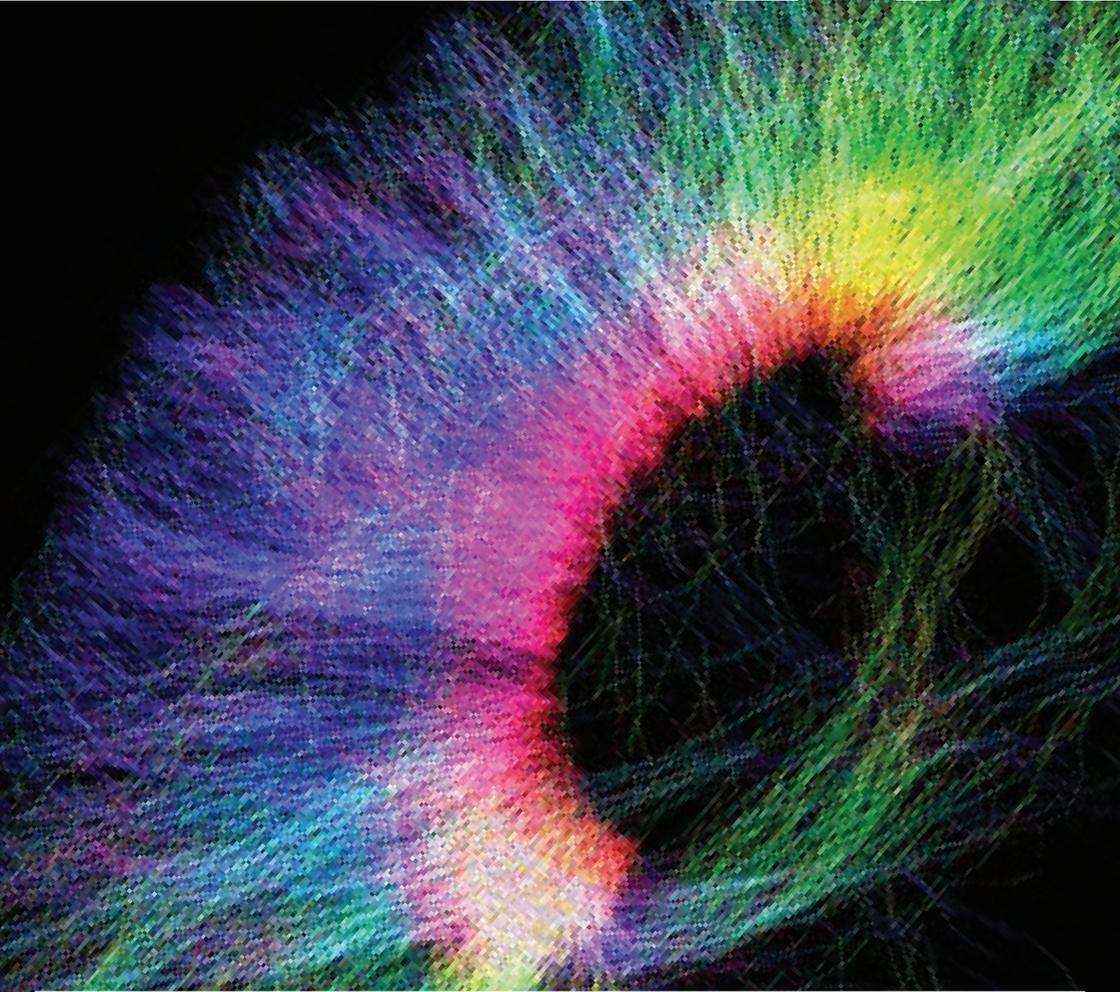


UCL GREAT ORMOND STREET  
INSTITUTE OF CHILD HEALTH



**UCL**



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DEVELOPMENTAL  
NEUROSCIENCES

# Introduction

## Professor Rosalind Smyth

It is a great pleasure to be able to introduce this informative brochure, which sets out the strategy and strengths of the Developmental Neurosciences Programme at the Great Ormond Street Institute of Child Health. Neurosciences has long been a very major strength at our institute, and indeed across Life and Medical sciences at UCL. However, it is the focus on developmental neurosciences that makes our work so unique and exciting.

From the beginning of my period here as Director four years ago, I always considered neurosciences as an exemplar of excellent integration between the clinical service at Great Ormond Street Hospital and the research programmes at the Great Ormond Street Institute of Child Health.

This synergy has been one of the key factors in the outstanding success of this programme, enabling us to focus on mechanisms of disease in epilepsy, neuromuscular disease, cognitive disorders, to name only a few. The insights gained by this research is now leading to major advances in diagnosis and treatments. In the coming pages, our colleagues highlight their exciting research objectives, and I hope that you will enjoy reading further.

**Professor Rosalind Smyth**  
Director  
UCL Institute of Child Health



## Executive summary

Using a life-span approach, we link laboratory-based neuroscience techniques with clinical research to investigate neurodevelopmental and acquired disorders affecting the young brain and peripheral nervous system. Our goal is to translate novel research findings into clinical practice. We use innovative technologies to relate genetic and anatomical markers of disease to normal and abnormal indices of cognitive, motor, behavioural, and mental health processes. We also undertake experimental clinical trials to develop novel therapies for neurological disorders, from early proof of concept, to more advanced confirmatory trials for children with neurodevelopmental disorders and/or rare diseases affecting central and peripheral nervous system function.



**Head of Programme**  
**Professor Helen Cross**



**Deputy Head  
of Programme**  
**Professor**  
**Torsten Baldeweg**

# Developmental Neurosciences Programme



The Developmental Neurosciences Programme is one of five academic programmes at the UCL Great Ormond Street Institute of Child Health.



The primary focus of the Developmental Neurosciences Programme is to minimise the impact of disorders affecting the developing central and peripheral nervous system by

- Studying the mechanisms of injury and repair
- Improving diagnosis and prognosis
- Evaluating therapeutic strategies
- Optimising functional outcome

The programme has four sections:



and has strong links with the Neuroscience division at Great Ormond Street Hospital for Children (GOSH).

# Clinical Neurosciences

Section Head: Dr Finbar O'Callaghan

**Clinical neurosciences is a multi-disciplinary section that conducts clinical research into epilepsy, cerebrovascular disease, visual impairment, movement disorders, demyelinating disease as well as the neurodevelopmental effects of early pain experience in children. The Section comprises 40 to 50 researchers at any one time, with eight senior staff/principal investigators. The Section attracts and welcomes visiting Fellows from throughout the world.**

## Neuroepidemiology:

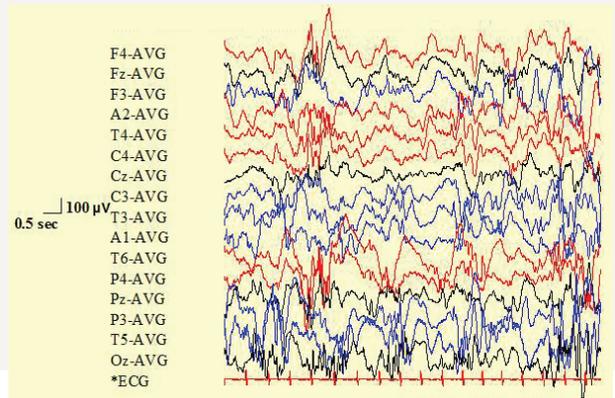
There is a strong emphasis on population based research in childhood stroke, infantile epilepsy and status epilepticus.

There is also strong emphasis on clinical trials in rare disease areas such as tuberous sclerosis complex and childhood stroke.

Infantile epilepsy is a particular interest of the Section with two current ongoing trials: the International Collaborative Infantile Spasm Study, and the Ketogenic Diet in Infants with Epilepsy Trial, as well as a further epidemiological study of newly diagnosed epilepsy in the first year of life; EPilepsy in Infancy; relating Phenotype to Genotype.



*EEG demonstrating hypsarrhythmia, as seen in West Syndrome*





## Pathogenesis of disease and disability:

This is focused on: i) study of the molecular basis of rare neurological disease, as well as interactions with environment, particularly with respect to early onset epilepsies, movement disorders, neurodegenerative, neurotransmitter and complex cerebrovascular disorders; ii) use of imaging tools to understand brain injury associated with convulsive status epilepticus, early onset epilepsy, sickle cell disease and cerebrovascular disorders; iii) use of model systems including cell culture (e.g. iPSC), fly models and rodent models to study mechanisms of movement disorders, seizures and comorbidities associated with epilepsy, and neurodevelopmental effects of early tissue injury and experience of pain. iv) use of long-term cohort studies of clinical patients to understand the neurodevelopmental consequences of epilepsy, early visual loss and early pain experience.

## Novel treatments and interventions:

We seek to evaluate novel targeted therapies in rare diseases in children followed at Great Ormond Street Hospital. Novel treatment evaluated in investigator led studies include Sickle Cell Disease, Multiple Sclerosis, Tuberculous Sclerosis and neonatal epilepsy. We have strong links with the pharmaceutical industry and members of the section are either Chief Investigator or Principle Investigator on national and international phase 2 and 3 industry studies in demyelinating disease and epilepsy. The clinical department is the national lead for paediatric epilepsy surgery and the Section leads both nationally and internationally in the evaluation of the impact of epilepsy surgery in children.



*Novel treatments and interventions*

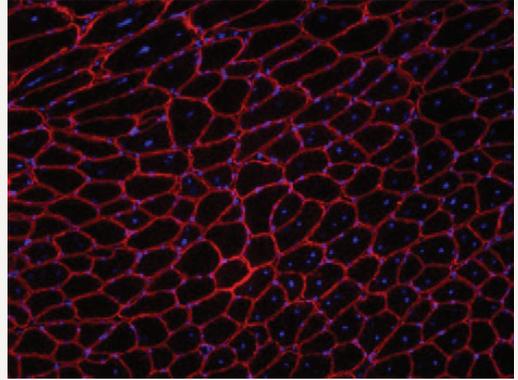
# Molecular Neurosciences

Section Head: Professor Jennifer Morgan

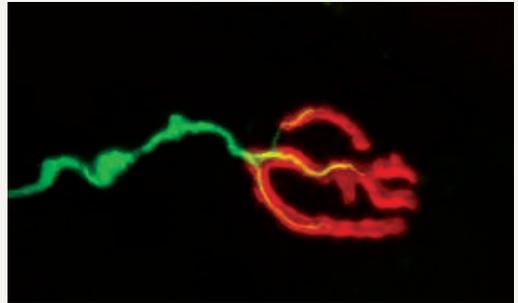
**The goals of the Molecular Neurosciences section are to understand the genetic and molecular causes of neuromuscular and neurodegenerative diseases, with the ultimate aim of translating this knowledge into treatment of patients.**

Regarding **Neuromuscular diseases**, there are two integrated activities, **The Dubowitz Neuromuscular Centre and the Translational Myology Laboratory.**

**The Dubowitz Centre** is a multidisciplinary centre with expertise in diagnostic and management aspects of childhood neuromuscular disorders, and in translational and basic neuromuscular research. The centre is the national lead for congenital muscular dystrophies and myopathies. Investigations on rare conditions led this centre to the identification of more than 30 disease genes. From a translational research perspective the Centre is part of the MRC Centre for Neuromuscular Diseases, in strong collaboration with the Institute of Neurology. A major research programme uses pre-clinical models and clinical trials to determine the efficacy of modifying gene splicing in neuromuscular diseases with antisense oligonucleotides in spinal muscular atrophy and Duchenne muscular dystrophy.



Sarcolemmal protein alpha-sarcoglycan on mouse muscle section

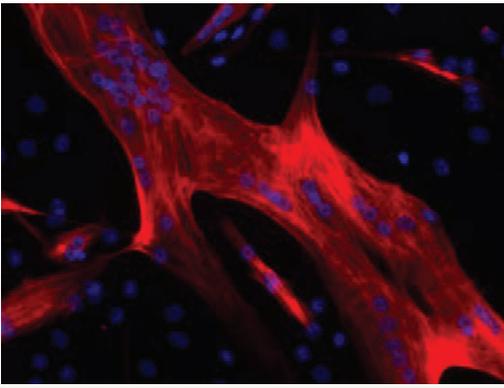


Neuromuscular junction

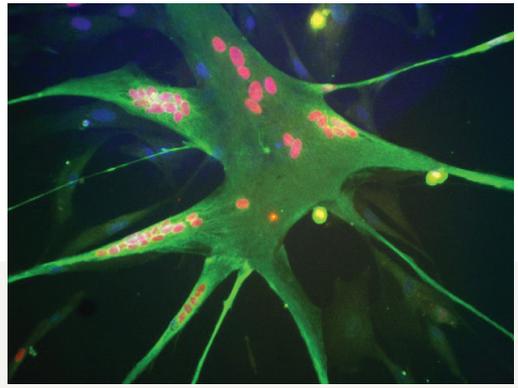
The Centre is currently involved in a dozen clinical trials, from first in man investigator led studies coordinated

with external funding obtained from the MRC, Department of Health and the European Union ([www.skip-nmd.eu](http://www.skip-nmd.eu)),





Myogenesis of human muscle-derived stem cells

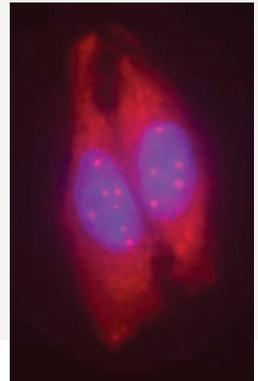


Myotubes in culture

to phase 2 and 3 studies, which have resulted in several successful drugs at different stages of approval. Another area of research relates to investigating the contribution of skeletal muscle stem cells to muscle regeneration and ways in which environmental changes within skeletal muscle, as a consequence of muscular dystrophies, ageing or injury, might affect muscle repair and regeneration. Viral gene delivery to muscle stem cells is also being investigated.

The **Translational Myology Laboratory** is also focused on the development of innovative treatment approaches for neuromuscular diseases. An adeno-associated-virus (AAV) platform and muscle cell immortalization or iPS techniques are used to both create disease-relevant cellular and animal models as well as treatment approaches. Current work addresses treatment approaches for Facio-scapulo-humeral muscular dystrophy (FSHD), Myotonic Dystrophy, and Duchenne- and Limb girdle muscular dystrophy. In addition, this laboratory investigates general aspects of muscle homeostasis such as myostatin mechanisms and how these can be exploited for ameliorating wasting muscle conditions.

The **Neurogenetics** Subdivision of Molecular Neurosciences focuses on elucidating underlying aetiology and disease mechanisms causing childhood neurological disorders, with a long term aim of developing novel therapeutic strategies. There is expertise on different forms of epilepsy (early infantile onset epileptic encephalopathy, Landau-Kleffner syndrome) movement disorders (dystonia and other hyperkinetic disorders, paroxysmal movement disorders, parkinsonism) and neurodegenerative conditions, such as NBIA (Neurodegeneration with Brain Iron Accumulation). The laboratory is focused on novel gene discovery and use cell models (including patient derived induced pluripotent stem cells) to investigate disease pathophysiology. There are strong local collaborations with the Institute of Neurology, Institute for Women's Health, School of Pharmacy, and Birkbeck College, for electrophysiological characterisation, gene therapy strategies, high throughput drug screening and homology modelling studies.



Nuclear protein SMN staining in HeLa cells

# Developmental Imaging and Biophysics

Section Head: Professor Chris Clark

The aim of DIBS is to develop and apply advanced MRI techniques for the diagnosis, prognosis and understanding of the biophysical mechanisms of disease in childhood. The primary focus of DIBS concerns imaging of the brain but there is also active research in imaging muscle and kidney as well as post mortem MRI.

## Advanced Imaging in Paediatric Brain Tumour Patients

In collaboration with Great Ormond Street Hospital, DIBS have led the introduction of advancing magnetic resonance imaging techniques into the clinical management of paediatric brain tumour patients. Perfusion-weighted imaging is now being applied routinely in new brain tumour patients, which allows us to measure the blood supply feeding a tumour. This is often linked to the malignancy of the tumour, so an imaging technique such as this can provide vital, non-invasive diagnostic information (Figure 1).

This can be used to help surgeons target the most malignant part of tumour during biopsy, and help stratify patients based on their likely tumour subtype at an earlier stage in their management.

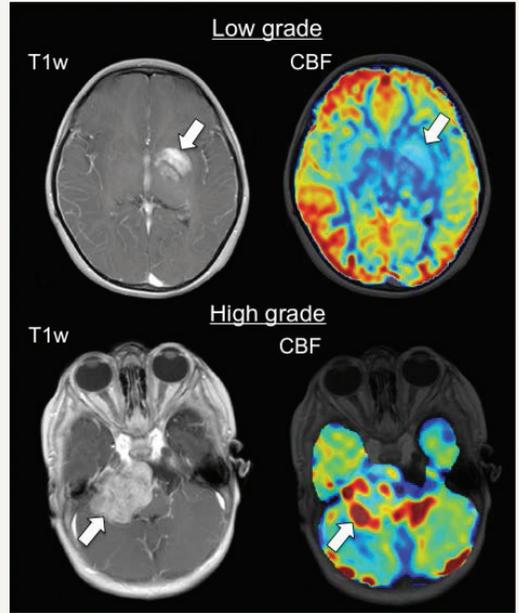


Figure 1: Illustrative MRI images in two paediatric brain tumour patients

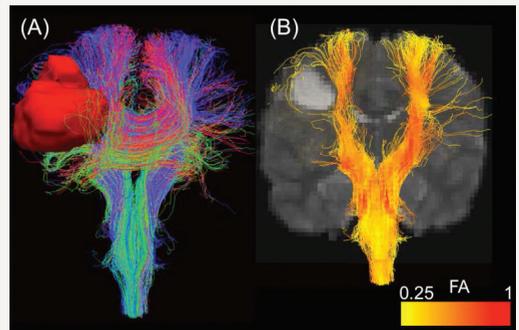


Figure 2: Diffusion tensor imaging (DTI) in a high-grade glioma patient

We have also introduced diffusion-weighted imaging into clinical management of brain tumour patients. Using Diffusion Tensor Imaging (DTI), we can use the diffusion of water molecules in the tissue as a probe to investigate the cellular structure. In particular, this technique gives us an excellent representation of white matter anatomy in the brain, and can be used to measure how much a tumour has invaded neighbouring white matter tracts (Figure 2). Again, this can help surgeons to assess the ‘tumour margin’ when planning surgical removal of the tumour.

## Reducing the effects of motion in functional MRI data

### Correcting motion in functional MRI

FIACH was a project inspired by the difficulties faced when trying to perform functional Magnetic Resonance Imaging (fMRI) on young children. This technique is used clinically to help inform brain surgery in children with epilepsy (so the surgeon can avoid cutting out a part of the brain that may impair speech). FIACH shows great promise in its ability to more comprehensively map language

areas (See Figure 3) and has the potential to provide improvements to all clinical services that utilise fMRI.

### Imaging in sickle cell disease

There are two main on-going studies on paediatric and adult SCD.

1. A follow-up of the Sleep Asthma Cohort (SAC) trial, in which patients underwent two sleep studies at GOSH between 2006-2014 to investigate the role of sleep-disordered breathing and pain.
2. A prospective phase II clinical trial (Prevention of Morbidity in SCD [POMS]) of 6 months of overnight positive airway pressure (APAP). The main aims are to investigate any improvement in cognition, particularly processing speed, and MRI biomarkers such as hippocampal size and white matter integrity.

Imaging on the 3T Prisma at GOSH has revealed a higher proportion of silent cerebral infarction than previous studies. Out of 86 SAC and POMS patients, 39 (45.3%) have SCI, usually distributed in the deep white matter of the frontal and parietal lobes.

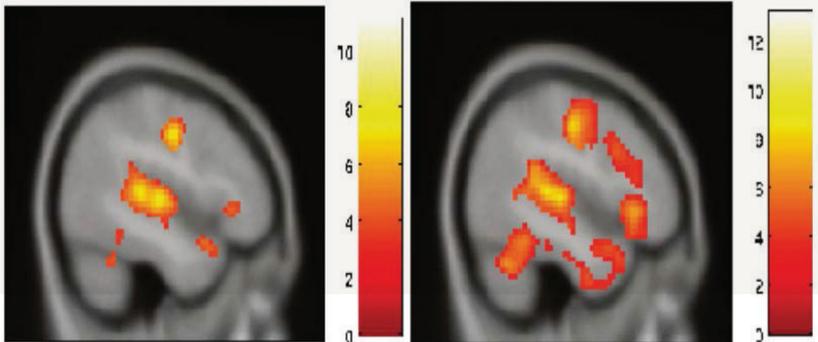


Figure 3: Comparing (A) Standard processing and (B) Processing with FIACH.

# Cognitive Neuroscience & Neuropsychiatry (CNN)

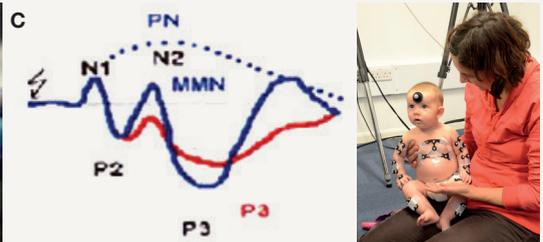
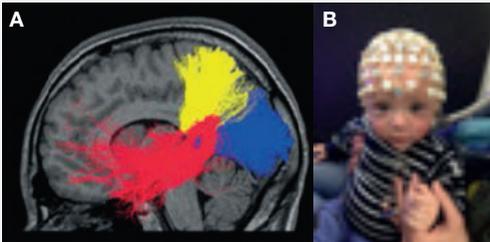
Section Head: Professor Faraneh Vargha-Khadem

**The goal of this Section is to identify brain networks underlying memory, language, sensorimotor, emotional, and behavioural function in patients with neurodevelopmental or acquired brain injury. We use electrophysiological, neuroimaging, and experimental techniques to study recovery and reorganisation of brain function thereby translating our research findings into improved clinical and educational outcomes.**

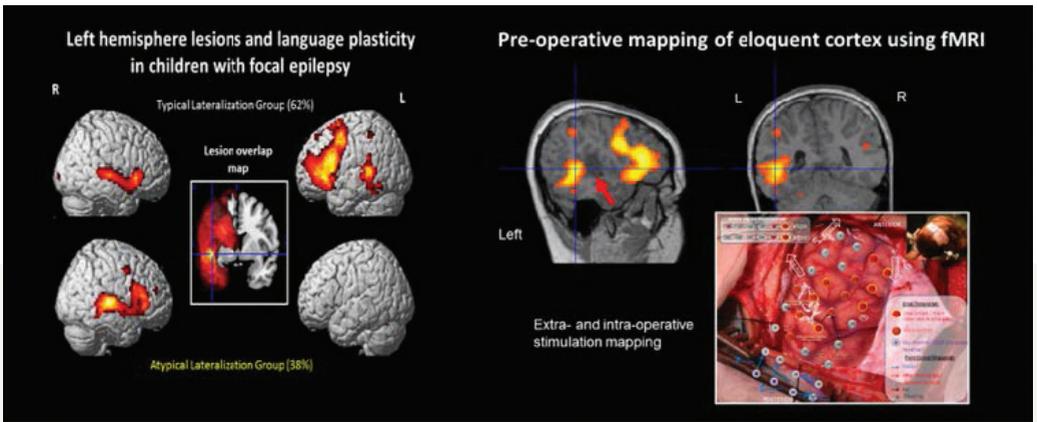
The PIs in the CNN lead their interdisciplinary teams of post doctoral fellows and PhD students in clinical research programmes, working closely with colleagues in the Department of Clinical Neuropsychology, and others in the Neurosciences Division of Great Ormond Street Hospital for Children. We conduct research on patient groups with epilepsy, cerebrovascular disorders, cardiorespiratory disease, demyelinating disorders, neurogenetic disorders, traumatic brain injury, preterm birth, and cortical blindness:

## Effects of early brain injury on the developing brain

Some neonates with a history of injury to the brain are at risk of problems with memory, language, movement coordination, and social skills later in childhood. Understanding the trajectory of brain-behaviour development in at-risk cohorts can identify those most likely to show later emerging difficulties. Using neuroimaging, eye tracking and movement analysis (kinematics) techniques, our work with young infants and toddlers focuses on identifying the neural correlates of specific cognitive and social skills and linking these measures to later outcomes via longitudinal studies.



(A) Magnetic resonance tractography reconstruction of interhemispheric pathways. (B) Electrophysiological recordings from a 6 month old infant. (C) Kinematic analysis of joint movements and rotations in a healthy baby at 6 months

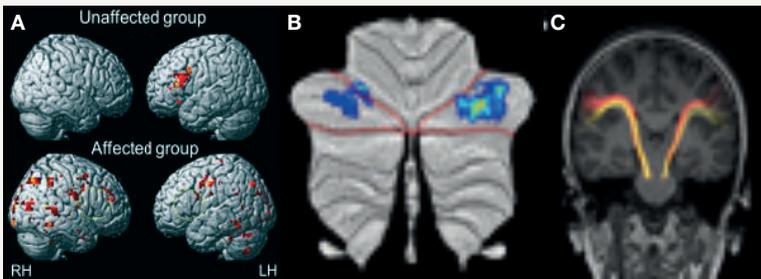


## Pre-operative functional mapping and long term outcome after epilepsy surgery

We are conducting large-scale studies into the plasticity of the developing brain in response to neurological insults to understand the root causes of learning problems of children with medication-resistant focal epilepsy. We are developing and applying non-invasive diagnostic neuroimaging methods for children who are candidates for epilepsy surgery. We then conduct longitudinal post-surgical outcome studies with the aim of improving cognitive and educational outcomes after such treatment. Another focus of interest is in diagnosis and treatment of neuropsychiatric disorders associated with epilepsy, including rare syndromes such as hypothalamic hamartoma.

## Brain-behaviour relationships in neurogenetic disorders

Here we focus on identifying deep phenotypes of rare genetic syndromes that result in motor speech, language, and limb movement deficits. We examine the physiological, behavioural, and neuropsychiatric sequelae of such disorders and relate them to their disrupted neural circuitry using structural and functional brain imaging techniques. Recently, we have expanded our remit to identify the neuroimaging correlates of other forms of neurodevelopmental disorders with the aim of isolating biological pathways from gene function to brain development to cognitive phenotypes.

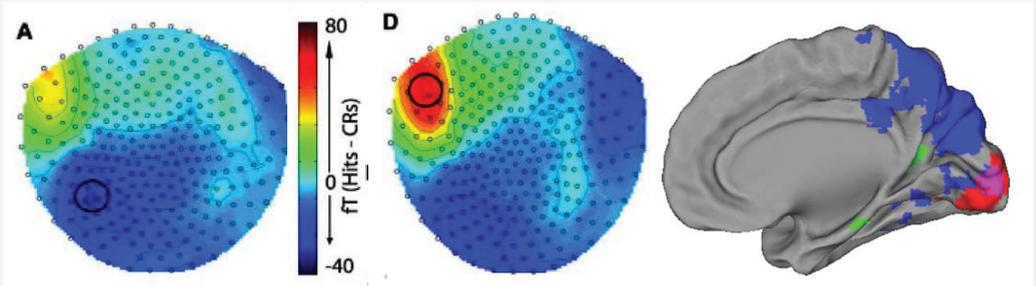


(A) Brain activation during language tasks in individuals with (affected) and without (unaffected) speech-language disorder caused by a mutation of the FOXP2 gene. (B) Flat-map of the cerebellum showing bilateral reduction in grey matter volume in lobule HVIIa Crus I (red lines) in cases with mutation of the FOXP2 gene. (C) Tractography reconstruction of the corticobulbar tracts

## Hypoxia, hippocampal damage and amnesia

Lack of oxygen to the brain can result in damage to the memory structures and interfere with the development of autobiographical memory and learning ability. Our research focuses on using MRI, fMRI and EEG to characterise the impact of hypoxic-ischaemic injury sustained at different points in infancy/childhood. Our

aim is to better understand the mechanism of hypoxic-ischaemic injury and its adverse effects on the hippocampus and memory retrieval and consolidation. By early identification of the memory problems, we provide accurate diagnosis and prognosis of outcome, and enable targeted educational support during the school years.



Patients with Developmental Amnesia (A and pink / blue areas in E) show a pattern of brain activity during memory tests that are quite different to the pattern shown by healthy controls (green areas in E)

**Our Section provides the only fully accredited MSc professional training programme in the UK in Paediatric Clinical Neuropsychology.**

# Collaboration with Great Ormond Street

Dr Sophia Varadkar

Head of Clinical Service



Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) is a national centre of excellence, currently delivering the widest range of paediatric specialties in the UK. With its status as a specialist Biomedical Research Centre for paediatrics, the partnership with UCL GOSH Institute of Child Health (ICH) forms the largest paediatric research and teaching centre in the UK. The Neurosciences Medicine clinical service is the largest paediatric neurology centre in the UK. The service is delivered across four main groups: Acute and General Neurology, Complex Epilepsy and the Children's Epilepsy Surgery Service, Dubowitz Neuromuscular Service and Clinical Neurophysiology. There are especially close links with the Neurosurgery, Neurodisability, Neuro-radiology Metabolic and Intensive Care Services at GOSH and with the National Hospital for Neurology and Neurosurgery, Queen Square, Institute of Neurology and Kings Health Partners.

The ethos is of one expert team, GOSH and ICH, exploring unanswered questions, sharing sub-specialist expertise and offering children the opportunity to participate in studies. The clinicians of the multidisciplinary teams have honorary contracts across GOSH and ICH and are actively involved in clinical and pre-clinical projects across all areas of the Developmental Neuroscience Programme, providing specialist clinical input at all stages. There are strong teaching and training collaborations with co-supervision of research students and education of clinical academic trainees. Together with ICH, there is a busy portfolio of investigator-led and industry-supported studies in the GOSH Somers Clinical Research Facility. The clinical service has particular experience in the translation of new investigative modalities and therapies from the ICH research platform into GOSH clinical practice.

# With thanks to our funders







# UCL

**UCL Great Ormond Street Institute of Child Health**

**Developmental Neurosciences Programme**

30 Guilford Street

London WC1N 1EH

