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A genomics revolution
Epilepsy genetics and precision medicine
Deb Pal | Stephanie Oates

Language of epilepsy – Richard Appleton

A history of stress – Christophe Bernard

Ultra long-term EEG – Duun-Henriksen | Richardson

In art, a little ambiguity can go a long way. Art is often 'open to interpretation' and an opportunity to share different perspectives. In science – and more specifically, medicine – ambiguity isn't so welcome. An ambiguous symptom, or test result, or diagnosis could be a big problem for doctor and patient alike.

One place where we can control ambiguity – but seemingly, sometimes don't – is in our literature and language. On page 16, Prof Appleton discusses some questionable terms we use in epilepsy which leave the door open for misunderstandings. He suggests ways in which we can avoid these and be a lot clearer when we discuss epilepsy.

And where an effort towards improved clarity is concerned, our other articles this issue follow suit. On page 10, Prof Pal and Stephanie Oates discuss how developments in genomics technology mean that we know a lot more about epilepsy causes than we did in the past. Dr Bernard's article on page 22 offers more clarity on why stress may be a catalyst for seizures, epileptogenesis and comorbidities in some – but not all – individuals. And on page 26, Dr Duun-Henriksen and Prof Richardson describe how ultra long-term EEG monitoring may be able to offer a more accurate picture of seizure frequency than seizure diaries.

Finally this issue, on page 31, Prof Seri pays a warm tribute to his friend and colleague, Prof Graham Harding, who died in 2018. If one thing *is* clear, it's that Prof Harding was very well loved and respected by everyone who knew him.

We hope you enjoy this issue.

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Ultra long-term EEG

Illuminating a blind spot in epilepsy care

Dr Duun-Henriksen and Prof Richardson look at a new device for ultra long-term EEG recording. They discuss the practicalities, possible value and potential issues and implications of using such a device to more accurately establish seizure frequency and activity

When optimising treatment for people with epilepsy, doctors are faced with two key blind spots. One is the exact number of seizures the patient is having and the other is how well the patient adheres to taking their medication. With the arrival of an entirely new medical device for continuous EEG monitoring in everyday life, it might be possible to shine a light on the first blind spot. We discuss this new device, its advantages and caveats, potential other ways to obtain the same kind of data and how it will impact clinical practice today and in the future.

Current tools for seizure detection

Seizure detection and monitoring has been an important area of research for many years. For example, sleep seizures are shown to be a risk factor for sudden unexpected death in epilepsy (SUDEP) [Nobili *et al*, 2011; Lamberts *et al*, 2012]. Effective monitoring of these and intervention from carers or family members can help reduce this risk. We also know that reducing the number of generalised tonic-clonic seizures (GTCS) is one of the biggest elements in reducing SUDEP risk [Hesdorffer *et al*, 2011]. Accurate detection and monitoring of seizures is therefore an essential part of managing these. Monitoring devices can offer promise with data collection, future possible seizure prediction and better epilepsy treatment.

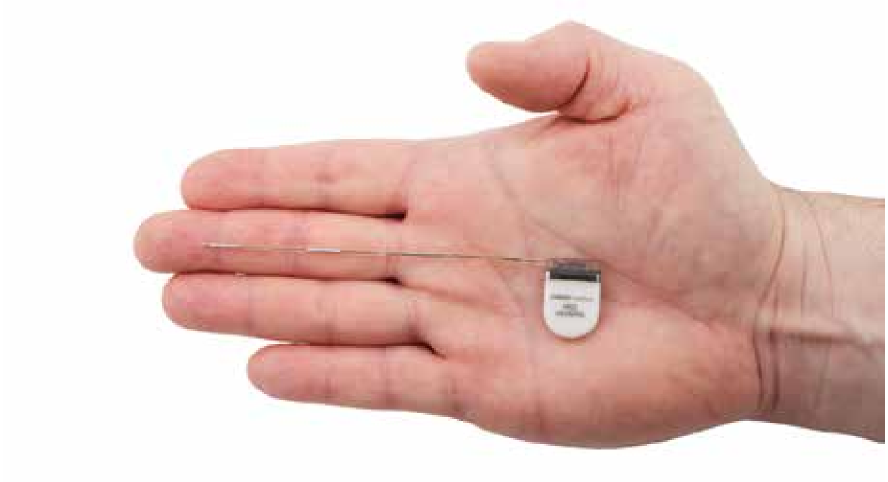
Different monitoring devices have been developed and studied, and while some have seen successes, they are not without their problems. For more than 25 years, patients have used a motion detector under the bed mattress for sleep seizure monitoring. However, a lot of patients and their caregivers complain that they are not sufficiently reliable [Bruno *et al*, 2018]. Recently, different wearable sensors have become available, but only a few are classified as medical devices for detecting seizures. One medical grade solution is the Empatica Embrace wristband. While it relies on measures such as movement, electrical skin conductivity and temperature of the skin, it is approved exclusively for

Many patients are unaware of their actual seizure frequency – studies have shown that self-reported sensitivity is as low as 30% in focal epilepsy and even lower for sleep seizures

GTCS. Another solution is the NightWatch from Livassured which bases its recordings on heart rate and movement. By focusing on sleep seizures, they have managed to get few false alarms. The device is approved for convulsive seizures and only during sleep.

Many patients are unaware of their actual seizure frequency. Studies have shown that self-reported sensitivity is as low as 30% in focal epilepsy and even lower for sleep seizures [Hoppe *et al*, 2007]. But even with the tools that are currently available, achieving an objective measure of the individual patient's seizure burden to guide treatment remains a challenge.

Figure 1: The 24/7 EEG SubQ implant, which gets placed in the sub-scalp layer under local anaesthesia



A more accurate seizure detection could be achieved with EEG. Current EEG monitoring is limited to five to 10 days, either as an in-hospital stay or an ambulatory home monitoring. While these methods yield a high sensitivity in epilepsy diagnosis, their value in treatment optimisation is limited as they are costly and can be a burden. Patients might have seizures too infrequently to be measured during a conventional EEG-recording.

A new EEG monitoring device

The 24/7 EEG SubQ device from UNEEG medical was just recently CE-marked. It was developed to get an objective measure of seizure burden in people with epilepsy by continuously recording in their everyday life in an unobtrusive and discreet way. A 10cm lead with electrodes to measure two-channel EEG as seen in *Figure 1* is implanted in the sub-scalp layer during a 20-minute procedure under local anaesthesia. The device was developed using standards from cochlear implants, so after implantation, it can stay implanted for up to 12 months. There is no battery in the implant, so an external device smaller than a £1 coin needs to be placed on the outside of the skin to transfer power wirelessly and receive the recorded data. This data is transferred by a small wire to a

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data recorder the size of a match box which can be worn underneath the patient's clothing. *Figure 2* gives an overview of how it is worn. This

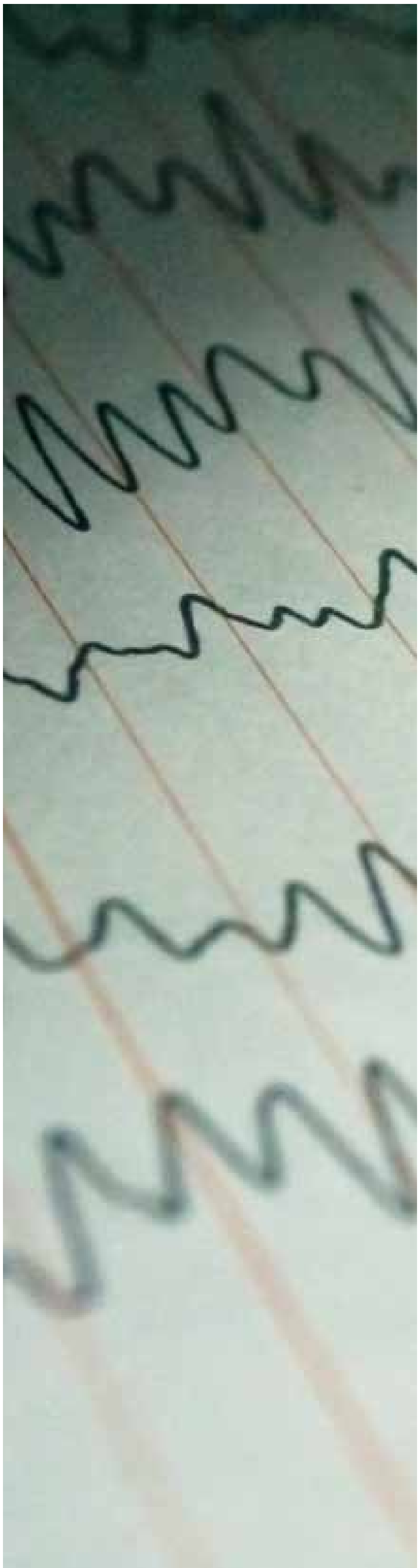


Figure 2: The UNEEG 24/7 as worn in everyday life. A disc smaller than a £1 coin is attached to the skin behind the ear by double adhesive tape while the storing- and battery-unit is worn underneath the clothes. Only a magnet to attach the logger and a small wire from the disc to the logger are visible

technology means the patient can be sent home with a discreet device which records brain activity day and night for as long as required.

All evidence of the performance of the device comes from studies in Denmark so far. A study at King's College London has just commenced, but no results are yet available. Thirty-five subjects, of whom nine have epilepsy [Weisdorf *et al*, 2018], have been using the device for between four and 13 weeks. A total of more than 1,500 days of continuous EEG have been collected without any device-related serious adverse events. Some patients reported headache as a result of surgery. One also had a minor rash due to continuous use of the double adhesive pad to attach the external device. However, all events were transient. One patient withdrew prematurely because the device was felt to be annoying.

The subcutaneous EEG device has the potential to provide crucial data when routine or video-EEG and patient seizure diaries are inadequate. However, the extensive amount of data the new device provides can pose a problem in clinical care. No epilepsy clinic will have resources to review months or years of data from a single patient. The solution thus comes with a specialised tool for visualisation of the two channels of EEG with machine learning capabilities to automatically detect EEG recorded seizures. An expert still needs to review all automated annotations, but instead of looking through huge amounts of continuous data, only epochs of interest need to be considered. EEG experts will need to widen their skills as they would no longer have the conventional full electrode array of the international 10-20 system. This is the case even though the signal is very similar to usual scalp recordings [Duun-Henriksen *et al*, 2015]

First results from subcutaneous recordings

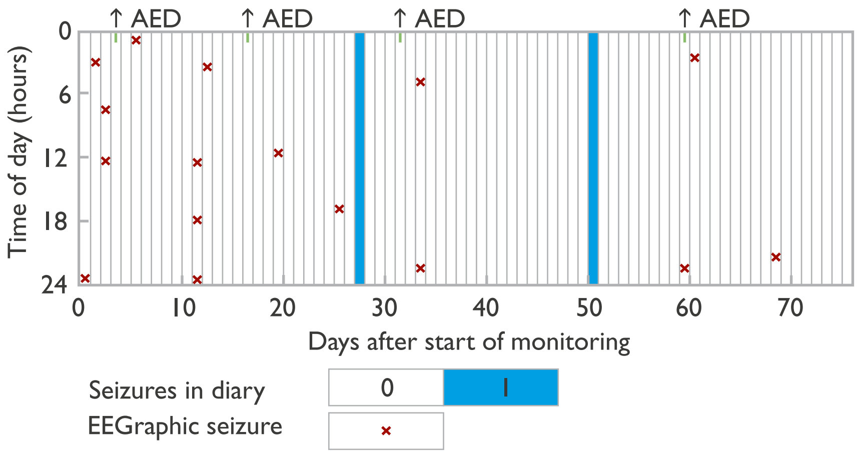
When investigating the Danish epilepsy recordings, a lot of new information is apparent. A journal article of all the results was recently submitted by Prof Kjaer and colleagues [Weisdorf et al, submitted for publication], but here we bring a case-study regarding a 44-year-old female diagnosed with epilepsy in childhood. Her seizures started again in 2016 after 15 years of seizure freedom. At this point, her medical history raised suspicion of temporal lobe epilepsy. This was confirmed by video-EEG with a left temporal onset of both focal to bilateral tonic-clonic seizures, as well as focal onset seizures with impaired awareness. MRI and CSF were normal. In her diary, she reported one to three seizures a month, but there was a strong suspicion of many more unrecognised seizures.

In *Figure 3* we see how 16 unreported seizures were identified in the 76 days of sub-scalp EEG recordings (red crosses), while only two were reported in the diary (blue lines). As sometimes seen, there is no correlation between the EEG recorded seizures and those reported in the patient's diary [Cook *et al*, 2013]. This is probably due to low seizure awareness, as she reported that seizures are usually noted by her boyfriend. At the top of *Figure 3* we see that her anti-epileptic drug (AED) dose was increased four times during the study. We can see that she had fewer EEG recorded seizures after the dose increases, but the same conclusion could not have been reached using the diary. We believe

We can see that the patient had fewer EEG recorded seizures after the AED dose increases, but the same conclusion could not have been reached using the diary

that more and longer studies are needed to confirm this observation. Recent reports have shown that multi-day rhythms of seizures are evident in both males and females [Karoly *et al*, 2018]. Understanding the occurrence of seizures in such patterns may be key for both patients and doctors.

Figure 3: EEG recorded seizures and diary seizures for one patient. ↑AED shows where the patient had an increase in anti-epileptic drug dose [based on Weisdorf et al, submitted for publication]



Impact on clinical practice

In a survey of 21 neurologists [Casson *et al*, 2010], 16 agreed that current ambulatory recordings are diagnostically useful over traditional inpatient recordings. Eighteen agreed that there is a need for wearable EEG devices. The questionnaire addresses standard ambulatory EEG. However, it does give a good indication that there is an unmet need that exceeds the 30-minute routine EEG and few days epilepsy monitoring unit stay. When asking people with epilepsy whether they would agree to wear a device on a daily basis, the participants saw the possible benefits for improved treatment. They said they valued this benefit more than they were put off by the possible inconvenience of wearing a sensor [Ozanne *et al*, 2017].

We suggest that the new ultra long-term EEG recordings can be useful for managing refractory epilepsy for patients. This is particularly where there is a suspicion of low reliability of their seizure diary or for patients with infrequent seizures where the doctor would like to see the morphology of the EEG. However, sufficient evidence of seizure onset is critical in order to position the two-channel recorder optimally for the EEG recording. Seizure occurrence cannot be ruled

out based on the lack of EEG recorded seizure activity, as it might not be apparent in the area of the brain covered by the device.

Finally, these new recordings might expose a fundamental issue that needs to be addressed – how should clinicians generally handle the possibility that seizure diaries are not reliable? Most management of epilepsy relies on the diary. If we are not able to rely on them, what can we then trust without implanting devices underneath the scalp in all patients? This will be left as an open question until more patients have been studied.

Future perspective

There seems to be a lot of future potential applications for this new ultra long-term EEG recording device which has just entered the market. For patients, reliable seizure alarms notifying family or caregivers when a seizure is occurring are likely to be desirable and should thus be prioritised for development. This would be especially valuable for children, although, currently the device is only approved for adults. Furthermore, as the recordings are based on EEG, one could speculate that the device could be used for recording sleep quality reliably. This could be important for the patient in providing information about recent seizures and sleep patterns. Whether seizures can be predicted, and patients thus warned before they happen, is still to be demonstrated. But some evidence shows that it might be possible [Cook *et al*, 2013], and something that would provide the largest improvement in quality of life for many patients. However, before ultra long-term EEG recordings are viable for widely distributed use, more evidence of clinical impact is needed from clinical trials, and a reimbursement code needs to be obtained.

Jonas Duun-Henriksen is a visiting researcher at King's College London on a secondment from the company manufacturing the device described in this article. Mark Richardson is on the advisory board for the company but has no other affiliation to UNEEG medical.

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Further reading

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For more information about the UNEEG 24/7 see *www.uneeg.com*