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FULL-LENGTH ORIGINAL RESEARCH

Ultra-long-term subcutaneous home monitoring of epilepsy—490 days of EEG from nine patients

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Abstract

Objective: To explore the feasibility of home monitoring of epilepsy patients with a novel subcutaneous electroencephalography (EEG) device, including clinical implications, safety, and compliance via the first real-life test.

Methods: We implanted a beta-version of the 24/7 EEG SubQ (UNEEG Medical A/S, Denmark) subcutaneously in nine participants with temporal lobe epilepsy. Data on seizures, adverse events, compliance in using the device, and use of anti-epileptic drugs (AEDs) were collected. EEG was recorded for up to 3 months, and all EEG data were reviewed visually to identify electrographic seizures. These were descriptively compared to seizure counts and AED changes reported in diaries from the same period.

Results: Four hundred ninety days of EEG and 338 electrographic seizures were collected. Eight participants completed at least 9 weeks of home monitoring, while one cancelled participation after 4 weeks due to postimplantation soreness. In total, 13 cases of device-related adverse events were registered, none of them serious. Recordings obtained from the device covered 73% of the time, on average (range 45%–91%). Descriptively, electrographic seizure counts were substantially different from diary seizure counts. We uncovered several cases of underreporting and revealed important information on AED response. Electrographic seizure counts revealed circadian distributions of seizures not visible from seizure diaries.

Significance: The study shows that home monitoring for up to 3 months with a subcutaneous EEG device is feasible and well tolerated. No serious adverse device-related events were reported. An objective seizure count can be derived, which often differs substantially from self-reported seizure counts. Larger clinical trials quantifying the benefits of objective seizure counting should be a priority for future research as well as development of algorithms for automated review of data.

KEY WORDS

EEG, epilepsy, home monitoring, long-term monitoring, subcutaneous EEG

1 | INTRODUCTION

Epilepsy is a brain disorder characterized by recurrent seizures. Thus, counting seizures is an essential part of tracking disease activity. Traditionally, patients record seizures in a seizure diary, but several studies show that such diaries are often unreliable.^{1–3} Many factors contribute to this problem, with unrecognized and undocumented seizures being the most important.^{4,5} Because the seizure count is a decisive factor in the choice of treatment, an imprecise seizure count could lead to suboptimal treatment with increased risk of complications. These clinical problems also concern the patients,⁶ and in the context of epilepsy research the problem of wrongful reporting is also well known.⁷

Objective and accurate seizure counting at home could be of great benefit in diagnosis, management, and research in epilepsy. An EEG acquisition system usable during everyday life could be the tool currently lacking in the toolbox of epilepsy diagnostics and management.^{8,9} Recently, many new EEG devices have appeared, combining various electrode configurations and data processing methods,^{10–15} but none of these have been tested in real-life. In this study, we present the first real-life data on a subcutaneous EEG device for continuous home monitoring of epilepsy. In our previous study, we found this device comparable to traditional scalp EEG in a controlled environment.¹⁶ In this study, we provide data on safety and compliance, and compare detection of seizures between seizure diaries and the new device using descriptive methods. Finally, we discuss the clinical relevance of our data relating to other seizure-detection devices.

2 | METHODS

2.1 | Study design and participants

The study was conducted according to the Helsinki Declaration following guidelines for good clinical practice. The committee of science ethics for Region Zealand approved the study (SJ-551). All participants provided written informed consent before any study activities were commenced. The study is registered in clinicaltrials.gov (NCT02946151).

The study was an exploratory, qualitative study. Patients from the outpatient epilepsy clinics were prescreened according to our eligibility criteria at Zealand University hospital (ZUH) from 2017-01-01 to 2018-10-31 and Odense University Hospital (OUH) from 2018-03-01 to 2018-10-31. Only adult patients with known or suspected temporal/frontotemporal seizure-onset zone (as corroborated by EEG or magnetic resonance imaging [MRI]) and self-reported seizure frequency of at least one seizure per month were eligible. Exclusion criteria included any disorders or activities that might infer additional risk at

Key Points

- First trial on subcutaneous electroencephalography (EEG) home monitoring over several months
- Subcutaneous EEG is feasible and well tolerated
- Subcutaneous EEG recordings can provide an objective seizure count
- Development of validated algorithms for automated review is the next step

participation or affect the quality of data. Patients with comorbid psychogenic nonepileptic seizures (PNES) were eligible only if they also had definite or probable genuine epilepsy fulfilling the inclusion criteria, and the genuine seizures were assessed to constitute a majority. All eligibility criteria are presented in Appendix S1. Due to limitations imposed by national data regulations, we had to pre-screen 1421 unselected patients referred to the epilepsy clinics. The main reasons for exclusion were as follows: lack of radiologic/electrographic corroboration of seizure-onset zone and treatment with anticoagulants/antiplatelets. Some patients met more than one exclusion criteria, but only the one considered the most important was documented. Figure S1 provides a flowchart of both the screening process and the study visits. Based on our eligibility criteria, 20 patients were invited for further information. Of these, three potential participants found the device too obtrusive, and declined to participate. Four declined, as they were preoccupied with intensive diagnostic workups in an epilepsy surgery program, and three were precluded from participation by the investigator as they were found unlikely to be able to complete the study protocol due to social or mental issues. In total, 10 participants were included, of whom 9 were implanted. Participants were scheduled to use the subcutaneous EEG device for approximately 3 months with no restrictions on activities, except from the eligibility criteria. Because monitoring duration by far exceeds that of traditional long-term monitoring, we henceforth refer to monitoring times exceeding 1 month as “ultra-long-term monitoring.” After completing the study, participants continued their customary follow-up in the outpatient epilepsy clinic.

2.2 | The device

The novel EEG acquisition system consists of an EEG electrode designed for subcutaneous implantation (termed “the implant”) and an external logging device for power supply and data transfer (termed “the external logging device,” ELD). The implant has three leads (one reference, two active) resulting in two bipolar channels recording at 207 Hz. The

implant and ELD together will be referred to as “the SubQ system.”

Surgical procedures were performed under local anesthesia by a surgeon who had undergone video training. In brief, a short incision (approximately 3 cm) was made behind the ear and the electrode was tunneled approximately 10 centimeters subcutaneously parallel to the temporal lobe. A small subcutaneous pocket was made to host the house of the electrode. The subcutis was sutured with resorbable suture (Vicryl 4-0) and cutis was sutured with Nylon (4-0). After approximately 10 days, the transceiver was attached to the skin by double-sided adhesive pads and the ELD itself was attached to the clothing by a strong magnet. The ELD used in the study was a beta version of the 24/7 EEG SubQ produced by UNEEG Medical A/S. Figure S2 shows the ELD in vivo. The system and surgical procedures have previously been described in greater detail in our proof-of-concept study.¹⁶

2.3 | Data collection and analysis

2.3.1 | Usage, adverse events, antiepileptic drugs, and self-reported seizures

Participants were instructed to wear the ELD all the time, except during bathing/showering or similar activities. Data on usage times for each participant were derived from the time stamps and duration of the recorded EEGs as saved by the ELD. MATLAB R2018a (MathWorks) was used to create the visual presentations.

Adverse device events (ADEs) were defined as any unintended or unfavorable response to the system during the study period possibly related to the use of the device or related procedures. We classified all ADEs according to severity based on their impact on daily life as the following: mild (does not interfere with everyday activities), moderate (interferes with some everyday activities), and severe (prevents some everyday activities). Serious ADEs were defined as ADEs requiring hospitalization, leading to death (or would have done so in the absence of treatment), congenital anomalies, or lasting disability. These definitions were preset prior to the commencement of the study.

Data on the use of antiepileptic drugs (AEDs) were collected at every study visit. Commencement, adjustments, and discontinuation of AEDs were noted.

Participants were instructed to document all events that they believed to be seizures in a seizure diary. The seizure diary was available either as an app or in a paper form. In the app, collection of the time and date was integrated with the registration of each event. In the paper form, participants had to note time and date by themselves. Participants were also instructed to provide a detailed seizure description form (Appendix S2).

Family members or caregivers were also allowed to fill out the seizure description forms. Upon collection, the participants had an opportunity to comment on the entries to the seizure diary and the seizure descriptions. Based on all the information available, self-reported events were categorized into a two-step process. First we evaluated whether each entry was an epileptic seizure at all and labeled each self-reported event as probably epileptic or nonepileptic seizures. Second, we evaluated each epileptic seizure and added a further semiology label as “focal aware seizure (FAS),” “focal impaired awareness seizure (FIAS),” or “uncertain.” This distinction was made by an experienced epileptologist (S.W.).

2.3.2 | EEG analysis

Prior to the review of the collected EEG data, all available previous scalp EEG recordings and/or reports for each participant were thoroughly reviewed to establish one or more personal spectrographic seizure signatures (henceforth simply referred to as a “seizure signature”), under the assumption that each seizure type in each participant had a unique signature. We then reviewed all the EEG data from the SubQ system by visual inspection of time-frequency spectrograms. We relied on the built-in spectrograms of the EEG reader, which utilizes a fast Fourier transformation (1-second resolution, Hamming window, 50% overlap). Figure 1 shows a screenshot of a seizure signature and the corresponding raw EEG presented in the same way we reviewed data.

Duration of the spectrogram shown on the screen was set at 10 minutes and the frequency scale from 0 to 30 Hz. These settings were selected as a trade-off between analysis speed and level of detail visible. Whenever the predefined signature was identified, we reviewed the event in the time domain to confirm or reject the event as a seizure and made a seizure annotation if relevant. We also reviewed the raw EEG if any other unusual spectrographic pattern appeared. By default, we reviewed 5 minutes of raw EEG before and after any event, but if circumstances dictated it, we reviewed as much as needed to make a decision. The entire review was performed by a trained epileptologist with several years of experience in visual EEG review (S.W.) using Nervus EEG Reader v. 5.95. All seizure annotations underwent secondary review by a board-certified neurophysiologist (T.W.K.), who made the final ruling. To avoid expectation bias, this procedure was performed before self-reported events were evaluated.

After the evaluation of self-reported events, we reviewed the time domain EEG of two examples of each kind of probable epileptic seizure reported by each participant, to ensure that no such self-reported events had an electrographic equivalent that was visible only in the time domain but not in the spectrograms.

For visualization of the circadian distribution of electrographic seizures, we binned the time stamps of all seizures

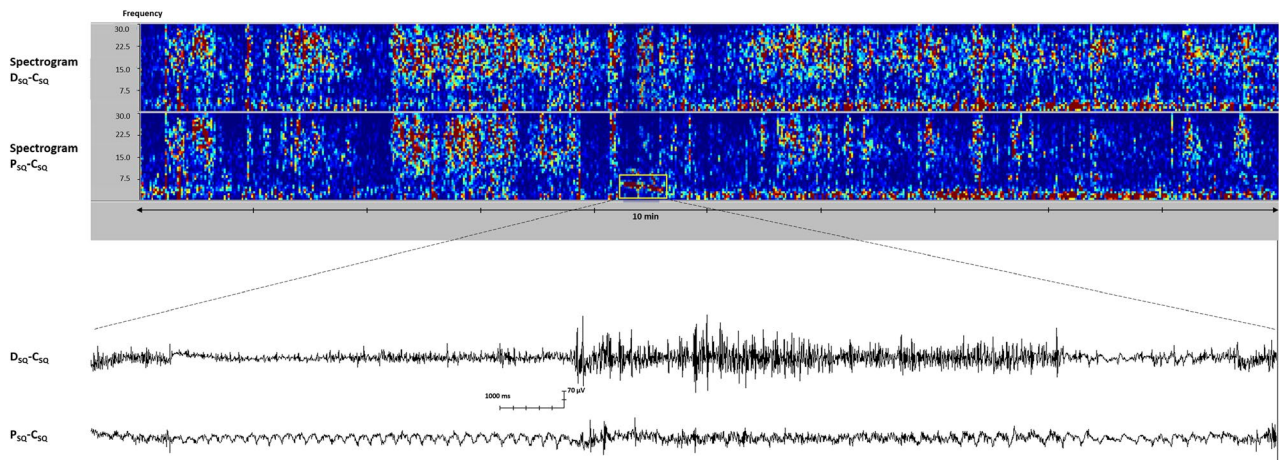


FIGURE 1 Seizure signature. The top panel shows the spectrograms of the two subcutaneous channels (DSQ-CSQ; PSQ-CSQ) as reviewed in the study. The yellow square highlights the spectrographic seizure signature, which, in this case, can be discerned only on spectrogram PSQ-CSQ. For each type of seizure from each participant, one signature was predefined from previous scalp electroencephalography (EEG) recordings. Shortly after the seizure, there is an increase in delta power (0.5-4 Hz), which could represent a postictal EEG pattern. Any spectrographic pattern resembling the relevant signature would be reviewed in the time domain for confirmation. The bottom panel shows the raw EEG at the time of the seizure with rhythmic theta activity in channel PSQ-CSQ and typical frequency dynamics. Thus, the raw EEG confirms the presence of a seizure

in 3-hour bins for each participant. For this analysis, we excluded all participants with fewer than 16 electrographic seizures, as we considered this the minimum requirement to discern any possible rhythmicity reliably.

In anticipation of considerable contamination of the EEG signal by electromyography (EMG) artifacts from the activity of the temporal muscles, we conceptualized high frequency noise as the EEG power above 20 Hz. We then visualized the signal-to-noise ratio (SNR) as: $P_{total\ signal}/P_{noise}$, with P being the power. This allowed us to estimate the effect of noise on seizure detection descriptively.

3 | RESULTS

We included 10 participants in the study. Eight participants completed the study according to protocol. One participant dropped out of the study before implantation for personal reasons and therefore provided no recordings; that participant is disregarded henceforth. One participant (ID A) dropped out of the study after 1 month due to discomfort from the implant. The mean age of participants was 43.7 years (range 27-64). There were two male and seven female participants who provided recordings. All participants except participant B, who was recently diagnosed, were medically refractory. No participants were involved in epilepsy surgery programs while using the SubQ system. Further characteristics of the participants and events of interest are summarized in Table 1.

Participants B and F are particularly noteworthy. They reported events with normal awareness only and a substantial

number of these events had no electrographic equivalent. Unfortunately, the lack of seizure-by-seizure time matching of electrographic and self-reported seizures prohibits statistical testing.

3.1 | Compliance and noise

We recorded 11 774 hours (490.6 days) of EEG of a possible 16 147 hours (73%). Participant C stopped using the ELD at night after approximately 1 month because he preferred sleeping undressed and the ELD requires clothing for attachment. This has taken a great toll on the overall compliance. The compliance of the participants along with the SNR and seizures is shown in Figure 2. For most participants, it can be seen how SNR decreases during the daytime but nonetheless, many electrographic seizures were detected.

3.2 | Seizure comparison

The visual review to identify electrographic seizures took one trained researcher approximately 3 months to perform. In all participants, except participant A, who had no seizures on record, definite signatures could be established, and we identified no seizures with incongruence between time domain and spectrogram. Two participants used the app for documentation of self-reported seizures and seven participants opted to use the analogue diary. In most analogue diaries participants frequently failed to provide seizure times (providing only dates). Therefore, we tabulated self-reported events by date only. Figure 3 shows self-reported probable epileptic seizures and electrographic

ID	Onset zone	Semiology ^a	Self-reported events ^b (epileptic; nonepileptic)	Electrographical seizures	Employment status
A	LT	FAS	0; 3	0	Unemployed
B	LT	FAS	55; 0	22	Unemployed
C	RT	FIAS with FBTCS	0; 3	5	Employed
D	RFT	FAS and FIAS	32; 0	232	Unemployed
E	LT	FIAS with FBTCS	0; 2	16	Employed
F	LT	FAS	21; 0	3	Employed
G	LT	Uncertain	13; 11	12	Employed
H	LT	FIAS with FBTCS	1; 5	2	Unemployed
I	LT	FIAS with FBTCS	133; 43	46	Employed

Abbreviations: FAS, focal aware seizure; FBTCS, focal to bilateral tonic-clonic seizure; FIAS, focal impaired awareness seizure; LT, left temporal; RFT, right frontotemporal; RT, right temporal.

^aObserved by participant or family/caregivers.

^bClassification by investigator.

seizures. Participants D and E had a substantial number of electrographic seizures without corresponding diary entries. In contrast, participants B and F had many diary entries without corresponding electrographic seizures. Participant I had both electrographic seizures without diary entries and vice versa. Participants A, C, and H had few events of any kind. For participant G there is almost complete congruence between self-reported and electrographic seizures.

Due to the limited number of participants, we did not perform hypothesis testing statistics.

For participant D, the commencement of perampanel treatment seems to reduce the number of self-reported seizures, whereas the electrographic seizure count seems to increase. For participant E, the electrographic seizure count seems to decrease after treatment is started. Participants C and F had too few electrographic seizures to establish a reliable pattern.

Concerning electrographic seizures, participants B, C, D, G, and I seem to have circadian rhythms based on Figure 3, but participants C and G have too few seizures to establish a trustworthy pattern. For participants with enough seizures (≥ 16), histograms of the electrographic seizures plotted against the time of day are shown in Figure 4, and this confirms the impression of rhythmicity. Participant E does not have any apparent circadian rhythmicity.

3.3 | Adverse events

No serious ADEs were reported and all the ADEs reported were anticipated, except one (“unclassified”). Table 2 summarizes all ADEs.

As expected, most participants experienced soreness at the implantation site after the surgery. For six participants, this soreness receded within approximately 1 week; one participant reported no soreness at all. Two had longer-lasting

soreness, for 2 weeks and 4 weeks, respectively. Soreness after explantation receded within a few days in all cases.

Two participants reported occasional headaches during the study. For one, the reported headaches were mild and did not require any response. For the other, the headaches were of moderate intensity and required over-the-counter pharmacologic treatment; in this case, the participant had also had occasional headaches prior to inclusion to the study. The headaches were similar in frequency and intensity before and during the study.

Two participants experienced minor irritation of the skin where the transceiver was attached; this was ameliorated by detaching the transceiver for short periods.

The unclassified event was described as a tingling sensation in the implant, but only when located at certain places in her house. Technical examinations of the implant after explantation revealed no malfunctions.

3.4 | User experience

Information on user experiences was collected only anecdotally. Most participants found the ELD easy to use and had no problems with the daily operations. Minor annoyances were noted, such as occasional nightly disconnections, having to adjust the usual position of glasses, and the necessity of wearing clothes at night. No participants felt constrained in their ability to perform jobs or leisure activities.

4 | DISCUSSION

This study is the first to describe ultra long-term monitoring of epilepsy patients with a minimally invasive EEG system in a real-life setting anywhere in the world. We have shown that home monitoring for approximately 3 months is feasible

TABLE 1 Participant characteristics

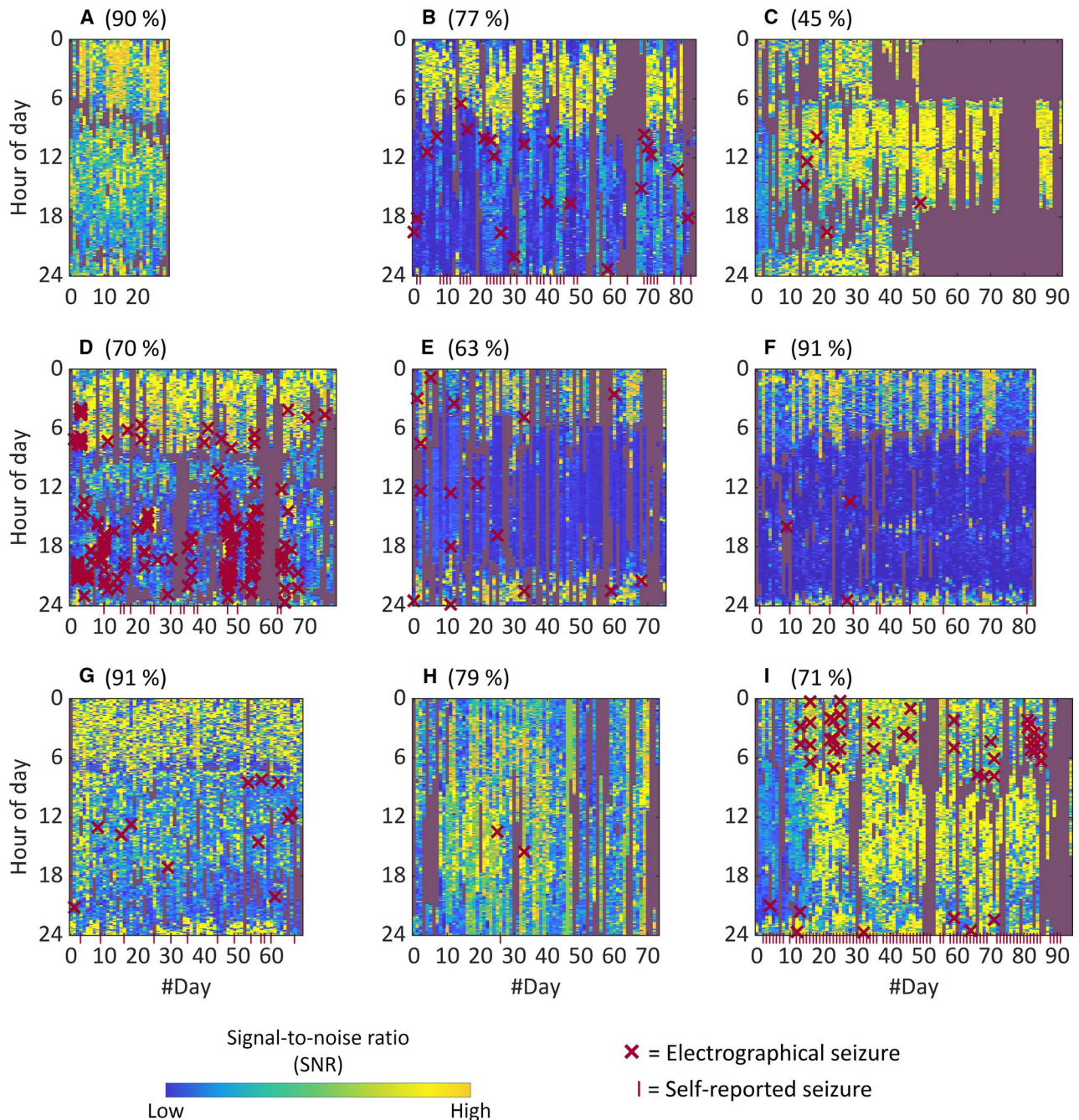


FIGURE 2 User compliance and signal-to-noise ratio. Charts for all participants displaying their compliance in using the external logging part of the device across the full study period by time of day. Total percentage for each participant in parentheses. Gray areas display epochs when the ELD was not used. No pattern of increased detection of electrographic seizures is apparent, suggesting that a detection bias due to noise is less plausible

without major adverse events or significant impact on activities of daily living. Total compliance was moderate (73%) with high interindividual variability (45%-91%). This variability was not related to adverse events but seemed to depend on everyday practicalities and hardware usability. The clinical implications of compliance issues should not be underestimated, and it warrants careful patient selection and thorough information about all parts of the SubQ system. For some participants, the electrographic seizures detected showed clear

circadian rhythmicity. This is well in line with the findings published by Baud et al.¹⁷ Qualitatively, the objective seizure count provided information on participants' response to changes in AEDs that would not have been revealed from the seizure diaries. Such information could affect the choice of treatment. Participants reported minimal impact on daily activities.

The participants are examples of clinical cases in which the information provided by the ultra long-term

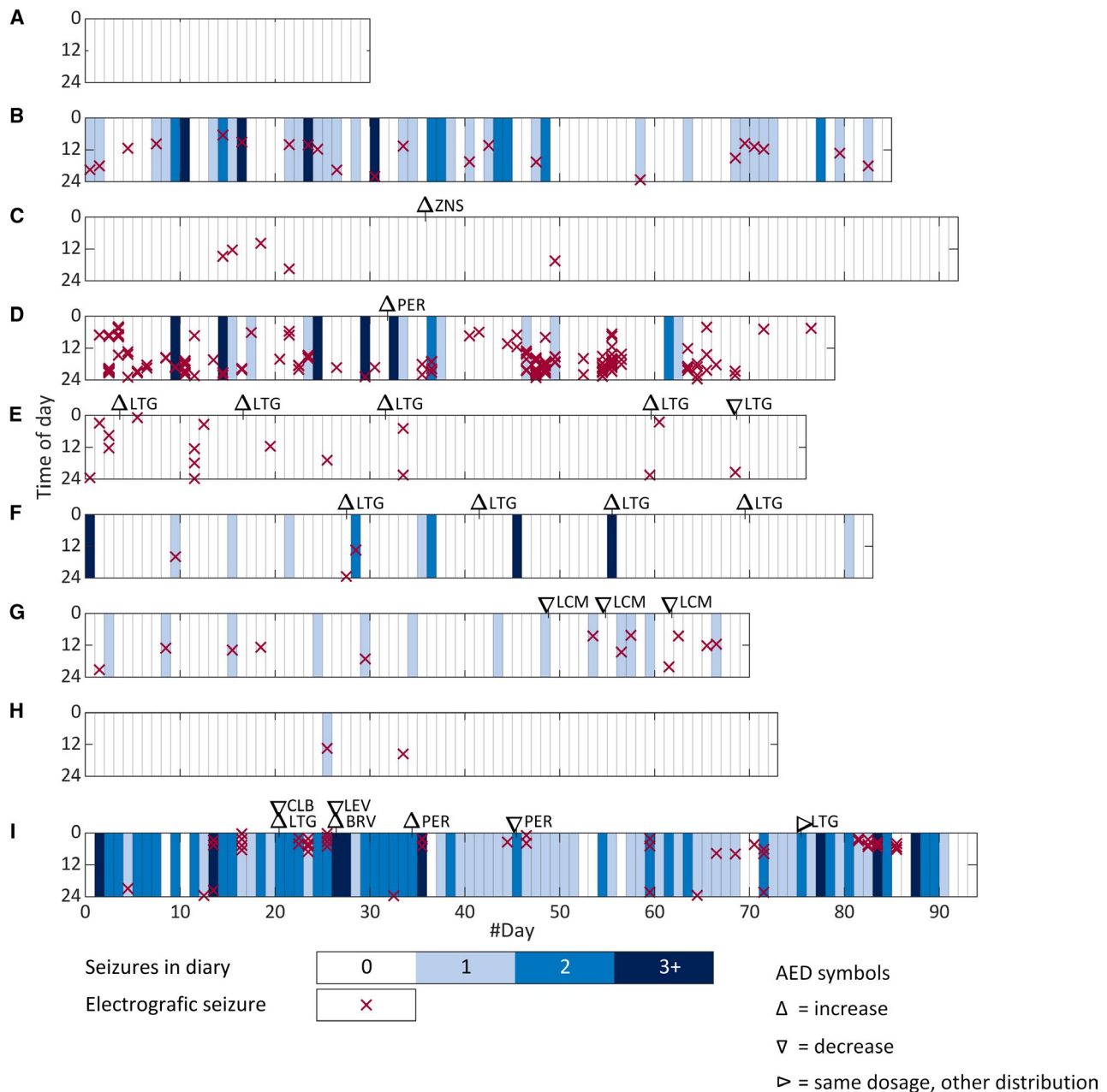


FIGURE 3 Seizure comparison and antiepileptic drugs. Charts for all participants showing electrographic seizures and self-reported events classified as probable epileptic seizures. Self-reported events are semiquantified and displayed by date only. Electrographic seizures are displayed by time of day. Changes in antiepileptic medication are shown on top of each chart. Participant E is a good example of underreporting, as she reported none of the electrographic seizures. BRV, brivaracetam; CLB, clobazam; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; PER, perampanel; ZNS, zonisamide

EEG would probably influence the treatment strategy. Controversially, we considered the electrographic seizures to be the ground truth and taking that into account, participants C, D, and E are cases of underreporting. The diary information alone would present the seizure burden as lower than it was. This could lead to a more passive treatment strategy, thereby increasing the risk of complications related to repeated seizures. All these participants had focal seizures with impaired awareness, which is a likely cause of the underreporting.

Participants B and F are seemingly cases of overreporting. These two participants had seizures with normal awareness, which is usually taken as an indication that a smaller cortical area has been involved in the abnormal activity. The precise area of cortical surface necessary for a seizure to be detected by electrodes placed outside the skull depends on many factors, but several studies have shown that smaller cortical surface involvement decreases the chance of detecting epileptic discharges using scalp electrodes.^{18–20} It seems likely that the same limitation applies to subcutaneous electrodes, such

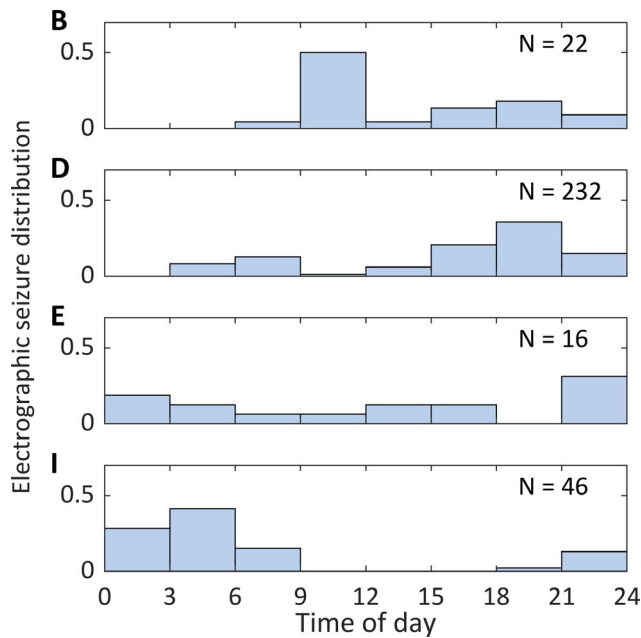


FIGURE 4 Circadian distribution of electrographic seizures. Histograms showing the circadian distribution of electrographic seizures for participants with ≥ 16 seizures. Days are divided into 3-h bins. All the presented participants, except participant E, seems to have a circadian pattern to their seizures

as the implant we tested. Therefore, we cannot say whether the self-reported events of these two participants are true seizures or not, without ambiguity. In the field of seizure-detection devices, overreporting of seizures seems to have received less attention than underreporting, but in our opinion, it is equally important. PNES could be considered a kind of overreporting, in which there is a great need for new diagnostic tools. Overreporting is more likely to lead to overtreatment and it holds risks of more adverse effects and interactions from AEDs.

Participant I was unique among our subjects. She misreported in a way that involved both underreporting and

overreporting. The electrographic seizure count revealed a very different pattern of seizure activity than the self-reported seizures. Such findings could be of great importance in uncovering potential seizure-precipitating factors, such as sleep deprivation or AED oversights.

Participant G was the only one among the included patients who was able to report her own seizures reliably, as seen by the high concordance between diary entries and electrographic seizures.

To the authors' knowledge, there are no equivalent devices at the same stage of development. Several other seizure-detection devices have appeared within the last decade, some employing EEG^{2,10,17,21,22} and some employing other technologies, such as EMG/accelerometry,^{23,24} heart rate variability,²⁵ electrodermal activity, or a combination of these.^{26,27} Describing the influence of an ultra-long-term EEG monitoring device on the mobility of the wearer is a key aspect of its usability. In 2017, Bateson et al²⁸ developed a mobility score for use in wearable EEG research going from 0 (least mobile) to 5 (most mobile). The device we tested does not exactly fit into the existing categories, but given the minimal impact on mobility, we assess it at a score of 4-5. Combined with the ease of use and minimal invasiveness, this makes for a very favorable usability profile for this system.

4.1 | Limitations

The present study had some shortcomings that must be considered when discussing the results. Several of these relate to the electrographic seizures.

First, we reviewed spectrograms rather than raw EEG. This was necessary to expedite the analysis, which even by this method took several months to perform. The process was monotonous, leaving room for human error due to lapses of attention. Reviewing the raw EEG would have exacerbated this problem, but also allowed for a more detailed analysis and we cannot exclude the possibility that reviewing the raw

TABLE 2 Summary of adverse device events

Event type	No. of occurrences	Severity	Anticipated
Pain/soreness at site of surgery up to 1 week after surgery	6	Mild	Yes
Pain/soreness at site of surgery more than 1 week after surgery	2	Mild	Yes
Headache not related to surgery	2	Mild	Yes
Skin irritation at transceiver contact position	2	Mild	Yes
Excessive bleeding	0	—	—
Infection	0	—	—
Unclassified	1	Mild	No

EEG would have yielded slightly different results. Second, there are some cases in which a true seizure could have occurred without being detected by the device:

1. The seizure did not involve a large enough cortical area to be visible in extracranial recordings of any kind.
2. The seizure did not propagate to a cortical area below the implant and was therefore not recorded.
3. The electrographic presentation of the seizure was discreet and would have required more spatial information to be detectable.
4. The electrographic seizure was not visible due to artifacts.

Although we took every precaution to avoid these issues by carefully selecting the participants and reviewing our data thoroughly, they might have occurred, adding a measure of imprecision to our electrographic seizure count. Participants B and F are examples of cases in whom we suspect these limitations influenced the electrographic seizure count. For statistical confirmation of this suspicion, we would have needed self-reported seizures with a precise time stamp for comparison with the electrographic seizures, which we did not have. Digital seizure diaries facilitate a more precise documentation of self-reported events, and we hope that the use of such diaries will grow more common in the future.

Validation of electrographic seizures is an obstacle that will require a major setup, preferably one employing intracranial EEG electrodes. Several studies have shown that intracranial electrodes, if positioned correctly in relation to the seizure focus, can be used to detect more seizures than scalp EEG electrodes.^{29–32} It seems likely that this relationship extends to subcutaneous electrodes, since the skull attenuates the EEG signal more than the other scalp tissue layers.³³ Another way to get around this problem is to perform large-scale trials comparing clinical outcomes for groups of patients in whom decision-making was based on traditional methods to other groups in whom decision-making was informed by whatever method in question. Such trials would be long and complicated, but also very informative. Recently, a proposal for standards for clinical trials of medical devices was presented.³⁴ Such standards should guide future studies on novel seizure-detection devices to facilitate comparison between studies and meta-analyses.

Using automated seizure detection algorithms would have been a very attractive solution for review of the massive amounts of data we collected. Such algorithms have been successfully employed previously in ultra-long-term monitoring scenarios.³⁵ However, automated algorithms must be validated properly to be reliable, and no algorithms had been validated properly on subcutaneous EEG when our dataset was ready for review.

Unfortunately, comparing detection of seizures from scalp EEG recordings and subcutaneous recordings during

the epilepsy monitoring unit (EMU) admission was not possible. This was due to the electrographically subtle seizures from participant D, which constituted most of the seizures recorded during admission; any comparison would have reflected the unusual electrographic presentation of the seizures, rather than any features of the devices compared.

Other limitations are the low number of participants in our study and the fact that we focused on persons with temporal lobe epilepsy. These decisions, although necessary for the feasibility of the study, decrease the generalizability of our findings. Despite this, the current study provides crucial safety and usability data, and the data we collected may be used to form hypotheses in future studies.

Finally, artifacts contaminated parts of our data, especially during the daytime. Considering the proximity of the implant to the temporal and mastoid muscles, this was anticipated. Potentially, artifacts could obscure the detection of electrographic seizures and thereby introduce a bias to our findings on circadian rhythmicity and our comparison of electrographic and self-reported seizures. Our findings, though, do not show a general preponderance of electrographic seizures during the nighttime, when the SNR is the highest, which seems to indicate that any potential bias in the detection of electrographic seizures is not severe. Methods for artifact rejection, both through improved surgical techniques and postprocessing of the electrographic data, should be explored further.

In conclusion, this is the first study to demonstrate that ultra long-term epilepsy home monitoring based on recordings from a minimally invasive, subcutaneous implant is feasible and safe. During almost 500 days of home monitoring, no serious ADEs occurred. Before implementing ultra long-term home monitoring EEG systems in clinical practice, larger trials with clinically relevant outcome measures are needed. In addition, algorithms for automated analysis of ultra long-term EEGs are an absolute necessity, as traditional visual analysis is both immensely time-consuming and a victim of subjectivity. Nonetheless, there seem to be several clinical scenarios for which the information yielded by such monitoring could provide better treatment and despite the limitations, we believe that devices for minimally invasive ultra-long-term monitoring will be an important contribution to the neurophysiology toolbox.

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CONFLICT OF INTERESTS

Authors Jonas Duun-Henriksen and Sirin Gangstad are full-time employees at UNEEG Medical A/S. Author Sigge Weisdorf has received support from UNEEG Medical A/S. Author Troels Kjær has performed consultancy for UNEEG Medical A/S. The remaining authors have no conflict of interests to disclose. 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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REFERENCES

- Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav*. 2012;24:304–10.
- Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol*. 2013;12:563–71.
- Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol*. 2007;64:1595–9.
- Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. *Neurology*. 1996;47:260–4.
- Tatum WO, Winters L, Gieron M, Passaro EA, Benbadis S, Ferreira J, et al. Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. *J Clin Neurophysiol*. 2001;18:14–9.
- Tovar Quiroga DF, Britton JW, Wirrell EC. Patient and caregiver view on seizure detection devices: a survey study. *Seizure*. 2016;41:179–81.
- Blachut B, Hoppe C, Surges R, Elger C, Helmstaedter C. Subjective seizure counts by epilepsy clinical drug trial participants are not reliable. *Epilepsy Behav*. 2017;67:122–7.
- Casson A, Yates D, Smith S, Duncan J, Rodriguez-Villegas E. Wearable electroencephalography. What is it, why is it needed, and what does it entail? *IEEE Eng Med Biol Mag*. 2010;29:44–56.
- Baumgartner C, Koren JP. Seizure detection using scalp-EEG. *Epilepsia*. 2018;59(Suppl 1):14–22.
- Do Valle BG, Cash SS, Sodini CG. Low-power, 8-channel EEG recorder and seizure detector ASIC for a subdermal implantable system. *IEEE Trans Biomed Circuits Syst*. 2016;10(6):1058–67.
- Debener S, Emkes R, De Vos M, Bleichner M. Unobtrusive ambulatory EEG using a smartphone and flexible printed electrodes around the ear. *Sci Rep*. 2015;5:16743.
- Bleichner MG, Lundbeck M, Selisky M, Minow F, Jäger M, Emkes R, et al. Exploring miniaturized EEG electrodes for brain-computer interfaces. *An EEG you do not see? Physiol Rep*. 2015;3:e12362.
- Zibrandtsen IC, Kidmose P, Christensen CB, Kjaer TW. Ear-EEG detects ictal and interictal abnormalities in focal and generalized epilepsy - A comparison with scalp EEG monitoring. *Clin Neurophysiol*. 2017;128:2454–61.
- Duun-Henriksen J, Kjaer TW, Looney D, Atkins M, Sorenson JA, Rose MH, et al. EEG signal quality of a subcutaneous recording system compared to standard surface electrodes. *J Sens*. 2015;(6):1–9.
- Kjaer TW, Sorensen HBD, Groenborg S, Pedersen CR, Duun-Henriksen J. Detection of paroxysms in long-term, single-channel EEG-monitoring of patients with typical absence seizures. *IEEE J Transl Eng Health Med*. 2017;5:2000108.
- Weisdorf S, Gangstad SW, Duun-Henriksen J, Mosholt KSS, Kjaer TW. High similarity between EEG from subcutaneous and proximate scalp electrodes in patients with temporal lobe epilepsy. *J Neurophysiol*. 2018;120:1451–60.
- Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. *Nat Commun*. 2018;9:88.
- Cooper R, Winter AL, Crow HJ, Walter WG. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalogr Clin Neurophysiol*. 1965;18:217–28.
- Cosandier-Rimé D, Merlet I, Badier JM, Chauvel P, Wendling F. The neuronal sources of EEG: modeling of simultaneous scalp and intracerebral recordings in epilepsy. *NeuroImage*. 2008;42:135–46.
- Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia*. 2005;46:669–76.
- Ives JR. New chronic EEG electrode for critical/intensive care unit monitoring. *J Clin Neurophysiol*. 2005;22:119–23.
- Geller EB, Skarpaas TL, Gross RE, Goodman RR, Barkley GL, Bazil CW, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. *Epilepsia*. 2017;58:994–1004.
- Beniczky S, Conradsen I, Wolf P. Detection of convulsive seizures using surface electromyography. *Epilepsia*. 2018;59(Suppl 1):23–9.
- Arends JBAM. Movement-based seizure detection. *Epilepsia*. 2018;59(Suppl 1):30–5.
- Jeppesen J, Beniczky S, Johansen P, Sidenius P, Fuglsang-Frederiksen A. Detection of epileptic seizures with a modified heart rate variability algorithm based on Lorenz plot. *Seizure*. 2015;24:1–7.
- Heldberg BE, Kautz T, Leutheuser H, Hopfengartner R, Kasper BS, Eskofier BM. Using wearable sensors for semiology-independent seizure detection - towards ambulatory monitoring of epilepsy. *Conf Proc Annu Int Conf IEEE Eng Med Biol*. 2015;2015:5593–6.
- Cogan D, Birjandtalab J, Nourani M, Harvey J, Nagaraddi V. Multi-biosignal analysis for epileptic seizure monitoring. *Int J Neural Syst*. 2016;27:1650031.
- Bateson AD, Baseler HA, Paulson KS, Ahmed F, Asghar AUR. Categorisation of mobile EEG: a researcher's perspective. *Biomed Res Int*. 2017;2017:5496196.
- Lieb JP, Walsh GO, Babb TL, Walter RD, Crandall PH. A comparison of EEG seizure patterns recorded with surface and depth electrodes in patients with temporal lobe epilepsy. *Epilepsia*. 1976;17:137–60.
- Pacia SV, Ebersole JS. Intracranial EEG substrates of scalp ictal patterns from temporal lobe foci. *Epilepsia*. 1997;38:642–54.
- Sakai Y, Nagano H, Sakata A, Kinoshita S, Hamasaki N, Shima F, et al. Localization of epileptogenic zone in temporal lobe epilepsy by ictal scalp EEG. *Seizure*. 2002;11:163–8.

32. Tao JX, Baldwin M, Ray A, Hawes-Ebersole S, Ebersole JS. The impact of cerebral source area and synchrony on recording scalp electroencephalography ictal patterns. *Epilepsia*. 2007;48:2167–76.
33. Karoly P, Goldenholz DM, Cook M. Are the days of counting seizures numbered? *Curr Opin Neurol*. 2018;31:162–8.
34. Beniczky S, Ryvlin P. Standards for testing and clinical validation of seizure detection devices. *Epilepsia*. 2018;59(Suppl 1):9–13.
35. Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology*. 2015;84:810–7.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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