Title

A new era in EEG monitoring? Sub-scalp devices for ultra long-term recordings

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Summary

Inaccurate subjective seizure counting poses treatment and diagnostic challenges and thus sub-optimal quality in epilepsy management. The limitations of existing hospital- and home-based monitoring solutions are motivating the development of minimally-invasive, sub-scalp, implantable EEG systems with accompanying cloud-based software. This new generation of ultra long-term brain monitoring systems is setting expectations for a sea of change in the field of clinical epilepsy. From definitive diagnoses and reliable seizure logs to treatment optimization or pre-surgical seizure foci localization, the clinical need for continuous monitoring of brain electrophysiological activity in epilepsy patients is evident. This paper presents the converging solutions developed independently by researchers and organizations working at the forefront of next-generation EEG monitoring. The immediate value of these devices is discussed as well as the potential drivers and hurdles to adoption. Additionally, this paper discusses what the expected value of ultra long-term EEG data might be in the future with respect to alarms for especially focal seizures, seizure forecasting, and treatment personalization.

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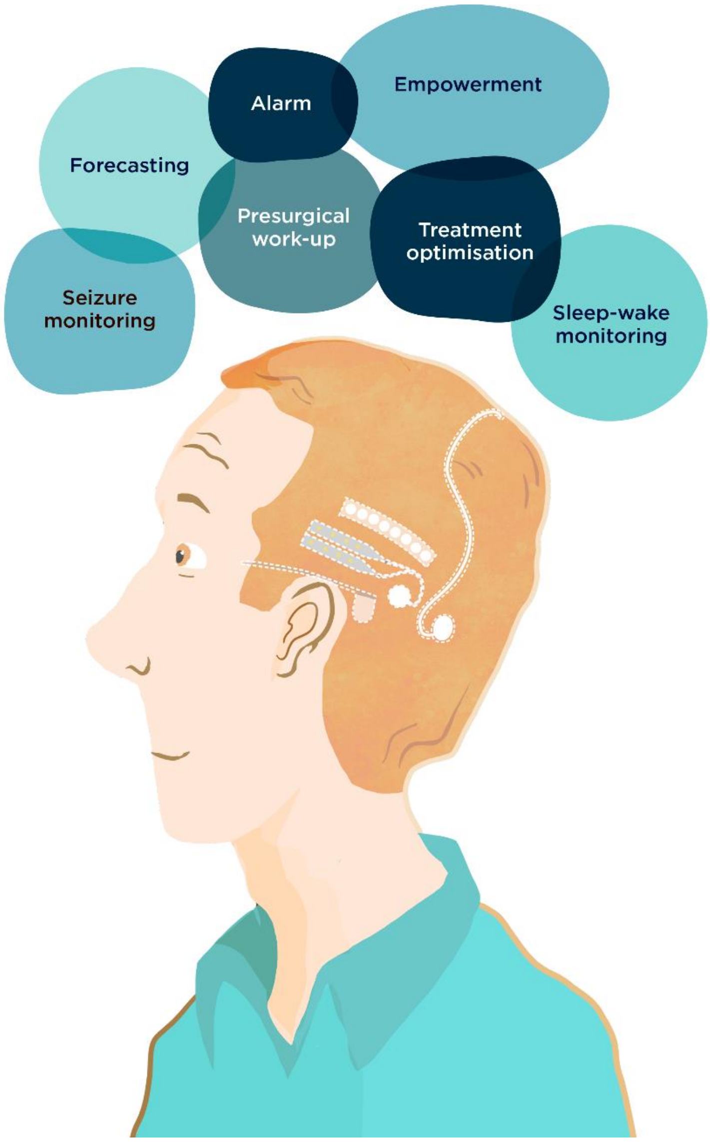

1 Introduction

The average accuracy of seizure diaries is below 50% and this complicates diagnosis and management of epilepsy.[1,2] Recent progress in the development of wearable EEG [3–6] and non-EEG seizure detection devices was reviewed in a number of papers,[3,7–10] all revealing the unmet need for devices that could chronically monitor epileptic brain activity. Implantable sub-scalp EEG devices meet this need by detecting electrographic seizures, which has been shown to be a robust objective measure that correlates to clinical symptoms.[11,12] In cardiology, the invention of Holter-ECG and the implantable loop recorder (ILR) provided a solution for the problem of monitoring rare cardiac events.[13,14] We anticipate a similar advance in neurology with respect to long term monitoring of brain activity in epilepsy.

Currently, scalp-EEG have several critical limitations for long-term monitoring. Electrodes must be held fixed to the skin either with a cap or an adhesive, such as collodion, and the skin-electrode interface must be maintained regularly to provide good recording quality. Despite intense research on dry-electrode technology, the quality attained so far is not sufficient to warrant broad applicability. Moreover, scalp electrodes are generally acceptable for periods of up to 1-2 weeks at most which might be insufficient if seizures are infrequent, and surveys show that esthetic appearance is an important variable to determine patients choice of a method for ambulatory monitoring.[15]

Two commercially available intracranial devices enable chronic EEG monitoring. The *RNS® System* (NeuroPace, Mountain View, USA), continuously records counts of epileptic events per hour bin and provides neurostimulation. But only snippets of raw data can be extracted amounting to several minutes per 24 hours of monitoring. *Percept*™ *PC*, Medtronic, provides neurostimulation treatment for symptoms associated with movement disorders, obsessive-compulsive disorder (OCD) as well as epilepsy, where *BrainSense*™ technology can also provide a limited form of EEG monitoring (manually triggered 30-second EEG storage and bandpass average power every 10 minutes). However, these are invasive intracranial systems with a clear emphasis on therapeutic neurostimulation rather than diagnostics.

With this gap in mind, a handful of researchers and organizations have individually pioneered the development of sub-scalp EEG recording devices, reaching converging technical solutions in recent years, and are currently working on translating the invention to the clinic and market. One sub-scalp device has recently been launched in Europe (*24/7 EEG™ SubQ*, UNEEG medical, Lynge, Denmark), but more are in development at centers and companies around the world. In providing previously unobtainable data, these minimally-invasive solutions may lead to a paradigm shift in the management of epilepsy, where clinical decisions will be based on objective brain epileptic activity including seizure counts, sleep quality and vigilance.

This review describes the novel class of sub-scalp EEG recording devices that can be implanted subcutaneously between the scalp and the cranium. A search on PubMed in May 2020 for (((subcutaneous OR subgaleal OR subdermal OR sub-scalp OR epicranial OR epiosteal) AND EEG) AND (epilepsy OR seizure)) resulted in 116 results with only a few of the mentioned systems in the current manuscript appearing. Given the sparse literature we chose to perform a knowledge driven review of these EEG devices. The review is based on information obtained from literature, conferences, personal correspondence as well as manually reviewing references to articles mentioned in the literature of non-EEG and wearable EEG seizure detection devices mentioned above.

We describe and provide an overview of current efforts for sub-scalp EEG systems, commercially available or in development, and discuss the utility of ultra long-term monitoring using sub-scalp devices in epilepsy and the advantages that objective seizure counts can provide. We also speculate on future possibilities of mechanistic insights into the epileptic brain, seizure forecasting and combination with non-EEG modalities and, finally, we discuss current challenges and limitations of the sub-scalp technology.

2 Sub-scalp EEG as a new modality

EEG is the most important paraclinical modality in diagnosing epilepsy. In addition, it helps classifying seizure types and epilepsy syndromes.[16] When routine outpatient EEG provides insufficient information, long term monitoring in a hospital-based epilepsy monitoring unit is the next classical option. To mitigate the high costs of such inpatient investigations, many home-based solutions have been proposed often involving a few days of scalp-EEG and a webcam placed in the patients house.[17,18] Depending on the results of these investigations, surgical resection of the seizure focus may be an option, and an additional intracranial EEG study is often required.[19]

2.1 Motivation for sub-scalp EEG

The development of sub-scalp EEG devices is motivated by an unmet clinical need that neither scalp nor intracranial-EEG address: ultra long-term (i.e. > 1month) EEG data collection in a home-environment that can reveal temporal fluctuations in patterns of seizures. This may have many advantages for personalized epilepsy management in the context of rare seizures, cycles of epileptic brain activity in a majority of patients and alternating seizure localization in some individuals with multifocal epilepsies (e.g. bitemporal epilepsy) [20–24]. Before discussing its potential for clinical practice in details in section 3, a technical review of current solutions for sub-scalp EEG follows.

2.2 Key technical aspects

Technically, the electrodes are implanted subcutaneously under the scalp, but above the bone. Electrode location differ among devices and can be varied for some. The sub-scalp placement removes the need for electrode care, avoids skin abrasions and secures a stable and low impedance recording where several types of artifacts are attenuated.[25–27] Modeling studies show that sub-scalp electrodes provide more specific and accurate measurements compared to scalp electrodes but with lower spatial and temporal resolution than intracranial electrodes.[28] A comparison between sub-scalp and scalp electrodes shows that the signal quality of the sub-scalp electrodes were at least equally good during background activity with closed and open eyes, and might be better during bodily movements.[29] Sleep recordings are also improved by the fact that sub-scalp electrodes are less obtrusive than scalp electrodes in the recumbent (sleeping) position. Many algorithms have been proposed to remove noise from EEG,[30] however, especially for the modalities with only a few channels, this will be challenging although not entirely impossible.[31]

Besides the implant, an external unit for power, data storage and transmission is needed. Five out of six solutions have opted for transmission of the data out of the implant (see below). This requires an external battery that is simple to recharge, .easy to use, discreet and unobtrusive. The system should be able to function for prolonged monitoring longer than 30 days but potentially for many months or years. Such devices should also be connected to a secure, cloud-based database supported by software applications to help organize and analyze the recorded data. The same five solutions that opted for external battery also provides continuous raw EEG signals for later expert interpretation aided by detection algorithms. Some solutions also include embedded software for real-time EEG analysis and some solutions are aiming to enhance classification accuracy with multimodal detection algorithms by including other physiological modalities such as ECG, accelerometry, or voice recordings. Table 1 gives an overview of the different current sub-scalp EEG systems that are described below.

2.3 Overview of current sub-scalp EEG systems

Different sub-scalp devices are proposed and they vary with respect to the number of channels (from two to thirty-two), degree of invasiveness (one incision under local anesthesia or up to four incisions under local or general anesthesia), and main application (seizure counting, alarming, forecasting, localization, neurofeedback or neuro-stimulation). This section provides an overview of the characteristics of different sub-scalp EEG devices that are presented below in alphabetical order. Figure 1 gives an overview over several of the systems described below as well as main application areas.

24/7 EEG™ SubQ from UNEEG medical A/S, Lynge, Denmark, features two bipolar channels introduced under local anesthesia. The SubQ was used to record EEG in healthy subjects,[29] as well as detecting clinically relevant electrographic seizures in epilepsy patients showing high reliability and tolerance.[32,33] The device comes with dedicated software for automatic seizure detection and EEG visualization. The device is CE-marked and multiple clinical trials are ongoing.[34]

The *Epicranial Application of Stimulation Electrodes for Epilepsy* (EASEE) from Precisis AG, Heidelberg, Germany uses 5 sub-scalp platelet electrodes (four smaller arranged around a larger center one). This arrangement is inspired by the surface Laplacian concept for improved stimulation depth. It is meant to be implanted above a lesioned brain area and/or epileptogenic focus and is capable of recording as well as delivering neuro-stimulation at an individualized closed-loop setting.[35] A clinical trial is ongoing.

The *Epios™ system* from the Wyss Center for Bio and Neuroengineering, Geneva, Switzerland, aims to offer flexible configurations: from focal or bi-temporal electrode layouts to broad coverage transposing the locations of the full 10-20 scalp EEG montage to the sub-scalp compartment. Implantation of the full montage is done under general anesthesia in less than one hour, through 2-4 small incisions (< 1cm) using specialized epiosteal tunneling tools. With lower coverage, implantation under mild sedation or nerve blocking is being considered. EEG data is transferred wirelessly to a head-piece and on to a body-worn unit for power and temporary storage.[36] The body-worn unit also supports multimodal co-registration (ECG, audio, accelerometry) that is then transmitted to a secure cloud-based application developed to support long-term data visualization and analysis. Preclinical trials are currently ongoing with the *Epios™* implant and a clinical trial is expected to start in 2020.

MINDER from EpiMinder Pty Ltd, Melbourne, Australia, is a sub-scalp device that implants a multi-channel electrode lead across the skull using a tunneling procedure so that both hemispheres are covered. Minder has the potential to provide long-term and continuous measures of the EEG which will provide a platform to support improved diagnosis and management of epilepsy. A clinical trial is ongoing.

The *Neuroview Technology* Ally, Englewood, USA is being developed as a fully implantable, sub-scalp EEG recording system to quantify seizures and aid in the diagnosis of infrequent paroxysmal episodes of altered consciousness or convulsive activity.[37] The fully-implanted device can record for a year of continuous use without the need to recharge. Low-power, on-board algorithms identify epochs of sub-scalp EEG activity suspicious for seizures and patient-identified event. EEG epochs are transferred to a cloud platform via a connected smartphone-based application for the neurologist to review with the aid of cloud-based machine learning algorithms to verify seizures and display and quantify seizure activity between clinic visits. On-device detection algorithms can subsequently be customized to improve the specificity of seizure detection. Clinical trials are expected to commence in 2020.

UltimateEEG from BrainCare Oy Ltd., Tampere, Finland, uses platinum on silicon electrodes of custom order sizes, number of channels and distance between electrodes. With support for up to 8 channels, the device offers mapping of seizure propagation. The planar electrodes are directionally focused towards the electrical sources to reduce EMG noise. Clinical trial is expected to commence in 2020.

2.4 Other sub-scalp EEG systems

Several studies have helped clarify other aspects of sub-scalp EEG recordings, but none of these seem to have evolved into a commercial concept. Jochum et al.[38] experimented with an implanted EEG system on a sheep and found a correlation coefficient of 0.86-0.92 with simultaneous scalp-EEG at the same location. Ahmed et al.[39] investigated high-density sub-dermal EEG probes subjected to artificial aging and compared volume conduction simulations based on 4-layered head models and found that recordings from the sub-dermal electrodes were less attenuated at higher frequencies than scalp-EEG recordings. Do Valle et al.[40] investigated an 8-channel implanted EEG-recorder with electrode arrays projecting cranially in a fan-like pattern from behind the ear and used it to test a seizure detection algorithm. Xu et al.[41] did a proof-of-concept of sub-scalp EEG sensors that were comparatively insensitive to motion related artifacts that can be expected to occur more in daily life. In an ICU setting, low-maintenance subdermal wire electrodes have been used, but while they are quick to set up, they can also easily be dislodged and thus require additional fixation and do not appear to be practical for chronic monitoring in daily life.[27]

2.5 Other modalities

Multi-modal monitoring, combining measurements of two or more different modalities, can be used to improve classification accuracy above what can be achieved by using one modality.[10,42] Heart rate variability (HRV) features are correlated with para- and sympathetic activity and this can be used to detect focal seizures or added to EEG based detection to improve accuracy.[42] Electrodermal activity (EDA) exhibits changes during generalized tonic-clonic (GTCS) and focal seizures [43] and is positively correlated with longer duration of postictal EEG suppression.[44] Audio recording could be useful to detect the initial vocalization or noise sometimes occuring during a seizure (ictal cries), or noise that can be characteristic of the postictal period.

Home-video combined with ambulatory EEG has demonstrated clinical utility aiding in interpretation in 14/17 (82%) cases in one study.[17] Sub-scalp EEG recordings could be combined with video or other modalities in a similar way. Video quality at a home setting can be at the same level as in-hospital video recordings and a majority of patients would prefer home monitoring. Cognitive and behavioral testing during seizures matter for seizure classification and could possibly be implemented in the home setting if online seizure detection algorithms were sufficiently accurate with low latency of detection after onset. Standardized ictal test batteries have been proposed and are feasible for all but very short seizures.[45]

2.6 Tolerance and safety

A review of the literature on complication rates with similar devices for deep-brain neurostimulation and occipital nerve stimulation revealed that expected complications include infections (<2%), lead migration (~20%), fracture (~4%), or skin erosion (~4%).[46–49] Infections, a dreaded complication with intracranial material would here be limited to the sub-scalp compartment, as the skull would act as an additional protective barrier for the brain. Sub-scalp hematoma and scalp fibrosis are expected to be very rare.

Prospective tolerance and safety data specific to sub-scalp EEG comes from a single trial.[33] No serious adverse device related events occurred, and the patients generally found the device easy to use although this was only collected anecdotally. Minor annoyances were reported, such as simultaneous wearing glasses, occasional nightly disconnections, and the necessity of wearing clothes at night to fix the external device. No participants felt constrained in their ability to perform jobs or leisure activities although six of the nine reported mild headache up to one week after surgery. One participant reported uncommon mild headaches that were tolerated without analgesics or other interventions.

In a study with a partially implanted subdermal wire electrode for 60 days in the intensive care unit, no safety concerns were noted.[50]

3 Utility of sub-scalp EEG recording

It is estimated that 50% of seizures are unreported, particularly nocturnal seizures or focal seizures with impaired awareness.[2] The direct consequence is the inability to ascertain therapeutic response: How often is epilepsy undertreated when seizures are underreported, and are true changes in seizure frequency overlooked? Patients may also misclassify non-epileptic events as seizures in their diaries, potentially causing over-treatment. Further, the issue of comorbid epileptic seizures and non-epileptic seizures is not uncommon.[51] In this section we outline the most important aspects and discuss the practical utility of sub-scalp EEG.

3.1 The value of personal long data

Today, there is an ongoing debate on the importance of detecting purely electroencephalographic seizures that patients are unaware of and don't feel negatively affected by.[52] This discussion is important for sub-scalp EEG as its ambulatory nature makes simultaneous video unviable and thus difficult to classify seizures as clinical or not. Neuroimaging studies in patients with temporal lobe epilepsy (TLE) have identified widespread anatomical abnormalities [53] and longitudinal studies in patients with chronic epilepsy show declines in memory and IQ,[54] so it is possible that repeated seizures have negative consequences or perhaps these results come from preferential sampling of the most severely affected patients with chronic refractory epilepsy. In either case, ultra long-term monitoring technology will be useful in clarifying this important question.

3.2 The challenge of personal long data

With limited resources available for data review, a prerequisite for ultra long-term EEG systems is algorithms for analysis of the vast amount of recorded data. A trained EEG technician can analyze 24 hours of 2-channel EEG in 2-3 hours. Use of trending tools alone can reduce the time for analysis by a factor of 8-10. Whether the algorithms need to be online or offline, simple or complex and patient-specific or generic will very much depend on the application. The actual time series will always be valuable to validate the findings of the algorithms such that algorithms might be considered as a data reduction method, while the final validation is still made by expert EEG reviewers supported by the algorithms. The right level of sensitivity must minimize the number of false-negatives, since going through a tractable number of false-positive clips is highly feasible in daily clinical routine. In addition to underlying algorithms, data visualization is also an important issue: If a patient has worn the system for six months, a way to obtain an overview of the seizure frequency, seizure duration, periodicity and time of day would be crucial. With machine learning and big data analysis, the prospects for automated detections are considerable.

3.3 Objective seizure counting

Treatment decisions are informed by seizure counts and there have long been calls for more reliable measures than what seizure diaries provide.[1,2,55,56] While wearables for the detection of tonic-clonic seizures in particular are gaining approval, the ability to automatically detect focal seizures, particularly with impaired awareness or without major motor features, remains unmet.[57] Objective seizure counts may inform clinical decisions to avoid that an effective treatment is abandoned because no discernible effect in self-reported measures was apparent[58] or that an inefficacious treatment is maintained or initiated on the basis of non-epileptic events, because non-seizure events (e.g. AED side effects, non-epileptic seizures) are incorrectly classified as seizures by the patient.

Ultra long-term EEG data have identified periodic patterns in seizure and spike occurrences operating on different time-scales.[22] Importantly, cycles appear to be stable within individuals and thus potentially constitutes interesting targets for therapeutic intervention.[22,59]

3.4 Initial epilepsy diagnosis

The differential diagnosis of epilepsy is broad: syncope and non-epileptic seizures (NES) are commonly misdiagnosed as epilepsy, less commonly, hypoglycemia, paroxysmal disorders of movement, sleep disorders, transient ischemic attack, migraines with aura and transitory global amnesia.[51] On top of that there also is the risk of not being diagnosed with epilepsy when recurring seizures are present but not identified. Before establishing a definitive diagnosis of epilepsy, characterization of the events is a key step. Inpatient video-EEG monitoring is regularly successful but may not capture events if they are too infrequent. Figure 2 visualizes the cumulative probability functions for seizure detection as a function of monitoring duration assuming a constant seizure frequency where each day can be conceived as a Bernoulli trial for a seizure occurring. Many patients will have seizure frequencies below 1/w and are thus unlikely to have a seizure during a standard EMU visit.

3.5 Seizure localization

When seizures are refractory to medical treatment, surgery is often indicated and increasingly used with improving results in the past decades.[60] Presurgical work-up regularly require the implantation of intracranial electrodes to refine the localization of the seizure-onset zone, sometimes in brain areas inaccessible to scalp or sub-scalp EEG. However, sub-scalp EEG that include bilateral electrode coverage would enable lateralization of seizures. A study of outpatient after inpatient intracranial EEG monitoring in 82 patients with mesial temporal lobe epilepsy of unknown laterality reclassified 16 (20%) as having unilateral or bilateral onset, which can help evaluating candidates for epilepsy surgery.[23,24]

Sub-scalp EEG that offers broad head electrode coverage could localize to a given cerebral lobe, although studies will be needed to confirm this. Basing surgical decisions on dozens to hundreds of electrographic seizures instead of a handful typically collected in hospital is a promising possibility for the future. Sub-scalp EEG will improve the continuum between optimization of medical treatment and presurgical planning, and represents a bridge partially mitigating both the critical lack of information in outpatient epileptology and the somewhat artificial conditions imposed in the epilepsy monitoring unit.[11]

3.6 Seizure alarting

A majority of patients and caregivers want some form of seizure monitoring, either at night only or 24/7, to feel more safe and less stigmatized.[61] This is where sub-scalp EEG are most likely to improve the every-day life of a person with epilepsy. A large study on quality of life (QoL) in epilepsy describes problems in terms of lower self-esteem, higher levels of anxiety and depression, social isolation, stigmatization, risk of sudden unexpected death in epilepsy (SUDEP) and higher rate of unemployment.[62] Injuries (burns, head- and dental injuries) increase with higher seizure frequency. Feelings of stigmatization were common and 48% worried about epilepsy some or a lot of the time. Hopefully, a reliable online alarm can alleviate such issues.

SUDEP is a major cause of anxiety and is one of the primary motivations some people with epilepsy have for wanting a seizure alarm. Death following a seizure may be preceded by a critical interval, where an intervention could potentially save lives.[63] Since GTCS are the main risk factor for SUDEP,[63] the motivation for seizure alarming for SUDEP prevention may be weaker for focal non-tonic-clonic seizures. For a sub-scalp device to be relevant for SUDEP prevention, it needs to provide at least equivalent performance to wearables or it could be part of a multi-modal system that is more robust. It could also be used to assess whether the risk of SUDEP changes over time for a certain patient by estimating changes in the post-ictal EEG, although this has to be shown in a clinical trial. [64–66]

3.7 Seizure forecasting

When patients are asked directly about the impact of seizure unpredictability, 66-68% consider it an important or very important aspect.[67] Developing systems that can predict the occurrence of a future seizure event with sufficient time to act would be a game changer. Instead of a binary output, the prediction could be expressed as elevated seizure risk, referred to as seizure forecasting. One successful demonstration of seizure forecasting used intracranial EEG recordings to provide visual feedback to patients minutes in advance of seizures.[68] Much effort has been put in developing solutions for seizure prediction combining intracranial EEG dataset and online competitions reaching classification accuracies of 81%.[69]

However, as intracranial recordings are unlikely to become wide-spread due to their invasiveness it will be relevant to test if good forecasting performance can be achieved on sub-scalp recordings. Although no prospective study with good forecasting results on extracranial EEG has yet been carried out, the authors are aware of several ongoing studies that will hopefully shed new light on predictability when ultra long-term recordings are available. Such systems should always be trained and tested on at least several months of labeled data to cover natural physiological variation [70] and circadian and multidien cycles in epilepsy.[22]

3.8 Using sub-scalp EEG in the future

Ultra long-term monitoring can be used both before and after establishing a diagnosis of epilepsy. Long monitoring durations are necessary to detect rare paroxysmal events as shown in Figure 2. Routinely used solutions of drug tapering, sleep deprivation and other provocations may in some cases induce events that differ from spontaneous seizures and cloud the interpretation. Therefore, an outpatient-based solution may under these circumstances outperform the EMU. Currently, clinicians will estimate the underlying seizure frequency before referring a patient to the EMU, but if ultra long-term EEG monitoring was an option, a probability plot like in figure 2 could be informative when deciding the optimal diagnostic strategy. Further, having a sub-scalp EEG implant does not prohibit an EMU stay for full video-EEG characterization and, on the contrary, given multidien cycles of seizures are highly prevalent among epilepsy patients,[22] the hospital stay could be timed to take place during a period of high likelihood of seizures.[11]

We envisage a toolkit, where sub-scalp devices for ultra long-term EEG monitoring can help detect focal or generalized seizures, but where non-EEG modalities (EMG, ECG, others) could be “added on” to the setup depending on the specific circumstances. Furthermore, while the relationship between sleep quality/duration and seizure risk has been suggested, the ability to record objective sleep quality and seizures is critical to understand if strategies to improve sleep can help seizure control. One study has even shown that two-channel sub-scalp EEG is sufficient to do robust sleep staging.[71,72]

4 Readiness for sub-scalp devices

As no published studies have dealt with the usability of sub-scalp devices, we must look into the readiness for wearables, scalp EEG and intracranial EEG.

4.1 Neurologist readiness

In a survey of 21 neurologists,[73] 16 agreed that current ambulatory recordings are diagnostically useful over traditional inpatient recordings, and 18 agreed that they thought that there is a further need for wearable EEG devices. Even though the questionnaire addresses standard ambulatory EEG, it does give a good indication that there is an unmet need that exceeds the 30-min routine EEG and 1-3 weeks EMU stay.

Surveys of medical doctors' views on the usefulness of seizure detection devices found that most considered alarms with major motor seizures and seizures associated with fall important while 53% gave a 4 or 5 on a 0 to 5 scale of necessity for alarms for impaired awareness during focal seizure and absences.[61]

4.2 Patient readiness

Patients have heterogeneous expectations for the seizure tracking device's performance but describe desirable features in medication reminders, water-proof design, real-time data analysis, improved diagnostics and seizure management.[74] Surveys suggest that patients would accept devices for seizure registrations provided that they have only small negative effect on daily lives,[75] but patients are concerned about appearance and visibility of sensors, so concealed sensors could help increase user acceptance.[15] Sub-scalp sensors are concealed but may use an external device for power and/or data storage that can be hidden under the users clothing. The majority (82%) of surveyed patients expected a seizure detection sensitivity at 90% or better.[61]

When asking the patients whether they would agree to wear a device on a daily basis, the participants saw the possible benefits for improved treatment effect and valued this benefit more than possible inconvenience of wearing a sensor.[15] Most (90%) would prefer a size of wristwatch or smaller. Obviously, acceptance will vary on an individual basis and depend on the trade-off between perceived benefit and the sum of inconveniences and potential side-effects. It must be kept in mind, that the questionnaires mentioned deal in hypotheticals regarding implantable devices and what patients might imagine when posed such questions may not accurately reflect their reactions towards the real devices detailed in this review. The implantable cardiac loop recorder is well accepted and so it seems likely that with sufficient benefit for the recipient implantable sub-scalp EEG devices will also be well accepted.

Some surveys suggest that up to 45.8% of patients think documentation of seizures is an either “important” or “essential” feature in a long-term seizure detection system.[75] Seizure alarming can help to reduce anxiety and assist autonomy. 60.6% of caregivers found that the seizure alarm gave them more freedom and 30.3% believed that it gave the patients more autonomy.[76]

5 Challenges and limitations of sub-scalp EEG recorders

In this section, we outline proposed objectives in future trials, considerations about low spatial resolution, logistical considerations relating to implantation, data management and safety.

5.1 Future trials

Future trials involving ultra long-term monitoring in epilepsy using sub-scalp EEG will be required to explore the value proposition of the technology. While the first safety and feasibility studies have been completed, evidence of clinical usefulness of ultra long-term EEG recordings is not available at the current stage of development, though multiple studies are in preparation or have commenced.

Development of seizure detection algorithms should follow the standards for reporting diagnostic accuracy proposed in [77] or [65]. We should be moving from small sample sizes and repeated training on retrospective data to prospective trials with larger samples and pre-defined thresholds for the algorithm's detection. It should be clear if the goal of the trial is seizure alarming or counting. Detection of interictal abnormalities should also adhere to published standards.[4]

Trials on seizure detection devices focus on reliable and accurate seizure counting, which rapidly raises the question of the clinical relevance of the many electrographic seizures typically recorded with ultra long-term EEG. This is an opportunity to improve the quality of how seizures are defined, although the question is not trivial [52]. More advanced trials aimed at optimizing medical management, increasing the ability to identify a change in seizure frequency, or informing epilepsy surgery will be necessary after this first step is achieved. Using the classical patient-reported outcomes for such trials (including seizures self-report) would defy the purpose. Other impacts could be quantified in terms of QoL scores, changes in level of disability, number of accidents and mortality, or simply whether the neurologist found a treatment improvement or was aided in reaching his therapeutic decisions.

Without a full understanding of the real seizure burden, outcomes of medication trials are often set for failure prolonging patients suffering. Simulations based on self-reported seizure events in the SeizureTracker database have investigated factors that can reduce costs of randomized clinical trials on AED efficacy without lowering statistical power, but did not attempt to incorporate seizure event uncertainty directly in the model.[79] Simulations could be useful in clarifying the impact of objective vs. subjective seizure counts in epilepsy for randomized controlled trials on AED in advance of real data having been accumulated, which will take many years.

5.2 Considerations about reduced spatial resolution

One disadvantage of most suggested sub-scalp devices except one compared to standard scalp EEG is reduced spatial resolution. For focal abnormalities, this can result in a lower sensitivity compared to standard scalp EEG, but strategically selecting the location of the sub-scalp electrodes for example guided by abnormality seen on standard-EEG or in MRI might be useful to inform placement in individual cases. Spikes in the interictal EEG might inform implantation strategy, but unilateral implantation will likely miss seizures confined to the contralateral hemisphere, precluding a discovery of bilateral seizure onset in such cases. In the absence of interictal spikes and lateralizing semiology from the patient history, but where a strong suspicion of epilepsy is present, a bilateral implantation strategy could be considered. One development has shown that it is possible to place electrodes according to the 10-20 system in the sub-scalp space in a minimally-invasive surgery, although it is done under general anesthesia. Importantly, a major limitation of sub-scalp EEG as compared to intracranial EEG is that it cannot monitor deep structures of the brain and has in that sense the same “field of view” as scalp EEG.

6 Conclusions

Sub-scalp EEG recording is an emergent technology. Studies comparing sub-scalp recordings with scalp-EEG are favorable and show that seizures can be documented electrographically. Different devices are being developed to offer a range of sub-scalp electrode coverage, all with minimally-invasive implantation of just a few electrodes under local anesthesia, others increasing coverage to the full head with general anesthesia. Some devices are fit for seizure counting, while others aim at localization.

The true value of ultra long-term EEG has yet to be established. It could give novel insights into brain function and is likely to open-up new avenues for biomarker discovery, personalized treatment and population analytics, especially when combined with other complementary information like movement and heart rate. Only when data has been collected over long periods of time will the true value of algorithm development for seizure prediction in patients be apparent.

Adoption of sub-scalp EEG for ultra long-term monitoring in epilepsy will cause a shift away from subjective seizure reporting in favor of objective seizure counting, a long-awaited change. This could have a broad impact on the daily management of epilepsy and place patients at the center of management of the disorder.

For clinical science, the technology will also facilitate the collection of otherwise very rare ultra long-term EEG recordings that could provide novel insights not only into epilepsy and other brain diseases but also provide high temporal resolution of physiological short- and long-term rhythms over time.

Key Points Box

- A new generation of sub-scalp, continuous brain monitoring systems have the potential to advance treatment and diagnosis in epilepsy
- First Studies comparing sub-scalp recordings with scalp-EEG are favorable and show that seizures can be documented electrographically
- Adoption of sub-scalp, ultra long-term EEG monitoring may cause a shift from subjective seizure reporting to objective seizure counting
- The true value of ultra long-term EEG has yet to be proven. More data collected over long periods of time is essential to show the benefit

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Disclosure of Conflicts of Interest:

Jonas Duun-Henriksen is a full-time employee at UNEEG medical. A company developing and producing a sub-scalp EEG device.

Maxime Baud is a part-time employee at Wyss Center for Bio and Neuroengineering, a not for profit foundation, and co-inventor on an international patent application under the Patent Cooperation Treaty number 62665486 entitled “Neural Interface System”.

Prof Richardson holds research funding from MRC, NIHR, Wellcome, EPSRC, Epilepsy Research UK, Epilepsy Foundation of America, European Commission, and Canadian Institutes of Health Research. He is UK CI of a trial sponsored by Xenon Pharma and has research collaborations with UNEEG, UCB, ANT Neuro, J&J and Seer Medical. He has been an advisory board member for UNEEG. He holds a patent WO2013182848A1.

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Daniel Friedman is a co-founder of Neuroview Technology and holds equity interests in the company. He also receives salary support for consulting and clinical trial related activities performed on behalf of The Epilepsy Study Consortium, a non-profit organization. Dr. Friedman receives no personal income for these activities. NYU receives a fixed amount from the Epilepsy Study Consortium towards Dr. Friedman's salary. Within the past year, The Epilepsy Study Consortium received payments for research services performed by Dr. Friedman from: Adamas, Axcella, Biogen, Crossject, CuroNZ, Engage Pharmaceuticals, Eisai, GW Pharmaceuticals, Pfizer, SK Life Science, Takeda, Xenon, and Zynerba. He has also served as a paid consultant for Eisai. He has received honorarium from Neuropace, Inc. He has received travel support from Medtronics, Eisai and the Epilepsy Foundation. He receives research support from the CDC, NINDS, Epilepsy Foundation, Empatica, Epitel, UCB, Inc and Neuropace. He serves on the scientific advisory board for Receptor Life Sciences and holds equity interests in the company.

Jukka Peltola has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Med- tronic, and UCB; and participated in advisory boards for LivaNova, Eisai, Medtronic, UCB, and Pfizer. He is a co-founder of Neuroeventlabs and holds equity interest in the company. He is also medical advisor to Braincare.

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Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure legends

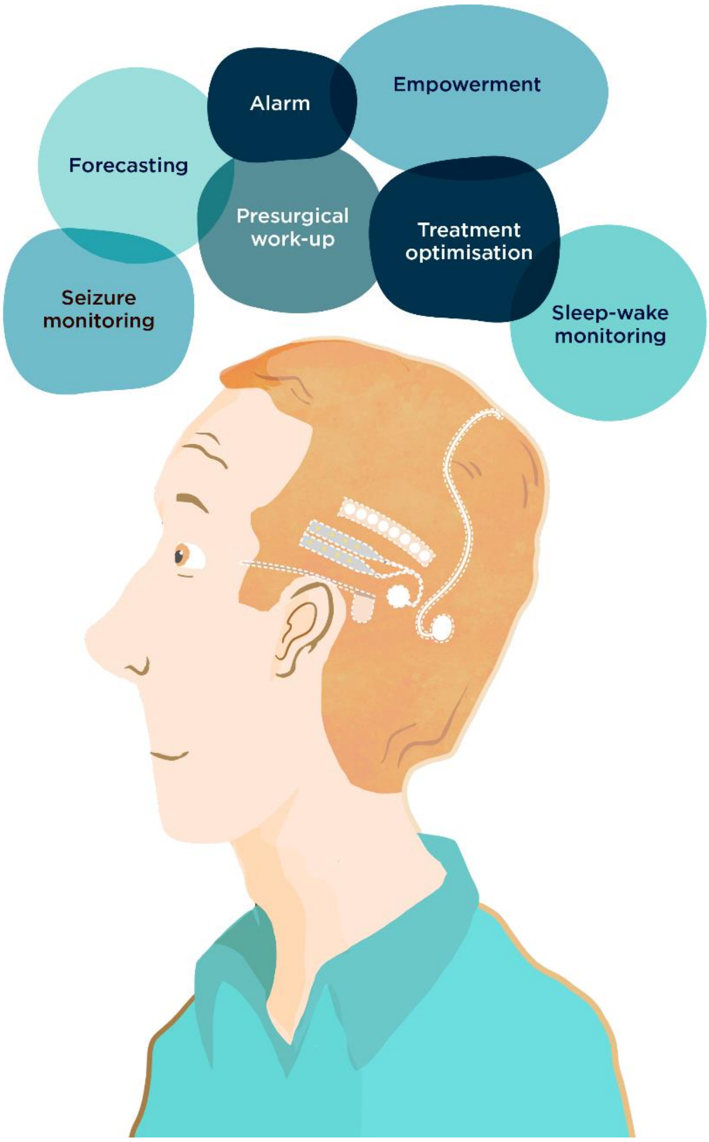

Figure 1. Overview of different implantable parts of sub-scalp devices as well as application areas. From lower left and up: *24/7 EEG™ SubQ* from UNEEG medical A/S, Denmark, The *Epios™ system* from the Wyss Center for Bio and Neuroengineering, Switzerland, *UltimateEEG* from BrainCare Oy Ltd., Finland, *MINDER* from EpiMinder Pty Ltd, Australia.

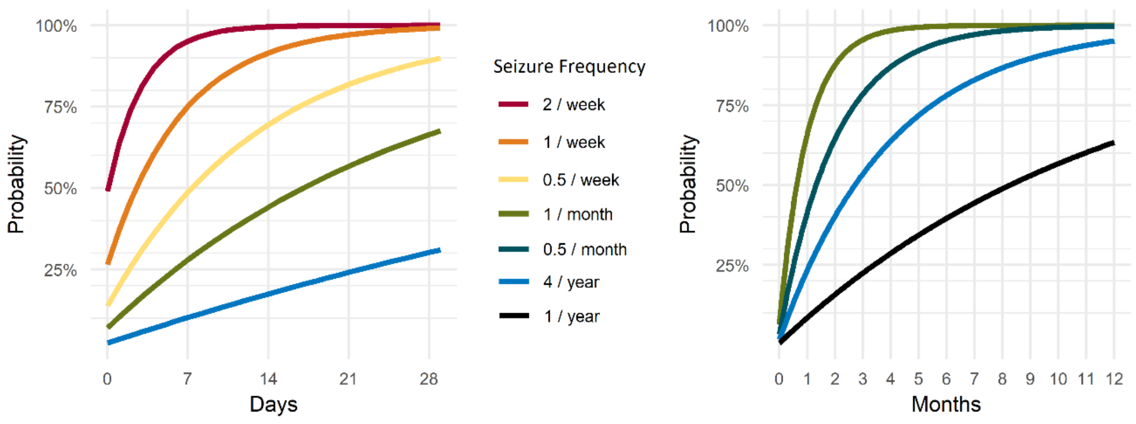

Figure 2. Cumulative probability functions for seizure detection as a function of monitoring duration.

Table legends

Table 1. Overview and core characteristics of known sub-scalp EEG systems certified or currently in development.

Device	# Channels / montage	Recording modalities	EEG sampling rate	Battery	Wearable companion	Continuous raw-data available	Status
CE-approved devices							
24/7 EEG™ SubQ	2 channels / unilateral	EEG + 3 axis accelerometry	207 Hz	External / 24h rechargeable	Yes	Yes	CE-marked by April 2019
Devices in validation phase							
MINDER	2 channels / bilateral	EEG	*	External / 24h rechargeable	Yes	Yes	Clinical trial is ongoing
EASEE	4 channel / unilateral Laplacian	EEG	*	*	Yes	*	Clinical trial is ongoing
Epios	7 channels / temporal OR 14 channels / bitemporal OR 28 channels / full	EEG + ECG + Audio + 3 Axis Accelerometer	250 Hz	External / 24h rechargeable	Yes	Yes	Clinical trial to start in 2020

	montage						
NeuroView Technology	1 or 2 channels / unilateral	EEG + 3 axis accelerometry	256	Internal / 1 year	No	No – only relevant epochs	Clinical trial to start in 2020
Ultimate EEG	Up to 8 channels / unilateral	*	*	*	*	*	Clinical trial to start in 2020