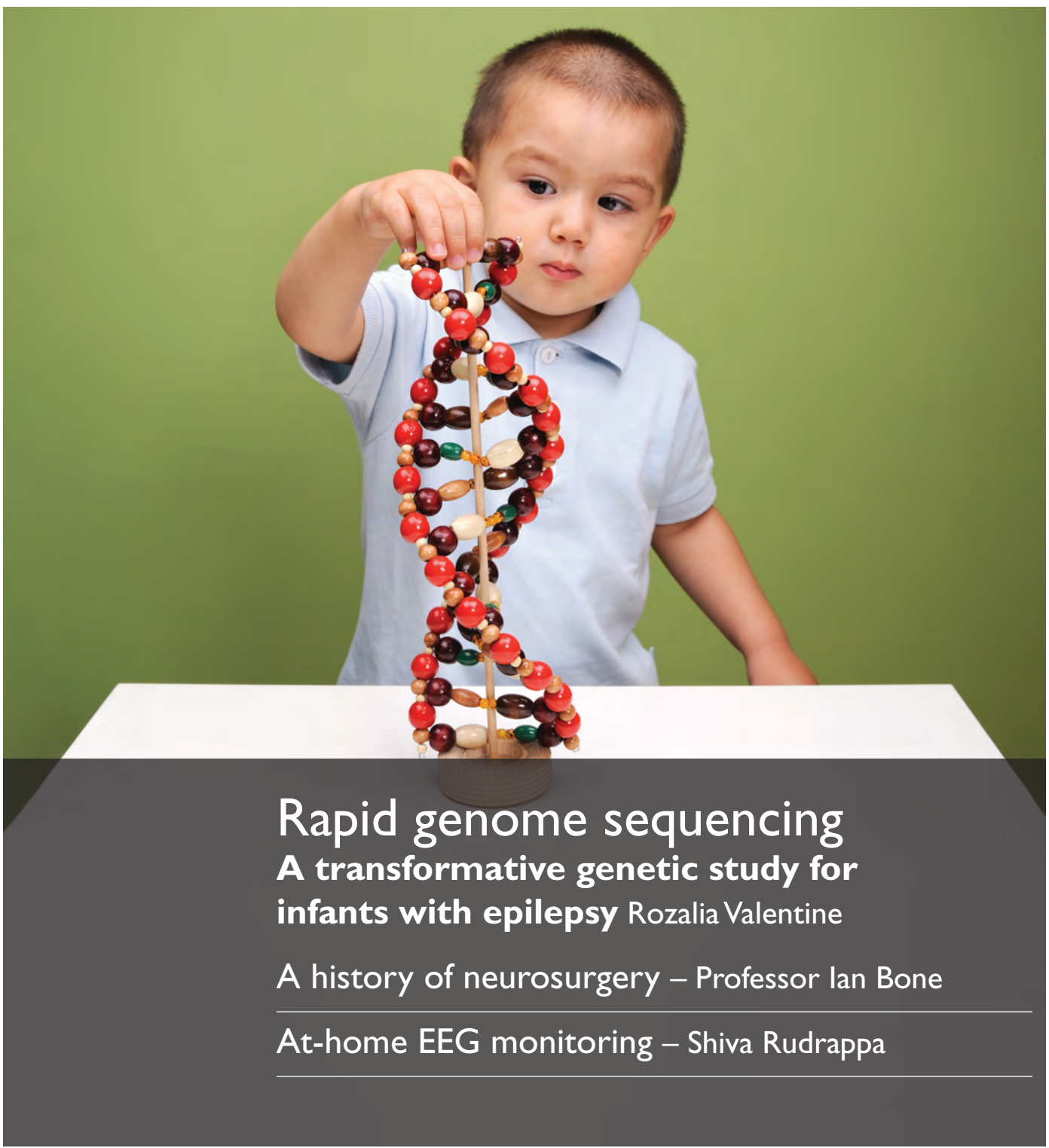
epilepsy action

Issue seventy one / Winter 2023
(Free to Epilepsy Action professional members)

epilepsy professional



Rapid genome sequencing
A transformative genetic study for infants with epilepsy Rozalia Valentine

A history of neurosurgery – Professor Ian Bone

At-home EEG monitoring – Shiva Rudrappa

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1. Elliott, RE., et al., (2011) Epilepsy & Behavior. 20; 478–483.
2. Patient's Guide for Epilepsy 2021, LivaNova USA, Inc.
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5. Spindler, et al., (2019) Seizure, 69:77-79.

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LivaNova Epilepsy

Welcome to the winter edition of Epilepsy Professional. We have some fantastic articles this edition.

One of the most difficult aspects in the management of patients with epilepsy is being certain about the seizure burden. We all struggle differentiating between seizures and certain behaviours, especially in those with intellectual disability. Remote monitoring of EEG and/or video offers potential help in these situations. Lance Watkins and colleagues discuss the potential for this in clinical practice and what the pros and cons of various options are.

Ian Bone from Glasgow takes us through the history of epilepsy surgery and the crucial role animal experimentation made to progress in the field. It is a fascinating look at how early neurology and neurosurgery developed. He also charts the parallel development of anti-vivisection groups and the development of animal cruelty regulations.

Having a definitive aetiological diagnosis for our patients makes managing their epilepsy more targeted. The world of genetic testing is ever evolving, but most genetic tests take months and sometimes even years before a result is available. Rozalia Valentine and colleagues describe a recent trial of using rapid whole genome sequencing to look for a genetic diagnosis in infants with epilepsy. The rapid whole genome sequencing used in the trial meant the result was available in a month with significant benefits in terms of prognosis, and individualisation of a patient's management.

I hope you enjoy the edition.

Seán Slaght
Consultant neurologist
Executive medical adviser
Epilepsy Professional

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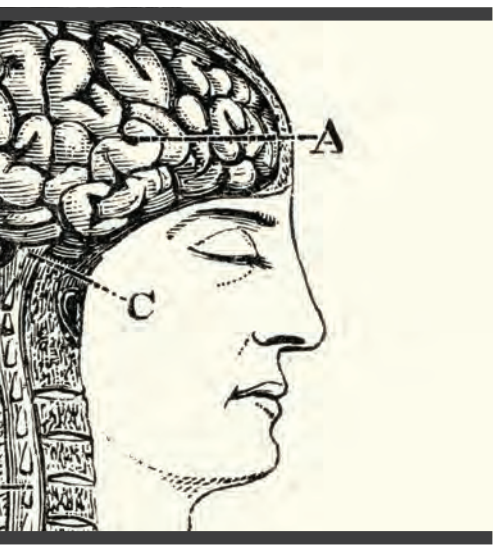

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Genome sequencing

Rozalia Valentine

A team from Harvard, Boston Children's Hospital and Great Ormond Street Hospital explain their research into the genome sequencing of infants

In this issue of Epilepsy Professional we're looking back into the history of our profession, while looking forward to what the future might hold.

On pages 12-18, Professor Ian Bone, a retired neurologist who is now writing about medical history, looks at the history of epilepsy surgery: from ancient trepanation to the first cerebral surgeries in the 19th century. He celebrates the 'martyrs of neuroscience' and looks at the anti-vivisection movement, which campaigned against the use of animal research.

Looking forward, on pages 24-28, Rozalia Valentine and team explain how their research into genome sequencing is speeding up diagnosis and treatment for infants. And on pages 20-23, Shiva Rudrappa, Lance Watkins and team talk about the benefits of allowing patients to undergo EEGs at home.

At Epilepsy Action, we are also looking towards the future. From this issue Epilepsy Professional will become an online-only publication. This will allow us to reduce our carbon footprint by cutting our paper use and limiting transportation by road. We hope it will also allow you to access the magazine more easily, it will be sent by email so you can read it wherever and whenever you choose. You should have received a letter with this edition that tells you what to do to access your digital magazine.

I hope that in reading this edition you learn as much about the future as the past, and we look forward to sharing our online version with you in the New Year.

Grace Wood
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Valproate restrictions to begin in January

New restrictions for sodium valproate are to come into effect from January 31, 2024.

The changes, announced by the Medicines and Healthcare products Regulatory Agency (MHRA) last year, affect men and boys for the first time.

The restrictions mean no one under the age of 55 will be newly prescribed sodium valproate unless two specialists agree there is no other effective or tolerated treatment, or unless there are "compelling reasons the reproductive risks do not apply".

The update means all women who could become pregnant and girls who are currently taking valproate will be reviewed at their next annual specialist appointment, and will require a second opinion to continue taking it. This will be done using an Annual Risk Acknowledgement Form, which will also be introduced for men in 2024.

According to the MHRA, about one in nine babies born to mothers taking valproate will have birth defects and about 30-40 of 100 will have learning difficulties. The MHRA has also said there is a risk of reduced fertility in men and boys.

Epilepsy Action understands that for 10% of people with generalised epilepsies, valproate is the first-line defence against hospitalisation and the risk of sudden unexpected death in epilepsy (SUDEP).

Epilepsy Action chief executive Philip Lee said: "Throughout 2023, we have raised our concerns around the new sodium valproate policies as part of a group of epilepsy charities and organisations. The new regulations represent a dramatic shift in clinical practice, and the group expressed concerns when it came to the impact on patient safety and workability for healthcare professionals.

"The group gave the MHRA constructive feedback on proposed patient materials, as well as the development and implementation of the policy. These changes were necessary so that patients and families could be empowered with all the insight they needed to make informed choices about their treatment.

"With the new policy being rolled out from the end of January 2024, we hope that all healthcare providers will be given the time to safely implement it at a time when these systems face unprecedented waiting times, resource limitations and access issues."

Autumn budget 2023: welfare reforms announced

The government has announced reforms to welfare for disabled people and those who are out of work.

As part of the autumn budget, chancellor Jeremy Hunt said he wanted to reduce "workless households" through a Back to Work plan.

The Back to Work plan seeks to help about one million people with long-term health conditions, disabilities or long-term unemployment to look for and stay in work.

However, it also introduces stricter benefit sanctions for people who can work but refuse to engage with their Jobcentre or decline work offered to them, including stopping people's benefits if they don't do enough to look for a job in six months.

Many people with epilepsy currently qualify for welfare benefits.

Hunt also announced that Universal Credit and other benefits would increase from next April by 6.7% in line with September 2023's inflation rate.

Epilepsy Action's senior policy and campaigns officer Daniel Jennings said: "We know that only 42% of people with epilepsy are in employment so we welcome efforts to get more people with disabilities and long-term health conditions into work.

"However, the way to do this is to provide tailored support for specific conditions to address the barriers to employment faced by people with disabilities, and not by pursuing harsher and harsher punishments for people already struggling on benefits during a cost-of-living crisis."

Meanwhile, cost-of-living payments for people on disability benefits have been dropped this winter. A £150 cost-of-living payment was given between 20 June 2023 and 4 July 2023 to people in receipt of certain benefits, including personal independence payment (PIP), but will not be given out this autumn.

Valproate boxes must now contain warnings

The MHRA has updated its guidance on dispensing valproate-containing medicines.

The medication will now be dispensed in the manufacturer's original full packaging.

The change was made to ensure patients receive safety warnings, including a patient card and information leaflet.

Sodium valproate is also sold under the names: Epilim, Epilim Chrono, Epilim Chronosphere MR, Episenta, Episenta MR, Epival CR, Dyzantil MR and Depakin.

The move follows concerns that some people taking the medicine were unaware of the risks to an unborn baby if taken during pregnancy.

Pharmacists will be able to make exceptions, but only where a risk assessment is in place that refers to the need for different packaging.

The change came into force in England, Scotland and Wales on 11 October.

In 2018, a review by the MHRA led to the introduction of the Valproate Pregnancy Prevention Programme, which is a condition of prescribing and dispensing valproate medicines to women of childbearing potential.

MHRA chief executive Dr June Raine said: "It is essential that patients on valproate-containing medicines receive the latest safety information every time their prescription is dispensed. These changes in the law ensure this happens. People's situation may change, especially with regard to the possibility of pregnancy, so it is vital the warnings about the harms of valproate are always brought to mind."

Northern Irish neurologist removed from medical register

Northern Irish consultant neurologist Dr Michael Watt is to be removed from the medical register, a fitness to practice hearing has ruled.

Dr Watt was at the centre of Northern Ireland's biggest patient recall. The tribunal previously ruled the neurologist's performance was "unacceptable".

The panel said his behaviour was "unacceptable in the areas of maintaining professional performance, assessment, clinical management, record keeping and relationship with patients".

The tribunal determined Dr Watt's failures were "stark, serious, repeated and numerous".

Epilepsy Action Northern Ireland's policy and campaigns officer Jack Morgan said the charity welcomed the decision of the tribunal.

He said: "Patients and families deserve answers, accountability and to feel that their experiences have been heard and considered. It is vital that lessons are learned so a situation like this is never allowed to happen again.

"We thank all the affected families who have spoken out about their situation. It is important the Department of Health now engages with patients regarding the implementation of the recommendations arising from the Independent Neurology Inquiry.

Sanofi sells Frisium to Pharmanovia

Sanofi has sold the epilepsy medicine Frisium, along with 10 more of its central nervous system (CNS) medicine brands, to Pharmanovia.

Frisium, a brand name for the benzodiazepine clobazam, is an adjunctive treatment used alongside other epilepsy medicines.

Pharmanovia is a global healthcare company with headquarters in Basildon, Essex.

Pharmanovia MSL director Fernando Osorio reassured people that very little would change.

He said: "We'll be working very closely with Sanofi to make sure there is no disruption. We fully understand that these are critical medicines and that there are patients in need."

Pharmanovia added that it intends to keep the same branding for Frisium, with the only likely change being the packaging.

The acquired medicine brands also include Sentil, Urbanyl, Urbanil, Urbanol, Urbadan, Noiafren and Castilium, Phenobarbital (Gardenal), Cyamemazine (brand: Tercian) and Prochlorperazine (brand: Stemetil).

Pharmanovia CEO Dr James Burt said: "Sanofi's decision to divest this established CNS portfolio, with leading brands such as Frisium, to Pharmanovia is recognition of our neurology expertise, our capabilities in lifecycle management and reputation of being a trusted divestment partner."

NHS announces 'bundle of care' for children and young people

A report from NHS England, supported by Epilepsy Action, has made a number of recommendations to improve care and outcomes for children and young people with epilepsy.

NHS England's Children and Young People's Transformation Programme includes guidance for Integrated Care Boards (ICBs). The recommendations include:

- Addressing variation in care between epilepsy services
- Supporting the mental health and wellbeing of children and young people with epilepsy
- Improving referrals into tertiary services and the Children's Epilepsy Surgery Service
- Improving the transition from paediatric to adult epilepsy services.

The recommendations were developed using data from Epilepsy12 and are aligned to guidance from NICE (NG217 & QS27).

Epilepsy Action's director of health improvement and influencing Alison Fuller said: "It has been fantastic to work alongside Young Epilepsy to help develop these key recommendations, which have been announced by NHS England. These recommendations are essential to ensure that children and young people with epilepsy receive the best possible care and can access the support they need.

"Findings from the Epilepsy12 report showed improvements in many aspects of epilepsy services for children and young people, however there were clear areas that needed improvement. These recommendations will help to close the gap on regional

disparities in epilepsy services, improve mental health support for children and young people with epilepsy, and will ensure they experience joined up care across the services, and when transitioning from paediatric to adult care.

"We hope these recommendations will help to improve services for children and young people so they can receive the comprehensive and harmonious care they deserve."

The report claims that implementing the recommendations would reduce the overall costs of delivering care by reducing unplanned hospital admissions, appropriate referral into hospital services and supporting early identification of comorbidities.

This programme of work has been supported by children and young people diagnosed with epilepsy, their families and a number of organisations including the charities Epilepsy Action and Young Epilepsy.

The report encourages ICBs to develop improvement plans in line with the recommendations, identify gaps in services by focusing on the provision of epilepsy specialist nurses, and ensure that children and young people receive timely access to appropriate EEG and MRI investigations with clearly defined waiting times.

One anonymous young person quoted in the report said: "Having access to an epilepsy specialist nurse would really help with communication and make it easier to get in contact with a [healthcare] professional."

The report also recommends that all children and young people who meet the criteria for tertiary neurology referral and surgery should have timely access to specialists.

It adds that all children and young people should have an agreed and comprehensive care plan and should receive personalised and appropriate information on the risks of sudden unexpected death in epilepsy.

Another anonymous young person quoted in the report said: "I have never had a conversation with a healthcare professional about sudden unexpected death in epilepsy. You end up looking on the internet and doing your own research."

The report also calls for improvements in the provision of mental health care. It says all children and young people with epilepsy over the age of five should have their mental health screened routinely. Those identified as requiring additional support should be referred to an appropriate service.

To improve the transfer of care from paediatric to adult neurology, the recommendations include designating a named worker who is responsible for initiating and planning that transition.

Guidance released to avoid maternal deaths from epilepsy

A report into maternal deaths in the UK and Ireland has found 40% of maternal deaths from a neurological condition were linked to epilepsy.

The report considered people who died during pregnancy or up to a year afterwards.

Between 2019 and 2021, 17 died from causes related to epilepsy. Of those, 14 died from Sudden Unexpected Death in Epilepsy (SUDEP). This is almost twice the rate of 2013-15.

The report concluded that five of those people could have survived if there had been improvements to their care.

Of the general population – with or without epilepsy – 241 people died during or up to six weeks after pregnancy. They were four times more likely to be black and twice as likely to live in a deprived area.

The MBRRACE report was published on 12 October. It is titled: Saving Lives, Improving Mothers' Care – Lessons Learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2019-21.

One of the key themes of the chapter on epilepsy was adherence to anti-seizure medications, which the authors said continues to be a concern.

The report also claimed that many "clinicians did not feel able to hold conversations, which may need to be repeated, about non-adherence to medication".

It is recommended that healthcare providers "develop training resources concerning shared decision making and counselling regarding medication

use in pregnancy and breastfeeding, including specific information on the benefits and risks of different medications and non-adherence".

During the period the report covers, the guidance on prescribing valproate for women and girls changed. This meant a large number of women of reproductive age were changing medication in this period. None of the women who died were taking sodium valproate.

Of the 14 women with an epilepsy diagnosis prior to or during pregnancy, eight did not receive pre-pregnancy counselling. The report also found that in many instances women had no or very little input from, or access to, neurology or epilepsy services.

According to the report, one woman waited seven months for two separate pre-conception appointments.

The report explains that effective pre-conception counselling provides an opportunity to ensure patients are taking the right medications. It also provides an opportunity to build trusting relationships, give advice and formulate a plan for future pregnancies.

Epilepsy Action wins Helpline of the Year award

Epilepsy Action won Helpline of the Year at the Helplines Partnership Awards 2023.

Advice and information officer, Diane Wallace, was given the Lifetime Service Award for her 30 years of dedicated service. In her time with the charity, she has answered more than 100,000 enquiries.

Advice team leader, David Thornton, also received a runner-up award for Mentor of the Year, in recognition of the guidance and support he provides to the helpline team and wider organisation.

The Helpline Awards recognise the exceptional work done by individuals and teams across the helpline sector. The ceremony was held in November at Birmingham Crowne Plaza Hotel.

The awards are organised by Helplines Partnership, the membership body for organisations that provide information, support or advice via phone, email, text or online.

Helplines Partnership praised recent improvements made by the service to reach more people, including the successful introduction of a live chat support.

Epilepsy Action's advice and service improvement manager Tom Beddow said: "We are incredibly proud to have received these three awards. The helpline team has worked tirelessly over the past few years to update and improve our services, while consistently providing the same high-quality, empathetic support. This amazing result recognises our advisers' ongoing commitment to delivering the best possible service to anyone who is affected by epilepsy."

Epilepsy Research Institute launched

The Epilepsy Research Institute was launched in October at the International League Against Epilepsy British Branch's annual scientific meeting in Gateshead.

The institute began as medical research charity Epilepsy Research UK – founded in 1985 – and received permission from the government to become an institute earlier this year.

Institute status is controlled by the government.

It said its mission was to "radically advance research into the causes, prevention and treatment of epilepsy and its associated conditions".

Epilepsy Action is a founding partner, along with Young Epilepsy, Epilepsy Scotland and the International League Against Epilepsy British Branch.

Epilepsy Action's CEO Philip Lee said: "The institute will drive much-needed investment into epilepsy research, putting the voices of people with the condition at the heart of that work.

"The lived experiences and views of our members and supporters are at the core of our involvement."

The institute's strategy was developed using the national research project #Every1EndingEpilepsy, which supports researchers to study new treatments and ways to improve quality of life for people with epilepsy.

SUDEP guidance launched in memory of Clive Treacey

Guidance to reduce risks to people with epilepsy and learning disabilities has been launched by NHS England and SUDEP Action.

The Clive Treacey Safety Checklist has been developed by NHS England Midlands, the University of Plymouth, NHS Cornwall Partnership and the charity SUDEP Action.

The checklist includes measures that help ensure people with epilepsy have up-to-date risk assessments, that their concerns are listened to and that staff who work with them are trained appropriately.

It is named after Clive Treacey who died from sudden unexpected death in epilepsy (SUDEP) aged 47 on 31 January 2017. He had learning disabilities and Lennox-Gastaut Syndrome.

Following his death, an independent review was launched into the care he received.

It found that his death was potentially avoidable and that there were multiple, system-wide failures in delivering his care and treatment.

Clive's sister, Elaine Clarke, said: "I can only hope that the transparency, dedication ambition and bravery continues. A movement in health is rare but to see so many people determined to address the gaps is absolutely indescribable. I used to say Clive is famous for all the wrong reasons, but now he is famous for a million good reasons."

Professor Mike Kerr from Cardiff University and Professor Rohit Shankar from the University of Plymouth were also involved in the project.

Drugwatch updates

20 November: Epistatus
Epistatus (Midazolam) 2.5mg/0.25ml oromucosal solution pre-filled oral syringes made by Veriton Pharma are out of stock until early 2024.

Epilepsy Action understands that there are no supply problems with other strengths of Epistatus.

8 November: Tegretol
Novartis, the maker of Tegretol has said 100mg tablets are now in stock and are being distributed to wholesalers. They should be available for pharmacies to order shortly.

Novartis also confirmed that Tegretol 200mg and 400mg remain available, but that demand had increased due to the shortage of 100mg tablets. The company encouraged pharmacies that are unable to get supply to contact Novartis Customer Services directly.

23 October: Zonegran
Advanz Pharma, the manufacturers of Zonegran, has said supply problems are affecting all forms of Zonegran in Northern Ireland.

19 October: Teva zonisamide
Teva has provided an update on the stock of Teva zonisamide capsules after they were out of stock in the summer. The company has said all strengths are back in stock.

10 October: Tapclob
Tapclob is now known as Clobazam Martindale Pharma Oral Suspension. Epilepsy Action has been assured by the manufacturer that it is the same product, just with a new name. Pack sizes remain the same, with 150ml and 250ml available in both strengths.

ILAE British Branch: driving, JME and amnesia

The ILAE British Branch held its Annual Scientific Meeting in Gateshead in October. **Tom Shillito** discusses some of the highlights

Dr Paul Cooper, a neurologist and chair of the DVLA medical panel for neurological disorders, gave an update on driving regulations and epilepsy.

People with epilepsy were first banned from driving in the 1930s. This ban remained until the 1970s, when regulations started to come into place that allowed for people with epilepsy to drive under conditions. Currently, people with epilepsy are allowed to drive if they have been seizure free for a year, or if their seizures don't affect their consciousness.

While the DVLA manages driving licences, the laws can only be changed by parliament. In driving law, you are considered to have epilepsy if you've had two or more seizures that were more than 24 hours apart within a five-year period. In medicine, epilepsy can be defined as having two seizures more than 24 hours apart over any period of time, or having the probability of seizures, or having an epilepsy diagnosis. This mismatch and the misunderstandings that can occur from it, can make it difficult to understand what is needed to get a licence, and when to stop driving.

The DVLA receives more than 3,000 medical forms a day, and there can be long waiting times. Dr Cooper's advice was to contact the organisation by email, and to make sure patients and doctors are providing any information as quickly as possible.

Juvenile myoclonic epilepsy

Professor Arjune Sen from the University of Oxford gave some updated findings about juvenile myoclonic epilepsy (JME)

JME affects about one in ten people with epilepsy. It usually begins when someone is a teenager or young adult, and affects slightly more women than men.

This research focused on predicting treatments. It looked at a large amount of data from men and women with JME, including what their seizure triggers were and whether anti-seizure medications (ASMs) had been effective.

It found that men with JME who had absence seizures were more likely to have drug-resistant epilepsy.

For women, the picture was more complicated. Women with JME were more likely to have drug-resistant epilepsy if their seizures began before they were 12. Women who had absence seizures were also more likely to have drug-resistant epilepsy than those who didn't. Among the women who had absence seizures, those who did not have photosensitive epilepsy were more likely to be drug-resistant. Women with JME who didn't have absence seizures were more likely to have drug-resistant epilepsy if their seizures were triggered by stress, sleep deprivation, their menstrual cycle and concentration. Photosensitivity also played a role – if their seizures were triggered by one of those things, and they were not photosensitive, they were even more likely to have drug-resistant epilepsy.

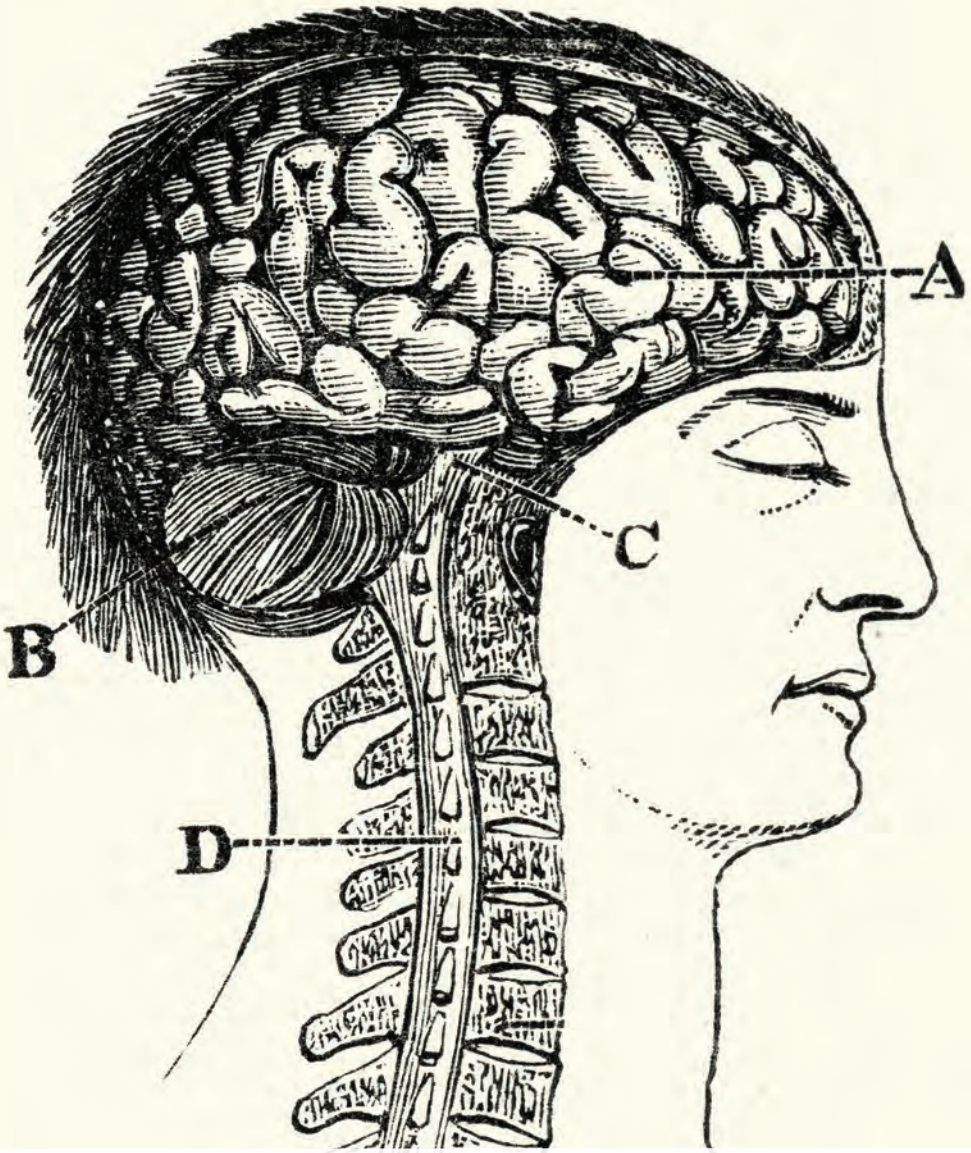
Transient epileptic amnesia

Professor Chris Butler from Imperial College London gave an overview of transient epileptic amnesia. This is a rare but recognisable condition that can affect people with temporal lobe epilepsy. Patients will have short (about 15-30 minute) periods when they can't remember anything from that day or the previous few days. This often happens just after they wake up. During this time they can't form new memories. They are usually able to remember who they are and who their family is, and can communicate and move around as normal. Once this period is over, their memories return.

People who experience this may feel more emotional. It is also common for them to experience accelerated long-term forgetting and autobiographical amnesia. These symptoms are easily missed.

More than two thirds of people who have transient epileptic amnesia are men, and it often starts in their 60s. Episodes happen about once a month.

One study found 98% of people with transient epileptic amnesia had their seizures become less frequent or stop completely by using ASMs.



A history of neurosurgery

The dawn of epilepsy surgery and the debt to animal experimentation

Ian Bone is a retired neurologist from the University of Glasgow. He is the author of Sacred Lives: An account of the history, cultural associations and social impact of epilepsy. Here he discusses the history of vivisection

In 1879, William Macewen of Glasgow performed what was most likely the world's first targeted epilepsy surgery. This was followed in 1881 in London by Rickman Godlee's meticulously documented case, and by 1890 Victor Horsley was able to publish a case series with outcomes. All three surgeons were knighted for their achievements and the courage of their first patients was widely acclaimed. How was all this accomplished? The potential of X-rays was still to be realised by Wilhelm Röntgen, Hans Berger's electroencephalogram was half a century away and the concept of CT and MRI would have seemed to belong to the science fiction of Jules Verne or HG Wells.

The martyrs of neuroscience

Frank Stahnisch refers to the "martyrs of neuroscience" in his account of the role of animal experimentation in the history of neurology [Stahnisch, 2010]. He points out that, in the ancient world, both Aristotle (384-322 BCE) and Galen (129-216 CE) were accomplished dissectors. Vivisection, defined as the use of living animals in experiments intended to increase human knowledge of human diseases, remained unregulated until the late nineteenth century when a Royal Commission was set up, culminating in the 1876 Cruelty to Animals Act. This was the first legislation worldwide to regulate the welfare of live animals in

All three surgeons were knighted for their achievements and the courage of their first patients was widely acclaimed

medical research and was alternatively named the Vivisection Act. It prohibited painful experiments on animals and the public demonstration of vivisection except to fellow practitioners and students. It also made mandatory a registry of places where such experiments might be performed with the power to certificate their practitioners [An act to amend the law relating to cruelty to animals, 1876]. The driving force behind the act had been Frances Power Cobbe (1822-1904) an Anglo-Irish social reformer (*pictured below*) [Mitchell, 2004]. The foremost feminist intellectual of her day, Cobbe advocated for women's suffrage, criticised the role of women in Victorian marriage and championed improvement in education and employment opportunities. She published widely in periodicals and produced many books and pamphlets on feminism, science and medicine, became the leader of the Victorian anti-vivisection movement and produced a two-volume autobiographical account of her life and works [Cobbe, 1894].

Frances Power Cobbe

Cobbe's movement, The Victoria Street Society, felt the Cruelty to Animals Act gave medical scientists too much latitude and continued, with Queen Victoria as patron, to campaign for the total abolition of vivisection, thus becoming a thorn in the flesh of the newly formed Physiological Society.

By the mid-nineteenth century, the functions of the brain were disputed and surgery only directed to skull injuries or the ancient unguided art of trepanation [Espinosa et al, 2022]. René Descartes (1596 –1650) had sought the seat of the soul in the pineal gland, Franz Joseph Gall (1758-1828) championed phrenology, the relevance of contours of the skull to character and personality, and Pierre Flourens (1794-1867) believed in the unity of the brain in that large parts could be removed without loss of function [Finger, 2000].

The Victoria Street Society, with Queen Victoria as patron, felt the Cruelty to Animals Act gave medical scientists too much latitude

Into this uncertainty stepped the English neurologist John Hughlings Jackson (1835-1911) and the Scottish neurologist and physiologist David Ferrier (1843-1907).

The French physicians Jean Baptiste Bouillaud (1796-1881) and Paul Broca (1824-80) had already noted that focal brain lesions could result in paralysis, loss of speech and seizures, but it was Hughlings Jackson in his observations on epilepsy, published as 'A study of convulsions' [Jackson, 1870], that led to the concept that motor functions within the brain were organised in a topographical manner. Jackson's work was supported in the laboratory by two Berlin scientists Gustav Fritsch (1838-1927) and Eduard Hitzig (1838-1907) who showed, in studies on dogs, that galvanic stimulation of the frontal cortex evoked movements in the opposite limbs [Walker, 1957].

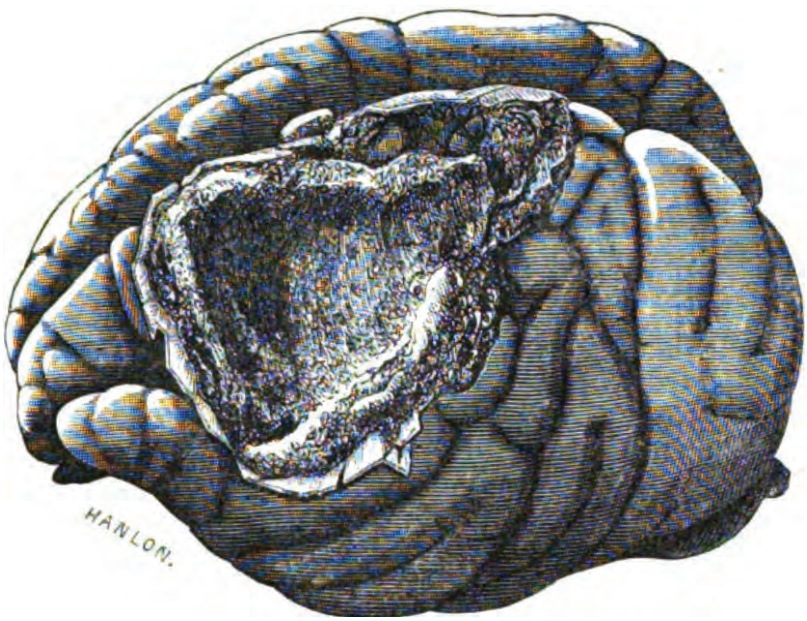


Fig 2 Drawing of lesion causing hemiplegia: Monkey demonstrated by Ferrier at the International Medical Congress 1881 (MacCormac 1881, 243)

David Ferrier and vivisection

Aberdeen born Ferrier received his medical training at Edinburgh University and thereafter took up an appointment at King's College London. In the spring of 1873 he visited the West Riding Lunatic Asylum, in Wakefield, West Yorkshire, where his former Edinburgh classmate James Crichton-Browne was physician superintendent. Like Ferrier, Crichton-Browne had, as a student, fallen under the spell of Thomas Laycock and was influenced by the latter's book Mind and Brain [Laycock, 1869]. Crichton-Browne sought to establish a research programme at the asylum to investigate brain function, with Ferrier's initial remit being to discover the sources of mental illness [Leyland, 1888] but, inspired by Jackson's theories, he immediately turned his attention to cerebral function mapping. By applying faradic stimulation to the brain surfaces of guinea pigs, cats, dogs and monkeys he was able to map out the cortical areas that elicited movement and moved on to study the areas implicated in sensation, vision and hearing. Preliminary results were published in the British Medical Journal [Ferrier, 1873a] and soon after in the West Riding Asylum Reports with a full account of methodology

accompanied by illustrations [Ferrier, 1873b]. Ferrier continued this work at The Brown Institute in London, in collaboration with fellow physiologist Gerald Francis Yeo, with further monkey studies involving the removal of brain regions. This work culminated in the publication of Functions of the Brain [Ferrier, 1876] and the equally acclaimed Localisation of Cerebral Disease [Ferrier, 1878]. Ferrier and Yeo's monkeys were anaesthetised with chloroform, operated on using antiseptic techniques and awoken to observe the effects of their brain injuries before being sacrificed for post-mortem examination.

Ferrier's work was not universally accepted and many were critical of his techniques. Foremost was Friedrich Goltz (1834-1902), professor of physiology at the University of Strasburg. A disciple of Flourens, Goltz believed in the indivisibility of the brain and not in the localisation of function. In 1881 they were to clash in a debate at The Seventh International Medical Congress. Goltz presented a dog and Ferrier two monkeys each having had areas of their brain ablated some months beforehand and observed thereafter. Goltz's dog had no focal deficit, while Ferrier's monkeys were hemiplegic and deaf respectively. The dog and the hemiplegic monkey were then slaughtered with a panel of experts agreeing that the dog's lesions were not as big as claimed and the monkey's lesion was just where Ferrier and Yeo had predicted [MacCormac, 1881] (*figure 2*). Ferrier had carried the day. Localisation of function was accepted and brain mapping tantalisingly opened the door to the possibility of human brain surgery. Ferrier's triumph was short lived. In months, The Victoria Street Society through Cobbe had investigated and found he had no licence to conduct the experiments that he had so victoriously presented. He was prosecuted under the Cruelty to Animals Act at Bow Street Court but found not guilty to the dismay of Cobbe and her fellow anti-vivisectionists who questioned the truthfulness of the defence witnesses.

Ferrier's work was not universally accepted and many were critical of his techniques

The advent of epilepsy surgery

William Macewen (1848-1924)

The concept of localising symptoms and signs to specific regions of the brain made targeted cerebral surgery feasible. Ferrier's work had confirmed Jackson's hypothesis that the nature of a seizure allowed it to be localised to a specific brain area. Macewen, widely regarded as one of the most innovative surgeons of his generation, had knowledge of cerebral localisation through following the writings of Jackson and the research of Ferrier. In July 1879, aged 31, he encountered 14-year-old Barbara Watson in the wards of Glasgow Royal Infirmary. Barbara had complained of a swelling over her left eye where a year previously a periosteal growth had been removed. Macewen and the nursing staff, formally trained by him, noticed short episodes of right face and arm twitching. These became progressively more frequent and a fatal outcome was felt imminent. Macewen initially explored the supraorbital swelling and then, on the basis of where he felt the seizures originated, trephined over the left frontal lobe and found a dural based tumour that he resected. Apart from transient right-sided paralysis and aphasia, Barbara made a full recovery with no further seizures until her death seven years later from an unrelated cause. Though no histology was taken, a meningioma has been assumed [Cushing, 1927]. Macewen first published Barbara's case in the Glasgow Medical Journal [Macewen, 1879], attracting scant attention, and then in The Lancet [Macewen, 1881]. Between 1879 and 1884 he operated on a further five patients and, though documentation is incomplete, localisation of symptoms appears to have informed the surgical approach in some if not all [Bone and Stone, 2023].

Rickman Godlee (1849-1925)

Godlee became a leading thoracic surgeon but earlier in his career, as a talented junior, he was asked to perform his one and only cranial operation. The patient, a 25-year-old Scottish male, known simply as Henderson, gave a six-month history of worsening generalised and left-sided focal seizures. Admitted to London's Hospital for the Relief and Cure of Epilepsy and Paralysis under the care of the neurologist Alexander Hughes Bennett he was diagnosed, on the nature of his seizures, with a possible tumour "in the neighbourhood of the upper third of the fissure of Rolando" and as a result of his parlous state was operated on November 25, 1884, with doctors Hughes Bennett, Jackson and Ferrier in attendance. A small glioma the size

Barbara made a full recovery with no further seizures

Victor Horsley with his pet dog

of a walnut was removed successfully but Henderson succumbed to sepsis and died three weeks later. The case was published to universal acclaim [Bennett and Godlee, 1884] with news of its tragic outcome soon to follow [Bennett and Godlee, 1885]. The publicity evoked by the surgery led to a tsunami of correspondence on the pros and cons of vivisection as well as whom, Macewen or Godlee, could claim to be the first. Before Henderson's death was known, Crichton-Browne, Ferrier's university classmate and former mentor, published a letter decrying the intellectuals who had denounced animal experimentation, claiming that "the case will be a living monument to the value of vivisection" and "the medical profession will declare with one voice that he owes his life to Ferrier" [Crichton-Browne, 1884]. The Bishop of Oxford, John Fielder Mackarness, one of those intellectuals so disparagingly referred to, responded immediately commenting on the "joyful enthusiasm" displayed by some physiologists when going about their animal work [Oxon, 1884]. Over the following weeks, with the controversy now ignited, 64 letters for or against vivisection appeared in The London Times alone [MacMillan, 2004].

Over the following weeks 64 letters for or against vivisection appeared in The London Times alone

Victor Horsley (1857-1916)

Unlike Macewen or Godlee, Horsley was both surgeon and vivisectionist, sharing with Cobbe a support of woman's suffrage. Horsley graduated in medicine from University College London before studying in Berlin and returning to London to complete his surgical training. On the April 27, 1886, James B, a 22-year-old Scottish male, was admitted to the National Hospital for Paralysis and Epilepsy under the care of Dr Hughlings Jackson. Following a childhood depressed skull fracture he had developed a worsening seizure disorder that was unresponsive to paraldehyde. The seizures were felt due to a focus of discharge around the posterior end of the superior frontal sulcus and, with Horsley having worked out the operation site from his knowledge of skull topography, surgery was undertaken. It revealed a cortical scar that was excised with cessation of seizures and full recovery [Horsley, 1886]. Horsley went on to publish a series of his and other surgeons' outcomes after epilepsy surgery [Horsley, 1890] as well as developing intra-operative brain stimulation.

He was soon to clash with the anti-vivisectionists and it was the book The Nine Circles of the Hell of the Innocent [Rhodes, 1892] that inflamed matters. Supervised by Cobbe and styled on Dante's Inferno, it catalogued animal experimentations, called out vivisectionists and frequently cited Horsley's work. Horsley, in correspondence in The Times, described the book as one of the "rankest impostures that for many years had defaced English literature being full of fraudulent misrepresentations" [Mitchell, 2004]. Cobbe replied by apologising for any minor inaccuracy but conceded little else [Cobbe, 1892]. Horsley responded by calling Cobbe a liar who had been accusing medical men of "murder, cruelty and falsehood" [Horsley, 1892]. Edward Berdoe, a supporter of The Victoria Street Society, wrote to the editor of The Times on Cobbe's behalf calling an end to the correspondence that "was not fitting for her to continue taking part in".

Epilogue

Cobbe in The Modern Rack: Papers on Vivisection [Cobbe, 1889] made it clear that she considered Ferrier's 1881 acquittal the result of medical collusion and campaigned up until her death for the total abolition of animal experimentation. By the end of the nineteenth century, Cobbe's enthusiasm and royal patronage had led to widespread support with emotive publicity for the movement (*see poster pictured below left*). In 1898 she left The Victoria Street Society, who found her aims unrealistic, and in 1898 formed the British Union for the Abolition of Vivisection (BUAV) [French, 1975].

Ferrier left animal experimentation to become a leading neurologist. In 1886 he founded the Neurological Society, becoming president in 1894, he was one of the founders of the journal Brain, and in 1890 he received the Royal Medal of the Royal Society, with a knighthood conferred in 1911 [Sherrington, 1928]. Ferrier suffered some reputational damage from his trial and was parodied by the writer Wilkie Collins, a friend of Cobbe, in The Heart of Science [Larner, 2023].

Macewen practised across a range of surgical specialties but continued to develop his interest in cranial and spinal surgery. Having never conducted animal research, he distanced himself from the vivisection debate. Appointed professor of surgery at Glasgow University in 1882, he was knighted for services to medicine in 1902 [Bowman, 1942].

Godlee's place in the history of neurosurgery was on the basis of a single operation. In 1892 he was appointed emeritus professor of surgery at University College Hospital and served as the president of the Royal College of Surgeons (1911-13). He was surgeon to the household of Queen Victoria and Kings Edward VII and George V, made a baronet in 1912 and made Knight Commander of the Royal Victorian Order (KCVO) in 1914 [British Medical Journal 1925].

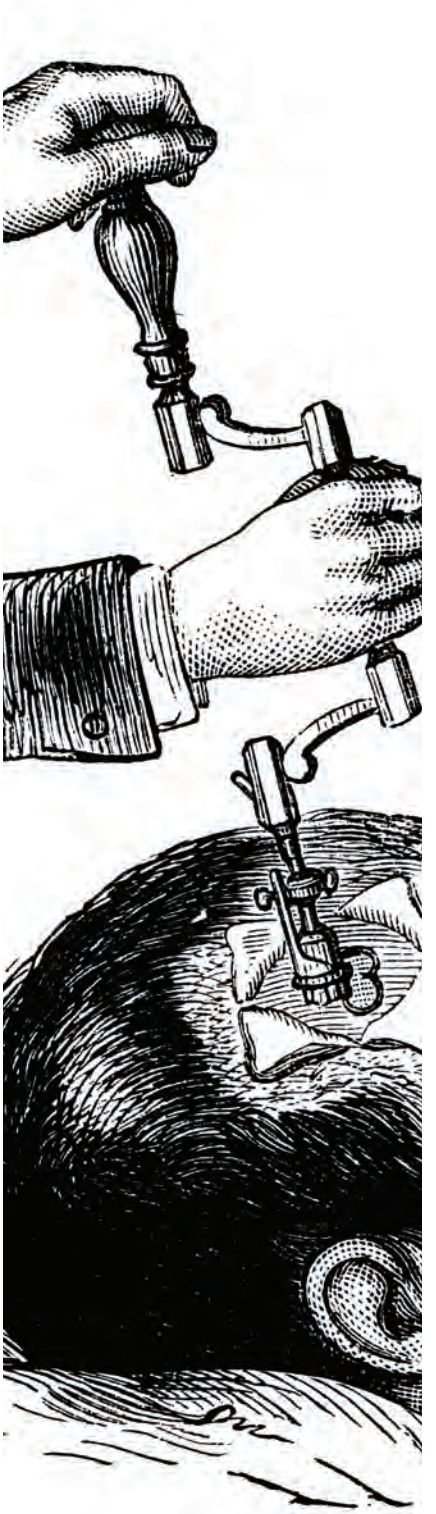
Without Ferrier's monkeys, epilepsy surgery would have taken decades longer to evolve

From 1884 to 1890, Horsley was professor-superintendent at London's Brown Institute, becoming the first fully practicing neurosurgeon at the National Hospital of Epilepsy and Paralysis in 1886. He subsequently became professor of Clinical Surgery at University College and was knighted in 1902 for his services to medicine. Among his many operative innovations was stereotactic surgery. At the outbreak of the First World War, he volunteered for active duty and died of heatstroke in Mesopotamia [Aminoff, 2022].

In the early 20th century there was increased public recognition of the medical benefits of vivisection with a decline in anti-vivisectionism. A second Royal Commission in 1912 found no need for further legal restrictions on animal experiments. The work of Wilder Penfield and Herbert Jasper in electrically stimulating the brains of hundreds of patients undergoing operative exploration for seizures under local anaesthesia [Penfield and Jasper, 1954], and the developments in imaging, meant there was no longer a role for animal studies in elucidating the functional anatomy of the brain.

Conclusion

Without Ferrier's monkeys, epilepsy surgery would have taken decades



longer to evolve and the operations of Macewen, Godlee and Horsley would not have happened. The basics of cortical localisation, derived from his work, proved essential building blocks for the likes of Penfield, Jasper and others to progress the science necessary for today's epilepsy surgery. The brutality of Ferrier's work is difficult to countenance now, but it was of its time and place and cannot be judged by current standards.

The last thought is for the martyrs of neuroscience who suffered pain, loss of function and life for the benefit of humankind without any say in the matter.

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At home EEG monitoring

The future for complex epilepsy populations?

Shiva Rudrappa from Swansea Bay University Health Board and a team from across Wales and the South of England discuss how at-home EEG testing is helping to diagnose patients with intellectual disabilities

The last two decades have seen a significant expansion in the diagnostic definitions of epilepsy. In the 1990s and before, major epidemiological studies explicitly required two or more unprovoked seizures to fulfil a diagnosis of epilepsy [Hauser *et al*, 1991]. In 2005, the International League Against Epilepsy (ILAE) conceptually defined epilepsy as a neurological disorder with enduring predisposition towards the generation of epileptic seizures [Fisher *et al*, 2005].

In 2014, a practical clinical definition of this theoretical construct was developed, with a diagnosis of epilepsy requiring two or more unprovoked seizures occurring more than 24 hours apart, or the occurrence of at least one unprovoked seizure in the presence of evidence of an enduring risk of further seizures. The qualification of the latter definition is based on the recurrence risk (at least 60% over 10 years) after two unprovoked seizures [Fisher *et al*, 2014].

Introduction

Electroencephalography (EEG) is an important investigation tool in diagnosing and managing epilepsy. However, standard out-patient EEG are often not sufficient for individuals who have a low frequency of seizure activity. Video EEG may be considered the 'gold standard' in neurophysiological testing and is useful in differentiating epileptic from non-epileptic events [Taufik *et al*, 2004]. Some people may find it challenging to access out-patient neurophysiological testing. This includes people with neurodevelopmental disorders such as intellectual disability (ID) and/or autism. Reasonable adjustments need to be made to services to help facilitate diagnostic testing (Table 1). However, even with such adjustments, in-hospital testing, particularly for extended periods, may not be tolerable. Alternatives, such as remote long-term EEG with video monitoring in the person's living environment, could be an alternative way of getting the data to help inform management.

Complex populations
An estimated 25% people with ID have epilepsy, making it the most common chronic condition associated with ID. The prevalence of epilepsy increases with the severity of ID. Furthermore, people with ID are more likely to have treatment resistance (failed two adequate trials of different anti-seizure medications (ASMs), suffer adverse effects of ASMs, and are at higher risk of sudden unexpected death in epilepsy (SUDEP) [McGrother *et al*, 2006; Young *et al,* 2015].

For people with ID and other neurodevelopmental disorders, there are a number of diagnostic conundrums. There may be challenges with cognition, communication, and a heavy reliance on accurate informant history. Differentiating an epileptic seizure from behaviour may pose the biggest challenge. Focal seizure disorders are common and may have complex presentations. Seizures can mimic behaviour, behaviour can mimic seizures [Watkins *et al*, 2022]. With the added complexity of higher prevalence of any psychiatric disorder and the impact of adverse effects of psychotropic medications including ASMs [Cooper *et al*, 2007]. Therefore, access to supportive diagnostic tools is even more relevant for those who find them the most challenging to access [Kerr *et al*, 2016]. Clarifying whether the presentation is seizure related is key to adopting an appropriate management plan and reducing risk of iatrogenic harm.

Recently, the first comprehensive scoping review of remote EEG monitoring interventions was conducted. It summarises the current evidence base to help inform choices for clinicians and adults with epilepsy [Milne-Ives *et al*, 2023]. The review was limited to studies of at-home EEG monitoring of epileptiform activity with wearable or implanted devices. A total of 23 studies were included, one study specifically looked at people with ID.

This is a cost-effective prolonged monitoring approach that can be done in the comfort of the home environment

Ambulatory EEG (including EEG-NIRS)
Ambulatory EEG (standard EEG electrodes on a portable cap, without video recording) and portable EEG-NIRS (near infrared spectroscopy; which measured change of oxygen in the blood when a brain region is active) was shown to have diagnostic utility and provide useful information that informed clinical management plans (51-72% of the time). This is a cost-effective prolonged monitoring approach that can be done in the comfort of the home and the patient can be engaged in activities (artefact possible). The main limitations of such devices are technological sophistication with no video recording, and the limitation of scalp EEG to detect seizure activity. This reinforces the reliance on detailed information from observers, which may be interpreted differently to a trained clinician [Dash D *et al,* 2012; Faulkner H J *et al*, 2012; Sawan M *et al*, 2013].

Home video EEG telemetry
This may be an option to provide the best approach to neurophysiological testing in a real-life context. It would be suitable for those people unable to tolerate in-patient hospital assessment, or for those who have significant commitments at home such as caring responsibilities. This approach may be particularly useful for people with neurodevelopmental disorders, to help minimise change to routine and provoking anxiety. For best implementation in such scenarios, a multidisciplinary approach is sensible, with support from community healthcare professionals. Home video EEG telemetry is usually conducted over a few days and so will only provide a 'snapshot'. This technology would be most useful when there are regular events and for diagnostic purposes. Other more complex scenarios, such as ASM changes (discontinuation), sleep deprivation and other interventions, are not possible due to lack of hospital environment and staffing for safety.

Weighing up the cost analysis is not straightforward, as the equipment needs to be purchased and technician time accounted for.

Table 1. Reasonable adjustments to generic services for people with neurodevelopmental disorders

Reasonable Adjustments – Preparation
- Information in an accessible format (specific to the individual)
- Site visits
- Empty waiting area
- First/last appointment
- Easy access-including minimal distance/avoiding busy public areas
- Longer appointment times
- Additional support staff
- Consideration of sensory needs
- Opportunities for engagement in preferred activities

However, overall, this is a more cost-effective method and more accessible when established. The clinical utility has been shown to be comparable to in-patient EEG monitoring (91-97%), with most people preferring to be tested at home than in hospital [Kandler R *et al*, 2017; Slater J D *et al*, 2019; Syed TU *et al*, 2019; Brunnhuber F *et al*, 2020; Elmali AD et al, 2021].

Wearable EEGs

Wearable EEGs have the advantage of being low-profile, low-maintenance, non-invasive, more comfortable than multiple electrodes and possibly cost effective. They have the potential to be a first step investigation in some patients and aid long-term monitoring, even empowering people with epilepsy to help direct treatment plans. There are limitations in how data is collected, reducing sensitivity and specificity. Such devices can be an aid to the epilepsy treatment toolkit, but have less utility in diagnostics, particularly if accurate seizure localisation is required (eg: epilepsy surgery assessment). Wearable devices have been shown to better predict seizure activity than clinical decision making alone, although the false positive rate is higher [Cook MJ *et al*, 2013; Coşgun E *et al*, 2021].

Sub-scalp EEG

Although sub-scalp EEG is minimally invasive, it is not tolerable for all. Sub-scalp EEG allows for long-term monitoring and seizure prediction that influences management. The signal is comparable to scalp EEG and less noisy. It may be sensitive to small neurological events such as sleep transients and only covers a small cortical surface area. The data obtained would need an extensive analysis from a neurophysiologist and may be susceptible to artefacts. However, it is better tolerated by patients, with no impact on patients' mobility, and does not require hospitalisation [Weisdorf S *et al*, 2018; Weisdorf S *et al*, 2019; Stirling *et al* 2021; Viana PF *et al,* 2021].

Intracranial EEG

With an invasive option there is a risk of trauma, inflammation and induced seizure activity on implantation that settles over time. This application is multifunctional, offering monitoring and seizure prediction. Beyond this it offers the opportunity for therapeutic electrical stimulation and adaptive deep brain stimulation (DBS). It allows for long-term monitoring with no impact on mobility or necessity for long-term hospitalisation [Cook MJ *et al*, 2013; Ung H *et al,* 2017; Constantino AC *et al* 2021].

Conclusion

This review provides a summary of the different avenues of technology available rather than specific devices. In general, the studies observed that remote EEG monitoring provided clinically useful results, often largely comparable to in-patient recordings. Home EEG monitoring was generally acceptable to patients. There are a variety of remote-monitoring tools being developed and evaluated. More research is required in complex populations to inform which monitoring systems are suitable.

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Genome sequencing

A transformative genetic study for infants with epilepsy

A team from Harvard, Boston Children's Hospital and Great Ormond Street Hospital explain their research into the genome sequencing of infants

Infantile onset epilepsies are frequently genetic in origin and the number of known monogenetic causes has exploded in the last decade. Genetic etiologies for epilepsies are important knowledge for a variety of reasons, including recurrence chances in families, understanding of the ion channels and proteins involved and potentially targeted therapies dependent on the gene identified [McTague *et al*, 2016].

A recent systematic evidence review (SER) and metanalyses determined that overall diagnostic yield over all test modalities is 17% in the epilepsies. However, yield differed greatly between test type, with genome sequencing the highest at 48%, exome at 24%, multi-gene panels at 19% and microarray at 9%. Both the presence of neurodevelopmental comorbidities and/or the presence of a developmental and epileptic encephalopathy increased yield [Sheidley *et al*, 2021].

The National Society of Genetic Counselors published a practice guideline for genetic testing and counseling for the epilepsies, based on the outcomes of the SER. The guideline has also been endorsed by the American Epilepsy Society. In this guideline, genetic testing is strongly recommended for all individuals with unexplained epilepsy of all ages. Exome and genome testing are conditionally recommended over a multi-gene panel, but any of the three can be first-tier testing followed by chromosomal microarray. The second strong recommendation is that genetic testing be ordered in the setting of qualified healthcare providers in the setting of appropriate pre and post-test genetic counseling [Smith *et al*, 2021].

Early genetic diagnosis can guide urgent treatment decisions and provide critical information to families

Our pioneering new study demonstrates the immense clinical potential of rapid broad-based genetic testing for infants with epilepsy. Published in *The Lancet Neurology*, this research shows that early genetic diagnosis can guide urgent treatment decisions and provide critical information to families of babies with unexplained seizures.

The study, termed Gene-STEPS (Shortening Time of Evaluation in Paediatric Epilepsy Services) was conducted by the International Precision Child Health Partnership, a collaboration of four children's hospitals in Australia, Canada, the UK and the USA. We enrolled 100 infants who developed new-onset epilepsy or complex febrile seizures at <12 months old and presented to one of our sites. Using rapid genome sequencing, primarily trio sequencing with samples from the infant and both biological parents, our teams identified a genetic cause of epilepsy in 43% of infants by just over a month after seizure onset.

This diagnostic rate represents a remarkably high yield for rapid genetic testing and is similar to the 48% diagnostic rate for (non-rapid) genome sequencing in the unexplained epilepsies SER [Sheidley *et al*, 2021]. The development of next-generation sequencing has revolutionized genomic medicine over the past decade. However, this study is the first to demonstrate the power of applying rapid genomic sequencing to a disease-specific cohort, specifically infants with new-onset epilepsy.

The findings suggest certain infants with new-onset epilepsy are more likely to have a genetic diagnosis identified, although a larger sample size is needed for a multivariable prediction model. Infants with neonatal-onset seizures had a higher diagnostic yield (74%) than those with onset outside the neonatal period, suggesting that rapid genetic testing may be especially useful for guiding treatment in babies who develop seizures in the first weeks of life.

For those referred from neonatal or pediatric intensive care units, the diagnostic yield (71%) was higher than for those referred from other inpatient or outpatient units, suggesting that infants who require intensive care and often have more severe seizures or other associated comorbidities are more likely to have a detectable genetic etiology.

The diagnostic yield also varied by epilepsy syndrome, with high yield for self-limited epilepsies (87%) and early infantile developmental and epileptic encephalopathies (54%), and a lower yet still important yield for infantile epileptic spasms syndrome (19%).

Across the diverse cohort, the genetics of underlying infantile epilepsy turned out to be highly heterogeneous. The study found 34 different genes or genomic regions implicated in epilepsy among the 43 diagnosed infants. There were very few repeating variants. Instead, the causes were wide ranging.

This research shows the advantage of scanning across the entire genome to identify novel genetic drivers

Previously, a 2022 review found the most seen genes in NGS studies included SCN1A, KCNQ2, CDKL5, SCN2A, PRRT2 and STXBP1 [Symonds and McTague, 2021]. This was reinforced by a 2023 paper regarding 103 individuals with developmental and epileptic encephalopathies who received exome sequencing [Scheffer *et al*, 2022] and a retrospective cohort study of 152 individuals with a genetic diagnosis [Haviland *et al*, 2022].

In our study, we did not see a predominance of KCNQ2, PRRT2 or SCN1A, although we anticipate seeing more individuals with these genes as the study continues. This is also likely due to the prospective nature of our study design and small sample size. However, this diversity highlights the power of rapid genome sequencing to cast a wide diagnostic net. Previous studies utilising gene panels could only search for a limited selection of known epilepsy genes. This research shows the advantage of scanning across the entire genome to identify novel genetic drivers.

For the vast majority of genetic diagnoses, there was immediate clinical utility for the infants and families. In a remarkable 98% of positive cases, the results informed urgent treatment decisions, avoidance of unnecessary tests, prognostic information and genetic counseling. Similar to other exome sequencing studies for the epilepsies [Graifman *et al*, 2023], a genetic counselor provided anticipatory guidance regarding prognosis, relevant foundations and support groups.

This demonstrates the immense, tangible value of early genetic diagnosis. Identifying the underlying variant provides personalised information to guide precision care, even when no specific treatment exists for that gene.

For example, certain genetic variants can indicate likely seizure control outcomes in that individual child. Other DNA variants suggest potential developmental impacts, allowing monitoring and interventions targeted to the infant's needs. Some implicate high risks of associated health conditions.

If the specific genetic cause indicates a favorable prognosis,

anti-seizure medications may be weaned or discontinued according to the treating neurologist. If it signals likely drug-resistant epilepsy, more intensive treatments might be considered earlier.

The genetic results also provide vital information and guidance regarding recurrence risk for future pregnancies and family planning. For families, simply identifying the cause can provide closure after the trauma of sudden infantile seizures. Meanwhile, clinical care can be tailored based on the gene variants found.

This study represents a shift towards genomic sequencing as a first-line diagnostic work-up for infants with unexplained epilepsy. The research provides a blueprint for integrating rapid genetic testing into routine clinical practice worldwide.

Rapid sequencing of children with rare diseases is already gaining ground in some specialised centres and neonatal intensive care units. However, this study is the first demonstration of its power in a disease-specific cohort across clinical settings.

Currently, in most hospitals, genetic testing for infants with epilepsy can take months to years to complete. Results are usually not available until after key treatment decisions are made. But this research shows, for the first time, that rapid genetic answers are feasible in real-world practice, even primarily in outpatient settings.

More than 90% of parents who were approached consented to enroll their infants in the study. This remarkably high percentage demonstrates that parents are highly motivated to identify the underlying cause of their child's seizures.

This study ushers in a new paradigm for evaluating infantile epilepsy. In the past, clinical diagnosis focused on observing the outward signs and symptoms. Genetic testing, if done at all, was an afterthought – but this research shifts genetics to the forefront.

Rapid sequencing promises to reduce diagnostic delays, allow earlier genetic-guided intervention and empower families with critical information. For vulnerable babies with treatment-resistant seizures, early answers can be life changing.

Looking forward, there is more work to be done. This initial study only begins to scratch the surface of understanding genetics in infantile epilepsy.

The cohort was relatively small at 100 infants. Expanding the study population and genetic analyses will likely implicate even more epilepsy genes. It will be important to build large databases of variants linked to clinical outcomes.

Additionally, future studies must investigate the lifelong impacts of rapid genomic diagnosis. Long-term follow up will further elucidate benefits across neurodevelopmental, educational, quality of life and economic realms.

There are also essential questions surrounding how to responsibly implement rapid genetic screening. Infrastructure must be developed for consistent genetic counseling, family support and longitudinal monitoring after sequencing. Widespread adoption will require major investments in training physicians, genetic counselors and clinical staff.

Ethical issues around screening for secondary findings unrelated to epilepsy will also need to be addressed. But this study provides the first evidence that early sequencing is likely to yield significant advantages that outweigh these considerations.

In summary, this transformative research marks a turning point in the

clinical approach to infants with epilepsy. It will pave the way for accelerated genetic diagnosis to become standard care. The possibilities of precision medicine are now clearly visible on the horizon.

For clinicians, this work should ignite a sense of urgency to integrate rapid sequencing capabilities and advocating for financial policies that support these accelerated tests. We now have evidence that early genetics can guide targeted interventions, reduce diagnostic delays and give families hope. This study provides a playbook for how to implement rapid testing in both inpatient and outpatient settings.

Rapid genome sequencing promises to shed light for infants and families struggling with the devastating impacts of early life epilepsy. This work represents a major milestone on the path towards more optimal outcomes through gene-guided care.

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epilepsy action

Epilepsy Action is here for you

helpline

Epilepsy can be very confusing. Our Helpline team are ready to answer any questions you might have on the phone, via live chat or email.

talk and support

If you want to talk to other people about life with epilepsy, you're welcome to come to one of our Talk and support groups to meet and share your experiences either on line or face-to-face.

befriending

Not everyone's ready for a group, though – one-to-one support through Befriending might be better for you. We'll connect you to a volunteer who will offer you a friendly listening ear either on the phone or online.

counselling

Counselling can be really helpful when things get tough – we're ready to help in Wales and Northern Ireland. Our professional Counselling team can provide the support you need online or over the phone.

family support Northern Ireland

Epilepsy doesn't just affect the person with the diagnosis – that's why our Family support service is there for family members and carers in Northern Ireland.

"Epilepsy Action has made such a big difference in my life... they have helped me learn to live with my condition"

epilepsy.org.uk/support

Epilepsy Action Helpline: freephone 0808 800 5050
email helpline@epilepsy.org.uk **epilepsy.org.uk**

Tom Shillito

Research update

Epilepsy Action health improvement and research manager, Tom Shillito shares updates from Epilepsy Action's research work

Step Together

The Step Together toolkit is a self-assessment tool that Epilepsy Action has created in collaboration with Professor Rohit Shankar. The toolkit assesses the quality and cohesiveness of care being provided to people with epilepsy and a learning disability. It can be used at place, service, system and regional levels, and is free to access through our website. It has been completed by many systems and services already, including a region-wide project in the Midlands, which was a finalist for a HSJ Patient Safety Award this year.

The toolkit is continuing its rollout across the UK. Cornwall is the latest ICS to adopt the toolkit, and it is completing the self-assessment over the festive period, with results expected in March 2024.

If you would like more information about how the toolkit can be used in your area, please contact Tom Shillito on tshillito@epilepsy.org.uk.

The toolkit can be downloaded at www.epilepsy.org.uk/professional/step-together.

Our preliminary results show that access to healthcare professionals varies drastically across the UK

Epilepsy workforce figures

The neurology workforce crisis continues to cause problems for patients and healthcare professionals. This crisis is especially prominent within epilepsy, with long waiting lists and limited access to support. To investigate this further, Epilepsy Action recently requested workforce figures from every NHS Trust in England. The aim of this is to find out how many neurologists, epilepsy specialist nurses and other related healthcare professionals are available in each region.

The analysis of this data is ongoing, but our preliminary results show that access to healthcare professionals varies drastically across the UK. The number of neurologists per person with epilepsy is highest in London, where epilepsy prevalence is lowest, and lower in more deprived areas where epilepsy prevalence is higher. Access to epileptologists is even more limited, with some regions having five or fewer epileptologists to care for tens of thousands of people with epilepsy. Access to epilepsy specialist nurses is also varied across the country.

The full analysis will be reported on the Epilepsy Action website when it has been completed.

Epilepsy and maternity

Epilepsy Action, in collaboration with NHS England's North West Region Midwifery Service, is undertaking a project to map the services available to pregnant people with epilepsy, as well as services offered pre-conception and perinatally. This project will also be investigating what excellent care for pregnant people with epilepsy looks like through consultation with both service users and healthcare professionals.

The risk of maternal mortality is up to 10 times higher for people with epilepsy compared to the general population. There is also a significantly higher risk of preterm birth, stillbirth and miscarriage. It is also known that many anti-seizure medications significantly increase the risk of birth defects and that these risks are not adequately discussed with the people taking those medications. Babies born to someone with epilepsy also have a higher risk of neonatal intensive care admission and neonatal or infant death.

A UK report from 2021 demonstrated that the number of deaths from Sudden Unexpected Death in Epilepsy (SUDEP) had almost doubled compared with the previous three years. Most women who died had clear risk factors for SUDEP, but had not had prevention measures discussed with them, or a medication review.

The 2023 MBRRACE report has further highlighted the need for work such as this. The report found that 40% of neurological maternal deaths caused by a neurological condition were people with epilepsy. It found

The risk of maternal mortality is up to 10 times higher for people with epilepsy compared to the general population

that between 2019 and 2021, 17 people died from causes related to epilepsy, 14 of these were SUDEP cases, which is twice the rate of SUDEP cases between 2013-2015. This project is currently being set up and will run from January to December 2024.

Research volunteers

Our research development volunteer group continues to grow, with nearly 100 members. These volunteers are trained in patient and public engagement, and can offer feedback on both research projects, documents and processes involved in healthcare.

In recent months they have been involved in a national tendering process, given feedback on many research project proposals and patient information sheets, and attended focus groups and one to one interviews. If you'd like to find out more about how our volunteers can support your research, please contact researchadmin@epilepsy.org.uk.

Further reading

Shankar R, Scheepers M, Liew A, Cross H, McLean B, Tittensor P, Slowie D, Toker-Lester H, Pullen A & Walker M (2020) Step Together Integrating Care for People with Epilepsy and a Learning Disability

If you are interested in completing the toolkit for your service, trust or system, all of the details can be found here: www.epilepsy.org.uk/professional/step-together

Markus Reuber

Highlights

Top picks from *Seizure*

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

My editor's choice from volume 111 of Seizure is a retrospective observational cohort study by Colin B. Josephson et al. intended to explore clinical and socio-economic features affecting the mortality risk of patients with late onset epilepsy [Josephson *et al,* 2023]. Based on the records of more than 1,000 older adults thought to have epilepsy and more than 10,000 controls (>65 years) – identified from more than one million primary care patients – the study describes 10 feature clusters associated with different outcomes. Cases with epilepsy were selected from the primary care database using a method initially developed for the Secure Anonymised Information Linkage (SAIL) databank (Wales, UK), which had previously been shown to spot people with epilepsy with a sensitivity of 88% and specificity of 98% [Fonferko-Shadrach *et al*, 2017]. The study's findings were derived from the linkage of primary care and electronic hospital episode statistics (HES) data. Additional information about cause of death was obtained from the linked UK Office for National Statistics (ONS). An unsupervised machine learning approach was used to characterise the clusters. While the hazard ratio (HR) of premature death was elevated to 1.7 (95% CI 1.5-2.0) across individuals with late onset epilepsy, the risk was found to be much higher in some of the clusters, including those named 'dementia and anxiety' (HR 5.4; 95%CI 3.3-8.7), 'brain tumour' (HR 5.0; 95%CI 2. 9-8. 6), 'intracranial haemorrhage (ICH) and alcohol misuse' (HR 2.9; 95%CI 1.8-4.8), and 'ischaemic stroke' (HR 2.83; 95%CI 1.8-4.0). Seizure-related cause of death was uncommon and restricted to the 'ICH and alcohol misuse' and 'healthy female' clusters.

This study is a good example of a research approach that has been used increasingly over recent years – facilitated by linkable electronic databases and advances in machine learning. This 'big data' approach has given rise to a debate reflected in two other publications in volume 111 of Seizure: an editorial by Randi van Wrede et al [Von Wrede *et al,* 2023] and a response by Julie W. Dreier [Dreier *et al*, 2023]. Van Wrede et al. make the point that 'big data' studies often draw broad conclusions without taking sufficient account of intra-individual variability. They state that some 'big data' studies in the field of epilepsy fail to differentiate between epilepsy as a cause, consequence or association of comorbidities or other relevant pathological findings. Furthermore, they highlight the risk of simplistic headlines and secondary reports promoting misunderstandings of epilepsy – even if the limitations of the original work had been discussed by the authors in the initial publication [Von Wrede *et al,* 2023]. In contrast, Dreier et al. point to the great potential and achievements of 'big data' studies. They refer to the ready availability of data, ensuring cost-effective use of limited research funds, as well as the large size of the cohorts, allowing for the inclusion of millions of subjects and exploration of rare exposures or outcomes. They list the reduction of selection bias, availability of longitudinal data, enabling researchers to investigate long-term effects, and the elimination of recall bias through prospective data collection as strengths of the 'big data' approach. They remind readers of the confirmation of the teratogenic effects of valproate as an important discovery based on 'big data' studies.

My editor's choice gives readers an opportunity to make up their own minds

My editor's choice gives readers an opportunity to make up their own minds: are the feature clusters identifying some patients as being at particularly high risk of early death clinically useful? Could they encourage clinicians to focus their attention on patient groups at particular risk – such as 'healthy females'? Or are the 'big data' diagnoses so often incorrect and the features so vague that the analysis by Josephson et al. is likely to promote pointless anxiety and a waste of resources?

Modified Atkins diet for drug-resistant epilepsy

Fasting and other manipulations of ordinary diets have been used as treatments of epilepsy for more than 2,500 years. The scientific era of diet treatment for epilepsy goes back to the 1920s when the ketogenic diet (KD) was introduced to mimic the beneficial effects that had been observed of fasting on seizures. This diet was commonly used into the 1940s but fell into decline with the advent of more effective pharmacological treatments for epilepsy such as phenytoin. Its "rediscovery" in the 1990s has been linked to the dramatic effects this diet had on the seizure control of a two-year old boy called Charlie. His amazing improvement with the KD caused his father to form The Charlie Foundation, and it inspired a movie starring Meryl Streep, which rekindled interest in this non-pharmacological treatment in the USA and elsewhere [Wheless, 2008].

Over the last three decades there has been accumulating evidence of the effectiveness of the KD with a 4:1 ratio of fat to protein and carbohydrates, and the KD has become the gold standard treatment for epilepsy in metabolic disorders such as Glucose Transporter Protein 1 (GLUT-1) deficiency syndrome or Pyruvate Dehydrogenase Deficiency [D'Andrea Meira *et al*, 2019]. While the evidence of effectiveness beyond these rare conditions has been rated as being of relatively low quality, in view of the lack of blinding and the small size of most studies, a recent Cochrane review concluded that up to 55% of children can achieve seizure freedom with the KD after three months while up to 85% of children achieve a >50% seizure reduction [Martin-McGill *et al*, 2020]. The mechanisms by which the KD achieves an anti-seizure effect remain uncertain. It is possible that different mechanisms are relevant in different patients [Youngson *et al*, 2017].

Over the last three decades there has been accumulating evidence of the effectiveness of the ketogenic diet

Unfortunately, the clinical use of the KD is associated with several practical problems that have only partly been overcome by the availability of specially formulated dietary products. The introduction of the diet typically involves hospitalisation, close metabolic monitoring with blood and urine tests is required to maintain it, and the low carbohydrate content of the KD poses an adherence challenge for people who can help themselves to foods they like. In addition, the KD can be associated with side effects such as nausea, vomiting, diarrhea and kidney stones, and there are concerns about its long-term safety.

The fact that many patients abandon the KD for these reasons has stimulated interest in diets with positive effects on epilepsy that are easier to adhere to – such as the Modified Atkins Diet (MAD). Like the KD, this diet limits the amount of carbohydrates, but aims at a much more easily achievable 1:1 ratio of fat to carbohydrates without meal-specific restrictions [Kossoff *et al*, 2008].

My editor's choice from volume 112 of Seizure, a systematic review and meta-analysis, is based on studies involving 575 patients, of whom 288 used the MAD as a treatment for epilepsy. It makes an important addition to the literature by combining the results of several smaller studies. It concludes that both adults and children receiving MAD plus standard drug therapy are more than six times more likely to achieve a >50% seizure frequency reduction than those receiving usual diet plus drug therapy. While there is still much to learn about which patients are likely to respond best to MAD, the combination of previous primary research allowed the authors to draw new conclusions about the likely effectiveness of the MAD in adults with epilepsy, the incidence of side effects, and it improved the precision of the estimated effect size of this diet.

Exome analysis focusing on epilepsy-related genes in children and adults with sudden unexplained death

When Darwin described its basic principles, natural selection was thought to be the key driver for evolutionary change – an idea characterised by Herbert Spencer in 1864 as the "survival of the fittest". What Spencer and Darwin meant to say was that individuals or species that are better adapted to their environment have a relative reproductive advantage. Since then, we have learned a lot more about gene-environment and gene-gene interactions. We have begun to understand how epigenetic mechanisms can contribute to the heritability of learned patterns of behaviour – and thereby how our ancestors' experiences can ensure we are optimally prepared for the environment we have inherited from them [Ladd-Acosta *et al*, 2016].

In parallel with the evolution of our genetic adaptation, there has been an evolution of its comprehension. This evolution has been driven by our low tolerance of being unable to understand the things

happening to or around us. As a species, and as individuals, we have an urge to explain our experiences. We are more likely to get distressed by experiences we cannot explain than by those we have an explanation for (even if the explanation is incorrect).

One context in which this becomes evident in medicine is when a person dies unexpectedly and without explanation. In children this scenario is called Sudden Infant Death (SID), in adults Sudden Unexpected Death (SUD). While many might prefer a sudden and unexpected death for themselves over one following a long period of suffering, death often causes particular trauma to those left behind when it is unexpected and unexplained.

My editor's choice from volume 113 of Seizure is a paper by Sarah E. Buerki et al. exploring the possible explanatory genetic contributions to SID and SUD [Buerki *et al,* 2023]. Previous genetic postmortem studies mainly focussed on genes associated with cardiomyopathies and cardiac arrhythmias. Potentially relevant genetic variants in such genes have been identified in around 20% of individuals whose deaths had been categorised as SID, with similar detection rates in adults who died of SUD [Neubauer *et al*, 2017], [Tester *et al,* 2018], [Guo *et al,* 2021]. Genes associated with cardiac pathology have also been examined in people thought to have died of SUD in the context of epilepsy (SUDEP). A recent review of such studies reported likely pathogenic gene discovery rates of around 11% [Chahal *et al*, 2020].

The genetic postmortem study by Buerki et al. focused especially on 365 epilepsy-associated variants – on the basis that a proportion of SUD may be attributable to SUDEP rather than primarily cardiac causes. Likely pathogenic variants were found in 19/155 (12.2%) of SIDS and in 6/45 (13.3%) of SUD cases. The potential relevance of this discovery is supported by the observation that genetic variants linked to epilepsy were found more commonly in the subgroup of SUD cases that were likely to have been linked to epilepsy (i.e. SUDEP): 4 of these 9 cases (44.4%) harboured such variants. Of course, the presence of a genetic variant linked to epilepsy does not mean all these individuals had experienced seizures or died of SUDEP. However, this finding supports the idea that SUDEP may explain more cases of SID and SUD than previously assumed – and that greater priority should be given to the prevention of SUDEP through the improvement of epilepsy services.

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Dates for the diary

Dates and events may be subject to change – please check on the relevant websites.

2024

24-26 January
BPNA 2024 Annual Conference
Bristol, UK
bpna.org.uk/conference/2024

3-8 March
4th International Training Course on Neuropsychology in Epilepsy
Lyon, France
bit.ly/3gLFWD4

25-28 March
ILAE teaching course:
EEG in the First Year of Life
Cambridge, UK & Online
bit.ly/3uvZZM9

5-8 May
Seventeenth Eilat Conference on new Antiepileptic Drugs and Devices (EILAT XVII)
Madrid, Spain
bit.ly/3u7Mzm6

11-12 May 2024
ILAE British Branch 19th Epilepsy SPR Teaching Weekend.
Birmingham University, UK
bit.ly/47ysQy4

29 June-2 July
10th Congress of the European Academy of Neurology
Helsinki, Finland
bit.ly/47LSi3L

7-15 September
15th European Epilepsy Congress
Rome, Italy
bit.ly/45p17Pg

23 September
ILAE British Branch Annual Scientific Meeting
Liverpool, UK
bit.ly/3Gjx8gO

2025

30 August-3 September
36th International Epilepsy Congress
Lisbon, Portugal
bit.ly/3uz1ARq

Next issue:

Dr Louise Spiers

Dr Spiers discusses her research into people with epilepsy who might have what could be considered exceptional, anomalous and spiritual experiences.

If you are interested in submitting a research paper for inclusion in *Epilepsy Professional,* please contact the Editor:

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optima

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