

Paediatric Epilepsy Research Annual Report 2012



Introduction

It is with great pleasure that I introduce our research report for 2012 for the epilepsy unit across UCL-Institute of Child Health, Great Ormond Street Hospital and Young Epilepsy.

Our research continues to focus on all aspects of childhood epilepsy; looking toward optimising outcomes in children with epilepsy and exploring the health, psychosocial and educational impacts and interventions. New projects initiated over the past year have included a study investigating brain networks in Childhood Absence Epilepsy and Juvenile Myoclonic Epilepsy using EEG-fMRI, and a study evaluating the role of sleep in learning in children with epilepsy.

We have secured new grant monies totalling £919,098 over this period. Further, we have as a unit been responsible for 49 peer reviewed publications of primary research, as well as a further 30 publications including chapters, reviews and commentaries of expert opinion. I have with colleagues edited two books; one a comprehensive text on Childhood Epilepsy with contributions from 90 international experts across the world (including members of the unit), and one a cookery book for parents of children on the ketogenic diet. Also Dr Liz Neal has edited a book on the ketogenic diet for professionals.

We hosted our third annual research retreat for researchers and collaborators in January, moderated by Professor Sam Berkovic from Melbourne. Here, many of our projects were presented and discussed enabling further ideas to be explored.

Over the last 12 months Rod Scott, Chair of the Research Development Board, has been promoted to Professor (from Reader) by University College London. Many congratulations to him. Also, I have been bestowed the honour of being the first woman in the 100-year history of the International League Against Epilepsy (ILAE) to be elected to the Executive Committee as Secretary General for the term 2013-2017.

Our research team continues to work towards finding ways to improve recognition of epilepsy as a healthcare priority in every part of the world and our aim over the next year is to continue to widen our focus of research into education to look at interventions following on from research into underlying mechanisms.

Professor Helen Cross

The Prince of Wales's Chair of Childhood Epilepsy



Research Partners

Young Epilepsy

Young Epilepsy is the national charity working exclusively on behalf of children and young people with epilepsy. With over 100 years expertise it provides world class diagnosis, assessment and rehabilitation for children and young people with epilepsy. The charity also operates an internationally renowned research programme. Young Epilepsy has a specialist school and college, providing day, residential and short break services, up to the age of 25, offering education and healthcare for children and young people with epilepsy, autism and other neurological conditions.

Young Epilepsy aims to achieve better futures for young lives with epilepsy and to raise awareness and understanding of epilepsy and issues associated with the condition. The charity provides support and information for parents, children and young people and training for professionals. It campaigns for better access to, and quality of, health and education services. It offers tailor-made training across the country for parents, teenagers and health, social care and education professionals and also work in schools.

UCL Institute of Child Health

UCL Institute of Child Health (ICH) is one of the world's pioneering paediatric research centres and represents the largest concentration of people dedicated to advancing paediatrics outside of the United States.

ICH pursues an integrated, multidisciplinary approach to enhance understanding, diagnosis, therapy and prevention of childhood disease. A broad range of paediatric issues is covered, from molecular genetics to population health sciences. All specialties as they relate to children's health are included so that ICH fulfils the role of a world-leading academic establishment in paediatrics.

In keeping with a commitment to disease prevention, ICH is active in teaching and research aimed at developing interventions to promote health both during childhood and in the later years of life.

Great Ormond Street Hospital for Children

Great Ormond Street Hospital (GOSH) is an international centre of excellence in child healthcare. The hospital is dedicated to children's healthcare and to finding new and better ways to treat childhood illnesses. There are more than 50 different clinical specialties at GOSH.

GOSH is also at the forefront of paediatric training in the UK and trains more children's nurses than any other hospital. They also play a leading role in training paediatric doctors.

The hospital is committed to carrying out pioneering research to find treatments and cures for some of the most complex illnesses, for the benefit of children here in the UK and worldwide and does so in partnership with UCL-Institute of Child Health.

Research Strategy for Childhood Epilepsy

Young Epilepsy, UCL-Institute of Child Health and Great Ormond Street Hospital

The overriding goal of epilepsy research within this joint unit is to enable a better long term outcome and to reduce the overall burden for children with epilepsy. The unit – encompassing Young Epilepsy, UCL-Institute of Child Health and Great Ormond Street Hospital for Children – is in a unique position of incorporating review of children with a range of severity from newly diagnosed to complex. Further collaboration across UCL allows continuation of work into adulthood, allowing study across the whole age range. The educational and behavioural expertise within Young Epilepsy allows interventional study beyond medical treatment.

Goal 1: To gain a better understanding of underlying mechanisms and aetiologies responsible for seizures. This will be achieved by:

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

Goal 2: To widen our understanding of the underlying mechanisms of neurodevelopmental and behavioural compromise in childhood epilepsy by including:

- The development of experimental animal studies to examine the effects of epileptiform discharges on development.
- Cohort studies to evaluate prevalence, natural history and outcome of comorbidities in childhood epilepsy.
- Correlative neurophysiology/neuropsychology studies.
- Collaborative outcome studies across the age range.



Goal 3: To determine the benefits of early interventions in improving long-term outcome in childhood epilepsy:

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

Goal 4: To reduce the overall burden of epilepsy in childhood to the individual, family and agencies involved through:

- Interventional behaviour programmes for families, education and health professionals.
- Rehabilitation

Goal 5: To develop a milieu of senior researchers working both together and independently towards overriding goals of unit, so enhancing training for academia, promoting a collegiate environment for junior staff and moving forward academic careers.

- Development of training fellowships.
- Projects involve working towards higher degrees with encouragement for independent working thereafter.
- Joint working between UCL-ICH and Young Epilepsy.
- Enhancing research across all areas of expertise.

Research Funding

Central to the research programme is the ability to apply for and manage research grants and funding. The various research activities are funded through a combination of research grants associated with specific projects and donations from individuals and other charitable organisations.

Funders of our 2012 research projects included The Wolfson Foundation, Action Medical Research, Great Ormond Street Hospital Children's Charity, University College London, Kings College London, Charles Wolfson Foundation, McGrath Foundation, Esmée Fairbairn Foundation, Vitaflo Limited and the Reta Lila Howard Foundation.

Research Update

Below is a brief update on the research projects being carried out within the unit:

Epilepsy in infancy: relating phenotype to genotype

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

Investigators: Helen Cross, Manju Kurian, Rod Scott, Christin Eltze, Finbar O'Callaghan, Elaine Hughes

Update: Funding has been secured for phase one of the project. Application for ethical approval is underway and recruitment is due to begin in September 2013.

The impact of reducing antiepileptic drug load on quality of life in children with refractory epilepsy

Project Aim: To prospectively determine the effect of reducing antiepileptic drug (AED) load on the quality of life and seizure control in children with refractory epilepsy who are on AED polytherapy.

Investigators: Rod Scott, Krishna Das, Suresh Pujar, Sarah Aylett, Archana Desurkar, Kirsten McHale, Brian Neville

Update: Recruitment of research participants from St Piers School and College at Young Epilepsy is underway.

Educational problems of children with epilepsy: their identification and management

Project Aim: To determine the prevalence of learning and behaviour difficulties in school-age children with epilepsy.

Investigators: Brian Neville, Colin Reilly, Patricia Atkinson, Rod Scott, Victoria Burch, Paul McCrone, Richard Chin, Sarah Aylett, Krishna Das, Dame Philippa Russell, Christopher Gillberg

Update: All of the participants, a cohort of children with epilepsy of school age in the Crawley area, have undergone initial screening and detailed psychological assessments. Data collection will be complete by end of March 2013. Some of the initial findings were presented at the BPNA conference in Manchester in January 2013 and further publications and conference presentations will follow in the second half of 2013.

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, Manju Kurian, Helen Cross



Update: The team have already successfully identified a few new genes causing severe seizure disorders of infancy (such as infantile spasms and migrating partial seizures of infancy) and is carrying out whole exome sequencing of a cohort of children with early onset seizures.

Prevalence and clinical outcome of Rasmussen Encephalitis in children

Project Aim: To collate information on the prevalence, symptomology, management and outcome of children with Rasmussen syndrome in the UK. This monitoring study of the rare but significant syndrome will provide us with information as to initial history, and response to treatment, including timing of surgery. We hope this will lead to plans for further trials.

Investigators: Kate Lamb, Will Scott, Robert Robinson, Sophia Varadkar, Helen Cross

Update: Information has been collated from clinicians across the UK who had previously managed or were managing a child with Rasmussen Encephalitis between March 2010 to March 2012. 21 cases were identified (12 male, 9 female) including 4 new diagnoses during the study period. The data is being reviewed and initial findings were presented at the BPNA 2013. Further analysis is being undertaken and the results will be published in the coming year.

Epilepsy genomics in childhood: finding the causes, directing treatment

Project Aim: To determine the frequency of genetic deletions as a cause of epilepsy.

Investigators: Anna Tostevin, Helen Cross, Sanjay M. Sisodiya

Update: Collection of the genetic and clinical data from 299 children with epilepsy is complete. The data is currently being analysed to look for novel genetic changes, combinations of genetic changes and the overall burden of genetic variability to see if these factors predispose to epilepsy in childhood.

Sleep and memory in children with focal epilepsy

Project Aim: To evaluate the role of sleep in learning (specifically memory consolidation) in children with different types of focal epilepsy, and determine whether this is disrupted compared to healthy children. This should lead to a better understanding of the causes of cognitive impairment in epilepsy.

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

Update: The PhD fellow took up post in March 2012. Full ethics and registration are in place and training is being undertaken. Research participants will be recruited from Great Ormond Street Hospital from April/May 2013, and from other hospitals in the North Thames Epilepsy Network from July 2013.



The encephalopathy of infantile spasms

Project Aim: To describe the encephalopathy of infantile spasms using ERPs and MRIs with controls.

Investigators: Brian Neville, Rod Scott, Stewart Boyd, Klaus Werner, Tang Fosi

Update: Three papers have been written up for publication and the thesis is being prepared for submission.

Improving epilepsy surgery in childhood using fMRI and EEG

Project Aim: To have a better understanding of the feasibility and the utility of EEG-fMRI in the presurgical evaluation of children with drug resistant focal epilepsy.

Investigators: David Carmichael, Maria Centeno, Daniel Konn, Chris Clark, Jonathan Clayden, Ronit Pressler, Helen Cross

Update: Led by the clinical research fellow, Dr Maria Centeno, nearly 20 patients undergoing presurgical evaluation at Great Ormond Street Hospital and a number of control subjects have been recruited. The data is being analysed and some interesting results have already been found.

A genetic basis for response to the Ketogenic Diet

Project Aim: To determine whether there is a genetic basis to treatment outcome with the Ketogenic Diet in drug-resistant epilepsy.

Investigators: Natasha Payne, Helen Cross, Sanjay M. Sisodiya,

Update: Approximately 275 participants have been recruited from Great Ormond Street Hospital, Evelina Children's Hospital, Young Epilepsy (in conjunction with Matthew's Friends), The National Hospital for Neurology and Neurosurgery, Birmingham Children's Hospital, St George's, Addenbrooke's and Bristol Children's Hospital. Candidate gene analysis and exome sequencing is in progress. Also, blood samples are being collected for RNA extraction.

Elucidation of the biochemical mechanisms responsible for the efficacy of the Ketogenic Diet

Project Aim: To determine changes seen in medium chain fatty acids in children treated with the Ketogenic Diet, and determine their possible role in the underlying mechanism of effect.

Investigators: Sean Hughes, Helen Cross, Simon Heales

Update: This project is in collaboration with the Department of Biochemistry, UCL-ICH. Decanoic acid has been identified as a possible candidate for proliferating mitochondria in a neural cell-line, indicating a possible mechanism of action for the ketogenic diet. Blood from participants recruited from Great Ormond Street Hospital Ketogenic Diet clinic is now being assessed for medium chain fatty acids.

The spectrum of epileptic spasms in children

Project Aim: Retrospective study to evaluate the range of phenotype of epileptic spasms in children captured on video-EEG.

Investigators: Daniel Carranza, Helen Cross, Ingrid Scheffer

Update: This is a collaborative study with investigators from Melbourne, Australia. Over 600 cases have been exclusively confirmed on video-EEG from a wide retrospective cohort of children with epileptic spasms from the UK and Australia. The data is being reviewed and a paper will be prepared for publication later in 2013.

Neurological, cognitive and neuroimaging outcomes within 10 years after childhood status epilepticus: a population-based study

Project Aim: To determine prevalence of epilepsy, motor and cognitive problems within 10 years after an episode of status epilepticus in childhood and investigate the predictors of poor outcomes.

Investigators: Suresh Pujar, Marina Martinos, Kling Chong, Michelle De Haan, Brian Neville, Chris Clark, Richard Chin, Rod Scott

Update: The data collection for the study is now complete and data analysis is being undertaken. Preliminary results suggest that the cause of status epilepticus is the main predictor of outcomes within 10 years. Children with no prior neurological impairments have a good outcome, and those with prior neurological impairments and/or epilepsy have poor neurological outcome.

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

Project Aim: The project aims to look at brain networks involved in the clinical expression of epilepsy as an approach to fully understand the common and distinct pathways existing across epilepsy syndromes.

Investigators: Suejen Perani, Helen Cross, Mark Richardson, David Carmichael

Update: This is a collaborative study with Professor Mark Richardson at Kings College. Application for ethical approval is underway.



The Research Team

The research team contribute to a wide spectrum of activities from basic range of experts working across UCL-Institute of Child Health, Great Ormond

Principal investigators

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

Professor Christopher Gillberg *Visiting Professor in Child and Adolescent Psychiatry*

Dr Manju Kurian *Consultant and Clinician Scientist*

Professor Brian Neville *Emeritus Professor of Childhood Epilepsy*

Dr Ronit Pressler *Consultant and Honorary Senior Lecturer in Clinical Neurophysiology*

Professor Rod Scott *Professor in Paediatric Neurology*

PhD students

Samantha Chan – *Sleep and memory in children with focal epilepsy*

Ben Duffy – *Experimental imaging studies post-status epilepticus*

Tang Fosi – *The neurological basis for cognitive and autistic regression in infants with West syndrome (infantile spasms)*

Sean Hughes (jointly with Biochemistry, ICH) – *Elucidation of the biochemical mechanisms responsible for the efficacy of the Ketogenic Diet*

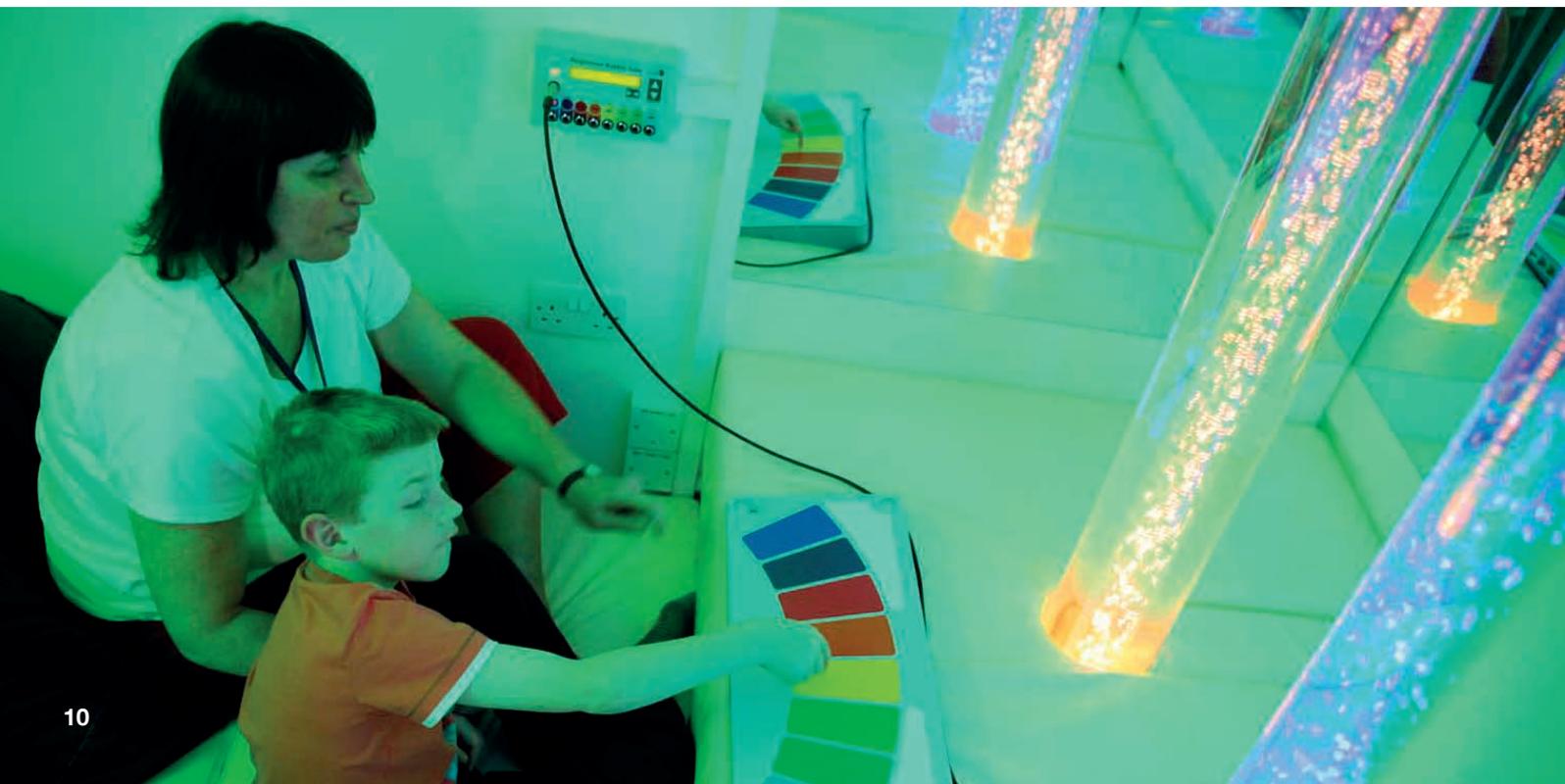
Amy Mctague – *The genetics of early onset epileptic encephalopathy*

Natasha Payne (jointly with ION) – *A genetic basis for response to the Ketogenic Diet in epilepsy*

Suejen Perani (jointly with Kings College) – *Investigation of brain networks in Childhood Absence Epilepsy and Juvenile Myoclonic Epilepsy using EEG-fMRI*

Suresh Pujar – *The outcomes 5-10 years after childhood convulsive status epilepticus: a population based study*

Fatma Scerif (jointly with Neural Developmental Unit, ICH) – *Identification of gene networks in childhood epilepsy*



science through to patient care and consists of a multidisciplinary
and Street Hospital for Children and Young Epilepsy.

Research staff

Daniel Carranza *Clinical/Research Fellow*
Antionietta Coppola *Research Fellow*
Virginia Fenton *Inclusion Project Researcher*
Havinder Hara *NEMO Coordinator*
Marina Martinos *Postdoctoral Neuropsychologist*
Kirsten McHale *Research Nurse*
Angela Mensah *Research Coordinator*
Esther Meyer *Post Doctoral Research Scientist*
Colin Reilly *Research Psychologist*
Anna Tostevin *Research Assistant*
Liz Neal *Honorary Research Dietician*
Anna Tyler *Postdoctoral Research Fellow*

Clinicians in neuroscience active in epilepsy research

Dr Patricia Atkinson *Consultant Community Paediatrician*
Dr Sarah Aylett *Consultant Paediatric Neurologist*
Dr Stewart Boyd *Consultant Neurophysiologist*
Dr Maria Clark *Consultant Paediatric Neurologist*
Dr Krishna Das *Consultant Paediatric Neurologist*
Dr Christin Eltze *Consultant Paediatric Neurologist*
Mr William Harkness *Consultant Paediatric Neurosurgeon*
Dr Cheryl Hemingway *Consultant Paediatric Neurologist*
Dr Isobel Heyman *Consultant Child and Adolescent Psychiatrist*
Dr Robert Robinson *Consultant Paediatric Neurologist*
Dr Sophia Varadkar *Consultant Paediatric Neurologist*

Active collaborators

Dr Torsten Baldeweg *Reader in Developmental Cognitive Neuroscience, UCL-Institute of Child Health*
Dr David Carmichael *Lecturer in Neuroimaging and Biophysics, UCL-Institute of Child Health*
Dr Richard Chin *Senior Lecturer in Paediatric Neurology, University of Edinburgh*
Dr Michelle de Haan *Reader in Developmental Cognitive Neuroscience, UCL-Institute of Child Health*
Professor Simon Heales *Professor of Clinical Chemistry, Great Ormond Street Hospital*
Professor Gregory Holmes *Professor of Neurology and Paediatrics, Dartmouth Medical School, USA*
Dr Thomas Jacques *Clinical Senior Lecturer and Honorary Consultant Neuropathologist, UCL-Institute of Child Health*
Dr Pierre-Pascal Lenck-Santini *Assistant Professor of Neurology, Dartmouth Medical School, USA*
Professor Sanjay Sisodiya *Professor of Neurology, UCL-Institute of Neurology*
Professor Faraneh Vargha-Khadem *Professor of Developmental Cognitive Neuroscience, UCL-Institute of Child Health*

Epilepsy Research Retreat

The Epilepsy Research Retreat serves as an annual get together of researchers and collaborators across the unit. This has followed models from other centres around the world and gives researchers the opportunity to discuss ongoing projects, completed projects and possible future directions of research.

The 2013 research retreat took place on 17-18 January in East Grinstead with Professor Sam Berkovic as the moderator. Professor Berkovic is Laureate Professor in the Department of Medicine, University of Melbourne, and Director of the Epilepsy Research Centre at Austin Health, Melbourne, Australia.

The meeting brought together more than 80 researchers and collaborators from Young Epilepsy, UCL-Institute of Child Health, UCL-Institute of Neurology, Great Ormond Street Hospital and Dartmouth College, USA. There were presentations on 22 of the projects taking place across the unit ranging from neuropathology to neuroimaging, genetics to educational exclusion as well as results of animal work from our collaborators in Dartmouth. Discussions at the end of each presentation gave investigators the opportunity to receive comments and feedback from fellow researchers and principal investigators.

The retreat also proved to be a highly social occasion. This aside, it successfully highlighted the breadth of epilepsy research being undertaken across the unit and also served as a way of motivating young researchers who may not have previously had the opportunity to meet other members of the unit.

'I thoroughly enjoyed the retreat and found it most stimulating and inspiring. It is quite amazing to learn that so much research is going on in our vicinity.'

Consultant Community Paediatrician

'It was a terrific meeting – both stimulating and relaxing at the same time.'

Senior Lecturer

'I enjoyed the opportunity to see the breadth of research occurring across the different units. I also found the opportunity to meet members of the wider research unit very beneficial, as I have not had this opportunity previously.'

PhD student

'I found the retreat to be well organised, interesting and entertaining. The programme was balanced and the mixing of all fields of research (animal, psychology, clinical, genetic) in most sessions maintained the continued attention of the broad audience.'

Clinical Research Fellow



Publications – 2012

Peer Reviewed Publications

1. Riney CJ, Chong WK, Clark CA , **Cross JH**. Voxel based morphometry in children with intractable focal epilepsy: implications for surgical intervention. *European Journal of Radiology* 2012;(81)6:1299-305
2. Cormack F, Vargha Khadem F, Wood SJ, **Cross JH**, Baldeweg T. Memory in paediatric temporal lobe epilepsy: effects of lesion type and side. *Epilepsy Res* 2012;98(2-3):255-259
3. Christodoulides SS, Neal EG, Fitzsimmons G, Chaffe H, Jeanes Y, Aitkinhead H, **Cross JH**. Vitamin A and E, Zinc, Selenium and Magnesium Levels over 12 months on the classical and MCT Ketogenic Diet. *J Hum Nutr Diet* 2012;25(1):16-26
4. Colonnelli MC, **Cross JH**, Davies S, D'Argenzio L, **Scott RC**, Pickles A, Hannan S, Harkness W, Heyman I. Psychopathology in children before and after surgery for extratemporal lobe epilepsy. *Dev Med Child Neurol*. 2012 Jun;54(6):521-6
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6. D'Argenzio L, Colonnelli MC, Harrison S, Jacques TS, Harkness W, **Scott RC**, **Cross JH**. Seizure outcome after extratemporal epilepsy surgery in childhood. *Dev Med Child Neurol*. 2012 Nov;54(11):995-1000
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11. Martinos MM, Yoong M, Patil S, Chin RF, **Neville BG**, **Scott RC**, de Haan M. Recognition memory is impaired in children after prolonged febrile seizures. *Brain*. 2012 Oct;135(Pt 10):3153-64
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14. Heinzen EL, Swoboda KJ, Hitomi Y, Gurrieri F, et al. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. *Nat Genet*. 2012 Sep;44(9):1030-4
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