Bristol Brain Research
Showcase and Networking Day
Poster Abstracts
The Bristol Brain Research: Showcase and Networking Day
Steering and Scientific Committee
(in alphabetical order)

Catherine Brown  Elizabeth Blackwell Institute/Research Development
Robbie Drake  Physiology, Pharmacology and Neuroscience
Hannah Gill  University Hospitals Bristol
John Grogan  BMS/Translational Health Sciences
Kevin Kemp  BMS/Translational Health Sciences
Gaurav Malhotra  Experimental Psychology
Karen Mifsud  BMS/Translational Health Sciences
Jacqui Oakley  Research and Enterprise Development
Zoë Reed  BMS/Population Health Sciences
Tamsin Sharp  BMS/Population Health Sciences
Alfie Wearn  BMS/Translational Health Sciences
**PROGRAMME**

8.30-8.45  **Registration and poster set-up** (refreshments available)

8.45-8.50  **Opening Address**
            [George Banting](#) (Dean of the Faculty of Biomedical Sciences)

8.50-10.20  **Oral Session 1**
            **Chair:** Robbie Drake (Senior Research Associate, School of Physiology, Pharmacology and Neuroscience)

   8.50-9.05  **Catherine Morgan** (Clinical Researcher, Centre for Medical Education)
            *Use of SPHERE house technology in feasibility study looking at Parkinson’s disease outcome measures*

   9.05-9.20  **Elanor Hinton** (Senior Research Associate, Bristol Medical School, Dept of Translational Health Sciences)
            *Functional connectivity analysis of the effect of eating rate during lunch on post-meal resting state fMRI data: An analysis conundrum*

   9.20-9.35  **Aleksander Domanski** (Postdoctoral Research Associate, School of Physiology, Pharmacology and Neuroscience)
            *Towards modulation of decision making through online manipulation of frontal cortical network dynamics*

   9.35-9.50  **Elizabeth Mallam** (Consultant Neurologist, Southmead Hospital, North Bristol Trust) and **Dane Rayment** (Consultant Neuropsychiatrist, Southmead Hospital, North Bristol Trust)
            *Relaunching Rosa Burden Centre: Functional Neurological Disorders and Sleep Disorders Services*

   9.50-10.05  **Robin Damion** (Postdoctoral Research Associate, School of Experimental Psychology)
            *Stroke onset time and tissue state evaluation in acute ischaemic stroke patients using quantitative MRI*

10.05-10.20  **Invited Speaker:** [Kathreena Kurian](#) (Reader in Brain Tumour Research, Bristol Medical School, Dept of Translational Health Sciences)
            *The Interactive Replica Neuroscience Research Lab exhibition at We the Curious*

10.20-11.50  **Poster Session 1** & refreshments

11.50-12.25  **Invited Speaker**
            **Chair:** Prof Astrid Linthorst (Professor of Neuroscience, Deputy Head of Bristol Medical School)
John Isaac  (Senior Director, External Scientific Innovation, Neuroscience, Johnson & Johnson Innovation)

*Academia-industry collaborations in neuroscience - opportunities and challenges*

**12.25-13.25  Oral Session 2**

**Chair:** Zoë Reed (PhD student, Bristol Medical School, Dept of Population Health Sciences)

12.25-12.40  Laura Palmer  (South West Dementia Brain Bank Manager)

*The South West Dementia Brain Bank: An invaluable research resource*

12.40-12.55  Vikki Neville  (PhD student, Bristol Veterinary School)

*The effect of reward and punisher experience on rodent decision-making*

12.55-13.10  Gareth Barker  (Senior Research Associate, School of Physiology, Pharmacology and Neuroscience)

*Investigating the role of projections from the nucleus reuniens to medial prefrontal cortex and hippocampus in associative recognition memory formation*

13.10-13.25  Invited Speaker: Emily Henderson  (Research Fellow, Bristol Medical School, Dept of Population Health Sciences)

*Preventing falls in Parkinson’s disease: The ReSPonD trial*

Emily is the winner of the 2017 *Bristol Neuroscience Grey Walter Prize* for best paper published by a PhD student within two years of graduation. We will present Emily with her certificate and prize following her talk.

**13.25-15.25  Lunch & Poster Session 2**

**15.25 - 16.00  Invited speaker**

**Chair:** Hans Reul (Professor of Neuroscience, Bristol Medical School, Dept of Translational Health Sciences)

Stephen Hicks  (Research Fellow in Neuroscience and Visual Prosthetics, Nuffield Department of Clinical Neurosciences, University of Oxford)

*Believing is seeing. Using augmented reality to improve vision and see the future.*

**16.00-16.40  Panel Pitches**

**Panel members:** Richard Apps (Professor of Neuroscience), Matt Jones (Professorial Research Fellow in Neuroscience), Jack Mellor (Professor in Neuroscience) (all from the School of Physiology, Pharmacology & Neuroscience); Jacqui Oakley (Research Development Manager, Research and Enterprise Development)

16.00-16.20  Ullrich Bartsch  (Postdoctoral Fellow, School of Physiology, Pharmacology and Neuroscience)

*Investigating the genetic mechanism of sleep abnormalities in schizophrenia*

16.20-16.40  Marcus Drake  (Professor of Physiological Urology, Bristol Medical School, Dept of Translational Health Sciences)

*Continence management in people with long-term health problems: Developing a programme grant application for a randomised controlled trial (RCT) of therapy in primary care*
16.40-17.10  Refreshments break

17.10-17.50  Oral Session 3
Chair: Tamsin Sharp (PhD student, Bristol Medical School, Dept of Population Health Sciences)

17.10-17.25  Elizabeth Coulthard (Consultant Senior Lecturer, Bristol Medical School, Dept of Translational Health Sciences)
Enhancing sleep to improve memory

17.25-17.40  Ella Gale (Postdoctoral Research Associate, School of Experimental Psychology)
Characterising the conditions in which feed-forward neural networks learn local (‘grandmother cell’) representations

17.40-17.55  Amy Howell (PhD student, Bristol Medical School, Dept of Translational Health Sciences)
Investigating novel risk factor for glioblastoma using population level genetic data

17.55-18.10  Juliana Redondo (Research Associate, Bristol Medical School, Dept of Translational Health Sciences)
Dysregulation of MSC expansion potential and antioxidant responses in progressive multiple sclerosis

18.10-18.45  Invited Speaker
Chair: Matt Jones (Professorial Research Fellow in Neuroscience, School of Physiology, Pharmacology & Neuroscience)
Martin Pearson (Senior Research Fellow: Robotics, University of the West of England)
Neurorobotics: What, why and how?

18.45-18.50  Closing Remarks and Prizes

18.50-19.45  Drinks and nibbles Reception

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New discoveries in the brain Renin Angiotensin System in Alzheimer’s disease

Al Mulhim N, Miners S, Kehoe P

Areas of research focus: Biochemical, neuropathological

Keywords: RAS, Alzheimer’s disease, pathogenesis

Brain region: Frontal cortex

Aim/Background: The classical brain RAS axis (ACE-1/Ang-II/AT1R) exerts damaging effects in the brain in both animal and human studies. Hyperactivity of this axis contributes to the pathogenesis of Alzheimer’s disease (AD). Alternative RAS pathways ((ACE-2/Ang(1-7)/MasR) and (APN/Ang-IV/IRAP)) have recently been discovered that counter-regulate the damaging effects of classical RAS signalling whilst are also implicated in boosting learning and memory. However, the involvement of these alternative RAS pathways in relation to AD pathogenesis remains unclear. We have measured brain angiotensins and their receptors involved in the alternative RAS signalling in relation to AD in a well-characterised cohort of post-mortem brains.

Methods: Human post-mortem brain tissue was obtained from the South West Dementia Brain Bank, University of Bristol, with local Research Ethics Committee approval. The AD cases (n=72) and the age-matched controls (n=48) were matched closely for age-at-death and post-mortem delay. The levels of Ang(1-7) and Ang-IV were measured in the mid-frontal cortex (Brodmann area 8/9) by ELISA. The expression and distribution of MasR, and insulin-regulated aminopeptidase (IRAP) (Ang-IV receptor) were determined by ELISA and immunohistochemistry. Pre-existing data on Ang-II level, and amyloid (Aβ) level (by ELISA) and Tau load (field fraction analysis), Braak staging information was also available for analyses.

Results: MasR level was significantly reduced in AD however Ang(1-7) remained unchanged. Ang-IV level was also reduced in AD with no changes in IRAP level in AD group.

Conclusion: Our recent studies show that dysregulation of alternative brain regulatory RAS components that are modifiable pharmacologically, are associated with the pathogenesis of AD.

References:
Investigating the role of miR-21 in hippocampal neural functions

Alahdal HM, Caldwell M, Warburton C, Uney J, Wong L-F
ha14787@bristol.ac.uk

Areas of research focus: Behavioural, clinical
Keywords: MicroRNAs, neurogenesis, hippocampus
Brain region: Hippocampus
Can offer: Immunohistochemistry, in situ hybridisation

MicroRNAs (miRNAs) are a class of small non-coding RNAs that act as post-transcriptional regulators. Recent studies suggested that miRNAs play a role in neurodegenerative diseases and brain disorders (Qureshi & Mehler, 2012). MiR-21, a miRNA that is dysregulated in cancers including glioblastomas, targets many cellular processes including cell proliferation and apoptosis cell proliferation (Si et al., 2007) and has been shown to be upregulated following post-traumatic brain injury and spinal cord injury to reduce lesion size, enhance cell survival and confer better neurological outcome after injury (Bhalala et al., 2012). Due to its effects on cell proliferation and survival, we speculate that miR-21 may play a role in adult neurogenesis in the mammalian brain. Here we investigate the effect of altering miR-21 levels on the cell fate of new-born neurons in the adult hippocampus. Using transgenic mice that globally either overexpress miR-21 or lack miR-21, we demonstrate that miR-21 overexpression led to increased neurogenesis in the dentate gyrus (DG), while its deletion showed a decreased neurogenesis in the same area. We show that miR-21 has a significant role in regulating hippocampal adult neurogenesis through altering cell survival. The decreased adult neurogenesis in the hippocampus led to impairment in learning and memory in the Morris water maze task. These results suggest that miR-21 plays an important role in hippocampal adult neurogenesis and therefore impacts on hippocampal-based learning and memory acquisition behaviours.

References:
Measuring information transfer via gonadotropin-releasing hormone (GnRH) receptors

Alobaid H, Voliotis M, Tsaneva-Atanasova K, McArdle CA
ha15132@bristol.ac.uk

Area of research focus: Cellular
Keywords: G protein-coupled receptor, gonadotropin-releasing hormone, mutual information
Brain region: Anterior pituitary
Can offer: Immunohistochemistry, signalling pathways, live cell-imaging, adenovirus purification

Aim/Background: GnRH is a neuropeptide that mediates central control of reproduction. It acts via GPCRs on pituitary gonadotrophs, causing PKC-mediated activation of ERK, and Ca\(^{2+}\)-mediated activation of Nuclear Factor of Activated T-cells (NFAT). Information theory derived statistical measures are increasingly used to quantify information transfer via receptors. Typically, single cell responses are used so the impact of cell-cell heterogeneity on information transfer is considered. We quantified GnRH effects on pppERK, Ca\(^{2+}\) and the nuclear fraction of NFAT (NFAT-NF), and calculated mutual information (MI) between GnRH and these measures. We found pronounced loss of information through signalling (3Bit input, <1Bit transferred) [1,2]. Here, we explore mechanisms that might mitigate such loss.

Methods: Gonadotroph-derived LbT2 cells were stimulated before staining for pppERK (immunohistochemistry) or for Ca\(^{2+}\) measurement (Fluo4). For some experiments, cells were infected with adenovirus for NFAT-EFP expression. Image acquisition and analysis was with a high content imaging platform, and MI between GnRH and the responses [I(response;GnRH)] was calculated (MatLab) using single cell responses from full concentration-response curves [1,2].

Results: I(ppERK;GnRH) values were maximal (~0.5Bits) after 5min GnRH stimulation and remained elevated for 60 min. I(NFAT-NF;GnRH) values increased to a maximum of ~0.5Bits at 60 min. I(Ca\(^{2+}\);GnRH) values increased to a maximum of ~0.8Bits at ~25 sec and reduced to 0.5Bits at~2min, then remained constant for10 min. Joint sensing (pppERK/NFAT-NF) increased the MI values but the increase was small (<0.2Bits). For the live cell measures we also considered response trajectory and this yielded only small increases (from ~0.45 to 0.5 for NFAT-NF and from ~0.8 to 1 for Ca\(^{2+}\)).

Conclusion: Individual LβT2 cells are unreliable sensors of GnRH with most information lost through signalling. Joint sensing and trajectory sensing both increase MI values but the increases were small. Marked information loss occurs early in the GnRH signalling network, prior to Ca\(^{2+}\) mobilisation.

References:
Life on hold: Torpor as a model of resilience

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Areas of research focus: Clinical, neurophysiological
Keywords: Torpor, chemogenetics, metabolism
Brain regions: Rostal ventromedial medulla, arcuate, paraventricular hypothalamus, dorsomedial hypothalamus, pre-optic hypothalamus
Can offer: Chemogenetics, torpor induction, thermal imaging, working heart brainstem preparation

Background: Torpor is a natural hypothermic, hypometabolic behaviour exhibited by many species, which represents a potent organ-protective strategy in times of physiological stress. The suppression of body temperature and metabolism associated with torpor allows animals to tolerate profound reductions in cardiac output, respiratory rate, and organ perfusion(1). If mimicked in a clinical setting, torpor could improve outcomes in critical illness as well as stroke and myocardial infarction(2).

Aims:
• Identify the neural circuits responsible for torpor induction in the mouse
• Characterise the physiology of torpor and its relationship to ‘normal’ physiological states including sleep
• Test the hypothesis that ‘synthetic torpor’ can be induced in species that does not ordinarily enter torpor, such as the rat

Methods to be used: This project will employ chemogenetic techniques in both transgenic mice and through viral vector injection to characterise the neural circuitry required for torpor induction. Using the ‘TRAP’ (Targeted Recombination in Active Populations)(3) transgenic mouse model, I will render the circuitry activated during torpor under the control of designer receptors (DREADDs)(4). This will allow generation of a ‘synthetic’ torpor, and identification of the circuits involved in torpor induction. A vectorised chemogenetic approach using both excitatory and inhibitory DREADDs in the TRAP mouse will allow identification of the necessary and sufficient neural circuit for torpor induction. Telemetric recordings and the working heart brainstem preparation will be used to explore the physiology of both natural torpor and synthetic torpor. Finally, using the knowledge gained in the earlier experiments, vectorised DREADD delivery in the rat will allow me to test the hypothesis that synthetic torpor can be induced in a species that does not naturally enter torpor.

References:
The combination of the CDK4/6 inhibitor palbociclib with the rapalogue temsirolimus inhibits DIPG cell proliferation via synergistic attenuation of cell cycle regulators

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Area of research focus: Cellular
Keywords: DIPG, palbociclib, temsirolimus
Brain region: Pons

Aim/Background: Diffuse Intrinsic Pontine Glioma (DIPG) accounts for up to 15% of all childhood central nervous system tumours and has a two-year survival rate of less than 10%. DIPG is highly chemotherapy-resistant and children show little response to conventional chemotherapies. Palbociclib has the potential to treat DIPG by selectively inhibiting the proliferation of cancer cells via inhibition of cyclin-dependent kinase (CDK) 4 and CDK6, which triggers cell cycle arrest at the G1 checkpoint. However, it has been shown that CDK inhibitors alone are ineffective as long-term brain tumour therapies. We aimed to use palbociclib to inhibit DIPG cell proliferation by inducing cell cycle arrest via targeted disruption of cyclin D -CDK4/6 complexes, in combination with the rapamycin analogue temsirolimus, used to attenuate cyclin D protein expression.

Methods: We tested palbociclib and temsirolimus on three patient-derived DIPG cell lines. We investigated the effectiveness of the drugs on cell viability, cell proliferation and the G0-G1 cell cycle checkpoint. We also assessed alterations in the expression of numerous key proteins in both the CDK4/6-cycD1-RB and PI3K/AKT/mTOR signalling pathways.

Results: We demonstrated that palbociclib and temsirolimus both inhibit proliferation in DIPG cells and that their effects were potentiated when used in combination. This was substantiated via flow cytometric and clonogenic analyses, the latter revealing longer-term dose-dependent reductions in colony formation. Quantitative analysis of the dose-effect relationship between the two drugs indicated a synergistic relationship when used in combination. Furthermore, immunoblot analyses showed inhibition of CDK4/6 and mTOR signalling using palbociclib and temsirolimus, respectively, each of which was enhanced in combination.

Conclusion: This work illustrates the in vitro effectiveness of these drugs against DIPG when used individually, and the amplified effects when used concurrently. The combination of these two clinically-approved therapeutics represents a putative fast-track approach to developing a much-needed treatment for DIPG.
Noradrenergic modulation of hippocampal function

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Areas of research focus: Cellular, behavioural, cognitive, neurophysiological
Keywords: Synaptic plasticity, learning and memory, optogenetics
Brain regions: Hippocampus and locus coeruleus
Can offer: Expertise in analysis using MATLAB, stereotaxic brainstem injections, whole-cell patch-clamp recording, opto- and chemogenetics, immunohistochemistry

The hippocampus is heavily involved in learning and memory, receiving inputs from a variety of sensory modalities as well as innervation by modulatory brain areas. The locus coeruleus (LC) is a brainstem nucleus that projects diffusely throughout the cortex, releasing noradrenaline to coordinate multiple brain areas and mediate a variety of cognitive processes, such as learning, memory, vigilance, and sleep\(^1\)\(^2\). Within the hippocampus this noradrenaline release acts as a novelty signal, with the LC switching from tonic firing in familiar spaces to burst firing when an animal enters a novel environment\(^3\). The effects of such a switch on synaptic dynamics, neuronal ensemble recruitment and memory formation are still poorly understood.

The function of LC hippocampal inputs will be examined using a combination of whole-cell patch-clamp recording in ex vivo hippocampal slices, opto- and chemogenetic manipulations, computational modelling and in vivo behavioural assays. Preliminary data with bath-applied NA has shown contrasting effects at different hippocampal synapses: at Schaffer Collateral-CA1 (SC-CA1) synapses it attenuates excitatory and inhibitory responses, whereas NA augments mossy fibre-CA3 (MF-CA3) excitatory responses. Such distinct effects will shape incoming cortical signals and experiments examining the effects of NA on physiological mossy fibre firing patterns are currently underway. These recordings will be analysed using a computational model of the MF-CA3 synapse and a larger network model of neuronal ensemble formation, the results of which will enable predictions of memory function that can be tested in vivo.

It is likely that bath-applied saturating NA provides an inaccurate picture of in vivo hippocampal noradrenergic modulation\(^4\), therefore opto- and chemogenetic approaches to induce the release of physiological concentrations of NA are being explored. At present, optogenetic activation of LC hippocampal fibres shows little effect, but chemogenetic manipulation shows modulation of a NA-sensitive current (the slow afterhyperpolarisation, sAHP).

References:
Functional assessment of multipotent mesenchymal stromal cells in progressive multiple sclerosis

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Areas of research focus: Cellular, clinical
Keywords: Multipotent mesenchymal stromal cells, cell therapy, multiple sclerosis

Novel treatment approaches are being explored for the treatment of progressive multiple sclerosis (MS), focusing on anti-inflammatory, neuroprotective and remyelinating therapies. Data from animal studies suggest that intravenous infusion of multipotent mesenchymal stromal cells (MSC) improves repair in animal models of MS, and cell-based therapy employing MSC is currently being evaluated in clinical trials. Multiple putative therapeutic mechanisms have been proposed, including paracrine-mediated immunomodulation and neuroprotection and cell fusion. However, despite early clinical translation, little is known about the effect of MS on MSC function.

In ongoing studies, we are performing a systematic analysis of MSC in progressive MS (MS-MSC) as part of the back-translational arm of the phase II, double-blind, placebo-controlled, randomised trial, ‘Assessment of bone marrow-derived Cellular Therapy in progressive Multiple Sclerosis’ (ACTiMuS; NCT01815632). Control MSC (C-MSC) are isolated from femoral head marrow obtained during elective total hip replacement.

Compared with C-MSC, MS-MSC have reduced ex vivo expansion potential, dysregulated antioxidant responses and display a phenotype consistent with premature ageing (see abstract submitted by Redondo et al). In ongoing studies, we are examining whether autophagy is differentially regulated in MS-MSC. We have also shown that the MS-MSC secretome has reduced neuroprotective potential in vitro and that this is due, at least in part, to reduced secretion of mitochondrial fumarate hydratase. Additional changes in the MS-MSC secretome include increased levels of thrombospondin-1 and we are currently investigating the functional effects of this in models of blood brain barrier permeability.

Future work will exploit recent advances facilitating identification of MSC in vivo and will include an assessment of MSC number and distribution in brain tissue affected by MS as well as in vivo tracking of MSC in models of MS.
Using optogenetics to examine recognition memory circuitry in vitro

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Areas of research focus: Cellular, neurophysiological
Keywords: Optogenetics, electrophysiology, prefrontal cortex
Brain region: Prefrontal cortex
Can offer: Optogenetics, electrophysiology, acute brain slicing, viral transduction

Aim/Background: The hippocampus, medial prefrontal cortex and thalamic nucleus reuniens are interconnected brain regions that is crucial for cognitive processes including associative recognition memory and spatial working memory. Little, however, is known about the physiology of the synapses connecting these regions and how it may contribute to these processes. Here I investigate in vitro the synaptic input from the hippocampus and nucleus reuniens into the medial prefrontal cortex.

Methods: Adeno-associated virus encoding channelrhodopsin-2 (ChR2) is injected into the nucleus reuniens of adult Lister Hooded rats. 14 days later acute modified coronal brain slices are prepared from the medial prefrontal cortex. Whole-cell patch clamp recordings are made from layer 5 pyramidal cells in the prelimbic cortex, nucleus reuniens afferents are activated with 470 nm light and hippocampal afferents are activated by electrical stimulation of their discrete fibre bundle (Banks et al., 2015).

Results: 1) Validation of the viral-ChR2 method to evoke synaptic transmission showed that ChR2 is ineffective at transmission frequencies at and above 20 Hz. 2) Nucleus reuniens inputs to prefrontal cortex show a strong short-term depression when stimulated at theta frequency. The mechanisms underlying this are not yet determined. 3) Hippocampal afferents are strongly modulated by cholinergic agonist carbachol whilst nucleus reuniens transmission is unaffected.

Conclusion: ChR2 has frequency-dependent limitations for evoking synaptic transmission. Nucleus reuniens and hippocampal inputs to prefrontal cortex show differential short-term plasticity and modulation by cholinergic transmission.

References:
Transcription factors PRDM8 and BHLHB5 regulate neuronal differentiation during development of the mammalian dentate gyrus

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Area of research focus: Developmental
Keywords: Dentate gyrus, gene regulation, immunohistochemistry
Brain region: Hippocampus
Can offer: Molecular techniques

Aim/Background: This work explores the genetic mechanisms that regulate neurogenesis and cell differentiation in the developing DG. Previously we have shown that transcription factors PRDM8 and BHLHB5 are expressed by granule cells in the adult dentate gyrus (Ross et al., 2012). PRDM8 and BHLHB5 form a repressive transcription factor complex that has an important role in neuronal circuit formation during cortical development (Ross et al., 2012). The aim of this study was to determine the influence of these transcription factors on hippocampal development.

Methods: We used confocal imaging of hippocampal cryosections labelled with cell type specific markers of immature and differentiated hippocampal neurons from Prdm8- and Bhlhb5- null animals taken between postnatal day 6 (PN6) and PN35.

Results: We found that loss of Prdm8 or Bhlhb5 resulted in the absence of calretinin+ (CR) mossy cells from the hilum of the developing DG at all observed time points and an expansion of immature granule cells (GCs) in the subgranular zone (SGZ) of the DG between PN14- PN35, but not in adult (>8 weeks old). These immature post-mitotic GCs were identified by their expression of doublecortin (DCX) and CR.

Conclusions: Our results suggest that PRDM8 and BHLHB5 regulate the differentiation of newborn GCs in the SGZ and mossy cells (MCs) in the DG hilum. Absence of either Prdm8 or Bhlhb5 results in the failure of MCs to develop and in an expanded population of immature post-mitotic GCs during postnatal development. The electrophysiological impact of these changes is under investigation.

References:
The effect of harmaline on coherent oscillations across the cerebellar-thalamo-cortical network

Bennett KM, Cerminara N, Goodfellow M, Whone A, Apps R

Area of research focus: Neurophysiological
Keywords: Essential tremor, harmaline, in vivo electrophysiology
Brain region: Cerebellum
Can offer: Local Field Potentials and single unit recordings

Essential Tremor (ET) is the most common movement disorder, affecting around 4% of the population over the age of 65 years (Louis & Ferreira, 2010). Currently, the underlying neurophysiological mechanisms which generate ET are unknown. However, synchronised oscillations at tremor frequency (4-12Hz) have been recorded within the motor cortex, thalamus, and muscles in patients, suggesting the involvement of pathological synchronous activity in the motor network (Schnitzler et al., 2009). Reduction of tremor symptoms in response to thalamic deep brain stimulation also provides evidence for thalamic involvement in the maintenance, if not also the generation of these oscillations (Flora et al., 2010). Converging evidence also suggests the cerebellum may have a key role in the origins of pathological oscillations in ET, although the underlying pathology may be heterogeneous (Louis, 2016). The harmaline model of ET has been shown to produce pathological oscillations within the olive-cerebellar pathway by increasing climbing fibre activation (De Montigny & Lamarre, 1973). However, the effect of harmaline on the cerebellar-thalamo-cortical network is not known. In the present experiments in awake rats, activity across the cerebellar-thalamo-cortical network was monitored, before and after systemic administration of harmaline (10mg/kg i.p.). An increase in coherent activity at the tremor frequency, would further validate the drugs utility as a model of Essential Tremor.
Combined topotecan and carboplatin therapy for DIPG suppresses cell growth in vitro and is well tolerated when delivered by convection enhanced delivery in vivo

Bienemann AS, Killick-Cole CL, Singleton WGB, Arshad A, Wyatt MJ, Barua NU, Gill SS
Presented by Boulter L

Area of research focus: Translational: lab to clinic
Keywords: Diffuse intrinsic pontine glioma (DIPG), convection enhanced delivery (CED), topotecan and carboplatin

Despite clinical advances, diffuse intrinsic pontine glioma (DIPG) remains universally fatal and urgently requires new treatment modalities to improve prognosis. Topotecan and carboplatin have formed treatment regimes for paediatric cancers as single agents with limited success. Both drugs have poor central nervous system penetration which may explain the lack of efficacy in the clinic when delivered systemically, furthermore, as single agents they have been administered to children with DIPG by convection enhanced delivery (CED) in early phase clinical trials and compassionate use programmes. Here, we describe the use of topotecan and carboplatin as combinatorial therapy for the treatment of DIPG in vitro and its tolerance when administered in vivo in a small animal model of intermittent CED.

In this study, we assessed the in vitro cytotoxicity of combined topotecan and carboplatin in two ex vivo patient derived DIPG cell lines (SF7761 and SF8628). Combination therapy in vitro showed an additive effect on cell viability when compared to each single agent. Next, we determined the tolerance and toxicity of both drugs administered by CED using an implantable catheter system in juvenile wistar rats by clinical and neuropathological examination of infused brain 21 days after treatment.

Results show that topotecan and carboplatin have an enhanced effect on DIPG cell viability in vitro when used in combination. This combination is currently being explored in a wider cohort of DIPG cell lines. In vivo assessment of sequential drug therapy in normal rat brain, shows this combination to be well tolerated and exhibited minimal CNS toxicity. Further work is required to see if this combination is effective in pre-clinical models of DIPG when administered by CED.
The interplay between cognition, attention and the cholinergic system in Parkinson’s disease: A mouse model

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Area of research focus: Behavioural

Keywords: Attention, cholinergic system, Parkinson’s Disease

Brain regions: Basal forebrain, striatum and pedunculopontine nucleus

Can offer: A new model for testing attention in mice, and how this can be influenced by the cholinergic system. Behavioural task using mouse touchscreen equipment.

Aim/background: Parkinson’s disease (PD) is a common chronic neurological disease, affecting around 1% of over 65’s in the UK. (Grosset et al., 2010) Falling is a common complication for Parkinson’s patients and it can impact the patient and their families. (Stel et al., 2004; NICE, 2013; Pin and Spini, 2016) We hypothesise that one cause of these falls, is a deficit in attentional resources, from cognitive decline and loss of gait and postural control. The pathology interlinking these may be a loss of cholinergic neurons in the basal forebrain, pedunculopontine nucleus and/or striatum. (Henderson et al., 2016) Therefore, this study aims to use a sustained attention task (SAT) to observe the effects of ageing on performance in mice, and then the influence of attention modifying drugs amphetamine, donepezil, methylphenidate and oxybutynin on SAT performance.

Methods: Animals (12 C57bl/6 female mice) were previously trained and tested in a novel attention task, the rapid serial visual presentation task. This task is run in a touchscreen operant chamber, and animals had previously been tested at ~4-9mths of age. In this study, animals will first re-baseline following a 3-month period without testing, and the results will be compared with their data from early adulthood. In the second part, acute effects of different pharmacological manipulations on attention will be used to investigate the validity of the method. Psychostimulants (Amphetamine and Methylphenidate), Acetylcholinesterase inhibitor (Donepezil) and Anti-Cholinergics (Oxybutynin) and Tropsium chloride will be studied.

Expected conclusion: Aged mice will be expected to have reduced attentional performance in the SAT. Furthermore, Amphetamine and Methylphenidate will be expected to increase attention in mice and therefore SAT performance. Acetylcholinesterase inhibitor, Donepezil, is predicted to have a positive effect on attention, by increasing acetylcholine availability. Finally, Oxybutynin, an acetylcholine diminishing drug, is expected to impair attention due to blockade of muscarinic acetylcholine receptor.

References:
Can OR37 ligands reduce an acute stress response in mice?

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**Areas of research focus:** Behavioural, neurophysiological

**Keywords:** Paraventricular hypothalamus, stress, olfactory

**Brain regions:** Olfactory system, paraventricular hypothalamus

**Can offer:** Olfactory behavioural testing

The overall aim of the project is to assess the potential for using OR37 ligand exposure to improve the welfare of laboratory mice. Long-chain aliphatic aldehydes, including pentadecanal, hexadecanal and heptadecanal have been identified as ligands for atypical OR37 main olfactory receptors. Unusually, these receptors project, via a single synapse in the main olfactory bulb, directly to the medial amygdala and paraventricular hypothalamus (PVN)\(^1\). Exposure of mice to a mixture of OR37 ligands has been found to decrease activation of corticotrophin releasing hormone expressing neurons in the PVN\(^2\), suggesting that OR37 ligands are prime candidates for social buffering pheromones, that are known to reduce the stress response in rodents via the main olfactory system. Using cFos expression as a marker of neural activity, we have confirmed that the OR37 ligand mixture is effective at reducing the activation of PVN neurons in a variety of anxiogenic contexts, including open field and elevated zero maze. However, we have so far been unable to detect significant effects on conventional behavioural measures of anxiety. This may reflect the relatively direct pathway for OR37 input to the PVN, which bypasses brain areas that are involved in the behavioural response to stressors. Current and future work aims to determine whether the inhibitory effect of OR37 ligand exposure on PVN cFos expression generalizes to other stressors, and whether a dissociation between endocrine and behavioural responses is evident in cFos expression in other brain areas involved in the stress response.

**References:**


Neuromodulation approach to controlling urinary incontinence in a rat model

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Area of research focus: Neurophysiological
Keywords: Neuromodulation, bladder, incontinence
Region: Pelvic nerve
Can offer: Rodent surgery, pelvic nerve stimulation, cystometry, urine output monitoring

Aim/Background: Neuromodulation of autonomic nerve activity as a means to regulate physiological processes is still an emerging field, with the potential to control different aspects of visceral function. We are investigating the potential for neuromodulation to control urinary voiding via stimulation of the pelvic nerve.

Methods: Rats were chronically implanted with a bipolar cuff electrode on the pelvic nerve. In addition, a bladder catheter was implanted via the dome to enable us to evoke repeated voids by infusing saline continuously into the bladder (11.2ml/h) whilst at the same time measuring changes in bladder pressure during filling and voiding via a T-junction in the catheter line.

Results: Each void (expulsion of urine) was accompanied by a sharp rise in bladder pressure. We showed that initiating high frequency stimulation (1-3kHz, 1-2mA sinusoidal waveform) of the pelvic nerve within 1-2s of the onset of the rise in bladder pressure signalling the start of an imminent void, could suppress the void.

In 13 trials (35%) voiding was suppressed completely (no urine expelled), whilst in 18 occasions (49% of trials) a small volume of urine was voided (46±3.7% of the volume expected from the mean of the preceding 2-3 voids). On 6 occasions (16%) the rat a void of expected volume occurred but was deferred for 24.5±5.2s after the onset of the stimulation. All rats resumed spontaneous voiding, typically within 1min of ceasing stimulation. The effects were repeatable over several weeks.

Conclusion: The experiments indicate that conditional or ‘on-demand’ closed loop stimulation has potential for developing as a new treatment for patients with urinary urge incontinence who have lost the ability to suppress voiding when their bladder is full but their social situation dictates that voiding would be inappropriate.
Light and temperature entrainment of the *Drosophila* circadian clock

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**Areas of research focus:** Behavioural, neurophysiological  
**Keywords:** *Drosophila*, electrophysiology, optogenetics  
**Brain region:** Circadian system  
**Can offer:** Electrophysiology, optogenetics, pharmacology, modelling

The *Drosophila* clock comprises 75 pairs of neurons grouped into identifiable clusters that sub-serve different circadian functions. They are defined by the expression of clock genes such as *period* (*per*) and *timeless* (*tim*) whose gene products negatively feedback to switch off their own expression forming the molecular clock. In the absence of environmental cycles, this clock free-runs with a period of approximately 24h and remarkably, this period length is maintained at different ambient temperatures, i.e. it is temperature compensated. Nevertheless, the same clock is extremely sensitive to daily temperature changes, because temperature cycles (TC) with an amplitude of only 2-3°C can synchronise behavioural and molecular rhythms. Synchronisation of the clock to environmental light:dark cycles is achieved by visual and non-visual pathways including *cryptochrome* (*cry*) and the newly discovered light input factor *quasimodo* (*qsm*).

Capitalising on fly genetics and pharmacology, we use a combined electrophysiological and optogenetic approach to characterize inputs and connections within this highly manipulable and compact clock circuit. We use paired whole-cell recordings in adult fly brains to directly demonstrate connections between the different neurons and characterise the neurotransmitters used by the system. In cases where neurons are not accessible for direct recordings we combine electrophysiology with optogenetic methods. We can activate a given set of neurons either using light-activated cation channels (ChR2, CsChrimson, ReaChR) or directly by electrophysiological stimulation, while simultaneously recording or imaging the membrane potential (ArcLight, Ace2N-2AA-mNeon) of potential postsynaptic neurons.

We could show that Ionotropic Receptor 25a (IR25a) acting in the chordotonal organs is required for behavioural synchronization to low-amplitude temperature cycles and that Qsm affects both daily and acute light effects in I-LNvs acting on the voltage-gated K⁺ channel Shaw and the Na⁺-K⁺-2Cl⁻ (NKCC) cotransporter. We are now trying to reveal the connections of the light and temperature input pathways to and within the circadian network which will lead to a better understanding of the circadian system.
Pupil diameter as a marker of locus coeruleus activity in humans

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Areas of research focus: Behavioural, cognitive, clinical, neurophysiological
Keywords: Pupil diameter, brainstem, auditory task
Brain region: Locus coeruleus
Can offer: Pupillometry

The Locus Coeruleus (LC) is a major norepinephrine nucleus residing deep in the brainstem, sending diffuse projections throughout the brain. The LC influences a plethora of functions so its dysfunction is likely to contribute to numerous disease states. Despite this, a measure of LC activity is yet to be validated in humans, and this is largely due to the intricate architecture of the brainstem, which prevents the use of non-invasive techniques. Evidence from electrophysiological animal studies suggests that LC activity fluctuates with pupil diameter so researchers have substituted more direct measures of LC activity with pupillometry (the measurement of pupil size) (Aston-Jones et al., 1994; Swick et al., 1994; Gilzerat et al., 2010).

The present study investigates the relationship between these two events in humans by measuring changes in pupil diameter with an eye tracker whilst administering an auditory oddball protocol, which has been shown to stimulate the LC in animals.

The data shows a pupil dilatory response to presentations of auditory oddball tones, similar to those reported by animal studies. This suggests that the relationship between LC activity and pupil diameter is also present in humans, which in turn suggests that pupillometry may be used as a proxy for LC activity in humans.

References:
Use of DREADDs to investigate the role of dopamine in control of urinary voiding

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Area of research focus: Neurophysiological
Keywords: Bladder, incontinence, DREADD
Brain region: Periaqueductal Grey Matter (PAG)
Can offer: Rodent surgery, electrophysiology, urine output monitoring, immunohistochemistry

Aim/Background: Control of urinary voiding is mediated by a spino-midbrain-spinal loop, under control of higher centres. A key relay in the ventrolateral PAG, appears to act as a neuronal switch that determines whether voiding is allowed to take place. The vlatPAG contains a cluster of dopamine (DA)-containing neurones. We are investigating the role of the DA cells in controlling voiding in rats, employing the ‘Designer Receptors Exclusively Activated by Designer Drugs’ (DREADDS) technique (Roth, 2016).

Methods: The viral vector (pAAV-hSyn-DIO-hM4D(Gi)-mCherry) was microinjected into the PAG of TH-Cre transgenic rats to selectively transfect dopamine-containing neurones with an inhibitory DREADD. Systemic injection of Clozapine-N-Oxide (CNO, 10mg/kg i.p.) was then used to temporarily silence dopaminergic neurones by activating this inhibitory receptor. 24h urinary voiding pattern was measured by housing rats in modified metabolic cages, which log the time and volume of each void. A video record of general behaviour was used to monitor overall activity and sleep-wakefulness pattern.

Results: Preliminary results from a limited number of rats (n=5) indicate that total volume voided did not change in the 4h period post injection of CNO (3.09±0.99ml post CNO vs 2.85±0.23ml post saline given at equivalent time of day, p=0.63 Wilcoxon signed rank test, n=5) nor was there a change in the proportion of time spent active (34.1±2.3% post CNO vs 38.1±7.2% saline control, p=0.63). However, there was a trend towards a change in the pattern of voiding such that voiding frequency increased post injection of CNO (5.4±1.4 voids in 4h after CNO vs. 3.4±0.4 post injection of saline, p=0.18) and the volume of each void decreased (0.58±0.12ml post CNO vs 0.92±0.18ml post saline control, p=0.063).

Conclusion: Although still at an early stage, we believe that the DREADDs approach will aid in determining the role of the DA cell population in the PAG in controlling micturition.

References:
Determining the pathways and synaptic mechanisms of the prefrontal cortex in recognition memory

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Areas of research focus: Cellular, behavioural, cognitive, neurophysiological  
Keywords: Associative recognition memory, medial prefrontal cortex, optogenetics  
Brain region: Medial prefrontal cortex  
Can offer: Electrophysiology, optogenetics

Previous work within the field has established interconnecting brain regions forming a neural circuitry for recognition memory. However, it is still unknown to what extent the connections between the regions are involved in encoding or retrieving memories. This project will focus on the projections from the medial prefrontal cortex (mPFC) and how they contribute to the proposed circuit.

Lesions of the mPFC have shown that no impairments are seen in novel object preference or object-location tasks after five minute or three hour delays, but impairments are apparent when associations must be made, such as in the object-in-place and temporal order tasks (Warburton & Brown, 2010; Cross et al., 2012). Disconnection studies show that interactions between the hippocampus, perirhinal cortex and mPFC are vital to perform these tasks, and many speculate the mPFC is important in integrating information and choosing context appropriate memories for successful completion (Eichenbaum, 2017). Whilst much work has studied inputs to the mPFC, little is known about its outward projections.

Within the neural circuit, the mPFC has three known, direct projections and these are to the perirhinal cortex, nucleus reuniens, and the lateral entorhinal cortex (De Souza Silva et al., 2016; Hernandez et al., 2017). It is unknown how these contribute in the encoding or retrieval of memories and how this information is communicated at a synaptic level.

This project will use a combined approach of optogenetics, to allow projection specific silencing or activation, in vivo with behavioural tests and in vitro with slice electrophysiology, respectively. This will uncover which pathways from the mPFC are involved in the encoding versus retrieval of memories, and the underlying synaptic mechanisms behind them.

References:
(4) De Souza Silva MA et al. (2016). Evidence for a specific integrative mechanism for episodic memory mediated by AMPA/kainate receptors in a circuit involving medial prefrontal cortex and hippocampal CA3 region. Cerebral Cortex. 26(7): 3000–3009.
Using *Drosophila* to study the impact of ageing on circadian rhythms and sleep

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**Area of research focus:** Neurophysiological  
**Keywords:** Circadian rhythms, ageing, *Drosophila*  
**Brain region:** *Drosophila* circadian clock (mammalian equivalent is the suprachiasmatic nucleus (SCN) of the hypothalamus)

**Aim/Background:** Circadian rhythms control a wide range of biological processes, ranging from metabolic activity to control of the sleep-wake cycle. It is well established that elderly individuals display fragmented sleep and a shift in sleep pattern to earlier in the day (Hofman & Swaab, 2006). We make use of the model organism, *Drosophila*, to investigate age-related changes on the circadian clock.

**Methods:** Behavioural changes were measured by recording locomotor activity of male flies of various ages; with flies housed individually in *Drosophila* activity monitors and analysed for circadian rhythms and sleep. At a neuronal level, whole cell patch-clamp recordings were made from clock neurons of different ages, using established protocols (Chen, Buhl, *et al.*, 2015).

**Results:** *Drosophila* show a significant linear decline in the strength of the circadian clock with increasing age, and an increase in circadian period. Sleep analysis found a significant increase in day-time sleep with age, while night-time sleep was unaffected. Current electrophysiological results have not found a significant effect of ageing on firing rates or membrane potential of clock neuron.

**Conclusion:** The linear decline seen in behavioural outputs of the clock demonstrate the suitability of *Drosophila* as a model to interrogate how ageing effects the circadian clock. Ongoing experiments aim to measure these effects on neuronal activity.

**References:**

Non-invasive cerebellar stimulation and motor adaptation. A stimulating story?

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Areas of research focus: Behavioural, neurophysiological
Keywords: Cerebellum, motor adaptation, non-invasive brain stimulation

Brain regions: Cerebellum and motor cortex
Can offer: Use of Transcranial Electrical Stimulation, EEG and extracellular electrophysiology

Aim/Background: Non-invasive electrical stimulation of the brain has been shown to affect performance in a variety of motor learning paradigms (Amadi et al., 2015), including visuomotor adaptation (Galea et al., 2011). The present study explored whether non-invasive stimulation over the cerebellum could influence visuomotor adaptation.

Methods: Eleven healthy participants performed a standard computer based visuomotor adaptation task, with concurrent EEG recording. Immediately prior to the adaptation phase, a localised anodal or sham transcranial direct current stimulation protocol was applied over the right cerebellar hemisphere.

Results: Modelling of behavioural adaptation parameters showed no observable difference between the anodal and sham stimulation protocols. Preliminary frequency domain analyses of the EEG signals recorded over the motor cortex and prefrontal cortex, revealed no statistically significant effect of the stimulation at the group level.

Conclusion: In this small-scale study, we were unable to detect any modulation of motor adaptation behaviour or neural activity as a result of cerebellar targeting of transcranial direct current stimulation. Possible reasons for the lack of effect will be discussed.

References:
In silico modelling and evolutionary relatedness of the OR37 subfamily of olfactory receptors

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Area of research focus: GPCRs
Keywords: G protein coupled receptor, modelling receptor ligand binding, olfactory
Brain regions: Olfactory system and HPA axis
Can offer: Olfactory behavioural testing

The OR37 subfamily of odorant receptors (ORs) represents a rather ancient gene cluster which exists exclusively in mammals. In mouse the OR37 main olfactory receptors A, B and C are activated by the long-chain aliphatic aldehydes pentadecanal, hexadecanal and heptadecanal, respectively\(^1\), and project via the main olfactory bulb to directly synapse on arginine vasopressin neurons in the paraventricular nucleus of the hypothalamus (PVN). Exposure to these aldehydes has been shown to inhibit hypothalamic corticotropin releasing hormone neuron activity and possibly the glucocorticoid stress response\(^2\), suggesting a role in mediating a phenomenon called social buffering. The OR37 olfactory receptor family that mediates the effects of the OR37 ligands is unusually conserved across species, suggesting there is the potential to open a new area of research in identifying similar ligand mixtures that are effective for other mammalian species.

Firstly, we identified the OR37 gene family repertoire in 13 species of placental mammals for which deep-coverage genome sequences are available. Those placentals with OR37A, B and C orthologs are candidates for ligand screening. Here we report for the first time the building of a novel 3-D mOR37 protein structure which we will use to develop an in silico screening model for characterisation of potential ligands that are predicted to functionally activate OR37 receptors in other mammalian species. This has potential impacts on animal welfare and productivity for food production, the welfare of companion animal and captive species, as well as potential applications in human and veterinary medicine.

References:
Assessing bacterial populations in Alzheimer brain

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Area of research focus: Clinical
Keywords: Microbiome, Alzheimer’s, Parkinson’s
Brain regions: Brain stem, basal ganglia, hippocampus, cortex
Can offer: Neurodegeneration, microbiome, 16S NGS

Aim/Background: Alzheimer’s (AD) and Parkinson’s disease (PD) are progressively disabling neurodegenerative diseases which hasten death. Neither can be cured as yet. The initiation of disease is largely unknown but its development centres on the production of misfolded proteins which, prion-like, spread through the brain via well defined pathways. Various neurodegenerative processes have been elucidated, and neuroinflammation is now thought to be a prime driver of progression. There is also substantial evidence that chronic, low level infections may provide the impetus for neuroinflammation; the two main protagonists being periodontitis and gut disorders. Our collaborative group (Bristol Dental School, Translational Health Sciences and Biochemistry) are investigating the presence of microbes in the brains from Alzheimer’s, Parkinson’s and Lewy body dementia patients with the aim of assessing their microbiome content and relative taxonomic ratios compared with normal. The preliminary findings are given here.

Methods: 16S ribosomal gene-specific Next Generation Sequencing (NGS) of extracted temporal lobe brain tissue from 16 AD cases and 16 control. qPCR and in situ PCR are currently being undertaken.

Results: A quantitative comparison was made of the bacterial content of both frozen and formaldehyde fixed sections of AD-affected cases with the cognitively unimpaired (normal). Our findings suggest a change in taxonomic profiles and a substantial increase in bacterial populations in AD brain tissue compared with normal.

Conclusion: The study presented here has shown, for the first time, that 16S NGS in terms of both PCR sensitivity and taxonomic coverage is extremely well suited to the detection and analysis of bacterial populations in both frozen and formalin-fixed temporal cortex, despite background human genomic DNA being present in overwhelming excess. Although this is only a pilot study with a limited cohort, these data strongly suggest that AD brains tend to have strikingly large bacterial loads compared to controls.

References:
The role of the nucleus reuniens of the thalamus in the recognition memory network

Exley BMS, Barker GRI, O'Donnell C, Warburton EC

Areas of research focus: Behavioural, cognitive
Keywords: Nucleus reuniens, recognition memory, neural network
Brain region: Nucleus reuniens
Can offer: Bow-tie maze behavioural experimentation, immunohistochemistry, confocal-microscopy image analysis

Recognition memory provides the ability to judge if a stimulus has been encountered before, a process which depends on a functional interaction between several key brain regions including the hippocampus, perirhinal cortex, medial prefrontal cortex, entorhinal cortex and thalamus. The nucleus reuniens of the thalamus (NRe) has previously been shown to synchronise activity between hippocampus and medial prefrontal cortex, along with entorhinal cortex. The project investigates the hypothesis that NRe plays a crucial role within the recognition memory circuit, using expression of the immediate early gene c-fos to map neural activity across the recognition memory network.

Rats were prepared with either a lesion in the NRe or a sham surgery and recognition memory was tested using a bow-tie maze recognition memory task (Albasser et al., 2010) with repeated training sessions in which the rats were presented with novel or familiar objects. In the final session, ninety minutes following exposure to either novel or highly familiar objects, the rats were sacrificed, and brain tissue prepared to quantify the expression of immediate early gene c-fos in selected brain regions using immunocytochemistry.

The effect of lesions in the NRe on neural activity in interconnected brain regions will be discussed. The data will enable modelling of the information flow within the network using statistical approaches. The results will further the understanding of the interactions within the neural network that drive recognition memory function.

References:
Targeting active brain protection through cell therapy in preterm infants at risk of cerebral palsy: Study of neural progenitor cells and molecular signalling in the cerebrospinal fluid of preterm infants

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Areas of research focus: Cellular, developmental, clinical
Keywords: Prenatal Intraventricular Haemorrhage (IVH), neural progenitor cells, cell signalling
Brain region: Subventricular zone and ventricles
Can offer: Neural stem cells cultures

Aim/Background: Preterm infants are highly vulnerable to intraventricular haemorrhage (IVH). One in five infants born under 32 weeks of gestation is affected by IVH and is major cause of long term developmental disruption [1]. IVH occurs at the subventricular zone (SVZ) of the lateral ventricles, due to the vulnerability of the vasculature in this area. If the SVZ disrupts, blood fills the ventricles and pro-inflammatory cytokines are released into the cerebrospinal fluid (CSF) [2]. The SVZ is rich in neural progenitor cells (NPCs)-which are important for brain development. Post-mortem and animal studies suggest that NPCs appear in the CSF after IVH [3,4] and CSF-NPCs interactions have been shown to influence NPC fate [5]. Our aims are to confirm the presence of NPCs within the CSF of preterm babies with IVH and the effect of pro-inflammatory CSF on human fetal NPCs (hfNPCs).

Methods: NPCs were isolated from IVH-CSF and cultured in NPC proliferation medium. hfNPCs were challenged with IVH-CSF and the cytokine inhibitors to study their differentiation profile by immunocytochemistry. CSF cytokine expression was determined by multiplex ELISA.

Results: We were able to expand NPCs from one early sample of our 20 CSF samples from 6 IVH-patients. These NPCs were able to proliferate, give rise to secondary neurospheres and differentiate into Tuj1+ and GFAP+ cells. We observed a decline in IL-1β and IL-6 CSF-expression and constitutively high CSF-levels of MCP-1. Our results show that IVH-CSF influences NPC fate causing an increase in astrocyte differentiation that can be rescued by PDGF/VEGF inhibition.

Conclusion: Our results support the presence of NPCs in the CSF at least in a subset of preterm babies with IVH. Furthermore, IVH-CSF may redirect NPC differentiation toward astrocytes and this may be mediated through PDGF/VEGF signaling. These findings may account for the compromised neuronal development observed in these patients.

References:
Using EEG to understand the mechanisms of Xenon-neuroprotection in anaesthetic-induced toxicity in developing brain

Gill H

Area of research focus: Developmental
Keywords: EEG, anaesthesia, neurotoxicity
Brain region: Cortex
Can offer: Pharmacology of anaesthesia, EEG recording

Background: Sevoflurane is a commonly used anaesthetic vapour shown to induce apoptosis and long-term neuro-deficit in immature rodents\(^1\). There are numerous reports of anaesthetic-induced apoptosis in the developing brains of immature rodents, but it can be argued that the doses used represent overdose\(^2\), as the resulting physiological derangement, mortality being reported, also induces apoptosis\(^3\). Processed electroencephalography (EEG) is used clinically to monitor depth-of-anaesthesia. A pattern of EEG called burst suppression (episodes of higher voltage activity interspersed with periods of very low voltage) is characteristic of very deep anaesthesia\(^4\). Similar activity in the EEG has been associated with isoflurane and sevoflurane-induced apoptosis in immature rodents\(^5,6\).

The addition of xenon, a rare anaesthetic gas, has been shown to prevent anaesthetic-induced apoptosis in a rodent model on postnatal day seven (P7)\(^7\) and is known to suppress high voltage activity in the EEG of rodents, pigs and humans\(^8\).

Aim: We propose to measure a dose of sevoflurane just high enough to produce burst-suppression pattern in the EEG of rodents on P7 and assess the effect of adding xenon to the inhaled gas mixture. We hope this will produce a rodent model of sevoflurane-xenon anaesthesia which removes the confounding variable of overdose and offers improved translation to the clinical setting.

Method: A modified up and down method\(^9\) will be used to measure the lowest concentration of sevoflurane producing burst suppression in individual Wistar rats on P7. Then, 0%, 40% or 70% xenon will be added. Assessment of the EEG changes will be performed by two researchers blinded to the combinations.

References:

Selective inhibition of the FK506-binding protein 51 alters ultradian and stress-induced corticosterone secretion in the rat

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Areas of research focus: Neurophysiological, neuroendocrine
Keywords: HPA axis, ultradian rhythms, stress
Brain region: Hypothalamus, pituitary
Can offer: Automated blood sampling in rats

The hypothalamic-pituitary-adrenal (HPA) axis regulates the release of glucocorticoids (CORT). CORT secretion is characterised by both circadian and ultradian rhythms which are strongly affected by age, gender, and disease states in the rat (1).

The FK506 binding protein 51 (FKBP51) regulates the effects of CORT by inhibiting nuclear translocation of the glucocorticoid receptor (GR), thus affects the negative feedback of CORT release. Indeed, clinical studies have shown that FKBP5 gene polymorphism (i.e. overexpression) is associated with elevated levels of CORT in patients affected by psychiatric disorders including major depression (2).

To further investigate the role of GR and FKBP51 in regulating ultradian rhythm of CORT, we used the FKBP51-specific antagonists SAFit2 (which has central and peripheral effects) and SAFit1 (peripheral effects only) (3). Adult male Sprague-Dawley were given SAFit2 (20mg/kg, 09.00h and 17.00h, SC) or SAFit1 (20mg/kg, 09.00h, 14.00h and 19.00h, SC) for five consecutive days. The ultradian rhythmicity of CORT was assessed using an automated blood-sampling system, collecting blood every 10 minutes for 24 hours. A noise stress was used to investigate the effects of SAFit2 and SAFit1 on stress-induced CORT secretion.

Both treatment with SAFit2 or SAFit1 decreased basal and stress-induced CORT concentrations. Furthermore, RTqPCR experiments showed enhanced GR-regulated gene expression in the hypothalamus of rats treated with SAFit2.

Our data provide insights into the role of FKBP51 and GR in regulating CORT synthesis and secretion, and suggest that inhibition of FKBP51 may represent a novel therapeutic approach for disorders associated with increased HPA axis activity.

References:
Reconsolidation in Parkinson’s disease, with and without dopamine

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Areas of research focus: Cognitive, clinical
Keywords: Dopamine, Parkinson’s disease, memory
Brain region: Hippocampus
Can offer: Behavioural testing, clinical populations, cognitive modelling

Aims/hypotheses: Parkinson’s disease (PD) patients show deficits on many cognitive functions, including episodic memory. We have previously shown that PD patients were impaired on long-term memory, and this was worsened when they were ON dopaminergic medication during learning (Grogan et al., 2015). In addition, dopamine during learning and early recognition testing affected response bias (the tendency to respond ‘yes’ or ‘no’ on a recognition test) 24 hours later. Modelling supported the hypothesis that these effects could have been due to dopamine affecting early consolidation or reconsolidation during the early tests.

Methods: PD patients learned a list of 100 words ON and OFF their dopaminergic medication and completed a 1-hour delayed recognition test. We also followed up patients for up to 2 weeks later with recognition memory tests over the phone, the last of which included a test of the words that were previously tested 1 hour after learning (and thus reconsolidated either ON or OFF dopaminergic medication), and untested words. We also tested Huntington’s disease patients, Mild Cognitive Impairment patients and Healthy age-matched Controls.

Results: PD patients showed some impairments in delayed recognition, with quicker decline over days, although by 14 days later there was little difference. PD patients OFF medication (cf ON medication) had larger increases in response bias over 24 hours.

After 14 days, target words which had been tested (and thus reconsolidated) were remembered much better than target words not seen since learning. PD patients had better accuracy if they had learned the words when OFF medication (vs ON), and there was a trend for greater benefit of reconsolidation when OFF medication.

Conclusions: We showed PD patients are impaired at long-term memory over days, although this becomes relatively smaller as healthy performance decreases to chance. Dopaminergic medication impaired some aspects of memory during learning and reconsolidation.

References:
Plasticity and learning on neuromorphic platforms

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Area of research focus: Computational and mathematical
Keywords: Plasticity and learning, neuromorphic systems, computational neuroscience
Brain region: Generic
Can offer: Neuromorphic platforms, modelling and simulation, software engineering

Aim/Background: In recent years a number of so-called neuromorphic platforms have come into existence both in Computational Neuroscience and in Machine Learning and both in academia and in industry (2; 4). Their purpose is two-fold: 1. for computational neuroscience, to provide a means to simulate large neural networks to test biological hypothesis, i.e. to understand the brain better; 2. as a next generation computation paradigm in machine learning, i.e. to utilise lessons learnt from natural neural information procession to build better Artificial Intelligence. So far the neuromorphic platforms could only simulate static synapses. We report here on our ongoing work within the Human Brain Project on bringing biologically inspired/plausible/realistic synaptic plasticity to neuromorphic platforms, in particular the SpiNNaker system (collaboration with U Manchester) (6) and the BrainScaleS system (collaboration with U Heidelberg) (5).

Methods: We concentrate on the implementation of the 1. so-called Fuse rule (1) which involves plasticity induction by Ca, 2. the Urbanczik-Senn rule (7) which involves interaction of dendrites, and 3. the INST/FILT rule (3) as these strike different balances between biological plausible, difficulty of implementation and technical performance.

Results: The above rules are being implemented on the SpiNNaker platform and the BrainScaleS system. We show here first results that demonstrate the agreement of neuromorphic simulation with the original models, and hence the underlying neuroscientific plasticity models.

Conclusion: These rules serve as an enabler on the neuromorphic platforms to simulate large plastic neural network with plasticity provided by similar custom plasticity rules. They therefore feed into an open modelling ecosystem that can be used for large scale simulations of neural network behaviour with plasticity.

References:
Dysregulated axonal transport in neurodegenerative disease

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Area of research focus: Clinical
Keywords: Axonal transport, kinesins, neurodegeneration
Brain region: Frontal cortex
Can offer: RNA/protein extraction from human brain tissue, qPCR

Defects in motor protein-mediated neuronal transport mechanisms have been implicated in several neurodegenerative disorders.1 Kinesin superfamily proteins (KIFs) comprise a large group of motor proteins whose primary role is the anterograde axonal transport and intraneuronal transport of protein cargoes through association with microtubule ‘rails’.2 KIF mutations have been associated with neurodegenerative disease. Of note, point mutations in KIF5A have been linked to several axonopathies3,4 and single nucleotide polymorphisms (SNPs) within the KIF5A gene locus have been linked to multiple sclerosis (MS) susceptibility5,6. KIF5A is believed to transport amyloid precursor protein (APP), phosphorylated neurofilaments, mitochondria and a range of pre-synaptic membrane proteins that form the SNARE complex7-9.

Axonal injury and loss are closely linked to disease progression in MS.10 Using a combination of qPCR and immunoblotting, we have found reduced KIF expression in post-mortem MS cortex and white matter and demonstrated significant inverse correlations between KIF5A and cargo expression, suggesting that lower levels of KIF5A contribute to the axonal aggregation of proteins that lead to the formation of axonal spheroids, commonly seen in the disease.11-12 Furthermore, we have found MS patients with risk alleles for SNPs within the KIF5A gene locus (linked to MS susceptibility), have significantly lower levels of KIF5A protein compared to MS patients without the risk allele. We have expanded our studies to explore KIF expression in post-mortem Alzheimer’s disease (AD) frontal lobe cortex. KIF5A protein expression also correlated inversely with levels of proteins pathologically associated with AD, including; APP and soluble Aβ.13 Our studies highlight the importance of KIFs in maintaining anterograde axonal transport for neuronal viability, which may be a potential early therapeutic target in neurodegenerative diseases.

References:
(8) Campbell PD et al. (2014) Unique function of Kinesin Kif5A in localization of mitochondria in axons.


Mutation of the Alzheimer disease associated gene, Ankyrin causes memory loss and shortened lifespan in *Drosophila*

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**Area of research focus:** Behavioural  
**Keywords:** Alzheimer’s disease, memory, *Drosophila*  
**Brain region:** Memory centres  
**Can offer:** *Drosophila* models

**Aim/Background:** Alzheimer’s disease (AD) is the most common form of dementia with patients suffering from accelerated cognitive decline including memory loss and early death. Postmortem AD brains reveal neurodegeneration that results from accumulation of amyloid plaques and intracellular tangles of tau. It is thought that 5% of the causes of AD are genetic, with the remaining 95% of causes being sporadic including non-inheritable genetic changes, ageing and environmental factors. AD causal genes include tau and amyloid precursor protein and its neurotoxic aggregating Amyloid b peptides (Ab42)\(^1\). In order to identify the largely non-inheritable contributory causes of AD, recent epigenome-wide association studies (EWAS) of AD have revealed a number of genetic loci that are associated with increased risk of AD with strongest association being with hypermethylation of the Ankyrin 1 (Ank1) gene\(^2\). This adaptor protein attaches membrane proteins such as ion channels to the spectrin-actin membrane cytoplasm and interacts with pro-apoptotic pathways.

**Methods:** We used *Drosophila* to model the effects of human tau (4R0N), human Ab42 and human tau co-expressed with Ab42 and compared their effects with misexpression of the *Drosophila* homologue of the human Ank1 gene (also in combination with human Ab42 and Tau) measuring the effect on longevity, neurodegeneration, locomotion and 1hr olfactory shock memory.

**Results:** Misexpression of human Ab42, tau or fly Ank caused the AD relevant phenotypes of:  
1) Shortened life span  
2) Neurodegeneration  
3) Locomotor defects  
4) Memory loss  
Correcting Ank expression was shown to rescue memory loss caused by overexpression of human Ab42 and Tau.

**Conclusion:** *Drosophila* provides an excellent genetic model to study AD pathology with a new AD candidate gene, Ankyrin causing AD relevant pathology in flies. Correcting Ank expression could reverse memory deficits of human Ab42 and tau models, suggesting its potential as a novel therapeutic target.

**References:**


Dopamine during retrieval or encoding does not enhance verbal recognition memory

Isotalus HK, Grogan JP, Irigoras Izagirre N, Howat A, Knight L, Coulthard EJ

Areas of research focus: Cognitive, clinical
Keywords: Memory, dopamine, learning
Can offer: sleep EEG, structural MRI, neuropsychology, statistical methods, coding in MATLAB

Aim/Background: Emerging evidence points at the importance of dopamine in successful memory performance. In Parkinson’s disease patients medication that increases dopamine availability in the brain enhances memory during consolidation and retrieval but not during encoding. In healthy ageing dopamine has been found to benefit long-term memory but it is not clear which processes it targets. We aimed to test if increasing dopamine activity improves either retrieval or encoding of verbal episodic information by administering L-DOPA to healthy older adults.

Methods: In this placebo-controlled double-blind randomised crossover trial 33 healthy older adults’ memory was tested using the remember-know paradigm. Volunteers first learnt a word-list on Day 1. On Day 2, to examine the effect of dopamine on retrieval, they were dosed with 150mg L-DOPA or placebo before their memory was tested. To target encoding, they then learnt a novel word-list for which they were tested immediately, and 1, 3, and 5 days later with unique targets at each test.

Results: There was no difference in verbal recognition accuracy or signal detection measures between L-DOPA and placebo when administered prior to retrieval or encoding (p>.05). In addition, these data provided moderate support against L-DOPA affecting retrieval (BF₀₁=4.243) or encoding (BF₀₁=4.300).

Conclusion: In healthy ageing increased dopamine activity in the brain does not enhance encoding or consolidation. Future research will investigate the efficacy of L-DOPA administration in targeting consolidation during sleep.
What is the relationship between apathy and disruption to normal biological rhythms?

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Areas of research focus: Behavioural, neurophysiological
Keywords: Apathy, circadian rhythms, ageing
Brain region: Amygdala
Can offer: Analysis of affective state, motivation and reward-sensitivity in rodents, including the use of touchscreen operant systems

Apathy is a complex neuropsychiatric symptom defined as a quantitative reduction in goal-directed behaviour(1). It is characterised by emotional blunting and lack of self-initiation. Apathy is a common behavioural symptom of aging, and is associated with a diminished quality of life, cognitive decline, and increased caregiver stress (Esposito, Rochat et al., 2014). Despite its prevalence in the elderly population, and the severe impact it has on daily living, no specific treatment has been approved. A greater understanding of the biological mechanisms that underlie apathy is urgently required.

Disruption to normal circadian/ultradian rhythms has previously been linked to psychiatric disorders including depression (Chase, 2011). The aged population have been shown to have disrupted circadian/ultradian rhythms, highlighted most clearly in their shifted sleep-wake cycle (Brown, Schmitt et al., 2011). Changes to other biological rhythms such as cortisol secretion have also been suggested (Sherman, Wysham et al., 1985). Therefore, we hypothesise that disruption to normal biological rhythms results in the psychological presentation of apathy, and restoration of these rhythms will improve symptoms.

The first project objective is to establish old age in rodents as a suitable model for apathy. This will be achieved by utilisation of several Behavioural tasks in both young and aged rodents that measure affective state, motivation and reward-sensitivity. The second objective is to establish how the sleep-wake cycle and corticosterone release change with age, and how these changes may impact on motivated behaviour. Corticosterone release will be assessed by automated blood-sampling and will be disrupted by adrenalectomy. The sleep-wake cycle will be measured by activity trackers and disrupted by altering animal housing lighting. Finally, the third objective is to determine the neural signature of apathy. We will utilise amperometry and voltammetry to probe dopamine release in the amygdala of the living rodent brain.

The outcome of this project will facilitate the development of novel treatments for apathy and give insight into healthy aging.

References:
Bone marrow cells for neural repair

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Areas of research focus: Cellular, clinical
Keywords: Bone marrow stem cells, neuro-regeneration, transplantation
Brain regions: Cerebellum, spinal cord, dorsal root ganglion
Can offer: Neuronal and stem cell culture, bone marrow stem cell transplantation, cerebellar neurodegeneration and ataxia

Background: Neuronal atrophy and dysfunctional glia are both known to contribute to neuropathology in neurodegenerative disease. Despite advances in the understanding of these diseases, current therapeutics show little ability to protect nervous tissue and no capacity to promote repair. Adult stem cell populations that reside within the bone marrow (BM) have been shown to both provide neurotrophic support and contribute to neuronal/gliial cell types in the brain through cell differentiation and/or fusion. The observation that BM cells can migrate and integrate within the nervous system may therefore offer a biological mechanism that can be exploited therapeutically.

Methods: Using *in vitro* and *in vivo* experimental techniques, in addition to analysing human post-mortem brain tissue, we have explored the process of BM-derived cells migrating and integrating within the nervous system of both murine models and patients with neurodegenerative disease.

Results: We provide evidence of extensive infiltration of BM-derived cells in areas of nervous tissue injury. Within these damaged areas, BM-derived cells contribute to the formation of mature neurons, neural precursors, neuroglial cells and myelinating Schwann cells by processes including cell fusion. We also show that in both genetic and acquired murine models of neurodegenerative disease, following cell fusion, genes derived from the donated BM-derived cell nucleus are expressed within the host neuronal cell. Moreover, we show that fusion between BM-derived cells and existing neuronal cells leads to the formation of electrically active neurons, restoring their function.

Conclusion: Our studies provide novel and fundamental insights into the ways in which nerve and glial cells can be protected and/or replaced within the adult nervous system. Harnessing BM transplantation as a neuro-regenerative gene therapy could be clinically valuable to a wide range of patients with otherwise untreatable neurological diseases.
An investigation into the stress-induced genomic action of the glucocorticoid receptor in the rat hippocampus using next-generation sequencing technologies

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Areas of research focus: Behavioural, computational and mathematical, neurophysiological

Keywords: Stress, glucocorticoids, next generation sequencing

Brain region: Hippocampus

Can offer: Chromatin immunoprecipitation and next generation sequencing

Aim/Background: During the acute stress response, activation of the hypothalamic-pituitary-adrenal axis results in a surge of glucocorticoid (GC) hormone secretion which facilitate an organism’s adaptation to stress by promoting behavioural changes and long-term memory formation (Reul, 2014). This activation results in elevated levels of corticosterone (cort) which bind to glucocorticoid receptors (GRs) in the hippocampus (Reul & de Kloet, 1985). Activated GRs translocate to the nucleus and exert genome-wide transcriptional changes by binding to glucocorticoid response elements (GREs) within the DNA (Mifsud & Reul, 2016). At present, however, little is known about the hippocampal genes regulated by GRs after stress in vivo.

Methods: Male Wistar rats underwent forced swimming (FS) and were killed at various time points after. Chromatin-immunoprecipitation (ChIP) and RNA extraction was performed on hippocampal tissue followed by next-generation sequencing (ChIP-/RNA-Seq). Extensive bioinformatic analysis was carried out to determine GR binding to GREs and associated transcriptional changes within the hippocampus. Pathway analysis was performed to elucidate the biological significance of genes exhibiting GR enrichment and transcriptional changes following acute stress.

Results: FS resulted in GR enrichment at >1,000 genomic loci. These loci were annotated to nearby genes and were predominantly associated with GREs. Over 3,000 genes exhibited changes in either heteronuclear (hnRNA) or mature (mRNA) RNA. Pathway analysis revealed that genes exhibiting GR enrichment and/or transcriptional changes following FS are involved in hippocampal specific processes including long-term potentiation of CA1 neurons, cognitive processes, and neuropsychiatric disorders such as major affective disorder.

Conclusion: This study has given extensive insight into the action of the GR during the acute stress response; a process critical for the maintenance of health and well-being. It has also highlighted a number of potential gene targets which may be important in studies aiming to elucidate how dysregulations in the acute stress response lead to the development of stress-related neuropsychiatric disorders.

References:
Preclinical analysis of sodium valproate for the treatment of DIPG by convection enhanced delivery

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Areas of research focus: Cellular, cancer biology, translational research
Keywords: Brain tumours, drug delivery, epigenetics
Brain region: Brainstem

There is a significant need to develop new treatment strategies to improve the prognosis of DIPG patients. We have previously shown that the HDAC inhibitor, sodium valproate (VPA), reduces the viability of DIPG cells \textit{in vitro}. Whilst, VPA does cross the blood brain barrier, only 15\% of serum concentrations reach the brain, therefore systemic delivery of VPA is unlikely to have significant anti-glioma effects without first incurring dose-limiting systemic toxicities. Convection enhanced delivery (CED) affords the direct administration of drugs to the tumour site, circumventing problems associated with central nervous system penetration of systemically administered drugs.

Live/Dead assays were used to assess the effect of VPA on DIPG cell viability after 72 hours and sequential 6-hour drug exposures. \textit{In vitro} neurotoxicity was determined by exposing normal hippocampal cells to VPA for 6 hours. To determine the feasibility of direct delivery to the brain, VPA was administered by CED to the brain of juvenile wistar rats. Toxicity was assessed by clinical and neuropathological examination of infused brain 21 days after treatment. In addition, clearance and stability was analysed by LC-MS/MS.

Results to date, demonstrate that VPA reduces cell viability in all DIPG cell lines tested. No significant differences were seen in cellular morphology and network of normal hippocampal derived glio-neuronal cultures \textit{in vitro}. This was further substantiated by \textit{in vivo} analysis of toxicity following acute VPA infusion by CED, showing minimal effect on neuronal and glial markers in normal brain. Mass spectrometric analysis determined VPA to be stable in artificial CSF and the half-life in rat brain to be two hours. This data suggests that VPA is well tolerated when delivered by CED in rat and supports further investigation into the \textit{in vivo} efficacy of VPA in an orthotopic DIPG model.
Collateral projections innervate the mammillary bodies and retrosplenial cortex: A new category of hippocampal cells

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Areas of research focus: Cellular, behavioural
Keywords: Neuroanatomy, memory circuits, hippocampus
Brain regions: Subiculum, retrosplenial cortex, mammillary bodies
Can offer: Anatomical tracing, immunohistochemistry, microscopy

Aim/Background: To understand the hippocampus it is necessary to understand the subiculum. Unlike other hippocampal subfields, the subiculum projects to almost all hippocampal targets, highlighting its critical importance for external networks. While many subicular efferents are segregated by their columnar and laminar origin, the hippocampal projections to the mammillary bodies and retrosplenial cortex (areas 29, 30) appear to arise from overlapping subicular regions in both rats and macaque monkeys.

Methods: To test for separation in these pathways pairs of retrograde tracers (Fast Blue and Cholera Toxin Subunit B) were inject in these two locations (rats and mice). The subiculum was examined for neurons labelled by a single tracer or co-labelled by both tracers. Immunofluorescence was then used to investigate the neurochemical properties of these projections, including staining for VGluT1 & 2, neurotensin, parvalbumin.

Results: We describe a new category of dorsal subiculum neurons that innervate both the mammillary bodies and the retrosplenial cortex. These bifurcating neurons comprise almost half of the hippocampal cells that project to retrosplenial cortex. The termination of these numerous collateral projections was visualized within the medial mammillary nucleus and the granular retrosplenial cortex (area 29). These collateral projections included subiculum efferents that cross to the contralateral mammillary bodies. Within the granular retrosplenial cortex, the collateral projections form a particularly dense plexus in deep layer II and layer III. This retrosplenial termination site co-localized with markers for VGluT2 and neurotensin.

Conclusion: Along with the anterior thalamic nuclei, the mammillary bodies and retrosplenial cortex are key members of a memory circuit (Papez circuit), which is usually described as both starting and finishing in the hippocampus. The present findings reveal how the hippocampus simultaneously engages different parts of this circuit, so forcing an important revision of this network. These findings challenge ideas of subiculum organisation and reverse information flow in Papez circuit.
Electrophysiological recordings of the cerebellum and periaqueductal grey during fear behaviours

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Areas of research focus: Behavioural, neurophysiological
Keywords: Fear behaviour, rodents, chronic electrophysiology
Brain regions: Cerebellum and Periaqueductal grey, survival circuits
Can offer: Electrophysiology

Many brain regions contribute to survival networks that co-ordinate fear responses. In the rodent, electrophysiological mapping has shown that neuronal connections exist between the periaqueductal grey (PAG) and cerebellum and lesioning studies targeting the pyramis of the cerebellum disrupt freezing behaviour in the rat (Koutsikou et al., 2014). Using electrophysiological techniques, we record from both the cerebellar fastigial nucleus (FN) and PAG during fear paradigms to investigate the contributions of each area to defensive behaviours e.g. freezing.

Rats under surgical anaesthesia (Ket/med) had tetrodes implanted into the FN and the periaqueductal grey. EMG wires were implanted into the neck to monitor motor activity. Following an appropriate recovery time, units were recorded from these areas whilst the animals underwent an auditory cued fear conditioning and/or predatory cat odour task.

Patterns of unit activity from the PAG and FN were compared to the unconditioned fear signal (auditory tone and cat odour). The units were also compared to EMG activity during freezing behaviour. Unit activity in the PAG was noticeably increased at the onset and offset of the fear signal (tone) (similar to that described by Watson et al., 2016) whilst there was no such observation in the FN. Units in the FN increased firing rate in response to cat odour.

These preliminary results suggest the FN isn’t responding to the specific auditory cue, but is potentially activated in a more generalised expression of fear, relating for example to freezing behaviour or autonomic responses. This data also suggests the FN responds to different sensory modalities in relation to fear as it responds to predatory odour but not an auditory tone. The PAG appears to be activated in response to signal the onset of an auditory tone, and with conditioning becomes entrained to the offset of the tone, in anticipation of an aversive response.
Amyloid-β plaque quantification in human brain parenchyma

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Area of research focus: Clinical

Keywords: Dementia, microscopy, immunohistochemistry

Brain regions: Frontal and parietal lobes

Can offer: Immunohistochemical staining, light microscopy, field fraction analysis

Aim/Background: Hypertension is associated with the accumulation of amyloid-β (Aβ) within the brain and mid-life hypertension may also increase the risk of developing Alzheimer’s disease (AD). Our project aims to elucidate the relationship between hypertension and Aβ accumulation by quantifying the protein levels of various vasoactive enzymes as well as enzymes responsible for Aβ clearance in a large cohort of post-mortem human brain tissue from individuals with a known hypertensive status, either with and without dementia (4 cohorts: controls, AD, vascular dementia and mixed vascular and AD pathology). In this study, we aimed to quantify the abundance of Aβ plaque load in the brain parenchyma to enable us to identify relationships between altered protein concentrations and Aβ abundance.

Methods: Brain tissue from 207 individuals was sourced from the South West Dementia Brain Bank. Sections of formalin-fixed and paraffin-embedded brain tissue from the frontal and parietal lobes were stained using an automated immunohistochemistry (IHC) protocol with an antibody specific for total Aβ (4G8). The stained sections were imaged using a light microscope (Leica) and field fraction analysis software (ImagePro) to quantify the percentage of Aβ in the brain parenchyma.

Results: Preliminary data indicates there is a significant difference in total Aβ between the control cohort, and the AD and mixed dementia cohorts in both the frontal and parietal lobes. In relation to previous IHC, a significant improvement was found by using the new automated IHC protocol in combination with a more specific Aβ antibody.

Conclusion: The Aβ abundance data clearly illustrates the differences in total Aβ plaque load in the different dementia cohorts. Data collection for this project is ongoing, and future analysis will examine the differences in total Aβ with hypertensive status as an additional variable.
Causal analysis of maternal substance use during pregnancy and offspring neurodevelopmental outcomes

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Areas of research focus: Epidemiology and population health, developmental
Keywords: Autism, substance use, prenatal
Brain regions: General, neurodevelopmental
Can offer: Statistical methodology

Aim/Background: Alcohol and tobacco use during pregnancy have been shown to influence fetal brain development [1,2]. These exposures have also been associated with intellectual disability, learning difficulties and autism spectrum disorder (ASD) [3-8]. Although such associations may be biologically plausible, whether they are causal or not is unclear. As a part of this project we aim to further investigate whether substance use by mothers during pregnancy is causally associated with childhood neurodevelopmental outcomes. The project will help to expand our understanding of the non-genetic causes of ASD, learning/intellectual disability and psychosis. Our research will provide a stronger evidence base to help future guidelines or policy regarding substance use during pregnancy.

Proposed Methods: We will first derive a new multisource variable of learning disability from record linkage, school data, GP records and questionnaire data from participants of the Avon Longitudinal Study of Parents and Children (ALSPAC). Similar multisource variables for autism, along with trait measures, have been derived previously [9]. Our initial analysis will use traditional regression methods to estimate the associations between the exposures and the outcomes detailed below adjusted for a range of potential confounders. This project will then make use of a variety of causal inference methods, each with their own underlying assumptions, advantages and constraints [10]. These methods include negative control designs, exposure-discordant siblings and Mendelian Randomisation (MR). Independent biases associated with each method are unlikely to lead to the same result. Therefore, if each method leads to a similar conclusion, this will provide support of that conclusions validity. If conclusions are contradictory then the assumptions of each method will be further investigated to identify potential violations. We will carry out cross cohort comparisons using other data sources, including the Stockholm Youth Cohort, which have complementary strengths.

References:


Distinguishing between evidence accumulation and temporal probability summation in perceptual decision making

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Areas of research focus: Cognitive, computational and mathematical
Keywords: Perception, vision, decision-making
Brain regions: Visual cortex, LGN, basal ganglia

Models of perceptual decision making typically assume temporal integration of a decision variable (e.g. sequential sampling models). However, the sensory input to these models, and therefore the precise input to the decision variable, is typically left unspecified. In contrast, models of early sensory system (e.g. probability summation models) specify that the ideal observer should generate the decision variable by matching a signal template with the stimulus. These models typically assume that the decision variable is not integrated but evaluated at each instant. We investigated how people identify signals in a stimulus that is temporally extended and contained additive and uncorrelated noise. When the signal-to-noise ratio (SNR) of this type of stimuli is varied, both models predict a shift in the reaction time distribution. But the models generate different predictions about how RT distributions shift with a change in SNR and the nature of this shift depends on whether the signal or noise component is varied. In an experiment where participants were asked to identify one of two numeric characters in a noisy animation, we found that the parameters of the fitted Ex-Gaussians shifted in line with the sequential sampling model. We also found the same pattern of parameter shifts irrespective of whether the SNR was manipulated through varying the signal (Session 1) or noise (Session 2). This finding suggests that the decision variable is related to the SNR of the stimulus, rather than the ideal decision variable that represents the difference in matched template responses.
Determining the optimal methods for testing for Chromosome 1p/19q codeletions and MGMT promoter methylation status in glioma

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Area of research focus: Epidemiology and population health
Keywords: Glioma, systematic review, MGMT, 1p/19q codeletion
Can offer: Systematic reviews

Aim/Background: Gliomas are brain tumours that are thought to be histogenetically related to glial cells and are the most common primary intracranial tumour. Two molecular markers that have diagnostic, prognostic and predictive importance in glioma are complete deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) (1p/19q codeletion), and MGMT promoter methylation status.

The optimal method of testing for 1p/19q codeletion and MGMT promoter methylation status has not been determined. The aim of this research is to determine the best way of testing for these markers, both from a clinical and economic standpoint.

Methods: We will perform a systematic review of studies which have performed 1p/19q testing using two or more techniques. Single nucleotide polymorphism array is the gold standard technique for testing for 1p/19q codeletion, however, few studies will have used this technique; therefore, we aim to use a latent class model to determine test accuracy when an imperfect test is used as the reference standard. The regions of the MGMT promoter that require methylation and the level of methylation which best predicts prognosis needs to be established. We will perform a systematic review of studies which have examined the association of MGMT promoter methylation status with overall survival, extracting information on how MGMT promoter methylation status was determined.

A final element of the reviews will be to consider the costs, and cost-effectiveness of alternative methods. This will be accomplished by completing a full integrated review of economic evidence, estimation of the resources used to provide the tests, and an economic model (a simple decision model).

Conclusion: This research aims to determine the optimal method of testing for Chromosome 1p/19q codeletions and MGMT promoter methylation status in glioma.
Utility of TOMM results in differentiating between FCD and dementia (TOMFAD)

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Areas of research focus: Cognitive, clinical
Keywords: Validity tests, dementia, cognitive impairment

Aim/Background: Performance Validity Tests (PVTs) are used in neuropsychological assessment to measure the degree to which test results accurately represent an individual’s level of ability. Anecdotally, we find that such tests are useful for differentiating between Functional Cognitive Disorder (FCD) and Mild Cognitive Impairment (MCI) or dementia. It is important to validate this observation empirically. Finding tools that help us to differentiate between FCD, MCI and dementia as early and accurately as possible is a key objective for research and clinical practice in this area. As well as this, some individuals with FCD or MCI may be misdiagnosed, leading to inaccurate prognosis or inappropriate inclusion in research.

Methods: In this study, we propose to examine archival data from our Cognitive Disorders Clinic in Southmead Hospital to (1) examine the distributions of a commonly used PVT score (the Test of Memory Malingering; TOMM) among people with different diagnoses and levels of cognitive impairment, and (2) determine whether including the TOMM score, in combination with the results of a battery of neurocognitive tests and psychological questionnaires, improves differential diagnosis.

Results/ Conclusion: We aim to determine if the TOMM is a useful component of the standard neurocognitive test battery with regard to early diagnosis and characterising participants in research trials.
Mineralocorticoid and glucocorticoid receptor binding to glucocorticoid target genes in the rat hippocampus after stress

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Areas of research focus: Behavioural, neurophysiological
Keywords: Stress, behaviour, corticosterone receptors
Brain region: Hippocampus
Can offer: Chromatin immunoprecipitation, bioruptor pico, behavioural tests

Glucocorticoids (GCs), secreted after stress or during the circadian rise, act on the brain through binding to mineralocorticoid (MRs) and glucocorticoid receptors (GRs). MRs and GRs then bind to glucocorticoid response elements (GREs) within target genes (e.g. FK506-binding protein 5 (Fkbp5), serum/GC-regulated kinase 1 (Sgk1), Period 1 (Per1)) to evoke changes in gene transcription. Until recently, this had not been studied under physiological conditions in vivo.

Male Wistar rats were killed under baseline conditions or at various time points after exposure to stress and hippocampus tissue was collected for chromatin immuno-precipitation (ChIP) to assess MR and GR binding to GREs within target genes or for RNA analysis by qPCR. In a separate experiment, rats were subjected to adrenalectomy (ADX) to remove endogenous CORT and the effect of ADX on MR and GR binding to target genes and subsequent RNA expression was assessed.

Different stressors resulted in similar levels of receptor binding to GREs, indicating that above a certain threshold these responses are independent of GC levels. MR and GR to GRE binding, as well as their binding as homo- versus heterodimers, was found to be GRE- and gene-dependent and resulted in associated changes in gene transcription. ADX abolished the stress-induced increase in MR and GR binding to target genes and prevented the associated stress-induced rise in RNA expression.

These findings highlight the complexity of GC receptor action, revealing new layers of regulatory control and opportunities for future investigation.
Later life depression and Alzheimer’s disease: Bystander or participant?

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Areas of research focus: Clinical, neurodegeneration
Keywords: Alzheimer’s disease, major depressive disorder, vascular dementia
Brain regions: Medial temporal, parietal white matter, dorsolateral prefrontal and orbitofrontal cortex
Can offer: ELISA, immunohistochemistry

Introduction: Alzheimer’s disease (AD) is estimated to effect 500,000 patients a year in the U.K. alone. This figure is projected to double by 2025. Depression has been associated with increased risk of Alzheimer’s and vascular dementia. Late life depression (>50) is most associated with this increased risk. It remains unclear whether depression is a risk factor for the development of AD or part of the AD prodrome.

Method: We will study individuals from 4 groups: early AD, early life depression, later life depression and controls. We will look at medial temporal cortex, parietal white matter, dorsolateral prefrontal cortex and orbitofrontal cortex. Amyloid-β (Aβ), tau and α-synuclein will be assessed by immunohistochemistry (the current gold standard). In addition, Aβ40, Aβ42 and α-synuclein will be measured by ELISA. Vascular function will be assessed by measuring biochemical markers of ante-mortem tissue oxygenation (proteolipid protein-1:myelin associated glycoprotein, and vascular endothelial growth factor) and of blood-brain barrier integrity (fibrinogen, adjusted for sample content of haemoglobin).

Predicted results: We hypothesise that brains from patients with late-life depression will show more severe AD pathology and vascular dysfunction than those from age-matched controls or from patients with early-onset depression, comparable to the findings in the early AD/MCI group.

Discussion: Delaying the onset of AD by even 5 years would reduce the number of sufferers by 36% by 2050. Identifying contributors to its development is a key part of finding ways of achieving this delay.

References:
Neuroscience in psychiatry training: A national project supported by the Gatsby Foundation and Wellcome Trust to strengthen the neuroscience content of core psychiatry training

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Areas of research focus: Clinical, medical education
Keywords: Psychiatry, education, neuroscience
Brain region: Whole brain
Can offer: Updates on the neuroscience component of psychiatric training and opportunities to develop local professional networks to support medical education

Aim/Background: Doctors wanting to become psychiatrists in the UK complete six-to-seven years of specialist postgraduate training. The first three “Core Training” years develop a foundation of clinical experience and knowledge of the fields underpinning our current understanding of mental illness. With support from the Gatsby Foundation and the Wellcome Trust, the Royal College of Psychiatrists (RCPsych) is reshaping psychiatry training by integrating neuroscience. This aims to introduce into clinical practice a modern neuroscience perspective reflecting the rapid and exciting advances in basic and clinical research that are transforming our understanding of how the brain works.

Methods: The project is led by a 15-member Commission of international experts in neuroscience and education. The primary focus of the first phase involved extensive stakeholder engagement across the country. This has been followed by a scoping exercise for the current Core Curriculum to formulate an updated, integrated neuroscience component accompanied by changes to the syllabus and written exam questions and the development of “Inspiring Excellence in Neuroscience” training days for clinical tutors. The project has also led to the establishment of the RCPsych’s first dedicated annual Neuroscience Conference to encourage and facilitate collaboration and integration among neuroscientists and psychiatrists.

Results: The response has been overwhelmingly positive and many psychiatrists have described this as a timely change. However, they have raised concerns over how new content is delivered, properly integrated with clinical practice and taught consistently across the training regions of the UK.

Conclusions: This shift in emphasis in psychiatric training offers a major opportunity to strengthen existing links between academic researchers and clinical professionals. Key to this process will be the creation of regional “Neuroscience in Psychiatry Networks” which will be essential in supporting delivery of the new training. Ultimately, we hope these developments will play a key part in shaping the influence of neuroscience in contemporary psychiatry.
Systematic review on neural correlates of lack of insight in frontotemporal dementia: Preliminary data

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Areas of research focus: Cognitive, neuropsychology
Keywords: Insight, neural correlates, frontotemporal dementia
Brain regions: Ventromedial-frontopolar cortex, temporoparietal junction
Can offer: Neuropsychological tools

Aim/Background: Lack of insight is a common clinical feature in different neuropsychiatric diseases, including schizophrenia, traumatic brain injury and dementia. Although this disorder is particularly prominent in frontotemporal dementia (FTD), its neural correlates has been underexplored across those syndromes resulting from frontotemporal involvement. Evidence suggests that global insight loss versus lack of insight into specific neuropsychological/behavioural domains might be underpinned by different brain areas in dementia. The main aim of this systematic review is to explore this further by identifying the neural correlates of lack of insight that has been reported in different variants of FTD.

Methods: Structural and functional brain imaging studies focused on lack of insight in FTD were the core of the search strategy designed. 5 databases, including MEDLINE, Embase, PsycInfo, Web of Science and BIOSIS, were explored. ProQuest Dissertations & Theses Global was also considered. Studies conducted in humans and published in English between 1995 and September 2017 made up the sample of articles revised.

Results: 14 papers out of 504 articles were finally selected. Most of the studies (~50%) observed global insight loss or lack of insight into social cognition. Functional studies associated global insight loss with frontal right dysfunction in the behavioural variant of FTD (bvFTD), whereas structural studies did with orbitofrontal cortex, ventromedial prefrontal cortex and frontopolar areas across behavioural and language variants of FTD. Lack of insight into social cognition was mainly explored with structural brain imaging studies in FTD, suggesting correlations with orbitofrontal cortex and areas placed throughout the limbic system.

Conclusion: Although neural correlates of lack of insight in FTD varied according to the brain imaging method and the type of neuropsychological assessment used, most of the studies reported correlations between general or specific insight loss and a widespread involvement of frontotemporal and limbic areas.

References:


Complement system activation & Alzheimer’s disease

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Area of research focus: Neuroinflammation
Keywords: Alzheimer’s brain, neuroinflammation, complement system
Brain region: Frontal and temporal cortex

Introduction: Neuroinflammation is a common feature of Alzheimer’s disease pathology, that is characterized by the presence of reactive astrocytes and activation of the microglia, as well as complement system activation & increased expression of pro-inflammatory cytokines. Amyloid beta protein accumulation in the brain of Alzheimer’s disease patients is the activator of the complement system. Its presence leads to glial cell activation and subsequent release of neurotoxic substances and free oxygen radicals, we looked at complement system to highlight its role as a part of neuroinflammation in the disease to determine if it should be considered as a potential target for treating Alzheimer’s disease.

Material and methods: We are studying different complement cascade proteins and regulators in a cohort of Alzheimer’s disease and age-matched controls in post-mortem human brain tissue. We are looking at different brain areas including frontal and temporal cortices, complement proteins are measured by ELISAs & WB analysis in homogenized brain tissue.

Results: Some of the complement proteins and regulators are increased in one or both brain areas in AD group compared to age-matched controls as C1q, iC3b & clusterin, while others show no significant difference between the groups.

Conclusion: The complement system is dysregulated in the brain of Alzheimer’s disease, also some of the complement system components was found to be correlated with the disease pathology according to Braak staging.
Failure of “cue-identification” in event-based prospective memory in mild cognitive impairment

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Areas of research focus: Cognitive, clinical, neurophysiological
Keywords: Alzheimer’s disease, neurodegeneration, memory
Brain regions: Hippocampus, prefrontal cortex
Can offer: Running MRI scans, performing cognitive and neuropsychological tests

Introduction: Prospective memory (PM) is the process of remembering when an action needs to take place following a cue (either event-based or time-based). PM is formed of a “cue-identification” component and a retrospective component (remembering the action to be performed). Alzheimer’s Disease (AD) patients have an impairment in PM and almost 50% of patients with mild cognitive impairment (MCI) are expected to develop AD. Therefore, we aim to investigate the following hypotheses i) event-based PM tasks are a good indicator of MCI and early stage AD and ii) changes in PFC volume are associated with poor PM.

Materials and Methods: 60 participants including healthy controls (HCs), people with subjective cognitive decline (SCD) and MCI were tested on 3 event-based PM tests as part of a neuropsychological battery and Clinical Dementia Rating scale. Each participant also had a T1-weighted whole-brain scan using a magnetisation-prepared rapid gradient-echo (MPRAGE) sequence.

Results: Statistical analyses revealed a significant decline in the overall PM scores in MCIs compared to HCs (p = 0.015). Further analyses demonstrated that the performance on the “cue-identification” component, but not the retrospective component, of PM is significantly worse in MCI compared to HC (p = 0.015). Changes in PFC volume associated with PM will be analysed using FreeSurfer Version 6.0.

Conclusions: These findings suggest that assessments of event-based PM, especially the “cue-identification” component, may be a useful clinical tool, which can distinguish between MCIs and HCs. The lack of “cue-identification” is thought to result in problems of self-initiation in patients with MCI, which impacts quality of daily life. We are currently analysing T1-weighted images to test the hypothesis that PFC is critical for event-based PM tasks.
Connectivity analysis of the attentional modulation of pain

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Areas of research focus: Cognitive, computational and mathematical  
Brain region: Brainstem  
Can offer: fMRI experiment design and analysis

Aim/Background: Distraction from pain is a robust strategy to transiently decrease pain perception without the need for pharmacological manipulation (Bushnell et al., 2013). A number of key regions in the pain modulatory pathways have been shown to be involved such as the anterior cingulate cortex (ACC), the periaqueductal grey (PAG) and the rostro-ventromedial medulla (RVM) (Tracey et al., 2002; Brooks et al., 2017, Bantick et al., 2002). However, how these regions interact to give rise to the distraction induced analgesic (DIA) effect is still unknown. We therefore investigated the effective connectivity between these regions during a DIA paradigm.

Methods: In an fMRI scanner, 40 healthy volunteers received a noxious or innocuous thermal stimulus while doing an visual attention task (Rapid Serial Visual Presentation) with two levels of difficulty. Both the stimulus intensity and the task difficulty were titrated for each individual against pain score and task success. The experiment had a 2x2 factorial design allowing us to define a task:pain interaction contrast. Effective connectivity was analysed using Psychophysiological interactions (PPI) in FEAT in FSL and dynamic causal modelling (DCM) in SPM12. Time-series for the analyses were extracted from brain regions showing an activation for main effects in Brooks et al. (2017).

Results: A permutation test showed the PAG and the RVM to increase coupling in the positive interaction contrast consistently in the studies analysed. Bayesian model selection on DCMs extended this result showing a modulation of the PAG to RVM connection caused by the hard task.

Conclusion: This finding identifies for the first time an increased functional connectivity in a descending control pathway in the brainstem that may be responsible for mediating DIA.

References:
Neural dynamics of survival circuits - Investigating the connections between cerebellum and periaqueductal grey

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Areas of research focus: Behavioural, computational and mathematical, neurophysiological
Keywords: Defensive behaviours, motor control, neural networks
Brain region: Cerebellum and PAG
Can offer: In vivo electrophysiology, immunohistochemistry

Aim/Background: Understanding mechanisms underlying emotional behaviours is important in the development of strategies to improve emotional disorders and animal welfare. Little is known about the way central ‘emotional’ circuits engage with the motor system to generate the highly characteristic responses essential for survival. My project explores the relationship between the cerebellum (CBM) and key components of survival networks, such as the periaqueductal grey (PAG).

Methods:
1) Retrograde viral neuronal tracers (e.g. CAV-2) to map anatomical connections between the PAG and CBM
2) Acute electrophysiological experiments in anesthetized animals to investigate functional connectivity between PAG and CBM
3) Modelling the survival network. Specifically, modelling spectral dynamics and their interaction in terms of power and phase coherence between the two structures

Results:
1) Analysis of brain tissue after injection of CAV-2 in the vlPAG
2) Stimulation of the lateral nuclei of the CBM evoked field responses in the vlPAG
3) Analysing the differences in LFP activity in the PAG and medial cerebellar nuclei during different phases of an auditory cued fear conditioning paradigm. These data will then be used to test dynamic causal modelling and to assess connectivity between these areas.

Conclusion: Initial pilot data and previous studies show that the PAG and CBM might be anatomically connected and communicating during fear behaviours e.g. freezing. One hypothesis is that these two structures contribute to the motor output, which can be studied further by correlating neural and EMG activity. The dynamics by which PAG and CBM are functionally connected will be explored further using the above techniques with the aim to characterise their contribution to defensive behaviours.
In vivo electrophysiological recording of hippocampal cells in head fixed but freely exploring mice

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Areas of research focus: Behavioural, neurophysiological  
Keywords: In vivo head fixed electrophysiology, spatial memory task, hippocampal networks  
Brain region: Hippocampus  
Can offer: In vivo head fixed electrophysiology and behaviour

Aim/Background: To fully understand the neuronal network mechanisms that underpin behaviour, it is necessary to record from individual neurons in the brain. Whilst extracellular recordings can detect the spiking activity of neurons, measuring the underlying subthreshold membrane dynamics requires intracellular recording. To achieve this in an awake, freely moving animal is almost impossible due to mechanical instability, therefore methods to reduce mobility by head-fixation have been developed in awake mice. A common technique involves head-fixed mice running on a treadmill in a virtual reality environment, but in these conditions naturalistic stimuli are limited, in particular the use of the whiskers which are a principle sensory input in mice. Our main aim is to be able to study neuronal responses in the hippocampus during decision-making tasks based on spatial memory, which will rely on the mice being able to freely explore in a minimally stressful environment.

Methods: Recently, a novel experimental system has been developed in which a head-fixed mouse can explore a large, air-lifted environment that is able to freely move around the animal in response to its movements. The Mobile HomeCage™ therefore offers the potential to perform high-precision electrophysiological recordings from individual neurons in the brain whilst the animal performs a behavioural task.

Results: Here we present our preliminary data showing recordings from principle hippocampal neurons (including extracellular, juxtacellular and whole-cell configurations) in freely moving mice and discuss refinements to the experimental design aimed at improving the behavioural performance of the head-fixed animals during recording.

Conclusion: Thus, we have proven that Mobile HomeCage™ is suitable to study neuronal membrane dynamics in the hippocampus that underlie spatial navigation behavioural task.
Studying G-CSF as a potential treatment for Friedreich’s Ataxia

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Areas of research focus: Cellular, clinical
Keywords: Ataxia, stem cells, cytokines
Brain regions: Cerebellum, spinal cord, DRG
Can offer: Human tissue / cellular analysis

Aim/Background: Friedreich’s Ataxia (FA) is the most common inherited ataxia. In most cases, FA is caused by homozygous GAA.TCC tri-nucleotide repeat expansion within intron 1 of the FXN gene, resulting in the transcriptional repression of frataxin; a small mitochondrial protein involved in iron-sulphur cluster biosynthesis. There is currently no proven treatment that effectively prevents or even slows the progressive neurodegeneration that characterises the disease. In murine models of FA, the cytokine Granulocyte Colony Stimulating Factor (G-CSF) has been shown to improve motor function, reverse pathological changes and have pronounced effects on levels of anti-oxidant molecules and the protein frataxin. G-CSF is a drug widely used clinically for bone marrow stem cell mobilisation prior to peripheral blood stem cell harvest.

Methods: We have studied in vitro the effects of G-CSF exposure on cultured lymphoblastoid cells derived from both patients with FA and age/sex-matched healthy controls. Specifically, using several proteomic techniques we have investigated the effects of G-CSF on cellular frataxin levels, anti-oxidant pathways and resistance to oxidative stress.

Results: To date, we have identified that levels of frataxin and associated anti-oxidants molecules are downregulated in lymphoblastoid cells derived from patients with FA. In response to G-CSF exposure, frataxin expression was significantly elevated in FA-derived cells and deficits in anti-oxidant cellular defences (specifically the expression of PGC1a, Nrf2, Catalase and glutathione peroxidase) were reversed.

Conclusion: In summary, our studies further show the potential of G-CSF as a future novel, rapidly translatable and disease-modifying treatment for patients with FA.
Cerebro-cerebellar interactions in goal-directed behaviour

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Areas of research focus: Behavioural, cognitive, neurophysiological
Keywords: Ataxia, stem cells, cytokines
Brain region: Cerebellum, electrophysiology, working memory
Can offer: Chronic electrophysiological recording techniques in rats

Goal directed behaviours involve a number of brain regions including the prefrontal cortex (PFC) and cerebellum. Traditionally, the cerebellum has been thought to mediate the motor aspects of such behaviours, however more recently there is evidence for involvement of the cerebellum in cognitive processes. This study aims to investigate cerebellar contributions to cognition by combining cognitive behavioural tests with recordings of neural activity within the cerebellum and PFC.

We used the delayed alternation T-maze paradigm, a task commonly used to assess the cognitive ability of rodents. In the sample phase of each trial, the animal is restricted to entering one goal arm, where it receives a reward. In the subsequent choice phase, the animal is returned to the start box and must enter the unsampled goal arm to receive a reward. Cognitive load was increased by increasing the time delay between the sample and choice phase, and in later stages by changing the rule so in the choice phase the animal must enter the previously sampled arm to receive a reward.

During this task, simultaneous multichannel electrophysiological recordings of neural activity within the cerebellum and PFC were obtained. In the cerebellum the medial nucleus (MN) was targeted for recording as previous studies in our lab have demonstrated behaviourally dependent coordinated activity between the MN and PFC (Watson et al., 2014). Ongoing analysis of single unit and local field potential recordings will allow MN-PFC interactions at different phases of the cognitive task to be investigated.

We hypothesise that during this task co-activation of the PFC and cerebellum will occur; that the direction of information flow will be from PFC to cerebellum when the cognitive load is high; and that the direction of information flow will switch (cerebellum to PFC) as the task is solved and cognitive demand decreases.

References:
Gaze characteristics in hemianopia during a naturalistic sandwich-making task and a table-top visual search task

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Area of research focus: Clinical
Keywords: Stroke, rehabilitation, hemianopia
Brain region: Visual cortex
Can offer: Eye tracking equipment and software

Aim/Background: Hemianopia impairs performance of lab-based visual search tasks (VSTs)\(^1\), resulting in longer search times\(^2\), increased fixations, and bias towards the hemianopic field\(^3\). However, these differences may diminish during real-world tasks\(^4\). This study examined visual behaviour during a VST, and a naturalistic sandwich-making task (SWT).

Methods: 5 participants with homonymous visual field defects, and 10 healthy age-matched controls completed a VST and SWT. Visual behaviour was recorded using an SMI eye tracker, and analysed using multivariate analysis of variance, controlling for age. Values presented are Mean±SEM.

6 sandwich-making items (SWT), or 13 recognisable objects (VST) were placed in pre-specified locations on a table. During VST trials (14 total), participants had to locate 2 of 13 objects. During the SWT, participants made 4 different sandwiches (4 trials, each repeated once).

Results: Patients took longer to complete the VST than controls (7.2±1.1 and 3.9±0.52 seconds, \(p=0.004\)) and made more fixations (6±2 and 4±1, \(p=0.013\)). Additionally, patients showed a trend of increased number of gaze shifts towards the hemianopic field (3±1 and 2±1, \(p=0.064\)).

During the SWT, patients and controls exhibited similar trial durations (74.9±5.5 and 60.1±5.6 seconds, \(p=0.121\)). Patients made more fixations than controls, (30±3 and 23±1 respectively, \(p=0.023\)), however there was no directional bias of gaze shifts (10±4 and 10±2, \(p=0.307\)).

Conclusion: Patients exhibited distinct visual behaviour to controls during the VST, but less so during the SWT. During real-world, visuo-motor tasks, patients appear to compensate for visual field defects that limit performance in lab-based VSTs. Further work is needed to elucidate these compensatory mechanisms.

References:


Influence of reward on offline brain activity: reactivation of reward-responsive neurons in the nucleus accumbens

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Areas of research focus: Behavioural, cognitive, computational and mathematical

Keywords: Hippocampal replay, reinforcement learning, memory

Brain region: Hippocampus and nucleus accumbens

Can offer: In vivo electrophysiology

Aim/Background: Replay of experience-dependent neural activity during sleep and rest, especially in the hippocampus, is thought to be a crucial mechanism for memory consolidation. During periods of awake rest and slow-wave sleep, patterns of neural activity that correlate with task-related events are replayed (Wilson & McNaughton, 1994), and the strength of this replay correlates with subsequent memory performance (Dupret et al., 2010). Preferential hippocampal replay of activity related to reward experiences has been reported in association with reactivation of reward-responsive cells in the nucleus accumbens, following learning (Lansink et al., 2009). This coordinated offline activity across the two brain regions may underlie the integration of reward into memory.

Methods: We have integrated experimental and modelling approaches to investigate how hippocampal-accumbens interactions promote reward-biased replay. Wildtype rats are trained to navigate a Y-shaped maze to receive a sucrose reward, with each of the three maze arms delivering reward with a different probability (12.5%, 50% and 87.5%, respectively). Electrophysiological recordings are made from silicon probes chronically implanted in accumbens and CA1 of the hippocampus, during training sessions and adjacent periods of sleep and rest. The probabilistic learning task is modelled using REINFORCE, a gradient-following reinforcement learning algorithm, implemented in an artificial neural network of stochastic logistic units in Matlab. The model is endowed with various plausible forms of replay to observe the effects on learning of biasing replay in different ways.

Results/Conclusion: The study is still in progress. We present preliminary results showing how the influence of reward and reward probability affect offline activity in the nucleus accumbens, and suggest from the model’s results how this offline activity might aid learning and subsequent memory performance.

References:
Exploratory investigation into the neural correlates of transient ischaemic attack

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Areas of research focus: Cognitive, clinical

Keywords: Transient ischaemic attack, electroencephalogram (EEG), visual evoked potentials

Brain region: All channels of an EEG; the area of the brain is dependent on the paradigm investigated

Can offer: I have a reasonable amount of experience using EEG. I also have experience in using Matlab with the subsequent data as well as producing various paradigms using Python. I’ve used the module “Psychopy” (Pearce, 2007) to do this.

Aim/Background: Transient Ischaemic attacks represent a form of stroke with no objective diagnostic criteria where very little rehabilitation is offered. The latter is likely due to the longstanding belief that TIAs do not produce lasting cognitive impairment. Additionally, the definition of TIA has been questioned and reconsidered (e.g. Albers et al., 2002; Easton, 2009) and long term cognitive impairment has been identified in a proportion of individuals, post-TIA. (Van Rooij et al., 2016). This study therefore aimed to investigate whether there were consistent neural correlates of TIA that were identifiable using relatively cheap and easy to set-up EEG equipment, the EPOC+, developed by Emotiv Systems. Such differences were investigated across a battery of tasks. A measure of cognitive impairment, the Montreal Cognitive Assessment, as well as behavioural data was included to evaluate the notion that TIA is often accompanied by long term cognitive impairment.

Methods: The battery of tasks included a 1-back task, a visual search paradigm, a semantic steady state visual evoked paradigm (see Stothart, Quadflieg & Milton, 2017 for methodology) and two resting state paradigms. Patient recruitment is still ongoing. However, we have collected a sample of healthy controls of a young age as well as an age matched sample.

Results: Preliminary findings include a proportion of TIA patients scoring below the threshold on the MoCA for mild cognitive impairment. These patients additionally scored the EPOC+ as highly acceptable. Statistical analysis will occur once a suitable sample has been recruited.

Conclusion: This project is still ongoing and therefore it is premature to draw any definitive conclusions at present. However, our initial data supports the findings of Van Rooij, et al., (2016) and initial investigation of the data related to the SSVEP paradigm indicates the EPOC+ may have the potential to accurately record steady state visual evoked potentials.

References:
Investigation into novel brain computer interface equipment’s ability to reliably detect semantic steady state visual evoked potentials

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Area of research focus: Techniques in neuroimaging
Keywords: (Semantic steady state visual evoked potential, electroencephalogram, frequency analysis
Brain region: Aim for significant findings when averaged over all channels of the EEG; strongest signal is normally around the occipito-temporal region
Can offer: Experience using Matlab in an EEG setting as well as Python for programming experiments; recording and manipulation of EEG data

Aim/Background: Conventional EEG equipment requires a substantial amount of time to set up and is expensive. Brain computer interface equipment such as the EPOC+ by Emotiv systems is relatively cheap and is far quicker to set up whilst having a poorer signal to noise ratio. Despite this, these headsets may be able to detect effects which have a strong signal such as those in visual evoked potential paradigms. To assess this, this study aimed to assess the ability of the EPOC+ to reliably detect the standard and deviant responses in a semantic steady state visual evoked potential paradigm, replicating the findings of Stothart, Quadflieg & Milton (2017).

Methods: This study uses data from a previously conducted study, using the age matched control group (N=21) of relatively older individuals and the second control group, which was primarily of University students of a much younger age (N = 29).

The SSVEP paradigm utilised similar stimuli as Stothart et al. (2017), presenting images at 6Hz. Standard stimuli contained living organisms, whilst the deviant stimuli, presented every fifth image (1.2Hz) were of non-living objects. Following a Fourier transform, we hypothesised that the EPOC+ would record a significant standard peak at 6Hz and deviant peak at 1.2Hz and its relative harmonics. We also hypothesised that the deviant peak would be significantly lower in a scrambled image control condition.

Results: Analyses are on-going, however initial data looks promising. Plotted on a graph (x = frequency, y= Signal to noise ratio), a reasonable proportion of participant data can visually be seen to contain the standard and deviant responses whilst averaging over participants suggests support for our hypotheses.

Conclusion: It is premature to draw strong conclusions; however, we hope that what is seen visually through plots of the data is found significant through analysis.

References:
Are visual hallucinations in Alzheimer’s disease a result of hypoperfusion of visual processing areas in the occipital cortex?

Sinclair LI, Mandagere V, Love S

Area of research focus: Cellular
Keywords: Alzheimer’s disease, neuropsychiatric symptoms, perfusion
Brain region: Occipital cortex
Can offer: ELISA, dot blot, immunohistochemistry

Background: Alzheimer’s disease (AD) is the most common form of late life dementia(1). Up to 20% of patients with AD experience hallucinations (2). Visual hallucinations (VH) are known to be more common in Lewy Body dementia (DLB) (3). In autopsy studies up to 60% of patients with AD had concomitant Lewy body pathology (3). Several studies have found that visual hallucinations are more likely in those with AD and Lewy body pathology (4–6).

Decreased perfusion of the occipital lobe has been shown in those with VH but as Lewy bodies are sparse in this region they cannot explain the hallucinations (7-9). Post-mortem studies have suggested decreased perfusion in the occipital cortex in DLB, which appeared to be a result of decreased microvessel density secondary to decreased VEGF (10).

Methods: We obtained tissue from a cohort matched for age, gender and post-mortem interval comprising 23 individuals with AD who had experienced visual hallucinations, 19 individuals with AD without hallucinations, 19 individuals with DLB and 36 controls. We studied BA18 (visual area V2) and BA19 (visual area V3) Von Willebrand factor (a marker of endothelial cell content), vascular endothelial growth factor (VEGF, a marker of tissue hypoxia), myelin-associated glycoprotein:proteolipid protein 1 (MAG:PLP1) ratio (a measure of tissue oxygenation relative to metabolic demand) and α-synuclein were quantified by ELISA (and in the case of α-synuclein also by immunohistochemistry), as in our previous studies (10). Data was analysed using parametric statistical tests with MAG:PLP ratio as the primary outcome.

Results: The MAG:PLP ratio was reduced in controls compared to the dementia groups in BA18 (p=0.034) and unchanged in BA19. There was no strong evidence of a between group difference in VEGF or vWF.

Conclusions: Our results do not support chronic hypoperfusion of visual processing areas in the occipital cortex as a cause of VH in those with dementia.

References:


Maternal micro-chimeric cells in MS affected brain

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Areas of research focus: Cellular, developmental
Keywords: Multiple sclerosis, micro-chimerism, human
Brain region: CNS- white matter/ grey matter
Can offer: Fluorescent in situ hybridisation

Maternal micro chimeric cells (MMC) pass across the placenta from a mother to her baby during pregnancy [1-5]. MMC have been reported in healthy adults but are often found more frequently and at a higher concentration in individuals with auto immune diseases [6-11]. This present study aims to identify and quantify MMC in adult human brain from control and multiple sclerosis (MS) affected individuals. Post mortem brain tissue from 6 male MS cases and 6 male control cases were examined using fluorescent in situ hybridisation (FISH) with a probe for the X and Y chromosomes. In further studies tissue sections were labelled with the FISH probe as well as being labelled for cell specific markers by immunofluorescence. Cell specific markers included CD45 for immune cells, beta III Tubulin for neuronal cells, Glial Fibrillary Acidic Protein for astrocytes and 2’3’-cyclic nucleotide 3’-phosphodiesterase for oligodendrocytes. Female cells presumed to be MMC were identified in 5/6 MS cases and 6/6 control cases. Cell specific labelling identified female cells of neuronal and immune phenotype in both control and active MS lesion tissue. This study shows that female cells presumed to be MMC are a common phenomenon in adult human brain where they appear to have embedded into brain tissue and do have the ability to express tissue specific markers.

References:
Developing a motor adaptation task for freely moving rats

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Areas of research focus: Behavioural, computational and mathematical, neurophysiological
Keywords: Motor adaptation, cerebellar nuclei, robotics
Brain region: Cerebellum

Animals, including humans, continuously make changes to their motor actions in response to external perturbations to maintain accurate goal-directed movements. This motor adaptation has been studied in humans using a range of tasks including applying visual perturbations using prism glasses, or motor perturbations by applying force with a robotic manipulandum, and measuring the subsequent errors in movement. Our aim is to develop an equivalent behavioural experiment in rodents, to further explore the underlying neural processes of motor adaptation.

Skilled forelimb reaching is commonly used to study motor control in rodents, but it is not suited to visual perturbations as rodents do not rely on their vision during such tasks. Mathis et al. (2017) introduced a method of motor perturbation to study forelimb adaptation in head fixed mice. Here we present a similar task developed for freely moving rats, and compatible with simultaneous recording of multiple brain structures.

Rats are trained to reach for and pull a joystick external to the training box. Successful pulls to a target zone are rewarded with the delivery of a sugar pellet at the rear of the training box. Once training is complete, a solenoid is used to apply a force on the joystick perpendicular to the pull axis during specified trials.

The joystick provides a more reliable method of reporting position over video tracking methods; a means of applying physical perturbation to the movement; and allows for automation of both the training and experiment.

References:
Predicting uncertainty in a natural task

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Areas of research focus: Behavioural, cognitive, visual attention and perception
Keywords: Wearable sensors, vision, natural tasks
Can offer: Eye tracking, computer vision, machine learning

Aim/Background: Wearable computing technology allows the opportunity to design behavioural monitoring and assistance systems. We propose a system to predict user uncertainty that would function similar to an interactive video how-to-guide. The system will use task-specific training data from novice to expert. Once trained, the online system will deliver relevant video segments from expert behaviour when uncertainty exceeds a threshold. To this end, we present data from on ongoing study with preliminary analysis of recorded behaviour from participants assembling a camping tent.

Methods: 24 participants answered a short survey about their experience setting up tents, then wore a head mounted first-person camera and eye tracker outdoors and were instructed to assemble a camping tent and to use printed instructions as needed. After completion, participants viewed the video from the first-person camera and rated their level of uncertainty frame-by-frame using a specialized video viewer developed in-house. Video data was manually annotated to delineate each step involved in assembly. Importantly, each time the participant referred to the instructions gave an overt indication of uncertainty.

Results: Using self-ratings of expertise, reference to instruction, and frame-by-frame uncertainty as ground truth, we analysed the data for insights into what behavioural cues might predict uncertainty. Features analysed include fixation and saccade measures, distribution and time series of assembly sequences. We are actively exploring hand tracking via the video data, and the use of neural networks to use eye tracking and video data to predict user attention and uncertainty.

Conclusion: Although preliminary, we have a rich dataset from a natural behaviour that allows analysis of eye gaze behaviour, visuo-motor coordination and possibly the prediction of attention and uncertainty as we develop computational models for this data set.
Patient databases reviews for recruitment purposes

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Area of research focus: Clinical
Keywords: Dementia, movement disorders, Parkinson’s disease
Brain region: Hippocampus
Can offer: Databases of volunteers and patients with neurological disorders

The Bristol Brain Centre at Southmead Hospital houses several research teams looking at neurological diseases. Here we present details of the patients we have registered on our various patient databases, as a possible resource for recruitment for new studies or for data-driven studies.

We have several databases in the Brain Centre, including Healthy Participants (~530 volunteers), Memory Clinic patients (~1,050 patients) and Movement Disorder patients (~140 patients). These databases have been running for several years, recruiting patients when they come in for appointments with their consultants, and when taking part in other studies.


The Movement Disorders database includes people with Parkinson’s disease (including Atypical Parkinson’s disease), Essential Tremor, Multiple Sclerosis Tremor, and Dystonia, REM-sleep behaviour disorder and Huntington’s disease. Patients range from 51-88 years old.

The Healthy Volunteer database has people without any serious neurological disorders (at time of recruitment) and has a wide range of ages (26-97), though it skews older (mean = 73 years).

These databases are a substantial research resource and can be useful for people looking to collaborate on patient studies, or for data-type studies using patient notes or following up patients over time.
Opioidergic transmission in the nucleus of the solitary tract brainstem circuitry

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Area of research focus: Neurophysiological  
Keywords: Endogenous opioids, brainstem  
Brain region: Brainstem  
Can offer: Electrophysiology (patch clamp) in acute slices

Aim/Background: Chronic pain is a prevalent problem and currently there are limited therapeutic options. Opioid treatments are the most commonly used option. Unfortunately, these drugs have very limited efficacy for chronic pain and are associated with unpleasant side effects. Opioids are often abused outside of the clinical setting, which can cause severe respiratory depression causing death. This has led to an opioid death epidemic in the USA and increasing harms in the UK (see Weisberg, et al., 2014). A better understanding of the brain’s endogenous opioidergic circuitry (which appears capable of producing analgesia without associated cardiorespiratory problems) (Rubinstein et al., 1996), could help differentiate the circuitry involved in the actions of exogenous opioids, to provide new therapeutic targets and neuron populations to avoid.

The nucleus of the solitary tract (NTS) located within the medulla has been shown to have a role in control of heart and respiration rate, as well as analgesia and gastrointestinal function (see Andresen and Paton, 2011). Some of these functions have been shown to be opioidergic in nature (Cerritelli, et al., 2016) suggesting that the endogenous opioid β-endorphin, which is produced in proopiomelanocortin (POMC) NTS neurons is involved. However, the mechanism of this opioidergic action has not been explored. I aim to identify the synapses involved in this opioidergic transmission and further explore the receptors being used and any regulatory mechanisms.

Methods:  
This will be achieved using mouse models which allow selective optogenetic activation of the POMC neurons to induce β-endorphin release (Cerritelli et al., 2016). Whole cell patch clamp recordings from brainstem populations of neurons involved in respiratory, cardiovascular and somatosensory control, targeted by the POMC neurons will be carried out. Selective pharmacological agents, will be used to determine the nature of the opioidergic transmission in these circuits in vitro.

Results and Conclusion: Project Ongoing

References:
An fMRI study of emotion during pulsatile glucocorticoid replacement in adrenal insufficiency

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Areas of research focus: Cognitive, clinical
Keywords: Stress, emotion, fMRI
Brain region: Amygdala plus many others
Can offer: Clinical research, fMRI

The Pulses Study is a clinical trial registered with World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.isrctn.com/ISRCTN67193733). This trial was designed to test whether a subcutaneous pulsatile infusion of hydrocortisone (8 pulses over 24 hours) using an infusion pump is an improved form of glucocorticoid replacement therapy for patients with adrenal insufficiency. Glucocorticoid replacement therapy in patients with adrenal insufficiency is a well-established treatment method. A typical treatment schedule includes three oral doses of hydrocortisone (10mg, 5mg, 5mg; amounting to a total 20mg) administered throughout the day. Regrettfully, many patients continue to complain of fatigue, weakness and a severe lack of motivation, despite their daily levels of hydrocortisone being replenished to those expected in healthy individuals. Previous studies in animals and healthy volunteers indicate that dynamic oscillations of glucocorticoids, are important for healthy neuroendocrine function affecting both fast non-genomic and slow genomic processes and that the ultradian rhythmicity of circulating cortisol is critical for the physiological response of the brain to emotional stimuli.

We conducted a double-blind, placebo-controlled, two-way crossover study in participants with conditions of adrenal insufficiency, 18 participants with Addison’s Disease (AD; 16 females, 2 left-handed). In one of two 6-week long study periods, each participant received one of two hydrocortisone replacement therapies: hydrocortisone oral tablets taken three times per day, or a pulsatile subcutaneous infusion of hydrocortisone delivered via an infusion pump (approximated to follow both the ultradian and circadian variations of cortisol in healthy individuals). Dosage varied from 20-40mg according to the individual's current prescription. At the end of each 6-week period, the patients took part in a functional magnetic resonance imaging (fMRI) study during which they underwent a facial expression recognition (FERT) task. Neuroimaging data are to be analysed using FSL software (fmrib Software Library), Statistical Parametric Mapping and Dynamic Causal Modelling.

(Due to the blinding strategy implemented in the clinical trial protocol, data analysis for this study will commence upon release of data on 30th January 2018 by the data monitoring committee. We will present results for the first time at the Bristol brain research day.)
The role of cholinergic and catecholaminergic neuromodulation in the nucleus reuniens in recognition memory

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Areas of research focus: Behavioural, cognitive
Keywords: Nucleus reuniens, recognition memory, neuromodulation
Brain region: Nucleus reuniens
Can offer: Animal behaviour, selective lesioning of brain areas, spontaneous exploration tasks

Recognition memory is defined as the ability to determine the relative familiarity of a stimulus. Recent work has implicated the nucleus reuniens (NRe) of the midline thalamus as a key component of a recognition memory neural circuit (which includes the hippocampus and medial prefrontal cortex (mPFC)). The NRe is critically important for the acquisition and retrieval of long-term associative recognition memory (Barker & Warburton, in press). While both dopamine and cholinergic neurotransmission in the hippocampus and mPFC is critical for recognition, the contribution of neuromodulatory systems within NRe has not yet been investigated. This study aimed to investigate the contribution of cholinergic and catecholaminergic systems within NRe to recognition memory formation.

Male Lister-hooded rats received intra-NRe injections of either the immunotoxin 192 IgG-saporin or the neurotoxin 6-OHDA to create selective cholinergic and catecholaminergic lesions, respectively. A sham control group also underwent surgery. Distinct components of recognition memory were assessed by using variations of a spontaneous preferential exploration task (Dix and Aggleton, 1999).

The results demonstrated that both IgG and 6-OHDA lesioned animals were impaired in the object-in-place task following a 3 hour delay but not following a 5 minute delay. Thus, the delay-dependent impairment suggests that both cholinergic and catecholaminergic neuromodulation in the NRe is required for processing long-term but not short-term associative recognition memory. Further work will assess performance in non-associative recognition memory and additional forms of associative recognition memory.

References:
The effect of mindfulness on psychological well-being of people with subjective cognitive decline

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Areas of research focus: Behavioural, cognitive, clinical
Keywords: Mindfulness, well-being, memory concerns
Can offer: Psychological interventions

Aim/Background: Subjective Cognitive Decline (SCD) describes a subjective worsening of the memory and thinking abilities in comparison to previous status, and is irrelevant of an acute event. People with SCD do not show any objective memory problems, as they normally perform within the normal range on cognitive testing. Even though SCD has been suggested as a symptomatic indicator of preclinical Alzheimer’s disease, it also constitutes quite a common experience among older people and other possible causes of such condition vary from normal ageing to psychological factors like depression and high health anxiety. Despite the high prevalence of these complaints, yet to date, there is limited evidence about interventions that could improve this condition. The present study contributes to the relevant literature by examining the effectiveness of two different non-pharmacological interventions on the psychological well-being of people with SCD.

Methods: For achieving this, researchers recruited 80 people (mean age= 63.2, 68.8% female) with SCD but no significant cognitive impairment. Participants were tested at baseline and 6 weeks follow-up. After the baseline visit, they were randomly assigned to one of three conditions: Mindfulness meditation, Lifestyle factors course, or Control group. Both intervention courses were delivered online for the duration of 4 weeks. Psychological well-being was measured by the WHO-5 Well-being Index. Change in well-being over time by group was examined with repeated measures ANOVA.

Results: A significant group by time interaction was observed on well-being (p<0.05), showing that the Mindfulness intervention group had an increase in well-being score at 6-week follow-up, while the other groups did not.

Conclusion: Such finding supports the link between Mindfulness and well-being and offers a potential intervention to improve well-being in the SCD population. A 6-month follow-up is underway to examine the longevity of this intervention on well-being, and to see the effects on cognitive function in people with SCD.
Optogenetic elucidation of hippocampal inhibitory synaptic plasticity

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Areas of research focus: Cellular, neurophysiological
Keywords: Synaptic plasticity, GABA, hippocampus
Brain region: Hippocampus
Can offer: Electrophysiology, optogenetics

The vast diversity of inhibitory interneurons within the hippocampus are integral for regulating its network function. Two of these interneurons, the parvalbumin (PV) and somatostatin (SST) expressing interneurons have distinct roles within the hippocampal network achieved via their diverse morphology and axonal projections (Pelkey et al., 2017). The plasticity mechanism and network consequence of altering the level of inhibition between these two interneurons and excitatory neurons within the hippocampus however remains uncertain.

We aim to address this by using a combination of whole cell patch clamp brain slice electrophysiology and optogenetics in transgenic mice. We aim to compare inhibitory synaptic plasticity induction at the synapses between parvalbumin and somatostatin interneurons to CA1 pyramidal neurons (Pyr).

Data so far has shown that theta burst activity at PV-Pyr synapses leads to long-term depression at inhibitory synapses (iLTD), which is AMPA, NMDA and GABAb receptor independent. Interestingly identical theta burst activity at SST-Pyr synapses results in inhibitory long-term potentiation (iLTP). We also show physiological relevant spike timing between these interneurons and pyramidal neurons leads to inhibitory spike timing dependent plasticity (iSTDP) that appears to be unique for each interneurons subtype.

By selectively activating distinct interneuron populations via optogenetics we are beginning to understand the requirements for induction of inhibitory plasticity for individual interneuron subtypes. Our findings of opposing change in inhibitory strength upon plasticity induction may provide a mechanism by which these two interneuron populations can regulate hippocampal network function. We aim to develop these findings further with ongoing electrophysiology experiments. Future aims will be to work with our computational neuroscience collaborators to model hippocampal network activity and study the consequence changes in inhibitory connections have on the network, with a focus on hippocampal place cell activity. This will hopefully lead to testable hypotheses that may foster new collaborations with in vivo electrophysiologists.

References:
What is the impact of regulatory guidance and expiry of drug patents on dementia drug prescriptions in England?

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Area of research focus: Epidemiology and population health
Keywords: Dementia, drugs, data
Brain region: Cortex
Can offer: Access to statistical software

Background: There have been several changes to national guidelines and initiatives that may have influenced prescribing of drugs for dementia in recent years. These include changes in National Institute for health and Care Excellence (NICE) guidance; several government dementia strategies; the addition of dementia to the Quality and Outcomes Framework; and the expiry of drug patents. Despite this, there has been little research into the effect of these events on prescribing. We examined prescribing trends in England using data from the Clinical Practice Research Datalink since the launch of these drugs up to 1st January 2016.

Methods: We considered the monthly proportion of patients eligible for treatment, with a diagnosis of probable Alzheimer’s disease, receiving their first prescription for each drug class – namely acetylcholinesterase (AChE) inhibitors and N-Methyl-D-aspartate (NMDA) receptor antagonists. Trend analysis using joinpoint models was then applied to identify up to two trend changes per drug class.

Results: Overall, prescriptions increased over the period studied with an average monthly percentage change of 6.0% (95% CI: -6.4 to 19.9; June 1997 to December 2015) for AChE inhibitors and 15.4% (95% CI: -77.1 to 480.9; January 2003 to December 2015) for NMDA receptor antagonists. Specifically, AChE inhibitor prescriptions increased at the end of 2012, probably due to a combination of the patent expiry of these drugs and the Prime Minister’s Dementia Challenge. However, neither of these factors appeared to influence NMDA receptor antagonist prescriptions, which were driven by NICE guidance released in 2011 that allowed access to these drugs outside of clinical trials.

Conclusions: Dementia drug prescribing does not always respond to factors such as regulatory guidance, recommendations or patent expiry and, when it does, not necessarily in a predictable way. This suggests that improved communication with clinicians may be needed to improve the cost-effective use of drugs for dementia.
Long term memory consolidation in preclinical Alzheimer’s disease

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Areas of research focus: Cognitive, clinical
Keywords: Alzheimer’s disease, memory consolidation, hippocampal subfields
Brain region: Hippocampus
Can offer: Structural MRI, neuropsychological tests, analysis of hippocampal subfield volumes from MRI

Alzheimer’s disease (AD) has long preclinical stage during which pathological changes are occurring within the brain but symptoms are not yet detectable with current tests. Despite the difficulties in diagnosing at this stage, preclinical AD (pre-AD) presents the most promise as a therapeutic window for effective treatment, as any treatment that could slow or halt the progression of AD would have to be administered before significant neurodegeneration has occurred [1]. Pre-AD sometimes presents as Mild Cognitive Impairment (MCI), however only ~40% of MCI patients ever receive a diagnosis of AD [2]. New biomarkers are required to identify AD in the preclinical phase.

Episodic memory impairment is a key symptom of AD. Clinically, however, delayed memory is tested over <30 minutes, and there is very little information about rates of forgetting over days and weeks in healthy ageing and AD. We hypothesise that long term memory consolidation ability over a 4-week period is a better predictor of cognitive decline than classical, ‘half-hour’ tests of delayed recall, as is alluded to in some previous studies [3-4].

Deficits in memory consolidation in AD are widely considered to be due to atrophy of the hippocampus and surrounding cortices. Pathologically, hippocampus is affected early in AD, with Entorhinal cortex, CA1, and subiculum, among the first subfields to lose volume [5]. Close examination of the structure of the constituent subfields of hippocampus may allow better predictions to be made about future cognitive decline.

We present here an overview and preliminary analyses of our ongoing longitudinal study to examine the predictive power of tests of long term memory consolidation and hippocampal subfield volumetry using high-resolution MRI for cognitive decline in older adults with mild cognitive impairment and subjective memory complaints. All participants will be followed-up after one year in order to assess any cognitive changes.

References:
Translational assessment of feedback sensitivity using acute pharmacological manipulations and early life stress

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Areas of research focus: Behavioural, developmental, cognitive, neurophysiological
Keywords: Affective disorders, reward learning, early life adversity
Brain region: Prefrontal cortex, limbic system, hippocampus
Can offer: Rodent behavioural tasks

Deficits in reward processing are a key feature of many psychiatric disorders including depression and anxiety with these deficits likely being crucial in the aetiology of these diseases (Der-Avakian, et al., 2016). Depressed patients have also been found to have altered sensitivity to positive and negative feedback in probabilistic learning tasks (Gorrindo et al., 2005; Pizzagalli et al., 2008). Early life adversity (ELA) is one of the major causes of psychiatric diseases worldwide and survivors of ELA have been found to have altered reward processing in probabilistic learning tasks (Pechtel & Pizzagalli, 2013). Translational behavioural tasks between humans and rodents allow better comparability and cross-species validity between studies and a rodent probabilistic learning task has been developed in rats (Bari et al., 2010). We plan on first further validating this paradigm using acute pharmacological manipulations before using it to probe the mechanistic link between early life adversity and the development of psychiatric disorders.

Adapting the paradigm developed by Bari et al. (2010) we trained a cohort of 12 rats in the Probabilistic Reversal Learning Task (PRLT). In this task, rats have to learn to spatially bias responses, touching either a left or right window on a touchscreen to receive a reward. Stimuli are probabilistically rewarded so that the “rich” stimulus is rewarded 80% of the time and the “lean” stimulus is rewarded only 20% of the time. After 8 consecutive choices for the rich stimulus, the reward contingencies switch so that the previous lean direction is now rich.

We will present data showing the effect of acute stress manipulations using corticosterone and restraint stress along with the effects of acute SSRI treatment with citalopram on probabilistic reversal learning and feedback sensitivity. We will additionally discuss plans for testing a future cohort of maternally separated rats in the PRLT in order to probe the cognitive changes that are underlying the predisposition of ELA animals to psychiatric disease.

References
The effect of increased end-point variability on the rate of motor adaptation

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Areas of research focus: Behavioural, neurophysiological
Keywords: Ageing, motor adaptation, accuracy
Brain region: Cerebellum, motor cortex

Aim/Background: Motor adaptation (MA)- or the ability to adjust movements to account for environmental or bodily changes- has repeatedly been shown to undergo age-related decline, resulting in slower MA of reduced magnitude. (Etnier & Landers, 1998; McNay & Willingham, 1998; Fernandez-Ruiz et al., 2000). This can affect the ability of older adults to perform everyday tasks, which in- turn reduces their quality of life.

Whilst numerous theories exist regarding the cause of age-related decline in MA, none have yet been proved conclusive. It is likely that several factors contribute, however an as-yet unexplored factor is movement accuracy. Accuracy declines with age, leading to increased variation in movement trajectory and end-point (Cooke et al., 1989; Pratt et al., 1994; Walker et al., 1997). We hypothesise that this may cause a decline in MA by creating uncertainty over the cause of movement error. In other words, inaccurate individuals may have difficulty determining whether a movement error was due to poor aim, or environmental/ bodily changes. Such a dilemma may delay the onset of adaptive motor changes, resulting in slower MA of reduced magnitude.

Methods: We aim to investigate whether decreased accuracy reduces MA in young adults, below that of age-matched controls and to the levels seen in older adults. To do so, we will use a standard visuomotor paradigm and apply a Gaussian error of a set standard deviation to every movement made to reduce participant accuracy. Control data will be used to characterise how accurate the reaching movements of young adults are and will be compared with the data of test participants to evaluate the role of decreased accuracy in the age-related decline of MA.

References:
The distribution, clearance and toxicity of panobinostat administered to juvenile rat and pig brainstem by convection enhanced delivery

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Areas of research focus: Translational: lab to clinic
Keywords: Convection enhanced delivery, panobinostat, animal models
Brain region: Pons
Can offer: In vivo

The pan-histone deacetylase inhibitor panobinostat has preclinical efficacy against DIPG and the oral formulation has entered a phase one clinical trial. However, panobinostat does not cross the blood brain barrier in humans. Convection enhanced delivery (CED) is a novel neurosurgical drug delivery technique that bypasses the blood brain barrier and is of considerable clinical interest in DIPG. We investigated the toxicity, distribution and clearance of a water-soluble formulation of panobinostat in small and large animal models of CED. 30 juvenile male Wistar rats received panobinostat administered to the pons by CED at increasing concentration and were compared to animals that received vehicle alone. Clinical observation continued for two weeks. Animals were sacrificed at 72 hours or two weeks following treatment and the brains were subjected to neuropathological analysis. A further 6 animals received panobinostat by CED to the striatum and were sacrificed zero, two or six hours after infusion, their brains explanted and snap-frozen. Brainstem drug concentration was determined by LC-MS/MS. Large animal toxicity was investigated using a clinically relevant MRI guided translational porcine model of CED using a drug delivery system designed for human use. 30 μM panobinostat was administered to the ventral pons of two juvenile Large White/Landrace-cross pigs and subject to clinical and neuropathological analysis compared to control after one or two weeks. Drug distribution was determined by LC-MS/MS in porcine white and gray matter immediately after CED. There were no clinical or neuropathological signs of toxicity up to an infused concentration of 30 μM in both small and large animal models. The half-life of panobinostat in rat brain after CED was 3 hours and the drug was observed to distribute in porcine white and gray matter with a volume infusion/distribution ratio of two and three respectively. CED of water-soluble panobinostat warrants investigation in children with DIPG.