# SHERRINGTON TALKS 2023

## DEPARTMENT OF PHYSIOLOGY, ANATOMY & GENETICS

**BLAKEMORE LECTURE THEATRE**
**SHERRINGTON BUILDING**

**FRIDAY 9TH JUNE AND FRIDAY 16TH JUNE**

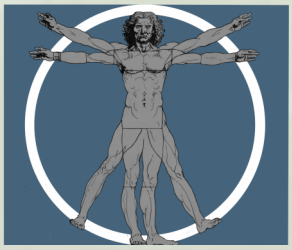
**FROM 1PM**

**'A Year of Progress' by DPAG Graduate Students in their 3rd year of DPhil research study**

**Chaired by DGS Professor Vladyslav Vyazovskiy, Associate Professor Carolyn Carr, Associate Professor Samira Lakhal-Littleton and Dr Armin Lak**

UNIVERSITY OF OXFORD

DPAG



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# SHERRINGTON TALKS DAY ONE 2023

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***Judged by Graduate Studies Committee Academics***

***Prize winners will be notified in the Digest on Monday 19th June***

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***Judged by Graduate Studies Committee Academics***

***Prize winners will be notified in the Digest on Monday 19th June***

**Judy Sayers**

## Regeneration of the Cardiac Conduction System

Supervisors: Professor Paul Riley & Dr Xin Sun

### Research Aim

Arrhythmias are a hallmark of myocardial infarction (MI) and contribute to poor prognosis. The cardiac conduction system is increasingly implicated in arrhythmia but how it is altered following MI is not well understood. I hypothesised there is a loss or impairment of the conduction system in adult infarcted hearts whereas it is preserved or rapidly restored in the regenerative neonatal setting, consistent with preserved normal rhythm.

### Methods and Results

Here, I utilised high-resolution wholemount imaging to characterise the cardiac conduction system in both intact and infarcted neonatal hearts across regenerative (post-natal day 1, P1), versus non-regenerative (post-natal day 7, P7) stages which recapitulate the mature injury response of fibrotic repair. In intact hearts I observed growth and expansion of the His/Purkinje network and changes in network morphology following MI between P1 and P7 stages. To ascertain whether there was a loss of specific subsets of conduction cells within the network and/or changes in the molecular response to injury across the regenerative to non-regenerative transition I utilised single-cell RNA sequencing of P1 and P7 hearts at 3-days post-injury. I detected a significant reduction in the electrical identity of the Purkinje populations of non-regenerating hearts after injury and a shift in cell type composition as compared to regenerative hearts. Imaging confirmed changes in conductivity in non-regenerative P7 hearts, with sustained loss of the fast conductance connexin-40 across broad regions of the His/Purkinje network remote from the infarct site. I am currently modelling the impact of connexin-40 loss on arrhythmogenesis and identifying functional targets to restore His/Purkinje conductivity in non-regenerative MI hearts.

### Conclusion

These findings elucidate both the transcriptional and cellular profile of the injured and regenerating cardiac conduction system after MI. I provide significant insights into conduction system pathophysiology during heart injury and identify molecular changes that might be targeted to maintain synchronous contraction in infarcted adult hearts.

**Kat Bochtler**

# Contextually and probabilistically weighted auditory selective attention

Supervisors: Associate Professor Kerry Walker

**Research Aim**

The ability to direct our attention towards a single sound source such as a friend's voice in a crowded room is necessary in our acoustical world. This process is thought to rely, in part, on directing attention to different sound dimensions, such as frequency. Previous investigations have shown task-dependent changes in the frequency tuning of auditory cortical neurons when ferrets actively detect or discriminate a particular frequency of sound (e.g. Fritz et al. 2010). However, questions remain about how attentional gain can arise based on sound statistics. Specifically, to what extent can this modulation occur even if frequency is not a necessary component of the task demands? Mondor & Bregman (1994) demonstrated that human listeners' reaction times on a tone duration task were slower when the presented tone frequency was unexpected (i.e. low probability). Here, we test the hypothesis that the statistical likelihood of sound frequencies alone can also affect animals' behavioural decisions on orthogonal dimensions of sounds.

**Methods and Results**

We trained ferrets on a 2-alternative forced choice tone duration discrimination task in which we manipulated the statistical likelihood of tone frequencies.

**Conclusion**

Our results show that, similar to humans, ferrets' reaction times on this duration judgement task increased for low-probability frequencies, while their accuracy remained stable across other frequencies. These results suggest that attentional filters are employed during listening, even for an acoustical dimension (frequency) that is orthogonal to the task demands (duration). Our future experiments will use this task in combination with microelectrode recordings to investigate the neurophysiological basis of statistical-based attentional filtering in the auditory cortex.

**Yitao Zhu**

# Sympathetic neuron-derived NPY protects from obesity by sustaining the mural progenitors of thermogenic adipocytes

Supervisors: Professor Ana Domingos Jansen and Associate Professor Neil Herring

## Research Aim

Neuropeptide Y (NPY) is secreted by sympathetic nerves, but its direct impact on thermogenic adipocytes is unknown. Here we uncover the mechanism by which peripheral NPY protects from obesity.

## Methods and Results

Our imaging of cleared murine brown and white adipose tissue (BAT and WAT) established that NPY+ sympathetic axons are only a minority that most maps to the peri-vasculature; our analysis of single-cell RNA -sequencing datasets identifies mural cells as the main NPY-responsive cells in adipose tissues. We show that NPY sustains mural cells, which are known to be a source of beige cells in both BAT and WAT and that NPY facilitates their differentiation to thermogenic adipocytes. We found that diet-induced obesity leads to neuropathy of NPY+ axons and concomitant depletion of the mural cell pool of beige fat progenitors. This defect is replicated in conditional knockout (cKO) mice with NPY specifically abrogated from sympathetic neurons. These cKO mice have whitened BAT with reduced thermogenic ability before the onset of obesity; they develop late-onset obesity on a regular chow diet and develop obesity more quickly when fed a high-fat diet without increasing food consumption.

## Conclusion

Our results indicate that relative to central NPY, which has an orexigenic function, peripheral NPY produced by the sympathetic nerves has the opposite effect on body weight homeostasis by sustaining the mural cell progenitor pool of thermogenic adipocytes. This finding is relevant to human epidemiological studies that NPY mutations lead to obesity independent of food intake.

**Naroa Ibarra Aizpurua**

# The role of astrocytes in Parkinson's disease pathogenesis in GBA N370S hiPSC-derived neuron-astrocyte co-cultures

Supervisors: Professor Richard Wade-Martins, Dr Nora Bengoa-Vergniory & Dr Sally Cowley

## Research Aim

Parkinson's disease (PD) is the second most common neurodegenerative disorder. To date, most studies investigating the mechanisms driving PD pathogenesis have focused on dopaminergic neurons (DAns), the cells most greatly affected in the disease, but emerging evidence has demonstrated that astrocytes also play a crucial role in its development. However, it is not clear whether astrocytes are neuroprotective to DAns or neurotoxic, potentially contributing to PD pathogenesis. Therefore, the aim of this project is to study the role astrocytes play in PD pathogenesis, focusing on astrocytes carrying the PD-associated GBA N370S mutation.

## Methods and Results

Using a recently published protocol, we generated control and GBA N370S iPSC-derived midbrain astrocytes (iASTROs) that express key astrocytic markers and respond to ATP by increasing their cytosolic calcium content. Additionally, we conducted a transcriptomics analysis to explore the inflammatory response of control iASTROs to different inflammatory cytokines and α-synuclein preformed fibrils (PFFs), both hallmarks of PD. Our results show that, after a 24h treatment, iASTROs do not undergo significant changes in response to PFFs, whereas when treated with inflammatory cytokines they respond by altering many cellular processes and acquire a reactive phenotype that does not fall into either the A1 (neurotoxic) or A2 (neuroprotective) categories previously described in the literature. Further in vitro studies with control and GBA N370S iASTROs corroborate these findings.
Furthermore, we established and optimised an in vitro co-culture system of iPSC-derived DAns (iDAns) and iASTROs. When co-cultured with iDAns, control and GBA N370S iASTROs enhance the survival of TH+ and MAP2+ neurons, as well as supporting the formation of more complex neurite trees. Moreover, control iASTROs promote the formation of synapses in GBA N370S iDAns. Lastly, our data suggests that, in co-culture with iDAns, control iASTROs retain their capacity to respond to inflammatory cytokines, and at the timepoint studied these reactive astrocytes enhance the survival of TH+ and MAP2+ neurons.

## Conclusion

In conclusion, iPSC-derived control and GBA N370S iASTROs undergo reactive astrogliosis in response to inflammatory cytokines but not α-synuclein PFFs, and these iASTROs support the growth and survival of iDAns regardless of their genotype.

**Kaitlyn Dennis**

# Selective palmitoylation of CD36 is associated with metabolic dysfunction in the type 2 diabetic heart

Supervisors: Associate Professor Lisa Heather & Professor Damian Tyler

## Research Aim

Cardiac metabolism is altered in type 2 diabetes (T2D) and is associated with impaired cardiac function. Membrane substrate transporters are the primary regulated step and are drivers of the metabolic dysfunction in T2D. We currently don't know what causes changes in membrane transporter subcellular location and function in T2D. Palmitoylation is a post-translational modification associated with protein trafficking. We questioned whether palmitoylation of the fatty acid transporter CD36 and glucose transporter GLUT4 was driving metabolic remodelling in the diabetic heart.

## Methods and Results

In a rat model of T2D, hearts were perfused in Langendorff mode with radioisotopes.
T2D hearts had abnormal substrate metabolism, with decreased glycolysis, decreased total and membrane GLUT4 protein content and no evidence of GLUT4 palmitoylation. In contrast, fatty acid oxidation and triacylglycerol storage were increased, with elevated total and membrane CD36 protein content. CD36 was palmitoylated in the heart and the palmitoylation of CD36 was significantly increased in T2D hearts. These findings were confirmed in insulin resistant human iPSC-CM and db/db mouse hearts.

## Conclusion

In conclusion, increased cardiac fat metabolism is associated with membrane CD36 relocation and selective palmitoylation of CD36 is a candidate for driving the metabolic derangements in T2D.

**Emma Haberman**

## Immunomodulatory Adipose Tissue Perineurial Cells Protect Against Obesity

Supervisors: Professor Ana Domingos Jansen & Professor Irina Udalova

### Research Aim

Obesity is a culmination of long-term energy imbalance, resulting in the storage of excess fats as triglycerides in adipose tissues (ATs). Sympathetically innervated ATs are key sites of both energy storage and hormone production. Leptin is one such hormone produced by adipocytes, released in proportion to AT mass. Leptin acts in the hypothalamus to diminish hunger and increase sympathetic drive onto ATs. This increase in sympathetic-derived norepinephrine stimulates adipocyte lipolysis and thermogenesis, providing a neuroendocrine negative feedback loop which broadly controls energy storage and energy expenditure. Obesity is closely associated with chronic, low-grade AT inflammation, mirrored by an increase in pro-inflammatory and a concomitant decrease in anti-inflammatory AT immune cells.

### Methods and Results

Here, we reveal a novel population of Leptin receptor+ perineurial cells ensheathing AT sympathetic neurons, which produce key anti-inflammatory cytokines, including IL33. We show that mice with a perineurial cell specific loss of IL33 gain more weight when fed high-fat diet despite comparable food intake - indicative of metabolic dysfunction. In the pre-obese state, a loss of perineurial cell derived IL33 reduces the frequency of anti-inflammatory regulatory immune cells, including regulatory T cells (Tregs) specifically within the brown adipose tissue (BAT). Along with this shift in BAT-populating immune cells, we show that these mice have impaired BAT thermogenesis, predisposing to obesity with both age and metabolic challenge.

### Conclusion

Together, this firmly implicates perineurial cells in the regulation of adipose tissue homeostasis.

**Florina Szabó**

# Does the abolition of synaptic vesicle release from deep-layer cortical projection neurons affect the development of GABAergic interneurons?

Supervisors: Professor Zoltán Molnár, Dr Anna Hoerder-Suabedissen & Associate Professor Ed Mann

**Research Aim**

Perturbations in cortical pyramidal cell numbers or activity have been shown to affect the survival of interneurons leading to aberrant network formation and functioning. The cellular and molecular mechanisms enabling pyramidal neurons to regulate the survival of interneurons are still unknown. We investigated whether regulated synaptic vesicle release from deep-layer projection neurons controls the distribution and number of GABAergic interneurons.

**Methods and Results**

To examine the role of pyramidal neuron activity in the maturation of parvalbumin-positive (PV) cells, we abolished calcium-dependent synaptic vesicle release in subsets of layer 5 and layer 6b pyramidal neurons across the entire cortical mantle using SNAP25 conditional knock-out mice. We examined the density of PV -expressing cells during and after development in the cortical and subcortical output target regions of layer 5 and 6b projection neurons. Chronic abolition of SNAP25 from layer 5 did not alter the density of cortical and subcortical PV+ cells at P21, but it altered their laminar distribution in S1. Layer 4 showed a significant decrease in PV cell density at P21, while the other cortical layers remained unaffected.

**Conclusion**

While the loss of Snap25 from layer 5 does not lead to area-specific changes in PV density, alterations in the cortical distribution and developmental trajectory of PV suggest that Ca2+-dependent neurotransmission from layer 5 pyramidal neurons may play a role in the development and maturation of PV cells. The neural activity of pyramidal cells may shape the formation of inhibitory circuits by regulating the laminar organisation of PV+ interneurons in the developing cortex.

**Anna Zerio**

## Dissecting the role of PDE2A2 in cardiac metabolism

Supervisors: Professor Manuela Zaccolo & Associate Professor Duncan Sparrow

### Research Aim

Mitochondria are recognized as organelles with tightly regulated cAMP signalling. Phosphodiesterases (PDE) regulate the level of intercellular cAMP and/or cGMP through hydrolysis to either AMP or GMP. In the heart, PDE2A2 localises to the mitochondria where it regulates mitochondrial morphology and functions.

Impaired myocardial metabolism plays a critical role in the pathogenesis of lipotoxic cardiomyopathy. Metabolic remodelling results in decreased oxidative metabolism and lipid accumulation, contributing to the progression of heart failure. However, the mechanisms of this dysregulation remain elusive. In my study, I propose that a PDE2A2 regulated pool of cAMP is present at the OMM, which modulates the uptake of FA by the mitochondria, contributing to a healthy cardiac metabolism.

### Methods and Results

The experimental body was conducted in mouse embryonic fibroblasts (wildtype or from a cardiac specific knock out of *pde2a*), or in cardiac myocytes. Coimmunoprecipitation confirmed interactions between PDE2A2 and elements the mitochondrial machinery for import of fatty acids (carnitine palmitoyltrasnferase 1, Cpt1). Radiolabelled fatty acids oxidation (FAO) assays revealed impaired FAO in PDE2A ko cells. A Cpt-1 assay showed reduced efficiency of the enzyme in importing fatty acids upon PDE2A inhibition. LipidTox staining revealed lipids accumulation in the absence of PDE2A.

### Conclusion

In conclusion, PDE2A2 localizes at the mitochondria where it may mediate the uptake of fatty acids aimed at the production of ATP. When PDEA2 is impaired, this results in a lipid accumulation, which replicates the clinical phenotype of lipotoxic cardiomyopathies.

PDE2A2 could lead to the discovery of novel therapeutic targets in metabolic syndromes.

## Conan O'Brien

# Investigating the form and function of adrenal gland macrophages

Supervisors: Professor Ana Domingos Jansen & Professor David Greaves

### Research Aim

The adrenal glands are hormone secreting glands that sit on top of the kidneys. Adrenal glands produce glucocorticoids, mineralocorticoids, and catecholamines, and are therefore critical regulators of the stress response, metabolism, and blood pressure. Despite being identified for more that 30 years, our understanding of adrenal macrophages reamins incomplete. In numerous other tissues, macrophages carry out a plethora of physiological and homeostatic roles in addition to their classical immune functions. The aim of this project was to characterise the macrophage compartment of the adrenal gland and assess its contribution to adrenal function.

### Methods and Results

Using an in vivo approach, complemented by cryosectioning, confocal microscopy, immunofluorescent assays, ELISA, and flow cytometry, we herein describe a subset of lipid-laden adrenal macrophages that accumulate in the adrenal cortex in an age and diet-dependent manner. Furthermore, we present data suggesting these foamy-like macrophages accumulate certain metabolites and thereby regulate adrenal hormonal output.

### Conclusion

We hereby provide novel insights into the physiological roles of macrophages in the adrenal gland and the mechanisms by which adrenal hormone production is regulated. Future investigations will establish whether adrenal macrophages regulate the hormonal changes that accompany obesity.

**Ajantha Abey**

## What makes some neurons vulnerable and others resilient to Alzheimer's and Parkinson's disease?

Supervisors: Professor Richard Wade-Martins, Professor Colin Akerman, Dr Nora Bengoa-Vergniory & Dr Becky Carlyle

### Research Aim

Alzheimer's and Parkinson's disease feature progressive neurodegeneration associated with protein aggregate formation in a regionally selective manner. The cortical neurons that are relatively vulnerable in Alzheimer's Disease (AD) are only affected late in Parkinson's Disease (PD), whereas midbrain dopaminergic neurons exhibit striking vulnerability in PD, but are relatively spared in AD. Here, we examined whether induced pluripotent stem cell (iPSC) derived neurons, which offer a rare opportunity to examine cell autonomous vulnerability in live human cells, can recapitulate this phenomenon of selective neuronal vulnerability to help determine common and contrasting disease mechanisms and identify therapeutic targets.

### Methods and Results

iPSCs from patients with AD-related presenilin-1 mutations (n=3), PD-related leucine rich repeat kinase 2 mutations (G2019S n=3, R1441C n=3), and isogenic corrected (n=3) and healthy controls (n=4) have been differentiated into both cortical neurons and midbrain dopaminergic neurons to enable comparison of vulnerability phenotypes in different neuronal subtypes from the same patient. AD cortical neurons insulted with alpha-synuclein pre-formed fibrils (PFFs) have impaired neurite outgrowth, reduced synaptic density, and extensive aggregate formation. Meanwhile, PFF insulted PD cortical neurons exhibit normal neurite outgrowth and relatively little aggregation, whereas PD dopamine neurons readily produce aggregates.

### Conclusion

These preliminary results show relative vulnerability of AD and resilience of PD cortical neurons to alpha synuclein aggregates for the first time. This suggests the selective vulnerability to proteinopathy exhibited in these diseases may be replicated by the iPSC neuronal model, and additionally supports the notion that cell intrinsic factors may partly determine this vulnerability.

## Ester Paolocci

# The Role of phosphodiesterase's in Autosomal Dominant Polycystic Kidney Disease

Supervisors: Professor Manuela Zaccolo, Dr Angus Wann & Dr David Henderson

### Research Aim

Autosomal Dominant Polycystic Kidney disease (ADPKD) is characterized by formation of fluid-filled kidney cysts which lead to renal failure, dialysis, and even transplant. Ciliopathies, such as ADPKD, arise when proteins of the Primary Cilium are mutated. In ADPKD, Polycystins 1 (PC1) or Polycystin 2 (PC2) mutations lead to decreased Ca2+ and enhanced cAMP signaling. Increased cAMP signaling from the cilium stimulates cell proliferation and fluid secretion, driving cystogenesis. A universal second messenger, cAMP is tightly regulated to achieve different functions in distinct subcellular domains. To control its signal, cAMP is hydrolyzed, at different intracellular subdomains, by phosphodiesterase's (PDEs). PDE4 inhibition aggravates cystogenesis, more PDE inhibition, more cAMP. However, evidence shows inhibition of PDE2 and PDE3 has a protective effect on cyst formation in vitro. The aim is to understand how PDE2 and PDE3 inhibition reduces cyst growth.

### Methods and Results

Fluorescence Resonance Energy Transfer (FRET) was used to measure cAMP signaling in response to cyst-inducing stimuli and PDE inhibitors in Inner Medullary Collecting Duct Cells (IMCD3). Split-GFP was transfected in IMCD3 to measure ER-mitochondrial contact in response to contact-forming treatments as well as PDE inhibition. FRET results show, PDE2 and PDE3 activity is decreased in non-ciliated cells compared to ciliated cells. Split-GFP results demonstrate upon starvation and PDE2 inhibition, short ER-Mitochondrial contacts are increased, implying a potential shift in bioenergetics, which could be mitigating cystogenesis in vitro.

### Conclusion

To conclude, PDE2 and PDE3 inhibition reduces cyst growth and PDE2 inhibition with starvation increases ER -mitochondrial contacts. Further understanding PDE involvement in renal cystogenesis could prove PDE isoforms as selective therapeutic targets for ADPKD.

**Benjamin Bréant**

## Investigating the dissociated states induced by psychedelics

Supervisors: Professor Vladyslav Vyazovskiy, Professor David Bannerman & Professor Trevor Sharp

### Research Aim

The administration of serotonergic psychedelics suppresses paradoxical sleep and results in increased sleep fragmentation. However, the possibility that potentiating the serotonergic system through psychedelics results in an occurrence of altered states of vigilance has received less attention. The aim of this study is to characterise the effects of a short-lasting psychedelic compound, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), on brain activity and sleep-wake states in mice.

### Methods and Results

EEG and EMG recordings were performed in freely behaving mice (C57BL6), as well as local field potential recordings, sleep deprivation, or exposure to sugar pellets or running wheels. Each animal received an IP injection of 5-MeO-DMT at either the beginning of the light period or after sleep deprivation. We observed that after 5-MeO-DMT administration animals kept interacting with their environment, and the cortical activity in awake animals showed occurrences of NREM-like neuronal population OFF-periods. These observations were supported by EEG spectral analysis showing a significant power increase in slow frequencies and reduction in theta-frequency immediately following the injection. The effects were short-lasting and largely dissipated 1 hour after the injection. The latency to REM sleep was significantly increased. Sleep deprivation, however, did not seem to alter this 5-MeO-DMT-induced slow oscillations.

### Conclusion

Our data support the notion that the effects of 5-MeO-DMT are short-lasting but significantly impact sleep-wake cycle. The main effect on vigilance states consisted in an acute suppression of REM sleep. Reduced theta activity and increased slow wave activity during waking suggest that 5-MeO-DMT induces a dissociated state of vigilance, having features of both wakefulness and sleep.

**Antara Majumdar**

## Graded Representations of Economic Value Across Frontal Cortex

Supervisors: Dr Armin Lak & Associate Professor Simon Butt

### Research Aim

Economic decision-making under risk - the process of selecting between options with different values and uncertain outcomes - concerns many aspects of our lives. Past studies demonstrated representations of economic decision variables in prefrontal cortical regions (PFC). These studies, however, either measured neural signals with coarse spatial and temporal resolution (e.g. using fMRI) or from small neural populations using electrophysiology. Therefore, it is unclear how neural populations across PFC encode economic decisions. To address this, we devised a two-alternative visual economic decision-making task in head-fixed mice.

### Methods and Results

We found that mice's choices were sensitive to expected value and observed diverse risk attitudes across mice. Using high-density large-scale electrophysiological recordings, we show that neural populations across various frontal regions encode economic value, albeit with graded strength. Moreover, we show that neural economic value representations depend on individual risk attitudes.

### Conclusion

Our work reveals graded representations of economic value across PFC and provides a platform for investigating the neural basis of economic decision-making at a large scale with high spatial and temporal resolution.

**Adam Wells**

# Dense-core granule biogenesis is regulated by a Rab6 to Rab11 transition and amyloidogenic proteins

Supervisors: Professor Clive Wilson & Professor Stephen Goodwin

**Research Aim**

Dense-core granules (DCGs) are compact stores of signalling proteins that play an important role in cell-cell communication in neurons and specialised secretory cells such as insulin-secreting β-cells. Formed within dedicated secretory endosomes, DCGs allow large numbers of signalling proteins to reversibly aggregate within amyloid-like granules which then disassemble following secretion. Notably however, DCG aggregates fail to disassemble normally in diseases such as type 2 diabetes, a defect that may contribute to neurodegenerative diseases like Alzheimer's Disease, where secreted β-amyloid forms cytotoxic extracellular plaques. Despite their importance, DCGs remain relatively poorly understood, largely due to their nanoscale dimensions.

**Methods and Results**

Therefore, I utilised the novel Drosophila secondary cell (SC) system, which features uniquely massive secretory endosomes and DCGs as well as clustered intraluminal vesicles (ILVs), to study DCG biogenesis and regulation.

Using SC-specific knockdowns and ex vivo imaging, I demonstrate that SC DCGs are regulated similarly to mammalian DCGs, being controlled by the conserved DCG regulators Arf1 and the AP-1 complex. I also show that Arf1 and AP1 control a novel Rab6 to Rab11 transition on secretory endosome membranes which triggers both DCG and ILV biogenesis. Through real-time imaging, I directly image the process of protein aggregation during DCG biogenesis and show that this process is severely disrupted following knockdown of neurodegeneration-linked proteins or expression of mutants involved in familial Alzheimer's Disease.

**Conclusion**

These results provide novel insights into fundamental DCG/endosomal biology and highlight links endosomal regulators, DCG aggregation and neurodegenerative processes.

**Lea Ballenberger**

# Dissecting the neuronal circuitry underlying sleep induction in the fly

Supervisors: Professor Gero Miesenböck & Professor Stephen Goodwin

## Research Aim

Sleep is crucial to our wellbeing and survival. While we all sleep every day, the exact neuronal basis of how sleep is controlled, has not been fully understood. To understand this further, I am using the fruit fly Drosophila melanogaster as a model organism, whose connectome of the central complex is publicly accessible. In detail, I am looking at a group of neurons in the fly brain, neurons projecting to the dorsal fan-shaped body (dFB neurons), whose activity is modulated by sleep pressure, and artificial activation induces sleep in the animal. I am working on identifying their downstream partners, their connection, as well as their function in the modulation of sleep.

## Methods and Results

Using behavioural, optical, and electrophysiological tools, I am studying the induction of sleep onto the organism. Using the connectome data, several potential downstream partners of dFB neurons were identified. Artificial activation and inhibition of these cells allows to study their involvement in the regulation of sleep. Using this approach, I have identified several neuronal groups that increase or decrease sleep of the fly, when neuronal activity was artificially controlled. Using 2-photon imaging and patch-clamp recordings, I am studying the response of downstream neurons to optogenetic activation of upstream neurons.

## Conclusion

After verifying the connection, I want to study the neurons' activity in relation to sleep pressure, as well as the neurons' function on the organism. Together, this data shall help our understanding how sleep pressure is transmitted onto the organism.

## Thijs van der Plas

# Perception and propagation of activity through the cortical hierarchy is determined by neural variability

Supervisors: Dr Adam Packer, Dr Sanjay Manohar & Professor Tim Vogels

### Research Aim

The brains of higher organisms are composed of anatomically and functionally distinct regions performing specialised tasks; but regions do not operate in isolation. Orchestration of complex behaviours requires communication between brain regions, but how neural activity dynamics are organised to facilitate reliable transmission is not well understood.

### Methods and Results

We studied this process directly by generating neural activity that propagates between brain regions and drives behaviour, allowing us to assess how populations of neurons in sensory cortex cooperate to transmit information. We achieved this by imaging two hierarchically organised and densely interconnected regions, the primary and secondary somatosensory cortex (S1 and S2) in mice while performing two-photon photostimulation of S1 neurons and assigning behavioural salience to the photostimulation.

### Conclusion

We found that the probability of perception is determined not only by the strength of the photostimulation signal, but also by the variability of S1 neural activity. Therefore, maximising the signal-to-noise ratio of the stimulus representation in cortex relative to the noise or variability in cortex is critical to facilitate activity propagation and perception. Further, we show that propagated, behaviourally salient activity elicits balanced, persistent, and generalised activation of the downstream region. Hence, our work adds to existing understanding of cortical function by identifying how population activity is formatted to ensure robust transmission of information, allowing specialised brain regions to communicate and coordinate behaviour.

**Luke Taylor**

## Cracking the neural code using brain-like computer models

Supervisors: Professor Andrew King, Associate Professor Nicol Harper & Assistant Professor Friedemann Zenke

### Research Aim

Can we learn more about our brains by emulating them on computers? Machine learning techniques have undergone rapid progress over the last decade, opening the door to more complex investigations of the nervous system using detailed brain-like spiking neural network (SNN) models. The primary focus of my DPhil uses these models to examine the neural code underlying the visual system. Here, I explore the hypothesis that the retina and primary visual cortex (V1) employ a predictive-like code, in which spikes encode features within sensory stimulus predictive of the future. Secondary to this, I set out to address a major shortcoming of SNNs, which are their slow simulation and training times, by developing computationally faster algorithms.

### Methods and Results

Using natural video stimuli, I trained a model of the retina and V1, both using a spike code optimised to predict the sensory future under metabolic constraints. I found the retinal model to capture the main ganglion cell types and their latency-like spike code; and the cortical model to capture the stereotypical V1 cell types, including key physiological differences between the inhibitory and excitatory neurons. Lastly, I developed a new technique for simulating and training SNNs, achieving up to a 50x training speedup and enabling quick and accurate fitting of electrophysiological recordings of cortical neurons on sub-millisecond timescales.

### Conclusion

The modelling findings suggest that the visual system employs a spike code predictive of the future, and the newly developed SNN algorithm provides a new basis for studying the brain using computers.

**Tara Diviney**

# Characterisation of a BAC-transgenic GBA-L444P mouse model of Parkinson's disease

Supervisors: Professor Richard Wade-Martins, Professor Stephanie Cragg & Dr Natalie Connor-Robson

## Research Aim

Parkinson's disease (PD), characterized by degeneration of dopaminergic neurons of the SNpc, is the 2nd most common neurodegenerative disorder in the world. Heterozygous mutations in the GBA gene, encoding for the lysosomal enzyme GCase, represent the strongest genetic risk factor for PD. However, the pathological mechanism underlying how GBA mutations contribute to PD pathology has not been fully elucidated and the lack of appropriate rodent models of GBA-associated PD is a barrier to future progress in this field.

## Methods and Results

In light of these limitations our lab created a novel BAC-transgenic mouse model of GBA-associated PD, which expresses the human wildtype or L444P mutant GBA transgene. A GCase activity deficit was identified in midbrain and cortex tissue and in cortical primary cultures from mutant mice. Also, the high molecular weight form of GCase predominated in the midbrain and cortex of L444P mice, supporting the hypothesis that immature, glycosylated GCase is trapped within the endoplasmic reticulum in the mutant mice. Furthermore, detection of dopamine release with fast-scan cyclic voltammetry identified a modest deficit in evoked striatal dopamine release in the CPu of L444P mice at 3 and 18-21 months. In spite of this, the striatal dopamine content is similar across genotypes at both ages, as measured by HPLC. The behavioural phenotype of the L444P mutant mice was mild, exhibiting some gait deficiencies.

## Conclusion

We can conclude that this BAC-transgenic mouse model shows promise to be a useful tool for future studies aiming to shed light on the role of GBA in early-stage PD pathology.

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