Research Projects

This section outlines the new, ongoing, and competed projects during July 2024 to June 2025

Young Epilepsy

Current projects

The projects are presented under the workstream they most contribute to. They have coloured, numbered icons in the top right corner which illustrate all the goals to which they contribute. Each project also features a purple 'What this means' box which gives a summary of the work and intended impact.

Workstream 1: Understanding Childhood Epilepsies

Gene-STEPS: Shortening Time of Evaluation in Paediatric epilepsy Services: a multi-centre prospective evaluation of the impact of early genetic diagnosis on patient outcomes

Project Aim: To implement rapid trio WGS for all children, utilise electronic healthcare records and research databases to unite phenotypic and genomic data and assess the impact of early genetic diagnosis on epilepsy, developmental, and health economic outcomes through formal longitudinal assessments of all children enrolled.

Investigators: Amy McTague, Helen Cross, Lyn Chitty, Neil Sebire

With: Annapurna Poduri, Katherine Howell, Ingrid Scheffer, Gregory Costain, Vann Chau

Summary: In the past decade, the genomic revolution has led to the identification of underlying genetic aetiologies for childhood epilepsy, in the form of monogenic disorders affecting ion channels, neurotransmitter receptors, synaptic proteins, and other families of proteins. In a growing number of cases, the specific genetic diagnosis informs prognosis and genetic counselling, leads to the opportunity to participate in natural history studies, and even to changes in treatment that, to date anecdotally, may change outcomes in seizures and in neurodevelopment. However, a major challenge in clinical practice is that early intervention requires early diagnosis. Currently the diagnostic odyssey in early-onset epilepsy is long and arduous for patients and their families. The timing and nature of genetic testing for such patients varies widely within and across countries and institutions. Our collective expertise includes epilepsy genetics research, genomic research, clinical epilepsy, clinical trials, and team science across four leading paediatric institutions in the IPCHiP Consortium: Boston Children's Hospital (US), Great Ormond Street Hospital and UCL Great Ormond Street Institute of Child Health (UK), Royal Children's Hospital Melbourne and Murdoch Children's Research Institute (Australia), and The Hospital for Sick Children ("Sick Kids", Canada). Each of our institutions has a proven track record of discovery and translation to patients, and our combined efforts in epilepsy will set a new standard for multi-institutional research, data sharing, and improvement. To investigate our hypothesis that rapid genetic diagnosis and tailored management could improve outcomes, we propose a novel approach to streamline and accelerate diagnostics in these severely affected children. We have now recruited over 500 patients internationally to the cohort and have published the first 100 probands in Lancet Neurology in 2023. Our paper on re-analysis was published in Neurology in November 2025

Funders: Young Epilepsy, GOSH charity, GOSH NIHR BRC, UCL International Office

Is there an episignature in the rare epilepsies?

Project Aim: To understand the role of DNA methylation in rare epilepsies

Investigators: Amy McTague, Manju Kurian

Summary: Sunflower syndrome is a rare, light-sensitive epilepsy, which affects females more than males, with an average starting age of 5-6 years. The seizures happen many times per day, and involve hand-waving followed by an episode of staring or eyelid flutter. They can significantly affect daily life- for example, children can find it hard to walk to school and cross the road safely. Most patients also have other seizure types including grand mal seizures. Sunflower syndrome is often associated with significant learning problems, autistic spectrum disorder, attention deficit hyperactivity disorder, anxiety and depression. The seizures are often resistant to most epilepsy treatments and there are no effective treatments for the significant developmental, psychological and behavioural problems which some people with Sunflower syndrome can suffer with. We have analysed the genetic information of our patients, and have found changes in 2 patients within certain genes that work towards switching other genes "on" or "off". These genes act by changing DNA to make it more or less likely to be expressed, a process called methylation. This has led us to wonder whether other patients with Sunflower syndrome might also have abnormal patterns of DNA methylation. We can check the "methylation fingerprint" with a DNA methylation array, a test that looks at 935,000 DNA locations in the genome per patient to see whether they are turned on, or methylated. We will also use long read sequencing to investigate regions of the genome with altered methylation. This project will allow us to use this unique DNA finger print as a new method of understanding rare epilepsies such as Sunflower syndrome.

What this means: This project will allow us to generate preliminary data regarding the role of epigenetic dysregulation in rare epilepsies.

Understanding the role of vitamin B6 dyshomeostasis in epilepsy disorders

Project Aim: Establish and characterise zebrafish models of different genetic disorders of vitamin B6 metabolism associated with early onset epilepsy.

Investigators: Karin Tuschl, Philippa Mills, Richard Rosch, Isaac Bianco, Stephen Wilson

Summary: Inherited disorders of vitamin B6 metabolism cause early-onset epilepsy that responds well to B6 treatment. However, despite seizure control, affected children show delayed neurodevelopment and brain malformations, suggesting additional disrupted pathways that may be targetable by novel treatments. Equally, there are types of epilepsy with no known links to B6 metabolism that respond to B6 for reasons that are currently not understood. Our research aims to determine how B6 dyshomeostasis leads to seizure generation with the view to identifying novel therapeutic targets and defining which epilepsy types respond to B6 treatment. Taking advantage of the unique characteristics of zebrafish, we will analyse B6-dependent epilepsy model (prosc, pnpo, aldh7a1 loss-of-function) and define shared and distinct phenotypes at multiple levels including cellular pathways, brain compartments and networks, and whole organism behaviour. This will be achieved using 1. Real-time in vivo, whole-brain calcium imaging to characterise epilepsy signatures, 2. Spatial transcriptomics to map whole-brain neuronal activity and neurochemistry at single cell resolution to identify those neuronal cell types relevant for seizure generation, 3. Free swimming locomotor activity assays to link neurochemistry to behavioural readouts, thereby, establishing robust animal models to elucidate the biology underlying phenotypes and to assess drug/treatment efficacy in the future.

Goal 1 Goal 3

What this means: We will be able to establish novel models for genetically distinct vitamin-B6-dependent epileptic disorders to test new and emerging treatments.

MELD Focal Epilepsies Project

Project Aim: To improve epilepsy surgery outcomes by developing Artificial Intelligence (AI) algorithms to automatically find subtle abnormalities on patients' MRI scans and help neurosurgeons to plan operations that will completely remove them.

Investigators: Sophie Adler, Konrad Wagstyl, Torsten Baldeweg, John Duncan, Juan Eugenio Iglesias, Helen Cross

Summary: In many patients with epilepsy, the seizures are caused by structural abnormalities, such as areas of the brain that have developed abnormally or certain types of tumours. These structural abnormalities often cause drug-resistant epilepsy, where drugs are unable to stop the seizures. For these patients, surgery to remove the abnormality can cure the seizures. However, the abnormalities can be hard to find and completely remove, and surgery is only successful in 6 out of every 10 patients.

This Multi-centre Epilepsy Lesion Detection (MELD) project has created the largest collection of anonymised MRI data from patients with epilepsy caused by structural abnormalities from hospitals world-wide (over 2000 patients). We have used this dataset to develop state-of-the-art algorithms to diagnose focal cortical dysplasias (Ripart et al., JAMA Neuro, 2025) and hippocampal sclerosis (Ripart et al., Annals of Neurology, 2025). We are now using this unique dataset to:

1) Create atlases of where structural abnormalities occur in the brain, helping us to understand why they cause epilepsy.

2) Train AI algorithms to find multiple different abnormalities causing epilepsy on MRI scans

3) Train AI algorithms to diagnose what is causing the epilepsy (e.g. developmental abnormality, tumour).

4) Develop an algorithm to predict which patients will be cured by surgery.

Funders: ERIUK

What this means: We hope to create useful, interpretable AI algorithms to better diagnose and plan epilepsy surgeries for patients with focal epilepsy.

Transforming neurodevelopmental disorders using multi scale imaging and genomics

Project Aims:

i) develop computational tools to identify individual subject-level imaging abnormalities in neurodevelopmental disorders

ii) create a multiscale genetic, cellular and imaging framework for understanding the common and diverging neurobiological causes of epilepsy and ASD

iii) test the potential of these tools for linking genetics, imaging and phenotypes with known mutations in genes associated with epilepsy and autism.

Investigators: Konrad Wagstyl, Sophie Adler, Helen Cross, Finbar O'Callaghan, Amy McTague, Andreas Brunklaus, Armin Raznahan, Juan Eugenio Iglesias

Summary: Epilepsy and Autism Spectrum Disorder are common clinical conditions that show high comorbidity. For some individuals structural brain abnormalities can be found, while for others genetic variations in shared risk genes have been identified. Imaging neuroscience and genetics have undergone a revolution, generating large, open datasets with the potential to characterise the brain at multiple scales in health and disease.

However, we currently lack the tools to reliably identify MRI subtle brain abnormalities in epilepsy and autism, to understand how risk genes pattern the developing brain and interact with imaging abnormalities, and how neuroimaging and genetic risk factors combine to produce a range of neurodevelopmental and seizure phenotypes.

We will i) develop computational tools to identify individual subject-level imaging abnormalities in neurodevelopmental disorders

ii) create a multiscale genetic, cellular and imaging framework for understanding the common and diverging neurobiological causes of epilepsy and ASD

iii) test the potential of these tools for linking genetics, imaging and phenotypes with known mutations in genes associated with epilepsy and autism.

What this means: We hope to create useful, interpretable AI algorithms to better understand, diagnose and treat patients with focal and genetic epilepsies.

The neuropathology of focal epilepsy in children

Goal 1 Goal 3

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

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

Summary: 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.

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

Goal 1 Goal 2

Project Aim: To characterise the memory profile of children and young people and 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.

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

Summary: 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.

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.

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.

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 have completed recruitment for 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 are in the process of collating the data and will analyse it to determine whether there are any correlations between clinical/laboratory findings and outcomes.

Goal 1 Goal 2 Goal 3

What this means: 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 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

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 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.

What this means: We want to know if data gathered during and between seizures can improve the use of SEEG electrodes to find the epileptogenic region.

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, Gemma Wilson

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. Data collection is on-going.

What this means: We are investigating past data to better inform future management and treatment of LKS.

EAGLET: EEG vs aEEG to improve the diagnosis of neonatal seizures and Epilepsy - a Randomised Trial

Project Aim: EAGLET is a prospective multicentre randomised controlled trial to evaluate whether the combination of cEEG with aEEG is superior to aEEG in the real time evaluation and diagnosis of neonatal seizures and in reducing time to treatment.

Investigators: Ronit Pressler, David Rowitch
Co-investigators: Topun Austin, Paul Clarke, Claudia Chetcuti-Ganado

Summary: Seizures are the most common neurological emergency in the neonatal period, affecting over 2000 infants per year in the UK. Diagnosing neonatal seizures is challenging because most have only subtle or no clinical manifestation. The gold standard for seizure detection is continuous electroencephalography (cEEG). However, there is limited availability in the UK due to lack of on-site specialist support. The more common amplitude-integrated EEG (aEEG) uses a limited number of electrodes and is easier to apply and interpret but has been shown to miss a significant number of seizures. Although studies have compared the diagnostic value of aEEG and cEEG retrospectively, the measured sensitivity of aEEG ranges widely (25-85%).

Goal 1 Goal 3

Method: This is a Pilot study to inform a lagger UK wide multicentre randomised clinical trial that aims to compare the real-time diagnostic rate of neonatal seizures of full EEG and CFM (or aEEG). In this pilot study up to 20 babies will be randomised to either standard of care (aEEG/CFM) or advance monitoring which is standard of care plus full EEG with remote monitoring. Outcome measures are diagnostic yield, time to diagnosis and time to treatment. We also ask parents and nurses to complete questionnaires to evaluate acceptance of EEG monitoring by parents and staff.

Funders: Evelyn Trust and BRC Cambridge

What this means: The result of this study will inform if advanced monitoring can diagnose seizures faster and more accurately.

The Meerkat Project

Project Aim: The Meerkat project aims to develop non-contact monitoring for neonates in intensive care. A collaboration between the Departments of Engineering and Paediatrics at the University of Cambridge, as well as universities in the UK and Europe, the project will leverage expertise in image processing and machine learning to improve neonatal care.

Investigators: Kathy Beardsall
Co-investigators: Alex Grafton, Peter Marschik, Ronit Pressler, Oliver Bonner

Summary: The research focusses on using a 3D camera to acquire data, which is non-contact, non-invasive, and does not interfere with routine care. Specific clinical areas of interest include monitoring vital signs, which currently requires multiple wires attached to the babies' fragile skin; activity monitoring, where detecting lethargic behaviour may provide useful clinical information; seizure detection, where seizure events can be fleeting and difficult to spot by clinical staff; General Movements Assessment, a method of detecting potential neurological disorders such as cerebral palsy, currently requiring assessment of video by trained experts. The equipment necessary to realise these clinical benefits will be housed in an integrated device, suitable for cot-side use. This equipment will also provide a platform for future applications of the imaging technology. We are currently in the process of setting this up.

Funders: Rosetrees Grant Collaboration

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 neurobehavioural phenotypes; identify risk factors for neurodevelopment and later intellectual disability.

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

Summary: 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 15% of the cohort. Variants of unknown significance in known epilepsy gene, requiring further evidence for proof of pathogenicity have been reported in 42%, and analysis for novel mutant genes is ongoing in 43%.

We plan to collect developmental follow up data from the 119 recruited participants 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.

Turning6 - A Clinical and Neurodevelopmental follow up of EpiPEG participants

Project Aim:

1. Characterise the neurodevelopmental (cognition, behaviour, sleep) status of children who had epilepsy in the first year of life.
2. Examine the association between initial neurodevelopmental and clinical assessment results and performance at follow-up.
3. 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, Finbar O'Callaghan, Manuela Pisch, Abigail Wooldridge, Lara Carr, and Helen Cross

Summary: Epilepsy in the first year of life is associated with difficult to treat epilepsy and poor neurodevelopmental outcomes severely affecting child and parent/caregiver quality of life and the child's educational outcomes. Despite this, there is a paucity of longitudinal data on children with early onset epilepsy with respect to neurodevelopment course and outcomes. This makes it difficult to understand the role of seizures, aetiology and treatment on outcome. Such data is vital to understanding prognosis in children with early onset epilepsy. Understanding factors associated with impairments will help direct prognosis but also management. The EpiPEG study recruited 115 infants who developed epilepsy in the first year of life. The children were reviewed clinically, where appropriate underwent genetic testing and underwent full neurodevelopmental assessment including measures of global development, sleep, and parent/caregiver wellbeing. We propose to follow up this unique cohort of children as they reach 6-8 years and undertake comprehensive psychological assessments with the child, their parent/caregivers and teachers. This will allow us to characterise the neurodevelopmental (cognition, autism and ADHD status, sleep, health related quality of life) status of children who had epilepsy but also examine the association between initial neurodevelopmental and clinical assessments, and performance at follow-up. We are also recruiting a control group of children (n=60-80) matched on age and gender with the children initially assessed in EpiPEG. Children in both groups will wear a Phillips Respironics Actiwatch2 for ten days, which measures several sleep variables such as sleep duration, fragmentation, and efficiency. Caregivers and parents of children also complete complementary measures of sleep (sleep diaries, survey) and behaviour. This will allow us to compare sleep in children with early onset epilepsy to age and gender matched controls. Both the assessment of the EpiPEG cohort and the recruitment of the control group are currently underway, and we have recruited 59 children to date.

SCN1A Horizon's: Natural history study of SCN1A related epilepsies in the UK

Project Aim: The SCN1A Horizons natural history study will establish a national UK platform for long term data collection on assessment and therapy of up to 400 child and adult patients with a genetically confirmed SCN1A variant. This study will increase our understanding of Dravet syndrome and SCN1A-related epilepsies by allowing us to learn more about the seizures, learning abilities and behavioural difficulties that children and adults with an SCN1A-related epilepsy live with.

Investigators: Andreas Brunklaus, Helen Cross, Amy McTague, Michael Absoud

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FG12-related epilepsy: putting the brake on sodium channels

Project aims:

1. Establish a patient-derived neuronal model of FGF12-epilepsy
2. Investigate disease phenotypes in patient-derived neurons
3. Assess novel therapeutic approaches to modulate FGF12

Investigators: Amy McTague, Serena Barral, Gabriele Lignani

Summary: FGF12-related epilepsy is a rare, severe disorder characterised by frequent seizures, status epilepticus, developmental delay, autistic spectrum disorder and increased mortality. FGF12 encodes fibroblast growth factor 12 which is expressed widely but particularly in the brain and heart and is a key modulator of voltage gated sodium channels, particularly Nav1.6 (SCN8A) and Nav1.2 (SCN2A). We have identified ten new patients with FGF12-related epilepsy and have delineated their epilepsy and developmental outcomes. A recurrent de novo variant R114H is responsible for 60% of cases of FGF12-epilepsy and has been suggested to result in a gain of function of the SCN8A channel in cell and mouse models. We will create a patient-derived neuronal model of FGF12 related epilepsy, generating a platform for testing of novel therapies using electrophysiology and other readouts. While some patients with FGF12 related epilepsy respond well to a precision medicine approach with sodium channel blocking medication such as phenytoin and carbamazepine, others have resistant status epilepticus and severe outcomes. Modulation of FGF12 thus represents a potential precision therapy for both this epilepsy and SCN8A/SCN2A-related epilepsies, which are amongst the commonest forms of genetic epilepsies.

International guidelines for Pyruvate Dehydrogenase Complex Deficiency (PDCD)

Project Aim: To develop international consensus guidelines for the diagnosis and management of PDCD

Investigators: Shamima Rahman, Jerry Bedoyan, Nandaki Keshavan

Summary: Guideline development will occur over a period of 1 year, followed by time for finalising the guideline and writing up for publication in JIMD (total ~18 months from first meeting to final publication). The guideline committee will initially meet remotely via videoconferencing on a monthly basis. The purpose of these meetings will be to:

1.Set the scope of the guideline
2.Formulate key guideline statements regarding diagnosis of pyruvate dehydrogenase deficiency
3.Form working groups to establish evidence base for clinical management
4.Formulate key guideline statements regarding management of pyruvate dehydrogenase deficiency, including pharmacological and non-pharmacological (including dietary) treatments and disease monitoring. At month 12, a face-to-face meeting over 2 days will be organised to enable voting on the statements of the guideline utilising a Delphi methodology to enable determination of consensus, utilising GRADE methodology. Evidence base for management will be presented at the face-to-face meeting, followed by discussion.

Goal 1

What this means: Having international consensus guidelines will hopefully shorten diagnostic odysseys and improve outcomes and access to therapies for children and adults affected by PDCD.

Multimodal approach to investigate pathomechanisms and biomarkers for early diagnosis of Rasmussen Encephalitis

Goal 1

Project Aim: This project, based at Great Ormond Street Hospital and UCL, aims to understand what causes RE and to discover early warning signs (biomarkers) that could allow earlier diagnosis and treatment. Using advanced techniques such as DNA sequencing, transcriptomics, and antibody profiling, the applicant will study brain tissue, blood, and spinal fluid from affected children. These tools may reveal hidden genetic mutations, immune responses, or infections linked to the disease.

Investigators: Evangelia Ioannidou, Tom Jacques, Suresh Pujar, Marios Kaliakatsos, Helen Cross

Current projects

Workstream 2 – Outstanding Treatments

The 7T Temporal Lobe Epilepsy Study

Project Aim: The 7-TLE study is a prospective neuroimaging study that is using super-high-field (7-Tesla) MRI to investigate the network abnormalities in children and adults with temporal lobe epilepsy.

Investigators: Rory Piper, Shan-Shan Tang, Alexander Hammers, Atta Siddiqui, John Duncan, Martin Tisdall, David Carmichael, Torsten Baldeweg

Summary: The 7-TLE study is a prospective neuroimaging study that is using super-high-field (7-Tesla) MRI to investigate the network abnormalities in children and adults with temporal lobe epilepsy. Patients with temporal lobe epilepsy and healthy controls will attend the KCL 7T MRI scanner at St Thomas' Hospital and have high-resolution functional and diffusion MRI acquired to investigate the brain connections that are associated with temporal lobe epilepsy. The study primarily will investigate the role of the piriform cortex (olfactory cortex) in the epileptogenic connectome of patients with temporal lobe epilepsy. The project recruitment period has ended and the data analysis is ongoing.

Goal 1

Funders: Funders: GOSH-CC

Comprehensive neuroimaging characterization of neurodegeneration and brain plasticity in children with Rasmussen Syndrome

Project Aim: The primary objective of the project is to identify predictors of successful cognitive recovery after surgical treatment.

Investigators: Torsten Baldeweg, Suresh Pujar, Patricia Sanfilippo, Marios Kaliakatsos

Summary: The PhD studentship will conduct a retrospective combined neuroimaging and neuropsychological study into the disease course of a rare inflammatory neurodegenerative condition, Rasmussen syndrome. The project will use quantitative neuroimaging data in connection with cognitive and clinical evaluation. The primary objective of the project is to identify predictors of successful cognitive recovery after surgical treatment.

Goal 1 Goal 2 Goal 3

What this means: We will provide firm evidence to inform the complex diagnostic process and clinical decision making for this challenging condition.

Dynamic variability in the epileptic brain

Goal 1 Goal 3

Project Aim: Investigate how epileptic brain activity changes over time at multiple scales (seconds, minutes, days), in order to understand how our diagnosis and interventions can be targeted appropriately.

Investigators: Richard Rosch, Jamie Norris, Stuart Smith, Martin Tisdall, Gerald Cooray, Karl Friston

Summary: It has long been recognised, that many aspects of epilepsy vary over time – the seizures themselves, the burden of interictal epileptiform discharges, the cognitive symptoms all vary over time. Yet our diagnostic tools and treatment modalities often rely only on snapshots. Through quantitative, artificial intelligence supported analysis of time varying SEEG signatures of epileptic brain activity we aim to identify predictors of certain changes in brain dynamics. We will then test whether this approach helps us predict the brain's response to interventions, such as single pulse electrical stimulation. Jamie Norris has completed an MRes on predicting interictal epileptiform discharges from ongoing EEG activity, and has started his PhD trying to build individualised brain models as part of his doctoral training programme in AI-enabled healthcare. Dr Stuart Smith is investigating infraslow changes in EEG activity as part of the Human Brain Project funding.

What this means: Prolonged EEG recordings offer a unique window into the variability of brain activity in patients with epilepsy. Explicitly accounting for the time varying nature of these signals in our analysis methods will allow us to understand better when seizures are more likely to occur, and when patients may best benefit from therapeutic interventions.

The CADET Trial: The Children's Adaptive Deep brain stimulation for Epilepsy Trial

Project Aim: To determine the safety and feasibility of a novel non CE licensed DBS device for children with Lennox Gastaut Syndrome.

Investigators: Martin Tisdall, Helen Cross, Tim Denison, Harutomo Hasegawa, Elaine Hughes, Marios Kaliakatsos, Kei Landin, Rory Piper, Richard Selway, Antonio Valentin

Summary: Lennox-Gastaut syndrome (LGS) is a rare yet severe form of childhood epilepsy - a disorder that causes seizures. LGS is typically resistant to medications and children continue to experience seizures that impair their quality of life and development. Early trials in adults with LGS have shown that deep brain stimulation (DBS) of a specific region of the thalamus of the brain (the centromedian nucleus (CMN) is effective in reducing the number of seizures. No such trials, however, have been performed to demonstrate this benefit in children. Providing this therapy earlier in the course of the disease may improve long-term seizure control, brain development, and quality of life.

We will engage with advancements in neuro-engineering in order to translate DBS technologies into an effective and tailored treatment for children with LGS. Our aims are to reduce the frequency of seizures and improve the quality of life of children with complex epilepsy.
The CADET Pilot will be a Phase II clinical trial of DBS for children with LGS. 4 children (5-15 years) will undergo DBS using a new device that allows continuous stimulation and has features attuned to the particular needs of children. All children will complete six-months of active stimulation and the change in seizure frequency in the last month will be the primary outcome that will determine effectiveness.

Funders: Royal Academy of Engineering

Determining the utility of OPM-MEG in a clinical context

Project Aim: This project aims to fast-track regulatory approval of a new OPM-MEG system, making it the first, and only OPM-MEG system in the world to be approved for human use.

Investigators: Christine Embury, Zelekha Seedat, Kelly St Pier, Lara Carr, Eliot Dawson, Freya Jackson, Dominic Sims, Rosemarie Pardington, Elena Boto, Matt Brookes, Caroline Scott, Helen Cross

Summary: Magnetoencephalography (MEG) measures the magnetic field of the brain and is a useful clinical tool. Despite this, conventional MEG has not been widely taken up as it is expensive and of limited in use. In particular, conventional MEG is inadequate for children and infants as helmets are sized for the average adult, reducing the signal captured, and movement relative to the sensors causes dramatic reductions in data quality (even 5mm movements render data unusable). Whilst the newly designed OPM-MEG system overcomes these issues, critically, the system needs regulatory approval for human use. This project will fast-track this process by amassing the required information. Specifically, the project will:

Demonstrate the safety of the system and complete all documentation to ensure compliance for human use.

1. Build devices to ensure system accuracy enabling system validation prior to use.

2. Test the system in humans to prove benefits over existing scanners
3. Demonstrate clinical utility in epilepsy by showing that we can accurately map aberrant brain tissue.

What this means: This project will attain regulatory approval for the OPM-MEG system, allowing this new clinical tool to be brought to market and, in turn, offering new hope to many suffering from neurological conditions, such as epilepsy.

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

Project Aims:

1. To create and characterise a patient-derived induced pluripotent stem cell (iPSC) organoid model Epilepsy of Infancy with Migrating Focal Seizures (EIMFS).
2. To investigate the neuronal phenotype of EIMFS at a cellular and network level.
3. To investigate the impact of novel therapies.

Investigators: Amy McTague, B Cerna, E O'Connell, Gabriele Lignani, H Zhou, 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, we 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. We have generated brain organoids from patients with SLC12A5 mutations and are testing a new form of gene therapy in this model.

What this means: We want 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

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

Goal 1 Goal 3

Project Aim: To 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. We have not been successful in obtaining funding for this project but despite this we are offering the dried blood spot PNPO assay to anyone who suspects a diagnosis of PNPO deficiency and we have diagnosed 3 new patients. The dried blood spot test for PNPO deficiency is fully set up in our lab and we are getting regular requests for the test.

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.

The Diagnosis and Management of Pyridoxamine 5’-Phosphate Oxidase Deficiency

Goal 1 Goal 3

Project Aim: To create guidelines for the diagnosis, treatment and follow up of Pyridoxamine 5'-Phosphate Oxidase Deficiency which will facilitate clinical decision making and improve the care for patients with PNPO-deficiency in a standardised manner.

Investigators: Philippa Mills and Emma Footitt

What this means: These guidelines will facilitate the clinical decision making and improve the care for patients with PNPO-deficiency in a standardised manner.

Improved diagnosis and monitoring of treatment for patients with epilepsy caused by mutations in ALDH7A1

Project Aims: To work out which compound is the most reliable marker for detection of ALDH7A1deficiency and could be used for newborn screening.

Investigators: Philippa Mills, Emma Footitt, Helen Aitkenhead, Peter Clayton, Alistair Horman, Youssef Khalil

Summary: Our team have shown that several seizure disorders that cannot be controlled with anti-epileptic drugs can be treated with vitamin B6. A rapid diagnosis for these disorders is important as patients may die without B6 treatment where a timely diagnosis is not made. The most common of these disorders is called ALDH7A1-deficiency. Whilst treatment with vitamin B6 stops the seizures it does not prevent the intellectual disability that is also part of this disorder and affects more than 75% of these children. We can help to prevent this by giving them a special diet. The earlier this diet is started the better the outcome. Ideally, we need a way to screen all babies at birth for this disorder so that we can start treatment early and prevent any irreversible damage from occurring.

The current test used to decide if a child has ALDH7A1-deficiency measures levels of a chemical called alpha-aminoadipic semialdehyde (AASA) however AASA can degrade if the sample does not reach the laboratory quickly, and is therefore not suitable for newborn screening. Recently other compounds that are also elevated in samples from ALDH7A1-deficient patients which may be suitable for analysis in newborn screening programmes have been reported. These, however, have only been looked at in a small number of samples.

The aim of this project is to measure the levels of these compounds in samples from a much larger group of ALDH7A1-deficient patients so that we can work out which is the most reliable marker for detection of this disorder and could be used for newborn screening. We will also look to see if measuring these compounds helps us to better monitor the patients and decide how to adjust the treatments given to achieve the best outcome.

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 performance in the lab and in vivo of an improved pyridoxal 5'-phosphate (PLP) option 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 this PLP. The new PLP formulation is in form of a powder in a sachet. The powder can be reconstituted water to give PLP solution (10 mg/ml). It can ensure accurate dosing to wide age range of paediatric population. In mice, the new formulation displayed B6 vitamers profile in the blood similar to pure PLP following oral administration. Liver histopathology findings after a 90 day repeated oral administration in CD -1 mice revealed no significant changes evidenced with any of the treatment groups (pure PLP-degraded pure PLP-new PLP formulation) suggesting that high dose PLP rather than photodegradants could be deleterious for the liver warranting a fine tuning dose finding study.

Funders: UCL Therapeutic Acceleration Support (TAS) Fund

What this means: Based on our work, we hope to find a pathway to confirm the clinical dose, produce a tolerable and regulated new formulation of PLP which will improve both safety and quality of life for children who are taking PLP.

Cooling in Mild Encephalopathy Trial (COMET)

Project aim: The goal of this randomised control trial is to evaluate the safety, efficacy, and cost-effectiveness of whole-body hypothermia as a therapy for babies with mild HIE.

Investigators: Prof Sudhin Thayyil, Seetha Shankaran, Dr Ronit Pressler, Prof Andrew Shannon, Dr Kerry Woolfall, Prof Samantha Johnson, Prof Patricia Grant, Dr Farah Alobeidi, Prof Stavros Petrou, Mrs Sarah Land, Mrs Mariam Mahmoud, Ms Stuti Pant, Mr Paul Basset, Mr Tony Brady, Prof Victoria Cornelius, Dr Aung Soe, Dr Eleri Adams, Prof Jon Dorling, Dr Ella Chakkarapani, Dr Balamurugan Palanisami, Dr Paolo Montaldo

Summary: Background: In the UK, around 800 babies (0.8 per 1000 livebirths) are admitted to neonatal units with mild HIE. These babies have lower cognitive scores at 2 years, and lower IQ during school age compared with healthy peers and 38% require special educational support. Whole-body hypothermia, an evidence-based intensive care therapy for babies with moderate or severe HIE, is increasingly used for babies with mild HIE in the NHS without adequate evaluation of the safety and efficacy. Observational reports suggest that hypothermia increases several adverse outcomes in these babies including need for invasive ventilation, opioid use, disseminated intravascular coagulation, hepatic dysfunction, cardiac dysfunction, thrombocytopenia, coagulopathy, metabolic acidosis and increases intensive care stay.
Methods: Multi-centre open label two-arm randomised controlled trial with an internal pilot and masked outcome assessments recruiting babies born at or after 36 weeks for 60 NHS hospitals over a 2 ½ year period. Babies with evidence of intrapartum asphyxia AND mild encephalopathy on neurological examination AND normal amplitude integrated EEG between 1 and 6 hours will be recruited, and randomised to whole-body hypothermia or targeted normothermia within 6h of birth. The primary outcome is the mean Cognitive Scale Composite score from the Bayley-III examination at 24 (+2) months. Decision-analytic modelling will be used to estimate long term cost effectiveness across the whole life span. Recruitment has now started. The primary outcome is the mean Cognitive Scale Composite score from the Bayley-III examination at 24 (+2) months, performed by a central team of three examiners masked to the allocation. Short term outcomes and adverse events will include mortality, duration of intensive care and hospital stay, duration of ventilatory and inotropic support, bloodstream positive infection, thrombocytopenia and coagulopathy requiring blood products, seizures, cerebral and pulmonary bleeding, opioid use, and breastfeeding at hospital discharge. Decision-analytic modelling will be used to estimate long term cost effectiveness across the whole life span. A sample size of 382 infants in total (191 in each group) was calculated to detect a clinically important minimum difference of 5 points (0.3 SD), at a 0.05 significance level and 90% power as the Bayley III Composite score has a mean of 100 and SD of 15. This increases to 426, after allowing for a conservative 10% drop-out rate.

What this means: The COMET trial was developed in response to a call from the British Association of Perinatal Medicine for urgent evaluation of the safety and efficacy of hypothermia in mild HIE and is likely to rapidly adopted into the national guidelines for implementation. On the other hand, if hypothermia is neither safe nor effective, therapeutic drift will be reversed leading to a cost saving of at least £5 million per annum as hypothermia increases intensive care stay by three days.

Functional brain connectomics: implications for post-surgical outcomes in children with focal epilepsy

Project Aim: In this project we will estimate how strongly seizure generating parts of the brain (the surgical target zones) are connected to other, healthy parts of the brain.

Investigators: Xiyu Feng, Jon Clayden, Torsten Baldeweg, Rory Piper

Summary: This measure is called 'functional connectivity' and can be derived from functional MRI (fMRI) scans that are routinely acquired in children evaluated before surgery. We have conducted a retrospective evaluation of over 80 children with temporal lobe epilepsy who had fMRI investigations at our centre, over half of which have undergone surgery during this period. We have characterised the functional connectivity alterations in this cohort compared to healthy controls with a focus on thalamic connectivity.

What this means: The project will inform the multidisciplinary diagnostic process for children who are candidates for neurosurgical treatment by helping to identify the brain network alterations in children with TLE and how this might impact on the success of surgical treatment.

Reconstruction and Computational Modelling for Inherited Metabolic Diseases [Recon4IMD]

Project Aim: Using personalised computational modelling to:

1. Accelerate the diagnosis of patients at risk of an inherited metabolic disorder [IMD].
2. Refine the diagnosis of patients at risk of an IMD.
3. Stratify IMD patients by clinically actionable compensatory and aggravating metabolic mechanisms that associate with phenotypic severity.

Investigators: Professor Shamima Rahman [UCL is one of 12 participating organisations in this Horizon Medicine grant being coordinated by Professor Ronan Fleming at the University of Galway]

Summary: Our overall objective is to accelerate and refine the diagnosis and stratification of inherited metabolic diseases using personalised computational modelling. Established academic technology for statistical genomic analysis, deep learning-based prediction of protein structure and whole-body metabolic network modelling shall be translated for clinical application, given genomic or metabolomic data. Human metabolic reconstruction, validated by tracer-based metabolomics, will enhance the predictive capacity of metabolic network models. Novel technology will be developed that uses deep learning, subject to physicochemical constraints, to enable classification using multimodal data (genome, metabolome, clinical). These personalised computational modelling approaches will be applied to accelerate the diagnosis of symptomatic patients, refine the diagnosis of asymptomatic at-risk patients identified by newborn screening, and develop personalised therapeutic approaches for a focussed subset of inherited metabolic diseases. Leveraging established clinical cohorts, we shall identify compensatory and aggravating mechanisms that associate with variation in clinical severity within the same disease. Clinically actionable predictions shall be tested using metabolomics and tracer-based metabolomics of established sets of patient-derived stem cell cultures. Personalised and conventional therapeutic approaches will be compared by leveraging disease trajectories within an established unified European registry of inherited metabolic diseases. To maximise the potential for impact, personalised modelling software will be designed in a way that is generally applicable to any inherited metabolic disease, and it will be implemented in a way that is both accessible to clinicians and admissible to regulatory authorities. To deliver effective impact, personalised computational modelling will be disseminated within the European Reference Network for Hereditary Metabolic Disorders.

What this means: We will use multimodal "Omics" technologies and computation modelling to improve the diagnosis and management of patients affected by inherited metabolic diseases.

Gene therapy for deoxyguanosine kinase deficiency

Project Aim: Our aim is to develop a gene therapy for deoxyguanosine kinase deficiency, a fatal mitochondrial disease of infancy.

Investigators: Shamima Rahman
Co-Investigators: Nandaki Keshavan. Simon Waddington, Rajvinder Karda, Mario Cortina-Borja

Summary: Our aim is to develop a gene therapy for deoxyguanosine kinase deficiency. We will utilise an excellent knock-out mouse model of DGUOK deficiency which we have characterised extensively and which recapitulates both liver and brain disease seen in patients. So far, our proof-of-principle experiments of intravenous (IV) gene therapy at 6 weeks have clearly demonstrated rescue of liver disease, including mtDNA copy number, OXPHOS deficiencies and blood alanine aminotransferase levels in knock-out mice. However, we observed insufficient brain transduction and no improvement in brain mtDNA depletion following IV gene transfer. To progress toward clinical translation, we now propose to use combined IV and direct brain injections to ameliorate both liver and brain disease in KO mice.

Goal 2

What this means: In this study, we aim to develop an innovative gene therapy approach to improve liver and brain disease manifestations of Deoxyguanosine kinase (DGUOK) deficiency, a mitochondrial disease, in a preclinical model.

Minimally invasive self-regulating gene therapy for neuropsychiatric disorders

Goal 2

Project Aim: Many neuropsychiatric disorders involve episodic symptoms arising from unstable brain circuits that become hyperactive, leading to seizures, psychotic episodes, or accelerated cognitive decline. Rather than targeting symptoms, we aim to address the underlying circuit instabilities by developing cell-state specific gene therapy that modulates only overactive neurons while sparing normally functioning ones.

What this means: We aim to create a potentially curative treatment that resets dysfunctional brain circuits to stable states through a single minimally invasive procedure, moving beyond symptom management toward disease modification.

Investigators: Gabriele Lignani, Dimitri Kullmann, Jerzy Szablowski, Mikhail Shapiro, Richard Rosch

Summary: We're developing a gene therapy approach that addresses a fundamental problem in neuropsychiatric medicine. Current treatments for conditions like epilepsy, Alzheimer's disease, and schizophrenia typically involve medications that affect the entire brain, often causing significant side effects while leaving many patients with persistent symptoms. About 30% of people with epilepsy and schizophrenia don't respond adequately to available treatments. Our approach targets the root problem: specific brain circuits that become hyperactive and unstable, creating conditions that lead to seizures, memory loss, or psychotic episodes. We've developed a "smart" gene therapy that only activates in these overactive neurons, using the brain's own activity sensors (immediate early genes) to detect when neurons are firing excessively. When hyperactivity is detected, the therapy automatically releases inhibitory proteins to calm the neurons down, then switches itself off once normal activity resumes. The key innovation is delivery method. Instead of requiring brain surgery, we use focused ultrasound to temporarily open the blood-brain barrier at precise locations, allowing gene therapy delivery through intravenous injection. This technique uses sound waves to create temporary access to problem areas, letting the therapy selectively target only the neurons that need treatment while leaving healthy brain function intact.

Neurological digital twins: precision surgical planning of epilepsy treatment

Project Aim: The aim of this project is to develop precision digital twins of human brain function to tailor surgical intervention for focal epilepsies. This will involve:

- Development of novel geometric-deep learning technologies that simulate human brain functional dynamics in response to stimuli;
- Precisely locate the sites of epileptogenic brain lesions;
- Build in silico trials of surgical treatment

Investigators: Emma Robinson, Joel Winston, David Carmichael

Summary: Structural abnormalities that can cause epileptic seizures can be difficult to detect from imaging, and even when they can, removing them by performing a surgical resection does not always stop seizures. This project seeks to model whether we can characterise alterations in brain dynamics - measured with functional imaging, such as EEG and fMRI - to improve localisation of focal epilepsies and ultimately predict how individual patients will respond to treatment

Goal 2

What this means: This technical project aims to utilise a particular type of AI modelling that can currently predict movie clips people are watching. We want to translate these models to functional and structural MRI data to predict features such as the localisation of focal epilepsy.

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7 Tesla Sodium MRI for Identifying Focal Brain Lesions Causing Paediatric Epilepsy.

Project Aim: To explore the utility of sodium MRI as a structural and functional biomarker in paediatric focal epilepsy patients.

Investigators: Jon Cleary, Jonathan O'Muircheartaigh, Ozlem Ipek, Alexander Hammers, Shaihan Malik, David Carmichael

Summary: In this study we are aiming to scan children both with and without focal lesions on standard hydrogen MRI with sodium MRI. TSC and sodium T2* images offer exciting potential as new biomarkers of epileptogenic regions. In limited studies in adult focal epilepsy, correlating to stereotactic-EEG, Total Sodium Concentration is elevated and greatest in the epileptic zone (EZ) compared to controls. Several mechanisms have been proposed for this including dysfunction/abnormal distribution of voltage-gated sodium channels in the EZ or seizure-related dysfunction of the Na+/K+ ATPase leading to sodium accumulation. However, to our knowledge, no studies have been performed to characterise sodium in paediatric focal epilepsy, proof-of-concept data in patients is needed for larger scale translational studies to define diagnostic performance.

Goal 2

What this means: We want to establish the potential for a new type of MRI scan that measures sodium for identifying abnormalities related to focal epilepsy in children.

Current projects

Workstream 3 – Outstanding Support

Epilepsy Carers Uniting with Researchers (E-Cure) PPI network

Project aim: Strengthen the voice of children and young people with epilepsy in our research by establishing the UKs first network of parents, carers and young people who volunteer to shape childhood epilepsy research.

Investigators: Lara Carr, Susi Khan, Samantha Chan, Amy McTague, Helen Cross

Summary: The sole purpose of the network is to consult on the development of research ideas, methodologies, and delivery to ensure research reflects the true needs of patients and families. Members choose their level of participation and interests. Roles for members can be as simple as participating in surveys, up to becoming formal members of project management groups as patient representatives. The network currently has over 195 members.

Goal 5

What this means: Working with patients and their families is critical to the success of research. This network is a key component of research design across the unit.

Epilepsy Pathway Innovation in Africa (EPInA) Project Aims:

• Societal change: *ensure* an enduring, positive change by improving public awareness and reducing the stigma experienced by people with epilepsy in sub-Saharan Africa.
• Diagnose: To improve the rate of accurate diagnosis of epilepsy by primary health care workers with app-based technologies.
• Treatment: increase the adherence to medication using text messaging.
• Prevent: reduce the incidence of infection and peri-natal injury in an endemic region in Tanzania and the subsequent risk of epilepsy.

Investigators: Charles Newton, Arjune Sen, Helen Cross, Josemir Sander, Albert Akpalu, Patrick Adjei, Symon Kariuki, Damazo Kadengye, Gershim Asiki, Thomas Kwasa, Bruno Mmbando, Dan Bhwana, Tarun Dua, William Matuja, Sloan Mahone, David McDaid, Richard Walker

Summary: Epilepsy is one of the most common serious neurological conditions and is particularly widespread in sub-Saharan Africa (SSA). This high incidence is, in at least a quarter of cases, because of preventable factors, yet many people who may have had seizures are not diagnosed and even fewer receive appropriate treatments. These factors are compounded by enduring social stigma that can make it hard for Africans with epilepsy to obtain employment, form relationships or feel valued. We have chosen to work in three countries – Ghana, Kenya and Tanzania. We will bring together work across all three countries to better understand the history of epilepsy, investigate why people with epilepsy are so disadvantaged and then set out to improve things. We will develop an app to help healthcare workers to better diagnose epilepsy, and pilot a text messaging scheme to help people to remember to take their medication. We will train local people in epilepsy care and develop epilepsy healthcare specialists to lead future projects. In Tanzania, which has a higher incidence of epilepsy, possibly due to onchocerciasis infection, we are also going to see if reducing the rate of onchocerciasis infection can lower the number of people with epilepsy.

Funders: NIHR

What this means: By implementing measures to improve the prevention, diagnosis, treatment and cultural understanding of epilepsy, we think this project can dramatically change the lives of people with epilepsy in sub-Saharan Africa. If successful we will use all that we learn to ensure similar work is carried out across other low-income countries.

European Reference Network on rare and complex epilepsies (EpiCARE)

Project aims:

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

Investigators: Professor Alexis Arzimanoglou

Summary: 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.

The European Reference Networks (ERNs) were launched in 2017. They involve more than 900 highly specialised health care teams, located in more than 300 hospitals in 26 European countries. The main mission of the ERNs is to help patients with rare or low-prevalence complex diseases.

The ERN EpiCARE brings together highly specialized health centres (28 full members and 15 affiliated partners) in 24 European countries with expertise in rare and complex epilepsies. The centres closely collaborate with the scientific societies (ILAE, EAN, EPNS, Epilepsy Alliance Europe) and a number of other epilepsy teams in the EU with expertise in specific domains. EpiCARE offers a coordinated approach for epilepsy diagnostics and treatment by using e-tools and cross-country e-consultancy.

One of 24 approved ERNs on rare disorders, EpiCARE now has 52 members, spanning 13 countries. EpiCARE aims to improve access for patients to diagnostic and therapeutic expertise, by engaging multidisciplinary experts through the network.

Prevention of Epilepsy by reducing Neonatal Encephalopathy (PREVENT) study

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

Investigators: Sudhin Thayyil, recruiting centres in Bangalore, Hubli and Calicut.
Co-investigators from UCL: Ronit Pressler, Helen Cross and Charles Newton

Summary: Around 50 million people worldwide have epilepsy, of which 80% live in low- and middle income countries. In India, birth related brain injury is estimated to account for up to 1/8th of these cases. The aim of PREVENT is to examine if a pragmatic intrapartum care bundle will reduce birth injury related epilepsy at 18 months of age in India. The four key elements of the care bundle are:

1. Birth companion.
2. Intrapartum fetal surveillance.
3. Electronic partogram.
4. Brain oriented early newborn care.

The care bundle will be evaluated using a prospective interrupted time series design, recruiting 80,000 women delivering in 3 centres in south India, over two years. Baseline data will be collected during the first year and the optimised care bundle will be introduced during the second year. All full-term newborn infants with perinatal brain injury during both periods, will have detailed assessments including video EEG, and MRI. Primary outcome is the number of infants with epilepsy at 18 months of age expressed as per 1000 term livebirths. The total duration of the study is four years including 24 months of recruitment and 18 months of follow-up. Recruitment and follow up is now completed and data locked for data analysis.

Analysis of EEG has resulted in a prospective study on the efficacy of second line antiseizure medication in neonates in LMIC (Krishnan et al, Lancet Regional Health, 2024).

What this means: There is a high incidence of epilepsy in India due to complications during birth. We want to address the issues surrounding safe childbirth and through this aim to reduce the incidence of epilepsy due to birth complications.

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, Steve Rose, Karen Ray

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 that is meaningful for their families and allows them to be included in research or outcome data. We used a small grant through the Patient Public Involvement scheme at GOSH to run some focus groups with families and are now trialling assessment using scripted home videos.

Physical Activity in Primary School-Aged Children with Epilepsy (PACE) - Prime

Project Aims:

1.Conduct a prospective observational study to compare levels of Physical Activity (PA), sedentary behaviour and sleep in primary school-aged children with and without epilepsy using accelerometers and survey methods.

2.Identify factors associated with levels of PA, sedentary behaviour and sleep in primary school aged Children with Epilepsy (CWE).

3.Explore CWE, parental and school staff views on barriers/facilitators for CWE engaging in PA.

Investigators: Colin Reilly, Natalie Pearson, Lauren Sherar, Monica Lakhanpaul, Kerry Robinson, Lara Carr and Helen Cross

Summary: This study aims to investigate physical activity (PA) in primary school-aged children (6–10 years) with active epilepsy compared to age- and gender-matched healthy controls. Using both questionnaires and eight-day accelerometer monitoring, the study will assess overall PA levels, time spent at different activity intensities, and participation in structured exercise or sports. Parents will provide additional information on child behaviour, sleep, and quality of life. The study will also explore factors influencing PA, such as seizure characteristics, psychological and socioeconomic variables, and parental wellbeing, as well as barriers and facilitators to engaging in PA.

What this means: Findings will provide pilot data on PA levels, identify potential intervention targets, and evaluate the feasibility of using wearable activity trackers to promote PA in children with

Acceptance & Commitment Therapy (ACT) in Children and Young People with epilepsy

Project Aim: To develop, deliver and evaluate pilot ACT intervention groups to improve mental health support for young people with epilepsy living in the South of England

Investigators: Natasha Hughes, Emily Rhidian, Lara Carr, Alexander Marsh, Ingram Wright

Summary: The ACT project is designed to support young people with epilepsy and their families in managing the psychosocial challenges associated with epilepsy. It uses the DNA-V model, an evidence-based and practical model grounded in ACT, positive psychology, and behavioural science.

The project consists of three components: a group for young people, a group for parents, and self-help resources which can be accessed at the users' own pace, all of which are online. All components have been co-produced with young people with epilepsy, their families, and experts in clinical neuropsychology to ensure that the content is relevant, accessible, and tailored to their needs.

The project aims to improve psychological flexibility through equipping participants with practical skills to manage uncertainty and distress and improve wellbeing. These include acceptance, mindfulness, self-compassion, techniques to manage unhelpful thoughts, building intrinsic motivation through identifying personal values, and strengthening healthy behavioural repertoires of value-aligned actions. The sessions also aim to reduce isolation by connecting participants with peers and empower participants with the knowledge and resources to self-manage the difficulties associated with epilepsy. The project will assess feasibility, acceptability, and effectiveness of the groups and self-help resources using both quantitative and qualitative measures.

Epilepsy in Schools: Developing web-based training for educational staff who support children with epilepsy in mainstream schools

Project aims: The overall aim of this project is to develop, pilot and assess the feasibility of web-based interventions for staff currently supporting children with epilepsy. The specific aims of this project are to:

1. Co-develop web-based training for teachers and other educational staff who support children with epilepsy in mainstream schools.
2. Conduct a pilot study of the developed web training focusing on the knowledge and attitudes of educational staff in mainstream schools before and after the training.

Investigators: Collette Meades, Joan Idowu, Bhavna Sidhpara, Lara Carr, Helen Cross, Colin Reilly

Summary: Knowledge about and attitudes towards epilepsy among teachers and staff working in mainstream schools is frequently deficient. Staff express concerns about seizure management and in particular the administration of emergency medication. In addition to seizures, children with epilepsy frequently have learning and behavioural-emotional difficulties which often have a greater impact on Health-Related Quality of Life (HRQoL) than seizures.
However, these difficulties are often not recognised or supported further adding to the potential exclusion of the children We propose to explore the views of young people with epilepsy, caregivers and school staff regarding the content of training materials on epilepsy for staff in the schools (Phase 1). We will then use this data to develop web-based training materials for staff in mainstream schools in the UK (Phase 2). We will subsequently conduct a pilot study of the developed web-training focussing on the knowledge and attitudes of educational staff in mainstream schools before and after the intervention (Phase 3).

We have now completed phase one of the project after running focus groups and interviews with young people with epilepsy (n=5), caregivers (n=10), and teachers (n=4). Four main themes were identified regarding the content of a training programme: need for information, importance of effective communication, support for children with epilepsy in school and support for staff. The current findings will be used to develop (phase 2) and evaluate a training programme for school staff with a focus on improving staff attitudes towards, and knowledge about epilepsy (Phase 3).

Transition from paediatric healthcare to adult healthcare for young people with epilepsy in the UK: A scoping review and focus group study

Goal 3

Project Aims:

- To identify and synthesize published research on transition from paediatric to adult healthcare for Young People with Epilepsy (YPE) in the UK.
- To conduct focus groups with young people with epilepsy and caregivers to better understand experiences of transition
- To understand the experiences and needs of health care professionals who work with young people with epilepsy during the transition process

Investigators: Joe Paternoster, Abigail Wooldridge, Rainne Gooselink, Lara Carr, Helen Cross, Colin Reilly

Summary: Lack of continuity in the healthcare system results in poor experiences of the transition process in the UK. Few NHS providers have epilepsy specific resources, and quality of existing materials is inconsistent. More studies are needed to understand the key components of effective transition. Epilepsy transition resources would benefit from co-creation with YPE and caregivers., and parental wellbeing, as well as barriers and facilitators to engaging in PA.

Funders: Angelini Pharma

What this means: Transition resources would benefit from co-creation with young people/caregivers. There is a need for further work with Health care professionals to understand their needs and experiences.

Completed projects

Workstream 1: Understanding Childhood Epilepsies

Multicentre Epilepsy Lesion Detection (MELD) Project

Project Aim: 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, Mathilde Ripart, Hannah Spitzer, MELD consortium, Helen Cross, Torsten Baldeweg, Konrad Wagstyl

Summary: The MELD project has created the largest neuroimaging cohort of FCDs to date, including data from over 1000 participants. Using this unique dataset alongside statistical and machine learning techniques, we have 1) Mapped the distribution of FCDs across the brain and created predictive models of lesion location and seizure freedom (Wagstyl et al., Epilepsia, 2020), 2) Created and deployed an interpretable machine-learning algorithm to automatically detect FCDs (Spitzer*, Ripart* et al., Brain, 2022) 3) Developed a state-of-the-art new machine-learning algorithm with improved performance at detecting FCDs on MRI scans (Spitzer, Ripart et al., MICCAI 2023).

Funders: Rosetrees Trust

What this means: Through the MELD project we have a better understanding of where FCDs occur in the brain and how this impacts patients and we have created tools that can be used to inform clinical decision making. These include predictive maps of lesion locations, deep learning tools for the detection of FCDs and models for the prediction of post-surgical seizure freedom. These tools have been validated on data from 22 hospitals and have been made openly accessible for any hospital to use when evaluating a patient with a suspected FCD.

Management of seizures in patients with primary mitochondrial diseases: consensus statement from the InterERNs Mitochondrial Working Group

Project Aim: We aim to develop guidelines and consensus recommendations on safe medication use and seizure management in mitochondrial epilepsy using Delphi methodology.

Investigators: Michelangelo Mancuso, Maria T Papadopoulou, Yi Shiau Ng, Anna Ardissone, Marcello Bellusci, Enrico Bertini, Lidia Di Vito, Teresinha Evangelista, Carmen Fons, Omar Hikmat, Rita Horvath, Thomas Klopstock, Cornelia Kornblum, Costanza Lamperti, Laura Licchetta, Maria Judit Molnar, Kristin N Varhaug, Mar O'Callaghan, Ronit M Pressler, Manuel Schiff, Serenella Servidei, Nora Szabo, Gráinne S Gorman, Helen J Cross, Shamima Rahman

Summary: Epilepsy is a frequent manifestation of primary mitochondrial diseases (PMDs), affecting up to 40% of patients. Seizures in PMD are typically difficult to treat and often represent a poor prognostic feature. As PMD are rare no randomised controlled trials can be performed and treatment is often empirically and not evidence based. We aimed to develop guidelines and consensus recommendations on safe medication use and seizure management in mitochondrial epilepsy using Delphi methodology.

Method: Twenty-four experts in mitochondrial medicine, pharmacology, and epilepsy management of adults and/or children from seven countries, who were members of five different European Reference Networks - known as the Mito InterERN Working Group - formed a Delphi panel, together with two patient organisation representatives. The Delphi methodology was followed to allow the panellists to consider draft recommendations on safe medication use and seizure management in mitochondrial epilepsy, using two survey rounds with predetermined levels of agreement

Conclusion: There was a high level of consensus regarding safety of 14 of 25 drugs reviewed, resulting in endorsement of NICE guidelines for seizure management, with some modifications. The experts caution against using sodium valproate in POLG disease, vigabatrin in GABA transaminase deficiency and topiramate in patients at risk of renal tubular acidosis.

Goal 1 Goal 3

What this means: These consensus recommendations have the potential to improve seizure control and reduce the risk of drug-related adverse events in individuals living with PMD-related epilepsy.

Completed projects

Workstream 2 – Outstanding Treatments

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, Sila Dokumaci, Fred Dick, Dr Simon Richardson, Serena Counsell, Alex Hammers, Jonathan O'Muircheartagh

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.

We have been developed a full scan protocol for Paediatric Epilepsy patients. This has been used in around 40 patients so far. In parallel, we have been developing patient[1] friendly head cushions to improve scan performance and tolerance which led to a patent and a £1M NIHR i4i grant to develop this device towards NHS adoption to reduce scan failures with associated costs. We will be visiting young epilepsy soon to get feedback on our device! [1] PCT Patent Application No. PCT/GB2023/050932
Claiming Priority to GB Patent Application No. 2205139.5
Head Immobilisation in MRI Head Coils
King's College London

What this means: We are working to understand the potential of this enhanced imaging technology and how best to use it for children. We are working to enable this imaging capability to be available across the CESS network.

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

Summary: This project is now finalised, and we have published a small case series to test our new EEG-fMRI acquisition [1].

[1] Steinbrenner et al., 2023, DOI:10.1007/s10548-023-00945-0.

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

Project Aim: To provide better informed diagnosis of memory impairments in children with epilepsy and predict outcome after surgery in the temporal lobe, using the Pair Test.

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

Summary: 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:

1. Diagnose the status of memory and learning.
2. Monitor progression of disease.
3. 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.

What this means: 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.

Research Funding

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

Our collaborative funding strategy has enabled us to build the world's largest paediatric epilepsy research unit and network of multidisciplinary practitioners.

Alongside academic grants raised by the researchers and their academic institutions, we rely on the additional multidisciplinary fundraising by Young Epilepsy, which allow us to redirect funds where the need is greatest within a project. This flexibility is vital and provides stability during challenges, such as delays due to unforeseen circumstances.

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.

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We remain ever grateful for the generosity and dedication of the organisations and individuals who support out work. Thank you!

To find out how you can get involved in our vital work, visit:

www.youngepilepsy.org.uk/get-involved