Research in Dementia & Neurodegeneration
Welcome

This handbook is designed to be a directory of King’s researchers currently working on Dementia and Neurodegenerative disorders. It maps out ‘who is doing what’ at King’s, which we hope will foster internal collaborations within the College and enable researchers from around the world to link up with ~60 outstanding Principal Investigators in this field. At King’s we are deliberately outward facing as we seek to build strong international collaborative networks involving Academia and Industry, which are essential if we are to make the step-change required to improve the therapeutic options for people with these disorders.

Discovering effective treatments for the dementias and other neurodegenerative disorders is one of the greatest therapeutic challenges facing developed countries. The number of people with dementia in the UK will reach >1 million by 2020 and the annual cost of their care will reach ~£25bn. Biomedical science has made tremendous progress in discovering therapies for many diseases but not dementia. We can cure most infections and combat a great many cancers, however neurodegenerative disorders remain in the ‘Too Hard’ basket. Remarkable technical advances in genetics, transcriptomics, proteomics, cellular and molecular biology are poised to transform our understanding of disease pathogenesis and deliver new therapies for our patients.

In order to target therapies to the right patients, we must improve the accuracy of our diagnosis and be able to monitor their response to treatment. We now know that neuronal dysfunction and degeneration often begins years or even decades before symptoms begin. Revolutionary advances in gene sequencing technologies are generating a comprehensive map of the major neurodegeneration risk genes. By discovering who is at greatest genetic risk and exploiting sensitive brain imaging and protein biomarkers we can make early diagnoses and intervene to prevent further neuronal loss or even before symptoms arise.
Our gene discoveries have allowed us to generate informative cellular and animal models which closely reflect the disease process in man. These are providing invaluable insights into the earliest molecular events that initiate and propagate the degenerative process and the endogenous defence mechanisms that eventually fail. Remarkably, the same pathogenic and protective pathways are also evident in human neurons derived from our patient stem cells. These cellular and animal models are revealing novel drug targets and accelerating our drug discovery efforts in partnership with Industry.

Our discovery of protein biomarkers in blood and CSF as well as MRI and PET imaging biomarkers are facilitating early diagnosis and the development of personalised therapies. We have run more clinical trials in Alzheimer’s, Parkinson’s and motor neuron disease than any other centre in Europe. We also have had an impact on addressing the diagnosis and care of people with dementia globally as we host the 10/66 Dementia Research Group and co-authored the WHO World Dementia (2012) and UK Dementia Reports (2014).

King’s has prioritised dementia and neurodegeneration research for investment having recently opened the £50m Maurice Wohl Clinical Neuroscience Institute with £10m of cutting edge equipment and is undertaking a major recruitment drive. It is adjacent to King’s College Hospital, a major tertiary neuroscience referral centre, with a neuroscience-dedicated Clinical Research Facility supported by a £50m Biomedical Research Centre and Unit in Dementia dedicated to bringing new therapies to our patients.

Thus we have an integrated research pipeline ranging from basic molecular and cellular research up to large-scale human trials with global outreach. We offer our academic and industrial partners world-class expertise and unparalleled facilities and hope that this handbook will generate new connections and collaborations.

Professor Christopher E Shaw
Director, Maurice Wohl Clinical Neuroscience Institute
Professor Dag Aarsland

Research interests
I am a psychiatrist who has focused my clinical and research work on the neuropsychiatric issues in Parkinson’s Disease (PD) including psychosis, mild cognitive impairment, dementia, and depression, among others. My clinical dementia research includes interdisciplinary and translation projects related to PD dementia, dementia with Lewy Bodies (DLB), aging and Alzheimer’s disease. I have longstanding experience in these areas and have conducted clinical research trials of therapeutic interventions for neuropsychiatric problems including PD dementia and DLB. I have experience in conducting longitudinal studies including incident cases of PD detailing mild cognitive impairment and prevalent PD cases detailing risk of psychosis, nursing home placement and caregiver burden.

More recently my main interest has been translational aspects of cognitive impairment in PD and DLB. Using post-mortem brain tissue from carefully followed patients we have studied the detailed morphological and neurochemical changes and their clinical correlates. We have analysed cerebrospinal fluid in different patient groups, and have explored how a variety of biomarkers are associated with the clinical symptoms. We have used similar approaches by a variety of structural and functional imaging techniques to investigate brain changes in neurodegenerative disease and their clinical correlates. I have established several large international multicentre studies to study the clinical course and biomarkers of patients with DLB and PD. By joining forces with other multicentre cohorts we have brought together large cohorts required for genetic studies, and are currently studying how genotypes are related to clinical and biomarker phenotypes. A focus for future work is to build on these findings from postmortem, CSF and blood-based studies to develop novel treatment targets, with the aim of performing first-in-man studies of novel and promising drugs with the potential for disease-modification in PD and DLB.

Publications
**Research interests**

For the last two decades I have been working on proteins associated with neurodegenerative diseases with major interest in Friedreich’s ataxia. In particular using different biochemical and biophysical techniques like multiple sequence alignment, enzyme biology, UV-VIS and circular dichroism (CD) spectroscopy and pull-down assay, I was able to observe that:

i) Frataxin and its bacterial orthologue CyaY bind iron without promoting ferritin-like higher aggregates formation,

ii) CyaY participates in iron-sulfur (Fe-S) cluster assembly as inhibitor of cluster formation, through direct binding to the desulfurase IscS,

iii) The interaction with IscS involves the iron binding surface of CyaY, which is conserved throughout the frataxin family leading to propose that frataxins are iron sensors that act as regulators of Fe-S cluster formation.

Recently I have been using a metabolomic approach to investigate frataxin function in vivo in different organisms and started a new project in characterizing M. tuberculosis iron-sulphur cluster biogenesis.

In 2013 I moved to the Maurice Wohl where I started to collaborate with Professor Shaw on amyotrophic lateral sclerosis (ALS). I would like to carry on the biochemical and biophysical characterization of the N-terminus of Annexin11. Recently, mutations in the N-terminal region of this protein have been associated with ALS. Indeed these mutations promote aggregation of Annexin11 in patients. The N-terminal region of Annexin11 shows a low complexity with few portions predicted to have secondary structures. I am currently investigating the structural differences between wild type and mutants of this region to identify the cause of the aggregation propensity in the mutants.

**Publications**

**Professor Ammar Al-Chalabi**

**Research interests**

Our research focuses on identifying the nature and risks of amyotrophic lateral sclerosis (ALS, also known as motor neuron disease, MND). I am Director of the King’s MND Care and Research Centre, a specialist motor nerve clinic of international standing that has an extensive portfolio of clinical and laboratory based research.

We collect detailed clinical information, allied with DNA samples and environmental questionnaires, both from the clinic and from a population register aiming to identify everyone with ALS in the South East of England. Working with colleagues across Europe, the USA and Australia, we use this information to identify subtypes of ALS, find genetic and environmental risk factors, and discover factors that modify survival and other features of the disease.

I lead a European Joint Programme on Neurodegeneration Research (JPND) consortium called STRENGTH, in which researchers from 11 countries work together to stratify patients into subgroups that may have specific risk factors or respond to specific treatments. I co-lead a large international consortium, Project MinE, which is sequencing the whole genomes of 22,500 samples, 15,000 from people with ALS, and analysing the epigenetic (methylation) profile of the samples to gain an insight into environmental and gene regulation risk factors. This consortium has recently completed a genome-wide association study involving 40,000 samples each genotyped at 10 million loci. I also co-lead the UK National MND Register, which aims to identify every person with ALS in the country and map service need with social factors underlying decision making by patients, carers and health care professionals in ALS, clinical patterns of the disease, and to run clinical trials.

**Publications**

Professor Safa Al-Sarraj

Research interests
Pathology and molecular genetics of MND. We identified a new pathological subtype of familial and sporadic MND, of MND/FTLD associated with C9orf72 mutations. We described the brain pathology of FUS and Profilin 1 mutations in MND.

I extended my interest in the heterogeneity of MND pathology to investigate its muscle pathology. We described the morphology and several molecular markers in muscle biopsies from 132 MND patients and controls. We identified novel changes in mitochondrial morphology and low grade inflammation, which supports the hypothesis that motor neuron degeneration, begins as a dying back axonopathy, a finding that has important therapeutic implications. We are further planning to investigate the TDP43 pathology in the peripheral nerves and muscles from MND patients.

Recently we have begun to investigate the link between traumatic brain injury and neurodegenerative disorders such as AD and more broadly in the pathology of post traumatic encephalopathy. I have established a new set of pathological criteria for head injury, based on molecular biological markers such as βAPP and ApoJ. We were the first to report diffuse TDP43 deposition and increased expression of APOJ in the brains of patients with chronic traumatic encephalopathy (CTE). In progress is a study to look at the link between ApoJ/DDK1/Tau/TDP43/A4 in AD (with or without trauma) and the wider pathology of post-traumatic encephalopathy.

In the clinical department we are interested to contribute to the large number of discoveries of molecular markers and genetic alterations in brain tumours and apply them for diagnosis and patient’s treatment and management. We have reported on genetics on subtype of glioblastoma and currently finishing a large study on the molecular genetics of infiltrative lower grade glioma (grad II and III) such as IDH1/2, ATRX, 1p/19 deletions, p53 and their implication for diagnosis, prognosis and treatment.

Publications
**Professor Clive Ballard**

**Research interests**
Experimental approaches and clinical trials focussing on improvement treatment of neuropsychiatric symptoms and pain in people with dementia. Pivotal studies have demonstrated the mortality risk of antipsychotics, highlighted the value of pimavanserin as an antipsychotic in people with Parkinson’s disease and large RCTs of non-pharmacological treatments have demonstrated the benefits of social interaction for the treatment of agitation. Our large RCT of stepped analgesia demonstrated clear benefits in the treatment of pain, agitation and depression in people with Alzheimer’s disease. Ongoing experimental work will allow us to refine treatment targets and interventions in the future.

Developed on-line PROTECT platform, enabling more than 30,000 healthy older people to participate in a longitudinal cohort study and providing a fantastic platform for nested clinical trials tackling both pragmatic treatment issues regarding the maintenance of cognitive health and enabling us to address experimental questions regarding polygenic risk and key genes mediating response to specific treatment interventions.

Microarray based approaches to drug discovery, with a specific focus on candidate compounds for repositioning as treatments for Alzheimer’s disease and synuclein dementias, with active ongoing programmes funded by the Wellcome Trust and Edmund J Safra foundation.

Identifying treatment targets and evaluating new therapies to delay the onset of dementia in people with Down’s syndrome, with published GWAS studies, a large published RCT of memantine for the treatment of dementia in people with Down’s syndrome and ongoing work identifying novel treatment targets and novel therapeutics.

**Publications**

Research interests

I have worked in Magnetic Resonance Imaging research as applied to neurological and psychological disorders for over 25 years. In the neurological field, my particular interests are in multiple sclerosis, epilepsy and neurodegenerative disorder; in psychiatry, I have interests in schizophrenia, bipolar disorder and depression. In parallel, my work also involves healthy controls, and has applications in the more fundamental questions of brain structure and function.

Much of my work has been on technique development, both for image acquisition and processing, and on the optimisation of protocols that make these techniques applicable to patient populations. (I currently hold an ethical approval for the development and optimisation of such scanning techniques in normal controls, along with a separate approval to allow the further optimisation sometimes required to make the techniques acceptable to clinical patients). I have a particular interest in quantitative MRI techniques; these include relaxation time measurements (which can probe the molecular environment of water within tissue (and in certain circumstances can reveal information such as the myelin water fraction)); magnetization transfer (another marker of myelination), perfusion (quantitatively and non-invasively measuring blood perfusion) and diffusion tensor imaging (providing a probe of the structure and integrity of neuronal tissue).

Publications

Mitochondrial dysfunction is an almost universal feature of dementia and may be an early causative factor. Loss of mitochondrial function reprograms neurons, affecting bioenergetics, metabolic status, synapse homeostasis and transcription. We are only beginning to understand how this altered cellular landscape leads to loss of neuronal function and dementia. Our aim is to investigate the mechanisms involved in responding to mitochondrial dysfunction in the nervous system and to exploit this knowledge to develop new treatments.

We are particularly interested in mitochondrial retrograde signalling. Mitochondrial retrograde signalling is a pathway of communication from mitochondria to the nucleus that enables cellular reprogramming, to respond to changes in mitochondrial activity. Studies in disease models suggest that retrograde signalling is active in patients with neurodegenerative disease, as a result of mitochondrial dysfunction. Manipulation of retrograde signalling is therefore a potential novel therapeutic strategy for neurodegeneration and dementia. We have developed a Drosophila model of neuronal specific mitochondrial dysfunction and used this to identify the gene HIFα as a key regulator of retrograde signalling (Cagin et al. 2015, PNAS). We further showed that inhibition of HIFα improves function in a Drosophila model of Parkinson’s disease.

We also use human tissue from patients to study the changes in mitochondrial activity associated with dementia. We recently showed that the activity of mitochondrial respiratory complex I is reduced in the frontal cortex of patients with Parkinson’s disease dementia (Gatt et al. 2016, Mov Dis). We are continuing to study patient tissue to identify molecular pathways that are altered in dementia patients and that may be therapeutic targets.

**Publications**

- Bateman JM, Iacovino M, Perlman PS, Butow RA. Mitochondrial DNA instability mutants of the bifunctional protein Ilv5p have altered organization in mitochondria and are targeted for degradation by Hsp78 and the Pim1p protease. *J Biol Chem.* 2002;277:47946-53. PMID: 12381727
Professor Richard Brown

Research interests

Research has addressed aspects of motor and non-motor aspects of movement disorders (especially Parkinson’s disease – PD), and other neurodegenerative conditions including Alzheimer’s disease, Dementia with Lewy Body/PD-dementia and ALS. The particular focus in recent years has been on neurocognitive and neuropsychiatric psychiatric aspects, using a range of approaches including surveys, experimental methods and imaging. The PD research has investigated the nature and psychological impact of distressing and disabling problems including fatigue, depression, anxiety and impulse control disorders. My group has undertaken the largest ever longitudinal study of affective symptoms, using data-driven approaches to identify mood-related clinical phenotypes (Landau et al 2015) and linked work into psychological processes (Julien et al 2016). Current work is examining neurocognitive processes in anxiety related to threat processing and using this evidence to test potential brief non-pharmacological interventions. I have also undertaken the first successful trial of a psychological intervention for the management of impulse control behaviour such as gambling and hypersexuality that can emerge following dopamine agonist treatment in a significant proportion of patients (Okai et al 2013).

Publications

Professor K. Ray Chaudhuri

Research interests
Over the past 15 years my team has led an international group of multi-disciplinary clinical scientists to develop the first ever holistic tools for assessment of non motor symptoms (NMS) of PD recognised as a key unmet need in the care and research of Parkinson's disease, the second commonest neurodegenerative disorder. (Chaudhuri et al 2006). These tools have now been adopted worldwide with translation to clinical epidemiological studies as well as outcome measures in clinical trials addressing key NMS of PD such as pain (Trenkwalder, Chaudhuri et al. 2016).

My group and work has led to recognition and awareness of the importance of measuring NMS in PD and changed the landscape of PD leading to a revision of the diagnostic criteria for PD which now includes some key NMS (Chaudhuri and Sauerbier 2016). In addition my group has led work identifying for the first time specific NMS dominant endophenotypes in PD (non motor subtypes, Chaudhuri and Sauerbier 2016). Further work has now identified specific neuropeptide deficiencies in these subtypes such as central limbic serotonergic deficiencies in PD fatigue (Park fatigue) subtype while raphe serotonergic dysfunction dominates in the park sleep subtypes with excessive daytime somnolence (Chaudhuri and Schapira, 2009).

My work has also underpinned clinical translation of the multi-peptide deficiency disorder model of PD to clinical trials with several non oral advanced therapy options in PD being studied for effect on non motor symptoms on PD for the first time. My group has led world first comparisons in a multi-centre initiative across Europe, comparing apomorphine infusion with levodopa infusion, for instance. The aforementioned scales developed from my group (such as the PD sleep scale) were also used for the first time as a co primary outcome variable in the RECOVER study which has established non oral therapy options as a key management strategy for sleep problems in PD.

Widely regarded as the foremost key opinion leader in the field of clinical non motor research in PD, I have also edited the first comprehensive text book on NMS in PD (twice recipient of the British Medical Association book commendation award) bringing together over 25 opinion leaders from across the globe.

Publications
Dr Anne Corbett

Research interests
My research spans the dementia field and draws on my diverse background in molecular biology, dementia care, translational research, online technologies and user engagement. A common theme across all of my research is translation and implementation.

Broadly, my work falls into three main themes. Firstly, online interventions and prevention of cognitive decline. I lead the online PROTECT study, a cohort of almost 20,000 older adults, which collects rich cognitive and medical data, and genetic samples to answer questions about the factors influencing ageing in the brain. PROTECT enables us to deliver clinical trials online, and I am currently leading a trial of brain training games in 8500 people, with the aim of improving understanding the role of genetics in cognition.

Secondly, I lead our large drug repositioning study which seeks to identify novel compounds for treatment of Alzheimer’s Disease and other dementias. This work utilises high-throughput transcriptional analysis, in vitro testing and pipeline pull-through to in vivo and clinical trial. We aim to bring promising drugs to trial faster than the traditional drug discovery route, whilst developing new data on the underlying biological substrates of dementia.

Thirdly, my research focuses on care home settings, and the development of interventions to improve the lives of people living in these environments. Currently this work is focussed on the management of pain, including studies to develop complex interventions for care staff, primary care physicians and residents to improve how pain is identified and treated. My care home work also spans a number of other key issues, including night-time care, the use of technology, psychosocial interventions and the challenge of implementation in these settings.

Publications
Professor Jonathan Corcoran

Research interests
I lead the Neuroscience Drug Discovery Unit, which was founded in 2010 and is project managed by Dr Maria Goncalves. We have focused our research on nuclear receptor signalling and how these pathways are modulated in maintenance and regeneration of the CNS. We have to date identified two lead candidates one as a therapeutic for Alzheimer’s disease (AD) the other for CNS repair. We carry out hit to lead and lead optimisation using a variety of in vitro and in vivo assays. We develop in vitro assays to determine EC50 and IC50 of various small molecules. We develop in vitro screens to identify pathways in AD and spinal cord injury (SCI). We then take these hits forward into in vivo assays in rodent models of AD and SCI. Hits from these screens are then taken forward for further preclinical and clinical development. We have established a network of CROs to carry out ADMET, GMP production, toxicology and regulatory affairs to enable phase I/IIA trials. We have also been successful in obtaining Venture capital funding to commercialise our lead candidate drug for AD. We have submitted a clinical trial application for our current lead candidate for CNS injury that has been accepted for phase I trials by the MHRA. Laterally we have adapted our assays as screening platforms for FDA approved drugs for drug repositioning for the treatment of AD.

Publications
Dr Richard Dobson

Research interests
The main areas of bioinformatics research have focused on the genomics of complex disease, with a special focus on biomarkers of Alzheimer’s Disease. Research has required the analysis, integration and modelling of complex large molecular datasets. The group has a range of experience which includes the analysis of data produced by expression arrays, SNP arrays, next generation sequencing (NGS) and network and pathway studies. Specific projects include in-silico drug repositioning screening to find new uses of old drugs.

In collaboration with the Clinical Informatics group, the group has developed expertise in natural language processing (NLP) for mining electronic patient records (eg for adverse drug reactions) and developed infrastructure to link the records to high throughput omics (H2020 http://kconnect.eu; 100k Genomics England).

The group are performing development work on Multi-Agent based computer systems using JADE to exploit big biomedical data for clinician aided decision support. More recently, the group have developed a significant programme in use of wearable devices to monitor epilepsy, major depression and MS through the remote monitoring of speech, cognition, activity, sleep, sociability and memory (IMI2 €22m euros; RADAR-CNS.org).

This builds on their work in developing a wearables and phone based system to detect relapse in schizophrenia.

The research has required the extensive use of computational approaches such as machine learning methods and the creation of software tools as well as the construction and administration of high performance computing infrastructure which has been uniquely developed behind the NHS rewall as part of the Centre for translational Informatics.

Large collaborative projects include the EU IMI2 RADAR-CNS, European Medical Informatics Framework (EMIF) for which the group lead on integrative biomarker analysis in Alzheimer’s. Other active collaborators include Janssen, GE, SomaLogic (US Biotech), FitBit, Intel, IBM, Illumina, SAGE Bionetworks, TwinsUK, HipSci, GENAROAD.

Publications
Research interests

Research in this group is focused on finding new disease-modifying treatments for Parkinson’s disease (PD). So far the group has identified a particular type of glutamate receptor (the mGluR4 receptor) that is present at presynaptic locations in select regions of the basal ganglia motor loop that experience abnormally-elevated neurotransmitter release in the disease state (Broadstock et al., 2012). When activated directly, these receptors reduced GABA release in the globus pallidus (MacInnes and Duty, 2008) and glutamate release in the substantia nigra (Austin et al., 2010), both of which can dampen down excitotoxicity in the substantia nigra. Accordingly, the group has shown that mGluR4 activating drugs, infused directly into the substantia nigra, preserve the dopaminergic neurones and motor function in rodent models of PD (Betts et al., 2012). Current studies are underway to identify systemically-active drugs to achieve similar targeting of this mGluR4 in a more clinically-relevant manner. The group has also shown that the growth factor, FGF-20, is a key player in the survival of dopaminergic neurones and motor function in rodent models of PD (Bets et al., 2012). Current studies are underway to identify systemically-active drugs to achieve similar targeting of this mGluR4 in a more clinically-relevant manner. The group is increasingly interested in the non-motor features of PD including pain and cognitive impairment in PD and other Lewy body diseases.

Publications

Research interests

The Fanto lab focuses on the essential question of how an organism keeps a functional nervous system throughout adult life and on the failure of these processes in neurodegeneration. Much of our attention is related to autophagy, a catabolic pathway fundamental for the maintenance of long-lived neurons. A second focus is on the role of glial cells and their interactions with neurons in the maintenance of the nervous system.

Our starting point was modelling in Drosophila melanogaster Dentatorubropallidoluysian Atrophy (DRPLA), a neurodegenerative disease due to expansion of a polyglutamine tract in the human Atrophin. Through these investigations we have established that neurodegeneration arises through a block in autophagy at the level of lysosomal clearance. Of even greater importance, and wider relevance, was the discovery, made through functional genomic analysis of transcription, that the Fat/Hippo tumour suppressor pathway is essential for neuronal homeostasis and mediates neurodegeneration by polyglutamine Atrophins. This finding has identified a whole new pathway of interest in this field.

Autophagy in DRPLA is not only disrupted in neurons, but also in glia. These cells are crucial for the maintenance of brain activity. We are interested in understanding how glial cells with autophagy defects interfere with the function and survival of the neighbouring cells, especially focusing on the effect that dysfunctional glial cells have on neuronal activity, circuits and behaviour.

Recently, we have expanded our expertise to in-vivo mouse studies, in which we have been able to validate our model for pathogenesis of DRPLA, specifically in the cerebellum, the area most affected in patients and we have also extended our interests to other neurodevelopmental (Vici Syndrome) and neurodegenerative (FTD/ALS) pathologies associated with significant dysfunctions in autophagy.

Dr Manolis Fanto

Research interests

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Publications

**Research interests**

My research focuses on visual perceptual pathology in neurodegenerative and eye disease, particularly visual hallucinations and related perceptual symptoms. Work carried out in my lab showed the phenomenological content of a visual hallucination (whether a face, object, colour or pattern, for example) is defined by where in the visual cortex spontaneous increases in activity occur. For example, activity within colour specialised cortex is associated with hallucinations of colour while activity within cortex specialised for faces is associated with hallucinations of faces. Beyond eye disease, this principle has been confirmed in clinical contexts such as schizophrenia.

Our work on visual hallucination phenomenology led to the idea that clinical associations between different visual hallucination contents reflect neurobiological mechanisms. Examining the phenomenology of visual hallucinations across different clinical contexts, we characterised three, overlapping but distinct visual hallucinatory syndromes. One syndrome is found in a spectrum of neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease and Dementia with Lewy Bodies; one is found in eye disease (Charles Bonnet Syndrome) and one is found in a range of conditions that share dysfunction in the serotonergic system. These syndromes not only differ in phenomenological but also have distinct prognostic implications. In Parkinson’s disease and Alzheimer’s disease, for example, visual hallucinations are associated with faster rates of cognitive decline and the move from independent living into care. This is not the case in eye disease, raising the possibility of understanding mechanisms of poor outcome by comparative studies of visual hallucination susceptibility.

These ideas formed the basis of an NIHR programme grant (Study of Hallucinations in Parkinson’s disease, Eye disease and Dementia [SHAPED] RP-PG-0610-10100) led by my group. Together with centres in Newcastle, Cambridge and Liverpool, SHAPED is tasked with establishing the prevalence, prognosis, comparative phenomenology, quality of life and economic impact of visual hallucinations across conditions and provide evidence from which to design future treatment trials. Alongside SHAPED, my group is involved in treatment trials of tDCS for visual hallucinations and developing advanced EEG techniques to characterise changes in high-frequency brain oscillations linked to hallucinations and delusions in psychosis.

**Publications**

- ffytche DH. The hodology of hallucinations. *Cortex.* 2008;44:1067-83. PMID: 18586234
- ffytche DH, Zeki S. The primary visual cortex, and feedback to it, are not necessary for conscious vision. *Brain.* 2011;134:247-57. PMID: 21097490
**Professor Paul Francis**

**Research interests**
I am interested in biochemical correlates of cognitive and non-cognitive changes in people with dementia so focus on the use of human post-mortem material. Major interests at present include understanding the contribution of changes in synaptic structure and function to cognition and behaviour. I direct a major UK initiative, Brains for Dementia Research with a cohort of people undergoing regular assessment with planned brain donation. Such material is available to researchers world-wide. I also collaborate on a major drug repositioning project (SMART AD) aiming to find new drugs for dementia. My research encompasses animal models and cell studies.

**Publications**
Research interests

Our current work is focused on the role of RNA processing in neurodegeneration as well as on the development of RNA-based therapeutic strategies. We also have a long standing interest on the cytoskeleton, another important target of neurodegenerative processes. We are particularly interested in motor neurone diseases, such as Amyotrophic Lateral Sclerosis, dementias of the Alzheimer's type, including frontotemporal dementia, and microsatellite expansion disorders.

An increasing number of neurodegenerative disorders are being linked to impairment of RNA processing. A prime example is provided by mutations in the MAPT gene, encoding tau, in Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17) that affect alternative splicing of tau. We have investigated the role of RNA-binding proteins, including TNRC4/CELF3 and TDP-43, in the regulation of tau splicing in sporadic tauopathies.

From a therapeutic standpoint, correcting aberrant RNA processing can be best achieved by direct intervention at the RNA level. We have successfully applied the spliceosome-mediated RNA trans-splicing technology to correct aberrant alternative splicing of tau in mouse models of tauopathies. The ability to reprogram alternative splicing has far reaching implications for the treatment of neurodegenerative and other neurological disorders linked to impairment of RNA processing.

The most common forms of amyotrophic lateral sclerosis and frontotemporal dementia are caused by a large GGGGCC repeat expansion in the first intron of the C9orf72 gene. We have identified polyadenylated C9orf72 RNA species retaining the repeat-containing intron and in which downstream exons are spliced correctly resulting in a C9orf72 mRNA with an enlarged 5'-UTR containing the GGGGCC repeat domain. Retention of the repeat-containing intron in C9orf72 mRNA potentially explains a number of pathological features of C9orf72-linked disease and suggests that the misprocessing of C9orf72 transcripts initiates the pathogenic process caused by C9orf72 repeat expansions as well as opens the way to novel therapeutic strategies.

Publications

• Anthony K, Gallo J-M. Aberrant RNA processing events in neurological disorders. Brain Res. 2010;1338:67-77. PMID: 20226177
• Malmqvist T, Anthony K, Gallo J-M. Tau mRNA is present in axonal RNA granules and is associated with elongation factor 1A. Brain Res. 2014;1584:22-27. PMID: 24398033
Research interests

About 17 years ago we started to work on the role of the CDK activator p25 in neurodegeneration. We found that transgenic overexpression of low levels of p25 do not cause neurodegeneration, but rather enhance long-term potentiation and memory formation (Angelo et al., 2003; Ris et al., 2005). Further, we found that p25/Cdk5 provide inhibitory crosstalk with GSK3β regarding tau hyperphosphorylation (Plattner et al., 2006). These findings suggested that p25 levels are reduced in Alzheimer’s disease brain, which we confirmed in post-mortem analyses (Engmann et al., 2011). Taken together, these studies suggested that p25 formation enhances synaptic function and memory formation, a process that is impaired already in the early stages of Alzheimer’s disease (Giese, 2014). Consequently, we used our p25 transgenic mice to screen for synaptic processes that may be impaired in Alzheimer’s disease. Among other things we identified the presynaptic protein CSPalpha and the regulator of local translation CYFIP2 as p25 regulated proteins (Engmann et al., 2011).

CSPalpha is a multifunctional presynaptic protein that is mutated in Kufs dementia. We found that CSPalpha expression is downregulated in post-mortem Alzheimer’s forebrain, whereas it is upregulated in Alzheimer’s cerebellum (Tiwari et al., 2015). Currently, we are testing the hypothesis that dysregulation of CSPalpha is critical for synaptic degeneration and that upregulation of CSPalpha may protect from synapse loss in models of Alzheimer’s disease.

CYFIP2 is thought to be a regulator of local mRNA translation at synapses and it might also regulate synapse morphology via influencing actin polymerization. We identified a downregulation of CYFIP2 expression in post-mortem Alzheimer’s forebrain. Modelling this reduced expression in mice leads to abnormal APP processing, increased tau phosphorylation and impaired spatial memory retention (unpublished data). Currently, we are testing the hypothesis that dysregulated CYFIP2 expression links abnormal APP processing together with enhanced tau phosphorylation and memory loss.

Publications

- Giese KP. Generation of the Cdk5 activator p25 is a memory mechanism that is affected in early Alzheimer’s disease. Front Mol Neurosci. 2014;7:36. PMID: 24822036
- Tiwari SS, d’Orange M, Troakes C, Shurov BN, Engmann O, Noble W, Hortobagyi T, Giese KP. Evidence that the presynaptic vesicle protein CSPalpha is a key player in synaptic degeneration and protection in Alzheimer’s disease. Mol Brain. 2015;8:6. PMID: 25631211
Research interests

My research into cognitive and psychological aspects of ALS/MND has been highly influential in the wider acceptance of cognitive/behavioural involvement in ALS/MND and the substantial change in the manner in which this disorder is viewed clinically. This is in contrast to when my research in this field began in 1990, when the prevailing view was that cognition was not affected in ALS/MND. The clinical world was slow to accept that this might be untrue. However, my group’s internationally-recognised work has helped to establish that ~50 per cent of people with MND may indeed have cognitive dysfunction; neuropsychological and neuroimaging research from my group has made an enormous contribution to this change in understanding, elucidating the involvement of brain regions outside the motor system.

This work has led to a growing awareness of how such cognitive change is relevant to a number of aspects of patients’ care. For example my group’s recent research has highlighted that language dysfunction is more prevalent than previously thought, with implications for communication of care-based decisions. Work has also recently demonstrated that a range of non-illness factors may be highly relevant to the potentially life-prolonging palliative care decisions that people with ALS make in later stages of the disease.

Other current (NIHR-funded) work involves the evaluation of self-management education courses for people with poorly controlled epilepsy and of the clinical and cost-effectiveness of cognitive behavioural therapy for adults with dissociative (nonepileptic) seizures.

Publications

Research interests

We have published a number of systematic reviews and meta-analyses of psychotherapy and pharmacotherapy interventions for mental and physical health disorders. These have investigated the efficacy of:

i) cognitive behavioural therapy (CBT) for anxiety and depression in older people (CBT was found to be effective, but effect sizes were small; Gould et al., 2012a, 2012b);

ii) interventions for reducing benzodiazepine use in older people (supervised benzodiazepine withdrawal augmented with psychotherapy interventions were most effective; Gould et al., 2014);

iii) interventions for improving cognition in people with dementia (beneficial effects were found with cognitive stimulation, but not cognitive training; Huntley et al., 2015);

iv) psychotherapy and pharmacotherapy interventions for reducing psychological distress or improving psychological wellbeing in people with Amyotrophic Lateral Sclerosis (we found insufficient evidence for these interventions; Gould et al., 2015).

We have also systematically reviewed the characteristics and validity of tasks that assess pattern separation and pattern completion in humans (Liu et al., 2016).

The evaluation of psychological therapies for older people with functional and organic disorders is ongoing. We have recently completed a pilot RCT of transdiagnostic CBT vs. delayed treatment for older people with comorbid anxiety and depression. We are currently examining the effects of brief mindfulness-based interventions in two studies: a pilot RCT in people with subjective memory complaints and an uncontrolled feasibility study in people with dementia with sleep disturbances. Our group is also currently assessing the effects of psychological therapies in members of staff working with people with mental and physical health disorders. An uncontrolled feasibility study of psychodynamic clinical supervision for mental health staff working with older people with personality disorders is in progress. In addition, we are currently investigating whether an online mindfulness-based intervention can improve compassionate care in nurses.

In other work we are examining the characteristics of psychotic and mood symptoms in people with Alzheimer’s disease (Reeves et al., 2012; Reeves et al., 2015), and developing a tool to assess frailty in older people with mental health disorders (Sutton et al., 2016).

Publications


**Research interests**

With a background in epilepsy research, we have long been faced with the analysis of brain images that present anatomical abnormalities. This has required adapting existing neuroscience tools, and developing entirely new ones.

For example, over the past 15 years we have created the world’s largest collection of single-investigator, truly manually delineated human brain atlases now containing 95 regions delineated on 30 MRIs of healthy young adults (Hammers A, Allom R et al. 2003, Gousias IS et al. 2008; atlases available via www.brain-development.org). We then developed a method for warping each atlas separately to a new MRI – thus cancelling out registration errors – and concatenating the information in target space, resulting in automatic anatomical segmentations of an accuracy comparable to that of human rater test-retest reliability (Heckemann RA et al. 2006, Hammers A et al. 2007).

Importantly for dementia, we then incorporated information about atrophy into the registration steps themselves (Heckemann RA et al. 2010) and were thus able to accurately label brains of very elderly controls and patients with Alzheimer’s disease; we have made ~1,000 labelled ADNI brains publicly available (Heckemann RA et al. 2011).

We have since applied these techniques not only to biological questions in epilepsy but also in the dementias, eg studying neuroinflammation in traumatic brain injury (Ramlacknansingh A et al.); the role of the amygdala in memory in mild cognitive impairment (Klein-Koerkamp Y et al.); or novel insights into emotion processing in early dementia (Sapey-Triomphe LA et al.).

Another domain of application has been automatic classification of Alzheimer’s disease, using region based, voxel-based, and also genetic measures, on cross-sectional (Gray KR et al. 2013) and longitudinal data (Gray KR et al. 2012), with some of the best results in the literature.

For the novel technology of simultaneous PET-MR, we have already contributed one of the top-performing algorithms for solving the problem of attenuation correction (Merida I et al. 2015 & submitted) and look forward to biological applications.

**Publications**

Research interests
My research centres on the biochemistry and cell biology of Alzheimer’s disease and related disorders and understanding the underlying molecular mechanisms. My primary research interests are on tau and α-synuclein, which form abnormal deposits in the brain in neurodegenerative disease. Tau is an important therapeutic target and work in my group has uncovered novel pathological functions.

New signalling functions for tau: we showed that neuronal tau release is a physiological process regulated by neuronal activity (Pooler et al, 2013), extending our previous findings that tau can act as a signalling protein (Reynolds et al, 2008). We identified Fyn-dependent trafficking of tau in neurons (Pooler et al, 2012) and we are investigating tau-Fyn interactions in Alzheimer’s disease (Lau et al, 2016). These findings give important insight into the prion-like spreading of tau pathology.

Tau phosphorylation in dementia: my comprehensive analyses of tau phosphorylation provide important mechanistic insight into Alzheimer’s disease (Hanger et al, 1998; 2007; 2009). I identified glycogen synthase kinase-3α/β (GSK3) and casein kinase 1δ as key tau kinases (Hanger et al, 1992; 2007); involved in tau toxicity and function. This work prompted international studies on inhibitors of GSK3 and casein kinase 1 as potential therapeutic targets for dementia.

Disease-associated tau mutations impair axonal transport: my work on tau kinases led to investigations of the effects of tau on axonal transport. This showed that phosphorylation modulates axonal transport of tau and mitochondria (Rodriguez-Martin et al, 2013; 2016; Gilley et al, 2012; 2015; Cuchillo-Ibanez et al, 2008), processes affected early in neurodegenerative disease.

Tau is pathogenic in animal models: my group identified a form of tau in human tauopathy brain (Wray et al, 2008) that, when expressed in mice (Tau35 mice), accurately recapitulates human disease. Tau35 mice will enable testing of potential therapies that are relevant to dementia (Bondulich et al, in press).

Publications
Dr Frank Hirth

Research interests
Current research in the lab addresses two fundamental questions: How is genetic information converted into neural circuits and behaviour? How are these processes affected in disorders of the brain? To address these questions in a systematic way in vivo, we are using the fruitfly Drosophila melanogaster as our principal study organism to investigate how identified stem cell lineages form neural circuit elements mediating sensorimotor integration and adaptive behaviour. We currently focus on the dopaminergic and GABAergic systems of the central complex, a group of brain centres that resemble structural and functional similarities to the vertebrate basal ganglia. In addition, we are studying two neuroblast lineages and their circuit derivatives in the adult fly brain, which resemble commonalities to midbrain-hindbrain-derived neural circuits in the vertebrate brain. Our findings identify a cerebellar-like structure and establish an ancestral ground pattern organization of the tripartite insect and vertebrate brain that extends from homologous gene expression and function to behavioural manifestations. We currently apply our insights into neural circuit formation and function to behavioural manifestations. We currently apply our insights into neural circuit formation and function to investigate mechanisms underlying neurodegenerative proteinopathies, including Parkinson’s and Motor Neurone Disease, as well as Frontotemporal Dementia. Specifically, we are investigating how mutation/dysfunction and accumulation of alpha-synuclein, TDP-43 and C9ALS/FTD-related repeat associated, non ATG-translated dipeptide repeat proteins (DPRs) can cause synaptic dysfunction and subsequent deficits of neural circuits and behaviour that ultimately result in cell type specific neurodegeneration.

Publications
Research interests

My group has extensively used transcriptomics to understand biological pathways underlying genetic vulnerability and for the development of biomarkers of disease to assist early diagnosis and identify disease mechanisms in Alzheimer’s disease.

Recent work has identified blood expression biomarkers able to distinguish people with cognitive impairment from those without cognitive impairment (Lunnon, 2012, Lunnon 2013 and Sood, 2015). Current collaborative projects with Professor Timmons (King’s & XR Genomics) and groups in the EU (EMIF, Dr Visser) and US (ADNI, Professor Saykin) AD biomarker consortia aim to test the performance of the blood biomarker in preparation for commercialisation.

Immune genes associated with a brain co-expression module have been sequenced in people with Alzheimer’s disease to identify new rare gene variants associated with disease risk which together define a functional pathway of vulnerability. Work is in progress to validate these candidate gene variants and undertake functional studies. This work includes developing microglial cell models of the Alzheimer’s neuroinflammatory susceptibility gene TREM2 and other functionally related Alzheimer’s disease risk genes, and developing assays and relevant markers for compound screening. The models are being evaluated using data generated from people with Alzheimer’s disease and brain tissue from people with and without the risk variants.

Publications

Professor Corinne Houart

Research interests

The Houart lab built its international reputation on its contributions in the understanding of cell fate decisions driving the formation of the forebrain during vertebrate early development. The team is continuing its investigation in this direction, with a focus on the temporal and quantitative changes driving forebrain complexity.

In the past 5 years, my lab also developed an interest in understanding transcripts dynamics in developing axons. A SFPQ mutant (isolated in a local zebrafish mutagenesis screen) led to the identification of a non-nuclear processing of cytoskeletal and synaptic transcripts, controlling neuronal connectivity (Thomas et al., in revision). The lab has used this mutant to build a convincing model of neurodegeneration, triggered by dysfunction of RNA processing events in axons and synapses. The ‘RNA processing’ section of my lab is planning to devote the next 5 years to understanding the role of splicing proteins and intron-retention in developing axons and synapses and use this knowledge to contribute to the effort in understanding neuronal aging and degeneration.

The team’s effort in understanding fate specification and forebrain organisation led to new findings regarding the transcription factor Foxg1, key driver of telencephalic fate in the embryo. My group found that this protein interacts with a centrosomal protein at the centre of microcephaly in human. This finding opens a new avenue in understanding the role of Foxg1 in both microcephaly and ASD. Sophisticated zebrafish genetic models are in the making to lead this new research avenue.

Publications


Current research interests are in four main areas as follows:

1. Understanding the processes and mechanisms that lead to neuronal cell death in Parkinson’s disease – these include disruption of iron homeostasis, altered mitochondrial function, changes in protein degradation by proteasomal action and autophagy and inflammation. These investigations can involve cell culture, primary neuronal cultures, in vivo toxin and genetic based models and post-mortem tissues from Parkinson’s disease.

2. The development and use of rodent and primate models of Parkinson’s disease that mimic both the motor and non-motor symptoms of the illness. These models are used to understand the basis of the symptomatology but also to devise and examine potential new therapeutic approaches to the treatment of both motor and non-motor signs of Parkinson’s disease.

3. Determination of the cause and treatment of motor complications of the dopaminergic treatment of Parkinson’s disease. The motor complications centre primarily on the development and reversal of levodopa induced dyskinesia but also explore the basis of dystonia and the ‘wearing off’ phenomenon. These investigations have led to the introduction of new drug treatment strategies for use in patients with Parkinson’s disease that has led to a marked decline in the appearance of troublesome dyskinesia.

4. The search for a ‘cure’ for Parkinson’s disease in its broadest sense with studies aimed and neuroprotection, disease modification and neurorestoration. The investigations use a range of approaches from cell culture, primary neuronal cultures and whole animal work. Protecting or improving the viability of dopaminergic neurones is the primary objective and this is looked at using drug molecules, trophic factors and genetic manipulation.

Publications:

- Brzozowski MJ, Jenner P, Rose S. Inhibition of i-NOS but not n-NOS protects rat primary cell cultures against MPP(+) induced neuronal toxicity. *J Neural Transm (Vienna)*. 2015;122:779-88. PMID: 25503828
- Broom L, Jenner P, Rose S. Increased neurotrophic factor levels in ventral mesencephalic cultures do not explain the protective effect of osteopontin and the synthetic 15-mer RGD domain against MPP+ toxicity. *Exp Neurol*. 2015;263:1-7. PMID: 25218309
Dr Steven Kiddle

Research interests
Starting off studying Mathematics and Systems Biology, I am now using a MRC Biostatistics Fellowship to research biomarkers of Alzheimer’s disease. This involves finding blood biomarkers of brain amyloid pathology or early cognitive decline, which could have potential for the enrichment of clinical trials. My research involves the comparison and integration of genetic, gene expression, protein and metabolite markers, and the integration of prevalence estimates through Bayesian priors. For example, I was involved in the first application of SOMAscan proteomic technology to the study of Alzheimer’s disease, both in the large EU AddNeuroMed cohort and the UK’s largest twin cohort (TwinsUK).

Continuing blood biomarker work through the supervision of students, I am now focusing on the development of longitudinal modelling approaches to study cognitive decline in dementia. Through this I hope to understand heterogeneity in cognitive decline, allowing the development of stratified medicine approaches. I am also collaborating with Zina Ibrahim on the topic of embedding clinical trials within hospital Electronic Health Records, an approach that will greatly facilitate stratified medicine.

Publications

Dr Richard Killick

Research interests
I am a molecular neurobiologist, with a background in sensory systems, particularly audition. As Lecturer and Principal Investigator I now lead a team whose scientific aim is to elucidate the molecular mechanisms of neurodegeneration, especially Alzheimer’s disease. Over the past twenty years, I have developed a broad knowledge of the neuroscience of Alzheimer’s disease and considerable expertise in the current techniques of investigative molecular neuroscience.

I received my DPhil from Sussex University in 1994 following investigations of molecular components forming the avian and mammalian auditory systems. I continued as a postdoctoral investigator at Sussex examining the developmental neurobiology of genes and proteins involved in Alzheimer’s disease, within the inner ear. In 1999 I moved to King’s College London, joining the Neuroscience department to further my investigations into the underlying cause of Alzheimer’s disease and other neurodegenerative disorders. During the coming years my attention was drawn to cellular signalling pathways thought to underpin the neuropathology of Alzheimer’s disease, particularly the Wingless/Wnt, Notch and Insulin pathways. In 2010 I established my own group at King’s, the current focus of which is the role of the non-canonical Wnt-Planar Cell Polarity pathway in Alzheimer’s disease neuropathology and the central role of Dickkopf-1 in the activation of this pathway following its induction by β-amyloid.

The group have recently moved to the Maurice Wohl Clinical Neuroscience Institute, where we collaborate closely with a range of other neuroscientists, clinicians and structural biologists and are involved in applying a pathway-driven approach to identify novel Alzheimer’s associated biomarkers and the uncovering of amenable therapeutic targets through which to treat the disease. Data gathered by the team now strongly support the further assessment of the only ROCK inhibitor in clinical use, Fasudil, for its repositioning for Alzheimer’s.

Publications
Research interests

My lab works in the chemistry and medicine interface. My team are experts in the analytical methodology used to detect thousands of small molecules namely metabolomics, as well as integrating multomics and endotypes such as MRI volumes (Whiley et al. 2012, Sen et al. 2013, Eshbiana et al. 2015, Voyle et al. 2016), and also technically validating biomarker panels for diagnostics (Casanova et al. 2016).

Over the last five years my team have been investigating the role of lipids in dementia. Using lipidomics they discovered that three phosphatidylcholines containing omega fatty acids are depleted in the blood of Alzheimer’s Disease (AD) patients (Whiley et al. 2013). These same lipids were found to be associated with memory loss in the healthy (Simpson et al. 2015). Working together with Dr Proitsi (IoP) two other lipid families in blood, cholesteryl esters and triglycerides, were found to have AD prediction qualities, results that were later validated in a second study (Proitsi et al. 2014 and 2016).

My group also explores the brain and liver axis, having shown that brain death produces inflammatory lipid mediator changes in the liver (Xu et al. 2015 and 2016). Equally we are interested in the role of the liver and gut flora in disease and are working on animal models of Parkinson’s Disease (PD) and AD to understand liver and gut metabolism in relation to the brain.

Currently the lab is involved in a number of academic-industry led consortia in the dementia field. The EMIF-AD project with a unique cohort of 1,000 participants that are stratified by amyloid-Beta and Tau in CSF aims to discover blood biomarkers of prodromal AD. Additional collaborations with the National Phenome Center (NPC) and the NIH NIA BLSA aim to validate their biomarker findings and understand the biology behind them.

Publications

Damage to a large number of cellular processes occurs in Alzheimer's disease, FTD/ALS and Parkinson's disease. These include damage to mitochondria, Ca\(^{2+}\) homeostasis, lipid metabolism, axonal transport, the ER involving activation of the unfolded protein response, autophagy and also inflammatory responses. The broad nature of this damage makes understanding pathogenic mechanisms difficult. How are so many different cellular functions collectively perturbed and can these different damaged functions be linked together in a common disease pathway? Moreover, the diversity of this damage makes devising new treatment strategies difficult; which disrupted cellular function should be prioritised as a therapeutic target? My group are interested in understanding common disease mechanisms in neurodegenerative diseases and using this information to devise novel treatment strategies. We are particularly interested in signalling between ER and mitochondria since this regulates many cellular processes that are damaged in neurodegenerative diseases. Recently, we identified the mechanism underlying ER-mitochondria signalling which involves binding of the integral ER protein VAPB to the outer mitochondrial membrane protein PTPIP51. VAPB and PTPIP51 form a 'molecular scaffold' that acts to tether the two organelles. Moreover, we have shown that the VAPB-PTPIP51 tethers are broken in neurodegenerative diseases and this reduces ER-mitochondria contacts and signalling. We are also interested in how key cargoes such as mitochondria, the amyloid precursor protein and kinases linked to neurodegeneration are transported through axons since axonal transport is damaged in neurodegenerative diseases and ER-mitochondria signaling can influence this transport. Finally, we are utilizing these findings to build novel cellular screens to identify small molecules that might correct damaged ER-mitochondria contacts in disease. We anticipate that such molecules will represent novel therapeutics.

**Publications**

Dr Jonathan Morris

Research interests
I have a background in the role of signalling proteins in cancer research and a major interest in the PSK family of protein kinases, which we identified and cloned 15 years ago.

In Alzheimer’s disease (AD), tau is highly phosphorylated and aggregated into neurofibrillary tangles, which likely contribute directly to neuronal cell death and neurodegeneration. Consequently, there is much interest in the identification of protein kinases responsible for the pathological phosphorylation of tau, as these enzymes could offer suitable targets for drug inhibition and therapy.

Recently, we have shown that PSKs bind and regulate microtubules, and also phosphorylate tau on more than 40 residues in vitro, including sites that control tau affinity for microtubules and their stability. Crucially, PSKs are activated catalytically where phosphorylated tau and neurofibrillary tangles occur in AD brain.

Our current work is investigating the roles for PSK kinases in targeting tau and microtubules in neurons and Alzheimer’s brain tissues. We are developing and characterizing small molecule inhibitors for these kinases, in addition to these target validation studies. Overall, our objective is to evaluate these proteins as therapeutic targets suitable for drug inhibition and potential treatment of dementia.

Publications
- Wojtala RL, Tavares IA, Morton PE, Valderrama F, Thomas NS, Morris JD. Prostate-derived sterile 20-like kinases (PSKs/TAOKs) are activated in mitosis and contribute to mitotic cell rounding and spindle positioning. J Biol Chem. 2011;286:30161-70. PMID: 21705329
Professor Robin Morris

Research interests
My research in dementia is from the perspective of a neuropsychologist and cognitive neuroscientist, but collaborating with neurologists, social scientists and health economists. Research has included investigating the neurocognitive systems that support awareness of cognitive deficit and applying this to dementias such as Alzheimer’s disease. This includes the development of the Cognitive Awareness Model (CAM), which is used to explain different facets of awareness loss, including the distinction between explicit and implicit awareness. This work recently showed how emotional reaction to task failure due to impairment can be dissociated from overt awareness of failure. I have also explored with Professor Linda Clare (University of Exeter) the psychosocial influences concerning awareness as part of the MIDAS study. I am investigating different aspects of the self, how this changes following the onset of dementia and how it can be understood in terms of brain changes and damage to neurocognitive systems supporting self representations. This work is integrated with an interest in the psychosocial aspects of dementia, in particular, recent work on ‘living well with dementia’ that explores different individual and social aspects that predict how a person with dementia can maximise their quality of life, as part of the multi-centre IDEAL study. I am also conducting research into the neuropsychology of cerebral small vessel disease, the largest cause of cerebrovascular cognitive impairment and dementia. Recent work in collaboration with Professor Hugh Markus (University of Cambridge), as part of the SCANS study, has shown which neuroimaging features best predict cognitive decline and dementia onset.

Publications
Dr Wendy Noble

Research interests
I first became involved in dementia research during my first postdoctoral position with Professor Karen Duff (Nathan S. Kline Institute/Columbia University, New York) where I began working to understand the contribution of tau phosphorylation to neurodegeneration in models of Alzheimer’s disease and tauopathies. Using newly developed mouse models of tauopathy I demonstrated for the first time in vivo that specific kinases phosphorylate tau to promote the development of tau pathology (Noble et al., 2003), and provided pre-clinical evidence that GSK-3 inhibitors have benefits for the treatment of neurodegenerative tauopathies (Noble et al., 2005).

Upon returning to the UK in 2004, I continued to investigate the mechanisms underlying the development of tauopathy (Utton et al., 2005; Kelleher et al., 2007; Garwood et al., 2010). This work led to the observation that alterations in glia, together with neuroinflammatory responses, are closely associated with the development of tau pathology in cell models, transgenic mouse models and in post-mortem human brain (Noble et al., 2009; Garwood et al., 2011). This work described that astrocytic inflammatory pathways influence tau phosphorylation, cleavage and aggregation, including in response to astrocyte activation by Aβ, in these models. Moreover, they demonstrated the potential of drug re-purposing for Alzheimer’s disease, showing that minocycline, a commonly used tetracycline antibiotic derivative, reduces inflammation and the development of tau pathology in vivo; these findings are now being pursued in clinical trials.

My group have also used post-mortem human brain to demonstrate changes in tau biology that are important for dementia, and investigating the mechanisms underlying prion-like tau propagation in tauopathies.

Publications

AT A GLANCE
Astrocytes as mediators of synaptotoxic Aβ-tau interactions
Neuroinflammation in dementia
Tau biology in health and disease
Pre-clinical testing of potential new therapies for dementia
Transgenic animal models, organotypic brain slices, co-cultures, and post-mortem human brain

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Publications
Dr Michael O’Sullivan

Research interests
I am a clinician scientist and Reader in Clinical Neuroscience at King’s College London. I trained as an undergraduate in Cambridge, and did specialist and research training in London and Munich. I was a Medical Research Council Clinician Scientist Fellow from 2008–12 at CUBRIC in Cardiff. The main clinical challenge of my work is cognitive impairment after stroke. In particular, I am interested in the interaction between focal damage and other processes involved in ageing and early cognitive decline, viewed from a network perspective. This work is based on investigation of structural and functional networks in the brain using MRI. I have a long-standing clinical interest in small vessel disease, including genetic forms such as CADASIL, and I am currently investigating new mechanisms of disease using PET. Ultimately, the thrust of the work is translational, with the purpose of promoting restoration of function.

Publications
Dr Richard Parsons

Research interests
My research has focussed upon the role of nicotinamide metabolism in the pathogenesis of Parkinson’s disease (PD). My seminal discovery that nicotinamide N-methyltransferase (NNMT) is significantly overexpressed in the brains of patients who have died of PD was the first to link an enzyme intimately involved in the regulation of NAD+ and thus ATP, synthesis with the disease. Subsequent studies have shown that elevated NNMT expression results in several neurotrophic effects, in particular increased Complex I activity, ATP synthesis and formation of functional synapses. I also demonstrated that increased NNMT expression is neuroprotective against PD-relevant mitotoxins such as MPP+, rotenone and 6-hydroxydopamine. My subsequent studies have elucidated the mechanisms underlying these effects: (1) increased energy production via the induction and activation of sirtuin-3 activity; (2) formation of functional synapses via the activation of the ephrin-B2 and Akt signalling pathways and (3) neuroprotection via the maintenance of cellular ATP levels.

I have also published a number of articles upon the regulation of β-secretase, in particular I have shown that statins regulate β-secretase activity, and subsequent amyloid-β production, via inhibition of its subcellular trafficking into lipid-rich rafts.

I have a number of national and international collaborations. With Dr Frank Hirth, Institute of Psychiatry, Psychology & Neuroscience, King’s, I have used Drosophila in vivo models to investigate mitochondrial bioenergetics in dopaminergic neurodegeneration. We are currently investigating the regulation of NAD+ biosynthesis by NNMT and its impact upon neurodegeneration using Drosophila. With Professor Fabio Klamt, UFRGS, Brazil, I am investigating the role of the cytoskeletal protein cofilin-1 in Parkinson’s disease, and I am currently investigating the genetic pathways underlying dopaminergic differentiation, substantia nigra specialisation, and PD pathogenesis. With Dr Nathanial Martin, University of Utrecht, the Netherlands, and Professor Monica Emanuelli, University of Ancona, Italy, I am investigating the bioactivation of endogenous neurotoxins by NNMT.

Publications:
Research interests
We are interested in studying the structure and function of proteins linked to neurodegenerative diseases in the attempt of understanding the events which lead to pathology and designing suitable therapeutic strategies. We focus on two distinct but converging families of diseases. We study proteins involved in diseases caused by protein aggregation and misfolding, such as Huntington’s chorea, Machado-Joseph disease and other types of spinocerebellar ataxias. We are interested in mitochondrial pathologies linked to misfunctioning of iron metabolism, such as Friedreich’s ataxia. Our approach uses different complementary biophysical, biochemical and bioinformatics techniques which range from various spectroscopies, to AFM, EM and ITC calorimetry. We are interested in structural, functional, evolutionary and thermodynamics aspects. We have made important contributions to understand the cellular role of frataxin in iron-sulfur cluster biogenesis as a regulator of the reaction speeds. We have also been the first to describe the interaction between frataxin and the IscS/IscU complex, central to the highly conserved machinery devoted to iron sulphur cluster assembly. In a different project we have proved that protein aggregation is the dark side of protein function. This knowledge will be used for drug design for the treatment of misfolding diseases.

Publications
Research interests
At Neurodegeneration Imaging Group (NIG), we primarily focus on the use of Positron Emission Tomography (PET) molecular imaging, Magnetic Resonance Imaging (MRI), and Clinical observation to study common (Parkinson’s disease, Alzheimer’s disease, Multiple Sclerosis) and less common (Huntington’s disease, Multiple System Atrophy, Progressive Supranuclear Palsy, Corticobasal degeneration) neurodegenerative disorders.

We use a range of brain imaging techniques for investigating aetiology, pathophysiology, diagnosis, progression, identification of novel molecular targets for pharmacotherapy, and brain response to conventional, novel and restorative treatments in neurodegenerative disorders. We are hoping that with our projects we will help accelerate novel therapeutic development for neurodegenerative disorders.

We are carrying out projects by applying optimizing neuroimaging methodology and working towards identifying key mechanisms involved in neurodegeneration such as neuroinflammation, protein accumulation (eg tau, amyloid and α-synuclein), brain metabolic dysfunction and dysregulation of neurotransmitters and enzyme.

Publications
Professor John Powell

Research interests
My work uses genetics to understand the biology of Neurodegenerative illnesses. We aim to identify genetic variation that contributes to susceptibility and behavioural phenotypes (psychosis, depression) in late onset sporadic Alzheimer’s disease (AD) and to identify genetic variation that contributes to susceptibility and endophenotypes (age of onset, survival and site of onset) of sporadic Amyotrophic lateral sclerosis (ALS). In addition to array based genotyping, we have used whole genome, exome and targeted exome sequencing approaches for the identification of genetic variation. All of our studies employ robust statistical techniques and we have used Mendelian randomisation and structural equation modelling as an approach to infer causality.

Publications
I founded the 10/66 Dementia Research Group (1998) to promote research into dementia in developing countries, where most of those affected live, but without evidence to guide policy and practice. The group conducted pilot studies (26 centres), and population-based surveys of prevalence and incidence (12 countries in Latin America, Asia and Africa). Key findings include:
1. a much higher prevalence and incidence of dementia than previously reported,
2. among chronic diseases, dementia is the leading contributor to disability and needs for care
3. dependence and social protection for older people are major societal and public health challenges
4. community-based interventions reduce carer strain and improve quality of life.

This evidence (140 peer-reviewed publications) changed perceptions of the global distribution of the dementia epidemic, and influenced intergovernmental policy initiatives (the Global Action on Dementia, and the WHO ‘Call for Action’). The Institute of Psychiatry, Psychology & Neuroscience Global Observatory for Ageing and Dementia Care has produced five annual Alzheimer’s Disease International World Alzheimer Reports (2009 – 15) covering global prevalence, incidence and costs of dementia, early intervention, long-term care, and modifiable risk factors. These data (adopted by the WHO) are the standard source on global dementia burden and impact for academic and media reports. I have made keynote presentations at the G7 Global Action on Dementia launch meeting, and at three subsequent G7 legacy events. I pioneered a public health model for scaling-up access to diagnosis and care, leading WHO mhGAP dementia guideline development, and co-chairing the WHO I-COPE Guideline Development Group for ‘Integrated Care for Older People’.

**Publications**

Dr Anto Praveen Rajkumar Rajamani

Research interests

I have a special interest in Psychiatric genetics. I have studied clinical (Rajkumar, 2011) and pharmacogenetic variables (Rajkumar, 2012, Rajkumar, 2013, Rajagopal, 2014) associated with clinical response to clozapine and serum clozapine levels (Rajkumar, 2013). We have demonstrated that the results of pharmacogenetic studies in schizophrenia depend heavily on their outcome definitions and that combined clinical and pharmacogenetic models have better predictive values. I moved to Aarhus University, Denmark, to pursue my Ph.D. in December 2010, and I started working with the Initiative for Integrative Psychiatric Research (iPsych), Denmark (Rajkumar, 2015). I studied the importance of BRD1 gene in affective behaviours using behavioural assays, 3-D neuronal image analyses, next generation RNA-sequencing (Rajkumar, 2015), miRNA sequencing, and micro-dialysis (Rajkumar, 2014). Findings of my research emphasised the importance of BRD1 and histone acetylation in the pathogenesis of affective disorders. We developed a novel mouse model for depression to evaluate the pertinent epigenetic changes and neurodevelopmental abnormalities.

I returned to clinical training in SLaM in February 2015, and I joined the department of Old Age Psychiatry, IoPPN, in March 2016. As I am interested in Old Age Psychiatry, and Psychiatric genetics, and I am currently studying the genetic aspects of Lewy Body Dementia.

Publications
Research interests
My research focuses on the problems experienced by older people and people with neurological disease living in the community and in care homes. It covers common daily problems such as incontinence, difficulties with mobility and other activities of daily living. We record the complications of immobility such as pain, postural deformity and muscle and joint contractures. I am particularly interested in the problems of co-morbidity, when people experience more than one long term condition at a time and the complexity that brings to their health care. I am interested in dementia after stroke and Parkinson’s disease and have completed randomised trials of rehabilitation interventions in these areas.

In my post at King’s as part of the Division of Health and Social Care, led by Professor Charles Wolfe I am privileged to have access to the South London Stroke register and an active group of stroke survivors who input to our work. The register is very useful for following up long term outcomes after stroke, including stroke related dementia. We are planning to look at immobility related complications and to develop outcome measures for people who have cognitive and communication impairments that limit their ability to use pen and paper measures or interviews. Our aim is to improve quality of life in this vulnerable group.

Publications
• Sackley C, Brittle N, Patel S, Ellins J, Scott M, Wright C, Dewey ME. The prevalence of joint contractures, pressure sores, painful shoulder, other pain, falls and depression in the year after a severely disabling stroke. Stroke. 2008;39:3329-34. PMID: 18797199
Research interests

Our goal is to find novel treatments, and to improve existing treatment strategies for both the motor and non-motor symptoms of Parkinson’s Disease (PD). Using animal models of PD and related movement disorders we investigate the effect of novel symptomatic and neuroprotective strategies. Using rodent models of motor dysfunction (6-OHDA-lesioned rat) we investigate the effect of novel drugs on rotational activity and expression of L-DOPA-induced abnormal involuntary movements. We extend these studies to their investigation in the primate MPTP-models of Parkinson’s disease, measuring locomotor activity, motor disability and dyskinesia (dystonia and chorea) using rating scales based on those used in man. In these studies we aim to find symptomatic drugs that improve motor function and/or reduce dyskinesia. In addition we investigate mechanisms of cell death using cell culture and 6-OHDA-, lipopolysaccharide(LPS)- and proteasome-inhibitor (PSI)-lesioned rats, and perform neuroprotection studies with behavioural and neurochemical correlates of cell death. Recently, we have started to characterise our rodent and primate models of PD for non-motor dysfunction and pathology. In these studies we aim to find treatment strategies that will slow the progression of PD. We are also keen to find improved treatments for the non-motor symptoms of PD. We have shown alterations in gut and bladder function/pathology in both the rodent and primate models, with evidence of changes in gut tissue electrophysiology, loss of cholinergic neurons and chronic glisosis (inflammation). In addition we are investigating cognitive function in our primate model of PD using the Wisconsin Generalised testing apparatus (WGTA), and preliminary data suggest cognitive deficits on tasks sensitive to executive function and visuospatial conditional learning consistent with PD.

Publications

- Broom L, Jenner P, Rose S. Increased neurotrophic factor levels in ventral mesencephalic cultures do not explain the protective effect of osteopontin and the synthetic 15-mer RGD domain against MPP+ toxicity. *Exp Neurol*. 2015;263:1-7. PMID: 25218309
Research interests

Over the past 20 years my team have collected one of the world’s largest biobanks of DNA samples, lymphoblast cell lines and post mortem tissues from patients with amyotrophic lateral sclerosis (ALS).

Following the discovery by Neumann et al. (2006) that TDP-43 was the dominant ubiquitinated protein within inclusions in ALS and non-tau FTD my lab were the first to identify mutations in familial and sporadic ALS and demonstrate their neurotoxicity (Sreedharan 2008). We have subsequently identified the proteins that regulate TDP-43 nucleo-cytoplasmic shuttling (Nishimura 2010), identified the major RNA binding targets, characterised splicing changes following TDP-43 knock-down, FTD-TDP and aging (Tollervey 2011a and b). IPS-derived neurons and glia from TDP-43 mutant patients recapitulate key features of ALS pathology (Bilican 2012, Serio 2013, Barmada 2014, Devlin 2015).

Using genome-wide linkage we identified a novel locus for familial ALS on chromosome 16q (Ruddy 2003) and subsequently identified mutations (FUS) in ~3 per cent of all familial cases (Vance 2009). We were the first to demonstrate that FUS mutations disrupt the nuclear localising signal leading to cytoplasmic aggregates. We subsequently generated a transgenic mouse model with FUS overexpression leading to an ALS phenotype (Mitchell 2013).

We were the first to demonstrate linkage to chromosome 9p in a Dutch ALS and FTD kindred (Vance 2006). An expanded hexanucleotide repeat was subsequently shown by two groups deJesus-Hernandez (2013) and Renton (2013) to be the most common mutation for ALS and FTD-TDP. Subsequently we demonstrated the hallmark cerebellar pathology (Al-Sarraj 2011) and that specific RNA binding proteins are sequestered in RNA foci.

Our exome sequencing effort in familial ALS is on going with a recent discovery of mutations in TUBA4A (Smith 2014) and several other unpublished candidates undergoing functional studies.

Publications

Dr Katherine Sleeman

Research interests
I am interested in palliative and end of life care for people with dementia, in the use of routinely collected clinical and administrative data in research, and in evidence-based policy making. From 2010–16 I held an NIHR Clinical Lectureship in palliative medicine, based at the Cicely Saunders Institute, KCL, working with Professor Irene Higginson. This work investigated place of death for people with neurological conditions and dementia, the use of routinely collected data to understand and improve end of life care, and outcome measures in advanced neurological conditions.

In March 2016 I took up an NIHR Clinician Scientist Fellowship to explore transitions between care settings (for example from care home into hospital) for people with dementia in their last months of life. Health care transitions have been suggested as a marker of poor quality of end of life care, but we know very little about the frequency with which people with dementia make transitions between care settings towards the end of life, or the factors that might help us prevent some of these. I am working with the NIHR Maudsley Biomedical Research Centre (BRC) Clinical Record Interactive Search (CRIS) database to investigate this question. The aim is to build a model of the individual, disease-related, and environmental factors associated with hospital transitions near the end of life. This data will then be used to influence policy and practice through National and Local partnerships.

Publications
Dr Claire Steves

Research interests
I am a Senior (Clinical) Lecturer at King’s College London and Locum Consultant Geriatrician at King’s College Hospital. I graduated first class from Cambridge University in 1997, and went on to pursue clinical studies in the heart of the East End of London, graduating with multiple distinctions in 2000. I trained in the prestigious St Thomas’s medical rotation before specializing in Geriatric Medicine. In 2009 I undertook a Wellcome Trust Clinical Research Training Fellowship, gaining a PhD in Epidemiology from King’s College London in the process. I took up my current post with the Department of Twin Research in 2014 and currently lead a team investigating frailty in this ageing cohort, including supervising PhD and MSc students. I remain clinically active specialising in the management of acute delirium in hospital settings and dementia in medically complex patients.

Research interests include using omics technology to investigating the development of frailty syndromes, including cognitive ageing and cognitive impairment, using twins to adjust for genetic confounding. At present I am focusing on the role of the gut, salivary and urinary microbiome in modulating the systemic inflammatory response which contributes to frailty, including impact on risk of delirium and cognitive decline.

Publications
Research interests

Most of my current activity focuses on the secondary use of routine healthcare data for research, through my leadership of the CRIS data resource. This has involved research across all age groups but has been particularly productive in dementia and late-life mental health, as well as in the impact of mental disorders on physical health which has been a longstanding interest. I began my research career investigating the inter-relationship between vascular risk factors and cognitive impairment/life affective disorder, and this has continued through analyses of a range of informative cohorts and in recent research on the potential impact on national dementia prevalence in populations at high vascular risk.

CRIS is an internationally unrivalled data resource in its size and in the depth of information now available on people receiving assessments and treatment for dementia and other mental disorders in routine clinical practice. Most of the cohorts we analyse have five thousand or more cases. As well as a range of external data linkages (eg with mortality and hospitalisation data), we have now developed a unique suite of natural language processing applications identifying over 70 individual affective and psychotic symptoms, as well as physical symptoms and conditions, interventions received and outcomes experienced.

In addition, I am Academic Lead for the Mental Health of Older Adults and Dementia CAG (Clinical Academic Group) at the South London and Maudsley NHS Trust and King’s Health Partners. As such, I am responsible for promoting research into dementia and late-life mental health in the Trust, developing research training and other infrastructures, and ensuring effective dissemination of the studies we support. I have particular interests in informatics as a tool for improving clinical practice and the patient experience.

Publications


Professor Rob Stewart
Professor Guy Tear

Research interests

Drosophila provides a model system to identify the normal and pathological roles of proteins associated with neurodegenerative disease. We are using the benefits of Drosophila to increase our understanding of gene products associated with Alzheimer’s and Batten disease.

Our Alzheimer’s work has focused on the critical role played by Tau hyperphosphorylation in Alzheimer’s disease pathology where it has become clear that a small number of kinases are responsible for the majority of the phosphorylation sites on tau in AD brain. We have established Drosophila as a whole animal assay to investigate which of these are responsible for the generation of toxic forms of tau in vivo. This makes use of humanised Drosophila that express human tau and specific identified human kinases to create an AD-like pathology. Using this system we are beginning to discriminate the specific involvement of the different kinases alone or together in the creation of toxic forms of tau.

Batten disease, also known as neuronal ceroid lipofuscinoses (NCLs), describes a group of at least nine fatal monogenetic neurodegenerative disorders that primarily affect infants and children. The genes mutated in several forms of the disorder have been identified recently, but very little is known about the precise roles of these gene products in normal neuronal tissue and how their mutation contributes to the disease. We have begun to combat this by investigating the role of the transmembrane proteins Cln7 and Cln3, which are affected in the most common forms of NCL. We have identified that the Drosophila Cln3 shares many properties with the vertebrate form, it is localised to the endosomal-lysosomal compartment in many cell type and found at the synapse. We are investigating the roles these proteins play in the normal function and development of the neuromuscular junction.

Publications

Dr Claire Troakes

Research interests
During the past 10 years I have undertaken a number of research studies in addition to my role as brain bank coordinator, working with colleagues both in the Basic & Clinical Neuroscience department and within the Clinical Neuropathology department of King’s College Hospital.

I have collaborated closely with Professor Chris Shaw and the MND genetics team at King’s and have been involved in a number of studies investigating the pathology associated with novel gene mutations. I played a vital role in the recognition of the characteristic pathology seen in the newly discovered C9ORF72 mutation ALS and FTLD cases. I have also led on projects investigating the role of Transportin in ALS-FUS cases and the pathology associated with Optineurin mutations.

Additionally, I have collaborated with a number of dementia researchers both at King’s and elsewhere and have co-authored numerous studies on the pathophysiology of a range of neurodegenerative, neurological and psychiatric diseases.

In the last couple of years I have been focusing my research on the association between head injury and neurodegeneration, investigating the pathological responses that occur after traumatic brain and spinal cord injury and how they may contribute to long-term degenerative processes.

Publications
Professor Federico Turkheimer

Research interests
My main interest is in the development of quantitative functional biomarkers using imaging, PET and MRI in particular. I head the Analysis and Pre-clinical Groups at the Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, Denmark Hill. I am an electronic engineer by training, hold a PhD in Nuclear Medicine and have worked in PET and neuroscience for the past 25 years holding appointments at the National Institute of Mental Health (Bethesda, USA), at the University of Cambridge, at the MRC Cyclotron Unit (then Imanet Ltd.) at Hammersmith Hospital. From 2002 to 2012, I was at Imperial College London where I was Reader in Mathematical Neuroscience and Head of the PET Methodology Group at the MRC Clinical Science Centre. My current research work in neurodegenerative conditions includes the methodological work-up of PET imaging of neuroinflammation (that we first demonstrated in dementia, Banati RB et al, Lancet 2001) as part of the Wellcome Consortium on Inflammation in Dementia and Depression. My Group is also developing a novel in-vivo MRI methodology to measure brain mitochondrial reserve and assess its relation to cognitive reserve in ageing (with BBSRC support), novel PET/MRI methods for the accurate quantification of brain myelin dynamics and PET techniques for imaging in-vivo glutamate toxicity (both with MRC support). We are also working on measurements of brain energetic entropy, its relation to oxidative stress and constructing biomarkers of brain biological age.

Publications
Dr Caroline Vance

Research interests
Having been involved in research into the genetics and pathobiology of motor neuron disease (MND) since 2002, I recently set up my own research team within the department that primarily focuses on the RNA-binding protein FUS and its role in neurodegeneration. Having first identified mutations in FUS as a cause of amyotrophic lateral sclerosis (ALS) (Vance et al., 2009), I have focused my research since on how these cause disease. With the subsequent discovery of wild-type FUS as a pathological protein in a subset of fronto-temporal dementia (FTD) patients (Neumann et al., 2009), this work has expanded to understanding both the normal function of the protein and its dysfunction in disease. My particular interests are studying the axonal transport and neuronal and synaptic function of FUS. This is partially done studying different neuronal populations using primary cultures and organotypic slice cultures from an existing transgenic mouse model that overexpresses the wildtype protein (Mitchell et al., 2013). As this model shows an aggressive degenerative phenotype it makes it an excellent one in which to further study the molecular changes occurring before and during disease onset. In addition we are developing novel knock-in zebrafish models to study the protein, its transport and its regulation in neurons at a more physiological expression level. My team also uses stable cells lines to investigate the molecular changes caused by mutations throughout the protein and the effect of these and on these of post-translational modifications.

Publications
Dr Anthony Vernon

Research interests
My research is focused on bridging scales between neuroimaging (macroscale) and cellular or molecular pathology (microscale) using an integrated biomedical imaging approach comprising in vivo Magnetic Resonance Imaging (MRI) clinically comparable technology, and ex vivo autoradiography, optical imaging of intact brain tissue (CLARITY) and standard molecular biology tools.

The main focus of research in my lab is mapping brain structural and functional abnormalities in rodent models of genetic and environmental factors that are associated with increased risk for schizophrenia (SCZ) and autism spectrum disorders (ASD). In particular, we are interested in the effects of prenatal immune activation, which has been linked to both SCZ and ASD, but also accelerated ageing and potentially, dementia. The methods we use are however also readily applicable to rodent models of neurological disorders. For example, I have a track record in applying MR imaging to rodent models of Parkinsonism and currently collaborate with Dr Diane Hanger at the Institute of Psychiatry, Psychology & Neuroscience in the MRI phenotyping of a novel mouse model of tauopathy.

Our long-term vision is to use this powerful systems-level approach increase our mechanistic understanding of these devastating disorders and provide validated cross-species biomarkers for testing novel therapeutic interventions.

My laboratory also has an enduring interest in psychopharmacology and we utilise the above systems-level approach to dissect the effects of drugs, both therapeutic (antipsychotics, levodopa) and illicit (ketamine, cannabinoids) on rodent brain structure and function, particularly when administered during vulnerable windows of brain development either in utero or during adolescence. The goal of this work is to increase our understanding of both the therapeutic and adverse effects of these compounds and provide mechanistic explanations for the links between illicit drug use in adolescence and increased risk for psychiatric disorders in adulthood.

Publications
Research interests

Historically, my research has focused on the application of brain imaging to enhance our understanding of CNS disorders. This includes the development of image collection and analysis strategies for improved diagnosis of dementia, earlier discrimination between parkinsonian syndromes, visualisation of corticospinal tract damage in motor neuron disease, robust neuroimaging measures of chronic pain and novel methods of mapping myelin loss in both brain and spine in multiple sclerosis.

My group’s current research interests include the use of artificial intelligence (eg machine learning of brain scans) to classify different patient cohorts, predict response to treatment and inform clinical management. Our lofty ambition is to make semi-automated neuroimaging a core clinical procedure in both precision psychiatry and neurology during the next 5 years. During this time my team will also continue to develop and appraise novel neuroimaging biomarkers of inflammation, plasticity, neurogenesis and metabolism in model systems for future clinical assessment.

My previous exposure to the pharmaceutical sector and translational research efforts in pre-clinical methods routinely leads me and my group to address experimental medicine questions regarding proof of target engagement, optimal dosing, pharmacodynamic profiling and potential indications for new chemical entities. This has resulted in significant pharmaceutical company collaboration (eg Roche, Lilly, Takeda, Bionomics and Janssen), close links with CROs (eg Quintiles and HMR) and regular engagement with the wider scientific community to roll out our expertise and best practice to numerous clinical and academic network partners (eg MRCAIMS, IMAGEN, BENEMIN, EUAIMS, MATRICS and TACTICS). With the establishment of robust, quantitative neuroimaging measures across studies and centres, we are now reaching a critical mass of data to better interrogate the impact of genetics on brain structure and function throughout life.

Publications

Campuses overview

Dementia & Neurodegeneration research at King’s takes place at Denmark Hill, Guy’s, St Thomas’ and Waterloo campuses.
Denmark Hill Campus (West)
Guy’s Campus
Waterloo Campus
Contact

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