Institute of Psychiatry, Psychology & Neuroscience

Division of Neuroscience
Research Strategy
2015–2020
Foreword

In September 2014, Neuroscience at King’s College London embarked on an ambitious new journey.

Over several previous decades, the relatively new field of neuroscience had spontaneously and rapidly emerged in several different areas of the university, resulting in considerable excellence and impact – but also fragmentation and lack of cohesion. At the beginning of the 2014-15 academic year, the four major neuroscience Departments were gathered into a single new Division of Neuroscience. At the same time, the world-renowned Institute of Psychiatry at King’s College London was expanded and renamed, to become the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) – comprising three Divisions: the Division of Academic Psychiatry, the Division of Psychology and System Sciences, and the Division of Neuroscience.

The Division of Neuroscience consists of 106 faculty-level research team leaders (Lecturer to Professor) distributed across four Departments, two on the Denmark Hill campus (the Department of Basic and Clinical Neuroscience; and the Department of Neuroimaging) and two on the Guy’s campus (the MRC Centre for Developmental Neurobiology; and the Wolfson Centre for Age-Related Diseases).

In the 2014 Research Excellence Framework (REF) – the nationwide review and benchmarking of university research performance in the UK – neuroscience was included in a larger category of psychiatry, psychology and neuroscience (known as Unit of Assessment 4, UoA4). King’s College London performed exceptionally well in UoA4, achieving greater research power in this area than Oxford or Cambridge, and higher overall quality in this area than UCL.

The Division of Neuroscience has enviable resources and infrastructure. We are housed in state-of-the-art facilities, including New Hunts House and the Wolfson Wing on the Guy’s Campus, and the Centre for Neuroimaging Sciences and the Maurice Wohl Clinical Neuroscience Institute on the Denmark Hill Campus. We were honoured to host a visit from HRH The Princess Royal, in June 2015, to officially open the Maurice Wohl Clinical Neurosciences Institute, a purpose-built 6500m² laboratory building – which will be exceptionally equipped through a £10 million grant from the UK Research Partnership Infrastructure Fund. The staff of the Division of Neuroscience have consistently been awarded more than £19 million annually in new research grants as lead applicant, and currently hold active research grants as lead or co-applicant worth in total more than £200 million. Clinical translational research is enhanced by a neuroscience-focussed NIHR Wellcome Trust King’s Clinical Research Facility, by an NIHR Biomedical Research Centre (which includes a substantial component of clinical neuroscience), and by an NIHR Biomedical Research Unit in Dementia.

This document sets out a brief portrait of the Division of Neuroscience at the end of its first year, and our aims and ambitions for the future.

1 www.timeshighereducation.co.uk/sites/default/files/Attachments/2014/12/17/g/o/l/sub-14-01.pdf
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Our vision

Our vision is to undertake world-leading research in neuroscience, spanning from molecules to mind, which will provide vital new knowledge and bring significant impact to people with conditions and diseases affecting the brain. We aim to provide the highest-quality neuroscience education and train the best of the next generation of neuroscience research and clinical leaders.

We have several particular strengths and unique qualities which will help us achieve our vision:

- Our neuroscience activity is based in a world-leading psychiatry and psychology environment, with extensive collaborations between these areas.

- We have excellent research activity related to the entire lifespan, from earliest embryonic development to late life neurodegeneration.

- Through King’s Health Partners, we have immediate access to very large and well-characterised patient populations in all areas of neurological and psychiatric disease, and access to very large collections of patient samples (such as DNA, living cell lines, and post-mortem brains).

- We especially aim to achieve major translational impact in common diseases of the brain and peripheral nervous system with substantial societal burden – such as dementia, neurodegeneration, stroke, traumatic brain and spinal cord injury, epilepsy, headache, neuropathic pain, autism and schizophrenia.

- Extremely close collaboration between basic scientists, clinical scientists, and clinical staff working in our hospitals provides an exceptionally clear line of sight between basic science and benefit for people with conditions and diseases affecting the nervous system.

- Our excellence in neuroscience research is reflected in excellence in neuroscience education, so that discoveries made in a King’s laboratory today are taught in a King’s classroom tomorrow.
The MRC Centre for Developmental Neurobiology

The mission of the MRC Centre for Developmental Neurobiology is to decipher how neural circuits assemble during development, from neural patterning to synapse formation and plasticity, and how disruption of this process leads to disease. Our research is organised around three main programmes: (i) Making a CNS from Models to Human; (ii) Assembly and Plasticity of Neural Circuits; and (iii) Neurodevelopmental Disorders.

Over the next four years, we aim to increase the productivity and impact of our research, develop new collaborations in translational neuroscience, and promote our international standing. Our goals include leading a bid for a new MRC Centre, attracting additional core funding for the Centre, and implementing a new four-year PhD programme.
Department of Basic and Clinical Neuroscience

The Department of Basic and Clinical Neuroscience has a greater diversity in terms of topics, methodologies and technologies than most other departments. Its mission is to change the therapeutic options for people affected by neurological and psychiatric disorders. Approximately a third of the research team leaders in the department are clinically qualified and clinically active.

Our vision is for clinicians and scientists to work together to gain a better understanding of disease aetiology, mechanisms and opportunities to test novel therapeutic interventions and evaluate the outcomes. Our main themes are: Neurodegeneration; Neurological Disorders; and the Cellular Basis of Behaviour. We utilise techniques from genetics and molecular biology, experimental models, experimental studies in human subjects, clinical trials, and health services research. Our work makes extensive use of human samples and observations – including studies of human genetics, experimental models incorporating human genetic defects, induced pluripotent stem cells from people with brain disorders, a wide array of human neuroimaging techniques, and behavioural studies.

Department of Neuroimaging

The Department of Neuroimaging is an interdisciplinary environment focused on the research and development of imaging methods to improve our understanding of brain disorders. This is achieved using a range of neuroimaging techniques which include perfusion, diffusion, functional, molecular and structural imaging.

Our current research projects span neurodegeneration, epilepsy, stroke, pain, psychosis, affective disorders, developmental disorders such as autism as well as studies of normal brain function. Basic scientific research is also performed in models of neurological and psychiatric disease, again using a diverse array of neuroimaging techniques, including pharmacological MRI and spectroscopy techniques. In conjunction with non-MR methods such as microscopy.
and autoradiography, this multifaceted approach enhances our understanding of the pathophysiological mechanisms underlying disease and informs the development of novel therapeutic interventions. Our longer-term objective is to translate these validated biomarkers to the clinic in order to improve diagnosis and treatment.

**Wolfson Centre for Age-Related Diseases**

The vision of the Wolfson Centre for Age-Related Diseases is to develop strategies aimed at restoring function to the ageing or damaged nervous system. To achieve this we need to understand how the normal adult nervous system functions, how it responds to stress and injury, and why repair mechanisms often fail.

We aim to understand nervous system dysfunction in disorders which result in cognitive impairments, loss of motor function, hearing loss and pain, with a large number of pre-clinical models used to evaluate therapeutic interventions in pain, Alzheimer’s and Parkinson’s disease, spinal cord injury and stroke. We have also recently established a drug discovery unit to help translate our efforts in these areas. The Centre is organised into five research areas:

(i) **Neurobiology and Pharmacology of Pain**;
(ii) **The Genetics of Age Related Hearing Loss**;
(iii) **Neurodegeneration and ageing**;
(iv) **Neural Regeneration and Adult Neurogenesis**;
(v) **Drug Discovery Unit**.
3.1 Enhancing impact through collaboration

In the next five years, we will greatly increase our collaboration with King’s Health Partners and the NIHR Biomedical Research Centres and Units. Direct access to large, well-characterised clinical populations and expert clinician-scientist colleagues will bring us every opportunity to successfully translate our research findings to clinical benefit.

King’s College London is a partner in the Francis Crick Institute. We anticipate vigorous collaboration, both through directly linking our scientists into the Francis Crick Institute, and through acting as a translational partner for Crick outputs. In particular we anticipate extending our current joint PhD programme, and putting some of our scientists directly into the Francis Crick Institute through secondments, satellite laboratories and sabbaticals.

We already have extensive collaboration with industry, but recognise the opportunity to extend beyond our current interactions to deepen scientific collaboration, exploiting the mutual expertise and advantages of an academic-industrial partnership. We aim to open up our labs to industry scientists and to work directly with them to achieve faster translational outcomes. We will appoint a researcher with extensive experience of industry collaboration as our Neuroscience Industry Champion.

Although we have many national and international leadership roles in large multicentre collaborations, we seek to enhance our prominence in this area. In particular we aim to capitalise on our extensive collections of patient specimens and data to enhance our value as collaborators.

3.2 Outreach to the public

The impact of science is greatly facilitated if there is a receptive public audience which fully understands the potential benefit of scientific discoveries. This understanding needs to begin at school. We will continue and further enhance our engagement with schools from primary to sixth form. For example, a sixth form Neuroscience conference in 2014 at one Kent secondary school featured a panel of our experts and one of our PhD students discussing all aspects of neuroscience research and careers arising from a neuroscience education. Our neuroscience students and principal investigators have hosted groups of primary school children on our campus as part of Brain Awareness Week, as well as organising interactive neuroscience engagement events.
demonstrations and workshops in primary schools across Lambeth. In addition, every summer our labs host secondary school students for two weeks for work experience as part of the In2Science UK scheme to help students from disadvantaged backgrounds to learn about research science. We also provide Nuffield Foundation Research Placements which enable students studying STEM subjects at school, particularly those who don’t have a family history of going to university, to spend the summer working alongside professional scientists.

Many of our research groups host open days and public meetings to make our work as accessible as possible. Furthermore, we routinely engage with patients and user groups in the design of research questions and research studies, supported by IoPPN’s exceptional track record of patient and public engagement in research. Recently we have initiated informal scientific discussions aimed at our local community, called Café Scientifique, jointly hosted with the Maudsley Charity at their Ortus centre which is open to the public.

Over the next five years, led by a Neuroscience Public Engagement Facilitator, we expect to see our activities in this area substantially increase.

### 3.3 Training future research leaders

There are extensive postgraduate training opportunities in the Division of Neuroscience, with our programmes inspired by and closely linked to our world-class neuroscience research. Particular emphases of our programmes are on cellular, developmental and clinical neuroscience. Students can choose from three MSc programmes in Neuroscience, Clinical Neuroscience or Neuroimaging. Our Neuroscience MSc programme, which consistently achieves exceptional levels of student satisfaction, provides a broad base in fundamental cellular and systems neuroscience but allows specialised options in topics such as Developmental Neuroscience, Nervous system disorders, Neurodegeneration and Tractography. Students taking Clinical Neuroscience benefit from neurological case studies and teaching by
experts in a wide range of neurological disorders. In addition to stand-alone MSc programmes, we also offer an integrated Masters in Neuroscience (MSci) due to commence in October 2015, whose fourth year offers advanced research training and optional modules shared with the MSc Neuroscience.

We offer a large range of four year and three year PhD training opportunities, including a one year MRes in the MRC Centre for Developmental Neurobiology, which can be teamed with a three year research project to provide four years of training. We also offer four year PhD Studentships under the King’s Bioscience Institute PhD Programme, of which Neuroscience is one of the four main themes; these are specifically aimed at translational science, with the student receiving dual supervision from both clinician and basic scientists. PhD training opportunities span all subjects within the Division of Neuroscience, but also allow participation in cross-Divisional and cross-Faculty programmes on topics such as neurodevelopmental disorders, translational neuroscience, computational science and mathematical modelling.

Student projects at both Masters and PhD level are based in the fantastic research facilities of the MRC Centre for Developmental Neurobiology, the Wolfson Centre for Age-Related Diseases, the Department of Neuroimaging and the newly built Maurice Wohl Clinical Neuroscience Institute. Students are fully integrated into our vibrant research culture, with a vast array of seminars, journal clubs, symposia and training opportunities. Given our research excellence across a panoply of topics, there is an unparalleled opportunity at King’s College London for students to explore their interests and develop state-of-the-art, marketable research skills.

At the post-PhD level we actively support the career development of promising post-doctoral researchers, inspiring them to become successful independent scientists and future research leaders. We provide mentorship, grant writing workshops, mock interview panels and schemes such as the King’s College London Prize Fellowship, which enables outstanding post-doctoral basic or clinical scientists to establish independent careers and to apply for competitive external fellowship funding. The Division of Neuroscience hosts numerous externally funded prestigious Fellowships, including MRC, Wellcome Trust, Royal Society and RCUK Career Development Awards and Senior Fellowship Awards. We provide close mentoring and support of these young researchers during their transition from post-doctoral scientist to group leader and strive to retain and support them through their career progression. Many previous Career Development Fellows within our neuroscience grouping have secured senior positions at King’s and have progressed to being leaders in their field.

3.4 Commitment to the Athena-SWAN charter

The Division of Neuroscience, as part of IoPPN, is committed to promoting inclusion and diversity in our workforce. We were delighted to be awarded a silver award from the Equality Challenge Unit’s Athena Scientific Women’s Academic Network (Athena-SWAN) in November 2014. The award recognises IoPPN’s commitment to recruit, retain and advance female academics working in science and that having an inclusive work environment benefits everyone.

In 2015, the Athena SWAN charter expanded to include transgendered and professional services staff and the ECU launched a new Race Equality Charter Mark.
3.5. Examples of the impact of our research

**Driving excellence in stroke care**

Each year, about 150,000 people in the UK have a stroke. Strokes happen when there is a blood clot or a bleed in the brain. At hyper acute units, people receive expert care, including immediate access to a brain scan to aid assessment and clot-busting drugs, if appropriate. Patients may then be transferred to a stroke unit closer to home for continued treatment and rehabilitation.

When our research began in the 1990s, all stroke patients were admitted to general medical wards where our researchers realised that many patients either died or had long-lasting disabilities.

They were involved in establishing a stroke unit staffed by a multi-disciplinary team and set out to investigate whether providing timely care in an organised way, based on assessment and setting goals, worked. Our researchers carried out several trials illustrating both the clinical and cost-effectiveness of stroke units.

They showed that patients cared for on general wards were more likely to die or be institutionalised following a stroke. People cared for on specialist stroke units, however, had fewer complications, were more likely to survive and more likely to return home and regain independence.

This work influenced Government policy leading to the creation of stroke units in hospitals throughout the UK. Now, admission to a specialist stroke unit is recommended in UK national guidelines, and around the world.

In the UK, there has been a steady increase in

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Patient receiving treatment on the Hyper Acute Stroke Unit at King’s College Hospital.

the number of patients receiving specialist care. In 2010, 88 per cent of patients were admitted to a stroke unit during their stay, compared to 46 per cent in 2004; and 56 per cent were admitted to an acute stroke unit within four hours in 2013, compared to 17 per cent in 2008.

*Research led by Professor Lalit Kalra.*

*Our research demonstrated that specialist stroke units help patients survive and recover more quickly – as a result, the services are available across the UK.*
Stem cell therapy to repair stroke damage

About 150,000 people have a stroke every year in the UK. Most are ischemic because the blood supply to the brain is blocked. As a result, billions of brain cells die because they are deprived of oxygen and are no longer able to send signals to other parts of the brain. About half of the people who survive a stroke are left with some sort of disability as a result.

Neural stem cells have the ability to become any of the cells that make up brain tissue. For more than a decade, our scientists have collaborated with the biotech and King’s College London spinout company ReNeuron to develop stem cell therapies to help the brain recover after a stroke. Early research was designed primarily to evaluate the safety of the stem cells and the technique used to implant them in the brain.

Our scientists helped devise the technology to generate neural stem cells that have the potential to be used for therapy. The procedure, called ‘conditional immortalisation’, enables one single neural stem cell to ‘expand’ to yield an infinite number of exact copies. This has allowed ReNeuron’s lab to generate enough CTX0E03 neural stem cells to provide thousands of doses of the therapeutic stem cell line ReN001.

With pivotal funding from the Charles Wolfson Charitable Trust, our researchers were then able demonstrate that rats disabled by a stroke ‘got better’ when CTX0E03 cells were injected into their brains.

These studies were used to support ReNeuron’s application for regulatory approval to test ReN001 in humans. ReN001 has now been tested on 12 stroke victims in the UK’s first ever clinical trial of a therapeutic product containing manufactured neural stem cells.

This therapy proved safe and the patients showed a clear, though modest, improvement in neurological symptoms. We are now moving into a Phase II trial in an attempt to prove efficacy.

*Research led by Professor Jack Price & Dr Mike Modo*

Our stem cell research underpinned the UK’s first ever clinical trial to treat stroke patients with manufactured neural stem cells.
Treating non-motor symptoms of Parkinson’s disease

Practically everyone who has Parkinson’s disease also has debilitating ‘non-motor’ symptoms that often have a greater impact on their quality of life than the movement difficulties caused by Parkinson’s. These include memory loss, sleep problems, mood changes, dribbling, apathy, concentration difficulties, fatigue and constipation.

Most people who have Parkinson’s disease experience at least six non-motor symptoms, but some people can have up to 30.

All non-motor symptoms are treatable but doctors need to be made aware of them. Our research showed that despite this, doctors and nurses across Europe did not discuss non-motor symptoms with their patients, and patients themselves did not mention them, either because they were embarrassed or because they did not think the symptoms were related to the disease.

Our researchers developed and validated NMSQuest (Non-Motor Symptoms Questionnaire), a simple questionnaire now used in clinics around the world to help ensure patients get the treatment they need for non-motor symptoms caused by Parkinson’s disease.

Patients can download the questionnaire from the Parkinson’s UK and International Parkinson’s and Movement Disorders Society websites. They simply fill it out and give it to their GP or specialist. NMSQuest is now recommended along with use of Parkinson’s Disease Sleep Scales (PDSS) by NICE as well as in the NHS Best Practice Tariff criteria for management of Parkinson’s.

Our researchers also led the development and validation of two scales that are regularly used in research studies to measure the effect of new treatments on non-motor symptoms. The Non-Motor Symptom Scale (NMSS) is now used in the majority of clinical trials of new drugs for Parkinson’s, and the PDSS and the updated PDSS-2 have been used in trials to measure the impact of medication on sleep disturbances.

Research led by Professor K Ray Chaudhuri

Our researchers developed questionnaires that are now used by doctors to help ensure patients with Parkinson’s get treatment for debilitating non-motor symptoms.
Genetic testing for motor neurone disease

Every day, almost 400 people around the world are diagnosed with amyotrophic lateral sclerosis (ALS), the most common form of motor neurone disease. Our researchers have identified genes that, when mutated, cause some types of this progressive and fatal condition.

Our researchers identified ALS-causing FUS and TARDBP genes, discovered mutations on SOD1 – and were the first to identify the location of C9orf72. Diagnostic tests are now available in laboratories around the world that can reveal whether someone carries a mutated version of the gene and therefore has an increased risk of developing ALS. They can also confirm diagnosis and inform treatment plans.

Our researchers have worked with Guy’s and St Thomas’ NHS Foundation Trust to develop ‘pre-implantation genetic diagnosis’ (PGD) for ALS caused by a mutation on the SOD1 gene. This allows people who carry a mutated gene the opportunity to avoid passing it on to their children.

The technique involves genetic testing of an embryo created through in-vitro fertilisation: only embryos free from the genetic mutation are implanted in the womb. It was successfully used for the first time in the UK at Guy’s Hospital in 2013 when a baby boy was born free of the mutated gene that his mother carries.

Discovering the genetic causes of inherited ALS can also help researchers understand more about the molecular mechanisms of the disease. Our research has shown, for example, that the proteins encoded by a mutated version of the FUS and TDP-43 genes are toxic to motor neurones. Identifying genetic mutations, and understanding the mechanisms, and how the disease develops, at a molecular level will ultimately enable the development of new and effective therapies.

Research led by Professors Chris Shaw, Ammar Al-Chalabi, Corrine Houart, Sarah Guthrie, Chris Miller & Drs Safa Al-Sarraj, Jean-Marc Gallo & Frank Hirth

Our researchers developed diagnostic tests that led to the first child being born free of the genetic mutation which causes motor neurone disease.

In ALS/MND motor neurones, like the one in the image, degenerate causing the muscles they control to weaken and waste away.
4.1. The developing brain: mechanisms and disorders

Understanding how the human brain develops is one of the great frontiers of discovery science. During normal human brain development, billions of neurons emerge and wire together correctly to form trillions of synapses. Studying this process is immensely challenging not only because of the complexity of the system but also because of the vast range of spatial and temporal scales needed to understand the process. However, the discovery of overarching rules behind the wiring of the brain, common to different neurons within and across species, have simplified the problem and given hope that the task at hand can be accomplished.

Our overall aim is to be able to understand how human brain circuits are formed and, to this end, a wide range of \textit{in vitro} and \textit{in vivo} approaches will be taken. The main challenge will be to approximate the diversity, connectivity and order of neurons and synapses normally found in the intact human brain. This approach will require us to solve substantial technical hurdles, but the insights into human brain development have the potential to be ground-breaking.

Neurodevelopmental disorders comprise a broad spectrum of neurological and psychiatric diseases including conditions as diverse as epilepsy, autism and schizophrenia. These disorders have broad sets of causes, but also overlapping phenotypes and genetics, which is suggestive of common deficits. Our current knowledge of these disorders is insufficient to inform drug development, and so we must gain insights into their biological basis to help design new therapies. For the first time, technological advances in genomics are beginning to shed light on the genetic and molecular bases of the most prevalent and severe developmental brain disorders. The identification of true susceptibility genes for autism and schizophrenia offers the opportunity to elucidate their biological underpinnings and, following the example of cancer and cardiovascular research, translate
these advances into rational therapies and individualised medicine. The main complexity, however, lies in the realisation that brain function emerges through specific neural circuits that we are only now beginning to understand. Addressing developmental brain disorders will therefore require the close integration of advances in neurology and psychiatry with fundamental neuroscience.

**Our strengths:**

- A substantial cohort of scientists focussed on brain development with established international excellence.
- Very close collaborative relationships with renowned clinical scientists working on developmental brain disorders in large patient populations, in the Division of Neuroscience, other Divisions in IoPPN, and in other areas of KCL.
- Genome editing, using TALE nuclease and CRISPR/Cas9 technology to generate targeted knock-out and knock-in mutants in zebrafish, mice, and human embryonic and induced pluripotent stem cells; developing TALEN-induced homologous recombination in vivo.
- Genetically-encoded activity reporters and modulators of neuronal/synaptic activity such as optogenetics.
- A wide range of experimental imaging technologies, from molecular and cellular imaging to whole-brain imaging, using calcium reporter systems and light-sheet microscopy.
- A wide range of human imaging techniques, including MRI, fMRI, DTI, EEG, PET, simultaneous EEG-MRI and simultaneous PET-MRI.

**Our goals:**

- Using primary neurons, neurons derived from stem cells, and ex-vivo slices, combined with technologies such as optogenetics, to define the core rules of how synaptic connections are formed and modulated in activity-dependent forms of plasticity.
- Experiments in more intact systems, such as imaging of these probes in fly, zebrafish and rodents will provide the link to the next step up in spatial resolution and allow for longer-term, repeated interrogation of circuits.
- Imaging of neuronal activity across an entire zebrafish brain using light sheet microscopy will reveal functional connectivity of circuits across different nuclei and inform the anatomy in ways that were previously unachievable.
- Human iPSCs will be used to derive human neurons, which will then be combined with glia and patterned such that they form structured neural networks, to create 2D and 3D functional networks of human neurons.
- At the other end of the spatial spectrum, we will draw a broad map of structural and functional brain connectivity, using fMRI, structural MRI, and DTI, to provide blueprints of the large-scale arrangement of neurons and axonal tracts in rodents and humans, from embryos through to adolescence.
- Creation of a Centre for Neurodevelopmental Disorders, which will bring together basic and clinical neuroscientists across different divisions of King’s College London, with the mission to advance our understanding of the pathophysiological mechanisms that cause conditions such as epilepsy, autism and schizophrenia and translate our understanding into clinical advances that change the lives of affected individuals.
4.2. Sensory systems: mechanisms and dysfunction

Human interaction with the environment is mediated through sensory systems. Their dysfunction, for example in chronic pain or deafness, leads to significant impairment, disability and suffering. Our work studies special senses and somatosensation, spanning from the development of these systems, the neurobiology of mature systems in both health and disease, to efforts to develop novel therapies to treat sensory disorders such as deafness and neuropathic pain. Experimental systems include model organisms such as fly, zebrafish and particularly mouse; and there is also considerable focus on studying humans in the context of both experimental medicine in healthy volunteers and clinical disease states. Our greatest concentration of effort relates to the study of pain, in which area King’s is internationally leading. Chronic pain is a debilitating disorder that affects millions of people world-wide and has a considerable detrimental impact on quality of life. Effective analgesic therapies are inadequate in the majority of chronic pain patients and are often associated with unpleasant side-effects. Consequently at present there is a substantial, unmet, clinical need for more effective analgesics for chronic pain.

We aim to elucidate the entire chain of processes from the molecular and cellular basis of detection of sensations, through to sensory perception at the level of the whole animal. We are studying the mechanisms of sensory transduction and signalling in neuronal and non-neuronal cells, especially how heat, cold and pain are detected in sensory neurons and how processes at the molecular level impact on pain and thermal sensation at the level of the whole animal. We are studying transduction molecules such as Transient Receptor Potential (TRP) ion channels that convert chemical and physical information into electrical and ionic signals. We are also investigating cannabinoid receptors and ligands, an important pathway for regulating pain responses. We study the role of chemokines in mediating neuron-glia communication, evaluating the contribution of neuronal chemokines and microglial receptors to persistent pain and neuronal survival.

Our work in pain includes studying the plasticity of the first pain synapse in the dorsal horn of the spinal cord. We study neuronal and immune cell-mediated mechanisms regulating the strength of sensory neuron-dorsal horn neuron synapse in the spinal cord to reveal new targets for chronic pain treatment. Our research also focuses on chemotherapy-induced painful peripheral neuropathies and persistent postoperative pain. Our drug discovery programmes aim to find blockers of ion channels important in pain.

King’s has an internationally-leading programme in the genetics of deafness, using the mouse as a model to identify the genes involved and to understand the molecular, cellular and physiological mechanisms.

Our strengths:

- A group of outstanding and well-funded groups collaborating on research into sensory systems, with a particular focus on pain and...
hearing. We have particular interests in the pathogenesis of neuropathic pain, in the mechanisms of thermal sensation, and in the genetic basis of age-related progressive hearing loss.

- Excellent infrastructure and equipment including facilities for state-of-the-art microscopy, molecular and cell biology, electrophysiology, mouse genetic manipulation, animal behavioural work and quantification of multiple aspects of animal auditory function.
- Broad and detailed understanding of the heterogeneity of pathological mechanisms underlying deafness, with a focus on age-related progressive hearing loss.
- Established collaborations with clinicians working on pathological pain and auditory dysfunction.
- Extensive international networks of collaborators working on pain, tinnitus and deafness in mouse and human.

**Our goals:**

- Develop our understanding of the molecular processes underlying normal pain sensation, thermal sensation and hearing in order to facilitate identification of suitable novel targets for treatment. Build molecular networks underlying normal hearing processes to facilitate identification of suitable targets for treatment.
- Develop validated targets and proof-of-principle for treatment of pathological forms of pain and progressive hearing loss.
- Develop improved diagnostic tools for stratification of different types of pain and auditory pathology so as to facilitate future clinical trials.
- Initiate drug development programmes with the aim of taking our basic research through into clinically useful treatments.
- Extend collaborations with clinical colleagues to enhance synergy between basic science and clinical practice.

### 4.3. Brain and spinal cord injury, regeneration and recovery

Injury to the brain, spinal cord or peripheral nerves, whether from trauma or a disease process such as neurodegeneration, can result in devastating disability. Consequently, repairing a damaged nervous system is one of the great challenges of contemporary neuroscience. Although recovery from nervous system injury is typically incomplete and limited, the nervous system is capable of substantial recovery – however, spontaneous recovery is often blocked by counterproductive tissue responses to injury.

Extrinsic factors include a paucity of positive influences in the environment (e.g. growth factors) and the presence of cavities and inhibitory cues (e.g. myelin inhibitors, proteoglycans). Intrinsically, mammalian CNS neurons downregulate many growth-promoting genes on maturation and consequently extend axons poorly after injury. CNS axon regeneration remains extremely limited in most experimental paradigms and effective restorative therapies remain to be developed. There is a substantial unmet clinical need to discover new therapies to repair injured brain, spinal cord and peripheral nerves.
The dogma for most of the 20th century was that the neurons we are born with need to last us a lifetime as all of the evidence suggested that we cannot make new neurons in the adult brain. However, recent evidence shows that not only do we continue to make new neurons in the brain, but this is important for learning and memory, and may be a key factor in some brain diseases. In the adult brain, neural stem cells make neuroblasts that populate the hippocampus or olfactory bulb with new neurons. Importantly, neuroblasts can also be attracted to injured areas in the brain where they might limit damage and restore function.

Spinal cord injury results in severe disability and there is currently no cure. However, recent advances at King’s have been made in identifying factors that prevent repair after injury and targeting these with novel treatments such as gene therapies, matrix modification and electrical stimulation. For example, our work has led to the development of an enzyme therapy that can digest inhibitory molecules associated with the spinal injury glial scar. This therapy has shown great promise in pre-clinical studies and can promote axon regeneration, neuroplasticity, neuroprotection and, most importantly, recovery of motor function in paralysed limbs.

Stroke is an extremely common cause of brain injury especially in older age. King’s Health Partners is one of the largest providers of stroke clinical services in the UK, with two highly effective Hyperacute Stroke Units and a Hyperacute Stroke Research Centre. Internationally leading work in stroke epidemiology and health services research is carried out in the Division of Health and Social Care Research, with which we collaborate closely. A substantial portfolio of academic-led and commercial clinical trials is carried out in the NHS clinical services. We are pursuing innovative studies using imaging and cognitive testing to identify factors which increase vulnerabilities to poor outcomes after stroke. We also make use of brains generously donated postmortem to our brain bank, to investigate the neuronal and synaptic plasticity underpinning preserved cognition after stroke. At the other end of the translational spectrum we have identified novel methods for improving sensorimotor function in experimental models of stroke.

On-going collaborations with Spinal Injury Units and Rehabilitation Centres working with stroke and spinal injured patients mean we are well positioned to be at the forefront of translating pre-clinical advances into therapies which could have a major impact on quality of life for patients, such as recovery of arm and hand function.

**Our strengths:**

- A highly collaborative grouping of scientists at the forefront of regenerative medicine, with a particular focus on understanding mechanisms underlying regeneration failure and identifying novel targets and strategies for restoring function to the damaged nervous system.
- Close collaboration with clinician-scientists and clinical services in stroke, brain injury and spinal cord injury; King’s Health Partners includes extensive clinical services in stroke and brain injury.
- Advanced imaging technology in patients to improve understanding of the natural recovery of memory and speech after stroke.
- Pioneering early human trials of stem cells to boost stroke recovery.
- Pioneering matrix modification strategies as therapeutic targets for spinal cord injury.
- Clinically relevant experimental models of stroke and traumatic brain and spinal cord injury.
- Systems wide approaches to map gene and protein changes involved in inflammation and...
tissue pathology after neurotrauma, leading to novel biomarkers and targets.

- Drug discovery unit for developing novel therapeutics.

**Our goals:**

- In experimental systems, determine the mechanisms underlying neuronal injury, regeneration and recovery, to facilitate developing optimised and targeted therapies.
- Develop an in-depth knowledge of the factors that regulate the generation of neuroblasts, their migration, and their decline in older age.
- Combine mechanistic studies with our expertise in reconstructing, through advanced imaging, the wiring of the brain and spinal cord.
- In experimental systems, elucidate the strategies to optimise the function of surviving systems to promote repair, since spontaneous functional recovery is known to occur in the majority of spinal injured and stroke patients.
- Elucidate the processes promoting plasticity and thus inducing compensatory changes in undamaged pathways and reorganisation of circuits as a strategy for future therapeutic intervention.
- Combine neuroplasticity promoting treatments with repetitive electrical stimulation and physical rehabilitation to maximise the potential for restoring directed and meaningful function.
- Identify novel targets and biomarkers for traumatic brain and spinal cord injury.
- Validate novel targets in human tissue samples and human cell lines and initiate drug development programmes with the aim of taking our basic research through into clinically useful treatments.
- Bring candidate therapies into first-in-man experimental studies.

**4.4. Neurodegeneration and dementia**

Neurodegenerative disorders are common and disabling yet no treatments alter disease progression. They exert an immense financial and social cost that will only increase with an ageing population. The number of people with dementia in the UK will reach more than 1 million by 2020, and cost approximately £25 billion per year. Yet research capacity is limited: for every UK researcher working on dementia, six work on cancer.

Despite the lack of treatments that alter disease progression, the current century has seen remarkable advances in our understanding of neurodegeneration. There are many emerging disease mechanisms that are gaining prominence following the identification of new disease-causing genes and informative disease models (e.g. templating, protein and vesicular trafficking, inflammation, ER-stress, autophagy, mitochondria, RNA processing and glial interaction). Our characterisation of disease mechanisms and development of assays for drug discovery has become increasingly sophisticated, including high-content imaging of tagged proteins in living cells in longitudinal studies. Advanced microscopy means that subcellular organelle structure and dynamic function can readily be visualised using advanced multiphoton microscopy.

We, and others, have demonstrated that patient-derived induced Pluripotent Stem Cells (iPSCs) can recapitulate key features of human neurodegenerative diseases. This has facilitated an exploration of disease mechanisms in a more physiological setting than transfected cell and transgenic animal models. Furthermore, new genome-editing tools allow us to correct pathological gene mutations, and rapidly
generate multiple isogenic lines in the absence of patient material. These tools allow us to map out factors that influence protein aggregation and cell death to identify potentially drugable targets. These findings will enhance our genomic, transcriptomic and proteomic research and allow us to fully exploit our exceptional patient tissue resources, (DNA, blood, CSF, fibroblasts, lymphoblasts). Genome editing will allow us to generate more informative animal models (Drosophila, zebrafish, mouse) using inducible/repressible gene expression tools and gene knock in strategies (e.g. TALEN, CRISPR/Cas9) to follow the sequence of events and evaluate the effects of therapeutic interventions.

Understanding neurodegeneration is key to developing and taking forward new treatments for Alzheimer’s disease, Parkinson’s disease, motor neuron disease and stroke. Central to our approach is translating basic science into improved clinical treatment. Key elements of our clinical work include a substantial focus on biomarkers and clinical trials. Major clinical trials have addressed psychiatric and behavioural symptoms associated with dementia and the use of antipsychotic and sedative drugs. King’s is internationally-leading in studies of non-motor symptoms of Parkinson’s disease and their treatment, and has an extensive portfolio of imaging studies (MRI, PET) in movement disorder, neurodegeneration and dementia. Our vision for neurodegeneration research is to build a continuous pipeline of ground-breaking molecular, cellular and human research that will advance our knowledge of disease mechanisms, reveal new avenues for therapy, and test innovative therapeutics.

**Our strengths:**

- The Maurice Wohl Clinical Neuroscience Institute, opened in June 2015, will be an international hub for neurodegeneration research, bringing together basic scientists and clinical researchers in a state-of-the-art 6500m2 laboratory building. Equipped with the help of a £10m UKRPIF grant awarded in 2015, equipment will include substantial tissue culture capacity and advanced microscopy.

- Working very closely with the clinical services of King’s Health Partners, we have access to some of the world’s largest and best characterised cohorts of patients with neurodegenerative disorders.

- We have large collections of DNA, tissue samples and post-mortem brains from patients with neurodegenerative disorders.
Highly developed expertise in induced pluripotent stem cells, animal models and genome editing.

**Our goals:**

- We intend to expand and strengthen our portfolio of research themes attracting Pharmaceutical and Biotechnology partners seeking our help to develop robust cellular assays for target identification, high-throughput compound screening, hit validation and de-convoluting therapeutic mechanisms. We will extend a range of informative animal models (fly, fish and mouse) to explore disease pathways in vivo and test potential therapeutics.

- Our microscopy centre and small animal 9.4T MRI scanner will generate many new insights allowing us to prioritise target selection and advance drug discovery.

- We will push further our studies to analyses of single molecular interactions using super resolution microscopy.

- Successful cellular assay and drug discovery programmes are well established and increased exchange of expertise in our new structure will advance our productivity and enhance the interactions with industry.

- We will develop in-vivo biomarker reporters to monitor disease activity longitudinally in transgenic animals, requiring whole animal imaging systems (MRI, bioluminescence).

- Mapping of temporal changes in the transcriptome will reveal the earliest changes that lead to cellular dysfunction and unveil endogenous neuro-protective strategies that cells and tissues employ to ameliorate degenerative processes. We have a well-established method of conducting meta-analyses of transcriptomic arrays across different cell types and species. We predict that large-scale transcriptomics studies will lead to identification of pathogenic disease signatures and of new candidate therapeutic targets.

**4.5. Drug discovery and drug repositioning**

The Division of Neuroscience has a dynamic and varied drug discovery programme, with the aim of accelerating translation of basic science discoveries to therapeutic options for people affected by neurodegenerative, neurological and psychiatric disorders. Moreover, it has the unique feature of coupling drug discovery to human brain imaging of drug action.

Two major strengths provide us a unique opportunity to pursue drug discovery: our research expertise encompasses a wide range of disorders that are in desperate need of novel therapies; and we have the capacity and the infrastructure to span the entire spectrum of drug discovery, from identifying promising targets with basic science research through to developing and testing lead compounds — ultimately taking a drug all the way from the bench into the clinic.

A prime example of our success in this area is the Neuroscience Drug Discovery Unit, founded in 2008 and supported by large drug discovery awards from the Wellcome Trust. Basic discovery science in the Division of Neuroscience, using patient samples of neurodegenerative disease, showed that retinoid-dependent pathways required for embryonic neuronal survival were deficient in Alzheimer’s disease patients. Based on these findings, work carried out by the Neuroscience Drug Discovery Unit identified novel optimised retinoids and now has two lead compounds for neurodegenerative disease. This research is currently commercialised via venture capital funding from Advent Ventures and the founding of CoCo therapeutics by King’s and the Wellcome Trust.
Our strengths:

- We are experienced in carrying out Phase I (first in man) and Phase IIA trials. This allows the investigators, from basic scientists to clinicians running the trials, to fully interact in the process of driving the drug into the clinic.

- The NIHR Wellcome Trust King’s Clinical Research Facility (CRF) provides a unique and remarkable infrastructure dedicated primarily to experimental medicine studies in neuroscience and mental health. It includes 3T MRI, shielded EEG rooms, TMS, virtual reality suite, multiple interview rooms, sampling and treatment rooms, and inpatient beds including ICU-level beds with MRI-compatible equipment.

- Established expertise of the Neuroscience Drug Discovery Unit.

- Funding partners for our drug discovery and development programs include the Wellcome Trust, Lundbeck, Novo Nordisk A/S, AstraZeneca, Ossianix, Auris Medical, Lilly and Takeda.

Our goals:

- We anticipate that this drug discovery research pipeline, combined with the world leading research and expertise of the Neuroscience Division of the IoPPN, will lead to the identification of many drug targets, and the development of novel therapeutics for a range of debilitating disorders that are studied in the Division of Neuroscience, including neurodegenerative diseases (Alzheimer’s and Parkinson’s diseases, Huntington’s, Myopathies, Fronto-Temporal Dementia, amyotrophic lateral sclerosis), neurological disorders (stroke, multiple sclerosis), traumatic injuries (spinal cord injury, traumatic brain injuries), rare genetic disorders (lysosomal storage disorders), chronic pain (neuropathic pain, chemotherapy-induced pain, headaches).

- We will also work with industry and utilise innovative funding mechanisms from the NIHR, EU and the MRC to engage in brain imaging studies to test the role of specific pathways in drug-induced changes of cognitive function in the context of normal brain and brains of patients affected by mental disorders.

- Principled discovery analyses will exploit our neuroimaging data to identify new potential in a wide range of drugs with pre-selected and unknown mechanisms. These newer analyses, based on multivariate statistics will allow comparison with existing compounds and prediction of response which will inform future treatments.

- Databasing across multiple drug mechanisms is also a major goal over the coming years. This will result in a better understanding of the differential effects of drug treatments in cognition and clinical symptoms. The role of pharmacological modulation in social cognitive processes represents a pressing need to enhance treatment in neurological and psychiatric disorders.
Our unique context

5.1 Psychiatry and Psychology

The Division of Neuroscience sits alongside extremely high-profile and high-volume work in psychiatry and clinical psychology. This is a central feature of our neuroscience context, which drives and enables specific areas of work at the interfaces between these disciplines. In particular, our emphasis on the basic neurobiology of mental health disorders stems directly from this.

Furthermore, we have an opportunity to further extend existing work on the psychological and mental health consequences of neurological and neurodegenerative disorders (which are extremely important causes of reduced quality of life), and work on psychological therapies.

5.2 King’s Health Partners and Clinical Academic Groups

The university has formed a partnership with three large NHS Foundation Trusts (King’s College Hospital, Guys & St Thomas’s Hospital, South London & Maudsley Hospital) to form King’s Health Partners. Amongst its many ambitions, King’s Health Partners coordinates research strategy and education strategy between the four partners, and leverages the advantages of large patient populations, their samples and their data for translational research; with the ultimate aim of enhancing clinical outcomes.

King’s Health Partners has a distinctive focus on the interface between mental and physical health, which speaks directly to priorities of the Division of Neuroscience. Furthermore, King’s Health Partners intends to develop a set of Institutes in a small set of priority areas, cutting across the four partners; one of these will be an Institute of Neuroscience. Currently, the delivery of King’s Health Partners priorities is devolved to Clinical Academic Groups, which are joint management fora; the Neuroscience Clinical Academic Group is jointly led by the Head of the Division of Neuroscience, and is a close partner of KCL neuroscience strategy. Clinical Academic Groups in mental health disorders also have close partnerships with KCL neuroscience.
5.3 NIHR Maudsley Biomedical Research Centre and Dementia Unit

The National Institute for Health Research (NIHR) has invested substantially in infrastructure and facilitation of translational research, in particular experimental medicine, delivered through the NIHR Maudsley Biomedical Research Centre; this Centre includes all areas of mental health, as well as clinical neuroscience in King’s College Hospital. The Biomedical Research Centre has a particular emphasis on large-scale collection of patient data, including medical records, neuroimaging, and patient samples; and on the related bioinformatics and clinical informatics. Building on this foundation of detailed phenotyping and stratification is a strategy to facilitate experimental medicine studies especially of novel therapies and novel disease biomarkers. Alongside the Biomedical Research Centre, and run in tandem, is the Biomedical Research Unit in Dementia, which takes a similar strategy but focussed on dementia.

5.4 KCL Health Schools

Neuroscience is thriving in a few areas in other parts of the Health Schools, particularly in the Division of Imaging and Bioengineering – especially the Centre for the Developing Brain, and the PET Centre. The Division of Neuroscience has close links with both of these areas and seeks actively to gain the greatest advantage from close collaboration.

5.5 Infrastructure, facilities and resources

We benefit from a wide range of excellent research facilities in Neuroscience. These facilities will be greatly enhanced by the award in 2015 of £10 million from the UK Research Partnership Infrastructure Fund, specifically to support new investment in facilities for neuroimaging at all scales, from molecules to man. A key priority in the next two years will be to ensure this award is used to maximum benefit.

Close working with clinical services in King’s Health Partners has provided the opportunity to build large collections of samples from well-characterised patients. Through the generosity of patients and their relatives, we have a very large post-mortem brain collection, mostly of neurodegenerative diseases. Substantial DNA collections have been assembled, as well as collections of living cell lines such as fibroblasts and lymphoblasts, and fluids such as blood and CSF. These specimen collections are linked to substantial phenotyping information.

King’s Health Partners has substantial clinical trials expertise, led by a joint clinical trials office which operates across all the Partners.
The NIHR Wellcome Trust King’s Clinical Research Facility is a neuroscience-focussed experimental medicine facility encompassing a wide range of exceptional resources including 3T MRI, EEG, and inpatient beds including ICU beds.

Human neuroimaging facilities are extensive. Across King’s Health Partners there are six 3T MRI scanners dedicated to neuroimaging. Facilities for PET in King’s Health Partners and Imanova, in which KCL is also a partner, include four PET-CT scanners and a PET-MRI at St Thomas’s PET Centre. Linked to these are a large number of hot cells capable of generating a full range of ligands with short and longer half-life.

Facilities for human neurophysiological investigation are also extensive. King’s Health Partners has the largest clinical neurophysiology department in the UK. University-based research facilities include five EEG systems with up to 128 channels, and to shielded recording rooms. There is also TMS, and capabilities for TMS-EEG, EEG-fMRI and PET-MRI-EEG.

Experimental facilities support work with fly, zebrafish and mouse. Extensive tissue and cell culture facilities are readily available. There is a genome editing unit which utilises TALEN and CRISPR/Cas9 technology to edit the genome in fish, mice and human stem cells. In addition we make extensive use of genetically-encoded activity reporters and modulators of neuronal/synaptic activity such as optogenetics.

Imaging of experimental systems is a particular strength and will be further strengthened through the award from UK Research Partnership Infrastructure Fund. The existing Nikon Centre, which supports advanced microscopy in collaboration with Nikon, will be extended into a satellite in the Maurice Wohl Clinical Neurosciences Institute, building on our already very wide range of experimental imaging technologies, from molecular and cellular imaging to whole-brain imaging, using calcium reporter systems and light-sheet microscopy.
Current research funding

Division of Neuroscience (snapshot taken August 2015)

The staff of the Division of Neuroscience have consistently been awarded more than £19 million annually in new research grants as lead applicant, and currently hold active research grants as lead or co-applicant worth in total more than £200 million.

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<th>Category</th>
<th>Number of current awards</th>
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Comprehensive information about each of the Neuroscience departments and researchers, as well as detailed information about our research grants and research outputs, can be found here: https://kclpure.kcl.ac.uk/portal/en/organisations/academic-neuroscience(29f8fb40-73c4-4d82-8ace-e44bf7ed3827).html
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