2019

Paediatric Epilepsy Research Report

Young Epilepsy

Great Ormond Street Hospital for Children NHS Foundation Trust

UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Inside

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Introduction

I am delighted to present our annual research report for the period July 2018 to June 2019 for the paediatric epilepsy research unit across Young Epilepsy, UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children.

We have initiated 13 new research projects, adding to 20 active projects spanning the clinical, educational and social elements of paediatric epilepsy. We have published 110 peer-reviewed items of primary research and a further 54 chapters in books, reviews and commentaries of expert opinion.

During this period, Young Epilepsy Chief Executive Carol Long caught the research bug and moved on to begin her PhD at Durham University. We welcomed our new Chief Executive, Mark Devlin at our Paediatric Epilepsy Research Retreat in January 2019. As an organisation, we are launching a new strategy which sets our research programme as one of the four key offers at Young Epilepsy, and we look forward to sharing our research more widely in the public sphere as this strategy matures.

We continue to share expertise with research and clinical colleagues and in December 2018, we held our 6th Paediatric Epilepsy Masterclass. The theme of this Masterclass was 'The Rare Epilepsies' and we were honoured to welcome Professor Alexis Arzimanoglou, Director of the Epilepsy, Sleep and Paediatric Neurophysiology Department at the University Hospital of Lyon, France, as our Key Note Speaker.

January 2018 saw our 9th International Paediatric Epilepsy Research Retreat for researchers and collaborators across the unit, moderated by Professor William Gaillard of The Children's Research Institute,Washington DC USA. The Retreat is a one-of-a-kind event where early career and seasoned researchers meet to constructively share their research and forge collaborations.

This report features a spotlight on a truly innovative project which will change the UK's diagnostic and surgical evaluation imaging suite for childhood epilepsy. The MEG Project is a collaboration, arising from the 2019 Paediatric Epilepsy Research Retreat, which will culminate in the world's first functional magnetically shielded room and OP-MEG system at Young Epilepsy's headquarters in Surrey. It will be the first MEG system accessible to children and people with complex needs without sedation.

Young Epilepsy's vision is to build a society where children and young people with epilepsy are enabled to thrive and fulfil their potential. Our research programme exists to establish successively better outcomes by driving early diagnosis and intervention in every aspect of childhood epilepsy.

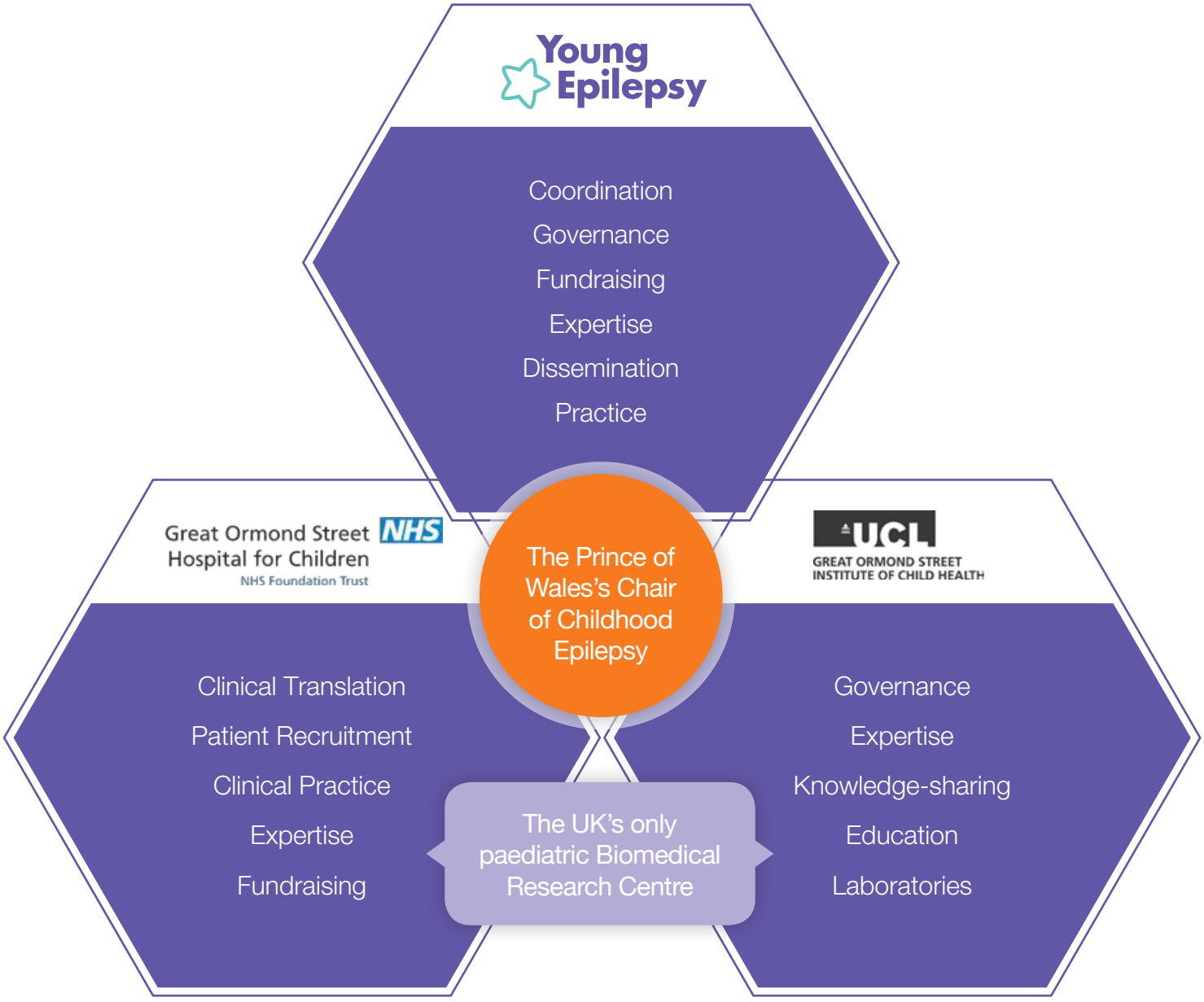
Professor Helen Cross OBE

The Prince of Wales's Chair of Childhood Epilepsy

Who we are

Research Partners

Led by the Prince of Wales's Chair of Childhood Epilepsy, Professor Helen Cross, our research programme is a collaborative scheme between Young Epilepsy, Great Ormond Street Hospital and UCL GOS - Institute of Child Health.



Young Epilepsy exists to create a society where children and young people with epilepsy are enabled to thrive and fulfil their potential. A society in which their voices are respected and their ambitions realised.

Under our four key offers; information, health, learning and research, we aim to:

- equip young people with knowledge and promote public awareness
- drive improvements in healthcare and advocate for young people's right to the highest standards of health
- deliver innovative education services and advocate for young people with epilepsy's right to an education
- coordinate and fund research into the causes, treatments and impact of childhood epilepsy

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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.

Research Funding

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

Our collaborative funding strategy 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 multidisciplinary fundraising, which allows us to keep the expertise within the unit and develop the impact of our work.

Alongside academic grants raised by researchers and academic institutions, we rely on the grace of designated funding from private individuals and Trusts, raised by Young Epilepsy, which allow us to redirect funds where the need is greatest within a project. This flexibility is vital and provides stability when the parameters of projects change.

The future of this programme rests on the ability to maintain and build the current infrastructure which allows us to maintain a base of operations to lead, coordinate and provide governance.

We remain ever grateful for the generosity and dedication of the organisations and individuals who support our work.

Thank you!

Action Medical Research

Brain Tumour Charity

Cancer Research UK

Child Health Research Trust

Children with Cancer UK

Epilepsy Research UK

Ethypharm

European Commission

Freya Foundation

Great Ormond Street Hospital Children's Charity

GW Pharmaceuticals

Innovate UK

James Lewis Foundation

Johnson and Johnson Innovation

Lily Foundation

Neville UK

National Institute of Health Research (NIHR)

NIHR GOSH Biomedical Research Centre

Novartis

Nutricia

Oakgrove Foundation

Olivia Hodson Cancer Fund

Rosetrees Trust

Science Foundation Ireland

Sobell Foundation

Sparks Charity

Syneos Health

VitafloPaediatric

Waterloo Foundation

Wellcome Foundation

Wolfson Foundation

Wyfold Charitable Trust

Research Team

The research team contribute to a wide spectrum of activities from basic science 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
Young Epilepsy; UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

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

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

Professor Michelle De Haan Professor in Infant and Child Development
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Isobel Heyman Consultant Child and Adolescent Psychiatrist
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Tom Jacques Reader in Paediatric Neuropathology
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NIHR Research Professor and Professor of Neurogenetics
UCL GOS - Institute of Child Health

Professor Finbar O'Callaghan Professor of Paediatric Neuroscience, Head of UCL GOS - ICH Clinical Neurosciences Section
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Shamima Rahman Professor of Paediatric Metabolic Medicine
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Rosamund Shafran Chair in Translational Psychology
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Rod Scott Professor of Paediatric Neuroscience
UCL GOS - Institute of Child Health; Great Ormond Street Hospital for Children and University of Vermont, USA

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Great Ormond Street Hospital for Children

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Young Epilepsy and Great Ormond Street Hospital for Children

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Dr Philippa Mills Associate Professor of Inherited Paediatric Metabolic Disease
UCL GOS - Institute of Child Health

Dr Friederike Moeller, Consultant Clinical Neurophysiologist
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Ronit Pressler Consultant in Clinical Neurophysiology and Clinical Lead of GOSH Telemetry Unit, Honorary Associate Professor in Clinical Neuroscience
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Colin Reilly Educational Psychologist
Young Epilepsy and UCL GOS - Institute of Child Health

Dr Robert Robinson Consultant Paediatric Neurologist
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Richard Scott Consultant in Clinical Genetics
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Rachel Thornton Consultant in Neurophysiology
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Mr Martin Tisdall Consultant Paediatric Neurosurgeon and Honorary Associate Professor
UCL GOS - Institute of Child Health; Great Ormond Street Hospital for Children and National Hospital for Neurology and Neurosurgery

Dr Sophia Varadkar Consultant Paediatric Neurologist
UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

PhD students

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

Filipa Bastos *Memory outcome after temporal lobectomy*

Victoria Bryant *Sudden Unexpected Death in Childhood; characteristics, autopsy findings and investigation*

Aswin Chari *Novel network evaluation of intracranial EEG to identify the epileptogenic zone*

Rosie Coleman *Functional and structural plasticity after epilepsy surgery*

Bianca De Blasi *Multi-parametric imaging using hybrid PET/MRI to investigate the epileptogenic brain*

Maria Eriksson *Cognitive outcomes after neurosurgical treatment for focal epilepsy: developing a neuroanatomical predictive model for clinical decision making*

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

Nandaki Keshavan *Gene Therapy for Deoxyguanosine Kinase Deficiency*

Jane Kung *Epilepsy in infancy - relating phenotype to genotype*

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

Dr Adeline Nogh *Molecular Genetic Investigation of Landau-Kleffner Syndrome*

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

Apostolos Papandreou *Investigation of disease mechanisms and screening for treatments in Beta-Propeller Protein- Associated Neurodegeneration (BPAN)*

Izabella Smolicz *The biology of paediatric central nervous system tumours at post-mortem*

Aitkaterini Vezyroglou *Deep phenotyping of alternating hemiplegia in childhood*

Research Staff

Sophie Adler-Wagstyl Research Associate

Konrad Adler-Wagstyl Research Associate

Amit Bali Clinical Leadership Fellow

Maryam Balogan Research Administrator - KIWE

Katy Barwick Genetics Associate - EpiPEG

Anne Brown Research Administrator

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Elaina Maldonado Research Associate

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Manuela Pisch Research Associate

Mirja Steinbrenner Research Associate

Natasha Schoeler Senior Research Dietitian

Tom Stone Research Associate

Active Collaborators

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Professor Matthew Walker Professor of Neurology
UCL - Institute of Neurology

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Dr Penny Fallon Consultant Neurologist
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Loughborough University

What we do

Programme strategy

Our research programme exists to establish successively better outcomes by improving early diagnosis and intervention in every aspect of childhood epilepsy.

Collaboration and integrated working across the partner organisations puts us in a unique position to incorporate data which spans:

- the entire range of complexity and comorbidity in epilepsy
- all stages of diagnosis and care
- the full age range, from neonates to young adults
- multidisciplinary expertise to improve holistic understanding of epilepsy and service design.

We operate under six strategic goals:

GOAL 01

Gain a better understanding of the medical causes of epilepsy

24% projects currently contribute to this goal

The majority of epilepsy treatment is symptomatic. The more we know about the underlying causes of the epilepsies, the more chance there is of developing curative, targeted treatments.

- 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 or genetic 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

22% projects currently contribute to this goal

Epilepsy is associated with myriad comorbidities. Evidence suggests that the effects of these comorbidities have a greater impact than seizures over the course of someone's life. This work will help us to understand how to treat epilepsy holistically.

- 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

GOAL 03

Improving diagnosis and treatment to determine the benefits of early interventions in improving long-term outcomes

26% projects currently contribute to this goal

The longer one has epilepsy, the longer its underlying cause is able to threaten or cause neurological damage. Effective diagnostic processes, optimal treatments and early intervention are vital in slowing or halting any damage.

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

GOAL 04

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

8% current projects contribute to this goal

We know that epilepsy can affect the way people learn and therefore may significantly affect someone's academic achievement if not properly understood. We want to know exactly what the challenges are and how best to support children with epilepsy in education.

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

GOAL 05

Make life better for children and families and make support systems more effective

15% projects currently contribute to this goal

Childhood epilepsy can affect the whole family and treatment must involve multiple disciplines and agencies. Support for families must be evidenced and treatment pathways must be made more efficient. Evidencing these needs allows service providers to plan more effective services.

- Interventional behaviour programmes ✓
- Rehabilitation and follow-up studies ✓
- Assessment of service provision ✓
- Evaluation of the impact of epilepsy on family life ✓
- Evaluation of the economic costs involved in epilepsy care ✓

GOAL 06

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

6% projects currently contribute to this goal

To ensure the continuation of excellent research in paediatric epilepsy by nurturing future talent and continually improving knowledge.

- 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 ✓
- Providing specialist education events and networking opportunities ✓

The MEG Project

What is MEG?

Magnetoencephalography (MEG) is a neuroimaging tool like EEG (electroencephalography), but MEG records brain function by measuring changes in magnetic fields rather than changes in electrical signalling. It can pick up deeper signals, with greater signal gain than EEG.

Current MEG systems are rarely used clinically due to their expense and the need to stay still during testing. They require a large chamber of liquid helium to cool the sensors.

The OP-MEG system is wearable and moveable and does not require cooling. The sensors are getting smaller, lighter and cheaper with each generation.

a typical current clinical MEG system

wearable OP-MEG - an early prototype

current size of new sensors

A world first wearable OP-MEG and Light Mu-Room System at Young Epilepsy.

MEG is an innovative collaboration between UCL GOS –Institute of Child Health (ICH), University of Nottingham (UoN), Magnetic Shields Ltd and Young Epilepsy, funded by Innovate UK.

We aim to develop and test the technical and clinical feasibility of the first lightweight magnetically shielded room for use with cutting edge, wearable Optically Pumped (OP) magnetoencephalography (MEG) technology. The room will be built in the Neville Childhood Epilepsy Centre at Young Epilepsy and will be the first and only set up of its kind once complete, and the only MEG system which is accessible by children and adults with complex needs and without the need for them to be sedated. MEG is a vital part of neurological diagnostics and surgical evaluation which clinicians currently have extremely limited access to.

This project has direct, near-future clinical and patient impact. Advances in imaging techniques over the last 10 years have been crucial to accurate diagnosis, early intervention and success in epilepsy surgery.

MEG itself offers an additional set of metrics, providing a far greater clarity of image, which other techniques do not and the development of imaging technologies such as the OP-MEG will lend great advantages to the assessment tools available to surgeons and clinicians when evaluating patients for surgery and diagnosis.

A vital outcome of this work is to make MEG accessible for children - specifically children with complex needs. Children present a notorious challenge to clinical imaging, including current MEG systems, because patients must stay absolutely still in an uncomfortable machine. The development of the wearable OP-MEG overcomes the need to stay still and has been developed to be significantly more accessible and accurate for children and people with complex needs. Greater accessibility for children means that clinicians will have a better chance of initiating earlier interventions and treatments for children with epilepsy.

Once the room is built, in winter 2020, we will design and run a series of clinical evaluations to determine the technical and clinical protocols for use, ensuring that the use of this technology is tailored to patient specific needs.

What are Mu-Rooms?

The wearable OP-MEG system allows patients to move provided they operate within a magnetically neutral zone. Mu-Rooms create a space shielded from any magnetic interference using Mu-metal and bespoke sheets of copper coils.

Light Mu-Rooms are much cheaper and lighter than current shielded rooms which makes them more feasible for more hospitals to host.

We are working with a specialist engagement team funded by The Wellcome Foundation to ensure that Young Epilepsy's Mu-Room looks and feels like a normal room and has a child-friendly interior.

New Reasearch Projects

Realising the potential of 7T MRI for paediatric imaging

Project Aim: To enable the first 7 Tesla (7T) magnetic resonance imaging (MRI) of paediatric patients with epilepsy being evaluated for surgery at GOSH and Kings College London Hospital (KCLH).

Investigators: David Carmichael, Helen Cross, Martina Callaghan, Shaihan Malik, Thomas Booth

Summary: The current standard resolution for clinical Magnetic Resonance Imaging (MRI) in neurology is 1.5 - 3 Tesla (a measure of the power of the magnet used). This study will look into the practical application and benefit of the 7 Tesla (7T) MRI machines at GOSH and KCLH.

3T MRI machines can show details of the brain as small as 1mm, a 7T machine can show details 50% smaller than this; small enough to detail network connectivity in real time. We believe that the potential of this technology will enable a significant increase in our ability to detect and stratify structural abnormalities causing epilepsy, particularly those due to cortical abnormalities, and through greater accuracy, allow more children to be considered for epilepsy surgery.

A natural history of Pyruvate Dehydrogenase Complex deficiency

Project Aim: To describe the natural history of Pyruvate Dehydrogenase Complex (PDC) deficiency from childhood to adulthood, including the spectrum of molecular diagnoses in affected patients in order to identify genotype/phenotype correlations and predictors of poor prognosis.

Investigators: Nandaki Keshavan, Shamima Rahman

Summary: PDC deficiency is one of the most common mitochondrial disorders. Patients with this condition develop a combination of problems including seizures, neurodisability and have a reduced life expectancy. It is essential to understand the mechanisms underlying the disease in order to identify new treatments, and to understand the natural history of disease in order to prepare for clinical trials. To date, a natural history study of PDC deficiency has not been undertaken in the UK. In collaboration with the Freya Foundation and tertiary paediatric metabolic and neurology centres nationally, we will undertake a multicentre retrospective study to describe the spectrum of symptoms, disease severity, molecular diagnosis, management and outcomes in both children and adult patients with PDC deficiency. We will then collate the data and analyse it to determine whether there are any correlations between clinical/laboratory findings and outcomes.

We will also biobank patient blood samples for future multi-omic studies in order to elucidate pathophysiological mechanisms.

We want to understand what are the predictors of poor outcomes in patients with PDC deficiency by undertaking the first natural history study of PDC deficiency in the UK. It is important that we understand how patients are currently being treated at different tertiary centres so as to inform best practice. At present we know little about the mechanisms that cause disease symptoms and in future aim to investigate this further in hope that we may be able to identify new effective treatments.

Modelling neuronal dysfunction in early onset epilepsies; a patient-centric approach

Project Aim: We have three overarching aims:

- **To create and characterise a patient-derived induced pluripotent stem cell (iPSC) organoid model of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS).**

  The creation of patient-derived cerebral organoids will enable study of the effects of the mutations in their native neuronal and genetic milieu. Fibroblasts from patients with *SLC12A5, KCNT1* or *SCN2A* mutations will be transformed into induced pluripotent stem cells (iPSCs) and differentiated into both cerebral organoids and medial ganglionic eminence-like organoids containing interneurons, which will be fused with the cerebral organoids.

- **To investigate the neuronal phenotype of EIMFS at a cellular and network level**

  A number of assays will be undertaken to investigate disease mechanisms including Western blotting and immunofluorescence to assess cell surface expression, patch clamping and multi-electrode array analysis to assess impact on channel and transporter function, multi-electrode array analysis to measure network formation and single-cell RNA sequencing to evaluate gene expression differences.

- **To investigate the impact of novel therapies**

  We will use a gene therapy approach *(SLC12A5)* or antisense oligonucleotides *(KCNT1)* to rescue the phenotype as an initial proof of concept. If successful, these approaches will be developed in future funding applications.

Investigators: Amy McTague, Dimitri Kullmann, Gabriele Lignani, Manju Kurian

Summary: In Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), affected babies have very frequent seizures, often up to sixty per day, which usually do not respond to currently available medications. Abnormalities in three genes,known as *KCNT1, SLC12A5* and *SCN2A* can cause EIMFS. These genes make important proteins in the brain that, when abnormal, cause seizures in young babies.

However, it is not clear how they lead to epilepsy.

Using a new state-of-the art brain cell model made from skin cells taken from patients in the study, Amy McTague will investigate how abnormalities in these genes lead to epilepsy and developmental problems in patients. Skin cells from each patient will be converted into stem cells. Stem cells have the potential to convert into any of the cell types in the body.

The stem cells will be converted into three dimensional structures, or organoids, which after maturation for several months will be made up of layers of neurons.

If we can work out precisely how the abnormal genes cause seizures, this may help us identify better drugs for both this form of epilepsy and other epilepsies. Our aim is to improve our understanding of how these abnormal genes lead to epilepsy and development problems which will help in the development of new treatments, with the ultimate aim of improving quality of life for patients and their families.

Prevention of Epilepsy by reducing Neonatal Encephalopathy (PREVENT) study

Project Aim: Our aim is to examine if a care bundle approach to improve the maternal care around delivery will reduce the number of babies sustaining serious birth related brain injury and epilepsy.

Investigators: Sudhin Thayyil, Helen Cross, Ronit Pressler, and many more

Summary: Led by Imperial College London, the PREVENT study is the world's largest study on babies with brain injuries. Brain injury during labour or childbirth is one of the leading causes of epilepsy in babies. The proportion of babies sustaining serious brain injury around the time of birth (40 per 1000 livebirths) in public sector hospitals in India is 10 times higher than that of the UK. Approximately 12 million people with epilepsy live in India.

Although epilepsy is not curable in most cases, by reducing birth related brain injury and substantial number of these cases can be prevented. In many cases, this can be prevented by simple, evidenced based and low-cost interventions tailored to the local needs. Our aim is to examine if a care bundle approach; a series of simple and interventions administered consistently, which includes intelligent foetal heart rate monitoring, an e-partogram, brain oriented neonatal resuscitation, and birth companions, will improve the maternal care around delivery will reduce the number of babies sustaining serious birth related brain injury and epilepsy.

We have assembled a team of experts in neonatal brain injury and neuroimaging, obstetrics, midwifery, qualitative research, epilepsy, global health, electrophysiology, care bundle development, health economics, public health, statistics, implementation research from leading academic centres in the UK and India, along with parent representatives to undertake this work.

The study will be conducted over 4 years in two adjacent public sector hospitals in Tamil Nadu, India, where the total number of babies sustaining birth related brain injury is the same as the total UK annual burden of birth related brain injury. During the first year of the study, we will collect accurate base-line data on brain injury, and develop and pilot the care bundle. The care bundle will be then implemented during the second year, and the outcome evaluated during the 3rd and 4th years.

The main outcome is to assess whether the proportion of babies (per 1000 live births) developing birth related brain injury is different before and after the introduction of this care bundle. We will also examine and compare the number of infants that develop epilepsy by their first birthday before and after the introduction of the care bundle.

We will compare our findings with data from 44 non-participating public sector hospitals to identify any natural reduction in the incidence of brain injuries. Finally, we will examine the views of the stakeholders and cost-effectiveness of this care bundle for adoption into the national health policy in India.

Novel network analysis of intracranial stereoelectroencephalography (SEEG)

Project Aim: To characterize interictal abnormalities in single unit neural dynamics and to establish whether the regions that display abnormal dynamics are consistent with the epileptogenic zone.

Investigators: Rod Scott, Martin Tisdall, Aswin Chari, Rachel Thornton

Summary: Epilepsy surgery is a neurosurgical operation to remove parts of the brain that generate seizures. A proportion of these children being evaluated for surgery have electrodes inserted into their brains as part of their clinical assessment, termed stereoelectroencephalography (SEEG), to help localise these regions. Subsequent surgery is not always successful - up to 40% of children will have ongoing seizures 5 years after surgery.

The purpose of this study is to assess the utility of specially designed SEEG electrodes which can measure signals from single brain cells. These electrodes record the same clinical information as normal SEEG electrodes and are implanted in the same way, but can give the research team extra information at the same time. The investigators aim to assess whether studying the changes in the firing of individual cells, both during and between seizures, improves our ability to localise seizures and therefore improve outcomes following surgery. This study will be carried out in children undergoing invasive recordings as part of evaluation for epilepsy surgery.

Development in Hypothalamic Hamartoma

Project Aim: To review the developmental profiles of children with hypothalamic hamartoma in relation to their medical presentation and treatment.

Investigators: Hanna Richardson, Leah Bull, Varsha Siyani

Summary: Hypothalamic hamartoma is a rare epilepsy caused by a benign tumour-like formation on the hypothalamus. The growth causes very difficult to control seizures, early puberty and developmental and cognitive problems.

We conducted a case note review of children with hypothalamic hamartoma to better understand how their development links to their medical presentation and treatment. Children with hypothalamic hamartoma have high levels of comorbidity and their profiles can change over time. The behavioural impact can be very severe and there are plans to look at this further with neuropsychiatry at GOSH.

The findings have been presented at the Royal College of Speech and Language Therapist's conference and also at the 4th International Symposium on Hypothalamic Hamartoma in Washington DC, US.

Antisense oligonucleotides for the treatment of ALDH7A1-deficiency

Project Aim: A proof of principal project to show that antisense oligonucleotide therapy can prevent the accumulation of the toxic metabolites that occur in patients with a-aminoadipic semialdehyde dehydrogenase (ALDH7A1) deficiency, a vitamin B6-dependent epilepsy disorder.

Investigators: Philippa Mills, Haiyan Zhou, Paul Gissen

Summary: Humans rely on vitamin B6 for the proper functioning of their nervous, endocrine and immune systems. They are not able to make this micronutrient themselves and must therefore get it from their diet. There are many different dietary forms of vitamin B6 which our bodies convert to the active form of this vitamin. This is known as pyridoxal phosphate (PLP). PLP is essential for enzymes involved in metabolism of proteins, fats and carbohydrates to work properly.

Whilst a dietary deficiency of vitamin B6 is rare, there are several genetic disorders which result in insufficient PLP within the cells of the body. PLP plays an important role in the brain therefore children with these disorders present with epilepsy. The most common of these epilepsy disorders occurs when there are mutations in a gene that is responsible for making an enzyme called a-aminoadipic semialdehyde dehydrogenase. This enzyme is involved in the pathway which converts lysine, an amino acid which is present in the food we eat, into energy. Mutations in this gene result in an accumulation of metabolites which interact with PLP thereby reducing the amount of PLP available for the brain. The resulting epilepsy can be treated by giving supraphysiological doses of vitamin B6.

Unfortunately, the compounds that accumulate, besides interacting with PLP, are also toxic to the brain. This toxicity results in intellectual disability and developmental problems. Treatment with B6 does not correct this. One way of preventing the accumulation of these compounds is to restrict the amount of lysine in the child's diet. Children do not like this diet and the improvements seen have only been partial. Better treatments are therefore needed.

We will investigate the use of antisense oligonucleotides as a way of preventing an accumulation of these toxic compounds in this disorder.

Landau-Kleffner syndrome: Patterns in the recovery phase

Project Aim: A retrospective case note review examining cognitive and language trajectories across different phases of Landau-Kleffner syndrome (LKS).

Investigators: Maria Clark, Christina Hawkins, Gemma Wilson, Harriet Holmes

Summary: LKS is a rare epilepsy which has an active phase, characterised by the loss of language skills and a distinct sleep EEG abnormality, referred to as Continuous Spike and Wave in Sleep (CSWS) or Electrical Status Epilepticus during Sleep (ESES). The active phase is followed by the recovery phase which continues for many years but in that time a child may regain skills.

There appears to be a variable course during the recovery phase of LKS, with some children maintaining a stable developmental trajectory during the course of the disease and into recovery and some children making significant developmental gains over this period.

We are currently looking into the longer-term outcomes, as well as functional-language outcomes, for children with LKS, post recovery phase.

LKS can be regarded as a sub-group of conditions which all share ESES, and we plan to broaden the research and to include the wider ESES group.

Turning 5 - A Clinical and Neurodevelopmental follow up of EpiPEG participants at 60 months

Project Aim: We aim to conduct a follow-up study of all 119 children which participated in the EpiPEG study (see page 31) to determine neurobehavioural and psychosocial outcome as they enter the school system.

Our project aims are to:

- ✓ Characterise the neurodevelopmental (cognition, behaviour, sleep) status of children who had infancy in the first year of life
- ✓ Examine the association between initial neurodevelopmental and clinical assessment results and performance at follow-up
- ✓ Examine factors including epilepsy factors and neurodevelopmental status associated with current performance and changes in performance between initial assessment and follow-up

Investigators: Colin Reilly, Manuela Pisch, Helen Cross

Summary: Children who develop epilepsy as babies often have significant learning and behavioural problems and seizures which are difficult to control. They rarely progress at the same rate as their peers in school, and their life chances are significantly diminished.

These early-onset epilepsies are hard to diagnose and equally hard to determine how well treatment will work. Many of these children remain without a specific diagnosis. This can be distressing for parents and worrying for doctors.

Epilepsy affects every aspect of a child's life and evidence shows that early intervention is key to improving outcomes in each area. This project aims to determine predictors of outcome in children with early onset epilepsy, ultimately improving treatment and outcomes in relation to their overall health and development, quality of life and life opportunities.

We will follow 119 children, who we saw as babies, as they grow up to gain a unique understanding of the early onset epilepsies. We will assess their clinical and developmental progress alongside their genetics and brain imaging. This will allow us to determine what predictors of outcome can be used by doctors.

We envisage this data being published and of benefit to patients in the short to medium term.

Physical Activity in Childhood Epilepsy (PACE)

Project Aim: The primary aim is to compare levels of physical activity in secondary school-aged children with 'active' epilepsy, and matched healthy controls, using both survey methods and activity trackers.

A secondary aim is to understand factors (e.g. age, gender, seizure related factors, sleep, behaviour-emotional functioning, school learning and parent wellbeing) which may be associated with physical activity, including structured exercise/sports participation, in children with epilepsy.

A third aim is to gather pilot data on physical activity levels in children with epilepsy and explore the feasibility of implementing an intervention to improve levels of physical activity in children with epilepsy.

Investigators: Colin Reilly, Emma Johnson, Helen Cross, Lauren Sherar, Monica Lakhanpaul, Kerry Robinson, Amit Bali, Patricia Atkinson, Natalie Pearson, Kathryn Simpson

Summary: Anecdotal evidence suggests that children with epilepsy engage in less physical activity than their peers. This does not mean engagement in team sports, rather, just being active. There is, however, limited research on this and no previous studies in the UK.

We will compare levels of physical activity in 150 secondary school-aged (11-15years) children. Half of them will have epilepsy and the other half not have epilepsy. Of the 150 children, 50 of them will attend special schools and 100 attend mainstream schools.

Activity will be measured by using activity trackers. We also want to know whether factors other than just their epilepsy may affect how active they are – things like their age, gender, how they feel, and sleep quality etc.

Depending on what we find, we may use this evidence to explore strategies which may improve access to being active, for children with epilepsy.

This project is fully funded and ethical approval has been granted. Recruitment began in November 2019. Three sites are currently open: St Piers School at Young Epilepsy, Whittington Health and Bart's Health. Two more sites are due to open by 2020: Sussex Community NHS Foundation Trust and North East London NHS Foundation Trust. The project is a collaboration between Young Epilepsy, Whittington Health and Loughborough Hospital.

Assessment of profound intellectual disability in complex epilepsy

Project Aim: To develop a robust assessment tool for children with complex epilepsy.

Investigators: Maria Clark, Gemma Wilson, Leah Bull, Karen Ray, Steve Rose

Summary: Current assessments do not capture the skills of children with complex epilepsy and are not sensitive enough to record change over time or after intervention. We are trying to develop new ways to assess this group.

This group are often not included in research or outcome data as there are no suitable measures for them. A new measure would allow them to be included and would also facilitate research that is relevant to them and their families.

A wearable OP-MEG and Light Mu-Room System at Young Epilepsy

Project Aim: To develop and test the technical and clinical feasibility of the first lightweight magnetically shielded mu-room for use with cutting edge, wearable Opticallly Pumped (OP) magnetoencephalography (MEG) technology.

Investigators: Tim Tierney, Stephanie Mellor, Geroge O'Neill, Gareth Barnes, Helen Cross, Rosemarie Pardington, Amy Muggeridge, Megan Brady, Kelly St Pier, Mark Devlin, Niall Holmes, Elena Boto, Ryan Hill, Gill Roberts, James Leggett, Richard Bowtell, Matt Brookes, Nick Murby, Eliot Dawson, Nick van de Wydeven, Courtney Veenswyk-Colvin, Peter Fierlinger, David Woolger, Cassandra Hugill, Sophie Perry, Vishal Shah, Torsten Baldeweg, Sarah Buck, Umesh Vivekananda, Matthew Walker, Vladimir Litvak, Eleanor Maguire, Daniel Barry, Andrew Levy, Sven Bestmann, Leo Dunque-Munoz, Jose Lopez

Summary: Magnetoencephalography (MEG) is a functional neuroimaging technique with high spatial and temporal resolution. It has been shown to provide useful information for presurgical planning in epilepsy but is not a readily available clinical tool, due largely to its high cost and low tolerance to movement. The latter is particularly problematic with children. However, advances in magnetic sensor technology mitigate many of the issues associated with MEG. OP-MEG uses optically pumped magnetometers (OPMs) in the place of cryogenically cooled MEG sensors. They can be worn directly on the head, which allows the patient to move naturally during a recording.

Unfortunately, like cryogenic MEG, OP-MEG must currently still be performed in a bulky, costly magnetically shielded room (MSR). The MEG Project at Young Epilepsy is a collaboration between UCL, the University of Nottingham, Magnetic Shields Limited and Young Epilepsy to design and build a new, lightweight MSR, tailored to the clinical setting. Both clinicians and young people with epilepsy will have a voice in its design; we are undertaking a public engagement project to gather their feedback throughout the design process.

Impact of the Ketogenic Diet on behavioural-emotional functioning and parental well-being in children with epilepsy (PsyKD)

Project Aim: To gain an understanding of the needs and experiences of families considering a Ketogenic Diet Therapy (KDT) and the subsequent impact of the diet on children and their parents.

Investigators: Natasha Schoeler, Colin Reilly, Helen Cross, Victoria Whiteley, Anita Devlin, Christin Eltze, Emma Williams

Summary: Adherence to a KDT may not always be easy and depends on physician, parental and healthcare system-related factors. Despite the range of prescriptible and non-prescriptible ketogenic products available, KDTs still require stringent dietary restriction, which places significant burden on families and requires major effort on the part of the child and family. Little is known about the impact of KDTs on child behavioural and emotional functioning and child quality of life. In order to have a better understanding of the impact of KDTs on children with epilepsy and on parental functioning, we propose to conduct a pilot study assessing functioning and views before commencement of dietary treatment and at at three months and one year follow up. The study would be the first of its kind, and would make a significant contribution to the research evidence-base for treatment of epilepsy with KDTs on psychosocial outcomes.

The project is currently seeking funding and is a collaboration between Young Epilepsy, Matthews Friends, GOSH, Addenbrookes Hospital, Royal Manchester Children's Hospital and Newcastle uopn Tyne Hospitals.

Research Project Update

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.

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

Update: This project is now being finalised. We have published our assessment of more rapid fMRI sequences for these and other fMRI studies. We have collected a small case series to test our new EEG-fMRI acquisition and are writing this up for publication. Mirja Steinbrenner, a neurologist from Berlin has joined the team on a research placement to do this.

What this means: This project has developed a system to improve the accuracy of brain imaging to better understand which parts of the brain are active just before and during a seizure. It has also been developed to improve accuracy when the patient is moving. Any movement, no matter how small, will affect most imaging techniques but it is not always possible to get a patient to stay perfectly still for a length of time, particularly if the patient is a child or a child with complex needs. This work will greatly improve the accuracy of imaging for these patients.

The neuropathology of focal epilepsy in children

Project Aim: To understand the biology underlying the diseases that cause focal epilepsy.

Investigators: Tom Jacques, Helen Cross, Martin Tisdall, Darren Hargrave

Update: We are focussing on brain tumours and on malformations of cortical development. This is leading to changes in our diagnostic practice for children undergoing epilepsy surgery and is improving our understanding of how these diseases develop.

What this means: This is a group of new projects which aim to define the causes of focal epilepsy. This work is vital to obtaining faster, more accurate diagnoses and also to improving and developing successively better treatment options. Currently, most epilepsy treatments are symptomatic and focus on seizures. We need to understand more about what causes epilepsy to be able to develop and offer curative rather than symptomatic treatment.

Effect of paroxysmal events in early onset neurological disease on cerebral tissue oxygenation & metabolism: a NIRS pilot study

Project Aim: To better understand energy consumption during epileptic seizures.

Investigators: Helen Cross, Aikaterini Vezyroglou, Ilias Tachtsidis, Rachel Thornton, David Carmichael.

Update: We are using broadband Near Infrared Spectroscopy (bNIRS) to investigate the changes of oxygenated and deoxygenated haemoglobin, as well as of cytochrome c oxidase during epileptic seizures alongside EEG. As cytochrome c oxidase is part of the mitochondrial respiratory chain, any changes in cytochrome c oxidase during epileptic events might be a biomarker of energy consumption during seizures. We designed headgear to record bNIRS simultaneously with routine EEG and recruited 15 patients to this pilot study. We were lucky to capture seizures in 9 patients. Analysis of our bNIRS and EEG data during repeated seizures in one of our patients showed a significant increase in blood oxygenation adjacent to the epileptic focus and a significant decrease in cytochrome c oxidase in the region of the epileptic focus. This might indicate a relative brain tissue hypoxia and energetic deficiency in the region of the epileptic focus during seizures. Data analysis in further patients is ongoing.

What this means: We are investigating how the bNIRS, and especially the cytochrome c oxidase measurement, is affected during an epileptic seizure. Better understanding of energy consumption during seizures will help us understand how seizures affect the brain in the long term.

Memory profile and reorganisation after epilepsy surgery in children with intractable Temporal Lobe Epilepsy (TLE)

Project Aim: The project aims to 1) characterise the memory profile of children and young people with TLE as well as their post-surgical memory outcome and 2) depict functional and structural reorganisation of memory networks in temporal lobe epilepsy before and after surgery, using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) magnetic resonance. We hope this may help to refine the prognostic accuracy of the preoperative workup, guide neurosurgical resection, and reduce the risk of memory impairment after surgery.

Investigators: Filipa Bastos, Faraneh Vargha- Khadem, Helen Cross, Jonathan Clayden, Sarah Buck

Update: Medically intractable temporal lobe epilepsy (TLE) is the main indication for epilepsy surgery in both adults and children and yields good outcome regarding seizure freedom. However, due to the medial temporal lobe's central role in memory, long-term memory and learning, difficulties are reported in patients with TLE. Routine pre-operative memory assessment in children with TLE consists of behavioural testing with protocols with suboptimal sensitivity to detect deficits in the paediatric population. Furthermore, memory lateralisation predictions are extrapolated from language lateralisation even though the interdependence of these two functions in children is not well documented, particularly in children with temporal lobe pathology.

This project involves memory testing using an application on a tablet developed by one of the investigators (Sarah Buck) as well as undertaking an MRI. Patients are seen before surgery and again 4 and 12 months after surgery. Patient recruitment will be ongoing until spring 2020 but data collection and analysis will carry on further as patients have to be seen 1 year after surgery.

What this means: We want to ensure that children with TLE undergoing surgery will have the best possible outcomes with regard to their memory function. To do this we have developed an app-based test to be used by the child, alongside MRI imaging which will help us to better understand how memory works and is organised in the brains of children rather than relying on evidence from adult research. This will enable much more accurate understanding of how the surgery could affect an individual and therefore, thus continually improving the process of surgical evaluation.

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.

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

Update: Investigation of this cohort is ongoing and our results have led to several publications including a Gene Reviews summary of *SLC12A5* and a review of the genetic landscape of epilepsy-dyskinesia. In addition we have taken part in an international cohort study on the genetics of Epilepsy of Migrating Focal Seizures of Infancy and have identified a novel gene for epilepsy-dyskinesia, *CACNA1B.*

What this means: We want to know what has caused 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. Recently, we have identified a new gene which causes both a severe early onset epilepsy and a movement disorder.

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 electrical stimulation (TES). We look to modulate brain connectivity and understand its relationship to epileptiform activity reduction.

We hypothesise that in epilepsy, brain networks can be targeted by weak electric fields applied to the scalp (TES) to modulate the brain's connectivity to reduce epileptic activity.

Investigators: David Carmichael, Frederike Moeller, David Sharp, Helen Cross, Mirja Steinbrenner, Martin Tisdall, Mark Richardson, Ines Violante, Rory Piper

Update: This project is funded by an ERUK pilot grant to commence study in patients with Juvenile Myoclonic Epilepsy. Rory Piper a surgeon training in Oxford has performed a research placement investigating thalamic connectivity in epilepsy.

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 infant baby enrichment research programme (ENRICH)

Project Aim: To explore the possibility of measuring the cortical response from the scalp of infants using standard non-invasive EEG techniques, due to the activation of C Tactile (CT) afferents and how the cortical response changes in regard to age.

Investigators: Ronit Pressler, Geraldine Boylan

Update: A total of 24 infants were recruited into the study, of which 20 attended both somatosensory nervous system pathway (SSEP) assessments at 4 weeks and 4 months of age and developmental assessments at 4 months. Group analysis of potentials during gentle stroking did not reveal a clear reproducible response. We are currently improving the test protocol and aim to test a further 20 infants. This second phase will be conducted in Cork, Ireland.

What this means: This study seeks to understand how responses in the brain to certain sensory stimuli are developed over the first four months of life. We want to understand whether if a pleasant touch is administered to a baby's forearm in the supine and prone positions, will we observe a cortical response, and if so, can it be recorded and how does it develop over time.

A multicentre, open-label, single-arm study to evaluate the pharmacokinetics, efficacy, and safety of Brivaracetam in neonates with repeated electroencephalographic seizures (PETITE)

Project Aim: The purpose of the study is to evaluate the pharmacokinetics of Brivaracetam in neonates who have seizures that are not adequately controlled with phenobarbital treatment and to identify the optimal Brivaracetam dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study.

Investigators: Ronit Pressler, Marios Kaliakatsos

Update: PETITE is a European, UCB Biopharma-led neonatal study exploring the efficacy of Brivaracetam. The study has now been set up and at present 6 sites are active across Europe (two UK sites - GOSH and Cambridge) and we have recruited our first participant.

The 'Exploratory Cohort' will receive a low dose of Brivaracetam intravenous (iv) solution for injection following one or multiple therapeutic doses of midazolam. 3 additional iv Brivaracetam doses, up to a total of 4 can be administered during the 48- hour Evaluation Period.

The dose and dosing frequency of Brivaracetam will be adjusted for the 'Confirmatory Cohorts' based on the analysis of the data collected for the Exploratory Cohort.

What this means: We are working with UCB Biopharma to understand the best way to use Brivaracetam in newborn babies with seizures who do not respond to Phenobarbital.

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

Update: This project has been granted ethical approval and is currently awaiting funding before work can begin.

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.

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 1 month to 2 years who have failed to respond to two or more pharmacological treatments.

Investigators: Helen Cross, Laura Lyons, Sally Halsall, Natasha Schoeler, Maryam Balogun, Christin Eltze, Simon Heales, Helen McCullagh, Rachel Kneen, Tim Martland, Jeen Tan, Andrew Mallick, Andrew Lux, Alasdair Parker, Helen McCullagh, Archana Desurkar, Penny Fallon, Helen Basu, Anita Devlin, Rajib Samanta, Shakti Agrawal, Manish Prasad, Rohini Rattihalli, Elma Stephen, Andreas Brunklaus, Martin Kirkpatrick, Ailsa McLellan, Nick Freemantle, Louise Marston, Irwin Nazareth.

Update: Since last year we have received 2 extensions for KIWE from the NIHR. The first for 5 months and the second for 24 months which allows us to continue the study until 30 June 2021. We have opened 6 new sites, so now have a total of 18 centres open across England and Scotland. We have recruited 106 patients to date, and aim to get as close as possible to the project's original 160 patient target.

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.

The "Pair Test": an App to diagnose learning and memory impairments in children with Temporal Lobe Epilepsy

Project Aim: The aims are to 1) provide better informed diagnosis of memory impairments in children with epilepsy and 2) predict outcome after surgery in the temporal lobe, using the Pair Test.

Investigators: Sarah Buck, Torsten Baldeweg, Filipa Bastos, Faraneh Vargha-Khadem

Update: The "Pair Test" uses a tablet-based paired-associate learning paradigm to disentangle impairments in different memory processes, and different components of the neural network within the medial temporal lobes. The test provides behavioural evidence regarding the functional integrity of the hippocampi and their interaction with the neocortical learning system. The Pair Games can be used to (a) diagnose the status of memory and learning, (b) monitor progression of disease, (c) assess the efficacy of pharmacological and/ or surgical interventions by providing pre- and post-treatment measures of function. Overall, the test provides better informed diagnoses than standardised tools, with more precise indication of the types of memory deficits and the underlying processing impairment. Filipa Bastos has joined the team and is working on this; combining new and current modalities.

What this means: The Pair Test is an app-based tool which will better help clinicians understand the type and complexity of learning and memory problems in children with Temporal Lobe Epilepsy (TLE). For instance, we may know that someone has trouble with their memory but we don't know if this is one memory problem or several. This test helps clinicians to see the full picture. They hope that this will not only lead to better support and treatment but also to make a more accurate predictions of how epilepsy surgery may affect someone's learning and memory.

Multicentre Epilepsy Lesion Detection (MELD) Project

Project Aim: : To create open-access, robust and generalisable tools for understanding and detecting focal cortical dysplasias (FCDs) that can assist the pre-surgical evaluation of patients with drug-resistant epilepsy.

Investigators: Sophie Adler-Wagstyl, Konrad Adler-Wagstyl, Kirstie Whitaker, MELD consortium, Helen Cross, Martin Tisdall, Torsten Baldeweg

Summary: The MELD project is a multi-centre collaboration for understanding and detecting FCDs involving the incorporation of data and sequences from multiple sites. Each site has been given detailed protocols to follow in order to pre-process the data from their site. The anonymised data matrices along with some clinical information (such as age, age of onset of epilepsy, surgery, histopathology and Engel outcome) has been shared. So far we have received data from over 550 patients and 350 controls. This will allow understanding of natural history of FCDs and the development of classifiers trained on the data from all participating centres to occur. Any developed classification tools and/or code will be shared. We hope that this will create open-access, robust and generalisable tools for FCD detection that can be used in the pre-surgical evaluation of patients with drug-resistant epilepsy.

What this means: We hope to create new and more robust tools to detect FCD in children and adults with drug resistant epilepsy. These tools will be co-created across many hospitals and will become openly accessible for any hospital to use when evaluating someone for FCD. The tools would then be continually improved to ensure that more and more people would have access to accurate diagnosis and possible surgery.

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 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, Emma Johnson, Helen Cross, Amy Muggeridge

Update: We have recruited over 60 young people across 2 sites and we expect to have recruited 70 young people by the end of the recruitment period in December 2019. Data regarding the experiences of children, parents and teachers is being gathered using surveys and semi-structured interviews.

Common experiences of children include frequently feeling that they are responsible for informing school staff about their epilepsy and that they feel anxious regarding peer responses to seizures. Children also want a greater awareness and increased monitoring of anti-epileptic drug (AED) side-effects in schools.

Parent reports suggest that the quality of communication between home and school regarding the child's epilepsy is often poor. Parents also report that risk assessments are not always appropriate (perceived as overly cautious or too relaxed).

Nearly half of teachers stated that they would not feel confident managing a child having a seizure, and the majority would like more training about epilepsy, including associated learning and behavioural difficulties. Out of a range of medical and behavioural conditions, including cerebral palsy, epilepsy is the condition school staff are most concerned about.

What this means: There is a lack of knowledge about epilepsy in schools. Our study involves interviewing young people with epilepsy their parents and their teachers about their experiences.

Our preliminary results suggest young people with epilepsy and their parents have significant concerns about knowledge and awareness of epilepsy in schools, and teachers report lacking confidence regarding managing seizures and associated learning and behavioural issues. There is a clear need for increased knowledge in schools and guidelines regarding seizure management and the impact of epilepsy on child learning and behaviour.
We hope this project will enable us to write guidelines for schools to support young people with epilepsy achieve their academic potential. We are also testing a screening instrument to help teachers and parents identify whether a child may have additional learning or behavioural needs. Knowing this will lead to getting the right support at school.

Multiscale modelling of epileptic networks from SEEG recordings

Project Aim: Epilepsy surgery aims to change epileptic brain networks in a way that will reduce the likelihood of future seizures. In this project we aim to use state of the art network modelling approaches to characterise these epileptic brain networks from intracranial EEG recordings, and in future help in predicting the effects of surgical intervention on those networks.

Investigators: Richard Rosch, Rachel Thornton, Martin Tisdall, Karl Friston

Summary: Resective surgery is an effective treatment for many focal epilepsies. Yet epilepsy is increasingly understood to be a disorder of brain networks, with abnormal brain activity emerging not from the isolated activity of individual regions, but from concerted activity of many coupled sources. Understanding this integrated epileptic network is far from intuitive – even apparently simple networks can show complex dynamics that are difficult to predict.

Computational models may offer a strategy to improve our understanding of epileptic networks. In this project, we are fitting computational network models of neuronal coupling to stereotactically recorded intracranial EEG (SEEG). Through the use of computational models, we are able to test what the network organisation that underlies epileptic dynamics on the SEEG is. This can be done at the level of microcircuits around focal brain abnormalities (e.g. looking at local coupling between tuber cores and peritubular cortex in tuberous sclerosis patients, see Tumpa et al (2019) bioRxiv doi.org/10.1101/691170), and at the level of whole brain circuits (e.g. identifying whole-network changes after interventions in patients undergoing therapeutic radiofrequency thermocoagulation).

What this means: We know that epilepsy is often a disorder of networks across the brain rather than the result of a single disruptive section. This means that entire networks must be considered when evaluating someone's suitability to undergo epilepsy surgery. This project sets out to really understand the workings of these networks so that the pre-surgical team can have a better grasp of the effect that any surgery, however relatively 'simple' may have on a person's functioning. We have just been awarded a PhD fellowship from the Oakgrove Foundation, and are recruiting for a new PhD student taking this project further.

Molecular Genetic Investigation of Landau-Kleffner Syndrome

Project Aim: To define the molecular genetic basis of Landau-Kleffner Syndrome (LKS)

Investigators: Adeline Ngoh, Maria Clark, Helen Cross, Dimitri Kullmann, Robert Harvey, Manju Kurian

Update: Adeline is coming towards the end of her PhD. She has successfully established a mutation frequency for *GRIN2A* mutations in her cohort, and defined the molecular basis for these loss-of-function mutations. She has also identified some new candidate genes for LKS.

What this means: We have been undertaking work to try and understand what genetic faults may cause or contribute to a rare epilepsy condition known as Landau Kleffner Syndrome (LKS). We found that some patients have a change in a gene known as *GRIN2A* and are working out how such genetic faults cause this condition. We also found some new genes that may be responsible for this condition, and we are currently evaluating these.

We hope to understand why LKS causes seizures and language difficulties. Understanding this will lead to more targeted and earlier treatment.

Mental Health in Children with Epilepsy (MICE)

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: Roz Shafran, Helen Cross, Sophie Bennett, Sarah Byford, Bruce Chorpita, Anna Coughtrey, Emma Dalrymple, Caroline Dore, Peter Fonagy, Tamsin Ford, Isobel Heyman, Rona Moss- Morris, Colin Reilly, Jonathan A Smith, Terence Stephenson, Sophia Varadkar

Update: Our NIHR funded Programme Grant began in October 2017. At therapists' requests we hosted a booster training session in March 2019 which gave therapists the opportunity to feedback on their experience on delivering the intervention during the training phase and discuss key learning points in preparation for the trial. During this session, we conducted qualitative interviews which provided further insight into their experience and the practicalities of physical healthcare staff delivering a telephone-based psychological intervention within epilepsy services. We also obtained participants' perspectives of receiving the intervention and the impact it has had on both their child's mental wellbeing and quality of family life. We received very positive, promising feedback from both therapists and families, and incorporated any feedback and suggestions into our planning for the main trial where necessary.

In April 2019 we were awarded the second half of our funding based on successful outcomes from the 6-month training phase. The trial commenced in May 2019 when the first participant was recruited and screening is now underway across all 7 sites. Due to demand we have trained additional therapists and staff to help with screening at other sites. We continue to meet with our Patient and Participant Involvement Research Advisory Group and Health Professionals Advisory group every 2-3 months. They advise on trial related procedures, for example the recruitment process in clinics and have contributed to plain English summary for families.

We are currently opening St Piers School at Young Epilepsy as a study site.

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 assessment 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.

Optimisation and bioperformance of a novel formulation of pyridoxal 5'-phosphate for treatment of pyridox(am)ine 5'-phosphate oxidase deficiency induced epilepsy in children

Project Aim: To test the efficacy of a new treatment for children with pyridox(am)ine 5'-phosphate oxidase deficiency induced epilepsy.

Investigators: Catherine Tuleu, Peter Clayton, Philippa Mills, Emma Footitt, Ahad Rahim, Simon Heales

Update: Some children have a specific type of epilepsy, called pyridox(am)ine 5'-phosphate oxidase deficiency induced epilepsy, which can be treated with a form of vitamin B6 called pyridoxal-5-phosphate (PLP). However, the current medication is not ideal. PLP is only available as a nutritional supplement in tablet or capsule forms. Unlike pharmacy-only medicines, this product is not regulated and can be problematic for clinical use. It is difficult to prepare and administer, unpalatable and unstable. Additionally, our preliminary data has shown that there is a high risk of inaccurate dosing and when mixed in water, these products are not stable, forming compounds that may be dangerously toxic to the liver. We have developed a more stable, formulation and have evaluated the purity and taste of this new drug. We are currently evaluating whether this product meets the safety requirements (i.e. not liver toxic) for administration to humans.

What this means: We hope to produce a tolerable and regulated formulation of PLP which will improve both safety and quality of life for children who are taking PLP.

Improving Care in Epilepsy (ICE) for children, young people and families

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, Helen Cross, Monica Lakhanpaul, Kerry Robinson, Dougal Hargreaves, Christina Petropoulos

Update: This is a collaborative programme of projects between Young Epilepsy, UCL Great Ormond Street Institute of Child Health, UCLPartners and Whittington Health, led by Amit Bali.

Current work streams include the development of a learning healthcare system for paediatric epilepsy, linked to individualised care plan; the co-creation of young people's networks; and the commissioning of an economic evaluation of the true economic impact of epilepsy at individual, family, service and national levels.

We have been struggling to fund the economic study. Bids are met with great interest and support but not with a dedication of funds. We are currently revising the approach to fund this study.

The development of a learning healthcare system has been incorporated into Young Epilepsy's Digital Strategy 2019-24 and will constitute one of two arms of the project. We aim to co-create and deliver a pilot patient held record in April 2020 for evaluation. This project will partner with the Epilepsy12 National Audit to record patient reported measures and we hope to integrate this as a patient held record and epilepsy registry within the NHS by 2024.

What this means: We want to ensure services for epilepsy are joined up, and are provided in partnership with young people and families and empowers them. 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.

Epilepsy in Infancy: relating phenotype to genotype (EPIPEG)

Project Aim: To identify and follow-up a cohort of children with new onset of epilepsy under 12 months of age to enable definition of neuro-behavioural phenotypes; identify risk factors for neurodevelopmental problems and later intellectual disability; determine novel genetic mutations as a cause for early onset epilepsy, and relate to clinical presentation.

Investigators: Helen Cross, Manju Kurian, Rod Scott, Christin Eltze, Finbar O'Callaghan, Michelle De Haan, Elaine Hughes, Jane Kung, Manuela Pisch, Katy Barwick, Aikaterini Vezyroglou

Update: We received 200 referrals, of these 186 were eligible and a further 119 were recruited to the assessment arm of the study. We are currently investigating the genetic aetiologies in patients from the study suspected to have an underlying disorder of genetic origin. A cohort of patients were recruited for whole exome triome analysis. To date, several genetic diagnoses (e.g. SCN-related genes, *PRRT2*) have been established in approximately 17% of the cohort.

We plan to collect developmental follow up data from the 119 recruited participants in 2020 as they turn five years old and begin to establish a long term data set or these individuals.

What this means: We have been looking at children following first presentation with seizures from the EPIPEG cohort. In some patients, we suspect that their epilepsy may be 'genetic', that is related to a fault or spelling mistake in their genetic makeup. We've investigated a number of children now and so far, found a genetic problem in 1/6 of the cases. We want to understand the specific areas of need in the early onset epilepsies and how to spot the earliest possible signs of epilepsy so that we can better help families know what to expect, and help doctors to understand what to look for and treat. Many people with epilepsy never learn what causes their epilepsy, which is why we are looking at the child as a whole, including a wide range of genetic testing to find an answer. Research like this aims to understand the unknown causes of epilepsy in the hope of paving the way to new and better treatments. This project will provide the basis for a longer study, which will follow these children as they grow up.

European Reference Network on rare and complex epilepsies (EpiCARE)

EpiCARE is a European Reference Network (ERN) for rare and complex epilepsies, coordinated by Professor Alexis Arzimanoglou, Director of the Epilepsy, Sleep and Paediatric Neurophysiology Department at the University Hospitals of Lyon, France. Advances in brain scanning as well as genetic and metabolic investigations have determined an increasing number of causes behind epileptic seizures, resulting in the description of more than 130 rare diseases.

One of 24 approved ERNs on rare disorders, EpiCARE has 28 members, spanning 13 countries. EpiCARE aims to improve access for patients to diagnostic and therapeutic expertise, by engaging multidisciplinary experts through the network.

EpiCARE aims to:

- ✔ To improve accessibility of detailed diagnostics to individuals of all ages with rare and complex epilepsies across Europe, including clinical evaluation and investigation.
- ✔ To develop treatment protocols and monitor standardised outcomes of rare and complex epilepsies.
- ✔ To improve awareness and accessibility to protocols for physicians and individuals with rare and complex epilepsies across Europe for treatment.
- ✔ To enhance educational activities and training opportunities across Europe by interchange across the network.
- ✔ To enhance opportunities for registries, and collaborative research for the benefit of individuals with rare and complex epilepsies across Europe.

Completed Projects

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

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

Ketogenic diet therapies (KDTs) are an effective option for drug-resistant epilepsy, although they are often associated with poor compliance and dissatisfaction. Medium chain triglycerides (MCT) can improve the palatability of KDTs, but their use is limited due to poor acceptability, taste and lack of convenience. Betashot, a ready-to-use, palatable emulsion of a unique blend of specific MCTs, aims to address these issues and improve tolerability of dietary treatment by avoiding the need to follow a ketosis-inducing KDT.

This study evaluated the compliance, tolerability and acceptability of Betashot in individuals with epilepsy.

Children aged over 3 years and adults with epilepsy took Betashot daily for 12 weeks. Dietetic and medical assessment, quality of life questionnaires and biochemical investigations were conducted at baseline, 5 weeks and 12 weeks.

The most frequently reported gastrointestinal symptoms were excessive flatulence, abdominal bloating or feeling full, and abdominal pain or discomfort. Overall, gastrointestinal symptoms decreased throughout the study period, following a peak during the initial introduction of Betashot. There was a statistically significant reduction in mean estimated number of seizures at visit C compared to visit A ($P<0.001$).

Adult and child participants with epilepsy who completed the study were able to comply with intakes of Betashot, and it was reported as acceptable when taken alongside their usual diet with minimal modifications. Side effects were predominantly mild and resolved satisfactorily with appropriate dietetic support and Betashot had a beneficial effect on mean seizure frequency.

Further study is warranted to determine the role of Betashot as a possible alternative or adjunct to KDTs for individuals with drug-resistant epilepsy.

Cardiac Arrhythmias in Dravet Syndrome (CADS)

Investigators: *Roland Thijs, Sharon Shmuely, Sanjay Sisodiya, Helen Cross*

People with Dravet syndrome face a substantial risk for sudden unexpected death in epilepsy (SUDEP), which affects one in 107 individuals per year. In more than 70% of these people an *SCN1A* gene mutation is found, encoding a sodium channel expressed in heart in brain.

Mouse models suggest an increased propensity to arrhythmias and may be indicated in SUDEP. In an attempt to explain the high SUDEP rates in Dravet syndrome, we ascertained the prevalence of seizure-induced cardiac arrhythmias in individuals with Dravet syndrome from four epilepsy centres in the Netherlands and the UK.

We included 59 people with Dravet syndrome and we obtained ictal ECG recordings in 45 cases, for 20 days continuously, which were compared to epilepsy controls.

We determined the prevalence of peri-ictal asystole, bradycardia and QTc changes. For convulsive seizures, we also assessed peri-ictal heart rate, heart rate variability, PR-interval and QRS-width. Generalised estimating equations were used to account for multiple seizures within subjects, seizure type and sleep/wakefulness.

No major cardiac arrhythmias which could directly explain high rates of SUDEP in Dravet syndrome were identified. Peri-ictal QTc-lengthening was, however, more common in Dravet syndrome, possibly reflecting unstable repolarisation. Whether QTc-lengthening affects risk of SUDEP is unknown and needs to be addressed in future studies.

Novel automated artefact-reduction to increase robustness of first-level fMRI analyses

Investigators: *Torsten Baldeweg, Marko Wilke*

We aimed to improve diagnostic fMRI scanning for children before epilepsy surgery. We developed a new software toolbox for clinical fMRI analysis, published a detailed report made freely available for all to use. This means clinical fMRI scans are less likely to fail due to signal artefact or motion and the results can be interpreted with greater confidence. A larger number of patients will have valid fMRI reports and images available for surgical image guidance.

This method is now in routine use at GOSH and other specialist centres and will be introduced for the new 3T interventional MRI scanner at GOSH.

This work will help to improve accuracy of fMRI evaluation for epilepsy surgery and diagnosis.

The early developmental course of babies with Sturge-Weber syndrome

Investigators: *Nisha Thapa, Tanganu Fosi, Jenny Sloneem, Varsha Siyani, Hanna Richardson, Sarah Aylett*

We conducted a retrospective case note review was conducted on 90 children aged below 3 years with Sturge-Weber syndrome (SWS) under clinical review at Great Ormond Street Hospital. We aimed to describe the clinical features of infants with SWS under 3 years and their developmental trajectory in relation to seizure onset. The medical history and standardised developmental test results (language, cognition, motor and visuospatial skills) contained in patients' assessment reports were analysed.

Clinical features of children with SWS aged under 3 years were: seizures in 81 patients (90%), hemiplegia in 52 patients (57.8%) and glaucoma in 42 patients (46.7%).

The developmental trajectory showed a decrease in the mean percentiles (for language, cognition and motor skills) and mean developmental quotients (for visuospatial skills) over the first 36 months.

Infants with unilateral brain involvement had significantly higher cognitive percentiles than those with bilateral brain involvement. Children with epilepsy had worse language and cognitive outcomes than children without seizure onset. Following treatment of early seizures in SWS language recovery appears to occur over time relative to cognition. The functional plasticity of language might account for these observations.

It is proposed that seizure prevention and optimal seizure control in the crucial first year of life will benefit cognitive and language development in patients with SWS.

We are now seeking funding for a study evaluating prophylactic treatment with anti-epileptic drugs for infants with SWS.

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

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

We wanted 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 Focal Cortical Dysplasia (FCD) lesions.

Sara Lorio has published an improved flexible proton density mapping method that can be used in clinical situations such as where there are large lesions or previous surgery. We have processed new advanced diffusion maps that show contrast changes radiologically and quantitatively and seem to differentiate between FCDIIa and FCDIIb.

These diffusion results have been submitted for publication.

We have also analysed quantitative susceptibility maps that showed strong visual contrast in a handful of cases – and changes in cortical structure in FCD patients when evaluated quantitatively. Working with Po-Wah So at Kings College London, we have compared our results to alterations in metal content using the diamond light source (https://www.diamond.ac.uk) to show changes in iron, calcium and zinc which we are being written up for publication.

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 in childhood epilepsy.

Involvement of the insula / opercula region in paediatric patients undergoing Stereotactic EEG (SEEG) exploration

Investigators: *Pablo Kappen, Christin Eltze, Martin Tisdall, Helen Cross, Rachel Thornton, Friederike Moeller*

Failure to recognise involvement of the insula / opercula (I/O) region is associated with poor outcome in epilepsy surgery. Recognition is challenging due to high connectivity with adjacent structures resulting in variable and misleading semiology, often subjective and therefore likely to be underreported by children. In this study we explored prevalence and characteristics of I/O involvement in paediatric patients undergoing SEEG exploration.

We included all consecutive patients undergoing SEEG at our centre between November 2014 and January 2018 with at least three contacts within the I/O. We compared pre-invasive characteristics, SEEG results, surgery and outcome for each of three groups:

1) seizure onset zone (SOZ) in the I/O

2) seizure spread to the I/O

3) no I/O involvement.

41 of all 53 consecutive patients had at least three contacts within the I/O and were included. 29% had I/O SOZ, 54% had I/O spread and 17 % had no I/O involvement. Insula associated symptoms described in adult literature were not statistically different between the three groups.

Complications due to SEEG were low (2 of 53 patients). Following I/O surgery, 63% were seizure free while an additional 26% of patients achieved seizure reduction. Postoperative deficits were seen in 75% of the patients but completely resolved in all but one patient.

Our data suggest an important role of the I/O region with frequent onset or propagation to the I/O region (83% of cases). Semiology appears less specific than in adults. Insula depth electrode insertion is safe with subsequent good surgical outcomes albeit common transient deficits.

Improving the standard of speech and language assessment for children with Dravet syndrome

Investigators: *Rosie Shuttleworth, Christina Hawkins, Maria Clark*

We aimed to improve speech and language assessment in Dravet Syndrome by clarifying profiles and community therapist experience and understanding.

Twelve children with Dravet Syndrome had a retrospective case note review, supplemented by questionnaires from community Speech and Language Therapists. This identified that children with Dravet syndrome tended to have uneven profiles, with weaker communication skills and high levels of autism. Community teams had limited experience and requested training and support to meet the children's needs.

The group have contributed to looking at national standards of care in Dravet Syndrome and hope to work with other centres to clarify speech and language profile by looking at larger numbers of children with the condition

We know that people with Dravet syndrome have significant developmental needs. Greater understanding of their profile and support for local teams will facilitate identification and support of these needs so that children can reach their potential.

Medical presentations of Sturge-Weber syndrome and an assessment of the predictive value of risk factors for intellectual and language impairments

Investigators: *Sebastian Yule, Tanganu Fosi, Jenny Sloneem, Christina Hawkins, Hanna Richardson, Sarah Aylett*

Sturge-Weber syndrome (SWS) is a rare congenital neurocutaneous disorder characterised by a facial capillary malformation (port wine stain) and an underlying leptomeningeal angioma. Common presentations include seizures, hemiplegia, visual field deficits, cognitive impairments and social communication disorders.

There is a variability in the medical presentations and neuropsychological outcome. The cause of these impairments remains controversial. The main challenge is to develop optimal treatment strategies and to improve prognosis.

This study evaluated the prevalence of medical presentations associated with SWS and risk factors which may be associated with intellectual and language impairments. We conducted a retrospective case note review with 140 children with SWS who were treated at Great Ormond Street Hospital.

The prevalence of intellectual disability (IQ ≤70) was 49.6% and the prevalence of a severe language disorder (core score ≤70) 48.3%. On regression analysis, the extent of lobar involvement significantly predicted an IQ ≤70. Intellectual functioning was found to be impaired by previous status epilepticus, whereas language functioning was found to have a greater degree of plasticity following status epilepticus but to be impaired by ongoing seizures.

The study gives results which are helpful in predicting outcome for this patient group and emphasises the importance of preventing status epilepticus and ongoing seizures.

We are now seeking funding for a study evaluating prophylactic treatment with anti-epileptic drugs for infants with SWS.

Awarded PhDs - Congratulations!

John Apps

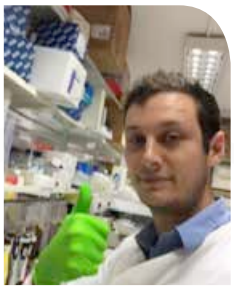
2018
Molecular characterisation of Childhood Craniopharyngioma and identification and testing of novel drug targets

John is continuing his training in Paediatric Oncology at Birmingham Children's Hospital. He was successfully awarded a Cancer Research UK Clinical Trials fellowship and spends 50% of his time spent at the Cancer Research UK Clinical Trials Unit, University of Birmingham, working on a range of trials for children and adults with brain tumours. He is an Honorary Lecturer at UCL GOS ICH where he continues to work with Prof Martinez-Barbera to understand the molecular pathology of craniopharyngioma through "omic" profiling studies.

David Nobbs

2018
Upper limb movement after hemispherectomy

David is now working at Hoffman-La Roche, improving efficacy endpoints in drug development by building novel digital health technology tools that measure the signs and symptoms of neurological conditions.



Matthew Wilson

2019
The biochemical investigation of vitamin B6 - responsive inborn errors of metabolism

After being successfully awarded his PhD, Matt was offered a position at the Laboratory for Molecular Diagnosis in the Department of Human Genetics at KU Leuven University to work with Professor Gert Matthijs. Matthew is now working on the diagnosis of Congenital Disorders of Glycosylation.

Richard Rosch

2019
Multiscale modelling of neuronal dynamics and their dysfunction in the developing brain

Richard is now the Sir Henry Wellcome Postdoctoral Fellow at Kings College London working on modelling epileptic network dynamics ranging from zebrafish to epilepsy surgery patients.

Paediatric Epilepsy Masterclass 2018

The Rare Epilepsies

In December 2018 we held a two-day Masterclass for paediatric epilepsy professionals hosted by Professor Helen Cross.

This meeting aimed to share the current position and knowledge on the rare epilepsies from a wide array of specialists, with many years of experience in epilepsy.

We were honoured to welcome Professor Alexis Arzimanoglou, Director of the Epilepsy, Sleep and Paediatric Neurophysiology Department at the University Hospitals of Lyon, France, to give the keynote speech before a full day's conference of talks and workshops from:

- Professor Stéphane Auvin, Professor of Epilepsy and Child Neurology *Université Denis Diderot, Paris*
- Professor Helen Cross OBE, The Prince of Wales's Chair of Childhood Epilepsy
- Professor Sanjay Sisodiya, Professor of Neurology and Honorary Consultant Neurologist *UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery*
- Dr Felice D'Arco, Consultant Paediatric Neuroradiologist *Great Ormond Street Hospital*
- Dr Anita Devlin, Consultant Paediatric Neurologist *Newcastle upon Tyne Hospitals NHS Foundation Trust*
- Dr Christin Eltze, Consultant Paediatric Neurologist *UCL GOS - ICH*
- Dr Amy McTague, Consultant Paediatric Neurologist *UCL GOS - ICH*
- Dr Richard Scott, Consultant in Clinical Genetics Great Ormond Street Hospital and *UCL GOS - ICH*
- Emma Williams, Founder, Chair of Trustees and CEO *Matthew's Friends*

The Masterclass was attended by over 50 epilepsy specialists. We aimed to challenge and support delegates to understand:

- the rare epilepsies and current research
- best practice and diagnostic processes
- support and networking opportunities for both clinicians and families

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 *Sleep, cognition and epilepsy: the relevance of sleep,* April 2017; *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 2019

The Young Epilepsy Research Retreat, hosted by The Prince of Wales's Chair of Childhood Epilepsy, is an annual gathering of researchers and collaborators across our research unit. This meeting gives researchers, at all stages of their careers, 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 70 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 year's work through sub-projects, collaborations and shared data.

2019 marked our 9th Retreat and we were honoured to welcome Professor Gaillard as Research Moderator this year. Bill is the Second Vice President of the American Epilepsy Society (President for 2020) and past Treasurer; past Chair of the International League Against Epilepsy (ILAE) Commission on Diagnostics, past Chair of the ILAE Paediatric Epilepsy Surgery Task Force, and past member of the Paediatric Commission. As Associate Director of the Children's Research Institute's Centre for Neuroscience Research, he is responsible for overseeing research in clinical neuroscience. His own research interests centres on advanced structural and functional imaging.

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

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 for discussion.

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 early-career researchers to recognise this diversity and to form the collaborations which underpin excellent science and practical outcomes.

The Research Retreat and additional meetings, such as the Young Epilepsy Masterclass, are a critical contributor to creating a collegiate environment across the unit and nurturing new talent in paediatric epilepsy research.

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

"A veritable feast of epileptology!"

Professor Ingrid Scheffer AO,
Moderator, Retreat 2017

The MEG project partnership with Young Epilepsy was the direct result of connection and collaboration following Tim Tierney's talk at the 2018 Retreat

Research Publications

Primary Research

1. Abdel-Mannan O, D'Argenzio L, Pitt M, **D'Arco F**, Bhate S, Hacohen Y, Kaliakatsos M (2019) **Two Cases of Guillain-Barré Syndrome Variants Presenting With Dysautonomia.** *Child Neurol Open.* 6:2329048X19856778.
2. Adler S, Blackwood M, Northam GB, Gunny R, Hong SJ, Bernhardt BC, Bernasconi A, Bernasconi N, **Jacques T**, **Tisdall M**, **Carmichael DW**, **Cross JH**, **Baldeweg T** (2018) **Multimodal computational neocortical anatomy in pediatric hippocampal sclerosis**. *Ann Clin Transl Neurol.* 5(10):1200-1210.
3. Alonazi BK, Keller SS, Fallon N, Adams V, **Das K**, Marson AG, Sluming V (2019) **Resting-state functional brain networks in adults with a new diagnosis of focal epilepsy.** *Brain Behav.* 9(1):e01168.
4. An S, Malhotra K, Dilley C, Han-Burgess E, Valdez JN, Robertson J, **Clark C**, Westover MB, Sun J (2018) **Predicting drug-resistant epilepsy - A machine learning approach based on administrative claims data.** *Epilepsy Behav.* 89:118-125.
5. Argyropoulos GPD, Watkins KE, Belton-Pagnamenta E, Liégeois F, Saleem KS, Mishkin M, **Vargha-Khadem F** (2019) **Neocerebellar Crus I Abnormalities Associated with a Speech and Language Disorder Due to a Mutation in FOXP2.** *Cerebellum.* 18(3):309-319.
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8. Bennett SD, **Heyman I**, Coughtrey AE, Buszewicz M, Byford S, Dore CJ, Fonagy P, Ford T, Moss-Morris R, Stephenson T, **Varadkar S**, Walker E, **Shafran R** (2019) **Assessing feasibility of routine identification tools for mental health disorder in neurology clinics.** *Arch Dis Child*. 104(12):1161-1166.
9. Benova B, **Jacques TS** (2019) **Genotype-phenotype correlations in focal malformations of cortical development: a pathway to integrated pathological diagnosis in epilepsy surgery.** *Brain Pathol.* 29(4):473-484.
10. Blümcke I, Coras R, Wefers AK, Capper C, Aronica E, Becker A, Honavar M, Stone TJ, **Jacques TS**, Miyata H, Mühlebner A, Pimentel J, Söylemezoğlu F, Thom M (2018) **Challenges in the histopathological classification of ganglioglioma and DNT: microscopic agreement studies and a preliminary genotype-phenotype analysis.** *Neuropathology and Applied Neurobiology.* 45:95-107.
11. Carecchio M, Invernizzi F, Gonzàlez-Latapi P, Panteghini C, Zorzi G, Romito L, Leuzzi V, Galosi S, Reale C, Zibordi F, Joseph AP, Topf M, Piano C, Bentivoglio AR, Girotti F, Morana P, Morana B, **Kurian MA**, Garavaglia B, Mencacci NE, Lubbe SJ, Nardocci N (2019) **Frequency and phenotypic spectrum of KMT2B dystonia in childhood: A single-center cohort study.** *Mov Disord.* 34(10):1516-1527.
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7. **Pressler R**, Yosawitz E (2018) **Neonatal seizures.** *In: Neuromonitoring in Neonatal and Pediatric Critical Care.* Editors: Wusthoff CJ, Hahn C. *Cambridge University Press.*

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Commission on Paediatrics of the ILAE

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North Thames Neurosciences Network for the Neurosurgical Child

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ILAE

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UK Paediatric Vagus Nerve Stimulation (VNS) expert group

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European Paediatric Neurology Society (EPNS)

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Elected to Board
International Child Neurology Association

Helen Cross
Clinical Advisor
Epilepsy Action

Helen Cross
Clinical Advisor
Children's Epilepsy Surgery Service (CESS)

Helen Cross
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Member of the Editorial Board
Epilepsia, Journal of the ILAE

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Member of the Workshop on Neurobiology of Epilepsy (WONOEP)
ILAE Neurobiology Commission Conference

Rod Scott
Reviewer
National Institute of Health Research (NIHR)

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Member of the Basic Science Committee
American Epilepsy Society

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Council Member
ILAE British Chapter

Sophie Varadkar
Member
RCPCH Epilepsy Programme Board

Faraneh Vargha-Khadem
Member of the Scientific Advisory Board
Max Planck Society

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Chairman of Exam Board, MSc Paediatric Neuropsychology
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Torsten Baldeweg
Module organiser and lecturer, MSc Paediatric Neuropsychology
University College London

Helen Cross
Member of the PhD Review Panel
UCL GOS - ICH

Helen Cross
Paediatric Epilepsy Masterclass
Young Epilepsy

Felice D'Arco
Honorary Senior Lecturer
UCL GOS - ICH and UCL Institute of Neurology

Felice D'Arco
Lecturer
European Course of Paediatric Neuroradiology

Michelle De Haan
Course Speaker, MSc in Cognitive Neuroscience, Translational Research Module
University College London

Michelle De Haan
Deputy Director, MSc in Clinical & Applied Paediatric Neuropsychology
UCL GOS - ICH

Michelle De Haan
Director, MSc in Infancy and Early Childhood Development
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Course Director, EEG in the First Year of Life teaching course
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Ronit Pressler
Lecturer in Neonatal Seizures
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Ronit Pressler
Web based teaching: e-brain: Epileptic Seizures and Syndromes in Neonates and Infants
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Training Advisor for Inherited Metabolic Medicine
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Society for the Study of Inborn Errors of Metabolism

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Course Contributor, Educational Psychology
University College London

Colin Reilly
Annual workshops for trainee educational psychologists
University College London

Martin Tisdall
Honorary Senior Lecturer
UCL GOS - ICH and UCL Institute of Neurology

Sophie Varadkar
Chair of the Steering Committee
BPNA Paediatric Epilepsy Training Programme

Professional Recognition and Awards

Rosamund Shafran and UCL GOS - ICH Psychological Medicine Research Team

Eric Taylor Translational Research into Practice Award
2019
The Association for Child and Adolescent Mental Health

Helen Cross

Frank Ford Award
2018
International Child Neurology Association

Manju Kurian

John Stobo Pritchard Award
2018
International Child Neurology Association

Adeline Ngoh

YES Best Presenter Award
2019
International League Against Epilepsy

Suejen Perani

Epilepsia Prize for Clinical Science Research
2019
International League Against Epilepsy

Birgit Pimpel

Adrian Prize
2019
British Society for Clinical Neurophysiology

Suresh Pujar

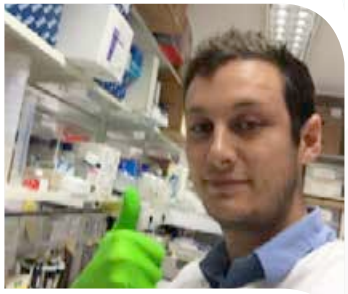
Dr Ronnie MacKeith Prize
2019
British Paediatric Neurology Association

Joyeeta Rahman

First Prize Poster
2018
UCL Great Ormond Street Institute of Child Health Open Day

Shamima Rahman

Adam Barsky Mitochondrial Lectureship
2019
Hospital for Sick Children, University of Toronto



Matthew Wilson

First Prize Poster
2018
UCL Faculty of Population and Health Sciences; Poster competition

At Young Epilepsy we want to build a society where children with epilepsy thrive.

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