12th International Expert Workshop
Epilepsy and Neurodevelopmental Disorders

14th - 15th March 2019
St Anne's College, Oxford
Foreword

I joined Epilepsy Research UK in 2004 after our son, Ivan, was diagnosed with Ohtahara Syndrome. Despite the excellent care Ivan received, it was apparent how little was known about the many types of epilepsy.

During my time with the charity, there has been significant research investment into the causes, diagnosis and clinical management of epilepsy. But equally as important as funding research, is the need to bring global experts together to build the overall research capacity and accelerate breakthroughs.

This workshop brings together experts from across the world to scrutinise the wide and varied aspects of neurodevelopmental disorders. More research is fundamental to ensuring families are able to access the best possible treatments for their children. I hope this workshop will help define the key research priorities, build on international collaboration, as well as encouraging further investment.

Thank you all for your wonderful support. This comes with my and Samantha’s very best wishes for a successful and productive workshop.

International Expert Workshop
Epilepsy and Neurodevelopmental Disorders
Dear colleagues,

Welcome to the ERUK International Expert Workshop on Epilepsy and Neurodevelopmental Disorders, organised by Professors Stuart Cobb, Oscar Marin and Sameer Zuberi.

The Expert Workshops are a flagship event in ERUK’s calendar. Occurring every two to three years, they are an opportunity to gather together experts from across the globe to critically appraise our understanding of the aetiology, pathophysiology, diagnosis and treatment of one aspect of the many faces of epilepsy. This year’s Workshop is the 12th in a series dating back to 1993, during which time the Workshops have addressed a wide range of topics including: epilepsy in pregnancy, the psychosocial burden of epilepsy, SUDEP, and tumour-associated epilepsy. The Workshops generate published proceedings in order that the material discussed at the Workshop can be shared with the wider community, with the view to promoting further investigation in that area.

This year the focus is on epilepsy associated with neurodevelopmental disorders. The birth of a child is a momentous and joyous occasion in the lives of the parents. However, for all too many parents this joy is curtailed by the realisation that there is something wrong with their child. This earth-shattering revelation often first manifests as the appearance of epileptic seizures, for which, unfortunately, there are limited treatment options. The Workshop is thus an opportunity for the expert community to consider the basis of neurodevelopmental epilepsy, to discuss the most appropriate animal models and diagnostic approaches, and to explore the potential treatment options for afflicted children.

Given the excellent program of sessions and speakers over the next two days, I have every expectation that these issues will be given detailed and authoritative scrutiny, and that the ensuing output will be valuable resource to the community.

On behalf of ERUK, I hope you enjoy the meeting and your stay in the elegant surroundings of St Anne’s College.

Professor Bruno Frenguelli
Chair, ERUK Scientific Advisory Committee
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<tr>
<td>08:15 onwards</td>
<td>Workshop registration and coffee</td>
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<tr>
<td>09:00</td>
<td>Welcome</td>
<td>Bruno Frenguelli</td>
<td>University of Warwick, UK</td>
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<td>Stuart Cobb</td>
<td>University of Edinburgh, UK</td>
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<td>Oscar Marin</td>
<td>King’s College London, UK</td>
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<td>Session 1</td>
<td>What is the broad relationship between neurodevelopmental disorders and epilepsy?</td>
<td>Sameer Zuberi</td>
<td>Royal Hospital for Children &amp; University of Glasgow, UK</td>
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<tr>
<td>09:10</td>
<td>Introduction</td>
<td>Sameer Zuberi</td>
<td>Royal Hospital for Children &amp; University of Glasgow, UK</td>
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<tr>
<td>09:15</td>
<td>The link between neurodevelopmental disorders and epilepsy (own clinical and research perspective)</td>
<td>Lucy Raymond</td>
<td>Cambridge Institute for Medical Research, UK</td>
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<td>09:35</td>
<td>Epilepsy gene discovery and its implications</td>
<td>Joseph Symonds</td>
<td>University of Glasgow, UK</td>
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<td>09:55</td>
<td>Use of epilepsy/NDD gene panels – does early diagnosis make a difference?</td>
<td>Amy McTague</td>
<td>University College London, UK</td>
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<td>10:15</td>
<td>Structural aetiologies in neurodevelopment and epilepsy</td>
<td>Renzo Guerrini</td>
<td>University of Florence, Italy</td>
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<td>10:35</td>
<td>Chaired discussion</td>
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<td>11:00</td>
<td>Refreshment break</td>
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<td>Session 2</td>
<td>How well can we model neurodevelopmental epilepsy disorders in experimental systems and what can they tell us? Chair: Lieven Lagae, KU Leuven, Belgium.</td>
<td>Lieven Lagae</td>
<td>KU Leuven, Belgium</td>
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<td>11:30</td>
<td>Introduction</td>
<td>Lieven Lagae</td>
<td>KU Leuven, Belgium</td>
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<td>11:35</td>
<td>Regulome-based computational anti-epileptic drug target discovery</td>
<td>Michael Johnson</td>
<td>Imperial College London, UK</td>
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<td>11:55</td>
<td>2-D and 3-D Stem Cell Models of Epilepsy</td>
<td>Jack Parent</td>
<td>University of Michigan, US</td>
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<td>12:15</td>
<td>Rodent models: where it all started</td>
<td>Solomon L. Moshe</td>
<td>Albert Einstein College of Medicine, US</td>
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<td>12:35</td>
<td>Epileptic networks in zebrafish - new insights from a novel animal model</td>
<td>Richard Rosch</td>
<td>King’s College London, UK</td>
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<td>12:55</td>
<td>Chaired discussion</td>
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<td>13:25</td>
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**Session 3:**

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<tr>
<td>14:30</td>
<td>Introduction</td>
<td>Floor Jansen</td>
<td>UMC Utrecht, Netherlands</td>
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<tr>
<td>14:35</td>
<td>What do we mean by the concept of epileptic encephalopathy?</td>
<td>Ingrid Scheffer</td>
<td>University of Melbourne, Australia</td>
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<td>14:55</td>
<td>Epilepsies with sleep activation – insights from functional neuroimaging</td>
<td>Patrick van Bogaert</td>
<td>Université d’Angers, France</td>
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<td>15:15</td>
<td>Early intervention in epileptic spasms</td>
<td>Finbar O’Callaghan</td>
<td>University College London, UK</td>
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<td>15:35</td>
<td>Influence of epilepsy surgery on developmental outcomes</td>
<td>Kees Braun</td>
<td>UMC Utrecht, Netherlands</td>
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<td>15:55</td>
<td>Chaired discussion</td>
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<td>16:25-16:40</td>
<td>Closing remarks for day one</td>
<td>Stuart Cobb</td>
<td>University of Edinburgh, UK</td>
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<td>Oscar Marin</td>
<td>King’s College London, UK</td>
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<td>19:00</td>
<td>Drinks reception followed by dinner</td>
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### Session 6: Molecular therapeutic strategies in epilepsy and neurodevelopmental disorders. What are the key questions and strategies for finding future treatments?
Chair: Dimitri Kullmann, University College London, UK.

**Time** | **Presentation Title** | **Speaker** | **Affiliation**
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14:10 | Introduction | Dimitri Kullmann | University College London, UK
14:15 | Genetic therapies | Stephanie Schorge | University College London, UK
14:35 | Targeting defective pathways in neurodevelopmental disorders: the example of the AnkyrinG interactome | Frank Kooy | University of Antwerp, Belgium
14:55 | Gene therapy in neurodevelopmental disorders | Stuart Cobb | University of Edinburgh, UK
15:15 | Cell therapies | Scott Baraban | University of California, San Francisco, US
15:35 | Chaired discussion
16:05 | Summary and closing remarks for day two | Stuart Cobb | University of Edinburgh, UK
  | Oscar Marin | King’s College London, UK
Speaker Profiles

Professor Alexis Arzimanoglou leads the Department of Paediatric Clinical Epileptology, Sleep Disorders and Functional Neurology of the Hospices Civils de Lyon, France and is the Epilepsy Research coordinator for the Child Neurology Department of the Sant Joan de Déu Barcelona Hospital in Spain. Together with Professor Helen Cross he coordinates the European Reference Network for rare and complex epilepsies, ERN EpCARE.

Professor Gus Baker is Emeritus Professor of Clinical Neuropsychology and Honorary Consultant Clinical Neuropsychologist at the University of Liverpool and the Walton Centre for Neurology and Neurosurgery. He was the principal researcher of the UK study on the neurodevelopment effects of antiepileptic drugs and co-principal researcher on the US/UK NIH funded study. The UK group have published over 25 papers in this field.

Professor Scott Baraban is the William K. Bowes Jr. Endowed Chair in Neuroscience Research at the University of California San Francisco. Dr Baraban is the recipient of awards from Klingenstein Fund, NIH (Javits), and AES (Basic Science Research Recognition). His laboratory established the (i) first interneuron-based cell transplantation strategies for intractable epilepsies, (ii) first zebrafish epilepsy models and (iii) first zebrafish-based drug screens for intractable epilepsies, (ii) first zebrafish epilepsy neurodevelopmental disorders and Functional Neurology at the University of Edinburgh, UK. His research focuses on the developmental and cellular mechanisms of epilepsy, intractable epilepsy, including epilepsy surgery, tuberous sclerosis, electrical status epilepticus in sleep (ESES of CSWS), and genetic epilepsy.

Professor Michael Johnson is Professor of Neurology and Genomic Medicine and Deputy Head of the Centre for Clinical Translation in the Division of Brain Sciences at Imperial College London, and Honorary Consultant Neurologist at Imperial College Healthcare NHS Trust. His research focuses on the systems-level integration of genetic, genomic and phenotypic data to infer causal functional pathways and their drugable regulators.

Professor Frank Kooy is a full Professor in Cognitive Genetics at the University of Antwerp. His research successfully focuses on the identification of genetic causes of cognitive disorders, such as intellectual disability and autism and to study the defective genes with the ultimate goal of developing rational therapies.

Professor Dimitri Kullmann is a professor of neurology at UCL. He trained in medicine and physiological sciences in Oxford and London. After a post-doctoral fellowship at UCSP he completed neurology training in London. His interests include synaptic physiology, mechanisms of neurological channopathies, and gene therapy for epilepsy. He is also the Editor of Brain.

Professor Liwen Laga is Full Professor at the University of Leuven, Belgium (KUL), Head of the Paediatric Neurology Department of the KUL University Hospitals, and Director of the Childhood Epilepsy Program at the KUL University Hospitals. Liwen Laga is the immediate past President of the European Paediatric Neurology Society and serves as an elected Board Member of the International Child Neurology Association (ICNA) and the Taskforce on Medical Treatment of Childhood Epilepsy of the International League against Epilepsy (ILAE).

Dr Floor Jansen specialised in Paediatric Neurology in 2007, and in the same year she obtained her PhD degree on a thesis entitled “identification of epileptogenic sources in patients with TSC”. Her clinical and scientific areas of expertise are: refractory paediatric epilepsy, personalised treatment.

Professor Renzo Guerrini is a Professor of Child Neurology and Psychiatry at the University of Florence, Italy. He is also Head of the Centre of Excellence for Neurosciences at Children’s Hospital A. Meyer, Florence. Professor Guerrini chaired the International League Against Epilepsy Commission on Paediatrics. In 2003, he received the ‘Ambassador of Epilepsy’ award from the International League Against Epilepsy and in 2012 the ‘Research Award for Clinical Science’ from the American Epilepsy Society (AES). He has coordinated the EU Project DESIRE on development of epilepsy.

Professor David C. Henshall is Professor of Molecular Physiology & Neurosciences and Director of the FutureNeuro Research Centre at the Royal College of Surgeons in Ireland. His research interests are cell and molecular mechanisms of epilepsy, biomarkers and novel therapies. He has authored over 175 original papers and book chapters.
Speaker Profiles

Professor Deb Pal is Professor of Pediatric Epilepsy at King’s College London and Honorary Consultant Paediatric Neurologist at King’s Health Partners where he heads the Epilepsy Genetics service for south east England. Deb graduated in natural sciences and medicine from Cambridge University and holds a Masters in epidemiology from the London School of Hygiene and Tropical Medicine. He completed a PhD in Neuroscience at UCL and postdoctoral training in statistical genetics and genetic epidemiology at Mount Sinai and Columbia University Medical Centers, New York. Professor Pal is interested in the genetic epidemiology and mechanisms of childhood epilepsy and its comorbidities in particular the common forms of childhood epilepsy with complex genetic inheritance.

Professor Jack M. Parent is the William J. Herdman Professor of Neurology and co-director of the Epilepsy Center at Michigan Medicine. He is a past Board member of the American Epilepsy Society and is Chief Editor of Epilepsy Currents. His research focuses on epileptogenic mechanisms in temporal lobe epilepsy and genetic epilepsies.

Professor Lucy Raymond is Professor of Medical Genetics and Neurodevelopment at the University of Cambridge and Honorary Consultant in Medical Genetics at Cambridge University Hospital, UK. Her research interest is understanding the genetic basis of disease and leads a number of collaborative efforts to identify the rare disease genes where intellectual disability, epilepsy or neurological conditions predominate.

Dr Richard Rosch is a Sir Henry Wellcome Fellow at King’s College London and the University of Pennsylvania, Philadelphia. He is a clinically trained neuroscientist and employs a variety of computational and empirical methods across patient data and model systems to link synaptic dysfunction and whole brain abnormal dynamics.

Laureate Professor Ingrid Scheffer AO is a physician-scientist whose work as a pediatric neurologist and epileptologist at the University of Melbourne and Austin Health has led the field of epilepsy genetics over more than 20 years, in collaboration with Professor Samuel Berkovic and molecular geneticists. This resulted in identification of the first epilepsy gene and many more genes subsequently. Her major interests are in the genetics of the epilepsies, epilepsy syndromology and classification, and translational research. She led the first major redescription of the epilepsies in three decades, published in March 2017, for the International League Against Epilepsy. She has received many awards, including 2007 American Epilepsy Society Clinical Research Recognition Award, ILAE Ambassador for Epilepsy Award, 2013 Australian Neuroscience Medalion, 2013 Emil Becker Prize for child neurology and the L’Oréal-UNESCO Women in Science Laureate for the Asia-Pacific region for 2012.

Professor Stephanie Schorge completed a PhD in Neuroscience at Brown University, and travelled to London to take on single channel biophysics. Her research quickly shifted to exploring how mutations in ion channels lead to neurological disorders, and conversely, how neurological disorders can change the regulation of ion channels. She is working with a larger collaboration to harness some of the insights gained into the altered excitability in epilepsy to a first-in-human trial for gene therapy for focal neocortical epilepsy.

Dr Joe Symonds is a paediatric neurology trainee at the Royal Hospital for Children in Glasgow. He is currently completing a PhD at the University of Glasgow on the impact of genotype-driven precision medicine for children with epilepsy.

Professor Patrick Van Bogaert is head of the department of Paediatric Neurology at CHU Angers, France, and Professor of Paediatric Neurology at the Université d’Angers, France, since 2016. Since then he has worked at the Laboratoire Angévin de Recherche en Ingénierie des Systèmes (LARIS), Université d’Angers, France. He has authored or co-authored 135 medical peer-reviewed articles, as well as 5 book chapters on Landau-Kleffner syndrome and epileptic encephalopathy with continuous spike-waves during slow-wave sleep.

Professor Hongjie Yuan is Assistant Professor and Deputy Director of Center for Functional Evaluation of Rare Variants, Emory University. His work focuses on human glutamate receptor variants associated with neurological disorders by utilizing a multidisciplinary approach that combines clinical experience, training in electrophysiology, and understanding of neurophysiology to translate basic research involving NMDAR/AMPA receptor variants toward therapeutic use.

Professor Sameer Zuberi is Consultant Paediatric Neurologist at the Royal Hospital for Children and Honorary Professor in the University of Glasgow. His clinical and research interests are in epilepsy and neurogenetics. He is past Chair of the ILAE Commission on Classification & Terminology & is President of the European Paediatric Neurology Society. ERUK funded research by his group is helping define the incidence and outcomes of the genetic epilepsies of early childhood.
Early brain development is extremely complex and requires the coordinated expression of thousands of genes at the required dose, location and function during development. Failure to achieve this is commonly due to constitutional abnormalities of the genome in the affected child. The majority of genetic variants are de novo in the affected child although familial rare variants may cause disease. Over recent years large-scale analysis of genomes of children with neurodevelopmental disorders or epilepsy has revealed many new genes that cause disease. The rate of gene identification is still high in this field both due to the extreme heterogeneity of the condition and the relative rarity of individuals who have a specific gene abnormality. The IMAGINE ID study has followed up 3,000 children diagnosed with a genetic cause of intellectual disability and identified that epilepsy is a frequent co-morbidity (30%). In children presenting with epilepsy as neonates in NICU and PICU the association with developmental delay is similarly common at 27%. The talk will focus on the range of molecular mechanisms of disease identified to date, the association of neurodevelopmental disorders and epilepsy and to put a diagnosis of epilepsy in context of other neurological features.

The development and application of next generation sequencing (NGS) technology has led to an exponential rise in the number of genes and genetic variants associated with epilepsy. The detection of highly penetrant and damaging variants in some patients can be sufficient to provide an adequate explanation for the entire disease process. Particularly high yields from such diagnostic genetic testing are observed in cohorts of children who present with early onset seizures. Obtaining a genetic diagnosis can be helpful to families in terms of informing further reproductive decisions, providing answers, and preventing further costly investigations. Evidence is emerging that certain anti-epileptic drug therapies may be more effective than others in specific genetic epilepsies. Early trials of gene-corrective therapy are now taking place. In a population-based cohort of all children presenting with epilepsy < 3 years identified a genetic cause in 29%. Genetic diagnosis is strongly associated with both early age of onset and the development of drug-resistant seizures. 84% of diagnoses involve the most frequently implicated 10 genes. Beyond the 10-20 most commonly implicated genes there is a long tail of more than 1000 extremely rare genetic disorders, most of which often present also with neurodevelopmental disorders in the absence of epileptic seizures. Using Whole Genome Sequencing (WGS) in a cohort of patients with drug-resistant seizures who have already had the more common genetic diagnoses excluded there is a long tail of more than 1000 extremely rare genetic disorders.

Use of epilepsy/NDD gene panels – does early diagnosis make a difference?
Dr Amy McClague, University College London, UK
09:55

Over the past decade, the use of next generation sequencing (NGS) panels has revolutionised diagnostics in early onset epilepsy and neurodevelopmental disorders. The diagnostic yield varies from 18-48% depending on epilepsy or developmental phenotype, age at seizure onset and panel-dependent factors such as number of genes included and sequence coverage. For some genetic epilepsies, treatment choice can be guided by variants identified on NGS panels. In the SCN1A-related epilepsies this includes avoidance of sodium channel blocking medications, early use of stiripentol and consideration of novel therapies such as cannabidiol and fenfluramine. Conversely, in SCN2A and SCN8A related epilepsies early use of sodium channel blockers such as carbamazepine for neonatal seizures and phenytoin for status epilepticus has led to reduced seizure frequency. In some genetic aetiologies, a more specific treatment is available. Identification of variants in SLC2A1 in an expanding range of phenotypes allows early consideration of the ketogenic diet. Repurposing of older medications such as quinidine for gain of function KCNT1 variants in epilepsy of infancy with migrating focal seizures and autosomal dominant nocturnal frontal lobe epilepsy has been successful in some, but not all, patients. Novel therapies under development include RNA-directed treatments and gene therapy and early diagnosis will allow recruitment of patients to appropriate clinical trials. The impact of an early genetic diagnosis also includes an end to the diagnostic odyssey, may avoid unnecessary invasive investigations and allows discussion of prognosis and access to patient support groups. However, the advent of NGS panels has also brought challenges including interpretation of multiple putative pathogenic variants, issues of reduced penetrance and somatic mosaicism and expansion of known phenotypes. As we move towards whole exome and whole genome sequencing and more rapid genetic diagnosis, it will be essential to prospectively monitor the impact of early diagnosis and aetiology-directed treatments on both seizures and neurodevelopmental outcome.

The malformations of the human cerebral cortex represent a major cause of a range of developmental disabilities, severe epilepsy and reproductive disadvantage. In general, it is estimated that up to 40% of individuals with drug-resistant epilepsy have a cortical malformation visible by good quality MRI scan. High-resolution MRI techniques have identified in vivo a growing group of cortical malformation phenotypes. Classical neuropathological studies have recently been confirmed by larger studies that have correlate abnormal cortical folding on high resolution imaging with specific neuropsychological deficits. Treatment options for alternative epilepsy are deceptively since drugs are scarcely effective and only a subset of patients apply for surgical treatment. Planning of surgical options needs a comprehensive electrophysiological and functional imaging approach, in relation to both the complex representation of eloquent cortical functions in the abnormally folded cortex and to the intricate networks that usually subserve the epileptogenic area. Intrinsic epileptogenic networks often involve the malformed cortex and distant cortical areas, as demonstrated by depth electrode explorations of the human brain and in vivo electrophysiological studies. The concept of structural aetiologies, after all, goes well beyond that of the MRI visible abnormality. Some genetic disorders, and now even channelopathies, challenge the classic distinction between the ‘pure’ genetic epilepsies, which used to be ideally epitomized exactly by ion channel alterations versus the structural/metabolic disorders in which a separate abnormality is interposed between the genetic defect and the epilepsy. On the other hand, epilepsy in non malformation ARX phenotypes (at least in relation to some of the mutations of this gene) or in patients with STXBP1 or CDKL5 mutations/deletions is difficult to assign to either the ‘genetic’ or the ‘structural’ category as they seem to carry both labels. It seems to be a primary expression of the genetic defect: since all patients have severe seizures but no structural lesion is recognizable as far as the diagnostic dimension can be pushed. Only development- and molecular-pathology studies can provide answers to these queries.
Session 2: How well can we model neurodevelopmental epilepsy disorders in experimental systems and what can they tell us?

Professor Michael Johnson, Imperial College London

11:35

Using integrated systems biology approaches we have previously shown that rare and common variants for genetic epilepsy converge on a gene co-expression network highly expressed in interneurons, and that integration of this epilepsy gene expression signature with drug perturbation data can reveal novel opportunities for drug repositioning in epilepsy (Delahaye-Durez A, et al. Genome Biology 2016;13:17245-263). More recently, we showed how a gene expression signature for acquired epilepsy could be leveraged to new drug target discovery using a novel gene-regulatory framework based on experimentally defined relationships between membrane receptors, transcription factors and target genes (Srivastava PK, et al. Nature Communications, 2018;9:3561. doi: 10.1038/s41467-018-06008-4). Although this later work established proof-of-concept for antiepilepsy drug target discovery based on gene regulatory networks (GRNs, regulomes), regulomes inferred from published knowledge lack tissue specificity and are limited by the incompleteness of the scientific archive as well as publication bias. In this presentation, I show how empirical gene expression data from epileptic brain tissue can also be used to infer gene regulatory relationships for drug target discovery at a disease context specific level, providing an improved framework for the discovery of novel disease modifying therapies for epilepsy.

2-D and 3-D Stem Cell Models of Genetic Epilepsies
Professor Jack Parent, University of Michigan, US

11:55

Reprogramming somatic cells to a pluripotent state via the induced pluripotent stem cell (iPSC) method offers an unparalleled approach for neurological disease modeling using patient-derived cells. Several groups, including ours, have applied the iPSC approach to model severe genetic developmental and epileptic encephalopathies (DEEs) with patient-derived cells. I will describe our findings using 2-D cultures of patient-derived neurons to model Dravet syndrome, also known as early infantile epileptic encephalopathy type 6 (EIEE6), caused by loss-of-function mutations in the SCN1A gene encoding the voltage-gated sodium channel Nav1.1. Then I will discuss similar studies of EIEE13 caused by gain-of-function mutations in the SCN1B gene encoding Nav1.1. Several groups are also beginning to explore epilepsy mechanisms using 3-D iPSC cultures, also known as cerebral or cortical organoids. Our laboratory and others are applying this approach to understand severe DEEs, including PMSE (Polyhydramnios, Megalencephaly and Symptomatic Epilepsy) syndrome and Rett Syndrome. Both 2-D and 3-D human iPSC models show epilepsy-relevant phenotypes and offer platforms for anti-seizure drug testing in patient-derived cells. Challenges include obtaining complete maturation of cells in vitro, and generating the complex repertoire of neuronal cell types. Nonetheless, the field is rapidly advancing and the findings suggest that human pluripotent stem cell approaches offer great promise for modeling neurodevelopmental epilepsies and identifying novel therapies.

Rodent models: where it all started
Professor Solomon L. Moshé, MD, Albert Einstein College of Medicine, US

12:15

The immature brain is not a miniature version of the adult brain and better understanding of the discrete windows of the developmental processes may indeed provide unique insights into factors that may mediate the expression and consequences of seizures and epilepsy as a function of sex. We have been fortunate in the past 40 years to witness an amazing growth of information in the field of developmental epilepsy. A major step was to the establishment of kindling as a model of epilepsy in infant rodents, the first such model of epileptogenesis followed by studies of post status epilepticus models. Kindling in developing rats provided unique insights in the expression of seizures including specific behavioral patterns of seizures, development of multifocal seizures and lack of postictal refractoriness that allows for clustering of seizures. These studies led to the development of a unique model of infantile spasms that replicates the human condition with recurrent spasms followed by other seizure types as the animals age. This model has been effectively used to identify new treatments for spasms. The post status epilepticus models provided insights on the extent of age-related seizure induced hippocampal injury. Nowadays, understanding the key features and possible biomarkers that may allow for the expression and consequences of seizures and related epileptogenesis taking into account the maturational patterns of the brain and gender differences will provide novel insights into creating therapeutic approaches leading to individualized treatments and precision based medicine.

Epileptic networks in zebrafish – new insights from a novel animal model
Dr Richard Rosch, King's College London, UK

12:35

Zebrafish have emerged as a promising new model in epilepsy research. This vertebrate model allows low-cost behavioural assays, provides well-established genetics, and has established lines with epilepsy-causing mutations. With advances in genetically encoded calcium indicators, fast volumetric microscopy, and improved computational image processing tools available, zebrafish now also offer a unique window into the whole-brain dynamics of a developing vertebrate brain – an aspect that's currently less well exploited in epilepsy research. Here I will be presenting initial results from functional recordings of the larval zebrafish brain during epileptic seizures. Combining calcium imaging with computational models of neuronal population activity allows insights into the specific synaptic deficits that give rise to the abnormal dynamics observed during epileptic seizures. By modelling the recorded calcium dynamics as emerging from networks of interacting excitatory-inhibitory neuronal oscillators, we can derive a map of transitions that occur during the acute seizure, and identify the synaptic changes associated with each. These insights from these acute seizure recordings will illustrate the kind of inference that is now possible when imaging novel zebrafish models of gene-associated infantile and childhood epileptic encephalopathies, such as SCN1A and GRIN2A-associated epilepsies. The combination of detailed functional imaging of whole-brain dynamics with (near) single cell resolution and the genetic deficits associated with human disease will allow insights into the dynamics of the epileptic brain not currently possible with other model systems.

Chair: Lieven Lagae, KU Leuven, Belgium

11:30 Thursday 14th March 2019

Chaired discussion 12:55-13:25
The concept of epileptic encephalopathy underpins the group of diseases known as the Developmental and Epileptic Encephalopathies (DEEs). Many infants and young children presenting with seizures develop an epileptic encephalopathy. This means that they have very frequent, often virtually continual, epileptiform activity. This epileptiform activity may be generalized, bilaterally synchronous, unifocal or multifocal. Patients typically have frequent seizures and multiple seizure types, but this is not universal. The third key component of an epileptic encephalopathy is that there is developmental slowing, arrest or regression. Why does an epileptic encephalopathy matter? Largely because there may be a remediable component if the process can be arrested. Such an improvement may be by simply changing anti-epileptic therapy from one that exacerbates seizures and epileptiform activity to optimal treatment for a DEE, ideally based on understanding the neurobiology. For example, in Dravet syndrome, typically due to SCN1A haplinsufficiency, sodium channel blockers such as carbamazepine increase both seizures and epileptiform activity. Often families will comment that the child is learning and more alert when the process is ameliorated. Many of the children with epileptic encephalopathies, which include a large number of epilepsy syndromes (eg Lennox-Gastaut syndrome, West syndrome, Epilepsy of Infancy with Migrating Focal Seizures), have a genetic basis for their disease, most commonly a de novo dominant pathogenic variant. The new terminology of ‘developmental and epileptic encephalopathy’ (DEE) was coined because many children with these diseases have developmental impairment due to the underlying mutation with the epileptic encephalopathy process superimposed on the underlying disorder. This means that suppressing the epileptic encephalopathy does not cure the disorder but understanding these two related but distinct components influences treatment approaches, providing the opportunity to optimise long term outcome.

Epilepsies with sleep activation – insights from functional neuroimaging
Professor Patrick Van Bogaert, MD, PhD. Université d’Angers, France
14:55

Epilepsies with sleep activation are epileptic encephalopathies in which intense interictal epileptiform activity during sleep is thought to play a major role in the cognitive and behavioural disturbances that occur in these children. This hypothesis is supported by studies showing an association between long duration of the continuous spike and waves during slow-wave sleep (CSWS) pattern on EEG and cognitive outcome. However, other possible contributing factors are the underlying etiology, which is likely to be genetic in patients with the absence of structural brain lesion on MRI, and side effects of anti-epileptic drugs. The aims of functional imaging in these epilepsies are to identify brain networks involved respectively in epileptogenesis and in cognitive dysfunction, to understand the functional dynamics between these two networks, and to study the impact of treatments on these networks. Studies performed at rest at the awake state using either PET with FDG or EEG-fMRI have shown relative hypermetabolism (or increased perfusion) in regions that belong to the epileptogenic network and hypometabolism (or decreased perfusion) in functionally connected regions that belong to the default mode network. These abnormalities may be reversible in patients who respond to antiepileptic treatments, evidencing the place of functional imaging as a biomarker of therapeutic response. Functional neuroimaging approaches combining the excellent temporal resolution of EEG and MEG with a good spatial resolution through sources reconstruction and co-registration with structural MRI, i.e. electrical and magnetic source imaging, are relevant to study the dynamics of these networks at the level of the millisecond.

Infantile spasms are the classic example of an epileptic encephalopathy. There are multiple reports describing the arrest or regression of development coincident with the onset of epileptic spasms and hypsarrhythmia. If the spasms themselves are causing developmental damage then the logical corollary is that rapid resolution of the epileptic encephalopathy with effective treatment should lead to improved cognitive and developmental outcomes compared to those children who are exposed to the encephalopathy for longer periods. Lead-time to treatment i.e. the interval between onset of spasms and the initiation of treatment, is a significant component in the total duration of exposure to the epileptic encephalopathy. Whether treatment is effective and how fast it works are two other factors influencing the duration of exposure to the encephalopathy. In this talk, drawing on data from ICSS and UKISS and other published clinical studies, I will discuss the effect of lead-time to treatment, speed of response and type of therapy on epilepsy and developmental outcomes. Infantile spasms may have many different underlying aetiologies. There have been suggestions in the literature that specific aetiologies may have specific responses to therapy. I will explore whether different aetiologies have different responses to treatment and different developmental outcomes and I will also discuss the inter-relationship between aetiology, lead-time and therapy on outcomes.

Cognitive development of paediatric epilepsy surgery candidates is determined by many variables, including their genetic and environmental “background”, the epileptogenic pathology, the seizure disorder itself – varying in severity from status epilepticus, epileptic encephalopathy, frequent seizures, to interictal EEG discharges – and the use of antiepileptic drugs. The majority of children with refractory epilepsy have cognitive impairments. Intellectual disability has been considered a contraindication for surgery in the past, whereas the child’s developmental capacity nowadays is an important perspective in surgical decision making. Cognitive functioning of the youngest surgical candidates, particularly those who undergo hemispherotomy, is almost always severely affected (with an IQ or DQ <55), and these children often have an arrest or regression of development due to an epileptic encephalopathy. Although a quantifiable postoperative increase of >8-15 DQ/IQ points is only seen in around 30%, mental age increases in almost all children, and their development seems to restart; one of the most gratifying experiences in paediatric epilepsy surgery. Eventual cognitive outcome after surgery, and the postoperative change in cognitive functioning, depend on etiology, contralateral MRI abnormalities, parental education, age at onset and surgery, presurgical IQ, and on seizure outcome. Most importantly, shorter epilepsy duration has been shown to not only increase the chance of reaching seizure-freedom, it also predicts better postoperative cognitive outcome and more cognitive improvement. Finally, AED withdrawal – which can be safely considered early after surgery in many children – is an independent predictor of eventual IQ and of postoperative IQ increase. Therefore, children with focal lesional epilepsy should be referred for presurgical evaluation early after diagnosis. Epilepsy surgery is an early treatment option, rather than a last resort.
Session 4: What is our understanding of underlying mechanisms linking genetic epilepsies and neurodevelopment?

From rare to polygenic epilepsies
Dr Dennis Lal, Broad Institute of MIT and Harvard, US

By accumulating a massive amount of genomic data, scientists have identified >100 genes associated with generalized, focal epilepsies and neurodevelopmental disorders with seizures. Part 1: The translation of these findings into the development of novel drugs or improved patient management is challenging, and the process is slow. Our group has developed a computational infrastructure for exploration of genetic variants on 3D protein structures to facilitate variant interpretation and drug target discovery, which will be presented at the meeting. Part 2: Recent research illustrates that genetic factors significantly contribute to the early onset and severe forms of epilepsy; they represent only one part of the puzzle. In the second part of the talk, recent data we will present new data on common risk variants and their role in the etiology of epilepsy.

Genetic Variations of NMDAR GRIN Genes in Epilepsy and Neurodevelopmental Disorders
Professor Hongjie Yuan, Emory University School of Medicine, US

N-methyl-D-aspartate receptors (NMDAR), ligand-gated ionotropic glutamatergic receptors, mediate a slow component of excitatory synaptic transmission in the brain that plays a key role in brain development and function. Genetic variations in multiple NMDAR subunits gene GRIN are implicated in a spectrum of neurodevelopmental disorders, including epileptic encephalopathy. There is a mismatch between the high volume of genetic information from sequencing and functional information about variants, which precludes understanding disease mechanism and treatment options. This presentation will focus on a set of GRIN missense variants identified in patients with developmental and epileptic encephalopathy (DEE). These variants are located in pre-M1, pre-M4, and M3/SYTANLAAF motif, critical regions for the channel gating and intolerant to genetic variation. Functional evaluation revealed that these variants influence NMDAR function in multiple ways with enhanced agonist potency, reduced sensitivity to negative modulators (Mg2+, Zn2+, H+), prolonged synaptic response time course, and/or increased single channel probability, leading to NMDAR hyperactivity and neuroexcitotoxicity. Overall, the data suggest these GRIN variants have complex influence on NMDAR function, which may underlie the patients’ phenotypes. A number of FDA-approved NMDAR drugs were assessed for their ability to rectify the altered NMDAR function to explore the potential for rescue pharmacology and clinical opportunity.

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PCDH19 variants using in vitro functional assays, in silico prediction and crystal structure modelling. We subsequently tested 25 variants; known disease-causing, VOUS as well as select, frequent population PCDH19 variants with high success rate. Our systematic review of 271 published cases showed that the penetrance of PCDH19 GCE is about 80%, much less than >90% we estimated from family studies in 2008. The review also showed significant behavioural comorbidities (60%) and significant association between age at seizure onset, before or after 12 months of age and disease severity. Subsequently we performed an online survey focusing on neurocognitive and neuropsychiatric aspects of PCDH19 GCE for which we received 111 completed responses, 33% from unpublished cases. The explanation of variable penetrance between e.g., mothers and daughters or discordant MZ twins, have been challenging to address. In this regard, we studied cellular and electrophysiological aspects of PCDH19 GCE using CRISPR/Cas9 modified mouse models with both, wt and KO PCDH19 alleles visualised. Only the heterozygous females showed altered brain EEG activity (altered SWDs). These mice also showed highly specific sorting and distribution of PCDH19 wt and PCDH19 KO neurons in their developing cortices (14.5dpc). We postulate that individually and tissue specific levels of cellular mosaicism, determined by either X-inactivation or somatic mutation timing, together with altered gene expression of the mutant PCDH19 cells, are the underlying forces of PCDH19 GCE.

Epigenetic mechanisms and noncoding RNAs
Professor David Henshall, Royal College of Surgeons, Ireland

Epigenetics refers broadly to processes that influence the medium- to long-term expression of genes through changes to the readability and accessibility of the genetic code. The mediators include biochemical modifications to DNA and the histones around which DNA is wrapped, as well as non-coding RNAs. This talk will provide an overview of these processes and how they promote open and closed states of chromatin and regulate transcription. Next, key examples of epigenetic processes found to be altered in models and patients with epilepsy will be reviewed with attention to how these influence gene expression, including mutations in genes with epigenetic functions. The talk will consider practical applications of this emerging area of research, including epigenetic marks as biomarkers for tissue- and biofluid-based diagnostics and precision medicine-based epigenetic editing of specific sites in the genome, as well as global approaches that might offer novel ways to correct dysregulated gene expression and treat or prevent epilepsy. Last, the talk will review the research gaps and the next challenges. In summary, epigenetic processes modulate brain excitability and epileptogenesis, shaping the transcriptional environment which together provides novel insight into patho-mechanisms, biomarkers and novel therapies for epilepsy.

Chaired discussion

PCDH19 Girls clustering epilepsy, a disorder of cellular mosaics.
Professor Josef Gecz, Adelaide Medical School, University of Adelaide, Australia


We have implicated PCDH19 in girls clustering epilepsy (GCE) in 2008. Hundreds of heterozygous females and >12 males with somatic mosaic PCDH19 mutations have been reported since. In addition to cell-cell adhesion function we found that PCDH19 protein acts as an intracellular signalling molecule with e.g. estrogen receptor alpha, ESR1, which leads to unexpected, but consistent deregulation of neurosteroid hormone levels in these GCE girls. We have developed a multidimensional pathogenicity assessment tool for
Epilepsy is a rather complex major public health disease, encompassing a large spectrum of epilepsy syndromes of variable aetiology. In addition to recurrent and unpredictable seizures, abnormalities in psychiatric status, cognition and social adaptive behaviours are potential major sources of disability in children and adults with epilepsy disorders. In children with epilepsy, findings have unequivocally documented a higher rate of neurobehavioral and attention deficit disorders, as well as psychiatric comorbidities, particularly emotional regulation disorders such as depression, anxiety, bipolar disorders, compared with both the general population and children with other medical disorders, neurological and non-neurological. For psychiatric comorbidities, a prevalence of 12% to 35% has been reported, compared to 3-8% in the general population. The link between an underlying brain disorder and psychiatric comorbidities has also emerged in recent literature, with evidence based on studies in adults, suggesting a bidirectional relationship between epilepsy and neurobehavioral comorbidities. Emotional regulation disorders can follow the onset of epilepsy; however, they can also precede it, thus serving as a possible risk factor. The clinical implication of such a bidirectional association is that neurobehavioral comorbidities might be present at diagnosis and even before epilepsy onset. The bidirectional relationship between psychopathology and epilepsy may also be unrelated to the severity of epilepsy, epilepsy syndrome, or type of mood or anxiety disorder. Nevertheless, controlled studies are relatively scarce and evidence-based data to strongly support such a statement are still lacking. Disparate findings are reported by: small sample sizes, heterogeneous epilepsy syndromes, and often inclusion of children suffering from established, chronic epilepsy rather than newly diagnosed patients. According to certain neurobiological models, the occurrence of mood/emotional disorders is linked to a biological and/or genetic susceptibility, which is influenced by stress factors. These elements may, in turn, potentially be affected by epilepsy; the repetition and propagation of seizures, disrupting or merely modifying the organization of specific neural networks. The pharmacological management of the epilepsies, particularly when frequent changes or polytherapy are necessary, further complicates a better understanding of the above. Up to 8% of patients with drug-resistant epilepsy develop treatment-emergent psychiatric adverse events of AED regardless of the mechanism of action of the drug and this is probably related to an underlying predisposition given by the previous psychiatric history. On the other hand, while some AEDs are successfully used for the treatment of mood disorders outside epilepsy, the same AEDs may be associated with paradoxical mood deterioration in people with epilepsy. The therapeutic challenges in clinical practice will be discussed.
Gene therapy offers the potential to change the expression of any gene in targeted cells. The potential for treatments to restore functional copies of genes in people who have mutations disrupting those genes is increasingly well-recognised. In epilepsy, which is frequently characterised by an imbalance between excitation and inhibition, there is a different opportunity for gene therapy. That is to alter expression of genes to restore this balance, even in individuals with no known causative mutation. This allows gene therapy to move from a focus on rare monogenic epilepsies to more common epilepsies, and the wealth of neurophysiological and molecular data revealing how neuronal excitability is modulated during epileptogenesis and epilepsy, means there are many potential target genes to investigate. This talk focuses on three different strategies in our collaboration that are aimed at reducing the likelihood of seizures: overexpression of potassium channels, use of designer receptors exclusively activated by designer drugs (DREADDs), and glutamate-gated chloride channels. The focus is on the technical and translational challenges and advantages of each approach and an analysis of how these approaches may be progressed to clinical trials, and how those clinical trials might be designed, using the strategy with the original potassium channel construct as a worked example.

Genetic variation in the AnkyrinG interactome causes a range of neurological disorders
Professor Frank Kooy, University of Antwerp, Antwerp, Belgium

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Numerous genes are involved in the pathogenesis of neurodevelopmental disorders. Several studies showed that a significant proportion of all putative disease genes converge on a relatively limited number of molecular pathways or protein networks. Thus far, the identification of the disease-networks followed the identification of the individual genes. To what extent this type of selection bias affects the detection of the disease-related pathways is unknown. We here took an unbiased approach by selecting a well-defined protein-protein interaction network and investigating the mutational load therein in a large cohort of patients with various neurodevelopmental disorders along with their parents. For our study, we selected the AnkyrinG PPI network. The AnkyrinG protein binds simultaneously to the spectrin cytoskeleton as well as to multiple members of all potassium channels and sodium channels as well as components of the calcium kinase 2. MIP sequencing of all proteins in the ANK3 PPI network was performed for over 1009 patient-parent trios. For this cohort, all nonsynonymous de novo variants that passed quality parameters, were selected for Sanger sequencing validation. A total number of 14 confirmed de novo variants were identified in multiple ANK3 PPI network members. Considering the average rate of base-substitutional mutations and size of the encoded genomic region by the network genes, a priori only one to two de novo mutations are expected in our screen assuming no selective pressure on the included genes. Thus our cohort, we detected a significant overrepresentation of de novo mutations in the AnkyrinG PPI network (p=0.007, Fisher’s exact test). Our finding stresses the importance of the AnkyrinG PPI network in neurodevelopmental disorders and suggests it as a potential target for future therapies.

Gene therapy in neurodevelopmental disorders
Professor Stuart Cobb, University of Edinburgh, UK

The potential for gene therapy in neurological disorders is finally being realised. Advances in diagnostic gene panels and sequencing technologies are giving earlier / definitive molecular diagnoses and identifying patient populations. At the same time, AAV vector-mediated gene therapy can target the root-cause in neurodevelopmental disorders (NDD) and genetic epilepsies. Importantly, gene therapy can attack genetic targets that are not readily ‘druggable’ by conventional therapeutic modalities. In the presentation, Rett syndrome will be given as an exemplar of translational progress in gene therapy. Rett syndrome is caused by loss-of-function mutations in the X-linked MECP2 gene and leads to seizures and lifelong cognitive, motor and other disabilities. It was the first genetic neurodevelopmental disorder to have been shown to respond to genetic rescue and these findings and others marked a paradigmatic change in the way we view and envision treating NDDs. Studies in accurate genetic models of the disorder have demonstrated the concept gene therapy and led to commercial and clinical development programmes NDDs. There are however many challenges and significant obstacles to translational success in NDD and genetic epilepsies. Many of the genes underlying the disorders are highly dosage sensitive and achieving appropriate control of levels and patterns of expression are as important as are the delivery, spread and distribution of the vector within the nervous system. As a result, ongoing efforts aim to make a new generation of gene therapy reagents with improved efficacy and safety necessary for clinical translation.

Interneuron-based cell therapy for intractable epilepsies
Professor Scott Baraban, University of California, San Francisco, US

Nearly 3 million Americans suffer from epilepsy. In one third of these patients, available antiepileptic drugs or invasive surgical procedures are not effective. With an increased understanding of the role of inhibitory GABAergic interneurons in the healthy and epileptic brain, hope for a cure emerges. During the past decade, transplantation of neuronal precursors into the CNS has shown great promise for the treatment of neurological diseases and epilepsy (often viewed as a deficit in inhibition) more specifically. Reports of neural progenitor cells with the ability to disperse and differentiate into neurons following transplantation have further raised expectations that defective brain circuits can be repaired. Using transplanted neural progenitors derived from the embryonic medial ganglionic eminence (or MGE) we are exploring the possibility that these cells will influence synaptic function in the host brain and reduce spontaneous seizures. Our work takes advantage of the unique ability of MGE progenitor cells to migrate and integrate as inhibitory GABAergic interneurons in the healthy and epileptic brain. The purpose of this presentation is to demonstrate the efficacy of these transplanted GABA progenitor cells in ameliorating spontaneous seizures and behavioral co-morbidities in a wide variety of rodent epilepsy models. Finally, the initial steps we are taking to translate these rodent studies to larger species will be discussed. Overall, these efforts provide proof-of-principle for the development of an interneuron-based cell transplantation therapy.
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Gus Baker, University of Liverpool
Torsten Bal deweg, University College London
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