Research Projects

This document outlines the new, ongoing, and competed projects during July 2021 to June 2022.

The projects are presented under the workstream they most contribute to. They have coloured, numbered icons in the top right corner which illustrate all of 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.

Young Epilepsy

Current projects

Workstream 1: Understanding Childhood Epilepsies

Functional effects of SCN1A mutations – New insights from biophysics and computational modelling

Project Aim: Linking functional properties of SCN1A mis-sense mutations with their resultant phenotypes

Investigators: Richard Rosch, Elaine Hughes, Kathleen Gorman, Colin Peters, Peter Ruben

Summary: Changes in the SCN1A gene are amongst of the most thoroughly investigated genetic causes of epilepsy. This gene controls sodium channel functionality – a critical component of cell structure. Yet even within the well-known SCN1A-related epilepsies, new phenotypes are still emerging, and the complexities of genotype-phenotype relationships remain only partially understood.

We combine biophysical measurements of the functional properties of the sodium channel variants found in patients with epilepsy, with computational modelling of neuronal function to understand better how different mis-sense mutation in the same gene – SCN1A – result in a wide range of phenotypes.

We have now published on a number of interesting cases from our patient cohort (e.g., Peter et al. 2017, Laura et al. 2021, Gorman et al. 2021). Data collection and analysis for our whole cohort has just finished and we are expecting to publish those results in the coming year.

Goal 1

What this means: Even when patients have apparently the same genetic mutation, there are still differences within the individual. This is because whilst we may have identified the cause of a particular epilepsy – such as a genetic mutation – we still might not understand exactly how it works or how each part of the mechanism of that gene/mutation results in the particular epilepsy syndrome of each patient.

By investigating in detail, the effects of specific mutations in a single gene, we hope to improve our understanding of the effects of genetic mutations in individual patients, and ultimately improve our treatments for each patient individually.

Neuro-LinK: Determining long-term outcomes in children with chronic neurological conditions (ICH Data science initiative)

Project Aim: Determine the long-term health outcomes of children treated at GOSH in three well-defined cohorts via data linkage with The Hospital Episode Statistics (HES) database.

Investigators: Jessica Pickles, Deborah Ridout, Torsten Baldeweg, Darren Hargrave, Thomas Jacques, Katie Harron, Vandana Ayyar Gupta, Francesco Muntoni

Summary: We are interested in obtaining long term outcome data, including hospital admissions and education outcome, for children with neurological conditions such as brain tumours, Duchenne Muscular Dystrophy and epilepsy surgery candidates. In particular, we are interested in those patients with neurological chronic disease who manage their condition over extensive periods, often require multiple interventions and may receive several forms of treatment. We will engage with PPI groups to discuss our project aims. Their feedback and advice will be instrumental in developing our application to seek approval.

Goal 1 Goal 2 Goal 3

There is a clear absence of long-term clinical outcomes associated with large paediatric cohorts, hindering the translation of research findings to our patients' life course and their expected clinical progression of disease. The project is aiming to access health outcomes for specific patient groups to appreciate the extent of the burden of disease for patients both during and after receiving their primary care at GOSH.

What this means: There is not enough information of the long-term outcome trajectory of children with chronic neurological conditions. We want to truly understand the burden of such conditions on patients so that we can better understand how to manage and treat them within the NHS.

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 Aims:

1. Implement rapid trio WGS for all children presenting to our health systems with epilepsy onset under 12 months of age
2. Utilize electronic healthcare records and research databases to unite phenotypic and genomic data and to create a "virtual" registry across all institutions that will promote ongoing discovery.
3. 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 (Boston Childrens), Katherine Howell, Ingrid Scheffer (Royal Childrens Hospital Melbourne), Gregory Costain, Vann Chau (The Hospital for Sick Children Toronto)

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.

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

Goal 1 Goal 2 Goal 3

Shining a light on the genetic basis of Sunflower syndrome

Project Aim: Investigate the genetic basis of this rare photosensitive epilepsy

Investigators: Amy McTague, Manju Kurian

Summary: Sunflower syndrome is a rare, photosensitive epilepsy, named for sun-seeking behaviour or stereotyped reflex seizures in bright light. Affected patients have many hand-waving episodes per day (the patient waves their hand in front of their own eyes and this stimulates a seizure). Hand-waving episodes are resistant to treatment and significantly impair quality of life.

Children with Sunflower Syndrome also experience other seizure types including absences, eyelid and other myoclonias and generalised tonic clonic seizures. Sunflower syndrome is often associated with significant neurodisability; many patients have co-morbid learning difficulties, autistic spectrum disorder, attention deficit hyperactivity disorder, anxiety and depression.

There remain a number of unanswered questions including whether the hand-waving episodes represent a reflex seizure or compulsive self-induction of seizures. We have established an international cohort of patients including families with significant family history and will undertake trio whole genome sequencing which will be analysed using Ingenuity and Alamut software, initially for known disease-causing genes followed by analysis for copy number variants and novel genes using differing inheritance models. Putative variants will be validated by Sanger sequencing and functional validation of likely disease-causing variants will be undertaken.

What this means: Sunflower Syndrome is a rare photosensitive epilepsy characterised by self-induction of seizures in children. We don't yet know what causes Sunflower Syndrome but we believe it has a genetic basis and we will be looking at an international cohort of patients and sequencing their entire genome alongside their biological parents. We will cross reference this with known epilepsy causing genes, against variations of these and will look for previously unknown epilepsy causing genes.

Short-term findings of this study will immediately improve the current genetic screening for epilepsy. We hope the long-term findings will reveal causal genes - giving a strong basis on which to develop targeted treatment for this condition.

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-Wagstyl, Kirstie Whitaker, Armin Raznahan, MELD consortium, Helen Cross, Torsten Baldeweg, Konrad Adler-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:

Mapped the distribution of FCDs across the brain and created predictive models of lesion location and seizure freedom (Wagstyl et al., Epilepsia, 2020).

Created an interpretable machine-learning algorithm to automatically detect FCDs on MRI scans (Spitzer*, Ripart* et al., Brain, 2022).

What this means: Through the MELD project we hope to better understand this important cause of medication-resistant epilepsy and create 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.

Modelling childhood genetic epilepsies in zebrafish larvae

Project Aim: Identifying whole-brain network dysfunction at single neuron resolution in larval zebrafish models of genetic epilepsies

Investigators: Richard Rosch, Dominic Burrows, Jade Lau, Martin Meyer

Summary: There are many limitations to what we can understand about epilepsy from measuring its effects in humans, or the commonly used rodent models with the recording methods currently available to us. Zebrafish larvae offer a unique perspective in that they are transparent and small enough in size so that they allow whole-brain calcium imaging at single cell resolution during epileptic seizures.

Zebrafish are a novel experimental model for the investigation of some of the most severe epilepsy syndromes of childhood, with the future potential to guide and trial novel therapeutic approaches for translation into human patients. In this research project we identify and characterise whole-brain abnormalities in genetic models of childhood epilepsies at single-cell resolutions, in order to develop a platform on which, in future, we may identify novel treatment strategies for some of the most complex epilepsy syndromes.

Goal 1 Goal 2

The PhD student, Dominic Burrows, has now successfully completed his viva and will be moving to the University of California, San Diego for a postdoctoral research fellowship. The funding for this project is now coming to a close and the relevant research papers are currently under review.

What this means: We are using Zebrafish larvae instead of mouse models to better understand some of the most severe genetic epilepsies of childhood. Zebrafish larvae are transparent, and this means we can see how each brain cell is functioning. This level of resolution will allow a much greater understanding of the brain networks involved in these complex epilepsies and lead to new, targeted, treatments.

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.

Goal 1

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)

Project Aims:

1. Characterise the memory profile of children and young people with TLE as well as their post-surgical memory outcome.
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

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.

Goal 1 Goal 2

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 Sarah Buck as well as undertaking an MRI. Patients are seen before surgery and again 4 and 12 months 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.

Goal 1 Goal 2

What this means: We want to know what has caused the epilepsy so we can better understand the processes in the brain that have gone wrong. We hope to use some new treatments for these processes that might not only apply to this rare epilepsy but also to some more common epilepsies.

Recently, we have identified a new gene which causes both a severe early onset epilepsy and a movement disorder.

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. Recruitment for this study is currently ongoing.

Goal 1 Goal 2

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.

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. 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. We conducted a case note review of children with hypothalamic hamartoma to better understand how their development links to their medical presentation and treatment.

Goal 2

What this means: The more we understand about how hypothalamic hamartoma affects development, the better we will be able to treat all aspects of the condition. This is particularly important in cases where we are unable to remove the hamartoma by surgery.

Novel network analysis of intracranial stereoelectroencephalography (SEEG)

Project Aim: To characterise 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.

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, Ulrich Stoof, James Wilsenach, Aswin Chari, Martin Tisdall, Gerald Cooray, 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).

Using computational models, we can test what the network organisations are that underly epileptic dynamics observed on the SEEG, as well as link these to additional data such as structural network recordings or known maps of neurotransmitter receptors across the brain. In future we hope that these tools help us identify the most promising candidates and approaches for epilepsy surgery. As part of this project, we have been awarded a Human Brain Project grant in order to link SEEG network analyses to structural networks as estimated from MR-imaging, which is funding the postdoctoral research fellow Dr James Wilsenach.

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.

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.

Goal 2 Goal 3

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.

Cis: Ronit Pressler and 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%). The set-up of this study is nearly completed, the start of recruitment is planned for January 2023.

Goal 3

Funders: Evelyn Trust and BRC Cambridge

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, Zachary Cohen

Update: This project is funded by an ERUK pilot grant to commence the study in patients with Juvenile Myoclonic Epilepsy. We had obtained the first data in a few patients just before COVID struck and are analysing the results as the basis for larger research grants. Rory Piper a surgeon training in Oxford performed a research placement investigating thalamic connectivity in epilepsy publishing a recent paper [1]. We have analysed the data and a current PhD student (Zachary Cohen) has been writing this up.

Goal 1 Goal 2 Goal 3

[1] https://pubmed.ncbi.nlm.nih.gov/34408719/

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 in a small number of subjects showed transcranial electrical stimulation appeared safe and well tolerated.

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.

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

Update: 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. 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 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

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 at 60 months

Goal 1 Goal 2 Goal 3 Goal 4 Goal 5

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, and their association with current performance and changes in performance between initial assessment and follow-up.

Investigators: Colin Reilly, Finbar O'Callaghan, Manuela Pisch, Colette Meades, Bhavna Sidphara, Amy Muggerdidge 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 outcomes. 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 119 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 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. The study is due to commence early in 2023.

What this means: This follow-up study of this unique cohort will significantly enhance understanding of neurodevelopmental course in children with early onset epilepsy. Additionally, understanding factors associated with impairments will help direct prognosis and management.

Realising the potential of 7T MRI for paediatric imaging

Goal 1 Goal 3 Goal 5

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 developing scan protocols for Paediatric Epilepsy patients and recently published a paper on one of these protocols [2], in parallel, we have been developing patient friendly head cushions that has led to a patent application [Patent 2205139.5, filed 7 April 2022] to improve scan performance and tolerance that we have been awarded an NIHR i4i grant (~1M) to continue. We are obtaining data with the advanced high-resolution scans and evaluating their utility.

[2] https://doi.org/10.1002/mrm.29479

Funders: GOSH-CC

What this means: We are working to understand the potential of this enhanced imaging technology and how best to use it for children.

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 and 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.

Goal 1

Funders: GOSH-CC

Dynamic variability in the epileptic brain

Project Aim: Variability in the EEG activity can be a challenge for diagnostics and treatments of epilepsy. However, with advanced methods of quantitative analysis, the variability in the brain activity itself may reveal important information about brain states, which this project aims to identify.

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 Brian Project funding.

Goal 1 Goal 3

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.

Current projects

Workstream 2 – Outstanding Treatments

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

Project Aim: To determine the efficacy of DBS in reducing seizure frequency in children with Lennox Gastaut Syndrome. We also wish to determine the effect on seizure severity and quality of life, the safety of the procedure (complications and adverse events) and the best stimulation patterns to provide seizure control.

Investigators: Martin Tisdall, J Helen Cross, Rory Piper, Marios Kaliakatsos, Hakim-Moulay Debhi, Harutomo Hasegawa, Elaine Hughes, John Fleming, Richard Selway, Ioannis Stavropoulos, Antonio Valentin, Tim Denison

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 Trial will be a Phase II clinical trial of DBS for children with LGS. 22 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. Patients will either be randomised to active ('on') versus inactive ('off') stimulation for three-months. All children will thereafter 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: LifeARC/GOSH-CC

Wearable magnetoencephalography (MEG) at Young Epilepsy

Project Aim: To develop a new Epilepsy Diagnostic Suite at Young Epilepsy centred around the installation and evaluation of the OPM-MEG technology.

Investigators: Gareth Barnes, Richard Bowtell, Matthew Brookes, Helen Cross, Tim Tierney, Torsten Baldeweg, Rosemarie Pardington, Kelly St Pier, Zelekha Seedat, Konrad Wagstyl, Umesh Vivekananda, David Woolger

Summary: The new Diagnostic Suite offers upgraded electroencephalogram (EEG), sleep telemetry and home telemetry services alongside an innovative wearable Optically Pumped (OP) magnetoencephalography (MEG) unit within a lightweight magnetically shielded room (Mu-Room). The overarching goal of the Young Epilepsy Diagnostic Suite is to offer world leading clinical neuroimaging technology in a comfortable and seamless environment for patients and their families. Currently MEG is a neuroimaging tool which is of very limited availability to children and young people with epilepsy, due to the equipment expense, weight, maintenance cost, fixed sensor location, intimidating aesthetic and the need to be perfectly still during the investigation. The OP-MEG and lightweight Mu-Room system overcomes each of these barriers to clinical use – chiefly the need to stay still. This makes MEG a clinically feasible tool in the diagnosis and surgical evaluation of children and young people with epilepsy – particularly those with complex needs who cannot tolerate other forms of neuroimaging such as EEG or magnetic resonance imaging (MRI).

What this means: The primary outcome of this project is to provide clinicians with an innovative technology which informs earlier and more accurate interventions for children with epilepsy. Epilepsy has enormous impact on a person's life and is usually present with additional developmental needs. The longer a child has uncontrolled seizures, the more likely there will be an impact in the longer term. Early, accurate intervention is critical to improving patient outcomes and quality of life in childhood epilepsy. Having developed the room and installed the equipment we are now in the process of clinical evaluation.

Development of a lifespan compliant magnetoencephalography system

Project Aim: Build an OP-MEG system for children aged 0-15years, that will offer direct clinical applicability, increased practicality, better data, and lower cost compared to current systems.

Investigators: Matthew Brookes, Richard Bowtell, Gareth Barnes, Helen Cross, Zelekha Seedat, Rosemarie Pardington

Summary: Conventional MEG systems use sensors that are cryogenically cooled and fixed in a one-size fits-all helmet. Performance is limited by a gap between the head and sensors, which is larger for infants, greatly reducing sensitivity. Further, movement relative to the sensors causes dramatic reductions in data quality (even 5mm movements render data unusable). For these reasons, conventional MEG is inadequate for infants.

Goal 3

The innovative OP-MEG sensors do not rely on cryogenics. They are small, lightweight, and can be mounted on the patient's head within a helmet. Because the sensors are closer to the head, OPMs afford vastly better performance, and removing cryogenics results in a much cheaper system. Based on this, we now have a unique opportunity to develop a MEG scanner for infants.

In this project we will look to solve the issues of different sensor arrangements according to head size and develop appropriate, tolerable helmets for the new wearable OP-MEG system.

What this means: The different head sizes of children and infants present a challenge to MEG scanning and we hope to develop a series of appropriate, comfortable and tolerable helmets for children aged 0-15 years.

Clinical deployment of wearable functional neuroimaging

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: Elena Boto, Prof. Matthew Brookes, Eliot Dawson, Freya Jackson, Rosemarie Pardington, Kelly St. Pier, Zelekha Seedat, David Woolger

Summary: Magnetencephalography (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 use. In particular, conventional MEG is inadequate for infants as 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:

Goal 3 Goal 5

1. Demonstrate the safety of the system and complete all documentation to ensure compliance for human use.
2. Build devices to ensure system accuracy enabling system validation prior to use.
3. Test the system in humans to prove benefits over existing scanners
4. Demonstrate clinical utility in epilepsy by showing that we can accurately map aberrant brain tissue.

What this means: This project will fast-track the regulatory approval process for the world's first OPM-MEG system, allowing this new clinical tool to be brought to market and offering new hope to many suffering from neurological conditions, such as epilepsy.

MELD (Multi-centre Epilepsy Lesion Detection) as an Adjunct for SEEG Trajectories (MAST) trial

Project Aim: Assess the utility of a novel machine learning algorithm in helping to plan electrode trajectories in children undergoing stereoelectroencephalography (SEEG).

Investigators: Aswin Chari, Sophie Adler-Wagstyl, Konrad Wagstyl, Zubair Tahir, Martin Tisdall

Summary: This clinical trial is a pilot study aimed at assessing the utility of a locally developed machine learning lesion detection algorithm in planning SEEG electrode trajectories. It is a rare prospective study of novel artificial intelligence technology and has recruited 20 patients.

Goal 3

Prior to setting up the trial, we assessed whether the algorithm may have been useful in previous SEEG cases and found that many of the lesions identified corresponded to where the seizures arose from. Interestingly, in 3/34 cases, a seizure onset zone was not found on SEEG and the algorithm identified lesions that were not being targeted.

What this means: We hope to show how useful a novel artificial intelligence software (that we developed here at ICH) is at improving the detection of abnormalities associated with epilepsy. We are starting with a first stage 'pilot' study to get a better idea of how we can use it and ensure it is safe before deciding on whether or not we should conduct a larger study.

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

We have three overarching aims:

1. **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 have been transformed into induced pluripotent stem cells (iPSCs) and are being differentiated into cerebral organoids. Currently we are validating organoids for layer specific and regional markers of neuronal identify and maturity. In the next year patient lines will also be differentiated into medial ganglionic eminence-like organoids containing interneurons, which will be fused with the cerebral organoids.

2. **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.

3. **To investigate the impact of novel therapies.**

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

Goal 1 Goal 2 Goal 3

Investigators: Amy McTague, Dimitri Kullmann, Gabriele Lignani, Jenny Lange, 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.

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 families.

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

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.

Goal 1 Goal 3

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

We have two aims:

1. Provide better informed diagnosis of memory impairments in children with epilepsy
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.

Goal 2 Goal 3 Goal 4

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.

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.

Goal 3 Goal 5

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.

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.

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.

Goal 2 Goal 3

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.

What this means: We are looking to develop a more tolerable treatment for ALDH7A1-deficiency.

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: Amy Muggeridge, Lara Carr, 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 almost 140 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)

We have four aims:

1. Societal change: ensure an enduring, positive change by improving public awareness and reducing the stigma experienced by people with epilepsy in sub-Saharan Africa.
2. Diagnose: To improve the rate of accurate diagnosis of epilepsy by primary health care workers with app-based technologies.
3. Treatment: increase the adherence to medication using text messaging.
4. 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: 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.

Goal 2 Goal 3 Goal 5 Goal 6

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.

Funding: 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)

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 centers 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.

EpiCARE aims to:

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.

To enhance opportunities for registries, and collaborative research for the benefit of individuals with rare and complex epilepsies across Europe.

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 a 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 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 nonparticipating 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. The PREVENT study is currently nearing the completion of recruitment.

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.

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.

We started recruiting patients into the main trial in 2019 and have now recruited over 130 participants of our planned 334. We were very pleased to be able to continue our research and support families during the COVID-19 pandemic as all of the assessment and treatment is completed over the telephone or via video conferencing. We've had some really good feedback from participants so far.

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.

Physical Activity in Childhood Epilepsy (PACE)

Project aims:

1. 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.
2. To better understand factors which may be associated with physical activity, including structured exercise/sports participation, in children with epilepsy.
3. Identify the barriers to engagement in physical activity for young people with epilepsy.
4. Explore the feasibility of implementing an intervention to improve levels of physical activity in children with epilepsy.

Investigators: Colin Reilly, Joan Idowu, Natalie Pearson, Colette Meades, Helen Cross, Lauren Sherar, Monica Lakhanpaul, Kerry Robinson, Amy Muggeridge and Helen Cross.

Summary: Anecdotal evidence suggests that children with epilepsy engage in less physical activity than their peers. There is, however, limited research on this and no previous studies in the UK. We have collected data on physical activity levels from 60 young people with epilepsy (11-15 years) and 49 control children without epilepsy.

Activity levels have been measured by using activity trackers. We are also exploring whether factors other than just their epilepsy may affect how active the children with epilepsy are including things like their age, gender, how they feel, and sleep quality etc. We have also explored perceived barriers to physical activity for young people with epilepsy and the supports needed to facilitate greater engagement in physical activity.

The study was suspended due to the COVID-19 pandemic and reopened as an entirely remote study in the Spring of 2021. Data collection was complete in August 2022 and initial findings suggest that children with epilepsy engage in less physical activity than peers.

What this means: We will use the findings from PACE to develop an intervention to reduce barriers faced by young people with epilepsy with respect to accessing physical activity.

Epilepsy Positive 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: Colin Reilly, Joan Idowu, Sophie Bennett and Helen Cross

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 co-develop web-based training for staff in mainstream schools in the UK with young people with epilepsy, their parents and staff who support them in school (Phase 1).

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 2).

Completed projects

Workstream 2 – Outstanding Treatments

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

Summary: 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. ENRICH was run by UCC (Cork) and GOSH was involved in a small part which was called Gentle Touch – evaluating the cortical response to gentle touch (like stroking or massage) using evoked potentials.

Goal 1 Goal 3

We finished the clinical part but unfortunately were not able to see a clear response. This was probably due to technical problems, so UCC had planned to take this further by using our data to make changes to the recording set up but this was impossible due to COVID-19 pandemic.

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 wanted to understand whether if a pleasant touch is administered to a baby's forearm in the supine and prone positions, will would observe a cortical response, and if so, could it be recorded and how did it develop over time.

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

Goal 3

Summary: The final report is currently in preparation. Recruitment continued until June 30 2021, by which time we had recruited 136 children. Results showed the KD to be similarly effective to further Anti-Seizure Medication (ASM) in infants with drug-resistant epilepsy . More infants in the ASM group however, had changes in ASMs during the intervention period compared to the KD group. The odds ratio of achieving seizure freedom at 8 weeks numerically favoured KD compared to further ASM.

Completed projects

Workstream 3 – Outstanding Support

Autism spectrum diagnosis (ASD) and epilepsy

Project aim: The assessment of autism for children with complex epilepsy poses many challenges; from fluctuating profiles to diagnostic overshadowing and atypical presentations. This project reviews the issues involved by drawing on more than 20 years' experience of neurodevelopmental assessment of children with complex epilepsy at GOSH.

Investigators: Harriet Holmes, Francesca Sawer, Maria Clark

Summary: The assessment of autism for children with complex epilepsy poses many challenges; from fluctuating profiles to diagnostic overshadowing and atypical presentations. This project reviews the issues involved by drawing on more than 20 years' experience of neurodevelopmental assessment of children with complex epilepsy at GOSH.

This project is now complete, and the findings published as a practice paper:

Holmes H, Sawer F, Clark M. Autism spectrum disorders and epilepsy in children: A commentary on the occurrence of autism in epilepsy; how it can present differently and the challenges associate d with diagnosis. Epilepsy Behav. 2021 Apr;117:107813. doi: 10.1016/j.yebeh.2021.107813. Epub 2021 Feb 26. PMID: 33642176.

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.

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

Action Medical Research
Anna Mueller Grocholski Foundation
Autistica
Brain Tumour Charity
BRC Cambridge
Cancer Research UK
Child Health Research Trust
Children with Cancer UK
D'Oyly Carte Charitable Trust
Epilepsy Research UK
Ethypharm
European Association of Neurosurgical Societies
European Commission
Evelyn Trust
Freya Foundation
The George E Neville Foundation
Google Cloud Platform Research Credit Award
GOSH NIHR BRC
GOSH-CC
Great Ormond Street Children's Charity
GW Pharmaceuticals
The Hospital Saturday Fund
Human Brain Project
Innovate UK
James Lewis Foundation
Medical Research Council Clinician Scientist Fellowship
Michael Cornish Charitable Trust
National Institute of Health Research (NIHR)
Nevilles PLC
NIHR GOSH Biomedical Research Centre
NIHR GOSH BRC PPIE Small Grants
Novartis
Nutricia
The Oakdale Trust
Oakgrove Foundation
Rosetree's Trust
Sir Henry Wellcome Fellowship
UCB BioPharma
UCL Child Health Research CIO Strategic Initiatives Pump-Priming Fund
Veriton Pharma
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Wellcome Research Enrichment - Public Engagement
Wolfson Foundation
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