Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Advancing availability of curative surgery to children with refractory focal epilepsy

Period when the underpinning research was undertaken: 2003- 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
J Helen Cross	**The Prince of Wales's Chair of Childhood Epilepsy & Head Developmental Neurosciences, UCL GOS ICH**	**2002 – present**
T Baldeweg	**Professor of Cognitive Neuroscience & Deputy Head Developmental Neurosciences, UCL GOS ICH**	**1999 - present**

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Epilepsy surgery can dramatically improve quality of life for some children with severe uncontrolled epilepsy, who endure continued unpredictable seizures, often multiple times a day. Research led by clinical scientists at UCL Great Ormond Street Institute of Child Health (GOS ICH) has led to a care pathway now applied across Europe, to identify suitable cases. The UCL team has established a centralised epilepsy surgery service for children in England that since 2013, has seen a three-fold increase in the number of children benefitting from surgery across 4 UK centres. In 2019, 345 children were treated in the UK and 85% of them are now seizure free. The team has also developed freely available MRI processing software for clinicians to identify candidates for surgery and established a European Specialist Network that is increasing awareness and availability of epilepsy surgery across Europe.

2. Underpinning research

Epilepsy affects 112,000 children and young people in the UK. Two thirds of patients will respond to antiepileptic medication or go into spontaneous remission. However, for 1 in 3 patients, seizures persist despite medication and many experience more than 30 seizures per day. This can have a devastating impact on families with patients experiencing cognitive and behavioural problems in addition to multiple seizures that impact quality of life and can result in injury. Research in the UCL GOS ICH Developmental Neurosciences department has been instrumental in developing ways to target surgical interventions to ensure more patients can live seizure free. These include validating functional imaging to relate brain abnormalities to areas of seizure onset, as well as delineate areas of function that should be preserved in surgery, and highlighting improvements post-surgery in cognitive function with long term follow up.

More recently, the UCL team has made improvements to structural MRI methodology and developed freely available machine learning software to support clinicians in identifying

cases. They have used advanced neurophysiology to determine where seizures may arise and demonstrated the link between early medication weaning post-surgery and improvements in cognitive function.

Identifying the link between EEG and structural brain abnormalities associated with epilepsy

Focal cortical dysplasia (FCD), an abnormality of cortical development, is the leading cause of surgically remediable drug-resistant epilepsy in children. Despite high-resolution MRI, post-operative histological studies demonstrate that 50-80% of FCD cases escape routine visual inspection. Incomplete resection of such lesions during surgery significantly reduces the chance that seizures will cease. To help correlate any structural abnormality with the electrical activity confirming the seizure onset zone, the UCL team have developed combined EEG-functional MRI (EEGfMRI) to link electrical activity to structural brain abnormalities and thus determine the source of the seizures (**R1**). They have also performed correlative advanced electrophysiological studies (electrical source imaging [ESI and EEGfMRI]) in children with focal onset seizures to improve the yield of location of responsible brain tissue (**R2**). This is providing increased confidence in determining which patients would benefit from surgery (**R3**).

Machine learning tools to identify surgical cases

The UCL team has developed several automated MRI analysis methods for the detection of subtle focal brain lesions. They have identified novel local morphological features allowing them to localise FCD lesions by developing cortical feature maps based on a machine learning method using artificial neural networks (**R4**). In collaboration with 26 European clinical centres, the team continues to develop freely available 'post-processing' machine learning tools for structural MRI (MELD consortium, https://meldproject.github.io). These tools have now been independently validated in three patient cohorts in the UK, US and China (**R5**).

Cognitive benefits post-surgery

Outcome studies from many centres worldwide demonstrate the long-term benefits of early surgery with regard to seizure freedom, but its impact on cognitive development has been unclear. The UCL team previously showed that the earlier the onset of epilepsy, the poorer cognitive performance in the longer term. More recently, they demonstrated that cognition is maintained in the short-term following surgery, but improvements in IQ are seen in longer follow-up assessments. Improvements are highly related to seizure freedom and weaning of medication as well as site of surgery and simultaneous cortical growth (**R6**). The team were integral to the design and data collection for a large pan-European study (TimeToStop cognitive outcomes study group) of over 300 children who had undergone surgery to treat epileptic seizures. This study provides further evidence for a link between early weaning from medication post-surgery and improvements in IQ (**R7**).

3. References to the research

R1 De Tiège X, Laufs H, Boyd SG, Harkness W, Allen PJ, Clark CA, Connelly A, **Cross JH**.(2007) EEG- Impact case study (REF3b) Page 2 fMRI in children with pharmacoresistant focal epilepsy. *Epilepsia*. Feb;48(2):385-9. doi:10.1111/j.1528-1167.00951.x

R2 Adler S, Wagstyl K; Gunny R; Ronan L; Carmichael D; **Cross J H**; Fletcher P C; **Baldeweg T** (2016) Novel Surface Features for Automated Detection of Focal Cortical Dysplasias in Paediatric Epilepsy *Neuroimage Clin*. Dec 30;14:18-27. DOI: 10.1016/j.nicl.2016.12.030

R3 Centeno M, Tierney T, Perani S, Shamshiri E, St Pier K, Wilkinson C, Konn D, Vulliemoz S, Grouiller F, Lemieux L, Pressler R, Clark C, **Cross JH,** Carmichael DW (2017) Combined EEG-fMRI and ESI improves localisation of paediatric focal epilepsy *Ann Neurol* Aug;82(2):278-287. DOI: 10.1002/ana.25003

R4 Wagstyl, K., Adler, S., Pimpel, B., Chari, A., Seunarine, K., Lorio, S., Thornton, R., **Baldeweg, T**., & Tisdall, M. (2020). Planning stereo-electroencephalography using automated lesion detection: Retrospective feasibility study. *Epilepsia*. Jul;61(7):1406-1416. doi: 10.1111/epi.16574

R5 Mo JJ, Zhang JG, Li WL, Chen C, Zhou NJ, Hu WH, Zhang C, Wang Y, Wang X, Liu C, Zhao BT, Zhou JJ, Zhang K. (2019) Clinical Value of Machine Learning in the Automated Detection of Focal Cortical Dysplasia Using Quantitative Multimodal Surface-Based Features. *Front Neurosci*. Jan 11;12:1008. doi: 10.3389/fnins.2018.01008.

R6 Skirrow C, **Cross JH**, Owens R, Weiss-Croft L, Martin-Sanfilippo P, Banks T, Shah E, Harkness W, Vargha-Khadem F, **Baldeweg T**, (2019) Determinants of IQ outcome after focal epilepsy surgery in childhood: a longitudinal case-control neuroimaging study. *Epilepsia* May;60(5):872-884. DOI: 10.1111/epi.14707

R7 Boshuisen K, van Schooneveld M, Uiterwaal C, **Cross JH,** Harrison S, Polster T, Daehn M, Djimjadi S, Yalnızoğlu D, Turanli G, Sassen R, Hoppe C, Kuczaty S, Barba C, Kahane P, Schubert S, Reuner G, Bast T, Strobl K, Mayer H, de Saint Martin, A, Seegmuller A, Laurent A, Arzimanoglou A, Braun K (2015) IQ improves after AED withdrawal following pediatric epilepsy surgery. *Ann Neurol.* Jul;78(1):104-14. DOI: 10.1002/ana.24427

4. Details of the impact

Approximately 35,000 children and young people in the UK experience severe uncontrolled epilepsy that is associated with a reduced quality of life and around 440 children each year could benefit from surgery. Clinical scientists at UCL GOS ICH led developments in MRI scanning that are now incorporated into international guidelines and help clinicians to identify children who will benefit from surgery, to reduce epileptic seizures and improve cognitive outcomes. In 2019, 345 children in the UK were treated with surgery and 85% of them have subsequently stopped having seizures completely. In addition, the UCL team has developed open access training tools and established international expert networks that mean in Europe many more children and young adults can now gain access to and benefit from epilepsy surgery.

Consensus recommendations for epilepsy surgery

The UCL GOS ICH team has led international initiatives to establish benchmarks and standards for epilepsy surgery in childhood. In 2014, Professor Cross led on a consensus document published by the International League Against Epilepsy (ILAE) on diagnostic techniques for use in presurgical evaluation in children. The published care pathway is now utilised worldwide as standard (**S1**). Cross was also part of the expert group selected by the ILAE that developed best practice recommendations for epilepsy surgery procedures to maximise chances of seizure control and help minimise cognitive deficits (**S2**).

Developments from UCL research are now embedded in new standards for paediatric epilepsy surgery centres worldwide, which state: “Level 1 care consists of children age 9 years and older, with discrete lesions including hippocampal sclerosis, undergoing lobectomy or lesionectomy, preferably on the cerebral convexity and not close to eloquent cortex, by a team … with access to video-electroencephalography and 1.5-T magnetic resonance imaging (MRI). Level 2 care, also encompassing Level 1 care, occurs across the age span and range of etiologies … associated with MRI lesions that may be ill-defined, multilobar, hemispheric, or multifocal, and includes children with normal MRI or foci in/abutting eloquent cortex. Available Level 2 technologies includes 3-T MRI, other advanced magnetic resonance technology including functional MRI and diffusion tensor imaging (tractography), positron emission tomography and/or single photon emission computed tomography, source localization with electroencephalography or magnetoencephalography, and the ability to perform intra- or extraoperative invasive monitoring and functional mapping.”(**S3**).

Open access software to support clinical assessment and selection for epilepsy surgery.

Since 2013, the UCL team has initiated a multi-centre effort to develop a large training data set - the 'Multi-centre Epilepsy Lesion Detection' (MELD) project (**S4**) that uses software tools developed at UCL to support identification of suitable cases for surgery. The consortium continues to contribute scan data to further develop the tools for lesion detection and normalisation techniques, through machine learning. The MELD cohort currently comprises over 550 FCD patients and 382 controls, with 26 participating centres internationally, including in Brazil, China, Finland, Spain and US. Participating sites use their own data for clinical planning comparing it to data from collaborating centres and allowing them to identify more patients suitable for epilepsy surgery who would have been missed using standard clinical evaluation (**S4**). The President of the American Epilepsy Society said, "This program has been at the forefront of investigation and advances that have demonstrated improved outcomes of paediatric epilepsy surgery in addition advocating for epilepsy surgery in children. Critical to success has been a series of elegant studies that have improved and broadened patient selection for epilepsy surgery, delineated benefits of surgery on seizure control and cognition, and introduced techniques and technology that have improved outcomes. Among these projects is MELD, an initiative that has organized collaboration of leading epilepsy centres from across the globe (including our centre), that has provided novel insights into the location and epileptogenic potential of focal cortical dysplasia (FCD)" (**S5**).

Increasing the number of children benefiting from epilepsy surgery

The UCL GOS ICH research has highlighted the value in increasing epilepsy surgery as an intervention for severe epilepsy, demonstrating that early surgery and subsequent weaning from medication can arrest cognitive decline and estimating that up to 440 children per year in England would benefit. The team has campaigned for change, driving the development of the Children's Epilepsy Surgery Service (CESS), established in 2012 and to which Professor Cross remains clinical advisor (**S6**). Since 2013, CESS has supported a three-fold increase in the number of children being assessed for and receiving epilepsy surgery in England. In 2019, 345 children were treated with surgery and 85% of them have stopped having seizures completely, with many discontinuing drug therapy, thereby arresting a progressive decline in IQ and educational attainment.

Cross co-led a successful bid to establish a European Union funded pilot network for epilepsy surgery – "E-pilepsy", to increase awareness and availability of epilepsy surgery across Europe. In 2016, Cross instigated the Reference Network for Rare and Complex Epilepsies (EpiCARE) with further EU funding. This is a network of 52 specialist health care providers/centres and a further 15 affiliated centres across 24 countries who work together to provide specialist advice on treatments for complex epilepsy cases. 'E-pilepsy' remains the surgical arm of EpiCARE. A care pathway exists for referral of patients into the pathway for discussion (**S7**). The Chair of the European Epilepsy Network said: "Their [Cross and Baldeweg's] work in advancing imaging options and outcomes has widened the spectrum of children suitable for surgery and established epilepsy surgery as an early management option in selected candidates, improving long term outcomes in these children… There is no question that the UCL group remain at the forefront of defining the selection and benefits of epilepsy surgery in children and have enhanced the awareness and availability throughout Europe and more globally." **(S8).**

The group meets virtually, twice a month to discuss 2-4 cases. A surgical case considered by the network was used for a video to advertise the work and success of the European Reference Networks overall, demonstrating how a boy of 5 years of age in Finland with a rare epilepsy related to a specific benign brain tumour, hypothalamic hamartoma, was brought for discussion with centres in the network and ultimately went to Marseille for specialised treatment (**S9**). This film won a silver dolphin award at the Cannes film festival in 2019. The patient's father said: "Thanks to this network, my son's doctor was able to seek

advice from the best specialists and they were able to work out the best treatment for my son."

5. Sources to corroborate the impact

S1 Jayakar P, Gaillard WG, Tripathi M, Libenson M, Mathern GW, Cross JH on behalf of the Task Force for Paediatric Epilepsy Surgery, Commission for Paediatrics, and the Diagnostic Commission of the International League Against Epilepsy (2014). Diagnostic Test Utilization in Evaluation for Resective Epilepsy Surgery in Children; Recommendations on behalf of the Task Force for Paediatric Epilepsy Surgery (of the Commission for Paediatrics) and the Diagnostic Commission of the ILAE. *Epilepsia*; 55(4):507–518. doi: 10.1111/epi.12544

S2 Jayakar P, Jayakar A, Libenson M, Arzimanoglou A, Rydenhag B, Cross JH, Bhatia S, Tassi L, Lachhwani D, Gaillard WD, On behalf of the Pediatric Epilepsy Surgery Task Force, International League Against Epilepsy Epilepsy (2018). Surgery near or in eloquent cortex: Practice patterns and recommendations for minimizing and reporting deficits. *Epilepsia*; Aug;59(8):1484-1491. doi: 10.1111/epi.14510

S3 Gaillard W, Jette N, Arnold S, Arzimanoglou A, Braun K, Cukiert A, Dick A, Harvey SA, Jacobs J, Rydenhag B, Udani V, Wilmshurst J, Cross, HJ, Jayakar P (2020). Establishing Criteria for Pediatric Epilepsy Surgery Centers Levels of Care: Report from the ILAE Pediatric Epilepsy Surgery Task Force. *Epilepsia;* Dec:61(21):2629-2642. doi: 10.1111/epi.16698.

S4 MELD (Multicentre Epilepsy Lesion Detection) – collaborative international project; able to utilise data for local clinical services https://meldproject.github.io.

S5 Letter from President of American Epilepsy Society.

S6 Childrens Epilepsy Surgery service https://www.epilepsy.org.uk/info/treatment/surgery/children (initiated 2012).

S7 www.epi-care.eu

S8 Letter from Co-ordinator, European Reference Network EpiCARE.

S9 https://europa.eu/euprotects/our-health/second-opinion-how-eu-networks-share-knowledge-save-lives_en