dementia and brain atrophy risks, we will collect prospectively blood-biomarkers (p-tau217, polygenic risk score) and evaluate cognitive trajectories with repeated MRI scans longitudinal cognitive tests. The effect of seizures and SE on cognition will be assessed in a population of patients with de-novo SE Study who are at greatest risk of cognitive decline. Machine learning algorithm Stage and Subtype Inference will be fitted for cognitive impairment staging.

Relevant publications 1

Tai XY et al. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: A study of temporal lobe resections. Brain. 2016;139(9):2441-2455

Relevant publications 2

Xiao F et al. Identification of different MRI atrophy progression trajectories in epilepsy by subtype and stage inference. Brain. 2023;146(11):4702-4716

Professor Martin Koltzenburg

Position: Professor of Clinical Neurophysiology
Department: Clinical and Movement Neurosciences
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/9050-martin-koltzenburg
Email contact: M.Koltzenburg@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Transcranial magnetic stimulation is a painless non-invasive method to explore the excitability of the human brain in health and disease. Using novel threshold tracking paradigms and advanced hardware we can now explore cortical excitability changes at sub-second resolution in combination with brain navigation and high-density recording of muscle responses.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

In a rotation project you will learn fundamentals of human neurophysiology including recording of surface electromyography in responses to transcranial magnetic stimulation (TMS) in healthy volunteers. You will be able to monitor cortical excitability to experimental interventions such as voluntary contraction or application of painless or painful cutaneous stimulation. Moreover, you will be able to study intrinsic excitatory and inhibitory cortical circuits and investigate how their balance fluctuates and contributes to movement control and processing of somatosensory stimulation This rotation project could evolve in studying the effect of neuroactive drugs that probe inhibitory and excitatory pathways of cortical excitability including analgesic drugs. Threshold tracking TMS has also emerged as a diagnostic biomarker in neurodegenerative conditions such as amyotrophic lateral sclerosis. This provides an opportunity to monitor disease progression and study target engagement of drugs that aim to reverse the abnormal inhibitory and excitatory brain circuitry in these diseases. Other projects could investigate how cortical excitability adapt in the hot brain to experimental challenges of temperature increases in health and disease that simulate challenges of the climate crisis.

Relevant publications 1

Samusyte G, Bostock H, Rothwell J and Koltzenburg M (2018) Short-interval intracortical inhibition: Comparison between conventional and threshold-tracking techniques. Brain Stimul 11:806-817.

Relevant publications 2

Tankisi H, Pia H, Strunge K, Howells J, Cengiz B, Samusyte G, Koltzenburg M, Fuglsang-Frederiksen A and Bostock H (2023) Three different short-interval intracortical inhibition methods in early diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 24:139-147.

Professor Dimitri Kullmann

Position: Professor of Neurology
Department: UCL Queen Square Institute of Neurology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/4318-dimitri-michael-kullmann
Email contact: d.kullmann@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My laboratory works at the interface between fundamental and translational neuroscience, with a focus on synaptic transmission and the operation of neural circuits. Current projects include optogenetic manipulation of population oscillations, mechanisms of seizure initiation and propagation, and gene therapies for epilepsy and cognitive/affective comorbidities.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Several projects are available. An in vivo project (which would require a Home Office licence) would be to test the ability of newly developed chemogenetic tools to affect mouse behaviour. This is part of a broader project that starts with molecular design, through testing in cell lines and ultimately leads to preclinical trials in epilepsy models with a view to clinical translation. Another in vivo project is to optimise an operant conditioning setup for unsupervised tests of visually-guided behaviour. This is part of a programme of research aimed to apply closed-loop optogenetic manipulation of cortical gamma oscillations as a test of their roles in perception and information propagation. A computational project would refine Hidden Markov Modelling applied to a large database of electrocorticograms and concurrent video in mouse models of epilepsy. An in vitro project would aim to understand how neurogliaform cells affect circuit function in the hippocampus and neocortex using acute brain slice electrophysiology, pharmacology and optogenetics.

Relevant publications 1

Extracellular glutamate and GABA transients at the transition from interictal spiking to seizures. Shimoda Y, Leite M, Graham RT, Marvin JS, Hasseman J, Kolb I, Looger LL, Magloire V, Kullmann DM. Brain. 2024 Mar 1;147(3):1011-1024. doi: 10.1093/brain/awad336.

Relevant publications 2

On-demand cell-autonomous gene therapy for brain circuit disorders. Qiu Y, O'Neill N, Maffei B, Zourray C, Almacellas-Barbanoj A, Carpenter JC, Jones SP, Leite M, Turner TJ, Moreira FC, Snowball A, Shekh-Ahmad T, Magloire V, Barral S, Kurian MA, Walker MC, Schorge S, Kullmann DM, Lignani G. Science. 2022 Nov 4;378(6619):523-532. doi: 10.1126/science.abq6656.

Dr Christian Lambert

Position: Principal Research Fellow
Department: Imaging Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/11034-christian-lambert
Email contact: christian.lambert@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

I lead a group focused anatomical phenomics, the link between brain structure and phenotypic variability. I run the "Quantitative MRI for Anatomical Phenotyping in Parkinson's disease" (qMAP-PD) longitudinal study that aims to: Identify PD earlier; Better anticipate disease trajectory; Provide non-invasive biomarkers; Understand the mechanistic basis of disease variability.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Parkinson's disease (PD) is a common neurodegenerative condition. It presents as a movement disorder with slowness of movement combined with tremor and/or rigidity. At diagnosis, ~40% of individuals will also have a deficit in one, or more, cognitive domains. In some people this remains reasonably static, where-as others progress rapidly to dementia. Whilst different cognitive patterns have been proposed in PD, how these relate to cortical microstructure and why there is such marked variability in progression remain poorly understood. The "Quantitative MRI for Anatomical Phenotyping in Parkinson's disease" study (qMAP-PD), is a longitudinal study using advanced quantitative MRI and anatomical methods in combination with deep clinical phenotyping, biomarkers, cellular models and genetics to understand phenotypic variability in PD. In this project, the student will initially characterise baseline patterns in cognition using an existing dataset of 113 early-stage PD and 90 healthy controls. Voxel-based morphometry and voxel-based quantification will be used to map the microstructural correlates of these clinical subtypes. Building on this during a PhD, they will use other techniques such as canonical correlation analyses to identify data-driven clusters, leveraging additional data sources (e.g., wet biomarkers), and compare these to longitudinal progression in life. There is a very rich expanded dataset the student can access to help further dissect the pathophysiological basis of different types of cognitive dysfunction, including matched longitudinal data from monogenic forms PD and the multiscale cohort with paired stem cell models (iPSC) to map the molecular mechanisms that underpin differences in progression.

Relevant publications 1

Smith N, Williams O, Ricciardi L, Morgante D, Barrick TR, Edwards M, Lambert C. Predicting Future Cognitive Impairment in De Novo Parkinson's Disease Using Clinical Data and Structural MRI. medRxiv 2021

Relevant publications 2

Lambert C, Lutti A, Helms G, Frackowiak R, Ashburner J. 2013, Multiparametric Brainstem Segmentation using a Modified Multivariate Mixture of Gaussians. Neuroimage:Clinical,

Professor Nilli Lavie

Position: Professor of Psychology and Brain Sciences
Department: Institute of Cognitive Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/7453-nilli-lavie
Email contact: n.lavie@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We research attention, cognitive control, awareness, memory, and emotion. We establish both the general neural and psychological mechanisms, and how they differ between people. We also apply our research to clinical conditions (e.g. Autism, ADHD). We use a variety of cognitive neuroscience methods with a recent focus on Electrophysiology.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Focusing attention on a task is vital for effective information processing and performance, however the ability to sustain attention focus declines over prolonged task periods, resulting in inefficient, slower and error-prone processing, and increased states of mind wandering. Although this has implications to many daily life tasks (e.g. studying for an exam), laboratory research has typically assessed 'sustained attention' during simple, monotonous tasks involving slow presentations of one item (e.g. a letter or digit) at a time. Real-world tasks are often far more demanding, and a sperate line of research from our lab has shown that increasing the processing demands in a task, can have a beneficial effect on attention: tasks of high perceptual load are found to improve people's ability to focus attention, compared to tasks of low load (e.g. Lavie, 2005). However the effects of perceptual load on the ability to sustain attention over prolonged task periods have not been established so far. The lab-rotation project will test the effects of perceptual load on sustained attention, using EEG to assess neural measures of attention capacity, and the mediating neural energy levels. The PhD research will be developed together with the student to extend the research to develop new tasks that capture better the impact of sustained attention decline on cognition (e.g. memory) and mood, considering also mental health states and conditions known to affect neural energy levels (e.g. depression and stress), and investigating manipulations aiming to improve attention and cognitive focus in these conditions

Relevant publications 1

Esterman, M. & Rothlein, D. Models of sustained attention. Curr. Opin. Psychol. 29, 174–180 (2019).

Relevant publications 2

Lavie, N. Attention, Distraction, and Cognitive Control Under Load. Curr. Dir. Psy. Sci. 19, 143–148 (2010).

Professor Glyn Lewis

Position: Professor of Epidemiological Psychiatry
Department: Division of Psychiatry
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/40255-glyn-lewis
Email contact: glyn.lewis@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

I am a psychiatric epidemiologist who also carries out randomised controlled trials. My research is focused on results that will change policy or improve the treatments for people with psychiatric illness. I will encourage students to pursue their own ideas and develop skills in the analysis and interpretation of epidemiological data.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

1) Epidemiology of Catatonia Catatonia is a condition that occurs in a variety of psychiatric disorders in which there are marked motor symptoms including abnormal movements, immobility and alterations in speech. Little is known about its epidemiology. With collaborators in the Karolinska Institute, we have access to a unique record linkage over the whole of Sweden (~10m people) over several decades. It will allow the first population based study of catatonia to examine a variety of questions. These include 1. What are the demographic and clinical characteristics of individuals with catatonia? 2. How does the mortality of individuals with schizophrenia with catatonia compare to those with schizophrenia without catatonia? 3. Is there evidence for a causal role of infection or autoimmunity in catatonia? The student would learn about the design, analysis and interpretation of longitudinal studies. A variety of statistical methods could be used including logistic regression and survival analysis. The project will involve learning how to choose confounders and adjust for them in statistical models. The project could be developed into a PhD. This would be jointly supervised with Dr Jonathan Rogers. 2) Contraceptive pill and mental health There is some evidence that hormonal contraceptives could increase the risk of depression in women. The current evidence is primarily from record linkages in Scandinavia. However, it is well known that people identified with depression via health records are a very biased group of people. The ideal method is to use standardised assessments to assess depressive symptoms in a longitudinal study. We would use data from the Avon Longitudinal Study of Parents and Children (ALSPAC) a large ~14,000 birth cohort of people born in 1991/92 in the Bristol area of the UK. ALSPAC is unique in having the most intensively phenotyped participants of any birth cohort in the world with about 78,000 variables for each participant. The student would learn about the design, analysis and interpretation of longitudinal cohort data. Analytical approaches towards adjusting for confounders and missing data would be taught.

Relevant publications 1

The association of alcohol dependence and consumption during adolescence with depression in young adulthoodhttps://pubmed.ncbi.nlm.nih.gov/37271164/

Relevant publications 2

Maintenance or discontinuation of antidepressants in primary care https://pubmed.ncbi.nlm.nih.gov/34587384/

Professor Vladimir Litvak

Position: Professor of Translational Neurophysiology
Department: UCL Queen Square Institute of Neurology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/10801-vladimir-litvak
Email contact: v.litvak@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Intracranial monitoring in patients with treatment-resistant epilepsy provides a unique opportunity to record and stimulate the brain in awake humans. Our research aims to leverage this opportunity to develop novel brains stimulation approaches for the treatment of psychiatric disorders.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The student will learn to reconstruct electrode locations using the Lead-DBS toolbox (https://www.lead-dbs.org/) and use electric field modelling combined with normative functional and structural connectomes to predict the cognitive tasks most likely to be affected by stimulation of particular electrode contacts. The full PhD will involve invasive and non-invasive brain recordings and brain stimulation in epilepsy patients combined with structural and functional mapping to identify stimulation targets that modulate circuits relevant to psychiatric symptoms.

Relevant publications 1

Allawala, A., Bijanki, K. R., Goodman, W., Cohn, J. F., Viswanathan, A., Yoshor, D., Borton, D. A., Pouratian, N., & Sheth, S. A. (2021). A Novel Framework for Network-Targeted Neuropsychiatric Deep Brain Stimulation. Neurosurgery, 89(2), E116–E121. https://doi.org/10.1093/neuros/nyab112

Relevant publications 2

Zhang, S., Cao, C., Quinn, A., Vivekananda, U., Zhan, S., Liu, W., Sun, B., Woolrich, M., Lu, Q., & Litvak, V. (2021). Dynamic analysis on simultaneous iEEG-MEG data via hidden Markov model. NeuroImage, 233, 117923. https://doi.org/10.1016/j.neuroimage.2021.117923

Dr Kenneth Man

Position: Lecturer in Pharmacoepidemiology and Drug Safety
Department: School of Pharmacy
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/67713-kenneth-man
Email contact: kenneth.man@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

his project uses population-based eHealth data, including the Clinical Practice Research Datalink, and advanced epidemiological techniques to investigate the impact of maternal psychiatric medication during pregnancy on the risk of central nervous system (CNS) disorders in offspring.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Rotation Project: Characterisation of Psychiatric Medication Utilisation and Clusters Before, During, and After Pregnancy Background: Pregnancy presents unique challenges in managing psychiatric conditions, often necessitating the use of medications that could impact both maternal and foetal health. Understanding medication utilisation patterns and their changes during pregnancy is critical for developing safe and effective treatment guidelines. Aims: 1. Determine the utilisation patterns of psychiatric medications before, during, and after pregnancy. 2. Analyse how psychiatric medication clusters change across these periods. 3. Investigate the prevalence and patterns of psychiatric co-medications during pregnancy. Methods: 1. Utilise the Clinical Practice Research Datalink (CPRD) to identify a cohort of pregnant women. 2. Calculate treatment episodes during pregnancy and generate results to represent medication use before, during, and after pregnancy. 3. Identify clusters within the medication networks, stratified by year, comorbidities, and pregnancy trimester. Activities: - Month-1: Training on data handling and cleaning, initial extraction of relevant data on psychiatric medications. - Month-2: Conduct preliminary analyses to calculate treatment episodes and create initial networks representing medication use. - Month-3: Perform clustering analyses and interpret results, preparing a summary report with findings and implications for further research. Potential for PhD Project: This rotation project will provide a comprehensive overview of psychiatric medication patterns during pregnancy, laying the foundation for a PhD project focused on in-depth analysis of specific medications, their safety profiles, and impacts on maternal and offspring health. The findings will inform clinical guidelines and promote safe prescribing practices for pregnant women with psychiatric conditions.

Relevant publications 1

Chan AYL et al. Maternal diabetes and risk of attention-deficit/hyperactivity disorder in offspring in a multinational cohort of 3.6 million mother-child pairs. Nat Med. 2024 May;30(5):1416-1423.

Relevant publications 2

Chan AYL et al. Maternal Benzodiazepines and Z-Drugs Use during Pregnancy and Adverse Birth and Neurodevelopmental Outcomes in Offspring: A Population-Based Cohort Study. Psychother Psychosom. 2023;92(2):113-123.

Associate Professor Torsten Marquardt

Position: Senior Lecturer
Department: Ear Institute
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/4881-torsten-marquardt
Email contact: t.marquardt@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Otoacoustic emissions: The dynamic range of sound pressures processed by the inner ear is astonishing, achieved by its highly compressive non-linearity. Otoacoustic emissions are byproduct of this nonlinearity, measurable noninvasively with a microphone in the ear canal. Although clinically applied worldwide, their diagnostic potential is yet to be fully exploited.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Dynamic range compression, which disappears with sensorineural hearing loss, is important feature of the healthy ear so that the limited firing rate range of the auditory nerve can encode a extremely wide range of sound levels (>120 dB!). Recently Dewey and Shera (2023) showed that otoacoustic emissions can non-invasively reveal the sharpness of cochlear frequency tuning, and recent experiments in my lab sparked the idea that they could also be used to quantify the compressive growth of cochlear vibrations as sound level increases. In this rotation project, this idea will be further verified with 8-10 young normal hearing participants by showing that the technique reveals the known increase of compression with increasing stimulus frequency, and also, that a frequency-specific reduction in compression is expected in cochlear region with reduced hearing sensitivity. Thus, audiograms (hearing threshold tests) will be obtained, from which a high and a low frequency of good hearing sensitivity will be picked, as well as a frequency within a region of elevated hearing loss (if existent). Then the otoacoustic emission technique will be applied with primary stimuli near these three frequencies to measure the compression ratio for cochlear regions coding these. The technique is based on the modulation of the emissions by an additional very low-frequency tone (<50 Hz), to which the cochlear response is known to grow linearly with sound level. The possible PhD project will then involve an objective verification in the gerbil in-vivo model using phase-sensitive Optical Coherence Tomography, like utilized by Dewey and Shera.

Relevant publications 1

General OAE review at https://journals.lww.com/ear-hearing/fulltext/2004/04000/mechanisms_of_mammalian_otoacoustic_emission_and.2.aspx

Relevant publications 2

Dewey and Shera (2023) at https://link.springer.com/article/10.1007/s10162-023-00892-4

Professor Andrew McQuillin

Position: Professor of Molecular Psychiatry
Department: Division of Psychiatry
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/4478-andrew-mcquillin
Email contact: a.mcquillin@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

This project aims to advance our understanding of schizophrenia's pathophysiology by identifying unique behavioural signatures (e.g., alterations in sleep or social behaviour), characterizing changes in brain function, and identifying anatomical changes unique to mutations responsible for risk of developing schizophrenia.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

This project aims to advance our understanding of schizophrenia's pathophysiology by identifying unique behavioural signatures (e.g., alterations in sleep or social behaviour), characterizing changes in brain function, and identifying anatomical changes unique to zebrafish models of mutations responsible for risk of developing schizophrenia.

Relevant publications 1

Singh et al., Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature 2022. PMID: 35396579

Relevant publications 2

Dreosti et al., Development of social behavior in young zebrafish. Front Neural Circuits 2015. PMID: 26347614

Professor Emad Moeendarbary

Position: Professor of Cell Mechanics and Mechanobiology
Department: Mechanical Engineering
University UCL
Faculty: Engineering Sciences
Profile: https://profiles.ucl.ac.uk/24395-emad-moeendarbary
Email contact: e.moeendarbary@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Myelination, driven by oligodendrocytes, is vital for brain development and cognitive functions like learning and memory. Current in vitro models lack physiological relevance. In this project, we address this shortcoming by combining hydrogel materials with 3D axon-like structures, mimicking brain tissue to study oligodendrocyte wrapping artificial axons more accurately.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The brain is one of the softest organs in our body, and oligodendrocytes are mechanosensitive, implying that the mechanical microenvironment governs their behaviour. However, one major obstacle in myelination studies is the use of conventional plastic/glass dishes or very hard fibrous materials that are much stiffer than the brain. During the rotation project, the student will focus on establishing the foundational skills necessary for the PhD project. Oligodendrocytes will be cultured on polyacrylamide using three different stiffnesses: (1) 0.5 kPa corresponding to the physiological range of brain elasticity, (2) 5 kPa comparable to the stiffness of axons and (3) 50 kPa representing a stiff material as a control (i.e. similar to conventional techniques). The impact of substrate material will also be investigated by comparing myelination on hydrogel versus plastic-based micropillar arrays. Aims/ steps/supervision/ timeline: 1. Culturing Techniques: Learn techniques for extracting and culturing oligodendrocytes. 2. Micropillar Setup: Establish micropillar assay and perform initial myelination assays (Moeendarbary). 3. Effects of changes in stiffness and material properties: Study the impact of changes in mechanical cues on OL myelination using immunofluorescence imaging. Learn immunofluorescence and imaging techniques. 4. Analysis: Learn and apply Image and data analysis. The PhD project uses a novel platform to explore how mechanical features of axon-like structures and biochemical cues from glial cells impact myelination. It integrates neurobiology, material science, and engineering, with Professors Moeendarbary and Pedarzani (joint supervisor of the project) providing expertise in microfabrication, mechanobiology, calcium imaging, and electrophysiology.

Relevant publications 1

Hall C. M., Moeendarbary E., & Sheridan G. K. Mechanobiology of the brain in ageing and Alzheimer's disease. Eur. J. Neurosci., 53, 3851–3878 (2021).

Relevant publications 2

Jagielska A., et al. Mechanical environment modulates biological properties of oligodendrocyte progenitor cells. Stem Cells Dev., 21, 2905–2914 (2012).

Dr Nicola Morant

Position: Professor of Qualitative Mental Health Research
Department: Division of Psychiatry, UCL
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/31284-nicola-morant
Email contact: n.morant@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

I am a specialist in qualitative mental health research. My interests centre around collaborative forms of psychiatric medication management, in particular antipsychotics, and the development of shared decision making in this field. I also lead qualitative work within larger mixed-methods projects across a broad spectrum of mental health topics. https://profiles.ucl.ac.uk/31284-nicola-morant

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Exploring experiences and processes of clinically guided antipsychotic reductions within the RADAR trial: Antipsychotic medication brings evidenced symptom control for people with psychosis but users often want to reduce or stop medication. Little is known about the feasibility or impact of this when done gradually with clinical support. The recently completed RADAR RCT compared reduction or discontinuation of antipsychotic medication with maintenance treatment over 24 months. Embedded qualitative studies that explored sub-samples of service users' and psychiatrists' experiences of reduction / discontinuation produced rich data. There are several opportunities for secondary analysis of these data sets in combination with quantitative trial data. Possibilities include exploring sub-groups of service users in terms of how they engaged with and experienced antipsychotic reduction processes; and investigations of how antipsychotic reduction processes were implemented within clinician-service user dyads. These could include using innovative qualitative data analysis techniques such as thematic narrative analysis or ideal type analysis. This rotation project provides opportunities to: i) learn about current research on antipsychotic medication; ii) develop or enhance qualitative data analysis skills. It could be developed into a full mixed-methods PhD in this area that would combine analysis of existing data with further primary quantitative / qualitative data collection to extend knowledge in a field that is highly clinically relevant but where the existing evidence base is limited.

Relevant publications 1

Morant N, Long M, Jayacodi S, Cooper R, Akther-Robertson J, Stansfeld J, Horowitz M, Priebe, Moncrieff J. (2023) Experiences of reduction and discontinuation of antipsychotics: A qualitative investigation within the 'RADAR' trial. eClinicalMedicine, 64: 102135. https://doi.org/10.1016/j.eclinm.2023.102135

Relevant publications 2

Morant, N., Kaminskiy, E. & Ramon, S. (2016) Shared Decision-Making for Psychiatric Medication Management: Beyond the micro-social. Health Expectations, 19 (2): 1002–1014. DOI - 10.1111/hex.12392.

Professor Jason Rihel

Position: Professor of Behavioural Genetics
Department: Cell and Developmental Biology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/35291-jason-rihel
Email contact: j.rihel@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We study the genes and neurons that regulate sleep, using the zebrafish as a model system. Zebrafish larvae exhibit periods of inactivity at night that fulfil the behavioural criteria for sleep. Their brains have critical sleep circuits, such as the orexin neurons, which are lost in humans with narcolepsy.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We have a variety of rotation projects using chemical biology, behavioural genetics, and neuroimaging to study sleep in zebrafish larvae. A few examples are listed here, but I am happy to discuss other potential projects focused on sleep. 1. What are the neuropeptides that regulate rebound sleep following sleep deprivation? We have recently developed several methods to reliably sleep deprive larval zebrafish, which induces rebound sleep. In this rotation project, the student will examine how neuropeptides change expression during and after sleep deprivation, will make genetic tools (e.g. Crispr generated mutants) to dissect the underlying mechanisms of rebound sleep, and will use small molecules to investigate how rebound sleep is affected by vigilance drugs. 2. What are the sleep-related phenotypes of autism and Alzheimer's disease (AD) risk genes? Disrupted sleep is a major component of neural disorders, and we have found that zebrafish autism and AD models have sleep phenotypes. In this rotation project, students will test mutants for sleep phenotypes, examine alterations in brain structure with confocal imaging, and test whether hypothalamic circuits are perturbed. 3. How do synapses change during sleep? The project will use optical imaging techniques to observe in vivo the dynamic changes to synapses in the larval zebrafish brain during sleep and wake states, following sleep deprivation, and in response to sleep-regulatory drugs and gene disruption. I list two relevant papers written by former PhD students.

Relevant publications 1

Suppermpool A, Lyons DG, Broom E, Rihel J* (2024). "Sleep pressure modulates single-neuron synapse dynamics in zebrafish". Nature 629, 639-45. https://doi.org/10.1038/s41586-024-07367-3

Relevant publications 2

Kroll F, Donnelly J, Özcan GG, Mackay E, and Rihel J* (2024) "Behavioural pharmacology predicts disrupted signalling pathways and candidate therapeutics from zebrafish mutants of Alzheimer's disease risk genes". eLife13:RP96839 https://doi.org/10.7554/eLife.96839.1

Professor Mala Shah

Position: Professor of Neuroscience
Department: Pharmacology, School of Pharmacy
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/19244-mala-shah
Email contact: mala.shah@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We focus on understanding the mechanisms by which G-protein coupled receptor (GPCR) activation by neurotransmitters alters intrinsic excitability in hippocampal neurons. We have also made significant contributions to understanding the role of K+ and Ca2+ channels in modifying neuronal activity in hippocampal and cortical neurons using electrophysiological and imaging approaches

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We can offer different types of rotation projects and I am happy to discuss projects with students. One potential rotation project would be to investigate modulation of GIRK channel function by M1 receptors in hippocampal dentate gyrus granule neurons. GIRK channels are constitutively active K+ channels that play a critical role in regulating the resting membrane potential and membrane conductance of granule neurons. Their activity is modified by G-proteins (Gonzalez et al., 2018). However, very little is known about their regulation of GPCRs. Our data shows that M1 receptor activation significantly depolarises the membrane potential and increases the membrane conductance of granule neurons (Martinello et al., 2015). We, however, do know the mechanism(s) by which M1 receptors exert these effects. One hypothesis is that M1 receptors inhibit GIRK channels to exert these effects. The project will test this hypothesis by making electrophysiological recordings from granule neurons present in brain slices. We have significant expertise in this method and it will be an opportunity for a student to learn this technique. A longer term research/Ph.D. project would entail using a combination of electrophysiological and imaging approaches to determine whether M1 receptors in granule neuron dendrites would alter synaptic potential shapes and integration by modulating GIRK and/or other K+ channel activity.

Relevant publications 1

§ Martinello, K., Huang, Z., Lujan, R., Tran, B., Watanabe, M., Cooper, E.C., Brown, D.A. & Shah, M.M (2015) Cholinergic afferent stimulation induces axonal function plasticity in adult hippocampal granule cells, Neuron, 85 (2), 346-363

Relevant publications 2

§ Gonzalez, J.C., Epps, S.J., Markwardt, J., Wadiche, J.I., and Overstreet-Wadiche, L. (2018) Constitutive and synaptic activation differentiates mature and newborn dentate gyrus granule neurons. Journal of Neuroscience, 38, 6513-6526.

Profesor Tali Sharot

Position: Professor of Cognitive Neuroscience
Department: Experimental Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/5515-tali-sharot
Email contact: t.sharot@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

I am especially interested in understanding human decision making, information processing, belief formation and motivation. My lab aims to bridge the gap between theory and real-world applications. Our research findings have a range of implications for improving mental health, reducing misinformation and improving the interactions between humans and technology. Our research is interdisciplinary, sitting at the intersection of psychology, neuroscience and economics. We leverage a multidisciplinary approach, combining computational modeling, virtual reality tools, neuroimaging techniques, behavioral experiments, psychopharmacology, analysis of web browsing behavior and natural language processing, to gain a comprehensive understanding of the human mind, brain and behavior.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Humans derive pleasure from cognitive activities (e.g., reading books, solving puzzles, playing chess). They may even engage with such activities at a cost. Why do some mental activities elicit hedonic reactions? What is the mechanism that ties cognition with pleasure? How does this mechanism develop and what happens when it is impaired? While a large literature is dedicated to the study of primary (food, sex) and secondary (material) reward processing, 'cognitive rewards' have been relatively overlooked. This is a critical gap in our understanding, given the important role cognitive rewards likely play in human flourishing. The proposed study's aim is to identify core features, common computations, and neural fingerprints of cognitive rewards. We will examine whether individual differences in sensitivity to cognitive rewards is related to mental health and how such sensitivity emerges. To that end, we will combine large online behavioral experiments with neuroimaging and computational methods.

Relevant publications 1

https://www.nature.com/articles/s44220-023-00116-x

Relevant publications 2

https://osf.io/preprints/psyarxiv/yd6j5

Dr Henrik Singmann

Position: Associate Professor
Department: Experimental Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/77922-henrik-singmann
Email contact: h.singmann@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My lab is focussed on two research streams: (1) Developing formal and/or computational models of memory and decision making focussing mostly on behavioural data. (2) The development and implementation of computational methods and statistical tools for psychology, neuroscience, and related disciplines using the statistical programming languages R and Stan.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

A key distinction in memory is between long-term memory (LTM) and working-memory (WM). While LTM is assumed to have an unlimited capacity, WM is limited to maintaining a handful of item-feature bindings. This distinction also has important mental health implications. Some disorders (e.g., depression) show specific LTM deficits (e.g., better memory for negative material), whereas others (e.g., ADHD) show reduced WM performance. Whereas the theoretical distinction between WM and LTM is well-established, the empirical distinction is not. The main difference between tasks in both domains is the number of items that participants need to encode, less than ten in WM tasks and typically much more (20+) in LTM tasks. However, not all tasks with small memory sets necessarily require cognitive processes that are assumed to be central to WM, binding and/or updating. The goal of the project is to provide empirical evidence which WM tasks require WM involvement and which can be solved solely through LTM alone. For this, we will use a formal empirical test that allows assessing whether memory judgments can be described by the general class of signal-detection theory (SDT) models, which assumes unlimited capacity and no WM limit. In earlier work (Kellen et al., 2021) we have shown that LTM judgements follow SDT. In the rotation project we test for one specific WM task whether it requires WM involvement or not. In the PhD project we aim to extend this work and exactly pinpoint which task features require WM involvement and which not.

Relevant publications 1

Kellen, D., Winiger, S., Dunn, J. C., & Singmann, H. (2021). Testing the foundations of signal detection theory in recognition memory. Psychological Review, 128(6), 1022-1050. https://doi.org/10.1037/rev0000288

Relevant publications 2

Singmann, H., Kellen, D., Cox, G. E., Chandramouli, S. H., Davis-Stober, C. P., Dunn, J. C., Gronau, Q. F., Kalish, M. L., McMullin, S. D., Navarro, D. J., & Shiffrin, R. M. (2023). Statistics in the Service of Science: Don't Let the Tail Wag the Dog. Computational Brain & Behavior, 6(1), 64–83. https://doi.org/10.1007/s42113-022-00129-2

Professor Trevor Smart

Position: Schild Professor of Pharmacology
Department: Neuroscience, Physiology & Pharmacology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/674-trevor-smart
Email contact: t.smart@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Our research focusses on how GABA receptors provide inhibition throughout healthy brains, and how dysfunction features in disease. We utilise an array of approaches including structural/molecular biology, electrophysiology, imaging and behaviour to study the molecular properties of these receptors, their roles in neuronal and network activity, and impact upon behaviour.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

The amygdala plays a centrally important role in anxiety and fear. Activity within the amygdala is critically controlled via inhibition provided by GABAA receptors. As in other brain centres, amygdala GABAA receptors are subject to modulation by innately synthesized neurosteroids whose levels vary depending upon behavioural state and pathophysiology. However, we know very little about how neurosteroids modulate specific populations of GABAA receptors to control amygdala-dependent anxiety and fear. Recent evidence suggests that neurosteroid modulation of parvalbumin-expressing interneurons (PV-INs) in the basolateral amygdala (BLA) may be important for controlling anxiety. However, and also important from a translational perspective, it is unclear what type of GABAA receptors are involved and how these may relate to neurosteroid modulation of excitatory principal neurons (PNs) within the BLA and mental health. Our rotation project will involve using immunohistochemistry to explore those GABAA receptors expressed by BLA INs, focusing on two specific subtypes: α2β3δ and α4β3δ. In parallel, neurosteroid modulation of these receptors will be assessed by using heterologous expression in cell lines and single cell patch clamp electrophysiology. The project will evolve from a rotation into a PhD study by (i) assessing the functional role of neurosteroids in modulating inhibition onto both BLA PNs and INs using acute brain slice electrophysiology; (ii) dissecting the role of specific GABAA receptors by the use of two unique transgenic mouse lines expressing either α2- or α4-GABAARs that are uniquely insensitive to neurosteroids; (iii) exploring the importance of neurosteroid modulation of these amygdala GABAA receptors for anxiety and fear by using a battery of behavioural tests; and (iv) investigating the translational potential of the neurosteroid binding site as a target in amygdala GABAA receptors for treating affective and anxiety disorders, using both established and novel neurosteroid ligands, assessed by electrophysiology and behavioural assays.

Relevant publications 1

3. Durkin EJ, Muessig L, Herlt T, Lumb MJ, Patel R, Thomas P, Bright DP, Jurd R, Moss SJ, Dickenson AH, Cacucci F, Trevor G Smart (2018). Brain neurosteroids are natural anxiolytics targeting α2 subunit γ-aminobutyric acid type-A receptors. BioRxiv 462457; doi: https://doi.org/10.1101/462457

Relevant publications 2

2. Kasaragod VB, et al. 2022 Mechanisms of inhibition and activation of extrasynaptic αβ GABAA receptors. Nature 602, 529-533.

Professor Aimee Spector

Position: Professor of Clinical Psychology of Ageing
Department: Clinical, Educational & Health Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/1239-aimee-spector
Email contact: a.spector@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My research focuses on the development, evaluation and implementation of psychosocial interventions in ageing. My interest in menopause transition, affecting half the world's population; stems from its neglect in research to date. I focus on understanding changes in cognitive and mental health and developing effective interventions, applying a cross-cultural lens.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Cognitive complaints at menopause transition, often described as 'brain fog'; include difficulty recalling words and numbers, misplacing items, trouble concentrating and forgetfulness. Longitudinal datasets suggest that around 10% of women show clinically significant changes in verbal learning and memory, although the data has many limitations including the use of unsuitable outcome measures with ceiling effects. Many questions remain unanswered, including the impact of hormone therapy and other factors on cognitive complaints, and cross-cultural differences. Whilst these difficulties resolve for most people, several years of reduced cognitive functioning can be highly damaging. Despite emerging data suggesting that approximately one in ten women leave the workforce during this time and that vulnerability to depression significantly increases, this is an area in which both research and provision of support have been vastly neglected to date. I am keen on a project that further develops our understanding of the notion of 'brain fog' including its presentation, mediating and moderating factors; potentially resulting in the development of some clearer guidelines / classification. The initial placement could involve a systematic review of the research to date. We also have related projects within the UCL Menopause Mind Lab that the student could get involved in, including the development of a measure of objective cognition and the development of an intervention to help manage cognitive problems in menopause transition.

Relevant publications 1

6. Spector, A., Li, Z., He, L., Badawy, Y., & Desai, R. (2024). The effectiveness of psychosocial interventions on non-physiological symptoms of menopause: A systematic review and meta-analysis. Journal of Affective Disorders.

Relevant publications 2

Badawy, Y., Spector, A., Lee, Z., & Desai, R. (2024). The risk of depression in the menopausal stages: A systematic review and meta-analysis. Journal of Affective Disorders.

Professor Hugo Spiers

Position: Professor of Cognitive Neuroscience
Department: Experimental Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/2293-hugo-spiers
Email contact: h.spiers@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My research group studies spatial cognition and neural representations of space and conduct research on the topic of Neuroarchitecture. We use a range of methods/facilities including: UCL PEARL, virtual reality, mobile apps, fMRI, fNIRS and other methods to test behaviour, cognition and record neural activity.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

We are seeking to explore fundamental principles in how the geometry of the environment and the density of people within it impact spatial behaviours such as exploration, wayfinding and escape behaviour, as well as the neural dynamics. We have set up a protocol at the UCL PEARL facility to record from over 100 people as they simultaneously navigate a light/temperature/sound controlled large maze-like environment. The rotation will help collect data from participants in this controlled environment and analyse the trajectory patterns and choices. The project would extend to a PhD by either further research on modelling the behaviour with generative models in collaboration with the Max Plank Centre for Collective Behaviour, or exploring mobile EEG data in collaboration with the Mobile Imaging Lab in Berlin, depending on the student's interests. This work leads on from past research we have done in VR simulating environments and artificial agents (Coutrot et al., 2022, Nature).

Relevant publications 1

Coutrot, A., Manley, E., Goodroe, S., Gahnstrom, C., Filomena, G., Yesiltepe, D., ... & Spiers, H. J. (2022). Entropy of city street networks linked to future spatial navigation ability. Nature, 604(7904), 104-110.

Relevant publications 2

De Cothi, W., Nyberg, N., Griesbauer, E. M., Ghanamé, C., Zisch, F., Lefort, J. M., ... & Spiers, H. J. (2022). Predictive maps in rats and humans for spatial navigation. Current Biology, 32(17), 3676-3689.

Professor Joshua Stott

Position: Professor of Ageing and Clinical Psychology
Department: Clinical, Educational, and Health Psychology
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/10969-joshua-stott
Email contact: j.stott@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

This project aims to improve understanding of neurodivergence in ageing and outcomes for older people who are 'AuDHD' (both autistic and ADHD). To do this, the student will analyse data from the AgeWellAutism (AWA) study. This is an opportunity to use unique data to research a topical, clinically-important area.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Ageing and neurodivergence and the impact of this intersection on health/wellbeing are key clinical concerns. ~40% of the UK's population are aged 50+, but only 0.4% of autism research has focussed on this group (1). Further, 90% of autistic people aged 50+ are undiagnosed (2), with similar rates likely in ADHD. PPI/lived-experience colleagues consistently raise the interaction of autism and ADHD, and how people with 'AuDHD' may have different health/wellbeing outcomes to those with only Autism or ADHD. This key clinical issue has not been addressed in people in mid-late life. The rotation project will explore: 1. Health/wellbeing profiles of a sub-sample of the AWA study, using questionnaire data from autistic participants with either low (N=296) or high (N=173) ADHD traits aged 40-90, to examine different outcomes in these groups. 2. Psychometric properties of the gold-standard ADHD trait screening measure (ASRS-5) in autistic people to understand its validity in this group, and whether a trait-based approach in research to address high levels of undiagnosed ADHD in older populations is possible. This will translate into student first-author publications. We have published >50 student-led papers previously. This can be expanded to a PhD using large-scale data our group has privileged access to (e.g., routine health records/treatment outcome data/ageing cohorts). The student will gain skills in quantitative (using advanced statistical modelling approaches [e.g., SEM/growth mixture modelling]), and, if they wish, qualitative (interviews and thematic analysis of experience) methods, to address important issues in mental health/neuroscience. Specialist support in methodologies is available throughout.

Relevant publications 1

Mason, D., Stewart, G. R., Capp, S. J., & Happé, F. (2022). Older age autism research: A rapidly growing field, but still a long way to go. Autism in Adulthood, 4(2), 164-172.

Relevant publications 2

O'Nions, E., Petersen, I., Buckman, J. E., Charlton, R., Cooper, C., Corbett, A., ... & Stott, J. (2023). Autism in England: assessing underdiagnosis in a population-based cohort study of prospectively collected primary care data. The Lancet Regional Health–Europe, 29.

Professor Kirill Volynski

Position: Professor of Neuroscience
Department: UCL Queen Square Institute of Neurology, Department of Clinical and Experimental Epilepsy
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/6950-kirill-volynski
Email contact: k.volynski@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

We have recently established a series of techniques to dissect the relationship between synaptic dysfunction and disease mechanisms at the protein, cellular, and network levels. The proposed project aims to provide insights into how disease-related mutations in synaptic proteins lead to disorders such as epilepsy, autism, and delayed neurodevelopment.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Mutations in presynaptic proteins that mediate synaptic neurotransmitter release cause severe neurodevelopmental disorders often associated with epilepsy and autism, collectively known as SNAREopathies. Our research targets mutations in vesicle-associated membrane protein 2 (VAMP2), a key component of synaptic vesicle exocytosis machinery. We have created an inducible transgenic knock-in mouse model with a VAMP2 disease mutant to study the relationship between altered synaptic transmission and disease and to develop targeted genetic therapies to restore normal function. The proposed rotation project will primarily focus on optimising gene therapy delivery. We will induce the disease at early developmental stages and use adeno-associated viral vectors expressing normal VAMP2 to rescue pathological phenotypes. The main goal is to compare the efficacy of gene therapy administration through both systemic (intravenous, intrathecal) and localised (intracerebral, intraventricular) delivery methods. Transduction efficiency and toxicity will be assessed using high-resolution imaging of fluorescent markers in fixed tissue. This rotation project will evolve into a PhD project, allowing the student to employ various strategies to further investigate the pathophysiology and treatment of SNAREopathies. These include screening pharmacological agents in vitro, performing glutamate imaging at single synapses in culture, investigating network electrophysiology in acute brain slices, conducting calcium imaging in awake mice, and using rodent telemetry and behaviour analysis to assess functional outcomes. Through these experimental approaches, the student will gain insights into operation of synaptic release machinery and the connection between synaptic dysfunction and the pathological network activity seen in epilepsy, autism, and other related disorders.

Relevant publications 1

Salpietro, V., Malintan, N. T., Llano-Rivas, I., Spaeth, C. G., Efthymiou, S., Striano, P., Vandrovcova, J., Cutrupi, M. C., Chimenz, R., David, E., Di Rosa, G., Marce-Grau, A., Raspall-Chaure, M., Martin-Hernandez, E., Zara, F., Minetti, C., Deciphering Developmental Disorders Study, SYNAPS Study Group, Bello, O. D., De Zorzi, R., … Houlden, H. (2019). Mutations in the Neuronal Vesicular SNARE VAMP2 Affect Synaptic Membrane Fusion and Impair Human Neurodevelopment. American journal of human genetics, 104(4), 721–730. https://doi.org/10.1016/j.ajhg.2019.02.016

Relevant publications 2

Qiu, Y., O'Neill, N., Maffei, B., Zourray, C., Almacellas-Barbanoj, A., Carpenter, J. C., Jones, S. P., Leite, M., Turner, T. J., Moreira, F. C., Snowball, A., Shekh-Ahmad, T., Magloire, V., Barral, S., Kurian, M. A., Walker, M. C., Schorge, S., Kullmann, D. M., & Lignani, G. (2022). On-demand cell-autonomous gene therapy for brain circuit disorders. Science (New York, N.Y.), 378(6619), 523–532. https://doi.org/10.1126/science.abq6656

Professor Jason Warren

Position: Professor of Neurology
Department: Dept of Neurodegenerative Disease (Dementia Research Centre)
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/9248-jason-warren
Email contact: jason.warren@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My group investigates how pathogenic proteins spreading through neural circuits produce symptoms of abnormal brain function in major dementias - particularly Alzheimer's disease, frontotemporal dementia and primary progressive aphasia. We seek to identify new, dynamic physiological mechanisms and biomarkers of dementia, as the key to earlier diagnosis and ultimately, treatments.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Title: A model paradigm for assessing crossmodal sensory integration in dementia. Outline: Crossmodal integration of auditory and visual information is essential for negotiating the complex environments of everyday life and places high computational demands on neural circuitry. Impaired audio-visual integration is likely to be a sensitive and dynamic readout of neural circuit dysfunction in major dementias such as Alzheimer's disease and primary progressive aphasia, with implications for earlier diagnosis, tracking daily life disability and guiding treatments. However, cross-modal sensory integration has been little explored in these diseases. This rotation project will focus on creation and piloting of a cognitive instrument for assessing audio-visual integration in patients with Alzheimer's disease and primary progressive aphasia, using a classical neuropsychological model paradigm of high ecological relevance: the McGurk effect, whereby observation of orofacial movements modulates perceived speech sounds. The strength of the effect will be manipulated by systematically degrading visual and auditory information, and performance of patients will be compared with healthy older controls. In the PhD to follow, the paradigm will be expanded to assess generic mechanisms of auditory and visual integration in natural scenes in Alzheimer's disease and frontotemporal dementia, manipulating factors of perceptual ambiguity, semantic predictability and emotional valence that are likely to expose the early effects of particular neurodegenerative pathologies. Underlying neural mechanisms will be established by correlating behavioural audio-visual integration measures with structural and functional neuroanatomical substrates, using voxel-based morphometry, task-activation functional MRI and MEG.

Relevant publications 1

Jiang J, et al. Comprehension of acoustically degraded speech in Alzheimer's disease and primary progressive aphasia. Brain 2023; 146: 4065-76. doi: 10.1093/brain/awad163.

Relevant publications 2

Marshall CR, et al. The functional neuroanatomy of emotion processing in frontotemporal dementias. Brain 2019; 142: 2873-87. doi: 10.1093/brain/awz204.

Professor Rimona Weil

Position: Professor of Neurology
Department: Neurodegeneration
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/21029-rimona-weil
Email contact: r.weil@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Our group aims to understand how dementia happens in Parkinson's and dementia with Lewy bodies. We use advanced brain imaging and fluid markers to understand these conditions better and to develop markers of disease progression.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Lewy body dementia (LBD) is the second commonest cause of degenerative dementia. The underlying brain mechanisms are not understood, but there is increasing research showing the importance of cholinergic pathways. The nucleus basalis of Meynert (NBM) in the basal forebrain is one of the key sources of cholinergic neurons, with widespread connections to the rest of the brain. Although early NBM degeneration in LBD is well-established, the effects of this degeneration on structural and functional NBM-cortical connections is not yet known. The aim of this rotation project is to examine functional connectivity between the NBM and cortical regions, using seed-based functional connectivity. You will make use of resting state MRI data we have collected in LBD patients. You will preprocess and analyse resting state data, supported by our lab who have a track-record in functional and structural connectivity. You will relate changes in functional connectivity with clinical measures of disease severity, such as scores on cognitive tests. This project will be the start point for a PhD. Next steps will be quantifying loss of structural connectivity, using diffusion weighted imaging; and investigating changes in relationship between functional and structural connectivity. You could relate changes to symptoms such as hallucinations. If you are interested, you could use dynamic causal modelling to examine the direction of changes in NBM connections. You could also investigate how early changes predict symptom severity after follow-up. You will have the opportunity to collect new MRI data, and to train in neuropsychology testing of LBD patients.

Relevant publications 1

Zarkali, Weil Neuroimaging and plasma evidence of early white matter loss in Parkinson's disease with poor outcomes, Brain Communications, 2024 PMID: 38715714: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11073930/

Relevant publications 2

Oswal A et al: Cortical connectivity of the nucleus basalis of Meynert in Parkinson's disease and Lewy body dementias, Brain 2021 PMID: 33521808: https://academic.oup.com/brain/article/144/3/781/6125159?login=true

Dr Sarah White

Position: Royal Society Dorothy Hodgkin Research Fellow
Department: Institute of Cognitive Neuroscience
University UCL
Faculty: Brain Sciences
Profile: https://profiles.ucl.ac.uk/11683-sarah-white
Email contact: s.white@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

• studying cognitive differences in the autistic mind through the lifespan, using neuropsychological tasks, eye-tracking and neuroimaging techniques; • how mentalizing affects other areas of cognition and behaviour (laughter, lie detection, mental time travel, mental health…); • whether mentalizing can be modulated through changes to the environment (social, cultural, linguistic, double empathy problem…)

Rotation project **(including a brief outline of how this will develop into a PHD project)**

Is mentalizing affected by how similar you feel to your partner? Mentalizing is the ability to represent other people's mental states that are distinct from our own. Intergroup biases affect many different cognitive mechanisms and it may affect mentalizing too. In the case of autism, the double empathy problem suggests that social-communication difficulties are due to a mismatch in neurotypes resulting from a lack of similarity between autistic and non-autistic people. One way of understanding this is as an intergroup bias, which may lead to the mentalizing difficulties that autistic individuals often experience, but predicts that these difficulties will be most prevalent during interactions with non-autistic people. This rotation project would test whether people are better at mentalizing about people who are "like them" by using an implicit mentalizing eyetracking paradigm. You can choose your own bias to study, dependent on your own areas of interest. This might be a gender, cultural, or racial bias. Or it could be a diagnostic bias. Or something completely different. This bias could either be explicitly primed or it might be implicitly presented. The placement would involve task set up/programming in Tobii Pro Lab eye-tracking software, recruitment, data collection/processing/analysis and writeup. This could develop into a PhD in a number of ways – to take a developmental approach, or explore this in autism at different IQ levels, or investigate the neural basis for this effect. Or some combinations of these. Other related projects are also available – happy to chat through ideas you may have.

Relevant publications 1

Wu R, Hamilton A & White SJ (2024). Can group membership modulate the social abilities of autistic people? An intergroup bias in smile perception. Cortex, 173, 150-60.

Relevant publications 2

Wu R, Leow K, Yu N, Rafter C, Rosenbaum K, F de C Hamilton A & White SJ (2024). Evaluative Contexts Facilitate Implicit Mentalizing: Relation to the Broader Autism Phenotype and Mental Health. Nature Scientific Reports, 14, 4697.

Professor Tom Wills

Position: Associate Professor
Department: Cell and Developmental Biology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/5085-thomas-wills
Email contact: t.wills@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

My group studies neural circuits in the hippocampal formation and how they support memory and navigation. Much of our work focuses on the post-natal development of place, grid and head direction cells: which intrinsic and experience-dependent factors are required for normal development, and how neural circuit development supports memory emergence.

Rotation project **(including a brief outline of how this will develop into a PHD project)**

How do animals navigate to find remembered goals? One important cue are the boundaries of the accessible environment, in particular their geometry. In a rectangular arena, many animals (including human children) search for goals at locations defined purely by geometry, ignoring separate landmark cues which could provide disambiguating information. Interestingly, mice raised in circular environments are less likely to rely on rectangular geometry, suggesting a role for environmental experience. In the Hippocampus, there are neurons coding for the position of an animal with respect to environment boundaries ('Boundary Vector Cells'; BVCs). Our group showed that the receptive fields of BVCs are influenced by boundary geometry: in a square, BVCs preferentially signal direction relative to straight walls. This effect was observed early in development, suggesting it could be experience-independent. To resolve the ambiguities suggested by the two results above, this project will explicitly test whether the effect of boundary geometry on the neural map of space (for example BVCs) is experience-dependent or not. Neuronal activity in animals reared in circular cages will be recorded, during the first exposure to square geometry. State-of-the-art Neuropixels 2 probes will be used to detect whether BVC (or other spatial neurons') firing is influenced by the square geometry, during this first experience. The project can be expanded into a PhD by either investigating mechanisms of plasticity (e.g. synaptic plasticity) for any experience-dependent effects found, or testing whether there is a critical period window in which experience of geometry effects the neural map of space.

Relevant publications 1

Environment geometry alters subiculum boundary vector cell receptive fields in adulthood and early development. Laurenz Muessig, Fabio Ribeiro Rodrigues, Tale L. Bjerknes, Benjamin W. Towse, Caswell Barry, Neil Burgess, Edvard I. Moser, May-Britt Moser, Francesca Cacucci & Thomas J. Wills. Nature Communications volume 15, Article number: 982 (2024).

Relevant publications 2

Twyman, A. D., Newcombe, N. S., & Gould, T. J. (2013). Malleability in the development of spatial reorientation. Developmental Psychobiology, 55(3), 243–255.

Professor Stephen Wilson

Position: Professor of Developmental Biology
Department: Cell and Developmental Biology
University UCL
Faculty: Life Sciences
Profile: https://profiles.ucl.ac.uk/2491-steve-wilson
Email contact: s.wilson@ucl.ac.uk
Theme: Neuroscience and Mental Health

Research overview

Our brains are left-right asymmetric with respect to neuroanatomy, processing of information and control of behaviour. Why is this and how do asymmetries arise? We know little about the origins of asymmetry and we use developmental, genetic, imaging and behavioural approaches to study brain asymmetry in zebrafish to address these issues.

Rotation project (including a brief outline of how this will develop into a PHD project)

To find out how brain asymmetry is established, we use genetic screens in zebrafish to identify genes that, when disrupted, lead to altered forebrain lateralisation. We have found mutations that lead to symmetric brains with either double-left or double-right sided character. For instance, we have identified mutations in a novel Wnt-pathway protein, Cachd1, in which neurons on the right side of the brain develops left-sided features. The rotation project will be to perform a Crispr-Cas9 based genetic screen in genetically sensitised backgrounds to identify genes that interact with Cachd1 to mediate the asymmetric development of these normally asymmetric neurons. Further studies of the genes and developmental pathways identified or the circuitry and behavioural changes in the new mutants could form the basis of a full PhD project.

Relevant publications 1

Gareth T. Powell, et al. (2024) Cachd1 is a novel Frizzled- and LRP6-interacting protein required for neurons to acquire left-right asymmetric character. Science 384: 573-579.

Relevant publications 2

Lekk, I., Duboc, V., Faro, A., Nicolaou, S., Blader, P., and Wilson SW (2019). Sox1a mediates the ability of the parapineal to impart habenular left-right asymmetry. eLife 8 e47376. PMID 31373552