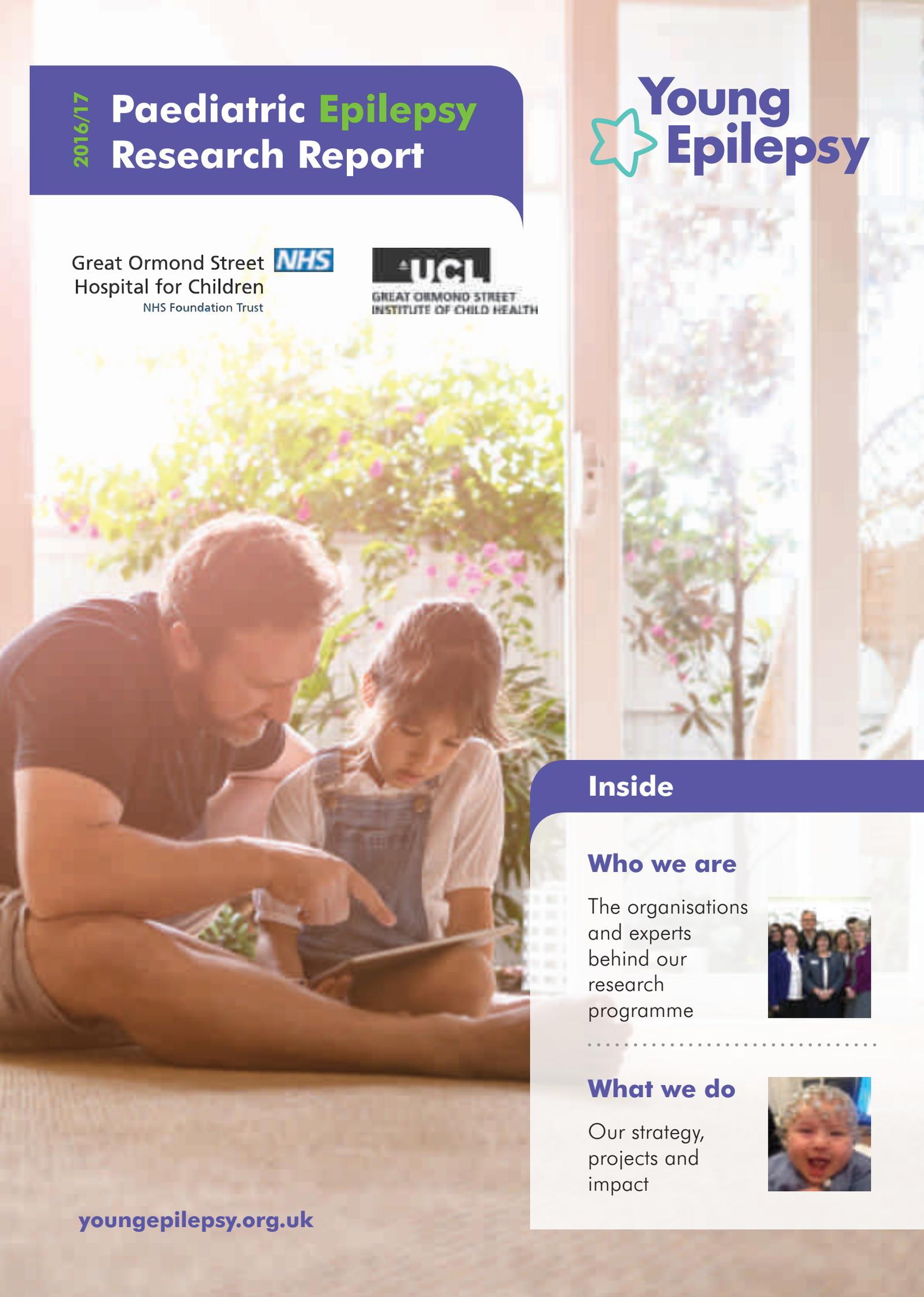


2016/17

Paediatric Epilepsy Research Report

Great Ormond Street
Hospital for Children
NHS Foundation Trust



Inside

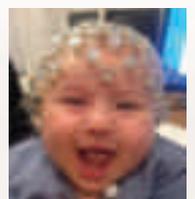
Who we are

The organisations and experts behind our research programme



What we do

Our strategy, projects and impact



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Introduction

I am delighted to present our annual Research Report for the period May 2016 to June 2017 for the epilepsy unit across Young Epilepsy, UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children.

Over the past year we have initiated 11 new research projects and been responsible for 88 peer-reviewed publications of primary research, as well as a further 31 publications of chapters, reviews and commentaries of expert opinion. As a wider research unit, we continue to work towards improving the recognition of epilepsy as a healthcare priority in every part of the world.

In January 2017, we hosted our 7th international Paediatric Epilepsy Research Retreat for researchers and collaborators, moderated by Professor Ingrid Scheffer AO of The Florey Institute of Neuroscience and Mental Health, Melbourne University, Australia. The Retreat is a one of a kind event where a uniquely broad range of experts can meet and constructively share current and future research.

The keystone of our research unit is The Prince of Wales's Chair of Childhood Epilepsy, an eminent position, unique in Europe, created and first held by Professor Brian Neville. Brian very sadly passed away in December 2016 leaving a monumental legacy in paediatric neurology, epileptology and philanthropy. One of the brightest minds in neurology, he nurtured and inspired so many others (myself included) and continues to provide insights and change lives as his final project comes to fruition; the Sussex Early Epilepsy and Neurobehaviour (SEEN) project.

Young Epilepsy's vision is to create better futures for young lives with epilepsy and associated conditions. We continue to vanguard practical outcomes for young people based on research



evidence and integrated services reflected in public policy. We cannot hope to make lasting, meaningful change without services governed by defensible fact in all disciplines of our work. It is central to all that we do.

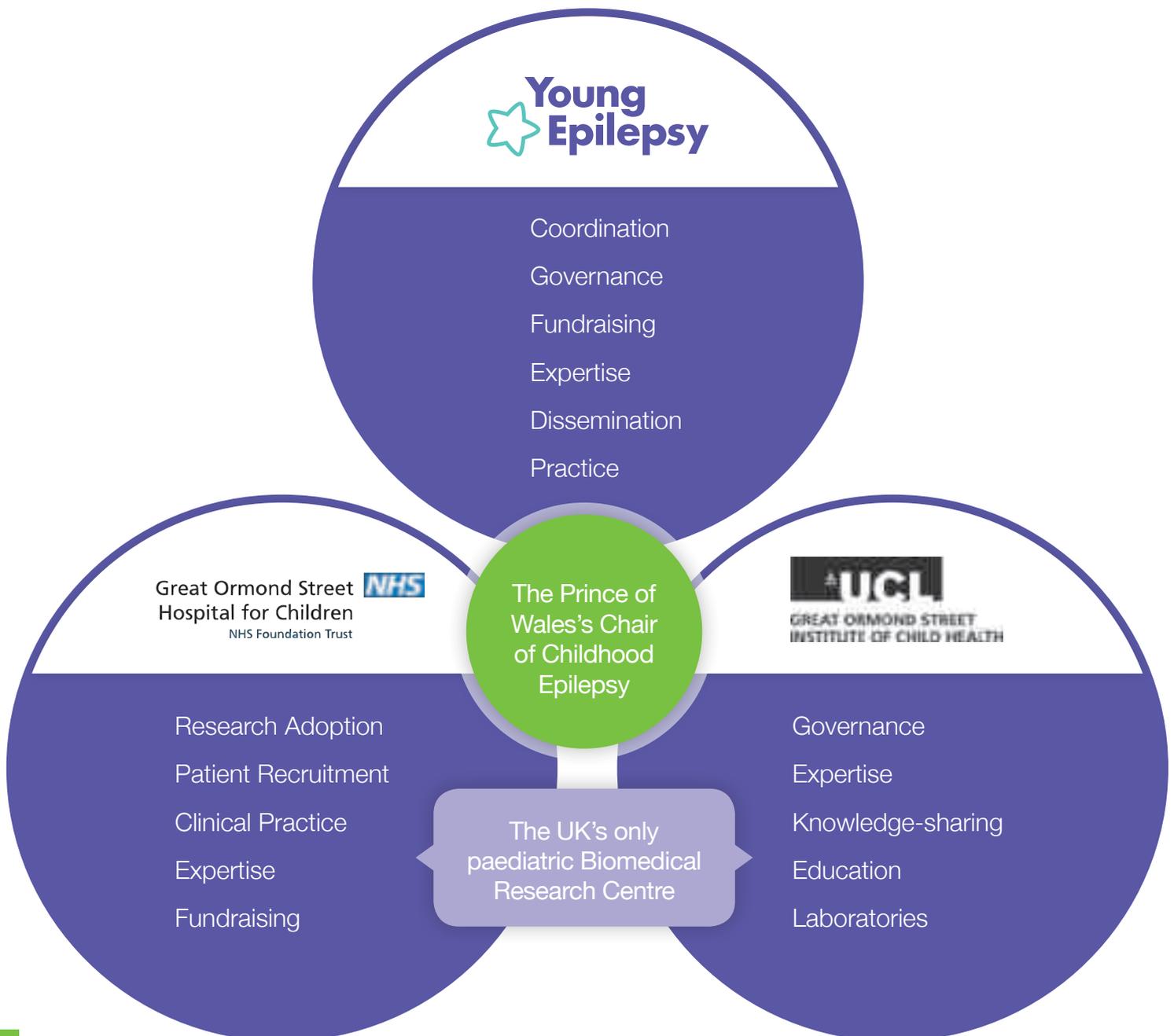
Professor Helen Cross OBE
The Prince of Wales's Chair of
Childhood Epilepsy

Who we are



Research Partners

Our research programme operates under the auspices of The Prince of Wales's Chair of Childhood Epilepsy, Professor Helen Cross OBE. It is a collaborative scheme between Young Epilepsy, Great Ormond Street Hospital for Children and UCL GOS – Institute for Child Health.



Who we are

Young Epilepsy is the national charity working exclusively on behalf of children and young people with epilepsy and associated conditions. With over 100 years expertise, it provides world class diagnosis, assessment and rehabilitation for children and young people with epilepsy.



Young Epilepsy has a specialist school and college, providing day, residential and short break services, for those up to 25 years of age, offering education and healthcare for children and young people with epilepsy, autism and other neurological conditions.

Young Epilepsy aims to achieve better futures for young lives with epilepsy and to raise awareness and understanding of epilepsy along with issues associated with the condition. The charity provides support and information for parents, children and young people as well as training for professionals. It campaigns for better access to, and quality of, health and education services.

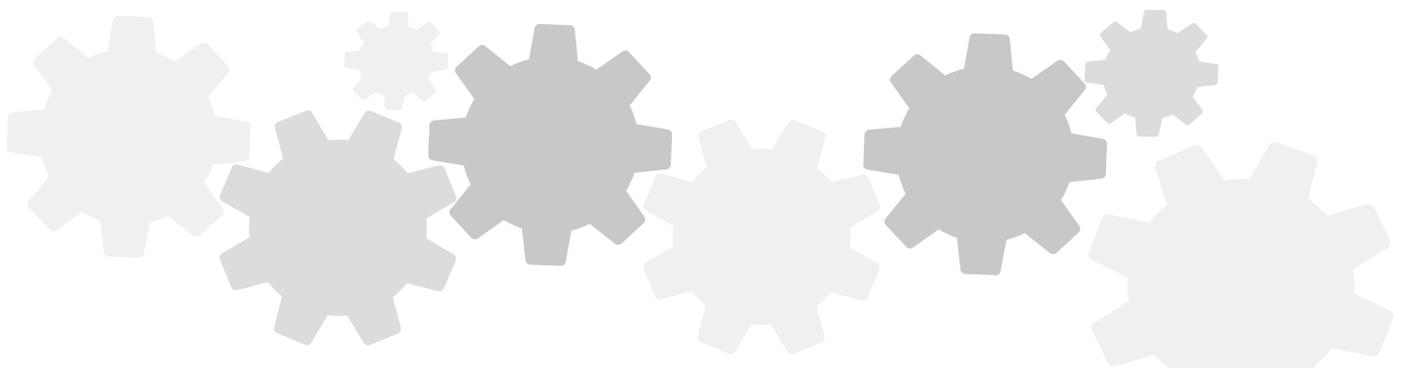
Great Ormond Street Hospital for Children (GOSH) is an international centre of excellence in child healthcare, at the forefront of paediatric training in the UK. GOSH plays a leading role in training paediatric doctors and training more children's nurses than any other hospital. The hospital is committed to carrying out pioneering research to find treatments and cures for some of the most complex illnesses. Together with UCL GOS - Institute of Child Health, GOSH forms the UK's only Biomedical Research Centre specialising in paediatrics.



University College London Great Ormond Street Institute of Child Health (ICH) together with its clinical partner GOSH, forms the largest concentration of children's health research in Europe.



ICH pursues an integrated, multidisciplinary approach to enhance understanding, diagnosis, therapy and prevention of childhood disease. All specialties as they relate to children's health are included so that ICH fulfils the role of a world-leading academic establishment in paediatrics. In keeping with a commitment to disease prevention, ICH is active in teaching and research aimed at developing interventions to promote health both during childhood and in the later years of life.





Professor Brian Neville 1939 - 2016

As the first Chair of Paediatric Neurology in the UK, and subsequently the first Prince of Wales's Chair of Childhood Epilepsy, Brian Neville made an immeasurable contribution to the understanding and care of neurological disease in childhood around the world.



Brian qualified in medicine from Guys Hospital Medical School, and trained in neurology at Great Ormond Street as well as the National Hospital for Neurology and Neurosurgery, UCLH. He was initially a consultant in paediatric neurology at Guys Hospital

where he was Director of the Newcomen Centre, developing a firm interest in cerebral palsy and epilepsy. He long realised research was key to moving forward in clinical practice, recognising the main questions that needed to be addressed arose from the patients themselves. His initial collaborations were with Kings College Hospital, however, in 1989 Brian was appointed the first UK Chair of Paediatric Neurology at University College London, Institute of Child Health and Great Ormond Street Hospital for Children (GOSH). His vision was for a unit that encompassed all aspects of paediatric neurology, from acute to chronic illness, with research embedded in clinical practice. He developed both the clinical and academic units to one of the largest in Europe. He specifically developed neurodisability services, firmly believing in the model of multidisciplinary team working. He additionally witnessed what could be achieved by epilepsy surgery through his collaboration with Kings, but felt children required a specific type of service. He pioneered the use of newly available MRI for a predominantly non-invasive programme, and also recognised the service had to be embedded in a complex epilepsy evaluation programme.

“His vision was for a unit that encompassed all aspects of paediatric neurology, from acute to chronic illness, with research embedded in clinical practice.”

The programme he started at Great Ormond Street Hospital is now one of the largest clinical units in the world. Recognising that children required continuation of services into adulthood, he also established links with the epilepsy unit at the National Hospital for Neurology and Neurosurgery, UCLH, and created one of the first transition clinics for teenagers with complex epilepsy.

Brian started working with Young Epilepsy in the 1980's, then St Piers, a school for children with epilepsy. He long recognised the potential of partnering with the NHS, and the possible reach of such expertise, if made available. Over the years he was key to the development of

the organisation, initially as a charity, subsequently as a medical and research resource. Brian campaigned and led fundraising for the creation of a chair in childhood epilepsy, establishing links with His Royal Highness The Prince of Wales who gave his name to The Prince of Wales's Chair of Childhood Epilepsy, a position of which Brian was the first incumbent (2004-2007). Brian

was a major driver for the creation of the medical and research centre in Lingfield, which now bears his name; the Neville Childhood Epilepsy Centre.

Brian's work was at the heart of the many issues where the secondary effects of epilepsy can affect a young person. The fundamental basis to his vision for the Chair was to greater understand the underlying mechanisms and secondary effects of the epilepsies and how intervention could improve outcomes. He also valued the relative contribution of different organisations in the research effort.

Who we are

It was at Young Epilepsy that he led the pioneering work into the use of buccal midazolam as rescue medication for prolonged seizures, now integrated into NICE guidelines. He led further work into the understanding of the effects of infantile spasms, optimising intervention in Landau Kleffner syndrome, the epidemiology of status epilepticus, and the rate of neurocognitive and neurobehavioural abnormalities in children with epilepsy in schools. He also led on establishing a European network for the study of Alternating Hemiplegia that now continues as a wider international effort. During his career he published 3 books, 45 chapters and more than 270 peer-reviewed publications. He created links across the community, UCL GOS – Institute of Child Health, Great Ormond Street Hospital, Young Epilepsy and ultimately the UCLH Institute of Neurology and Neurosurgery which would allow evaluation and intervention across a patient's entire age range.

He also valued the role of the parent support organisations and undertook an enormous amount of work over the years with *Contact a Family*. He acted as medical advisor to several condition-specific support groups, including as Executive Secretary of the Medical Education and Information Unit of the Spastics Society 1978-1992 (now Scope).

Brian long recognised the need to encourage and train junior colleagues in epilepsy and neurodisability research so the specialty could grow. As coordinator of postgraduate training for North London, UK and Europe, he was able to develop a training programme which allowed appropriate trainees (more than half at GOSH) to enrol for PhD's and develop into the present generation of clinical academics. He wrote the training programmes for Paediatric Neurology for Europe and the UK with the integration of neurodisability and child psychiatry, and established a European syllabus for paediatric neurology. In all, he supervised 15 higher degree (PhD or MD) students and many more visiting fellows from around the world. Brian was an outstanding mentor who always found the balance between getting the research project done and

allowing his mentee to develop their own ideas and direction. This had the wonderful effect of giving breadth to both the research programmes and clinical practice. He also pursued collaborative work with colleagues in countries with limited resources. Notable longstanding links were established with Kilifi, Kenya; Dhaka, Bangladesh and Chandigarh, India, enabling those countries to develop their own excellent paediatric neurology systems.

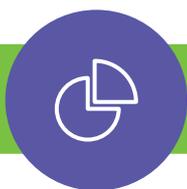
Brian was instrumental in the establishment of the British Paediatric Neurology Association (BPNA) serving on the council as Secretary (1980-1983) and President (1986-1989), Chair of the Training Subcommittee (1993-1999). Brian was one of the founding members of the European Paediatric Neurology Society and was subsequently elected to the board. He founded the European Academy of Childhood Disability (Chairman for 12 years) and also the European Society for Movement Analysis in Children (Chairman for 10 years). He was on the editorial board of the journal *Developmental Medicine and Child Neurology* for 15 years (1977-1992) and negotiated its becoming the Journal of the BPNA. On his retirement, Brian

was made an honorary member of the European Paediatric Neurology Society, awarded a Lifetime Achievement award from the International League Against Epilepsy (ILAE) UK Chapter and an honorary doctorate from University of Gothenburg.

Brian's legacy is colossal and his work will continue to shape the field of neurology for generations to come. His legacy remains in the many paediatric neurologists, paediatricians, therapists, children and families around the world who will be eternally grateful for his insights. At the heart of all he did, he was an extremely caring man who always put the child and family at the centre of all activity.

“At the heart of all he did, he was an extremely caring man who always put the child and family at the centre of all activity.”

We are immensely proud to have counted Brian as one of our own and he will be greatly missed.



Research Funding

Central to the research programme is the ability to apply for and manage research grants and donations.

Our approach to research is an admired model in the research community. It is our holistic and unified strategy that has enabled us to build the world's largest paediatric epilepsy research unit and network of multidisciplinary practitioners. We marry academic project grants with the safeguard of smart fundraising which allows us to keep the expertise within the unit and develop the impact of our work. Our unified approach ensures this work will endure.

The future of this programme rests on the ability to maintain the current infrastructure. We rely on the grace of unrestricted funding which allows us to design projects, review their impact, effectively disseminate findings and to ensure that excellent research outcomes are translated into direct, tangible benefits for young people with epilepsy, their families and supporting practitioners. It allows us to maintain a base of operations to both lead and support projects with administration whilst upholding excellent governance. Our growth and achievements as a unit have depended directly on the security this infrastructure provides.

We remain ever grateful for the generosity and dedication of the organisations and individuals who support our work. We simply could not achieve the outcomes we strive for without such aid.

Thank you!

Action Medical Research	NIHR EME Programme
Brain Tumour Charity	NIHR PGfAR Programme
Cancer Research UK	Rita Lila Howard Foundation
Charles and Elsie Sykes Trust	Rosetrees Trust
Charles Wolfson Foundation	Sanofi
Epilepsy Action	Science Foundation Ireland
Epilepsy Research UK	Sobell Foundation
EU- Chafea	Sparks Charity
European Commission	Special Products
FP7-HEALTH-2013-INNOVATION-1	True Colours Trust
George E Neville Foundation	University College London Hospital
Great Ormond Street Hospital Children's Charity	Biomedical Research Centre (UCL/BRC)
Johnson and Johnson Innovation	Fast Track Grant F203
LivaNova	Vitaflo Limited
Maurice Wohl Foundation	Willie and Mabel Morris Charitable Trust
McGrath Foundation	Wellcome Trust
Mrs Barbara Abbott and Family	Wolfson Foundation



Research Team

The research team contribute to a wide spectrum of activities from basic science through to patient care. The team consists of a multidisciplinary range of experts working across Young Epilepsy, UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children.

Principal Investigators

Professor Helen Cross OBE The Prince of Wales's Chair of Childhood Epilepsy and Head of UCL GOS - ICH Developmental Neurosciences Programme

Professor Torsten Baldeweg Professor of Developmental Cognitive Neuroscience, Deputy Head of UCL GOS - ICH Developmental Neurosciences Programme

Professor Chris Clark Professor of Imaging and Biophysics, Head of UCL GOS - ICH Developmental Imaging and Biophysics Section

Professor Christopher Gillberg Visiting Professor in Child and Adolescent Psychiatry

Professor Isobel Heyman Consultant Child and Adolescent Psychiatrist and Honorary Professor

Professor Manju Kurian Consultant Paediatric Neurologist and Clinician Scientist

Professor Finbar O'Callaghan Professor of Paediatric Neuroscience, Head of UCL GOS - ICH Clinical Neurosciences Section

Professor Shamima Rahman Professor of Paediatric Metabolic Medicine

Professor Rod Scott Professor in Paediatric Neurology

Professor Faraneh Vargha-Khadem Professor of Developmental Cognitive Neuroscience, Head of UCL GOS - ICH Cognitive Neurosciences Section

Dr Patricia Atkinson Consultant Community Paediatrician

Dr Sarah Aylett Consultant Paediatric Neurologist

Dr Stewart Boyd Consultant Clinical Neurophysiologist

Dr David Carmichael Lecturer in Neuroimaging and Biophysics

Dr Maria Clark Consultant Paediatric Neurologist

Dr Krishna Das Consultant Paediatric Neurologist

Dr Michelle De Haan Reader in Developmental Cognitive Neuroscience

Dr Christin Eltze Consultant Paediatric Neurologist

Mr William Harkness Consultant Paediatric Neurosurgeon

Dr Cheryl Hemingway Consultant Paediatric Neurologist

Dr Roxanna Gunny Consultant Neuroradiologist

Dr Tom Jacques Reader in Paediatric Neuropathology

Dr Marios Kaliakatsos Paediatric Neurologist

Dr Philippa Mills Senior Lecturer in Genetics and Genomic Medicine Programme

Dr Friederike Moeller Consultant Clinical Neurophysiologist

Dr Ronit Pressler Consultant in Clinical Neurophysiology and Clinical Lead of GOSH Telemetry Unit

Dr Colin Reilly Educational Psychologist

Dr Robert Robinson Consultant Paediatric Neurologist

Dr Richard Scott Consultant in Clinical Genetics

Dr Rachel Thornton Consultant in Neurophysiology

Mr Martin Tisdall Consultant Paediatric Neurosurgeon

Dr Sophia Varadkar Consultant Paediatric Neurologist

PhD students

Sophie Adler *Cortical infolding in paediatric epilepsy*

Sam Amin *An investigation into mTOR inhibitors in Tuberous Sclerosis Complex*

Sarah Buck *Organisation of the memory circuit in paediatric Temporal Lobe Epilepsy*

Rosie Coleman *Functional and structural plasticity after epilepsy surgery*

Bianca De Blasi *Quantitative PET analysis in paediatric epilepsy*

Amy Fairchild *Characterisation of high-risk paediatric brain tumours and their aberrant gene networks*

Jane Kung *EPIPEG: Epilepsy in infancy; relating genotype to phenotype*

Yao-Feng Li *Modelling cell-cell interactions in developmental cortical lesions*

Amy McTague *1. The genetics of early onset epileptic encephalopathy 2. Molecular genetic investigation of epilepsy of infancy with migratory focal seizures*

Adeline Ngoh *Molecular genetic investigation of Landau-Kleffner Syndrome*

Apostolos Papandreou *Translational approaches for beta-propeller associated neurodegeneration*

Birgit Pimpel *Neurophysiological methods to aid decision making in paediatric epilepsy surgery*

Joyeeta Rahman *Novel diagnostic and therapeutic approaches for mitochondrial disorders*

Richard Rosch *Dynamic causal modelling of large-scale networks in human development and their relationship to network abnormalities in paediatric patients with developmental epilepsies*

Tim Tierney *Retrospective motion correction in fMRI data*

Thomas Stone *Genomic classification and analysis of epilepsy-associated glioneuronal tumours.*

Siobhan Titre-Johnson *Ketogenic diet in infants with epilepsy*

Katharina Vezyroglou *Deep phenotyping of alternating hemiplegia in childhood*

Matthew Wilson *Rapid identification of children whose epilepsy can be treated with vitamin B6*

Research Staff

Amit Bali Clinical Leadership Fellow

Anne Brown Research Administrator

Rumana Jalil Trial Coordinator

Chloe Jones Assistant Research Psychologist

Louise Jones Research Administrator

Judith Kalser Clinical Research Fellow

Amy Muggeridge Research Manager

Liz Neal Honorary Research Dietician

Adeline Ngoh Clinical Training Fellow

Manuela Pisch Research Associate

Natasha Schoeler Research Dietician

Siobhan Titre-Johnson Trial Manager

Katharina Vezyroglou Clinical Fellow for Complex Epilepsy

Over the 14 year course of our research programme we have supervised over 40 PhD projects. The majority of our PhD students go on to further epilepsy research or clinical neurology specialities.

Our research network is global. We work with experts from over 30 universities and specialist research units across Europe, America and Australia.

Who we are

Active Collaborators

Professor Nick Freemantle Professor of Clinical Epidemiology and Biostatistics
PRIMENT Clinical Trials Unit, UCL Great Ormond Street - Institute of Child Health

Professor Simon Heales Professor of Clinical Chemistry
UCL Great Ormond Street - Institute of Child Health and Great Ormond Street Hospital

Professor Gregory Holmes Professor of Neurology and Paediatrics
University of Vermont, USA

Professor Matthias Koepp Professor of Neurology
UCL - Institute of Neurology

Professor Irwin Nazareth Professor of Primary Care
PRIMENT Clinical Trials Unit, UCL Great Ormond Street - Institute of Child Health

Professor Ingrid Scheffer AO Paediatric Neurologist and Physician Scientist
University of Melbourne & Florey Institute of Neuroscience and Mental Health

Professor Sanjay Sisodiya Professor of Neurology
UCL - Institute of Neurology

Professor Matthew Walker Professor of Neurology
UCL - Institute of Neurology

Professor Robin Williams Professor of Molecular Cell Biology
Royal Holloway Hospital

Dr Shakti Agrawal Consultant Paediatric Neurologist
Birmingham Children's Hospital

Dr Helen Basu Consultant Paediatric Neurologist
Lancashire Teaching Hospitals NHS Foundation Trust

Dr Bigna Bölsterli Paediatric Neurologist
University Children's Hospital Zurich, Switzerland

Dr Richard Chin Clinical Senior Lecturer
University of Edinburgh

Dr Archana Desurkar Consultant Paediatric Neurologist
Sheffield Children's NHS Foundation Trust

Dr Penny Fallon Consultant Neurologist
St Georges Hospital

Dr Anita Devlin Trustee, *Young Epilepsy*; Consultant Paediatric Neurologist
Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Dougal Hargreaves Health Foundation Improvement Science Fellow and Honorary Consultant Paediatrician
University College Hospital

Dr Elaine Hughes Consultant Paediatric Neurologist
Evelina Children's Hospital

Dr Rachel Kneen Consultant Paediatric Neurologist
Royal Liverpool University Hospital

Dr Andrew Lux Consultant Paediatric Neurologist
Bristol Children's Hospital

Dr Louise Marston Trial Statistician
PRIMENT Clinical Trials Unit, UCL Great Ormond Street - Institute of Child Health

Dr Tim Martland Consultant Paediatric Neurologist
Royal Manchester Children's Hospital

Dr Helen McCullagh Consultant Paediatric Neurologist
Leeds Teaching Hospital

Dr Ailsa McLellan Consultant Paediatric Neurologist
Royal Hospital for Sick Children, Edinburgh

Dr Alasdair Parker Consultant Paediatric Neurologist
Cambridge University Hospital

Dr Rajib Samanta Consultant Paediatric Neurologist
Leicester Royal Infirmary

Dr Ruth Williams Consultant Paediatric Neurologist
Evelina Children's Hospital

What we do



Research Strategy

The principle objective of research within the unit is to reduce the overall burden for children with epilepsy and establish successively better long-term outcomes.

Collaboration and integrated working across the unit puts us in a unique position to:

- ✓ incorporate reviews of children across the entire range of complexity and at all stages of diagnosis and care
- ✓ extend the continuation of our work into adulthood, through UCL, allowing study across the whole age range
- ✓ improve vital understanding beyond medical treatment, through the diagnostic, educational and behavioural expertise within Young Epilepsy.

We operate under six strategic goals:

GOAL 01

Gain a better understanding of the medical causes of epilepsy

21% current projects contribute to this goal

What are the underlying mechanisms and aetiologies responsible for seizures? | Q

How do we answer this?

- Cohort epidemiological studies to determine incidence, prevalence and outcome ✓
- Population and family studies to gain further insights into new treatments ✓
- Studies to determine the molecular basis to the epilepsies ✓
- Enhanced structural studies using neuroimaging to increase detection of structural correlates ✓
- Correlative studies in neurophysiology to enhance detection of origin ✓
- Pathological examination of tissue from surgical specimens to enhance our understanding of structural correlates and related epileptogenesis ✓

GOAL 02

Gain a better understanding of how epilepsy affects development and behaviour

19% projects currently contribute to this goal

What are the underlying mechanisms of neurodevelopmental and behavioural compromise in childhood epilepsy? | Q

How do we answer this?

- Cohort studies to evaluate prevalence, natural history and outcome of comorbidities ✓
- Experimental animal studies to examine the effects of epileptiform discharges on development ✓
- Correlative neurophysiology and neuropsychology studies ✓
- Collaborative outcome studies across the age range ✓

GOAL 03

Determine the benefits of early interventions in improving long-term outcomes

33% projects currently contribute to this goal

How does early intervention improve outcome? | Q

How do we answer this?

- Short and long-term evaluation of outcome following early epilepsy surgery ✓
- Evaluation of new medical treatments ✓
- Evaluation of educational intervention ✓

GOAL 04

Gain a better understanding of barriers to learning and determine the benefits of educational interventions

10% current projects contribute to this goal

How does epilepsy affect learning? | Q

How do we answer this?

- Evaluation of measures of progress in children with severe impairments ✓
- Evaluation of targeted educational interventions across all educational settings ✓
- Enhance the understanding of possible impairments and interventions of professionals working with children with epilepsy ✓

GOAL 05

Reduce the burden of epilepsy to the young person, family and agencies involved

10% projects currently contribute to this goal

How can we make life better for children and families and make support systems more effective? | Q

How do we answer this?

- Interventional behaviour programmes ✓
- Rehabilitation ✓
- Assessment of service provision ✓
- Evaluation of the impact of epilepsy on family life ✓

GOAL 06

Develop a network of multidisciplinary professionals to strengthen our research and shape the education of future practitioners

8% projects currently contribute to this goal

How can we better share our knowledge to promote a collegiate environment to nurture future research excellence? | Q

How do we answer this?

- Development of training fellowships ✓
- Projects working towards higher degrees with encouragement for independent working thereafter ✓
- Joint working between ICH, GOSH and Young Epilepsy ✓
- Enhancing research and interoperability across all areas of expertise ✓



Research Project Update

Epilepsy in Infancy: relating phenotype to genotype (EPIPEG)

Project Aim: To improve diagnosis and treatment outcome for young people with epilepsy by studying newly presenting patients, under 12 months of age, and their response to treatment. A clinical database will be established to be used as a resource for health practitioners when determining the best course of treatment for a particular diagnosis.

What this means: We aim to understand much more about early onset epilepsies to help families to understand what to expect in terms of prognosis, developmental outcome and treatment. We are investigating genetics in order to support targeted treatment and for this treatment to start as early as possible, thereby reducing the burden on the infant and family.



Investigators: Helen Cross, Manju Kurian, Rod Scott, Christin Eltze, Finbar O'Callaghan, Michelle De Haan, Elaine Hughes, Jane Kung, Manuela Pisch, Katharina Vezyroglou, Chloe Jones, Judith Kalser

Update: Site recruitment was closed in February 2017 with 53 active sites across South East England (80% uptake). Over 160 patients have been referred to date with emerging cohort trends such as greater proportion of patients being male and an unexpectedly high prevalence of family history of epilepsy. We have begun the sleep study arm of the project and are starting the genetic investigation phase. We have approval to extend the recruitment period until the 30 October 2017.

The genetics of early onset epileptic encephalopathy

Project Aim: The project aims to identify novel early onset epileptic encephalopathy genes which will contribute to the understanding of the disease mechanisms involved in such epilepsies.

What this means: We want to know what has caused the epilepsy so we can better understand the processes in the brain that have gone wrong. We hope to use some new treatments for these processes that might not only apply to this rare epilepsy but also to some more common epilepsies. So far, we have found a previously unidentified gene which causes a severe early onset epilepsy.



Investigators: Amy McTague, Helen Cross, Dimitri Kullmann, Rod Scott, Manju Kurian

Update: Following investigation in the early onset epileptic encephalopathy cohort, 12 patients have been identified to have mutations in KCNT1. This series has been described in a manuscript undergoing minor revision for *Neurology*. Further gene discovery work is ongoing and investigation of the cohort has also lead to expansion of the phenotypes of known genes such as RARS2, PLCB1, GABRB3, TBC1D24, FOXG1 and GNA01.



What we do



The genetics of Landau Kleffner Syndrome

Project Aim: The project aims to identify novel genes which will contribute to the understanding of the disease mechanisms causing language impairment and seizures in this epileptic disorder.

Investigators: Adeline Ngoh, Maria Clark, Brian Neville, Helen Cross, Rebecca Greenaway, Rob Harvey, Dimitri Kullmann, Manju Kurian

What this means: We aim to identify the genes responsible for Landau Kleffner Syndrome in the hope this will help us to understand why it causes seizures and language difficulties. Understanding this will lead to more targeted and earlier treatment.

Update: The team has screened 50 patients for mutations in the gene, GRIN2A, previously reported to be a cause of Landau Kleffner Syndrome and related epilepsy syndromes in 8-20% of patients. Mutations were identified in six patients (12%). GRIN2A negative patients have had coding regions of their DNA screened for other disease-causing genes and analysis of this data is currently underway.

The team has identified GRIN2A mutations in seven patients (approximately 12%). Currently, functional investigations are ongoing to determine the effect of the novel GRIN2A mutations identified. Analysis of whole exome sequencing data continues, along with functional experiments to evaluate interesting potential candidate genes are underway.

Corticosteroids or clobazam for ESES Syndrome: a European, multicentre, randomised, controlled clinical trial (RESCUE ESES)



Project Aim: An international multicentre randomised controlled clinical trial with blinded outcome assessment to determine the best treatment for children with Electrical Status Epilepticus in Sleep (ESES) Syndrome.

What this means: Encephalopathy with Electrical Status Epilepticus in Sleep (ESES) Syndrome is a rare epilepsy syndrome of childhood that is characterised by epileptic activity during sleep and problems with cognition or behaviour. ESES resolves spontaneously in puberty, but cognitive problems often remain. Adequate treatment is mandatory to prevent or reverse these cognitive deficits. However, it is unknown which treatment is the best. Treatment with “standard” antiepileptic drugs is not very effective. Some studies suggest that clobazam and steroid treatment may be the best option. The only way to prove which treatment is best is to let a lottery decide which treatment a child gets (randomisation) and then compare the effects of both treatments.

Chief Investigator: Floor Jansen, Utrecht

Local Principal Investigator: Helen Cross

Update: This condition is extremely rare and so recruitment is very slow but steady. We have opened at three UK sites (London, Edinburgh, Glasgow), and other European Union countries including Italy (Pavia), France (Paris, Lyon, Strasbourg), Belgium (Brussels, Leuven), Germany (Kehl, Freiburg, Kiel, Vogtareuth), Denmark (Dianalund), Finland (Helsinki), Romania (Bucharest), Bulgaria (Sofia) and Spain (Madrid).



Pilot study of cardiac rhythm in Dravet Syndrome: a cause of SUDEP?



Project Aim: To determine whether heart rhythm abnormalities are aggravated at times of illness in children with Dravet Syndrome and establish whether this in turn has implications for management and monitoring at times of illness. We hope this might lead to studies of acute preventative therapies at such times.

Investigators: Helen Cross, Juan Pablo Kaski, Sarah Aylett, Elaine Hughes, Sanjay Sisodiya, Katharina Vezyroglou

Update: This study involves parents retaining an ECG machine at home, and recording the heart rhythm during illness. Eight families have been recruited and have participated to date. Data collection is ongoing but slow as this is a rare condition.

What this means: We know that people with Dravet Syndrome are susceptible to additional heart problems. We want to know if heart problems can arise from periods of illness such as having a cold or a fever. If so, then we will work to change guidelines for support of patients with Dravet Syndrome in times of illness and ensure heart problems are considered.

Cardiac Arrhythmias in Dravet Syndrome (CADS)

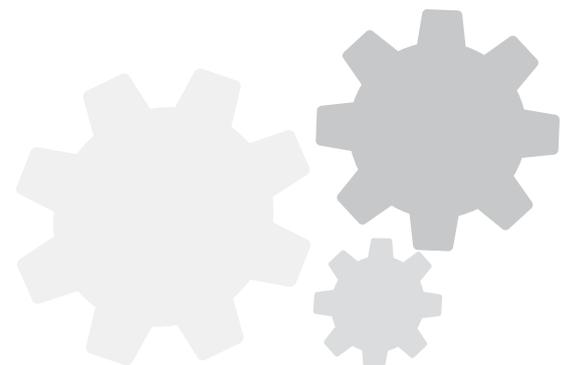


Project Aim: An international study to assess the prevalence of cardiac arrhythmias in patients with Dravet Syndrome and to compare the prevalence of cardiac arrhythmias between these patients and those with other types of epilepsy.

Investigators: Roland Thijs, Sharon Shmueli, Sanjay Sisodiya, Helen Cross

Update: We have ethical approval and are currently opening GOSH as a recruitment site. We hope to have data collection complete by Summer 2018.

What this means: This is an international study, lead by the Stichting Epilepsie Instellingen Nederland (SEIN) and conducted in the Netherlands, Germany and the UK. We know that people with Dravet Syndrome have a higher risk of Sudden Unexpected Death in Epilepsy (SUDEP) and we want to understand if this is connected to heart problems. We hope to evidence the need for treatment pathways to include both cardiac and neurological monitoring as standard care in Dravet Syndrome.



What we do

The fast without the spurious: developing a system for robust and rapid simultaneous EEG-fMRI measurements



Project Aim: To develop more advanced EEG-fMRI scans that may better detect brain areas active at the start of seizures. To do this we are trying new motion-correction technology that tells the scanner where the head is using a camera and a marker attached to a dental retainer and updates the scanner accordingly.

What this means: We are trying to understand exactly what parts of a patient's brain are active during a seizure and whether or not they may be contributing to seizure activity. This study will help us to better identify any abnormalities causing the seizures and, we hope, lead to more targeted treatment earlier.

Investigators: Amy McDowell, Danilo Maziero, David Carmichael, Helen Cross, Kelly St Pier, Nikolaus Weiskopf

Update: This project is now coming to a close and we are writing up both another advancement to improve EEG quality during subject movement and our assessment of more rapid fMRI sequences. We have been collecting a small case series so far to test our new EEG-fMRI acquisition and hope to capture the onset of seizures.

Betashot - a feasibility study of the use of Betashot, a medium chain triglyceride-based (MCT) formula for special medical purposes in children and adults with epilepsy



Project Aim: This feasibility study is to evaluate the use of Betashot, a MCT based food for special medical purposes. This study aims to determine whether a product, primarily consisting of Decanoic Acid (C10) is well tolerated in a population of individuals with epilepsy.

What this means: This is a tolerability study related to the ketogenic diet. We want to know if patients are happy to take it. We do not fully understand how the ketogenic diet works but research suggests that medium chain fatty acids (MCTs) may be key in the efficacy of the diet. We hope this product, if tolerable by patients, will ease the demanding ketogenic diet administration.

Investigators: Matthew Walker, Helen Cross, Sanjay Sisodiya, Simon Heales, Rumana Jalil, Natasha Schoeler

Update: This tolerability study is recruiting adults and children with complex epilepsy. Recruitment will be complete by the end of 2017. The first patient was recruited in July 2016 and we have recruited 60 patients into the trial.



Improving Care in Epilepsy (ICE) for children, young people and families (formerly the Darzi Fellowship Project)



Project Aim: To implement an innovative model of care that improves outcomes by better reflecting the broad impact epilepsy has on the individual person, by virtue of being young person and family-centred, integrated across different sectors providing care, and measured on meaningful outcomes.

Investigators: Amit Bali, Carol Long, Monica Lakhanpaul, Kerry Robinson, Helen Cross

Update: This is a collaborative project between Young Epilepsy, UCL Great Ormond Street Institute of Child Health, UCLPartners and Whittington Health.

Current work streams include the development of an epilepsy registry linked to individualised care plans, the co-creation of young people's networks, and the commissioning of an economic evaluation of the costs versus cost-savings of providing integrated epilepsy care.

To achieve this, we need to make intelligent use of relevant data, keeping young people and families at the centre, such that it improves care both for the individual and as a whole for the 112,000 young people under 25 in the UK with epilepsy.

What this means: We want to ensure services for epilepsy are joined up, and are provided in partnership with young people and families. We want to ensure they receive personalised, holistic care. Our work to date has told us this is imperative. This requires improved communication, understanding what outcomes really matter, tailoring care and thinking with a whole systems strategy across all sectors.

What I Need In School (WINS) - Developing guidelines for best practice for young people with epilepsy in schools in the UK

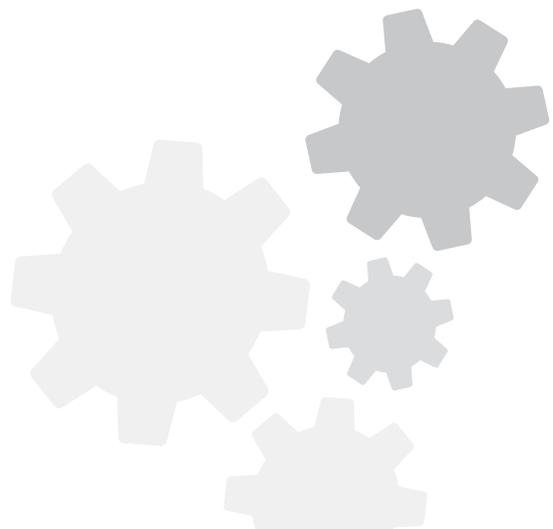


Project Aim: To garner the views and experiences of school age children (6-15 years) with epilepsy, their parents and teachers regarding the impact of epilepsy on school functioning and their current and desired educational supports for young people with epilepsy.

Investigators: Colin Reilly, Patricia Atkinson, Chloe Jones, Helen Cross

Update: This project is now fully funded and has been granted ethical approval. The project is due to commence in November 2017.

What this means: We know epilepsy can have a profound effect on a young person's learning and we want to ask them, their parents and their teachers to tell us what they feel they need support with and what type of support they would like. We hope this project will enable us to write guidelines for schools to support young people with epilepsy achieve their academic potential.



What we do

Validation of the Assessment of Behaviour and Learning in Epilepsy (ABLE) Tool, a screening instrument for the neurobehavioural comorbidities of childhood epilepsy

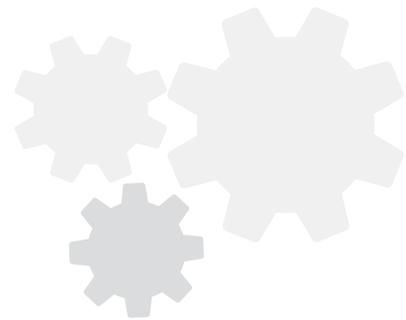


Project Aim: A pilot study to assess the validity of the ABLE Tool, a device developed as part of the Children with Epilepsy in Sussex Schools (CHESS) study. The ABLE tool is a screening tool for teachers and parents to use to identify additional learning and behavioural needs of children with epilepsy.

What this means: We have created a tool to help parents and teachers understand if a child with epilepsy has additional learning or behavioural needs. We want to know if this is an effective tool to identify such problems and whether this can help to improve support in school.

Investigators: Patricia Atkinson, Colin Reilly, Helen Cross

Update: We are currently applying for ethical approval for this project, having gained approval from the GOSH Clinical Research Adoptions Committee. We are now fundraising for the cost of the project. We hope to implement the project in early 2018.



Ketogenic diet in Infants With Epilepsy (KIWE)



Project Aim: This is a randomised controlled trial to determine the effectiveness on seizure control of the ketogenic diet compared to alternative further antiepileptic drug treatment. Patients are children with epilepsy aged 3 months to 2 years who have failed to respond to two or more pharmacological treatments.

What this means: We want to know if the ketogenic diet is an effective treatment for epilepsy in infants who have not responded to two or more antiepileptic drugs. We want to know if it is an effective alternative to trying additional antiepileptic drugs. We know the ketogenic diet works well for some older children but no-one has determined systematically if it works for infants. If it does, then it provides further options for early treatment.

Investigators: Christin Eltze, Ruth Williams, Nicholas Freemantle, Simon Heales, Rachel Kneen, Louise Marston, Tim Martland, Irwin Nazareth, Helen McCullagh, Alasdair Parker, Shakti Agrawal, Archana Desurkar, Anita Devlin, Helen Basu, Penny Fallon, Andrew Mallick, Andrew Lux, Rajib Samanta, Siobhan Titre-Johnson, Helen Cross, Natasha Schoeler

Update: The project is currently recruiting at 12 centres across the UK. We aim to complete recruitment by January 2019. There have been numerous barriers to recruitment, but have achieved 50 recruited patients to date, one third of the way to our target. With the addition of four extra centres, we hope that recruitment will continue to be maintained.



Non-invasive modulation of brain network dynamics to suppress epileptic activity and improve cognition (EPICONN TM)



Project Aim: A pilot study to measure a reduction in epileptiform activity associated with transcranial alternating current stimulation (tACS) and attention. We look to measure changes in brain connectivity and understand their relationship to epileptiform activity reduction. We hypothesise that in epilepsy brain networks can be targeted by weak electric fields applied to the scalp (tACS) to modulate the brain's connectivity to minimise epileptic activity and maximise cognitive performance.

Investigators: David Carmichael, Frederike Moeller, Elhum Shamshiri, Helen Cross

Update: This project has approval from the GOSH Clinical Research Adoptions Committee and an ethics application is underway with a view to open the study as soon as possible.

What this means: We want to know more about how non-invasive electrical stimulation of the brain affects the brain and how this may be used to control seizures. We know surgery is not always successful and not everyone responds to antiepileptic drugs (AEDs). This project looks at a pioneering, and cost effective, new treatment as an addition or alternative to surgery/AEDs.



The pharmacokinetics, efficacy and safety of brivaracetam in children with repeated electrographic seizures (PETITE)



Project Aim: An international project to provide data on the long-term safety and efficacy of brivaracetam (BRV) in paediatric patients with epilepsy.

1 month to <17 years whom have completed core studies, with at least another 100 participants between the ages of 4 years and <17 years of age who have been diagnosed with partial-onset seizures being directly enrolled into the study.

What this means: We want to understand the best way to use brivaracetam in children with epilepsy.

Participants will receive BRV for at least three years based on the development of approval for BRV, the establishment of a BRV access programme, or if the investigational product is stopped by the sponsor in the specific age group for the participant.

Investigators: Ronit Pressler, Marios Kaliakatsos

Update: We plan to recruit 600 participants across Europe, Mexico and the US with the possibility of adding more countries/regions as required. Participants will be aged between

Several assessments will be carried out during the period of participation in the study which is due to open late 2017.

What we do

Evaluating dietary intervention before surgical treatment for epilepsy (EDIBLE)



Project Aim: This is a work package of the European Union FP7 funded project DESIRE (Development and epilepsy – strategies for innovative research to improve diagnosis, prevention and treatment in children with difficult to treat epilepsy).

The work package is a randomised controlled trial to determine whether seizure freedom, in the treatment of epilepsy associated with focal cortical dysplasia type II, is more likely when resective surgery is performed after a ketogenic diet.

What this means: We are working with research teams across Europe to identify whether surgery is more likely to result in seizure freedom if patients with focal cortical dysplasia type II are on the ketogenic diet before surgery. If so, then we will look at creating new guidelines for pre-surgical treatment in order to increase the chances of seizure freedom after surgery for patients with this type of epilepsy.

Investigators: Helen Cross is the leader of this work package in the UK and Chief Investigator of the randomised controlled trial. It is coordinated through the Clinical Trials Unit at Liverpool University by the Research Coordinator Christiana Papamichael.

Update: Progress with this project has been extremely slow, not least due to the differing contractual and ethical requirements across sites in different countries in Europe. Unfortunately, due to the poor recruitment and lack of remaining time, the study closed to recruitment in July 2017. A continued study of neuropathology aims to achieve the secondary aims of the study; for instance, whether ketogenic diet leads to methylation changes in tissue.



Prognosis in Landau-Kleffner Syndrome and continuous spikes in slow-wave sleep syndromes – epileptic Encephalopathy Longitudinal Multicentre Omics study (ELMO)



Project Aim: This is an international, longitudinal, prospective multicentre cohort study which seeks to primarily determine if laboratory markers improve upon clinical prediction of disease course and response to treatment in children with difficult to treat epilepsy. Secondly the project will evaluate longitudinal changes in gene expression and gene methylation status that occur during the course of epilepsy from the time of diagnosis.

Chief Investigator: Deb Pal

Local Principal Investigator: Helen Cross

Update: This study has opened sites in the UK (London, Leeds, Edinburgh), France (Angers, Marseilles), Germany (Kiel) and Italy (Rome, Firenze, Milan) and is recruiting patients.

What this means: Epilepsies that seriously affect someone's normal development of cognition and behaviour are termed "epileptic encephalopathies" (EEs). However, the cause of 85% of cases remains unsolved. We want to better understand the effects these conditions have on the brain and to see if we can find a biomarker in the blood to better determine the cause of the problem in order to improve treatment and understanding of what to expect as the condition develops. We know this has been done for people with autism and Alzheimer's so we are hoping to use a similar approach with EE.

Identifying and treating mental health disorders in children and young people with epilepsy: a screening and brief intervention study



Project Aim: Establish the feasibility of routine screening and brief telephone intervention for mental health disorders in paediatric neurology clinics so children and young people with difficulties are able to access the support they need.

Investigators: Sophie Bennett, Isobel Heyman, Sophia Varadkar, Anna Coughtrey, Marta Buszewicz, Sarah Byford, Caroline Dore, Peter Fonagy, Rona Moss-Morris, Terence Stephenson, Susan Tebbs, Erin Walker, Roz Shafran, Helen Cross

What this means: Children and young people with epilepsy are more likely to have emotional or behavioural difficulties than children and young people who do not have a chronic illness. There are lots of studies showing that there are effective treatments for emotional and behavioural difficulties in children, but we don't know whether they also work in children who have epilepsy. We want to know if an online questionnaire and a talking treatment delivered over the telephone can help us to pick up and treat emotional and behavioural difficulties in children and young people with epilepsy.

Update: Our pilot study showed that the method of identification was feasible in terms of numbers completing the online questionnaire (n=406, of which n=232 had significant symptoms of a mental health disorder). Results are promising from the 40 families who took part in the brief intervention, with progress made towards families chosen goals and high levels of satisfaction reported by families and clinicians. Chief Investigators Roz Shafran & Helen Cross were very pleased to have received a grant from the National Institute for Health Research (NIHR) to continue this research over the next five years, which means we will be able to provide the treatment to children and young people from other hospitals across the country to find out if it works in these different settings. The first stage of this larger project will be to hold focus groups with families and clinicians so they can help us to develop the intervention and the research plan.

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Is pyridox(am)ine 5'-phosphate oxidase deficiency, an eminently treatable cause of epilepsy, under-recognised in children?



Project Aim: Improve diagnosis and treatment of children with pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency by using a novel rapid screening dry blood spot assay.

Investigators: Peter Clayton, Philippa Mills, Helen Cross, Ronit Pressler

What this means: The research team has developed a new, quick test to check if someone has an epilepsy disorder called pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency which responds to treatment with vitamin B6. We want to see how employing this test in clinical practice improves the diagnosis and treatment of children with PNPO as it is often overlooked. Early detection and treatment with vitamin B6 will help to prevent disability. We also hope this study may uncover other causes of epilepsy which may benefit from vitamin B6 treatment.

Update: This project has been granted ethical approval and an application for funding to Action Medical Research has been submitted.



What we do



The infant baby enrichment research programme - ENRICH

Project Aim: Discover the relationship between sleep and infant development through the work of two interlinked projects, BabySMART and GentleTouch.

What this means: This study is focused on understanding how sleep contributes to the healthy development of infants. Studies have shown that brain development and learning are heavily influenced by sleep. Regular, quality sleep helps to optimise physical growth and brain development, while a lack of sleep has been linked to long-term negative impacts on behaviour and learning ability. The ENRICH programme will research the effects of lifestyles, sensory experiences and sleep patterns on the cognitive development of healthy infants.

Investigators: Ronit Pressler, Geraldine Boylan

Update: We plan to recruit 75 babies in the UK across both projects. The study is due to open early 2018.



BabySMART (ENRICH)

This is a randomised study which includes a baby massage programme prior to sleep. Parents randomised to the intervention arm will be trained in massage with the aim of a more structured sleep routine, and improved development and cognitive outcomes. Those randomised to the non-intervention arm will follow their normal/planned sleep and care routine.

Participants will be recruited within the first week of life and will be seen at 2 weeks, 4 months and 18 months of age. A baby sleep/bathing diary will be kept by parents and questionnaires will be completed at appointments. A sleep EEG will be taken at both the 4 and 18 month appointments and developmental assessment (Griffiths III) will be conducted.

Gentle Touch (ENRICH)

A subset of 20 BabySMART participants will be approached to also take part in the GentleTouch part of the study. This will aim to determine the effects of pleasant touch administered to a baby's forearm in the supine

and prone positions and observe if a cortical response can be recorded. This will require additional EEGs being taken at the age of 4 weeks and also at 4 months.

Using new quantitative MRI tissue parameter maps to detect and delineate Focal Cortical Dysplasia (FCD)



Project Aim: To develop better imaging methodology by investigating whether using quantitative MRI parameter mapping together with quantitative analysis can provide improved detection, delineation and classification of FCD lesions. This is the first application of these scanning and analysis methods to epilepsy and may lead to a change in local, national and international practice in imaging childhood epilepsy.

Investigators: Sara Lorio, David Carmichael, Helen Cross, Nikolaus Weiskopf, Karin Shmueli, Thomas Jacques, Chris Clark, Kling Chong, Torsten Baldeweg

Update: The team has published a recent review and been busy collating patient and control data including our motion correction technology. Sara Lorio has been working on improving the proton density maps that we obtain and processing susceptibility and diffusion maps with help from our collaborators. These are now starting to be assessed radiologically.

What this means: We know that in FCD, lesions in the brain cause epilepsy. We are developing more accurate techniques for mapping these lesions using Magnetic Resonance Imaging (MRI) in order to greatly improve surgical planning and accuracy. We hope this will lead to better outcomes for children with FCD who have surgery and for us to be able to offer surgery to more children because we can map their lesions.

A European pilot network of reference centres in refractory epilepsy and epilepsy surgery (E-epilepsy)



Project Aim: To trigger accelerated development of epilepsy surgery by promoting cooperation between highly specialised neurology, clinical neurophysiology and neurosurgery centres in all EU regions.

Co-leads: Philippe Ryvlin, Helen Cross

Update: We have established a network of 52 centres across Europe. We have organised regular multidisciplinary discussion of patients, and a website with information for patients and clinicians; virtual multidisciplinary discussion of patients; systematic reviews on pre-surgical evaluation; and outcomes in progress with a view to the formation of guidelines. The network will be sustained as the surgical treatment arm of EpiCARE (see opposite).

What this means: We hope to increase the number and proportion of European children and adults cured of their refractory epilepsy by improving delivery of optimal epilepsy surgery throughout Europe.



What we do

European Reference Network on rare and complex epilepsies (EpiCARE)



Working for patients with rare, low-prevalence and complex diseases, the EpiCARE network seeks to increase the number of seizure free patients in Europe.

EpiCARE is a European Reference Network (ERN) coordinated by Professor Helen Cross for GOSH, which was launched in June 2017.

Traditionally, epilepsy has been treated as a single disease, but these conditions are increasingly viewed as a group of rare and complex diseases. ORPHANET, the portal for rare diseases and orphan drugs, lists 137 disorders with epilepsy as the predominant symptom, however many patients remain undiagnosed and without access to treatment.

One of 24 approved ERNs on rare disorders, EpiCARE has 26 members, spanning 13 countries. Aimed at improving access for patients to diagnostic and therapeutic expertise, we hope these networks will eliminate the need to travel for better care because complex cases will be discussed with the multidisciplinary experts through the network.

EpiCARE will develop and deliver highly specialised diagnostics and care to improve interventions and outcome in individuals with rare and complex epilepsies. Collecting common outcomes through specific disease registries will enhance optimal management in these rare conditions. Although the primary aim of the networks is clinical, a key part will be the development of registries, and ultimately research and clinical trials.



European
Reference
Network

for rare or low prevalence
complex diseases

Network
Epilepsies (ERN EpiCARE)

The EpiCARE network aims to:

- ✓ deliver full access and utilisation of pre-surgical evaluation and epilepsy surgery
- ✓ increase diagnosis of rare causes of the epilepsies
- ✓ enhance identification of patients with treatable rare causes of the epilepsies
- ✓ increase access to specialised care for rare causes, including the development of novel therapies
- ✓ foster research on innovative causal treatments in rare and complex epilepsies.

EpiCARE builds on the work of the pilot ERN E-epilepsy which worked to increase awareness and accessibility of epilepsy surgery, for carefully selected individuals, that effectively used e-tools and multidisciplinary team discussion.



Completed Projects in 2016: Next Steps

The disability complex of early onset epilepsies: Sussex Early Epilepsy and Neurobehaviour (SEEN)

Study team: Brian Neville, Colin Reilly, Patricia Atkinson, Chloe Jones, Ayesha Memon, KB Das, Christopher Gillberg, Rod Scott

This study found that parents (particularly mothers) of children with epilepsy are at greater risk of mental health and sleep problems than parents of children with non-epilepsy related neurodisabilities.

We determined that parents of children with epilepsy are at high risk of mental health and sleep difficulties. This study highlights the need for further understanding of the needs of families in order to provide better support. There is limited population-based research, or research which compares parents of children with epilepsy with parents of children with other neurodevelopmental or neurological conditions.

It was also noted that children with epilepsy have a high neurodevelopmental need and are at increased risk of learning and behavioural difficulties. Those who have epilepsy in early childhood are a particular risk group for such difficulties. Despite this, children with epilepsy rarely have their learning and behavioural needs identified as the focus is often on the need to manage seizures.

These findings highlight the need for epilepsy services to take a family-based approach to care; plus a further need to consider the developmental impact of epilepsy and its impact on families as a whole.

We will submit up to five articles to peer-reviewed journals, following this we will share the wider results of the study and launch our report which outlines our recommendations for service and policy.

Cannabidiol - Safety, tolerability and efficiency of Cannabidiol as add-on therapy in severe childhood epilepsies

Local study team: Helen Cross, Katharina Vezyroglou

This open label study determined that Cannabidiol is an effective add-on therapy for children with severe epilepsy. On average, the seizures experienced by the children were reduced by nearly 40%, and 43% of those taking Cannabidiol saw their seizures cut by half. Three children (5%) stopped having seizures altogether. Side effects included drowsiness, fatigue, diarrhoea and reduced appetite.

This study has added to the evidence base for the use of Cannabidiol in epilepsy. Helen Cross was also Chief Investigator for Europe for the randomised control trial (RCT) of Cannabidiol as add-on therapy in Dravet Syndrome, published in May 2017 (NEJM), and also an investigator in the Cannabidiol RCT in Lennox Gastaut syndrome due to publish soon.

GW Pharma, who sponsored these studies, is applying for a license for the product in the United States and in Europe. Should this be approved, the product will then need to be assessed further before it can be approved for use by the NHS.



Sleep and memory in children with focal epilepsy

Study team: *Samantha Chan, Torsten Baldeweg, Stewart Boyd, Rod Scott, Krishna Das, Ronit Pressler, Helen Cross*

Cognitive impairment is the major co-morbidity in childhood epilepsy, and in many cases will have a larger long-term impact than the seizures themselves. However, the mechanisms contributing to this are poorly understood, precluding targeted intervention. This project examined the structure and regulation of sleep in children with epilepsy. It provided direct evidence of the impact of sleep on cognitive function by correlating neurophysiological characteristics with performance on sleep-dependent neuropsychological tasks administered over the same interval as the sleep recorded. We found that, contrary to expectations, sleep benefits memory consolidation in children with epilepsy to the same degree as controls. However, the benefit of sleep showed an inverse relationship to the nocturnal interictal discharge load. We also employed quantitative EEG analysis of slow wave activity to examine sleep homeostasis in patients with epilepsy, studying a retrospective sample who had undergone partial sleep deprivation. Sleep homeostasis was fundamentally intact in these patients, who had similar clinical characteristics to the prospective sample.

Findings from this project provide the first direct evidence that sleep benefits intellectual functioning in children with epilepsy, particularly where its structure and regulation is intact. Sleep-related memory consolidation may represent a compensatory mechanism, perhaps accounting for the relative cognitive preservation in this cohort of children with epilepsy with a structural aetiology, despite the early onset of seizures.

Improving epilepsy surgery in childhood using fMRI and EEG

Study Team: *David Carmichael, Time Tierney, Elhum Shamshiri, Maria Centeno, Daniel Kohn, Chris Clark, Jonathan Clayden, Ronit Pressler, Helen Cross*

Surgical treatment in epilepsy is effective if the epileptogenic zone (EZ) can be correctly localised and characterised. Here we used simultaneous electroencephalography–functional magnetic resonance imaging (EEG-fMRI) data to derive EEG-fMRI and electrical source imaging (ESI) maps. We evaluated their yield, individual and combined ability to localise the EZ and predict seizure outcome.

Fifty-three children with drug-resistant epilepsy underwent EEG-fMRI. Interictal discharges were mapped using both EEG-fMRI hemodynamic responses and ESI.

EEG-fMRI combined with ESI was found to provide a simple unbiased localisation that may predict surgery better than each individual test, including in MRI-negative patients.

Our computerised classifier was able to correctly detect the epileptic abnormalities in 73% of the patients. It even worked in the very young patients. This shows great technological progress and now we are planning to go one step further by testing the programme on new patients with abnormalities that the neuroradiologist cannot currently identify. The hope is that more children with drug-resistant epilepsy will be able to be considered for epilepsy surgery, and the surgery itself will have greater accuracy and therefore higher chances of freedom from seizures.

We hope these results will motivate the development of clinical services for GOSH and Children's Epilepsy Surgery Service (CESS).

Cerebral blood flow changes preceding epileptic events in children

Study team: Elhum Shamshiri, David Carmichael, Helen Cross

We have found evidence that blood flow changes precede epileptic events in EEG-fMRI and that the changes are typically bi-phasic. This is currently being written up for publication by Ellie Shamshiri who was awarded her PhD this year and is now working as a Post-Doctoral Researcher in Geneva. Using measurements of EEG and near infrared spectroscopy, obtained by Ellie as pilot data, we recently obtained grant funding from GOSH Children's Charity to develop the outcomes of this study further.

Algorithm for neonatal seizure recognition (ANSeR)

Local study team: Ronit Pressler

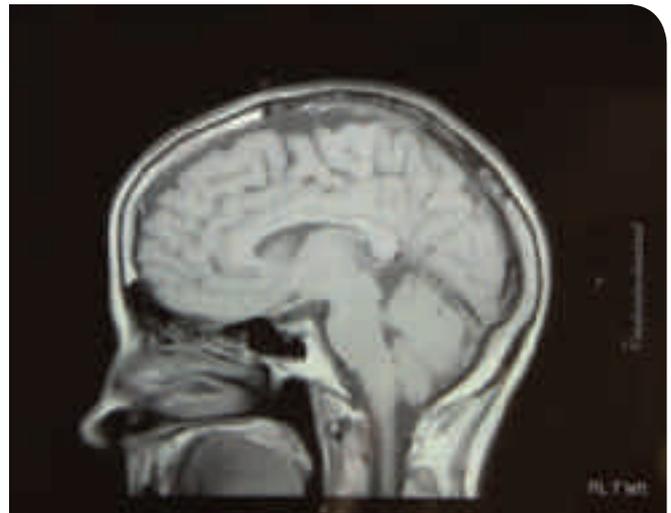
The ANSeR project was a collaborative project in hospitals across Europe, to test a computer algorithm that can detect seizures in babies.

Neurophysiologist expertise is not available in every hospital and certainly not available 24/7. People who have the knowledge and experience to read the EEGs of a newborn are in short supply. A multidisciplinary group of scientists, clinicians and engineers have been working for a number of years to design new equipment and computer programs that will monitor babies and automatically alert us if there are problems. The culmination of this work is now known as ANSeR. The project aim is to give every one of these babies an expert opinion when they need it.

EEG investigation of brain networks in Childhood Absence Epilepsy (CAE) and Juvenile Myoclonic Epilepsy (JME) using EEG-fMRI

Study team: Suejen Perani, Maria Centeno, Helen Cross, Mark Richardson, David Carmichael

We have been evaluating the data obtained. The first part of the study involved us determining if the brains of patients, who have just been diagnosed and have not yet received medication, have abnormalities. We found that the thalamus of these patients is smaller than in medicated patients. This means that the structural abnormality is not caused by medication or seizures but is part of the disease phenotype. We have also been analysing EEG-fMRI data with a number of findings regarding the networks underlying seizures that are currently being written up for publication. Suejen Perani recently received her PhD for this work.



Completed PhD projects 2016/2017 - Congratulations!



Samantha Chan

2017

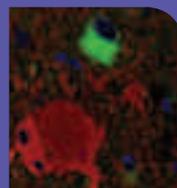
Sleep and cognition in epilepsy: Sleep and memory in children with focal epilepsy



Suejen Perani

2017

Investigations of brain networks in Childhood Absence Epilepsy and Juvenile Myoclonic Epilepsy using fMRI



Fatma Scerif

2016

Identification of gene networks in childhood epilepsy



Elhum Shamshiri

2016

Understanding cerebral blood flow changes preceding epileptic events in children



Paediatric Epilepsy Masterclass 2017

Sleep, cognition and epilepsy: the relevance of sleep

In April 2017 we held a two-day Masterclass for paediatric epilepsy professionals hosted by Professor Helen Cross. Following the outcomes of Dr Chan's project, *Sleep and memory in children with focal epilepsy*, this Masterclass brought together world-renowned sleep experts to discuss the importance of sleep hygiene in epilepsy treatment and wider care.

We were honoured to welcome Professor Patrick Van Bogaert, Paediatric Neurologist at the University of Angers, France, to give the keynote speech before a full day's conference of talks and workshops from:

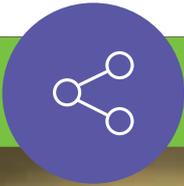
- ✓ Professor Helen Cross OBE, The Prince of Wales's Chair of Childhood Epilepsy
- ✓ Professor Matthew Walker, Head of Clinical and Experimental Epilepsy *UCL Institute of Neurology*
- ✓ Professor Paul Gringras, Professor of Children's Sleep Medicine and Neurodisability *Evelina London Children's Hospital*
- ✓ Dr Samantha Chan, Clinical Research Fellow *UCL GOS - ICH*
- ✓ Dr Bigna Bölsterli, Paediatric Neurologist *University Children's Hospital Zurich, Switzerland*
- ✓ Dr Manuela Pisch, Research Associate *UCL GOS - ICH*
- ✓ Dr Zenobia Zaiwalla, Consultant Neurophysiologist *John Radcliffe Hospital*

The Masterclass was attended by over 60 epilepsy specialists. We aimed to challenge and support delegates to:

- ✓ broaden their knowledge of the role of sleep in the treatment of epilepsy
- ✓ share best practice and diagnostic processes when considering sleep therapy
- ✓ offer networks opportunities of peer support with treatment and support for patients and families with difficult diagnoses.

We hold one Masterclass per year and aim to bring together as wide a professional audience as possible to encourage cross-discipline discussion and holistic outcomes.

Past themes have included *Is it epilepsy; the identification and management of non-epileptic events in children*, April 2016; *Acquired brain injury; consequences and management*, April 2015; *Transition from paediatric to adult services*, July 2014; *Early onset epilepsies*, November 2013.



Paediatric Epilepsy Research Retreat 2017



“An enjoyable feast of epileptology!”

Professor Ingrid Scheffer AO,
Research Moderator 2017

Over the past
7 years, 154
projects have been
discussed at the
Research Retreat

Our Research Retreat is hosted by Professor Helen Cross OBE, The Prince of Wales's Chair of Childhood Epilepsy, and serves as an annual gathering of researchers and collaborators across our research unit. This meeting gives researchers the opportunity to discuss ongoing projects, completed projects and future directions of research with a unique range of epilepsy specialists.

This year we presented 20 current projects and welcomed 89 guests from over 20 organisations and 6 countries. Almost every attendee has a direct clinical role in supporting children and young people with epilepsy. We welcomed back previous speakers and were able to see the outcomes of discussions started at previous Retreats reflected in the last year's work through sub-projects, collaborations and shared data.

2017 marked our 7th Retreat and we were honoured to welcome Professor Ingrid Scheffer AO as Research Moderator. Professor Scheffer joined us from University of Melbourne and Florey Institute of Neuroscience and Mental Health. She is Chair of Paediatric Neurology Research at the University of Melbourne, Senior Principal Research Fellow at the Florey Institute of Neuroscience and Mental Health, and Vice President and a founding Fellow of the Australian Academy of Health and Medical Sciences.

Discussions at the end of each presentation give investigators the opportunity to receive comments and feedback from fellow researchers and principal investigators representing a vast array of different fields. We altered the format to ensure every speaker had 30 minutes which allowed ample time to allow in depth discussion.

What we do



The Retreat is also a highly social occasion, giving international and domestic researchers what is often their single annual opportunity to meet colleagues and peers face to face. This vital networking truly highlights the breadth of epilepsy research being undertaken across the unit. The meeting critically serves as a way of motivating young researchers to understand this diversity whilst forming the collaborations which underpin excellent science.

This year, the refreshingly non-competitive and encouraging environment of the Research Retreat has been extended into a series of monthly satellite meetings held at ICH. Each meeting welcomes two researchers to present their work for discussion. This increases the opportunity for researchers to receive feedback and continues the momentum of the Research Retreat throughout the year. From these meetings we have initiated a multidisciplinary Rasmussen Syndrome Working Group, the aims of which are to assess and improve the clinical pathway of children with this syndrome. The Research Retreat and additional meetings are a critical contributor to creating a collegiate environment across the unit and nurturing new talent in paediatric epilepsy research.

“An excellent group of researchers...a lovely example of the global development of the field.”

Paediatric Neurologist

Speakers use half their time to present their project because leaving opportunity for discussion with the multidisciplinary audience is just as important

The Research Retreat is refreshingly non-competitive.

Research can be a very competitive world and we create a nurturing environment in which to support future stars



Research Publications 2016/17

Primary Research

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4. Amin S, Slaney K, **O'Callaghan F** (2017) **Musculoskeletal involvement in tuberous sclerosis.** *Arch Dis Child.* 102(2):178.
5. Apps JR, Hutchinson JC, Arthurs OJ, Virasami A, Joshi A, Zeller-Plumhoff B, Moulding D, **Jacques TS**, Sebire NJ, Martinez-Barbera JP (2016) **Imaging Invasion: Micro-CT imaging of adamantinomatous craniopharyngioma highlights cell type specific spatial relationships of tissue invasion.** *Acta Neuropathologica Communications.* 4(1):57.
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9. Barry JM, Sakkaki S, Barriere SJ, Patterson KP, Lenck-Santini PP, **Scott RC**, Baram TZ, Holmes GL (2016) **Temporal Coordination of Hippocampal Neurons Reflects Cognitive Outcome Post-febrile Status Epilepticus.** *EBioMedicine.* 7:175-90.
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11. Beniczky S, Neufeld M, Diehl B, Dobesberger J, Trinka E, Mameniski R, Rheims S, Gil-Nagel A, Craiu D, **Pressler R**, Krysl D, Lebedinsky A, Tassi L, Rubboli G, Ryvlin P (2016) **Testing patients during seizures: A European consensus procedure developed by a joint taskforce of the ILAE - Commission on European Affairs and the European Epilepsy Monitoring Unit Association.** *Epilepsia.* 57(9):1363-8.
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Reviews, editorials and letters

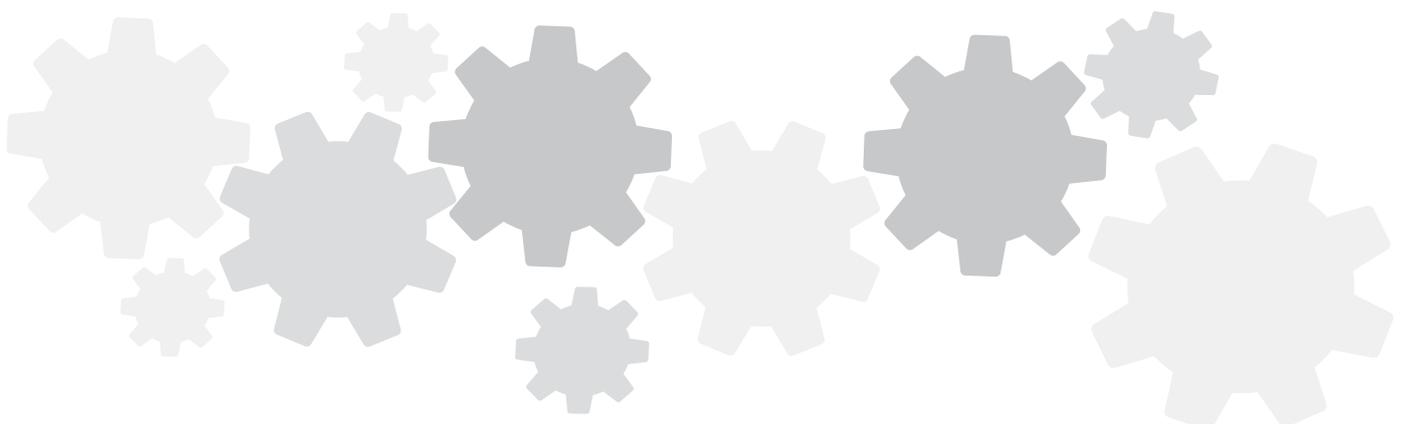
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University College London

Faraneh Vargha-Khadem

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5th UK Paediatric Neuropsychology Meeting

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UCL GOS - ICH and UCL Institute of Neurology and Genomics England

Helen Cross et al

Paediatric Epilepsy Masterclass 2017
Young Epilepsy

Krishna Das et al

PLEAT Trainee Day 2016
Young Epilepsy

Shamima Rahman

Professional workshops on Leigh syndrome and Pyruvate
dehydrogenase deficiency
Lily Foundation family weekend, London, November 2016

Shamima Rahman

Training Advisor for Inherited Metabolic Medicine
Royal College of Paediatrics and Child Health





Professional Recognition and Awards



Manju Kurian

L'Oréal - UNESCO Women in Science Award

May 2017

L'Oréal - UNESCO

Research Professorship to investigate genetic causes of cerebral palsy

August 2017

National Institute of Health Research (NIHR)

John Stobo Prichard Awards

2018

International Child Neurology Association (ICNA)



Helen Cross

2017 Sidney Carter Award in Child Neurology

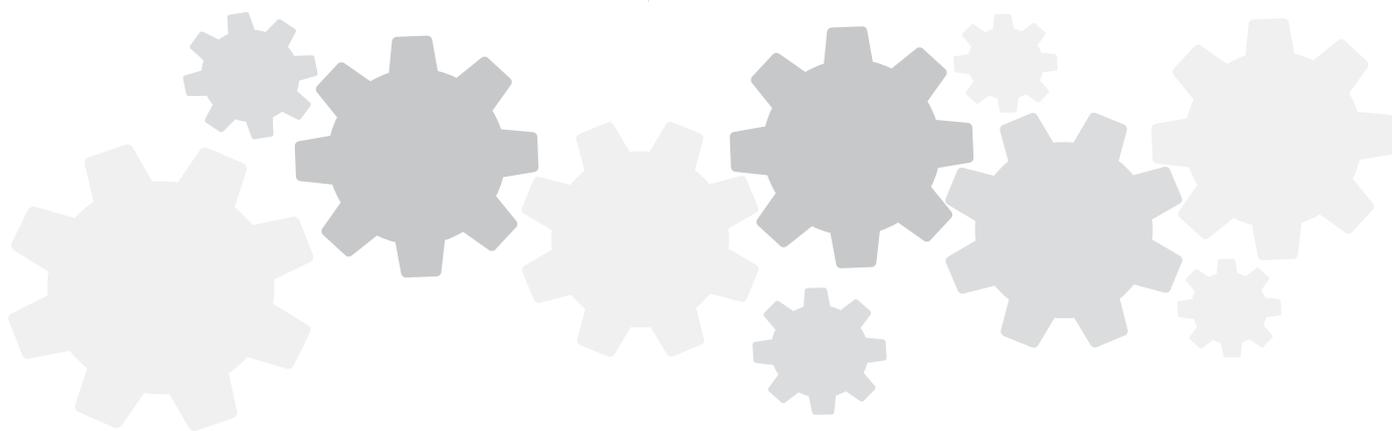
April 2017

American Academy of Neurology

Frank Ford Award

2018

International Child Neurology Association (ICNA)





Shamima Rahman

Archibald Garrod Award
September 2016
Society for the Study of Inborn Errors of Metabolism (SSIEM)



Torsten Baldeweg

Deputy Head of the Developmental Neurosciences Programme
April 2017
UCL GOS - ICH



Chris Gillberg

INSAR Lifetime Achievement Award for Autism Research
May 2016
International Society for Autism Research (INSAR)

Photo Credit: Emelie Asplund



Amy McTague

International Child Neurology Association (ICNA) Young Investigator
October 2016
British Paediatric Neurology Association (BPNA)



Finbar O'Callaghan

Professor of Paediatric Neuroscience
June 2017
UCL GOS - ICH



Philippa Mills

Senior Lecturer (GGM)
June 2017
UCL GOS - ICH



At Young Epilepsy we want to create better futures for young lives.

As a national charity and a centre of expertise for all young people with epilepsy, we have over 100 years experience to share.

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Young Epilepsy is the operating name of The National Centre for Young People with Epilepsy. Registered Charity No: 311877 (England and Wales).