epilepsy action

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epilepsy professional

Zebrafish in epilepsy research
Meet the tiny fish making a big splash

Dominic Burrows | Richard Rosch

Transitioning – Shelda-Jane Smith

CECTS – Sarah Collins

Seizure Highlights – Markus Reuber

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Welcome to the Spring edition of *Epilepsy Professional*. Oh, how I long for spring. I am sure like me, you can also see the signs of new life all around; crocuses budding and daffodils proudly swaying. Even as I write it's pancake Tuesday and Lent is just about to begin, yet earlier I was dashing between home, the car, work and home, still dodging heavy showers, sleet, wind and rain. As I said, oh how I long for spring.

In this edition of *Epilepsy Professional,* you could say that we have a special focus on the early years of the epilepsy age spectrum with special attention to zebrafish as models in epilepsy research, cognition and learning in childhood epilepsies and a fresh look at transitional epilepsy care in individuals with comorbid learning disability.

Dominic Burrows, a clinician and neuroscientist from King College London, tempts us with his fish tank back to bedside approach using zebrafish models in epilepsy research, in an article exploring their use in translational neuroscience. Though there are limitations with such models, due to the absence of a cortex, some of their other properties mean they have an emerging place in the research domain. These include the ability to study single cell and whole brain activity, neurodevelopmental visualisation and that they are amenable to genetic modification.

Sarah Collins, an epilepsy nurse specialist from Kent Community Health Foundation Trust, challenges us in her article on childhood epilepsy with centro-temporal spikes. Most of us, even adult neurologists are familiar with this childhood epilepsy traditionally thought to be fairly benign and often not requiring treatment. In her literature review, Sarah illustrates the need for larger cohort studies to explore the repeating themes of cognitive difficulties in terms of memory, attention and language. Maybe if borne out in larger scale studies, these factors, together with seizure frequency and severity at such a formative age, may pose a greater rationale for treatment of the condition with epilepsy drugs.

I am sure many readers are involved in epilepsy transition clinics, so you will enjoy Shelda-Jane Smith's article on anthropological reflection on epilepsy transition care. This is a novel reflection on how our traditional rite of passage style clinic, based on a model of biomedicine and funding streams, creates a tension for individuals with epilepsy and comorbid learning disability and their carers. I hope this article provides you due challenge as it did me. I was struck how maybe the goal of such a clinic should not always be to promote independence. In today's society we should strive to foster and acknowledge diversity when we see it and accept cultural care differences, and in Shelda-Jane's words, we must view transition as really being about moving into a new stage of life, something unique to us all.

I hope you enjoy this edition, including these articles on the early years and next time I write, I hope it will be spring.

Ann Johnston
Consultant neurologist
Executive medical adviser
Epilepsy Professional

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Sarah Collins

Childhood epilepsy with centro-temporal spikes has a huge impact on a child's neurodevelopment. What can be done to support children with this condition to help realise their full potential?

As I write, the NHS has just upgraded coronavirus to a level four incident, the highest category of emergency.

It's an outbreak that is beginning to test all levels of governmental and healthcare administration, from public health officials having to remind people to wash their hands and self-isolate, to DWP policy which is dictating the line on statutory sick pay.

The government is already preparing for the worst, with plans in place to close schools and cancel major public and sporting events. With the virus reported to be mutating into a more aggressive form, tracking and containment is going to only get more difficult. Reports indicate that now the best tactic is to try and slow the spread of the virus as much as possible, until a vaccine enters mass production.

Meanwhile, the general public have been whipped up into panic-buying, sending hand sanitiser sales through the roof. I've seen pictures of people on public transport wearing plastic bags and boxes as makeshift masks. And in China, a woman microwaved bank notes worth £300 in an attempt to kill off the virus, but only succeeded in burning them to a crisp.

The extra strain on resources means undoubtedly there will be some impact on epilepsy healthcare, whether the burden is on ICU beds, potential medicine shortages, even extra stress leading to worsened symptoms.

In these uncertain times, 'hope for the best, plan for the worst' is perhaps the best way forward. Look after each other out there, and yourselves.

Matt Ng
Editor
If you no longer wish to receive Epilepsy Professional *magazine, email us at editor@epilepsy.org.uk or call us on 0113 210 8800*

Editor/desktop publishing: Matt Ng (mng@epilepsy.org.uk)

Design: Suzanne Horvath (shorvath@epilepsy.org.uk)

Publishers: Epilepsy Action (External affairs department)

Advertising: Louise Cousins – 0113 210 8847 lcousins@epilepsy.org.uk

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New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY, UK
tel: 0113 210 8800 | **fax:** 0113 391 0300 | **Epilepsy Action Helpline freephone:** 0808 800 5050
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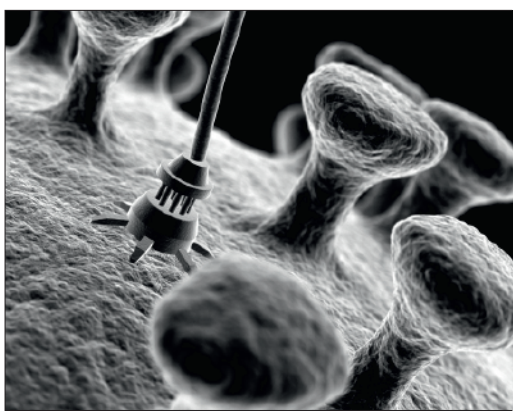
EU funds project to develop nanodevices against epilepsy



The use of nanotechnology is being investigated as a revolutionary method to treat neurological diseases such as epilepsy and Parkinson's.

It's theorised that nanodevices could be used as brain implants which modulate the activity of nerve cells electrochemically, reducing or even ceasing epileptic seizures entirely.

The IN-FET project (Ion Neuromodulation for Epilepsy Treatment), launched in January 2020, is looking at ions such as magnesium, potassium and calcium, the messengers underlying the communication between nerve cells.

Nanodevices could analyse and control the activity of ions and, in particular, their concentration. Through this method it should be possible to modify cell activity, thereby activating or turning them off. In epilepsy, the hyper-excitability of brain cells is due to the flow of ions. Here, the devices could work as an ion trap, so they no longer excite the cells, preventing seizures.

"Epilepsy is one of the most common neurological diseases, affecting 50 million people worldwide," explains Professor Michele Giugliano, director of the Neuronal Dynamics Lab at SISSA (Scuola Internazionale Superiore di Studi Avanzati) in Italy. "Pharmacological treatment is a widespread approach to fight the disease but for many patients medication is no help. Epilepsy drugs prove ineffective with 7% to 20% of children with the condition. Drug resistance amongst adults ranges between 30% and 40%. Alternative experimental therapies also have serious drawbacks."

The project brings together experts in nanoengineering, information technology and neurobiology. Funded by the European programme 'Future Emerging Technologies (FET) Open', the initiative will involve IBM Research, Multi-Channel Systems, the Universities of Geneva and Sheffield and the Italian Inter-University Consortium for Nanoelectronics, among others. Its goal will be to develop implantable devices able to alter the concentration of the most common ions on a microscopic scale. These devices will be able to measure the electrical activity of neurons and actively work to correct it.

"Today's cutting-edge experimental therapies for restoring or repairing brain functions in neural disorders often involve modulating or silencing hyperactive brain circuits," explains Professor Giugliano. "This can be done by pharmacological or genetic manipulations, or by delivering electrical, magnetic or optical stimuli to the brain. All of them, however, come with serious drawbacks, due to the unnatural means to regulate the activity of nerve cells. Our idea is to use what the brain normally uses to function: ions."

More than 40% of status epilepticus patients have adverse outcomes

Finnish researchers have been studying the short-term outcomes of patients treated for status epilepticus (SE) at Kuopio University Hospital. Published in *Seizure* journal, the team found there was a 9% risk of death and a 32% risk of functional loss one month after SE.

The study, carried out by the University of Eastern Finland and the Epilepsy Centre in Kuopio University Hospital, recruited 137 SE patients during 2015.

Fourteen patients were enrolled twice because of another episode of status epilepticus during the study period. Outcomes were analysed one month after discharge by phone interview and a patient record review. It was discovered that the risk of death could be predicted relatively accurately in the emergency room, through the use of SE prognosis tools.

The prognostic scores STESS (Status Epilepticus Severity Score) and EMSE (Epidemiology-based Mortality score in Status Epilepticus) were able to predict survival with a certainty of more than 95% in many episodes of SE with low risk features. These scores were determined from the aetiology and clinical presentation of SE, and the age and comorbidities of the patient.

For the full study visit *bit.ly/32IRGdX*

Fruit-flies shed light on brain plasticity

By studying the fruit-fly Drosophila, researchers at the University of Birmingham have uncovered the genetic mechanisms behind brain plasticity, the brain's ability to change and adapt.

Fruit-flies are a common study model in neuroscience, due to investigators being able to look at their entire nervous system. Their genes can be identified and linked all the way from specific neurons to neural circuits, brain structure and behaviour. The research could pave the way for a deeper understanding of how the human brain adapts over time, including comprehending the link between plasticity and neurodegeneration. It's been understood for some time that human brains are adaptable and plastic. Brains change as new things are learned, and enable people to adapt after limb amputation or brain injury. How it does this, however, is not yet fully known.

The study, published in *eLife* in February, identifies a specific set of genes that are responsible for brain plasticity. These genes encode proteins known as Toll receptors, responsible for receiving and transmitting signals within cells. Tolls are known to play a key role in the body's immune system, but the Birmingham team, led by Professor Alicia Hidalgo, have also discovered they influence nervous system formation. This link between Tolls and brain plasticity is an unexpected development.

Professor Hidalgo says: "The specific molecules we identified are well known for the role they play in regulating the body's immune system. Perhaps in evolution the nervous system and immune system shared a common origin, as they share similar functions. For example, the immune system helps to protect us from microbes, while our nervous system through behaviour plays a role in protecting us from larger dangers, like reacting to threats. It seems brain plasticity re-activates the mechanisms that operate during the formation of the brain in development."

The team found that the Toll receptors were present across different areas of the brain and dedicated to different functions. From there they can influence neuronal number and brain size.

"This arrangement of the Tolls suggests they can work independently of each other, perhaps to control the response to different sensory stimuli such as smell, or vision," says Professor Hidalgo. "These can then be modulated to influence the formation and maintenance of particular types of neurons in response to experience."

It's still unknown how close these mechanisms in fruit-flies match those in a human brain, but the study provides some insight into where to look at to further understand plasticity. "Drosophila is a powerful model organism because we can show that brain plasticity has a genetic basis and identify how genes control this process," says Professor Hidalgo.

For the full study visit: *bit.ly/2TuwJPQ*

Correction

In the last issue of *Epilepsy Professional*, we published an article written by Dr Heather Angus-Leppan titled *Living better, living safer with epilepsy: Time for a paradigm shift*. However, in error we truncated the end of the article. Please find below the fully restored paragraphs. We apologise for any inconvenience caused.

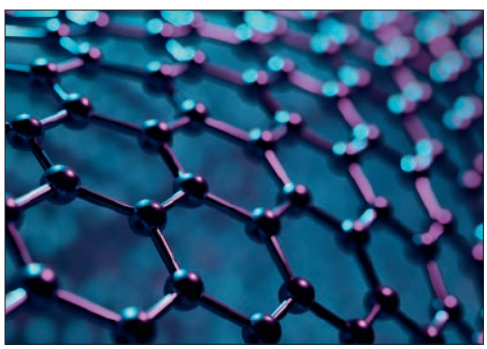
Campaigning and political action

Some think healthcare professionals and charities should stay out of politics, and leave it to the politicians. Should we keep ourselves detached? Clearly political action is complicated, outside the comfort zone of most nurses and doctors, and can be misinterpreted. I argue that if we don't take political action then we accept the status quo and things will not change. Social deprivation, which is clearly linked with higher risk of epilepsy-related deaths, will only change through unified political action. A first step is for joint working and a united voice across the epilepsy charities, starting with the key issues on which there is a clear consensus.

Dr Heather Angus-Leppan, Consultant Neurologist, Royal Free London NHS Foundation Trust; Lead, Epilepsy Initiative Group, Royal Free London; University College London. *heather.angus-leppan@nhs.net*

epilepsy.org.uk/info/sudep-sudden-unexpected-death-in-epilepsy

Graphene-based implant could lead to new epilepsy treatments



Wonder material graphene has been successfully used in recording electrical activity in the brain, potentially unlocking the door for new epilepsy treatments.

These new graphene-based brain implants have been developed by Graphene Flagship partners at the Barcelona Microelectronics Institute (IMB-CNM, CSIC), the Catalan Institute of Nanoscience and Nanotechnology (ICN2), and ICFO (The Institute of Photonic Sciences).

The devices were able to record brain activity at extremely low frequencies and over large areas, unlocking an extra fount of information found below the 0.1 Hz scale.

Electrode arrays have been used to record electrical signals in the brain for decades, mapping activity throughout the various areas. However, these arrays could only detect activity over a specific frequency threshold.

The new technology uses a transistor-based system which amplifies brain signals in situ, before transmitting them to a receiver. By using graphene, the implant can support more recording sites than electrodes can, and it is slim and flexible enough to be used over large areas of the cortex without interfering with normal brain functions. When in place, the implants offer unprecedented mapping of low-frequency brain activity, which is known to carry critical information about the onset and progression of seizures and strokes. These new brain implants could also pave the way for more advanced brain-computer interfaces.

In neurology, this may finally shed much more light about what we only loosely know about the human brain. Applications of this technology could reveal key insights into where and how seizures begin and end, eventually offering up new techniques into the diagnosis and treatment of epilepsy.

"Beyond epilepsy, this precise mapping and interaction with the brain has other exciting applications," says José Antonio Garrido, one of the leaders of the study working at Graphene Flagship Partner ICN2. "In contrast to the common standard passive electrodes, our active graphene-based transistor technology will boost the implementation of novel multiplexing strategies that can increase dramatically the number of recording sites in the brain, leading the development of a new generation of brain-computer interfaces."

"This work is a prime example of how a flexible, graphene-based transistor array technology can offer capabilities beyond what is achievable today and open up tremendous possibilities for reading at unexplored frequencies of neurological activity" commented Kostas Kostarelos, leader of the Health, Medicine and Sensors Division of the Graphene Flagship.

Cannabis-based drug fast-tracked for NHS access

Cannabis-based drug Epidyolex has been fast-tracked into the NHS, which could now help treat around 2,000 people a year.

Doctors are able to prescribe the medicine together with clobazam in adults and children aged two or over with Lennox-Gastaut or Dravet syndrome. Both are severe types of epilepsy and people with either Lennox-Gastaut or Dravet syndrome usually experience several seizures daily.

NICE has issued further guidance which states that the treatment should be reviewed every six months. For people with Lennox-Gastaut syndrome, NICE says treatment should stop if the number of drop seizures does not fall by at least 30% after six months compared to pre-treatment. For people with Dravet syndrome, NICE says treatment should stop if the number of convulsive seizures does not fall by at least 30% after six months compared to pre-treatment.

Based on clinical trials, combined treatment with Epidyolex and clobazam was shown to reduce the number of seizures by up to 40% in some children. This news follows the NICE recommendation in 2019, which stated Epidyolex should be covered under the NHS to help treat Dravet syndrome and Lennox-Gastaut syndrome. It's the first cannabis plant-based medicine for epilepsy to be recommended by NICE. In September, Epidyolex also gained approval from the European Medicines Agency (EMA) for medical use throughout the EU.

New therapy could stop seizures in childhood epilepsies

A type of gene therapy could help those with a rare form of childhood epilepsy. The breakthrough could pave the way for a treatment for rare developmental and epileptic encephalopathies forming from a single genetic mutation.

The gene SCN8A controls a sodium channel that allows neurons to transmit an electric signal. Mutated versions of the gene can cause these channels to become hyperactive, leading to recurrent seizures. The average age of onset of SCN8A-related encephalopathy is just four months old.

Neurologist Miriam Meisler and her team at U-M Medical School have been trying to develop new therapies to treat this type of epilepsy. A new therapy known as antisense oligonucleotide (ASOs) enabled researchers to control gene expression. ASOs are short DNA or RNA molecules designed to block messenger RNA molecules and their encoded proteins. This allows them to control the amount of RNA expressed by mutated genes, dampening their effects on the body. The research team looked into the potential of ASOs for this condition. They developed a mouse model which mimicked the disease in people. They generated a mouse with the same SCN8A mutation found in several patients but with the mutation turned off long enough to test the therapy. By designing mice with an 'on switch' they were able to apply the ASO, and activate the mutation.

"The effect was dramatic and unambiguous," says Meisler. "We had a four-fold increase in lifespan, with added effects of repeated treatments." There was no evidence of low-level seizure activity in the treated mice. The amount of mRNA expressed was reduced by half after ASO treatment, which was well tolerated. The treatment was also effective against other types of epilepsy, including Dravet syndrome. The team is now testing other models to see how effective they are against other seizure types. The team's work is published in *Annals of Neurology*. For the full study visit: *bit.ly/39n4Zn6*

Researchers can 'switch off' seizures

A team of US neuroscientists have discovered they can 'switch off' epileptic seizures in rats. The findings, published online in *Proceedings of the National Academy of Sciences (PNAS)*, provide the first evidence that while different types of seizures start in varied areas of the brain, they can all be controlled by targeting a very small set of neurons in the brain or their tendril-like neuronal axons.

Zeroing in on specific neurons suggests that treatment for epilepsy can be improved, researchers say. For example, the deep brain stimulation used today could be minutely targeted at the cell body of these neurons or at the areas their axons touch, depending on the type of seizure, says the study's senior investigator, Patrick Forcelli, an assistant professor in neuroscience and in pharmacology and physiology at Georgetown University Medical Center (GUMC).

"We have found a major choke point in epilepsy circuits in rat brains that we believe can be harnessed to disrupt the onset of seizures or to stop their propagation within the brain," he says. "Circuit-based therapy for people will help offset the known side effects that come with drug therapy and other techniques."

Researchers have known for about 30 years that while inhibiting a certain area of the brain, the substantia nigra pars recticulata (SNpr) can help stop a seizure. The circuits by which the SNpr controls a seizure have remained unclear. The SNpr is a small area deep within the brain. "It is usually thought to be involved in movement and movement disorders," says Forcelli. "We knew targeting SNpr can stop a seizure, but we didn't know how. Neurons in this area have axonal projections that go to many different parts in the brain."

This study, he says, is built upon the pioneering work done at GUMC in the 1980s when researchers, led by Karen Gale, PhD, "built a metaphorical Rand McNally-type atlas of neuronal pathways involved in seizures and epilepsy - these maps have moved forward both basic biology and for pharmacological treatment of epilepsy." The aim of his research is "to make a "Google maps" version with higher resolution and the ability to zoom in on each address, to improve brain stimulation therapy," says Forcelli.

With his team, Forcelli used four models of experimental epilepsy in seizure-prone rats, designed to reflect a different type of seizure (absence, forebrain tonic-clonic, brainstem tonic-clonic, and limbic) seen in human epilepsies. They were able to stop these seizures by placing light-sensitive ion channels into neurons in the SNpr; when exposed to light, the neurons can be turned on or off. They found that seizures could be turned off by either silencing activity of the SNpr cell bodies or, in some cases, the areas that these neurons project to.

"We can't target therapy if we don't know how the circuits work. Discovering that silencing one area that a SNpr projects to can turn off specific seizures suggests a much more targetable therapy. For example, deep brain stimulation could be aimed at that area," Forcelli says.

"These findings clarify a long-standing question in the field: the role these individual SNpr neural pathways play in the control of seizures," he says.

The findings are now published in the online journal *Proceedings of the National Academy of Sciences*.

For the full study visit *bit.ly/30rKFxf*

Study shows link between brain activity and memory

A US study has revealed how memory and abnormal brain activity are linked in patients with epilepsy who often report problems with memory. The data show that abnormal electrical pulses from specific brain cells in these patients are associated with a temporary kind of memory disruption called transient cognitive impairment.

Ueli Rutishauser, a neurologist from Cedars-Sinai, and his team investigated electrical activity in the hippocampus by implanting electrodes in the brains of 11 adult epilepsy patients and having them perform a memory task.

Published in *JNeurosci,* the results showed that interictal epileptiform discharges (IEDs) temporarily changed the firing of individual cells in the hippocampus. This change in the activity of the cells in turn disrupted the patients' ability to recall whether they previously had seen a presented image. Epilepsy patients commonly experience IEDs between seizures and report transitive cognitive impairment. However, it has so far remained unknown why IEDs cause such impairment.

During the task, the extent of memory disruption was related to exactly when an IED occurred, with the most severe impairment caused by IEDs that appeared within two seconds of the patient trying to recall an image, Rutishauser said. He added that the effect was specific to recall and that the presence of IEDs did not disrupt the encoding of new memories.

For the full study visit *bit.ly/382Wr3o*

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epilepsy.org.uk/yourchild

Your child and epilepsy

Grow your confidence managing epilepsy in your family

Your child and epilepsy is a new online course for parents and carers of children with epilepsy. It's been developed with parents, epilepsy nurses and psychologists.

This course is a helping hand to support families on their epilepsy journey. It's full of advice and stories from parents. It aims to give parents and carers the confidence, skills and knowledge to support their child to manage their epilepsy.

There are eight parts that cover:

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- The impact of epilepsy on family life
- Your child's wellbeing
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- Growing up and independence
- Sources of help and support

Free course

The course is free and flexible. It can be accessed at any time on a computer, tablet or smartphone with internet access.

Leaflets about the course to give to families can be requested by emailing **nurseorders@epilepsy.org.uk**

To view the course go to: **epilepsy.org.uk/yourchild**
Get in touch **learning@epilepsy.org.uk**

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Zebrafish models in epilepsy research

The tiny fish making a big splash

Dominic Burrows and Richard Rosch look to the fish tank to understand the intricate dynamics of epilepsy

Introduction

Epileptic seizures are characterised by abnormal electrical activity disrupting brain function. Yet our understanding of how this abnormal brain activity is generated remains limited. This is not least because of the limited data we usually have access to: conventional EEG records brain activity through layers of bone and skin, since they are placed on the scalp. Even in the context of epilepsy surgery, where electrodes are placed inside the skull, we can usually only measure the average activity of whole brain regions acting in unison.

Epileptic seizures however, emerge from the abnormal activity of groups of neurons in the brain which we cannot directly measure in patients. Using animal models of epilepsy in which we can capture cellular pathology has enabled us to identify the cellular mechanisms behind abnormal brain dynamics recorded using EEG. An animal that has already made a big splash in epilepsy research is the larval zebrafish. Zebrafish have quickly become popular model systems in translational neuroscience because they enable recordings of both single-cell and whole-brain activity during seizures.

In this article we will outline some of the exciting new approaches in epilepsy research now possible in zebrafish, and how these cutting-edge approaches may lead to novel treatments for patients with epilepsy.

A crystal-clear window into brain function

Zebrafish are fast emerging as a model of interest for the study of epileptic seizures. An initial study reported that administration of a seizure-causing drug (pentylenetetrazole, PTZ, which blocks inhibitory synaptic GABA receptors) caused seizures even in larval fish (Baraban et al, 2005). Applications of zebrafish in epilepsy research have since grown substantially.

In recent years, studies have used zebrafish to study seizure mechanisms (Rosch et al, 2018), genetic mutations that cause epilepsy in patients (Liao et al, 2019), and develop pharmacological drug screens for novel epilepsy treatments (Baraban et al, 2013). In fact, a recent review suggests that zebrafish may offer more reliable clinical relevance and pharmacological predictability than conventional rodent models (Griffin et al, 2018).

The zebrafish is a freshwater fish indigenous to South Asia, named for its horizontal blue stripes (Figure 1A). They reach 5cm in length as adults and have a lifespan of ~2.5 years. Eggs are laid by females and fertilised by male fish outside of the body. Only three days later, larvae will hatch, and start independently feeding at five days' post-fertilisation (DPF). At seven DPF, the larval zebrafish brain is simple (~100,000 neurons, one millionth of the human brain) and small (<1mm3 in volume), but shares key neuroanatomy and functional features with mammalian counterparts, producing a variety of complex behaviours (Figure 1B).

Studying the zebrafish brain at this early stage has multiple advantages: the larvae's external development enables the visualisation of normal and abnormal neurodevelopment from the start of life. Furthermore, the transparency of the larvae allows unhindered optical access into the developing brain (Figure 1B)

Zebrafish have been used to study seizure mechanisms, genetic mutations and develop drug screens for novel epilepsy treatments

(Antinucci et al, 2016). Combine this with recent advances in neuronal recordings with fluorescence-based light microscopy and we get whole-brain recordings of neuronal activity at single-cell resolution, even in freely

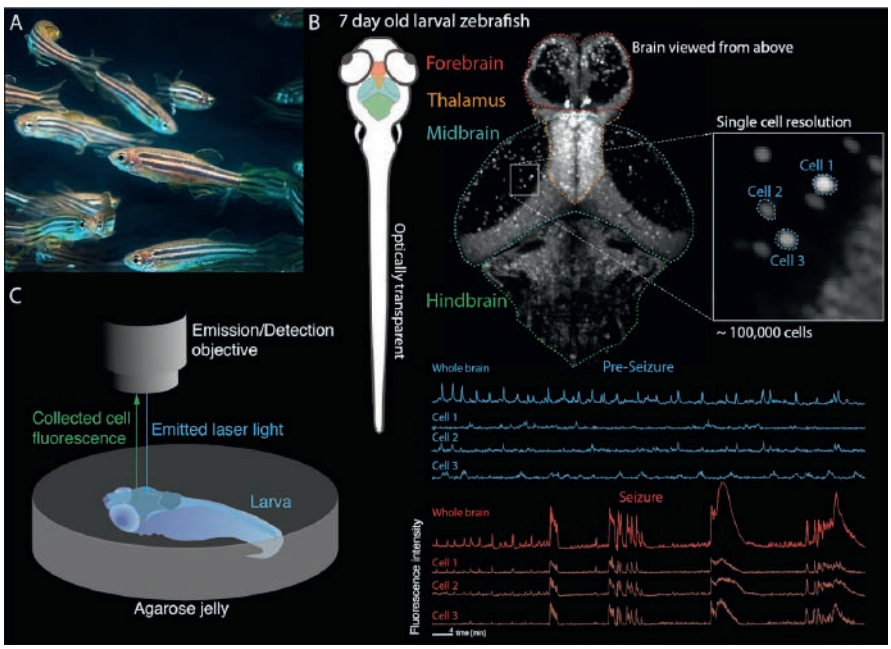

Figure 1: Calcium imaging of larval zebrafish
(A) Adult zebrafish. Photo by Lynn Ketchum, courtesy of Oregon State University.

(B, left) A seven-day old larval zebrafish viewed from above, illustrating the transparency of the embryo allowing visualisation of the entire brain.

(B, middle) A high resolution stack of the 7dpf zebrafish brain captured with a two-photon microscope, shown with gross anatomy traced out.

(B, right) Zoomed in image of three example cells.

(B, bottom) Fluorescence traces over time of the whole brain and individual cells (from B, right) which show large increases in fluorescence intensity and cellular synchrony during seizure (red) compared with pre-seizure (blue).

(C) Schematic of the fluorescence microscopy setup. The larval fish is restrained in agarose jelly while alive. The objective scans emitted laser light (blue) across the zebrafish brain exciting fluorescent proteins, causing fluorescence emission (green) which is detected via the objective.

behaving animals, a feat currently impossible in rodents (Figure 1B, C) (Ahrens et al, 2013).

When exposed to seizure-inducing drugs, importantly, various chemo-convulsants (PTZ, kainic acid) induce brief, inter-ictal and prolonged, multi-spike ictal discharges in zebrafish larvae alongside convulsive movements (Baraban et al, 2005). These behavioural and brain abnormalities are corrected following the administration of anti-epileptic drugs such as benzodiazepines and valproate (Afrikanova et al, 2013). Therefore, zebrafish can recapitulate key electrophysiological and behavioural features of seizures. However, these induced seizure models are unlikely to faithfully map on to seizure phenotypes from epilepsies with genetic aetiologies. With this in mind, various genetic models of epilepsy in zebrafish have been developed, which may harness the strengths of zebrafish as a model for the development of targeted treatments.

A model for the age of epilepsy genetics

The advent of genomic investigations in clinical neurology has brought with it an explosion in the number of patients whose epilepsy is now diagnosed as monogenic, i.e. being caused by a single mutation. This is particularly striking in the childhood epilepsies: population-wide data shows that approximately one quarter of children under three who have epilepsy have a diagnostic single gene mutation. These mutations are often de novo, i.e. new mutations which arise randomly rather than through inheritance, and the specific gene variation is so rare that they often only occur in one single patient. Yet about 85% of genetic epilepsies are caused by mutations which occur within 10 of the most common 'epilepsy genes' (Symonds et al 2019).

Data shows approximately one quarter of children under three who have epilepsy have a diagnostic single gene mutation

This diversity in the genetics of the epilepsies leaves us with an open question: what are the mechanisms that translate genetic causes to disruptions of whole-brain dynamics? Patients with similar genotypes may

have very different phenotypes, and patients with apparently similar epilepsies may carry causative mutations in unrelated genes. Over the past two decades, much progress has been made in addressing this challenge by deeply characterising human phenotypes associated with different genetic mutations ('top-down' approach, e.g. Wallace et al 2001, Sadleir et al 2017), or by studying in detail the effects of specific mutations on synaptic and neuronal function ('bottom-up' approach, e.g. Peters et al 2016, Ben-Shalom et al 2017).

In the current genetic era in epilepsy research, animal models offer the unique opportunity to combine the power of these two approaches to identify the mechanisms underlying epileptic brain dynamics in genetic epilepsies. With appropriate models, we can study both the whole-brain phenotypes, and their neuronal and synaptic causes concurrently. This is particularly the case in zebrafish, which not only allow advanced neuroimaging, but also genetic modification at scale. For example, in one unprecedented study, 132 different zebrafish lines were generated, each carrying knockout mutations for a single known human risk gene for schizophrenia. This allowed brain imaging and behavioural phenotyping across the diversity of genetic backgrounds associated with neurodevelopmental disorders. Similar studies are underway for epilepsy genes in zebrafish – and already today, there are a range of zebrafish models of human genetic epilepsies that have seizures as a result of their mutation in an 'epilepsy gene' - including DEPDC5 (Swaminathan et al 2018), GABRA1 (Samarut et al 2018), GABRG2 (Liao et al 2019), SCN1A (Baraban et al 2013), STX1B (Schubert et al 2014), TPP1 (Mahmood et al 2013) and more. Most of these genetic fish lines show paroxysmal convulsive movements in the context of epileptiform discharges when local field potentials are recorded through invasively placed electrodes. While fish do not have a cerebral cortex, seizures recorded from their midbrain regions nevertheless show fundamental homologies in their onset and offset dynamics to ictal recordings in humans and rodent models of epileptic seizures (Jirsa et al 2014). Furthermore, seizures are effectively treated with anti-epileptic medication in a number of these genetic lines. The first treatments identified from screening novel putative drugs in genetic zebrafish lines are now being trialled in patients, closing the translational loop (Griffin et al 2017).

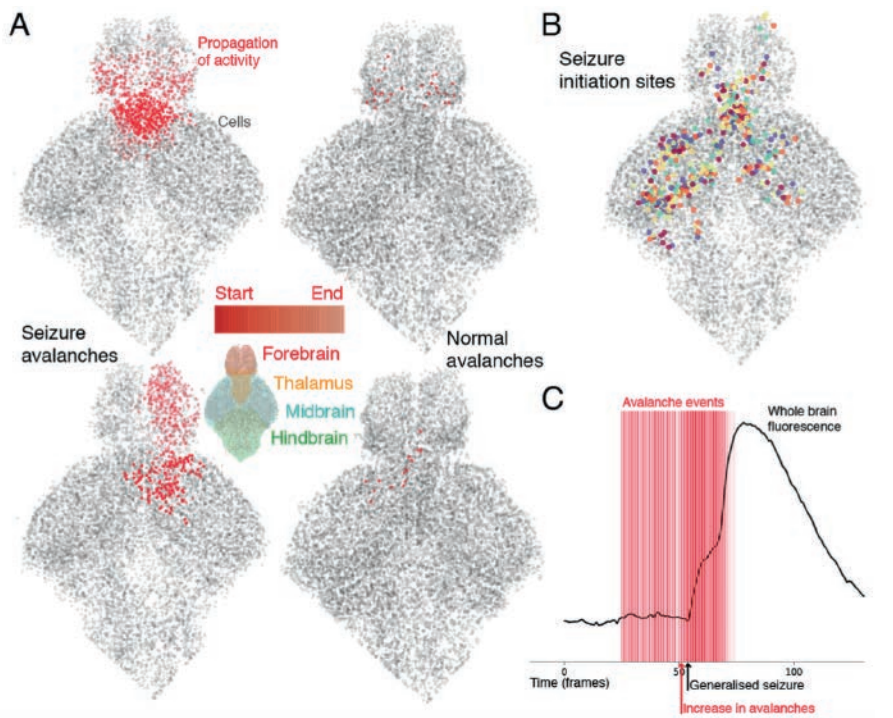

Figure 2: Avalanches of activity
(A) Avalanches, neuronal activity spreading throughout the brain, are visualised as cells coloured in red, with lowering colour intensity as the avalanche spreads. Avalanches which occur during seizures (left) are much larger and longer than avalanches corresponding to resting brain activity (right).

(B) Avalanche events which correspond to seizure events, plotted over the zebrafish brain by their spatial location (coloured randomly).

(C) Whole brain fluorescence (black) during a generalised seizure event, shown by a large increase in fluorescence. Distinct avalanche initiation points are plotted (red) demonstrating that an increase in avalanche events precedes the generalised seizure (red).

Seizures at single cell resolution
With the emergence of novel genetic models of epilepsy and the development of state-of-the-art

fluorescence microscopy techniques, we can begin to probe the cellular mechanisms underlying seizures. This has been made possible by the development of fluorescent, genetically-encoded reporters of cellular activity. These reporters are green fluorescent proteins (GFP) found in jellyfish that emit light following exposure to specific light wavelengths (Orm et al, 1996). Using genetic engineering we can modulate GFP structure so that it only glows following calcium binding, and express the re-structured protein (called GCaMP) in zebrafish neurons (Chen et al, 2013). In this way, the fluorescence intensity in a cell is proportional to intracellular calcium and thus can be taken as a measure of cell activity (Figure 1B). Using GCaMP in combination with powerful laser microscopes in an optically transparent brain allows for deep imaging of the entire brain, with single cell resolution across most neurons in the brain (Figure 1C) (Ahrens et al, 2013; Bianco et al, 2015).

Such approaches have already provided useful insights into the pathology of seizures. Studies have reported that seizures emerge as cellular ensembles, groups of cells that fire together, which are composed of more cells that are more distantly connected than during physiological activity (Liu et al, 2019). Multiple studies have also reported increases in synchrony across cells in the brain, even at great distances during epileptic seizures in zebrafish (Diaz Verdugo et al, 2019). This provides cellular-level evidence for the notion of seizures being 'hypersynchronous' events – which in clinical EEG may present itself as increased phase-locking between channels in ictal recordings. Furthermore, computational models of zebrafish seizures have helped to explain how changes in synaptic brain connectivity can result in the emergence of seizures (Rosch et al, 2018).

Given their amenability to genetic modification, these approaches can be taken further. Studies have also genetically re-engineered the zebrafish genome to express fluorescent proteins only in specific cell types – targeting for example neuronal subpopulations expressing specific neurotransmitters. Such approaches have shown that glial cells may contribute to widespread neuronal synchrony across large distances during generalised seizures (Diaz Verdugo et al, 2019). In this way, we can begin to understand the effect of different cell types in seizure generation. Identifying cell types preferentially impacted in different genetic epilepsies in this way has the potential to identify novel targeted treatments for patients, based on modulating specific neuronal subpopulations based on their individual gene mutation.

Avalanches of activity

One particular line of research in our lab is understanding the balance between excitation and inhibition in epilepsy. In the healthy brain, excitation and inhibition is balanced: activity spreads partially across neuronal networks in the brain, but will self-terminate, due to balanced local inhibition (Lombardi et al, 2012). These patterns of spreading activity have been described as avalanches, and much work has gone into understanding the biological basis of these events across species, including humans, mice and zebrafish (Beggs et al, 2003; Ponce-Alvarez et al, 2018; Tagliazucchi et al, 2012).

A key feature of epileptic seizures is a supposed loss of excitation-inhibition balance, tipping the scale towards more excitation. In our calcium imaging data of the zebrafish brain at rest and during epileptic seizures, we can measure the spread of avalanches from cell to cell, across the entire brain (Figure 2A). Interestingly we find much longer and larger avalanches during seizures, suggesting a loss of local inhibition and supporting the hypothesis that excitation-inhibition balance is lost in epilepsy. In fact, individually self-limiting, local avalanches may even precede and ultimately cause more global transitions into generalised seizure states (Figure 2C).

While this data is preliminary, we are beginning to look at different genetic models of epilepsy to understand how avalanches may be affected differently by different mutations. Of particular interest is understanding how different types of mutations affecting diverse neuronal mechanisms, can lead to altered brain dynamics and ultimately epileptic seizures. In fact, given that mutations affecting fundamentally different synaptic processes can lead to similar seizure types in patients, we hypothesise that there is a limited, convergent set of mechanisms leading to seizures. For example, one of the most severe childhood epilepsy syndromes, Dravet syndrome, which is caused by a sodium channel mutation, has shown to preferentially impair inhibitory neurons in the brain. If excitation-inhibition balance is altered then we should also find larger avalanches in Dravet zebrafish mutants, which could potentially be corrected by increasing inhibition in the brain (Martin et al, 2010). Furthermore, if we can demonstrate that avalanches are increased across many different mutations, then a loss of excitation-inhibition balance may be a key unifying mechanism to explain seizures in patients.

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From fish tank back to bedside

Zebrafish allow an unprecedented look into multiscale dynamics of the epileptic brain. There are clear limitations to the model – e.g. the lack of cerebral cortex, the early developmental stage at which most of the imaging takes place, and some inherent differences between human and zebrafish genome, to name but a few. Yet their small size, transparency, and amenability to genetic modification opens new avenues for translational epilepsy research.

These advantages are already being exploited in a range of rare diseases – where genetically modified zebrafish 'avatars' of patients with rare disorders are used to screen for potentially useful treatments rapidly (Culley et al 2019). Such approaches have been streamlined such that they can provide insights for treatment of individual patients in a 'bedside to fish tank, and back' approach (Li et al, 2019). Even imaging brain function is now scalable, with semi-automated calcium imaging in zebrafish identifying key signatures of SCN1A-related epilepsies that can be rescued with specific pharmacological interventions (Ghannad-Rezaeie et al, 2019).

But if we want to improve treatment for patients with genetic epilepsies, we will likely need to think of novel approaches alongside these above examples of reusing existing candidate drugs identified from drug screening. Targeted neuromodulation, for example, is already being used in patients with focal epilepsies – with a trial for optogenetic modulation awaiting clinical trial in patients. Transparent zebrafish 'avatars' of multiple genetic epilepsies that allow for whole-brain imaging and concurrent optogenetic control may be the perfect next step for identifying which patients with genetic disorders may benefit from future targeted neuromodulation therapies.

Often progress in neuroscience comes with the development of new tools. For epilepsy research, we are now in the lucky position of having several such tools come together: genomic diagnostic, advanced microscopy, and the molecular genetics necessary to harness both in this fascinating little fish, that will tell us so much about the epileptic brain.

Dominic Burrows, PhD Fellow, Richard Rosch, Clinical neuroscientist and paediatrician, King's College London

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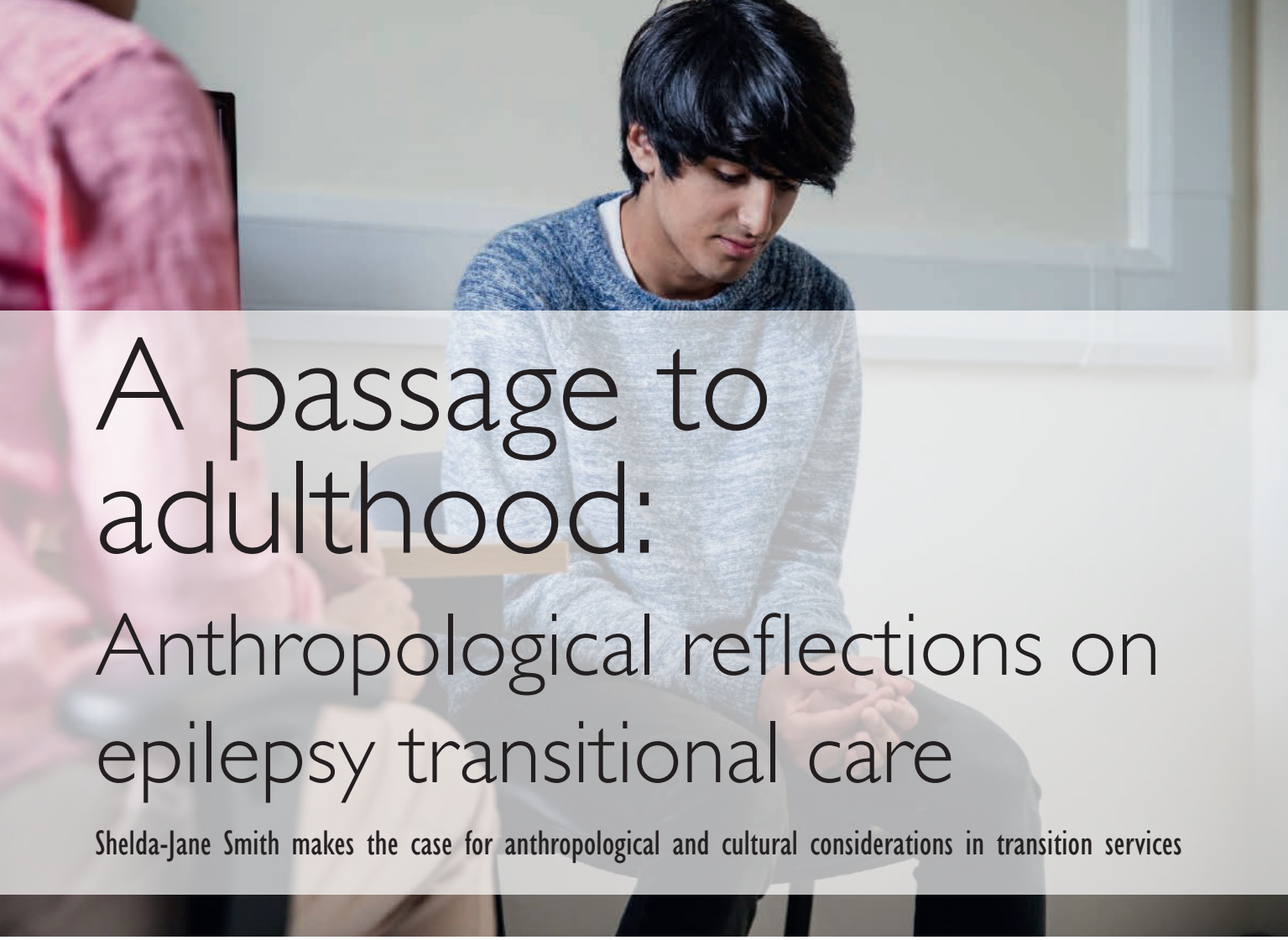

A passage to adulthood:

Anthropological reflections on epilepsy transitional care

Shelda-Jane Smith makes the case for anthropological and cultural considerations in transition services

There is a wealth of clinical literature documenting the need for improved epilepsy transitional services. However, while many studies have looked at epilepsy transitional care from within the broader discipline of health services research, such as applied psychological and clinical sciences, I chose to examine the practice of epilepsy transitional care from an anthropological perspective. The rationale for such an approach was based upon the need to explore the experiences of providing and receiving care in order to clarify how transitional care practices shaped patient and carer experiences. Furthermore, this study paid particular attention to the experience of transitional care for those with epilepsy and a co-morbid learning disability (henceforth referred to as ELD).

In this article, I wish to draw attention to three key insights taken from this study that may assist in the future development and delivery of epilepsy transitional care. I share these insights in the hope of generating awareness of the needs of young people with epilepsy and a comorbid learning disability, as well as their parents and their clinicians.

Epilepsy, transition and disability: An anthropological approach

From 2014 to 2016, I carried out ethnographic fieldwork that centred on a teenage epilepsy clinic [TEC] in England and any relevant clinical, social work and research activities associated with this TEC. The fieldwork revealed how institutions sought to address the so-called 'challenge' of transitional care. Within the transition literatures, these 'challenges' have tended to overemphasise the troublesome nature of adolescence, therefore making the adolescent patient population appear problematic. However, examining this care practice from a social scientific perspective enabled an understanding of the sociocultural influences that are also at play. For example, this study explored how the 'challenge' of epilepsy transitional care was predicated on funding, clinical commissioning, the culture of biomedicine, and sustained effort and motivation of a small number of epilepsy clinicians. In other words, the challenge of epilepsy transitional

healthcare was much more than the oversimplification that adolescents are a problematic patient group.

The rhetoric versus the reality

Analysis of transitional care practices revealed that the concept of traditional rites of passage (Turner, 1969; Van Gennep, 1909) were built into the practice of transitional care [see below field note extracts]. Briefly speaking, rites of passage consist of separation, transformation and reintegration phases that were reflected in the three-step approach to this particular TEC under study. However, while rites of passage were useful for guiding the transitional pathway from child to adult services they did not, however, map on to the experiences of transitioning for young people with ELD. For the patient group and their carers, a tension was created between the model of transitional care and their experiences of transitioning.

Furthermore, data revealed that the concepts of independence and responsibility were significant driving forces in the development and implementation of epilepsy transitional care. For example, within interviews with health professionals, adolescence was upheld as a period of increasing psychological, emotional and social independence. This meant that the practice of transitional care appealed to sociocultural norms concerning responsibility and citizenship upon entering adult services and adulthood. Yet, with these concepts emerging as the prevalent social values that transitional care was organised around, some patients and their families inevitably felt marginalised by the transitional care that they had received. Consequently, there was a schism between the ideals – or rhetoric – of transitional care and the reality of caregiving for those with ELD.

Concepts of independence and responsibility were driving forces in developing and implementing epilepsy transitional care

Independence

Considering that transitional care is embedded within a society that values individuals who are independent, it was unsurprising to find that independence became a key feature of this care practice. This was evidenced through transition care protocols that encouraged young people to attend clinic without an accompanying parent. The intention behind such suggestions was to foster patient independence. However, while this may be beneficial for some teenage patients, interview data showed it to be a significant concern for parents of those with ELD (See Table 1).

Contrasting the below interview extracts we see that independence, while a significant feature of adolescent developmental psychology, is also embedded within wider society and culture. Here we see references to an unequal distribution of healthcare infrastructure and clinical resources (Street, 2014; Street & Coleman, 2012), between paediatric and adult services. For example, longer clinic appointments within paediatric services, larger, and more accommodating physical space in the paediatric consultation rooms, allowing for several family members to attend the consultation together. Therefore, the care that young people are met with when they transition to adult services is markedly different from what they have previously received in a paediatric setting. This suggest that the cultures of care (i.e. the differences between of paediatric and adult services) play a part in this transition 'challenge'.

Responsibility

Significant to the process of transitional care was the notion of the

Table 1
Interview regarding independence during the transitional period.

Rhetoric	Reality
Neurologist [paediatrics]: At least in paediatrics we're hardwired to deal with families but in adults [services] they are often pushed for time and need to do their job as efficiently as possible. Parents unfortunately can get in the way. Don't get me wrong they can get in the way over here too but there's more space for that here.	Mother 1: Careers advice, housing, all these health plans and reviews that never happen. If I'm honest, kids like our son are just left to fend for themselves. This kind of thing [transitional care] is written for kids who are going to go on and have some sort of life. Where's the advice for people like us? We'll be caring for him until forever. Father 1: It makes sense to put all effort into 'normal' kids or those with mild difficulties because they're the next generation going into society, but he doesn't really go into society, does he? All this promise of health plans and reviews we just take it with a pinch of salt. Mother 1: When you've got a kid with disabilities, over the years you learn to lower your expectations of services and the government.

'good patient'. In the context of epilepsy, the good patient was the adolescent who engaged with their healthcare needs in a way deemed responsible and self-caring (see Table 2). Furthermore, within the data, notions of the 'good patient' and 'patient responsibility' were often tied up with what it means to be a good citizen which was often considered in social and economic terms. Crucially, responsibilised approaches to transitional care (i.e. making patients become more responsible for their own healthcare needs) was something that parents in the study felt were burdensome as the young people they cared for would never fit this ideal of the responsibilised patient.

These interview extracts highlight the problems within a responsibilised approach to transitional care for young people with ELD. However, both extracts speak of how care is practised against the backdrop of an increasingly constrained and underfunded national health service. This point suggests that transitional care adheres to the principles of a UK healthcare system that is based upon a moral economy, whereby obligations of citizens must be fulfilled to 'contribute', 'help' or 'ease the burden' of a publicly funded healthcare service (Kierans, 2018).

These quotes illustrate how clinicians, patients and their families were all caught within a system that did not allow for the extra needs, care and attention that was required by patients with profound and multiple disabilities as they moved into adulthood.

Acknowledging diversity in adolescent epilepsy

Studies within medical anthropology and the sociology of science prove useful for entangling the variety of (non-clinical) influences that shape contemporary clinical practices. For example, within transitional care discourse, psychological models of adolescence and normative trajectories of development were prevalent. Here, I am reminded of Fernando Vidal's (2009) essay *Brainhood, anthropological figure of modernity*, where he argues that the expansion of neuroscience in explaining human experience has produced the notion of 'brainhood' – the idea that humans are ultimately their brains. However, sociologist Nikolas Rose (2007) has argued that the proliferation of the neurology and psychology disciplines[1] is responsible for reshaping social policies, practices and organisation. As a result, we are beginning to witness a rise in the practical application of normative neuro-developmental pathways that likely require a more nuanced consideration of adolescent development. Crucially, as this study shows, there is a need to recognise the diversity of those who are considered neurodevelopmentally atypical.

From this study there are three key lessons that might aid the future development of transitional care. Firstly, transitioning has to be considered a negotiated and situated process. That is to say, transitional care is not simply moving from one service to another but is predominantly about patients moving into a new stage of life – something that is unique to us all (Beresford, 2004). Secondly, if

Table 2
Interview extracts exemplifying views on patient/parent responsibility during the transitional period.

Rhetoric	Reality
Neurologist [Adult Services]: We all need to take care of ourselves, not just those who are ill. When they [young patients] do self-care, and eventually take responsibility for their own health, everyone benefits. Knowing their type of epilepsy, medication, or even just the phone numbers of the hospital, all these little things, decreases the chance of making things worse in the future…. What's good for the patient is good for the taxpayer is good for everyone.	Father 2: When he was younger things ran smoothly but now everything seems to be getting taken away from him and, in a way, we either have to be ready to fight for that care or learn to let it go. You have to pick your battles. For example, one [adult services] nurse didn't know about specialist LD services in our area and I mean at times we've felt that we're doing their job for them…I think they expect you or your kids to know this sort of thing.

transitional care is to be inclusive, then the diversity of disability must be recognised within systems of care. The all too neat classifications of 'disability' and 'adolescence' discounts the complexities and contradictions of the range of cognitive capacities within a young epilepsy population. Finally, this study suggests that we need alternative ways of conceptualising adolescence in the context of disability and long-term conditions such as epilepsy. Transition services in this study were time-limited; i.e. transition occurred when the individual 'aged-out' of paediatrics. However, aged-defined approaches to care were not necessarily about supporting the process of transitioning to adulthood but more about supporting the ongoing structure of institutional clinical care. Crucially, this research shows that the problems or challenges associated with transitional care were not so much about the difficulties of adolescents. Rather, the challenge of transition also lay in cultural differences between clinical settings, the commissioning of clinical services and socio-cultural articulations of childhood, adolescence and adulthood. Each of these aspects had significant bearing upon how epilepsy transitional care was developed, practised and experienced.

Shelda-Jane Smith
PhD researcher
Institute of Population Health Sciences, The University of Liverpool

Shelda-Jane Smith is a researcher in psychological anthropology with interests in neuropsychology, adolescence and epilepsy.

[1]Where it was once psy that lent authority and expertise, it is now increasingly the case that the neurosciences are offering the dominant explanations of human behaviour (Rose & Abi-Rached, 2013). Rose and Abi-Rached (2013), employ the terms 'neuro' and 'psy' to signify the wide family of disciplines that fall under these prefixes.

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The impact of childhood epilepsy with centro-temporal spikes on learning and the implications for treatment – a literature review

CECTS occurs at an important time in a child's neurodevelopment. Sarah Collins takes a closer look at the evidence and options to promote the best outcomes.

Childhood epilepsy with centro-temporal spikes (CECTS), previously known as benign epilepsy with centrotemporal spikes (BECTS), accounts for 15-25% of all childhood epilepsy usually affecting children aged 3-14 years (Tovia et al. 2011; Vannest et al. 2015). It is characterised by relatively infrequent, brief focal seizures with hemifacial motor and somatosensory symptoms, often affecting speech, sometimes evolving into tonic-clonic seizures (Tacke et al. 2016; Vannest et al. 2015). Seizures generally occur in sleep or upon waking, but can occur during the day (Callenbach et al. 2010). The EEG typically shows high voltage centrotemporal spikes, often followed by slow waves activated by sleep, while clinical imaging is routinely normal (Callenbach et al. 2010; Gaillard et al. 2011).

CECTS has been traditionally regarded as a benign epilepsy with excellent prognosis as seizures are infrequent and cease by adulthood (Wickens et al. 2017). The majority of patients do not require treatment and many parents actively choose not to start their child on medication unless seizures are frequent or impact on activities of daily living (Miziara et al. 2012). However, while studies suggest that children with CECTS have normal intellectual capacity, there are a large number of studies demonstrating evidence of language, behavioural and cognitive deficits occurring in children with CECTS, which suggests that this epilepsy syndrome may have a bigger impact on children than previously recognised (Datta et al. 2013; Vannest et al. 2015). Jurkevičienė et al. (2012) suggest that these difficulties are often present early around diagnosis, and for clinicians working with young people with CECTS, it is important to have awareness of these issues to best support children and young people.

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Impact on learning

It is well recognised that epilepsy impacts on a child's learning, attention and memory, but Vannest et al. (2015) suggest that particular epilepsy syndromes have their own specific profile of cognitive difficulties that clinicians and educators need to be aware of.

Most learning difficulties identified in CECTS patients are related to language development and function (Goldberg-Stein et al. 2010). The abnormal interictal epileptiform discharges that cause the seizures in CECTS typically originate in the centrotemporal region of the brain. This region is directly related to speech and language functioning so it is logical to assume that seizures arising in this area could impact on the development of brain networks involved in language and cognitive functioning (Ebus et al. 2015; Neri et al. 2012; Ofer et al. 2018). In particular, studies have demonstrated a variety of problems with reading, learning of auditory-verbal material and phonological awareness (Ebus et al. 2015; Neri et al. 2012).

Studies by Ay et al. (2009), Miziara et al. (2012) and Filippini et al. (2013) suggest that reading ability such as accuracy and speed was more likely to be impaired in children with CECTS when compared to controls. Jurkevičienė et al. (2012) and Goldberg-Stein et al. (2010) compared language function in CECTS children against a control group and found that the CECTS children had more difficulties with verbal fluency and comprehension, which could impact on information retrieval from memory. Monjauze et al. (2011) found that

CECTS children had deficits in expressive and receptive language as well as sentence production which can impact on the development of literacy proficiency in children.

Vannest et al. (2013) compared a small group of CECTS children against a control group in neuropsychological testing of language functions. The study showed that the CECTS group had only mildly lower language skills, along with lower levels of visuospatial skills and processing speeds, although Vannest et al. (2013) failed to collect full neuropsychological and functional MRI (fMRI) for all the children in the study. However, of some interest to the Vannest study was the fMRI data that showed different patterns of brain activation during language processing between the two groups. Children without epilepsy showed predominantly left-sided brain activity during semantic word tasks, whereas the CECTS group showed higher activation in the right hemisphere. Both Monjauze et al. (2011) and Lillywhite et al. (2009) also identified atypical epileptiform discharges on either EEG or fMRI associated with expressive language assessments, suggesting that reorganisation of the neural network for language in CECTS children may occur, possibly as a result of persistent epileptiform discharges.

A number of studies suggest that IQ values are normal in children with CECTS (Monjauze et al. 2011; Nissenkorn et al., 2017). Garcia-Ramos et al. (2015) found in their study that CECTS children who were seizure-free had higher IQ scores than CECTS children who continued to have some seizures. However Vőlkl-Kernstock et al. (2009) failed to find a relationship between seizure freedom and IQ. Wickens et al. (2017) note that many of the studies looking at the cognitive impact of epilepsy exclude children with low IQ, so it is possible that this supposition of normal range IQ is not entirely accurate.

One of the areas of cognition that is often impacted by epilepsy is memory and this is often associated with difficulties in academic achievement in children with all epilepsies (Menlove and Reilly 2015). Northcott et al. (2007) found CECTS children showed impairments in both visual and auditory memory and Miziara et al. (2012) identified impairments in auditory memory in their study. Neri et al (2012) and Northcott et al. (2007) reported that the children with CECTS in their studies were more likely to have deficits in executive cognitive functioning, particularly in the areas of reasoning and planning which impacts on verbal and auditory memory.

However, Lopes et al. (2014) found that deficits in memory skills were minimal in CECTS children and appeared linked to poor attention.

One of the areas of cognition often impacted by epilepsy is memory and this is often associated with difficulties in academic achievement

Vőlkl-Kernstock et al. (2009) also reported increased difficulties in attention and social skills (particularly reading non-verbal cues and emotions in others), as well as aggressive behaviour, but this was based on subjective parental responses and not independently assessed by the authors.

Tovia et al. (2011) carried out a large retrospective study of 196 children. They found that 31% of the children with CECTS had attention deficit hyperactivity disorder (ADHD), though again, the children studied were not independently reviewed; merely their records studied. However, smaller and more recent studies by Kim et al. (2014) and Bektaş et al. (2019) also suggest that children with CECTS may have an increased risk of ADHD, poor attention and impulsive behaviours.

Risk factors for learning difficulties in CECTS

Filippini et al. (2013) proposed that increased frequency of nocturnal interictal epileptiform discharges was associated with increased risk of poorer outcomes in neuropsychological testing, in particular verbal functioning. Ebus et al. (2011, 2015) also reported an association between nocturnal interictal rolandic discharges and impaired reading skills, replicating similar findings to earlier studies by Ay et al. (2009) and Northcott et al. (2007). However other studies have failed to demonstrate a relationship between language function and interictal discharges suggesting that epileptiform activity alone might not be an important determinant of cognitive difficulties in CECTS (Goldberg-Stern et al., 2010; Jurkevičienė et al., 2012; Miziara et al., 2012; Nissenkorn et al., 2017; Tedrus et al., 2009; Vőlkl-Kernstock et al., 2009). Nevertheless it is logical to hypothesise that the interictal nocturnal discharges typically seen in CECTS have the potential for disrupting memory consolidation in sleep, therefore leading to academic underachievement (Asadi-Pooya et al. 2019).

An older study by Chaix et al. (2006) argues that children with increased epileptiform activity in sleep EEG were less proficient in semantic verbal fluency than children with minimal discharges. Semantic verbal fluency is typically a frontal

lobe function, and although frontal lobe interictal epileptic discharges are not characteristically seen in CECTS patients, the authors suggested that abnormal interictal discharges in other areas of the neural cortex may lead to language dysfunctions (Chaix et al. 2006).

Very few studies consider age of seizure onset or seizure frequency. Both Miziara et al. (2012) and Ebus et al. (2011) failed to identify any correlation with seizure frequency and cognitive difficulties in the CECTS patients they studied. Jurkevičienė et al. (2012) studied 61 children with CECTS and suggested that the younger the child was at seizure onset, the poorer they scored in language function testing. These findings were also mirrored by Filippini et al. (2013). Brektas et al. (2019) reported older age of seizure onset was linked to increased risk of ADHD symptoms in CECTS children. In contrast, Callenbach et al. (2010) found no correlation between age of onset and language or cognitive functioning.

Long-term outcomes in CECTS

The studies demonstrate good outcomes for seizure remission before adolescence in CECTS patients (Callenbach et al. 2010; Vannest et al., 2015). Asadi-Pooya et al. (2019) suggest that cognitive deficits may wane after a few years. However there is a significant lack of long-term studies that retest cognitive abilities in adolescence and adulthood.

Völkl-Kernstock et al. (2009) found that attention and behavioural difficulties had improved one year after seizure remission. Callenbach et al. (2010) followed CECTS children for up 17 years and found that none of the young people reported a significant cognitive or educational difficulty and nearly half of the 29 children studied were going onto university. Camfield and Camfield (2014) reported that their follow-up study of childhood-onset epilepsies over 30 years demonstrated not only were all patients with CECTS seizure free, there were only minimal adverse outcomes compared to other childhood epilepsies in areas such as poverty, employment and psycho-social problems. However it is important to recognise that both of these studies were conducted through interview and no formal assessments were made and therefore may not be representative of the wider population of CECTS patients.

As the cognitive and language deficits seen in CECTS patients occur during primary school years, the impact on the child's potential may be large

Conversely, a study by Garcia-Ramos et al. (2015) reported that children with CECTS who performed worse in a number of cognitive domains compared to a control group, continued to show the same deficits over a two-year period despite demonstrating parallel cognitive development to the control group, suggesting that learning problems may not diminish once seizures had stopped. Given that the cognitive and language deficits seen in CECTS patients occur during primary school years the impact on the child's potential may be large and there is a need for further long term follow-up.

Treatment of CECTS

Whether to start a child on treatment for CECTS is often a dilemma faced by clinicians and families, and customarily, children with CECTS are not started on treatment due to the short duration of the epilepsy and low number of seizures (Vannest et al. 2015). Several studies propose that cognitive difficulties are associated with increased interictal activity on EEG rather than number of clinical seizures (Ebus et al., 2011; Goldsberg-Stein et al., 2010; Nicholai et al., 2007). This suggests that reduction of this interictal activity may lead to improvements in cognitive functioning. Therefore clinicians must consider the potentially positive and negative outcomes that anti-epileptic drug (AED) treatment may have on cognition, and balance the need to treat seizures with the need to minimise any side effects the AEDs themselves may have (Menlove and Reilly, 2015).

Prescribing guidance in the UK (BNFc, 2020) recommends first line treatment of CECTS with carbamazepine or lamotrigine with guidance from the International League Against Epilepsy (ILAE) recommending carbamazepine or sodium valproate as first line monotherapy (Glauser et al. 2013), however MHRA guidance on the use of sodium valproate in girls should be followed.

Guidance from both the ILAE and BNFc suggest levetiracetam and oxcarbazepine may also be effective, but the ILAE recognises that there have been very few RCTs looking specifically at CECTS treatment (Glauser et al. 2013). Amended guidance from NICE in 2018, states that levetiracetam is not cost-effective and should only be considered if carbamazepine and lamotrigine have been ineffective.

Hermann et al. (2010) specifically reviewed the impact of AEDs on cognition and suggest that carbamazepine and valproate could have negative effects on sustained

attention, processing and motor speed, and memory, but lamotrigine and levetiracetam appear to have fewer cognitive side-effects, especially when compared with carbamazepine which also appeared to affect verbal fluency. A study comparing the impact of carbamazepine and levetiracetam on cognitive functioning, also suggested that carbamazepine can worsen speech problems but switching to levetiracetam can improve cognitive functioning (Kossoff et al. 2007). More recent studies also propose that cognitive functioning improved with levetiracetam monotherapy compared to carbamazepine (Helmstaedter and Witt, 2010; McNally and Kossoff, 2015). Furthermore a small number of studies suggest that levetiracetam is more effective than carbamazepine in suppressing interictal epileptiform discharges in CECTS (Kanemura et al., 2018; Tacke et al., 2016).

It is worth noting that many of the studies looking at CECTS patients fail to demonstrate a link between specific AED treatments and cognitive difficulties

Xiao et al. (2014) retrospectively compared the efficacy of low doses of levetiracetam and valproate on seizure frequency in CECTS children over an 18-month period. Their results showed that both medications were equally effective in reducing seizures, but valproate appeared more effective at improving EEG abnormalities.

It is worth noting that many of the studies looking at CECTS patients fail to demonstrate a link between specific AED treatments and cognitive difficulties. In the majority of studies assessing the cognitive impact of AED treatment in children with CECTS, very few children are given cognitive testing prior to commencing treatment, and therefore may have had pre-existing cognitive deficits that are not related to medication. Moreover, these studies include small sample groups with a wide variety of different medications, as well as CECTS patients not taking AEDs, thus making direct comparison of studies difficult. Therefore ongoing monitoring of cognitive functioning is essential for children with CECTS

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throughout the duration of any treatment and long after they are in seizure remission. Although there is a large amount of evidence to suggest that children with CECTS are at risk of neuropsychological deficits, the data in favour of AED treatment in improving cognitive problems is minimal. Using AEDs for children with CECTS may be effective in reducing interictal EEG abnormalities and thereby potentially improving cognitive functioning but given that seizure frequency is infrequent and seizures generally occur at night, the risk of treatment often outweighs the benefits, unless the child is having frequent or daytime seizures (Xiao et al. 2014).

Conclusion

While there are no large population-based studies looking at long-term outcomes in patients with CECTS, there are many studies consistently replicating similar results, with cognitive difficulties including memory and attention difficulties and language impairments. Left unrecognised, these difficulties may lead to academic underachievement in children leading to poorer employment opportunities and reduced quality of life in adulthood (Asadi-Pooya et al. 2019). The decision to treat or not to treat remains a difficult one as all AEDs have the risk of adverse effects which can often cause the child and family additional issues.

CECTS presents during a time that is crucial for the development of academic and social skills as well as acquisition of knowledge and learning strategies, and therefore could have a significant impact on a child's academic progress (Neri et al. 2012). The evidence suggests that close monitoring of the child's language development and cognitive functioning is essential for positive long-term outcomes, and treatment of interictal discharges may be indicated if significant cognitive impairments are present. Joint working with parents and education establishments, to ensure changes in the child's academic attainment are identified early, is essential. The epilepsy nurse specialist may be helpful in bridging this gap and raising awareness to ensure the child is given the appropriate support to enable them to achieve their full potential.

Sarah Collins
Children's Epilepsy Nurse Specialist
Kent Community Health NHS Foundation Trust

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Highlights

Top picks from *Seizure*

Editor of the journal *Seizure*, Professor Markus Reuber highlights his key papers from the latest editions

Seizure 2019, Vol 72, Editor's Choice: Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting

Although seizures and epileptic discharges in the brain are the cornerstones of the definition of epilepsy, the lived experience of the condition very much encompasses epilepsy-associated cognitive, emotional and social problems as well as the unwanted effects of the treatments offered for the disorder. In fact, in individuals whose epileptic seizures cannot be stopped completely with drugs or other medical interventions, health related quality of life (HRQoL) is affected more strongly by psychological variables and the side effects of anti-seizure medicines (ASMs) than by the frequency or severity of their seizures (Suurmeijer et al, 2001). While side-effects affecting cognition/coordination or mood/emotion are more frequent (and more closely associated with reduced quality of life) previous research has demonstrated a clear negative correlation between HRQoL and unwanted effects of ASMs on skin or mucosa ($r = 0.42$, $p = 0.01$) (Perucca et al, 2009). What is more, in routine clinical practice,

ASM-related skin reactions are particularly likely to lead to the discontinuation of potentially effective medicines.

My Editor's Choice paper from Volume 72 of *Seizure*, is a narrative review by Dora Lozsadi, Amolak Bansal and Thomas Fowler which summarises the evidence on the nature, frequency and optimal management of skin reactions associated with ASMs (Lozsadi et al, 2019). About one in 30 of all individuals with epilepsy will

Health-related quality of life is affected more strongly by psychological variables and side-effects of ASMs than by the frequency or severity of their seizures

experience such a drug reaction, but skin reactions are considerably more common in those taking aromatic ASMs (especially carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, lamotrigine, phenobarbitone and primidone) or sulphonamide-type drugs (especially zonisamide).

The typical management of unwanted skin reaction involves the discontinuation of the antiepileptic drug and recording of an "allergy" to the drug in question. The review by Loszsadi et al. suggests that this is not always necessary and may stop patients from using medication they may well have benefited from. Lozsadi et al argue that severe cutaneous drug reactions (such as Stevens Johnson Syndrome) are relatively rare and that many patients could tolerate treatments that have been associated with skin reaction if their particular skin rash is assessed carefully and the drug re-introduced very slowly. Their review provides a pragmatic management pathway for patients presenting with a suspected drug-induced rash. It includes suggestions for pre-treatment screening and assessment of potentially drug-associated rashes and associated symptoms to aid the early identification of patients at risk of severe allergic reactions.

Seizure 2019, Vol 73, Editor's Choice: The role of electroencephalography in the early diagnosis of non-convulsive status epilepticus in elderly patients with acute confusional state: Two possible strategies?

Those working near the "frontline" of emergency medicine in nations with an aging population will be acutely aware of the effects of the demographic changes on healthcare services. The United Kingdom is typical of many other countries facing similar demographic challenges. Between 2015 and 2020 – a period of only five years, in which the general population is expected to rise by 3%, the numbers of those aged over 65 are expected to increase by 12% (1.1 million); the numbers aged over 85 by 18%

(300,000); and the number of centenarians by 40% (7,000) (Parliament UK, 2019). One of the most common emergency presentations of older adults is an acute confusional state. Unfortunately, the differential diagnosis of this clinical presentation is extremely wide – ranging from general medical disorders (including urinary tract and chest infections, metabolic disorders, iatrogenic effects of drug treatments), psychiatric conditions (including delirium or psychosis) to neurological conditions such as stroke, neurodegenerative disorders, encephalopathy, traumatic brain injury, epileptic seizures or postictal states.

Most of the medical and neurological disorders causing hospital admissions with acute confusion can be diagnosed easily with simple investigations such as blood tests, urine analysis or imaging studies which are requested as a matter of routine and without much thought. However, there is one common neurological condition, which cannot be diagnosed effortlessly in this way: nonconvulsive status epilepticus (NCSE) (Beyenburg et al, 2007). The possible manifestations of NCSE are diverse. Most patients have selective rather than global cognitive deficits. Those involving consciousness, speech, praxis, memory, attention and effect are particularly prominent. Impairment of consciousness may be characterised by reduced vigilance, reactivity or orientation (Profitlich et al, 2008). With the limited exception of admissions to the few centres where emergency EEGs are readily available, this diagnosis can only be made if clinicians think about it – and make the considerable effort to arrange an EEG recording (often requiring transfer to another hospital). However, it is possible that many – perhaps most cases currently remain undiagnosed.

Unfortunately, as Francesco Manfredonia et al, in my Editor's Choice from Volume 73 of *Seizure* demonstrate, there is no easy way to optimise the diagnosis of NCSE (Manfredonia et al, 2019). Abbreviated EEG procedures or recordings with a limited number of electrodes improve the feasibility of capturing EEG from a confused patient in an emergency setting but have a diagnostic yield, which may be well below 50%. The test of choice is also the least practicable: continuous EEG recording. Simpler solutions are urgently needed. Unfortunately the fact that the diagnosis is likely to be routinely missed means that the urgency of the problem remains unnoticed - out of sight out of mind.

Seizure 2020, Vol 74, Editor's Choice: Socioeconomic outcome and access to care in adults with epilepsy in Sweden: a nationwide cohort study

The link between higher socioeconomic status and better health is beyond any doubt. The many strands of evidence which support this link have recently been summarised in a document produced by the British Medical Association (British Medical Association, 2017). In the UK, a high income country with free access to healthcare for all citizens, life expectancy in the most deprived areas is seven to eight years lower for men, and four to six years lower for women, than in the least deprived areas. Wealth-related differences in health status are detectable before birth: birth weight, a recognised marker of subsequent cognitive development, is, on average, 200 grams lower in babies born in the poorest areas in the UK than in those born in the most affluent areas. Babies living in poverty are more likely to die within their first year of life. In mothers, poverty increases the risk of postnatal depression and is associated with lower rates of breastfeeding. Children born into poverty are more likely to develop a range of chronic diseases as well as diet-related problems. In their first year of school, children living in the most deprived areas are twice as likely to be obese than children living in the least deprived areas (12.5% versus 5.5%). Poor children also have higher rates of fatal and non-fatal accidents, their risk of dying from unintentional injury is 13 times greater. A link with poverty even exists for genetic conditions such as cystic fibrosis, and poorer children experience worse growth, poorer lung function and higher risk of infection. The pattern continues into adulthood where most long-term conditions have been found to be more common among lower socio-economic groups, including diabetes, chronic obstructive pulmonary disease, arthritis and hypertension. Two-fifths of adults in England aged 45 to 64 with below-average incomes have a limiting long-term illness. This is twice the rate of adults of the same age with above-average incomes. The risk of developing epilepsy is also much greater in poorer areas in the UK (Steer et al, 2014). Not surprisingly, similar findings have been reported from other countries. For instance one study from the USA found the prevalence of active epilepsy to be 1% across the

country, but twice as high in low-income households (Centers for Disease C, Prevention, 2012).

My Editor's Choice paper from Volume 74 of *Seizure* is an original research paper by Klara Andersson et al (Andersson et al, 2020). Their cohort study data based on 126,406 adult patients with a diagnosis of epilepsy from the Swedish patient register and a control population of 379,131 adults without epilepsy confirmed that low income levels were associated with a higher risk of epilepsy and that people with epilepsy (PWE) had more somatic and psychiatric comorbidities and lower levels of education than controls. However, the findings of this study go beyond these well-known associations and shed additional light on some of the reasons for the poorer health outcomes observed in PWE of low socioeconomic status. For instance, the study demonstrates that – although the Swedish healthcare system aspires to offer the same free healthcare to all patients in need, regardless of their level of income – hospitalisations were more common among PWE from lower than higher income groups. Conversely, PWE in the high-income (and high education) groups were more likely to have received at least one medication prescription from a specialist in neurology in the five-year study period than those in the most disadvantaged groups. These findings mean that healthcare systems which are passively available to the whole population, but which do not reach out more actively to provide healthcare to patients in lower socioeconomic groups are unlikely to diminish health inequalities. In fact, even active healthcare outreach efforts are unlikely to level differences between socioeconomic groups in health outcomes and mortality without addressing differences in nutrition, housing, education and many other spheres of life from childhood onwards.

Low income levels were associated with a higher risk of epilepsy and people with epilepsy had more somatic and psychiatric comorbidities than controls

Further reading

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We need to update our pathways for status epilepticus

The end of 2019 saw a landmark in epilepsy research with the publication of the Established Status Epilepticus Treatment Trial (ESETT, Kapur et al. *N Engl J Med* 2019;381:2103-13). The trial was terminated early for futility at a planned interim analysis. But it showed that there was no difference in outcome between levetiracetam, fosphenytoin (pro-drug of phenytoin) and valproate, when used to treat benzodiazepine refractory status epilepticus.

While no difference was seen between the three drugs, it is still an important trial and should act as a trigger for all of us to evaluate the protocols and pathways in our departments. Status has an unacceptably high mortality and morbidity and there are often delays in getting the right treatment at a good dose.

Phenytoin remains the first-line drug used in many UK hospitals when benzodiazepines have failed. It is a drug with complex pharmacology and interactions, which is often not used at the right dose. The evidence that levetiracetam is as good is excellent news and an impetus to replace phenytoin as our first line agent. It is also very important that the right dose is used first time. The ESETT trial used 60 mg/kg up to a maximum of 4.5g.

The maxim *time is brain* is used a lot now in stroke medicine, but was coined originally in the treatment of status and is a phrase we should be taking back. We need rapid treatment for status with the right drugs at the right dose.

While ESETT shows that large randomised multicentre trials in the emergency treatment of epilepsy are possible, all three drugs showed less than a 50% response in terms of the primary endpoint (out of status and awareness improving at one hour).

The maxim 'time is brain' is used a lot now in stroke medicine, but was coined originally in the treatment of status and is a phrase we should be taking back.

What we do next in patients who do not respond is based on relatively poor evidence or expert opinion. We must learn how to do better for our patients with this most devastating form of epilepsy. I am hoping to see (and contribute patients to) more trials in this area.

In the meantime, let's get out to our emergency departments and medical teams and remind them that in status epilepticus time is brain and that they need to use the right drugs in the right doses according to the evidence we now have.

Dates for the diary

March 2020

26-28
4th ILAE British Branch Epilepsy Neuroimaging Course
Chalfont St Peter, UK
https://bit.ly/2rbePH9

26-29
14th World Congress on Controversies in Neurology
London, UK
cony.comtecmed.com

29-3 April
3rd International Training Course on Neuropsychology in Epilepsy
Bordeaux, France
https://bit.ly/2O2wlq0

April 2020

2-4 April
4th International Video-EEG in Paediatric Epilepsies from Seizures to Syndromes
Madrid, Spain
2020.videoeeg.es

22-24 April
Fetal and Neonatal Neurology Congress
Paris, France
mcascientificevents.eu/brain

22-25 April
Treatment Strategies in Pediatric Epilepsies
Girona, Spain
epiped-curse.com

May 2020

8-9
Epilepsy 2020: A vision of the future in epilepsy research
Montreal, Canada
https://bit.ly/2Ootjvr

July 2020

4-8
14th European Congress on Epileptology (ECE)
Geneva, Switzerland
epilepsycongress.org/ece

Meta-analysis of sleep problems in childhood epilepsy

Alice Winsor explores how we should consider sleep disturbances in the diagnosis of childhood epilepsies.

Epilepsy in those with intellectual disabilities

Phil Tittensor outlines the multidisciplinary health services that could better meet the needs of people with epilepsy and intellectual disabilities.

Epilepsy Professional's advisory panel

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