Clinical Neurophysiology 141 (2022) 77–87

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Sub-scalp electroencephalography: A next-generation technique to study human neurophysiology

Zulfi Haneef [a,*], Kaiyuan Yang [b,1], Sameer A. Sheth [c], Fuad Z. Aloor [d], Behnaam Aazhang [b], Vaishnav Krishnan [a,b], Cemal Karakas [e,f]

[a] Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA
[b] Department of Electrical and Computer Engineering, Rice University, Houston, TX 77005, USA
[c] Department of Neurosurgery, Baylor College of Medicine, Houston, TX 77030, USA
[d] Department of Medicine, Baylor College of Medicine, Houston, TX 77030, USA
[e] Division of Pediatric Neurology, Department of Neurology, University of Louisville, Louisville, KY 40202, USA
[f] Norton Children's Neuroscience Institute, Louisville, KY 40241, USA

ARTICLE INFO

Article history:
Accepted 3 July 2022
Available online 18 July 2022

Keywords:
Subscalp
EEG
Wearable
Epilepsy monitoring
Seizure detection

HIGHLIGHTS

- Sub-scalp EEG (ssEEG) is a promising next-generation technology for investigating human neurophysiology.
- It enables ultra-long-term EEG recording to improve diagnostic yield in epilepsy.
- Different ssEEG devices have been developed with unique strengths and limitations.

ABSTRACT

Sub-scalp electroencephalography (ssEEG) is emerging as a promising technology in ultra-long-term electroencephalography (EEG) recordings. Given the diversity of devices available in this nascent field, uncertainty persists about its utility in epilepsy evaluation. This review critically dissects the many proposed utilities of ssEEG devices including (1) seizure quantification, (2) seizure characterization, (3) seizure lateralization, (4) seizure localization, (5) seizure alarms, (6) seizure forecasting, (7) biomarker discovery, (8) sleep medicine, and (9) responsive stimulation. The different ssEEG devices in development have individual design philosophies with unique strengths and limitations. There are devices offering primarily unilateral recordings (24/7 EEG™ SubQ, Neuroview™, Soenia® UltimateEEG™), bilateral recordings (Minder™, Epios™), and even those with responsive stimulation capability (EASEE®). We synthesize the current knowledge of these ssEEG systems. We review the (1) ssEEG devices, (2) use case scenarios, (3) challenges and (4) suggest a roadmap for ideal ssEEG designs.

Contents

1. Introduction 78
2. ssEEG: A paradigm shift in epilepsy diagnostics 79

Abbreviations: Acc, Accelerometry; ASM, Antiseizure medications; CC-BY, Creative Common Attribution License; CE, Conformitè Europëenne; CEO, Chief Executive Officer; Cm, Centimeter; DRE, Drug-resistant epilepsy; EASEE, Epicranial Application of Stimulation Electrodes for Epilepsy; EEG, Electroencephalography; EMU, Epilepsy monitoring unit; FDA, Food and Drug Administration; GA, General anesthesia; Hz, Hertz; h, hours; LA, Local anesthesia; NJ, New Jersey; PIMIDES, Patient Individualized Modulation and Intervention by Epicranial Stimulation; PWE, Persons with epilepsy; ®, Registered; RNS, Responsive neurostimulation; ssEEG, Sub-scalp electroencephalography; SUDEP, Sudden unexpected death in epilepsy; TBI, Traumatic brain injury; Temp, Temporal; TM, Trade Mark; US, Unitad States.

* Corresponding author at: 7200 Cambridge St #9A, Houston, TX 77030, USA.
E-mail addresses: zulfi.haneef@bcm.edu (Z. Haneef), kyang@rice.edu (K. Yang).
[1] Co-corresponding author at: 6100 Main St MS366, Houston, TX 77005, USA.

https://doi.org/10.1016/j.clinph.2022.07.003
1388-2457/Published by Elsevier B.V. on behalf of International Federation of Clinical Neurophysiology.

2.1. Motivation for ssEEG, and current EEG recording systems . . . 79
2.2. Technical aspects of ssEEG . . . 79
2.3. Current ssEEG systems . . . 80
2.3.1. 24/7 EEG™ SubQ (UNEEG Medical, Alleroed, Denmark) . . . 80
2.3.2. Minder™ (Epi-Minder, Melbourne, Australia) . . . 80
2.3.3. Neuroview™ (Neuroview Technology Inc., Englewood, New Jersey, USA) . . . 81
2.3.4. Soenia® UltimateEEG™ (BrainCare Oy, Tampere, Finland) . . . 81
2.3.5. Epios™ (Wyss Center, Geneva, Switzerland) . . . 81
2.3.6. EASEE® (Precisis, Heidelberg, Germany) . . . 82
3. Use case scenarios . . . 82
3.1. Seizure quantification . . . 82
3.2. Seizure characterization . . . 82
3.3. Seizure lateralization . . . 82
3.4. Seizure localization . . . 83
3.5. Seizure alarms . . . 83
3.6. Seizure forecasting . . . 83
3.7. Biomarker discovery . . . 83
3.8. Sleep medicine . . . 83
3.9. Responsive neuro-stimulation . . . 83
4. Challenges . . . 84
4.1. Technical challenges . . . 84
4.2. Safety and tolerability . . . 84
4.3. Lack of standardized clinical protocols and guidelines . . . 84
5. Future roadmap . . . 84
5.1. Automatic seizure detection analysis with machine learning . . . 84
5.2. Wearable companion devices for ssEEG . . . 84
5.3. Clarification of technology and large clinical trials . . . 84
6. Conclusions . . . 85
Declaration of Competing Interest . . . 85
Acknowledgments . . . 85
Funding . . . 85
References . . . 85

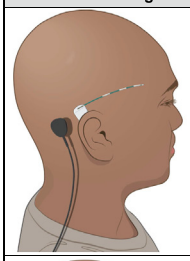
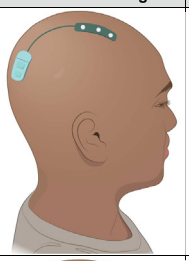
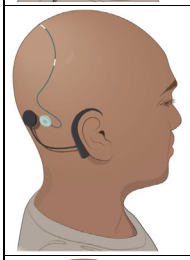
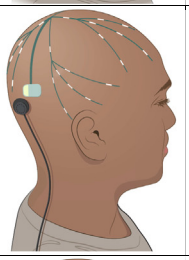
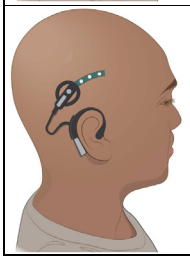
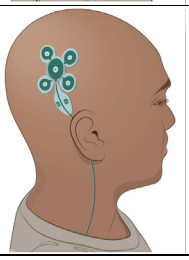
1. Introduction

Epilepsy is the second most common chronic brain disease worldwide, affecting approximately 3.4 million people (1.2% of the population) in the United States (US) (Zack and Kobau, 2017). Persons with epilepsy (PWE) experience substantial premature mortality and several medical comorbidities (Devinsky et al., 2016), and seizure-related variables including seizure frequency and the burden of antiseizure medications (ASM) impact the overall quality of life (Spencer et al., 2007). Technologies that improve our ability to accurately identify and quantify seizures are an essential component of data-driven medical and/or device-related management strategies for PWE. Current practice almost exclusively rely on self-reported seizure counts or electronic seizure diaries (Fisher et al., 2012), which are notoriously unreliable and, in some patients, may miss up to half of all seizures (Blachut et al., 2017), mostly due to lack of awareness that a seizure has occurred (Elger and Hoppe, 2018), leading to suboptimal seizure management.

Approximately one-third of PWE have drug-resistant epilepsy (DRE) and are candidates for epilepsy surgery evaluation which requires precise seizure localization (in cases of focal onset seizures) (Brodie et al., 2012; Englot et al., 2017). However, the presurgical evaluation does not always provide enough information to localize or lateralize seizures (Chan et al., 2018). Even with video electroencephalography (EEG) in an epilepsy monitoring unit (EMU) evaluation, definitive lateralization, and localization may prove elusive due to limitations in recording duration (Moseley et al., 2015), often leading to under-sampling and mislocalization of seizures that may be multifocal or bilateral in onset (King-Stephens et al., 2015; Smart et al., 2013). In chronic bihippocampal ambulatory electrocorticography recordings in suspected bitemporal epilepsy, we know that about a third of patients require at least a month before electrographic onsets can be recorded from both hemispheres (King-Stephens et al., 2015). Existing approaches to overcome these limitations have their own constraints. Ambulatory video-EEG provides high-quality recordings at home but is limited by short recording durations (2–3 days) and the need for trained EEG technologists for the setup, removal, and troubleshooting (Brunnhuber et al., 2020; González Otárula et al., 2021). Wearable technologies such as skin-adherent EEG (Lehmkuhle et al., 2015), behind-the-ear EEG (Bleichner and Debener, 2017; Swinnen et al., 2021), and intra-auricular EEG (Kappel et al., 2019) suffer from inconsistent signal quality, the need for regular maintenance, and the inability to record over longer time periods. The inevitable trade-off in mobile EEG technologies appears to be quality/need for electrode care vs. duration of recordings. Long-term intracranial EEG recording is possible using the responsive neurostimulation (RNS) system, but they are mainly built for neuromodulation for very particular indications and are too invasive for routine diagnostic applications (Duun-Henriksen et al., 2020).

These technical gaps have led to the development of sub-scalp EEG devices (ssEEG, also sometimes called subcutaneous, subgaleal, subdermal, epicranial, epiosteal, or subcutaneous EEG), where a subcutaneous recording electrode is implanted between the scalp and the skull. This approach may provide transformative advances in clinical epilepsy care, with superior signal quality by avoiding the typical artifacts of scalp EEG and prolonged recording durations without the need for recurrent electrode care. ssEEG devices may help improve diagnostic yield by capturing habitual seizures in a home environment without the need for ASM withdrawal and provocative maneuvers. Additional benefits include convenience, as it avoids EMU-related school/work disruptions,

Table 1
Details of subscalp encephalography (ssEEG) devices in development.

Illustrative Image	Device details	Approval/ other notes	Illustrative Image	Device details	Approval/ other notes
	**24/7 EEG™ SubQ** *(UNEEG, Alleroed, Denmark)* ° *Channels: 1 lead with 3 contacts* ° *Sampling:* EEG 207 Hz ° *Battery:* External, 24 h rechargeable ° *Wearable companion*: Yes ° *Raw data:* available ° *Incision:* ~3 cm, LA	° Typical implant location is unilateral temporal. ° Orientation can be changed. ° Multimodal recordings- EEG, 3-axis acc.		**Neuroview™** *(Englewood, NJ, USA)* ° *Channels:1 lead with 3 contacts* ° *Sampling:* EEG 256 Hz ° *Battery:* Internal, 3 years ° *Wearable companion*: No ° *Raw data:* available ° *Incision:* ~2 cm, LA	° Subscalp EEG electrodes can be placed at the cranial vertex or anywhere. ° Low-power, on-board algorithms identify epochs suspicious for seizures and patient-identified events. ° Multimodal recordings- EEG, 3-axis acc.
	**Minder®** *(Epi-Minder, Melbourne, Australia)* ° *Channels: 1 lead with 4 contacts* ° *Sampling:* EEG 250 Hz ° *Battery:* External, 24 h rechargeable ° *Wearable companion*: Yes ° *Raw data:* available ° *Incision:* unspecified, GA	° Bilateral scalp coverage achieved by tunneling a very long multi-channel electrode to contralateral head.		**Epios™** *(Wyss Center, Geneva, Switzerland)* ° *Channels: Each trident-shaped lead has 8 contacts. Total up to 4 leads (32 contacts)* ° *Sampling:* EEG 250 Hz, ° *Battery:* External, 24 h rechargeable ° *Wearable companion*: Yes ° *Raw data:* available ° *Incision:* 2-4 incisions each <1 cm, LA, or GA	° Full head coverage (10-20 montages) can be placed under GA. ° EEG data transferred wirelessly to headpiece and body-worn unit for power and storage. ° Multimodal recordings - EEG, audio, 3-axis acc., and ECG
	**Soenia® UltimateEEG™** *(BrainCare Oy, Finland)* ° *Channels: 1 lead with up to 8 contacts* ° *Sampling:* EEG 1000 Hz ° *Battery:* External, 24-48 h ° *Wearable companion*: Yes ° *Raw data:* available ° *Incision:* ~2-3 cm, LA	° Platinum on silicon electrodes, customizable electrode number (up to 8), size, and inter-electrode distance.		**EASEE®** *(Precisis, Heidelberg, Germany)* ° *Channels: 5 platelet contacts* ° *Sampling:* EEG 250 Hz ° *Battery:* Internal, >3 years ° *Wearable companion*: No ° *Raw data:* planned ° *Incision:* ~7 cm, GA	° Placed over epileptic focus ° Diagnostic and responsive neurostimulation planned ° Electrode design based on Laplacian montage.

Data and image representations are compiled/created by authors based on publicly available information and with input from development teams wherever possible. Final production details/ design may be different. Color schema for images: implanted device (cyan), electrodes (green), external transceiver, and wires (black).
Abbreviations: Acc- Accelerometry, CE- Conformitè Europëenne, cm-centimeter, EASEE- Epicranial Application of Stimulation Electrodes for Epilepsy, US FDA- United States Food and Drug Administration, GA- General anesthesia, h- hours, Hz-Hertz, LA-local anesthesia, NJ-New Jersey, ®-Registered, temp-temporal, ssEEG-subscalp electroencephalography, TM-Trade Mark.

and cost savings from repeated EMU evaluations to capture infrequent seizures- a single 4–5 day EMU study may cost up to $35–40,000 in hospital costs alone (Agrawal et al., 2015).

Several ssEEG systems have been developed by independent research groups around the world with different design philosophies rendering unique strengths and limitations. These devices vary in many ways, including the number of leads, degree of invasiveness, and primary intended purpose (seizure identification, quantification, lateralization, localization, and/or therapeutic stimulation). Despite publications about individual devices (Viana et al., 2021a; Weisdorf et al., 2018, 2019) and focused reviews (Duun-Henriksen et al., 2020; Pathmanathan et al., 2021), uncertainties persist among epilepsy specialists about their utility in epilepsy evaluations. Here, we review this literature to synthesize existing viewpoints about the utility of ssEEG and their potential roles in addressing the unmet needs of the epilepsy community. We discuss ideal case scenarios that may benefit from these currently emerging devices and suggest a roadmap for ssEEG implementation in future epilepsy care.

2. ssEEG: A paradigm shift in epilepsy diagnostics

2.1. Motivation for ssEEG, and current EEG recording systems

The motivation to develop ssEEG devices arises from an unmet clinical need in recording ultra-long term (months to years) high-quality EEG to provide accurate seizure quantification. Such devices may offer many advantages and solutions for personalized epilepsy management in the context of infrequent seizures (Chan et al., 2018), identifying multidien (multi-day) rhythms of seizure risk (Baud et al., 2018; Karoly et al., 2016; Stirling et al., 2021) and for prioritizing resective or neuromodulatory treatments in patients with two or more seizure onset zones (Hirsch et al., 2020; King-Stephens et al., 2015).

Two main recording approaches are prevalent for the diagnostic evaluation of seizures- scalp (surface) EEG and intracranial EEG. Scalp EEG is easy to set up and record, and has good spatial (whole head) coverage, but is limited by lower spatial resolution and unstable scalp contact necessitating greater involvement by EEG technologists. On the other extreme, high-fidelity, high-resolution, recordings are possible using implanted intracranial EEG. However, this is not feasible in most patients with epilepsy as they are invasive, require specialized neurosurgical support, and suffer from low spatial coverage. Both modalities are typically limited to recording over relatively short periods of time (1–2 weeks) and are performed in the hospital environment. ssEEG represents a compromise between these two extremes by enabling less noisy recordings than scalp EEG and by not requiring frequent technologist intervention to maintain EEG quality. They are also minimally invasive, thus making it possible to be used in a wider population than intracranial EEG. The ability to perform ultra-long-term recordings over weeks-months in a home environment is an additional theoretical advantage of ssEEG systems.

2.2. Technical aspects of ssEEG

Long-term ssEEG devices are new to the epilepsy diagnostic landscape (Table 1 and Fig. 1). The general design of these devices

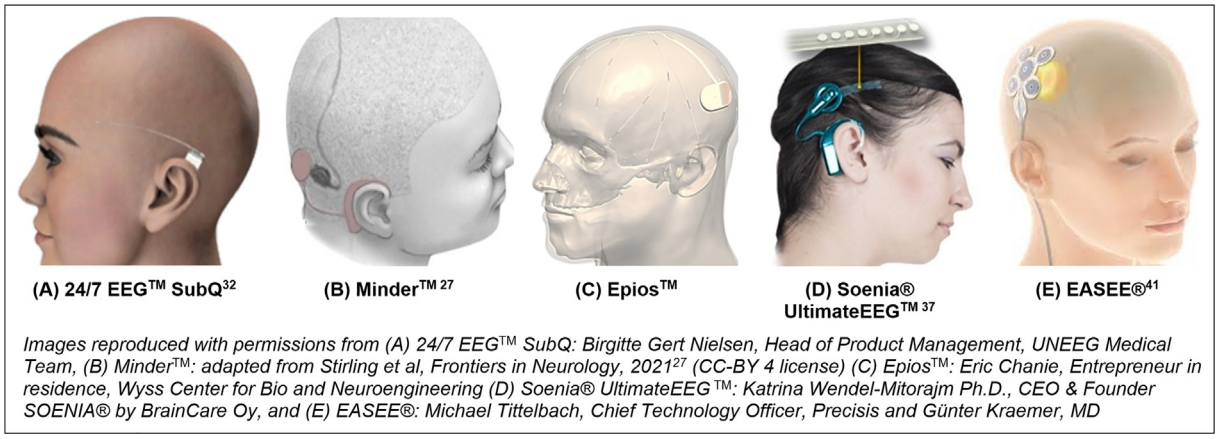


Fig. 1. Design renderings of the different subscalp-electroencephalography (ssEEG) systems – see description/images in Table 1 and text for details. *Abbreviations:* EEG-Electroencephalography, EASEE- Epicranial Application of Stimulation Electrodes for Epilepsy, ®-Registered, TM-Trade Mark.

includes leads with a range of sizes and contact numbers, which are tunneled subcutaneously under the scalp and attached to a recorder. Internalized electrodes, of varying designs, connect with an external unit necessary for power, data storage, and transmission, and may contain additional sensors to record audio, accelerometry, or photoplethysmography signals. In the following sections, we summarize our knowledge of current ssEEG systems aggregated from the literature and publicly available information, supplemented by personal communication with the development teams.

2.3. Current ssEEG systems

2.3.1. 24/7 EEG™ SubQ (UNEEG Medical, Alleroed, Denmark)

This is the sole device that is currently approved for clinical use with a Conformitè Europëenne (CE)-mark for Europe, and pending US Food and Drug Administration (FDA) approval (24/7 EEG™ SubQ, 2022, p. 7; Weisdorf et al., 2019, 2018). This system was originally developed for the detection of hypoglycemia in persons suffering from diabetes (Juhl et al., 2010), however, later obtained approval for use in epilepsy management (Table 2). The single implanted lead has three contacts creating two bipolar channels (the middle contact is a reference). The implant is inserted in a minimally invasive procedure under a local anesthesia (Pathmanathan et al., 2021), typically in a unilateral temporal location. However, a device may be implanted on both sides of the head and thereby bitemporal recording may be achieved (Table 3). An implanted lead connects to an external storage unit that also powers the implant through an inductive link. The housing is placed behind the ear and the lead can be inserted in various directions. This system features a complete data infrastructure enabling the daily transfer of data from the patient to the hospital and dedicated software for automatic seizure detection and ssEEG visualization. The external unit is attached to clothing with the disc placed on the skin overlying the device housing (Fig. 1). The external device requires daily charging, and patients are instructed to alternate between two external storage units. The external device features a pushbutton for patients to annotate their seizures. The device supports three-axis accelerometry data recording as well.

Real-world recordings have reported overall good signal quality, safety, tolerability, and a high adherence rate in home-monitoring up to three months (Duun-Henriksen et al., 2015; Weisdorf et al., 2019). A single case report described the longest period of ssEEG monitoring to date in a 35-year-old patient (230 days), which captured 22 patient-reported seizures and an additional 32 seizures identified with direct ssEEG review (Viana et al., 2021a). In another case series, three out of nine patients under-reported seizures compared to device detected seizures (Weisdorf et al., 2019). A similar number of over-reporting was also present, although this may represent missed seizures due to limited spatial EEG coverage. The spectral characteristics of ssEEG recordings with 24/7 EEG™ SubQ are similar to scalp EEG and signal quality is stationary, suggesting suitability for chronic implantation in various scenarios from seizure detection and forecasting to brain-computer interfaces (Viana et al., 2021b).

2.3.2. Minder™ (Epi-Minder, Melbourne, Australia)

This device has an implanted lead with four contacts (Cook, M, Personal Communication, 2022) and a telemetry unit (Stirling et al., 2021). Bilateral scalp coverage is achieved by tunneling a

Table 2
The original purpose and stage of clinical development.

	Original purpose	Stage of clinical development
24/7 EEG™ SubQ	The detection of hypoglycemia in diabetes,	○ CE-marked April 2019
Minder ®	n/a	○ Clinical trial ongoing
Neuroview™	Seizure quantification	○ Clinical trial ongoing
Soenia® UltimateEEG™	Monitoring for drug-resistant epilepsy	○ Clinical trial ongoing Pending CE approval Surface electrode version CE-marked.
Epios™	Seizure detection	○ Clinical trial ongoing
EASEE ®	Treatment of focal drug-resistant epilepsy	○ Pending CE approval US FDA- breakthrough device designation Clinical trials ongoing, primary endpoints reported

Abbreviations: CE- Conformitè Europëenne, EASEE- Epicranial Application of Stimulation Electrodes for Epilepsy, n/a- not available, US FDA-United States Food and Drug Administration.

Table 3
Advantages, disadvantages, and likely clinical use of the various ssEEG systems.

	24/7 EEG™ SubQ	Minder ®	Neuroview™	Soenia ® UltimateEEG™	Epios™	EASEE ®
Advantages						
Requires only local anesthesia	+		+	+		
Raw data availability	+	+	+	+	+	+*
Bilateral recording capacity	+/–	+	+/–	+/–	+	
Seizure localization (dense EEG coverage)					+	
Seizure lateralization	+/-	+	+/-	+/-	+	
Therapeutic capacity						+
Long-term battery (>3 years)			+			+
On-board algorithms to identify seizures			+			+*
Customizable contact number/size				+	+	
High sampling rate (1000 Hz)				+		
Multimodal recording capacity						
3-axis acc	+		+		+	
ECG					+	
Audio					+	
Disadvantages						
May require general anesthesia		+			+	+
Short-term battery (24–48 hours)	+			+	+	
Requires several scalp incisions					+	
External power/ wearable component	+	+		+	+	
Likely clinical use						
Diagnostic	+	+	+	+	+	+*
Seizure quantification	+	+	+	+	+	+*
Therapeutic						+

Abbreviations: acc-Acceleterometry, ssEEG-Subscalp EEG, EASEE- Epicranial Application of Stimulation Electrodes for Epilepsy.
+/– indicates the devices that may provide bilateral recording with a bilateral implant.
* Next-generation/clinical phase pending.

very long multi-channel lead to the contralateral sub-scalp region. It is powered by an external device placed behind the ear which communicates with a nearby paired phone. A custom mobile application permits the uploading of captured EEG data to a secure cloud where it can be reviewed by clinical staff. The application also captures synchronized audio and accelerometer data from the mobile hardware. Minder™ was reported to be safe and tolerable in a study with five patients with refractory epilepsy (Stirling et al., 2021) – a clinical trial ongoing to assess the safety of recording epileptic seizures.

2.3.3. Neuroview™ (Neuroview Technology Inc., Englewood, New Jersey, USA)

Neuroview™ is a fully implantable ssEEG recording device primarily intended to quantify seizures (Neuroview Technology Inc, 2022). A unique feature of the device is that it can record EEG data for up to three years without recharging. This device is completely subcutaneous and features one lead (each with three contacts including one reference contact) that is internally powered, with an onboard seizure detection algorithm and a cloud-based machine-learning platform. The device records three-axis accelerometry data as well. The lead can be placed in the desired orientations including across the vertex to provide limited bilateral recordings. Raw EEG data is uploaded to the cloud using an encrypted algorithm via a smart device (phone or tablet). The device can also be programmed to record EEG epochs at predetermined times and durations. In a study of 21 patients undergoing intracranial EEG evaluations for up to 13 days, concomitant ssEEG electrodes (placed at or near the cranial vertex) displayed a 98% sensitivity and 99% specificity for seizure detection compared to simultaneous intracranial recordings (Pacia et al., 2022). This device is currently being tested in a naturally occurring canine epilepsy before a human pilot study.

2.3.4. Soenia® UltimateEEG™ (BrainCare Oy, Tampere, Finland)

The UltimateEEG™ device has leads that resemble subdural strips used in intracranial EEG. Each device features up to 8 biosilicon contacts that can be geometrically customized to map seizure propagation. The planar design is believed to result in a low noise recording (BrainCare – Long-term epilepsy monitoring, 2022). The device is implanted beneath the skin under local anesthesia through an incision about 2–3 centimeters long with leads directionally focused toward the electrical source (Duun-Henriksen et al., 2020). If necessary, several strips can be used. These patented leads have been designed to survive extraction after years of implantation under local anesthesia. The external transceiver device wirelessly captures, and uploads data recorded by the implant to the cloud, negating the need for any external cable wires. The leads have appropriate approvals and Finnish Medical Device Authority permission for surgical implantation and clinical trials. The surface recording versions of the electrodes are CE-marked and available for use (UltimateEEG™, 2022). Patients can use a companion app (Soenia® Medical Diary) to report symptoms such as seizures.

2.3.5. Epios™ (Wyss Center, Geneva, Switzerland)

The Epios™ system comprises a series of thin leads incorporating sensing electrodes and a miniature implant that can be inserted under either local anesthesia or general anesthesia (depending on the extension of the incision and size of electrode coverage) through two to four small incisions (<1 centimeter) (Epios™, 2022). Each lead has a stem and three branches in a "trident" configuration containing a total of eight contacts. The electrode layout system in Epios™ offers a flexible configuration: one trident for unilateral monitoring, two tridents for bilateral, and four tridents for whole-brain coverage. A full system can provide full head coverage using up to four such tridents (i.e., 32 contacts in total) covering both temporal lobes, frontal, and occipital lobes (Fig. 1). ssEEG signals are wirelessly transferred to an external headpiece positioned on the skin directly over the implant with a magnet, and/or onto a body-worn unit for power and temporary storage (Epios™, 2022). The body-worn unit supports multimodal co-registration for electrocardiography, audio, and accelerometry data. The data acquired can be conveyed to the wearable data processor and is finally

securely stored in the cloud where long-term data visualization and analysis are supported. Clinical trials are currently underway to assess the feasibility of electrode insertion, adverse events related to the study device, and the capability of the EEG signal recording (Early Feasibility Study on Epios Leads, 2022).

2.3.6. EASEE® (Precisis, Heidelberg, Germany)

Epicranial Application of Stimulation Electrodes for Epilepsy (EASEE®) is the only ssEEG system reviewed that allows for therapeutic transcranial neurostimulation and will add diagnostic EEG recording capability to realize individualized closed-loop setting for focal epilepsy (About EASEE®, 2022). The device comprises an array of five sub-scalp "platelet" (disc electrode) contacts, four smaller and one larger contact in the middle (Fig. 1), which are positioned over the putative seizure onset zone (About EASEE®, 2022). The device is primarily developed for focal transcranial cortical stimulation and the contact layout is designed based on the surface Laplacian concept to improve stimulation depth by generating fields and current flows vertical to the contact plane. The EASEE® lead is fixed on the skull surface after the removal of the periosteum by a neurosurgeon, with the central contact being placed over the pre-determined epileptogenic brain area and connected subcutaneously to a pulse generator on the trunk (Kravalis and Schulze-Bonhage, 2020). Two stimulation modes are used: (1) For acute anti-seizure effects, a focal high frequency, short pulse, short-duration burst (100 Hz, 160 us, 0.5 seconds) of alternating current is applied every 2 minutes; (2) For long-term neuroplastic changes, a DC-like stimulation (DLS) consisting of a very long cathodal pulse (2000 μs) followed by a charge equalization pulse with a fifth of the amplitude of the active pulse is delivered for 20 minutes once a day (Kraemer G, Personal communication 2022; Schulze-Bonhage et al., 2022). As the sup-periosteal space is thought to be more sparsely innervated, stimulation is not painful or even perceivable by the patient (About EASEE®, 2022). If the patient can perceive stimulation, the electrical parameters can be adapted as needed to be below the patient's individual perception threshold.

There are two ongoing prospective multicenter pilot studies (Patient Individualized Modulation and Intervention by Epicranial Stimulation [PIMIDES] trial and the EASEE II trial, both University Medical Center in Freiburg, Germany) to assess the safety, feasibility, and performance of focal transcranial cortical stimulation including patient-controlled closed-loop neurostimulation with the first generation EASEE® system to treat medically refractory focal epilepsy (Kravalis and Schulze-Bonhage, 2020). Preliminary results showed that 17 out of 33 recipients experienced at least a 50% reduction in epileptic seizures after six months compared to their pre-implantation baseline (responder rate 53%) (Schulze-Bonhage et al., 2022). The EASEE® device is currently under review for the CE-marking and is expected to be available commercially in Europe soon. The US FDA recently granted EASEE® a breakthrough device designation (Minimally Invasive Epilepsy Treatment EASEE Receives FDA Breakthrough Device Designation, 2022; Precisis' EASEE Epilepsy Treatment Receives FDA Breakthrough Device Designation, 2022). Next-generation EASEE® System will include EEG recording and seizure detection means.

3. Use case scenarios

3.1. Seizure quantification

Patient-reported seizures are often inaccurate and underestimate the seizure burden. This results from several reasons including amnesia from hippocampal seizures, seizure occurrence in sleep, cognitive impairments impairing communication, and subclinical seizures. By some estimates, self-reporting of seizures misses almost half of all seizures, and nocturnal seizure reports may be reported only in around 14% (Hoppe et al., 2007; Swinnen et al., 2021). Underreporting of seizures can lead to inadequate treatment. Efforts to improve seizure quantification include wearable and home-based devices such as wristbands (Empatica Embrace®, EpiHunter®), bed seizure monitors (MedPage®), or a seizure movement monitor (Emfit®) (Bruno et al., 2020; Onorati et al., 2017). Although these devices are approved for detecting tonic-clonic seizures, their ability to recognize seizures without major motor features remains suboptimal (Bruno et al., 2020). Long-term EEG recordings are more likely to provide a more reliable seizure burden quantification (Viana et al., 2021a). In a study assessing the use of behind-the-ear EEG, a patient-specific seizure detection algorithm could detect more seizures automatically than what patients typically reported (Vandecasteele et al., 2020). Another benefit of long-term monitoring is the accurate assessment of treatment efficacy (Weisdorf et al., 2020). More accurate seizure quantification and assessment of treatment efficacy may potentially be of use in clinical trials rather than relying on seizure diaries as being practiced currently.

3.2. Seizure characterization

EMU monitoring is the gold standard for characterizing seizures and distinguishing epileptic seizures from conditions that mimic seizures such as syncope, hypoglycemia, paroxysmal movement disorders, transient ischemic attack, migraines with aura, and transitory global amnesia (Benbadis, 2009; Eddy and Cavanna, 2014). However, the diagnostic yield of EMU is limited by the duration of the monitoring (Faulkner et al., 2012; Moseley et al., 2015). A 7-day hospital stay has a >75% likelihood of capturing seizures with a baseline frequency of >1/week and drops to 50% with a frequency of once/2 weeks. Less frequent seizures would require weeks to months for similar diagnostic yields (Duun-Henriksen et al., 2020). Ideally, 2–3 events are needed to adequately characterize seizures, which is not always possible in a hospital setting. Furthermore, habitual seizures are more likely to happen at home without hospital-based variables including environmental stressors, ASM withdrawal, and altered sleep-wake cycles. Long-term ssEEG can improve the diagnostic yield in this scenario by ultra-long-term recordings. One limitation is that if seizures are not from the site of ssEEG implant, they may be mischaracterized as non-epileptic events. Additionally, focal seizures of deep origin may be under-sampled and undetected by ssEEG devices. Thus, the ssEEG devices should be used primarily for ruling in seizures, not ruling them out. As such, an a priori hypothesis is essential, perhaps by a preliminary EMU evaluation, before planning ssEEG for seizure characterization. To overcome some of these challenges, the combined use of wearable multimodal devices and ssEEG devices may help increase the sensitivity and specificity of seizure detection and characterization.

3.3. Seizure lateralization

For some patients, particularly patients with mesial temporal lobe epilepsy, a standard 4–7 day EEG monitoring may not be adequate to precisely establish the seizure laterality (King-Stephens et al., 2015). In a study of patients with bilateral hippocampal RNS implantations, some patients suspected to have bilateral seizures were found to display strictly unilateral electrographic onsets and vice versa (King-Stephens et al., 2015). Similar to RNS, ssEEG is not ideal for initial seizure localization due to limited coverage compared to conventional 10–20 EEG coverage but has the advantages of ultra-long-term recordings to quantify between a few high yield locations (King-Stephens et al., 2015). Basing surgi-

cal planning and decision-making on dozens or even hundreds of seizures rather than a handful of seizures is a promising possibility with the advent of ssEEG devices.

3.4. Seizure localization

The ability to record brain activity over months to years with ssEEG that offers broad head electrode coverage can help localize seizures without reducing medications. Devices designed to offer broader coverage may have an advantage in this scenario- for instance, Epios™ provides a full 10–20 coverage, and Minder™ provides bilateral, albeit more localized, coverage.

3.5. Seizure alarms

Epilepsy may be associated with various injuries (e.g., burns, cranial and dental injuries, drowning) and impaired quality of life (e.g., feeling of stigmatization, lower esteem, higher level of anxiety and depression, and social isolation), especially in patients with higher seizure frequency (Duun-Henriksen et al., 2020; Taylor et al., 2011). Seizure alarms may provide a greater sense of control for patients and boost resilience. ssEEG devices can communicate with an external device (e.g., a smartphone) that can activate an alarm. All the devices we reviewed except two (Neuroview™ and EASEE®) specifically note a companion wearable device. Even though an alarm system would not prevent seizures from happening, it may allow timely intervention to prevent injuries, severe seizures or status epilepticus, and sudden unexpected death in epilepsy (SUDEP) (van Westrhenen et al., 2022). Most patients and caregivers desire some form of seizure detection method to feel safer and have peace of mind (Van de Vel et al., 2016). Meaningful implementation of such systems, however, can be gained when the alarm device meets the user's needs and is successfully implemented in the care setting (van Westrhenen et al., 2022). For instance, with children, parental preferences for seizure alarm systems reported include ''introduction to use'', ''personalization'', ''interaction'', ''alert'' and ''interface'' capacity (van Westrhenen et al., 2022).

3.6. Seizure forecasting

The random and unexpected nature of seizure occurrence is one of the most debilitating aspects of epilepsy, particularly for people who experience less frequent seizures (monthly or yearly) (Dumanis et al., 2017; Taylor et al., 2011). The ability to anticipate seizure occurrence would revolutionize epilepsy management, leading to a dramatic change in the quality of life of PWE, and would enable preventative treatment strategies. It would provide PWE with a timely warning for their seizure and allow epilepsy providers to manage therapies accordingly to prevent impending seizures. Long-term patterns in seizure occurrence have long been described, and recently quantified revealing multidien and cluster organization (Baud et al., 2018). In a study involving 37 subjects with an implanted brain stimulation device, it was shown that interictal epileptiform activity and seizures oscillate with circadian and subject-specific multidien periods, most commonly 20–30 days in duration (Baud et al., 2018). Earlier studies have shown forecasting is possible with implantable intracranial devices (Karoly et al., 2021), however, it is unlikely that they will become widespread due to their invasiveness. Thus, forecasting capacity with less invasive studies would be much more relevant and optimal. In a recent study using an ssEEG device (Minder™), the data acquired allowed seizure forecasting to be successfully undertaken (Stirling et al., 2021).

3.7. Biomarker discovery

Biomarkers for various aspects of epilepsy may be discovered with the availability of chronic ssEEG recordings. SUDEP is an example (Kroner et al., 2014), where although the mechanisms remain elusive, EEG features such as post-ictal generalized suppression have been found to be associated with greater mortality (Bruno and Richardson, 2020). By using long-term ssEEG in patients with infrequent seizures, EEG biomarkers of SUDEP may be better clarified.

ssEEG can also assist in identifying the early epileptogenesis in various conditions such as traumatic brain injury (TBI) or tuberous sclerosis complex. Following TBI, quantitative EEG changes have been described in the acute, subacute, and chronic stages (Haneef et al., 2013). However, the difficulty in obtaining prolonged EEG recordings following TBI has limited the development of EEG biomarkers for early post-traumatic epilepsy. The availability of easily accessible, high-quality, homogeneous data can considerably help efforts to develop biomarkers in guiding anti-epileptogenesis therapy following TBI (Duncan et al., 2018). Another example is EEG surveillance in infants with tuberous sclerosis complex, where a high positive predictive value of epileptiform discharges for predicting infants who subsequently develop epilepsy was demonstrated (Wu et al., 2016). Thus, using ssEEG, predictive biomarkers may allow earlier intervention that may curtail epileptogenesis and its negative effects. As a neurophysiological biomarker, ssEEG could be used not only as a clinical diagnostic tool but also as a tool for early detection and predicting the stages of certain other neurologic and psychiatric conditions such as dementia or depression (Al-Qazzaz et al., 2014; Dev et al., 2022).

3.8. Sleep medicine

Sleep is one of the most studied human behaviors in relation to epilepsy (Frauscher and Gotman, 2019). A previous study showed that quantitative EEG measures of sleep architecture may provide insight into EEG traits and represent a"fingerprint" of brain activity (De Gennaro et al., 2005). Certain sleep-related neurophysiological biomarkers in epilepsy are dynamic over timescales of days to weeks (Gliske et al., 2018). To study brain activity during sleep, a limited EEG is routinely recorded during overnight sleep studies (Orr, 1985). However, sleep studies are usually limited by the duration of the study and an unnatural environment. As a long-term recording tool, ssEEG may prove advantageous in studying the sleep neurophysiology (Gangstad et al., 2019), particularly in quantifying sleep, determining sleep architecture over the long-term in a natural environment, and possibly combining with measures of oxygen and respiration to investigate the effect of sleep-related breathing disorders on brain activity. ssEEG may be useful for following the efficacy of interventions for sleep apnea, narcolepsy, and idiopathic hypersomnolence, among others.

3.9. Responsive neuro-stimulation

There is literature on the effectiveness of high-frequency intracranial stimulation (Morrell and Group, 2011), low-frequency intracranial stimulation (Manzouri et al., 2021; Schindler et al., 2007), and transcranial direct current stimulation (Assenza et al., 2014; Auvichayapat et al., 2013). Currently, the only US FDA-approved closed-loop device that provides direct EEG monitoring over the long term and delivers responsive cortical stimulation is the RNS system (Rao, 2021). However, the risk intrinsic to implantation of an intra-cranial device, and limited indications hinder widespread use (Rao, 2021). ssEEG devices may overcome these risks and promise transformative advances in clinical epilepsy. Although several ssEEG systems are in develop-

ment, only EASEE® offers both diagnostic and therapeutic neurostimulation capability in an individualized closed-loop setting. As noted earlier, there are two ongoing pilot studies to assess the feasibility of patient-controlled transcranial neurostimulation with the EASEE® system (Kravalis and Schulze-Bonhage, 2020) with some preliminary evidence that extracranial stimulation may help reduce the number of epileptic seizures (Schulze-Bonhage et al., 2022).

4. Challenges

4.1. Technical challenges

The limited spatial sampling of ssEEG devices may result in the under-detection of focal seizures arising from contralateral or deeper regions. ssEEG devices placed under the temporalis muscles may be affected by electromyography artifacts, especially with tonic seizures, and strategically positioning electrode locations may be important. The design of ssEEG electrodes has been reviewed elsewhere (Ahnood et al., 2022). Rhythmic artifacts mimicking seizures may need simultaneous video recording to differentiate, which is not possible natively with ssEEG devices. Due to the continuous long-term recording, ssEEG devices generate a large quantity of time-series information without the intrinsic capacity to automatically identify seizures. Thus, it is essential to develop algorithms for seizure detection. A recent study on 21 patients with ssEEG suggested that a simple seizure detection algorithm could provide sufficient accuracy and clinical utility (Bacher et al., 2021).

4.2. Safety and tolerability

The literature on the safety and tolerability of ssEEG devices is limited. Possible complications with sub-scalp electrode placement include infections, lead migration, fracture, skin erosion, mild headaches, sub-scalp hematoma, and rarely scalp fibrosis (Duun-Henriksen et al., 2020; Weisdorf et al., 2019). Infection is typically limited to the sub-scalp compartment. In a prospective study assessing the safety and tolerability of ssEEGs, there were no serious adverse device-related events (Weisdorf et al., 2019). In the same study, no patients felt any constrain to continue with their daily activities. However, only a few minor annoyances were reported, such as occasional nightly disconnections, having to adjust the usual position of glasses, and the necessity of wearing clothes at night (Weisdorf et al., 2019). Current and upcoming ssEEG devices are not magnetic resonance imaging compatible, and the need for future magnetic resonance imaging may represent a contra-indication presently. Another disadvantage of these devices includes the bulky size of their large external units.

4.3. Lack of standardized clinical protocols and guidelines

The development of multiple EEG recording systems with various design philosophies helps foster innovation and a better likelihood of a breakthrough device. However, this causes fragmentation of research in the field leading to smaller-scale clinical trials and the different study protocols limit comparison between trials. Similar challenges with wearable non-EEG automated seizure detection systems led to the development of clinical practice guidelines for such devices in outpatient settings by the Working Group of the International League Against Epilepsy (ILAE) and the International Federation of Clinical Neurophysiology (IFCN) (Beniczky et al., 2021). This could be a model for developing similar guidelines for ssEEG devices.

5. Future roadmap

5.1. Automatic seizure detection analysis with machine learning

Machine learning (ML) models have enabled rapid advances across multiple aspects of medicine (Rajkomar et al., 2019). It is of particular benefit in the analysis of large quantities of data ("big data") which is cumbersome to process with traditional statistical techniques. ML can reduce human effort and help in a variety of diagnostic applications, matching or exceeding the performance of clinical experts (De Fauw et al., 2018; Esteva et al., 2017; López Pineda et al., 2015). Continuous recording of physiological data such as with ssEEG generates big data which is ideal for developing ML models. A study assessing the accuracy of focal seizure detection by epileptologists, with and without an automated seizure detection algorithm applied to EEG data collected from a wearable device, found a better sensitivity and a slightly higher false alarm rate with automated seizure detection alone (with no epileptologist involvement) (Biondi et al., 2022). ML was used effectively to classify relative seizure frequency from chronic electrocorticography from intracranial devices (Sun et al., 2021). A study assessing behind-the-ear electrodes reduced the review time of 24-hour recording from 1-2 hours to around 5–10 minutes by using seizure detection algorithms through ML (Swinnen et al., 2021). Despite advances in ML and automatic seizure detection, the final validation of seizure data would still require an expert EEG reviewer at present.

5.2. Wearable companion devices for ssEEG

Wearable devices may have specialized roles in epilepsy by specialized sensors or by combining several distinct sensor streams. For instance, the wristbands such as Empatica Embrace® detect changes during seizures including accelerometry (body movement), photoplethysmography (heart rate, blood volume pulse changes), skin temperature, and electrodermal activity (capturing the vasodilatation and diaphoresis associated with autonomic arousal), all of which may reveal seizure- and patient-specific changes during seizures. These wristbands are easily deployed and there is accumulating evidence of their efficacy in detecting seizures (Meisel et al., 2020; Onorati et al., 2017; Vossler, 2021). The combined use of various wearable devices and ssEEG devices may lead to increase sensitivity and specificity of seizure detection, better help guide treatment, avoid morbidity and mortality from inadequate treatment, and improve health care expenses related to seizures from epilepsy. Multimodal recordings have been described to lead to a better understanding of the individual seizure semiology of PWE (Kjaer et al., 2021). The addition of movement, cardiac rhythms, or simultaneous video (e.g. using the Nelli® device) (Peltola et al., 2022), would greatly enhance the utility of ssEEG.

5.3. Clarification of technology and large clinical trials

ssEEG monitoring is an emerging concept in epilepsy care. As such, it is not clear how neurologists would implement this new technology, especially given the diverse models with distinctive features and associated technical limitations. For example, Epios™ could have specific advantages for localization due to its wider coverage, EASEE® may be used for treatment/stimulation purposes, Minder™ may be useful in lateralization due to its bilateral coverage with a single incision, and 24/7 EEG™ SubQ may be useful for seizure quantification once the location is better clarified. Several important questions remain to be answered, including sensitivity and specificity of ssEEG for seizure detection, handling of the large

volume of the data, device cost, and adaptability of patients, caregivers, and providers to the new technology. Clarification of all these questions through large clinical trials could lead to better treatment of patients. Additionally, clinical trials may clarify the interrelation between EEG and physiological or pathological phenomena such as the one between epilepsy and sleep, interictal epileptiform discharges and seizures, and post-ictal suppression and SUDEP. The knowledge gained through ultra-long-term EEG recording may lead to the identification of new biomarkers that can elucidate risk factors for the individual patient over time in addition to several other potential benefits (Pathmanathan et al., 2021).

6. Conclusions

ssEEG is emerging as a promising next-generation technology in the expanded evaluation of PWE. Different ssEEG devices have been developed with unique strengths and limitations. Although DRE reflects a limited segment of PWE, there may be additional use case scenarios with further technological advances. A future can be envisioned where there would be a shift away from subjective seizure reporting to much more accurate seizure detection, and ultra-long-term EEG monitoring becomes the standard of care for seizure quantification and pre-surgical evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank all the manufacturers and ssEEG device development teams, including UNEEG Medical, Neuroview Technology Inc, BrainCare Oy, Precisis and Wyss Center, and researchers including Katrina Wendel-Mitoraj, Ph.D. (UltimateEEG™), Ruben Kuzniecky, MD (Neuroview™), Daniel Friedman, MD (Neuroview™), Steven Pacia, MD (Neuroview™), John Heasman (Minder™), Mark Cook, MD (Minder™), Günter Kraemer, MD (EASEE®), Eric Chanie (Epios™), Birgitte Gert Nielsen (UNEEG), Mads Liebach Bjerregaard (UNEEG) and Michael Tittelbach (EASEE®) who provided critical data for ssEEG devices.

Funding

ZH, KY, and VK are supported by the Mike Hogg Fund. VK receives funding from the NINDS (K08NS110924). ZH is supported by the MEDVAMC bridge and seed award.

References

24/7 EEG™ SubQ; 2022. https://www.uneeg.com/en/epilepsy/products/subq [accessed April 22, 2022].

About EASEE®; 2022. https://easee.precisis.de/de/ [accessed June 10, 2022].

Agrawal S, Turco L, Goswami S, Faulkner M, Singh S. Yield of monitoring in an adult epilepsy monitoring unit (P2.097). Neurology 2015;84.

Ahnood A, Truong ND, Fleiss B, Nikpour A, Kavehei O. Novel electrode architecture for subgaleal electroencephalography: a feasibility study. Sens Diagn 2022;1(2):245–61. https://doi.org/10.1039/D1SD00020A.

Al-Qazzaz NK, Ali SHBMD, Ahmad SA, Chellappan K, Islam MS, Escudero J. Role of EEG as biomarker in the early detection and classification of dementia. Sci World J 2014;2014:1–16. https://doi.org/10.1155/2014/906038.

Assenza G, Campana C, Formica D, Schena E, Taffoni F, Di Pino G, et al. Efficacy of cathodal transcranial direct current stimulation in drug-resistant epilepsy: a proof of principle. In: 2014 36th annual international conference of the IEEE engineering in medicine and biology society, Chicago, IL: IEEE; 2014, p. 530–3. https://doi.org/10.1109/EMBC.2014.6943645.

Auvichayapat N, Rotenberg A, Gersner R, Ngodklang S, Tiamkao S, Tassaneeyakul W, et al. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimulat 2013;6:696–700. https://doi.org/10.1016/j.brs.2013.01.009.

Bacher D, Amini A, Friedman D, Doyle W, Pacia S, Kuzniecky R. Validation of an EEG seizure detection paradigm optimized for clinical use in a chronically implanted subcutaneous device. J Neurosci Methods 2021;358:109220. https://doi.org/10.1016/j.jneumeth.2021.109220.

Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, Rao VR. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun 2018;9(1). https://doi.org/10.1038/s41467-017-02577-y.

Benbadis S. The differential diagnosis of epilepsy: a critical review. Epilepsy Behav 2009;15(1):15–21. https://doi.org/10.1016/j.yebeh.2009.02.024.

Beniczky S, Wiebe S, Jeppesen J, Tatum WO, Brazdil M, Wang Y, Herman ST, Ryvlin P. Automated seizure detection using wearable devices: a clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology. Epilepsia 2021;62(3):632–46. https://doi.org/10.1111/epi.16818.

Biondi A, Santoro V, Viana PF, Laiou P, Pal DK, Bruno E, Richardson MP. Noninvasive mobile EEG as a tool for seizure monitoring and management: a systematic review. Epilepsia 2022;63(5):1041–63. https://doi.org/10.1111/epi.17220.

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. https://doi.org/10.1016/j.yebeh.2016.10.036.

Bleichner MG, Debener S. Concealed, unobtrusive ear-centered EEG acquisition: cEEGrids for transparent EEG. Front Hum Neurosci 2017;11:163. https://doi.org/10.3389/fnhum.2017.00163.

BrainCare – Long-term epilepsy monitoring; 2022. http://www.braincare.fi/index.html [accessed April 22, 2022].

Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78(20):1548–54. https://doi.org/10.1212/WNL.0b013e3182563b19.

Brunnhuber F, Slater J, Goyal S, Amin D, Thorvardsson G, Freestone DR, et al. Past, Present and Future of Home video-electroencephalographic telemetry: a review of the development of in-home video-electroencephalographic recordings. Epilepsia 2020;61(Suppl 1):S3–S10. https://doi.org/10.1111/epi.16578.

Bruno E, Richardson MP. Postictal generalized EEG suppression and postictal immobility: what do we know? Epileptic Disord 2020;22:245–51. https://doi.org/10.1684/epd.2020.1158.

Bruno E, Viana PF, Sperling MR, Richardson MP. Seizure detection at home: Do devices on the market match the needs of people living with epilepsy and their caregivers? Epilepsia 2020;61(Suppl 1):S11–24. https://doi.org/10.1111/epi.16521.

Chan AY, Knowlton RC, Chang EF, Rao VR. Seizure localization by chronic ambulatory electrocorticography. Clin Neurophysiol Pract 2018;3:174–6. https://doi.org/10.1016/j.cnp.2018.03.007.

De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, Askham H, Glorot X, O'Donoghue B, Visentin D, van den Driessche G, Lakshminarayanan B, Meyer C, Mackinder F, Bouton S, Ayoub K, Chopra R, King D, Karthikesalingam A, Hughes CO, Raine R, Hughes J, Sim DA, Egan C, Tufail A, Montgomery H, Hassabis D, Rees G, Back T, Khaw PT, Suleyman M, Cornebise J, Keane PA, Ronneberger O. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med 2018;24(9):1342–50. https://doi.org/10.1038/s41591-018-0107-6.

De Gennaro L, Ferrara M, Vecchio F, Curcio G, Bertini M. An electroencephalographic fingerprint of human sleep. NeuroImage 2005;26(1):114–22. https://doi.org/10.1016/j.neuroimage.2005.01.020.

Dev A, Roy N, Islam MK, Biswas C, Ahmed HU, Amin MA, Sarker F, Vaidyanathan R, Mamun KA. Exploration of EEG-based depression biomarkers identification techniques and their applications: a systematic review. IEEE Access 2022;10:16756–81. https://doi.org/10.1109/ACCESS.2022.3146711.

Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. Neurology 2016;86(8):779–86. https://doi.org/10.1212/WNL.0000000000002253.

Dumanis SB, French JA, Bernard C, Worrell GA, Fureman BE. Seizure forecasting from idea to reality. Outcomes of the My Seizure Gauge Epilepsy Innovation Institute Workshop ENEURO.0349-17.2017. ENeuro 2017;4. https://doi.org/10.1523/ENEURO.0349-17.2017.

Duncan D, Barisano G, Cabeen R, Sepehrband F, Garner R, Braimah A, Vespa P, Pitkänen A, Law M, Toga AW. Analytic tools for post-traumatic epileptogenesis biomarker search in multimodal dataset of an animal model and human patients. Front Neuroinform 2018;12. https://doi.org/10.3389/fninf.2018.00086.

Duun-Henriksen J, Baud M, Richardson MP, Cook M, Kouvas G, Heasman JM, Friedman D, Peltola J, Zibrandtsen IC, Kjaer TW. A new era in electroencephalographic monitoring? Subscalp devices for ultra-long-term recordings. Epilepsia 2020;61(9):1805–17. https://doi.org/10.1111/epi.16630.

Duun-Henriksen J, Kjaer TW, Looney D, Atkins MD, Sørensen JA, Rose M, Mandic DP, Madsen RE, Juhl CB. EEG signal quality of a subcutaneous recording system compared to standard surface electrodes. J Sensors 2015;2015:1–9. https://doi.org/10.1155/2015/341208.

Early Feasibility Study on Epios Leads; 2022. https://www.clinicaltrials.gov/ct2/show/record/NCT04796597?term=Epios&draw=2&rank=1 [accessed April 22, 2022].

Eddy CM, Cavanna AE. Video-electroencephalography investigation of ictal alterations of consciousness in epilepsy and nonepileptic attack disorder:

practical considerations. Epilepsy Behav 2014;30:24–7. https://doi.org/10.1016/j.yebeh.2013.09.003.
Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. Lancet Neurol 2018;17(3):279–88. https://doi.org/10.1016/S1474-4422(18)30038-3.
Englot DJ, Birk H, Chang EF. Seizure outcomes in nonresective epilepsy surgery: an update. Neurosurg Rev 2017;40(2):181–94. https://doi.org/10.1007/s10143-016-0725-8.
Epios™; 2022. https://wysscenter.ch/advances/epios-brain-monitoring [accessed June 10, 2022].
Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017;542(7639):115–8. https://doi.org/10.1038/nature21056.
Faulkner HJ, Arima H, Mohamed A. Latency to first interictal epileptiform discharge in epilepsy with outpatient ambulatory EEG. Clin Neurophysiol 2012;123(9):1732–5. https://doi.org/10.1016/j.clinph.2012.01.023.
Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, Herman ST, Fureman BE, French JA. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav 2012;24(3):304–10. https://doi.org/10.1016/j.yebeh.2012.04.128.
Frauscher B, Gotman J. Sleep, oscillations, interictal discharges, and seizures in human focal epilepsy. Neurobiol Dis 2019;127:545–53. https://doi.org/10.1016/j.nbd.2019.04.007.
Gangstad SW, Mikkelsen KB, Kidmose P, Tabar YR, Weisdorf S, Lauritzen MH, Hemmsen MC, Hansen LK, Kjaer TW, Duun-Henriksen J. Automatic sleep stage classification based on subcutaneous EEG in patients with epilepsy. Biomed Eng Online 2019;18(1). https://doi.org/10.1186/s12938-019-0725-3.
Gliske SV, Irwin ZT, Chestek C, Hegeman GL, Brinkmann B, Sagher O, Garton HJL, Worrell GA, Stacey WC. Variability in the location of high frequency oscillations during prolonged intracranial EEG recordings. Nat Commun 2018;9(1). https://doi.org/10.1038/s41467-018-04549-2.
González Otárula KA, Balaguera P, Schuele S. Ambulatory EEG to classify the epilepsy syndrome. J Clin Neurophysiol 2021;38:87–91. https://doi.org/10.1097/WNP.0000000000000678.
Haneef Z, Levin HS, Frost JD, Mizrahi EM. Electroencephalography and quantitative electroencephalography in mild traumatic brain injury. J Neurotrauma 2013;30(8):653–6. https://doi.org/10.1089/neu.2012.2585.
Hirsch LJ, Mirro EA, Salanova V, Witt TC, Drees CN, Brown M-G, Lee RW, Sadler TL, Felton EA, Rutecki P, Shin HW, Hadar E, Hegde M, Rao VR, Mnatsakanyan L, Madhavan DS, Zakaria TJ, Liu AA, Heck CN, Greenwood JE, Bigelow JK, Nair DR, Alexopoulos AV, Mackow M, Edwards JC, Sotudeh N, Kuzniecky RI, Gwinn RP, Doherty MJ, Geller EB, Morrell MJ. Mesial temporal resection following long-term ambulatory intracranial EEG monitoring with a direct brain-responsive neurostimulation system. Epilepsia 2020;61(3):408–20. https://doi.org/10.1111/epi.16442.
Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol 2007;64:1595–9. https://doi.org/10.1001/archneur.64.11.1595.
Juhl CB, Højlund K, Elsborg R, Poulsen MK, Selmar PE, Holst JJ, Christiansen C, Beck-Nielsen H. Automated detection of hypoglycemia-induced EEG changes recorded by subcutaneous electrodes in subjects with type 1 diabetes—the brain as a biosensor. Diab Res Clin Pract 2010;88(1):22–8. https://doi.org/10.1016/j.diabres.2010.01.007.
Kappel SL, Rank ML, Toft HO, Andersen M, Kidmose P. Dry-contact electrode ear-EEG. IEEE Trans Biomed Eng 2019;66(1):150–8. https://doi.org/10.1109/TBME.2018.2835778.
Karoly PJ, Freestone DR, Boston R, Grayden DB, Himes D, Leyde K, Seneviratne U, Berkovic S, O'Brien T, Cook MJ. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. Brain 2016;139(4):1066–78. https://doi.org/10.1093/brain/aww019.
Karoly PJ, Rao VR, Gregg NM, Worrell GA, Bernard C, Cook MJ, Baud MO. Cycles in epilepsy. Nat Rev Neurol 2021;17(5):267–84. https://doi.org/10.1038/s41582-021-00464-1.
King-Stephens D, Mirro E, Weber PB, Laxer KD, Van Ness PC, Salanova V, Spencer DC, Heck CN, Goldman A, Jobst B, Shields DC, Bergey GK, Eisenschenk S, Worrell GA, Rossi MA, Gross RE, Cole AJ, Sperling MR, Nair DR, Gwinn RP, Park YD, Rutecki PA, Fountain NB, Wharen RE, Hirsch LJ, Miller IO, Barkley GL, Edwards JC, Geller EB, Berg MJ, Sadler TL, Sun FT, Morrell MJ. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. Epilepsia 2015;56(6):959–67. https://doi.org/10.1111/epi.13010.
Kjaer TW, Remvig LS, Helge AW, Duun-Henriksen J. The individual ictal fingerprint: combining movement measures with ultra long-term subcutaneous EEG in people with epilepsy. Front Neurol 2021;12:718329. https://doi.org/10.3389/fneur.2021.718329.
Kravalis K, Schulze-Bonhage A. PIMIDES I: a pilot study to assess the feasibility of patient-controlled neurostimulation with the EASEE® system to treat medically refractory focal epilepsy. Neurol Res Pract 2020;2:15. https://doi.org/10.1186/s42466-020-00061-5.
Kroner BL, Wright C, Friedman D, Macher K, Preiss L, Misajon J, Devinsky O. Characteristics of epilepsy patients and caregivers who either have or have not heard of SUDEP. Epilepsia 2014;55(10):1486–94. https://doi.org/10.1111/epi.12799.
Lehmkuhle M, Elwood M, Wheeler J, Fisher F, Dudek E, Lervik K, et al. Development of a discrete, wearable, EEG device counting seizures. Proceedings of the 69th annual meeting of the American Epilepsy Society, 2015.
López Pineda A, Ye Y, Visweswaran S, Cooper GF, Wagner MM, Tsui FR. Comparison of machine learning classifiers for influenza detection from emergency department free-text reports. J Biomed Inform 2015;58:60–9. https://doi.org/10.1016/j.jbi.2015.08.019.
Manzouri F, Meisel C, Kunz L, Dümpelmann M, Stieglitz T, Schulze-Bonhage A. Low-frequency electrical stimulation reduces cortical excitability in the human brain. NeuroImage: Clin 2021;31:102778. https://doi.org/10.1016/j.nicl.2021.102778.
Meisel C, El Atrache R, Jackson M, Schubach S, Ufongene C, Loddenkemper T. Machine learning from wristband sensor data for wearable, noninvasive seizure forecasting. Epilepsia 2020;61(12):2653–66. https://doi.org/10.1111/epi.16719.
Minimally Invasive Epilepsy Treatment EASEE Receives FDA Breakthrough Device Designation; 2022. https://www.bloomberg.com/press-releases/2022-02-22/minimally-invasive-epilepsy-treatment-easee-receives-fda-breakthrough-device-designation [accessed April 8, 2022].
Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77(13):1295–304. https://doi.org/10.1212/WNL.0b013e3182302056.
Moseley BD, Dewar S, Haneef Z, Stern JM. How long is long enough? The utility of prolonged inpatient video EEG monitoring. Epilepsy Res 2015;109:9–12. https://doi.org/10.1016/j.eplepsyres.2014.10.011.
Neuroview Technology Inc.; 2022. https://neuroviewtech.com/ [accessed June 10, 2022].
Onorati F, Regalia G, Caborni C, Migliorini M, Bender D, Poh M-Z, Frazier C, Kovitch Thropp E, Mynatt ED, Bidwell J, Mai R, LaFrance WC, Blum AS, Friedman D, Loddenkemper T, Mohammadpour-Touserkani F, Reinsberger C, Tognetti S, Picard RW. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. Epilepsia 2017;58(11):1870–9. https://doi.org/10.1111/epi.13899.
Orr WC. Utilization of polysomnography in the assessment of sleep disorders. Med Clin of North Am 1985;69(6):1153–67. https://doi.org/10.1016/S0025-7125(16)30980-4.
Pacia SV, Doyle WK, Friedman D, Bacher DH, Kuzniecky RI. Intracranial EEG validation of single-channel subgaleal EEG for seizure identification. J Clin Neurophysiol 2022;39(4):283–8. https://doi.org/10.1097/WNP.0000000000000774.
Pathmanathan J, Kjaer TW, Cole AJ, Delanty N, Surges R, Duun-Henriksen J. Expert perspective: who may benefit most from the new ultra long-term subcutaneous EEG monitoring? Front Neurol 2021;12. https://doi.org/10.3389/fneur.2021.817733.
Peltola J, Basnyat P, Armand Larsen S, Østerkjaerhuus T, Vinding Merinder T, Terney D, et al. Semiautomated classification of nocturnal seizures using video recordings. Epilepsia 2022. https://doi.org/10.1111/epi.17207.
Precisis' EASEE Epilepsy Treatment Receives FDA Breakthrough Device Designation; 2022. https://www.fdanews.com/articles/206771-precisis-easee-epilepsy-treatment-receives-fda-breakthrough-device-designation [accessed April 8, 2022].
Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med 2019;380(14):1347–58. https://doi.org/10.1056/NEJMra1814259.
Rao VR. Chronic electroencephalography in epilepsy with a responsive neurostimulation device: current status and future prospects. Expert Rev Med Devices 2021;18(11):1093–105. https://doi.org/10.1080/17434440.2021.1994388.
Schindler K, Elger CE, Lehnertz K. Changes of EEG synchronization during low-frequency electric stimulation of the seizure onset zone. Epilepsy Res 2007;77(2-3):108–19. https://doi.org/10.1016/j.eplepsyres.2007.09.011.
Schulze-Bonhage A, Winter Y, Hirsch M, Kaufmann E, Kegele J, Knake S, et al. Antiepileptische Wirksamkeit fokaler Cortex- Stimulation (FCS) mit dem EASEE-System bei pharmakoresistenter fokaler Epilepsie (Antiepileptic effects of focal cortex stimulation (FCS) with the EASEE system in pharmacoresistant focal epilepsy); 2022. https://easee.precisis.de/static/9d9e5f542c7806ec19392038cdf97e5c/antiepileptische-wirksamkeit-fokaler-cortex-stimulation-fcs-mit-den-easee-system-2022-uni-freiburg.pdf [accessed June 10, 2022].
Smart O, Rolston JD, Epstein CM, Gross RE. Hippocampal seizure-onset laterality can change over long timescales: a same-patient observation over 500 days. Epilepsy Behav Case Rep 2013;1:56–61. https://doi.org/10.1016/j.ebcr.2013.03.003.
Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Haut S, Langfitt JT, Walczak TS, Devinsky O. Health-related quality of life over time since resective epilepsy surgery. Ann Neurol 2007;62(4):327–34. https://doi.org/10.1002/ana.21131.
Stirling RE, Maturana MI, Karoly PJ, Nurse ES, McCutcheon K, Grayden DB, Ringo SG, Heasman JM, Hoare RJ, Lai A, D'Souza W, Seneviratne U, Seiderer L, McLean KJ, Bulluss KJ, Murphy M, Brinkmann BH, Richardson MP, Freestone DR, Cook MJ. Seizure forecasting using a novel sub-scalp ultra-long term EEG monitoring system. Front Neurol 2021;12. https://doi.org/10.3389/fneur.2021.713794.
Sun Y, Friedman D, Dugan P, Holmes M, Wu X, Liu A. Machine learning to classify relative seizure frequency from chronic electrocorticography. J Clin Neurophysiol 2021. https://doi.org/10.1097/WNP.0000000000000858.
Swinnen L, Chatzichristos C, Jansen K, Lagae L, Depondt C, Seynaeve L, Vancaester E, Van Dycke A, Macea J, Vandecasteele K, Broux V, De Vos M, Van Paesschen W. Accurate detection of typical absence seizures in adults and children using a two-channel electroencephalographic wearable behind the ears. Epilepsia 2021;62(11):2741–52. https://doi.org/10.1111/epi.17061.
Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. Epilepsia 2011;52:2168–80. https://doi.org/10.1111/j.1528-1167.2011.03213.x.
UltimateEEG™; 2022. https://soenia.fi/electrode-implant [accessed April 22, 2022].

Van de Vel A, Smets K, Wouters K, Ceulemans B. Automated non-EEG based seizure detection: do users have a say? Epilepsy Behav 2016;62:121–8. https://doi.org/10.1016/j.yebeh.2016.06.029.

Vandecasteele K, De Cooman T, Dan J, Cleeren E, Van Huffel S, Hunyadi B, Van Paesschen W. Visual seizure annotation and automated seizure detection using behind-the-ear electroencephalographic channels. Epilepsia 2020;61(4):766–75. https://doi.org/10.1111/epi.16470.

Viana PF, Duun-Henriksen J, Glasstëter M, Dümpelmann M, Nurse ES, Martins IP, Dumanis SB, Schulze-Bonhage A, Freestone DR, Brinkmann BH, Richardson MP. 230 days of ultra long-term subcutaneous EEG: seizure cycle analysis and comparison to patient diary. Ann Clin Transl Neurol 2021a;8(1):288–93. https://doi.org/10.1002/acn3.51261.

Viana PF, Remvig LS, Duun-Henriksen J, Glasstetter M, Dümpelmann M, Nurse ES, Martins IP, Schulze-Bonhage A, Freestone DR, Brinkmann BH, Kjaer TW, Richardson MP. Signal quality and power spectrum analysis of remote ultra long-term subcutaneous EEG. Epilepsia 2021b;62(8):1820–8. https://doi.org/10.1111/epi.16969.

Vossler DG. Forecasting seizure storms using epilepsy wristband sensors. Epilepsy Curr 2021;21(2):99–101. https://doi.org/10.1177/1535759721990062.

Weisdorf S, Duun-Henriksen J, Kjeldsen MJ, Poulsen FR, Gangstad SW, Kjaer TW. Ultra-long-term subcutaneous home monitoring of epilepsy-490 days of EEG from nine patients. Epilepsia 2019;60:2204–14. https://doi.org/10.1111/epi.16360.

Weisdorf S, Gangstad SW, Duun-Henriksen J, Mosholt KSS, Kjær TW. High similarity between EEG from subcutaneous and proximate scalp electrodes in patients with temporal lobe epilepsy. J Neurophysiol 2018;120(3):1451–60. https://doi.org/10.1152/jn.00320.2018.

Weisdorf S, Zibrandtsen IC, Kjaer TW. Subcutaneous EEG monitoring reveals AED response and breakthrough seizures. Case Rep Neurol Med 2020;2020:1–6. https://doi.org/10.1155/2020/8756917.

Westrhenen A, Wijnen BFM, Thijs RD. Parental preferences for seizure detection devices: a discrete choice experiment. Epilepsia 2022;63(5):1152–63. https://doi.org/10.1111/epi.17202.

Wu JY, Peters JM, Goyal M, Krueger D, Sahin M, Northrup H, Au KS, Cutter G, Bebin EM. Clinical electroencephalographic biomarker for impending epilepsy in asymptomatic tuberous sclerosis complex infants. Pediat Neurol 2016;54:29–34. https://doi.org/10.1016/j.pediatrneurol.2015.09.013.

Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy—United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66(31):821–5.