

Current Techniques and Engineering Opportunities for Advancement and Improvement in Electroencephalographic Acquisition and Analyses

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Received date: September 17, 2024, **Accepted date:** November 20, 2024

Citation: Swaminathan A. Current Techniques and Engineering Opportunities for Advancement and Improvement in Electroencephalographic Acquisition and Analyses. J Exp Neurol. 2024;5(4):192-209.

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Abstract

Epilepsy is a highly prevalent condition and affects about 50-65 million people worldwide with great impact on health and quality of life, including medical and social aspects. Electroencephalography (EEG) represents the main diagnostic approach to evaluate patients with epilepsy. EEG techniques have achieved significant improvement over the years and keep evolving to meet increasing demands such as higher accuracy, innovation and better quality and technique to enable improved diagnosis and treatment of epilepsy and other conditions. We use this paper to discuss current techniques and future opportunities for advancement of different types of EEG and various aspects of its use, along with avenues for improving EEG related engineering and technology. We wish to enumerate various aspects of EEG hardware and capturing techniques to discuss opportunities for improvement, along with detailing the utility of software advances including quantitative EEG and EEG analyses. We also aim to discuss neurostimulation and its role in advancing the management of epilepsy. Finally, we also discuss the use of EEG in non-epilepsy conditions. We aim to showcase current capabilities and expand on these to describe opportunities for advancement in diagnosis and management using EEG for a variety of indications. Our paper seeks to detail various aspects of EEG advancement that can improve overall patient care and research.

Keywords: EEG, Video EEG, quantitative EEG, Biosignal monitoring, ECoG, Ambulatory EEG

Abbreviations: EEG: Electroencephalography; WHO: World Health Organization; AI: Artificial Intelligence; EMU: Epilepsy Monitoring Unit; ICU: Intensive Care Unit; AEEG: Ambulatory EEG; VEEG: Video EEG; QEEG: Quantitative EEG analyses; IEEG: Intracranial EEG; SEEG: Stereotactically Placed EEG Electrodes; ECoG: Electrocorticography; VNS: Vagal Nerve Stimulator; RNS: Responsive Neurostimulator; DBS: Deep Brain Stimulation; ASM: Anti-Seizure Medications; EMG: Electromyography; SUDEP: Sudden Death in Epilepsy; PD: Parkinson's Disease

Introduction

Epilepsy is a highly prevalent condition and affects about 50 million people worldwide, based on World Health Organization (WHO) estimates [1]. The medical and socioeconomic burdens on patients and their families are tremendous and the annual financial impact is in the billions [1]. Management of epilepsy is multifaceted and involves multidisciplinary efforts from physicians and other medical professionals, policy makers, patients and their families. Electroencephalography (EEG) forms the mainstay of diagnostic evaluation for patients with suspected or known epilepsy. EEG studies are primarily

performed to capture seizures and associated abnormalities, confirm or exclude a diagnosis of epilepsy, define the type of epilepsy, localize the parts of the brain affected by epilepsy, determine their numerical burden and offer guidance in determining the optimal treatment or combination of treatments. Non epileptic conditions like sleep or movement disorders or dementia have also benefited from use of EEG for purposes of research and patient care. Extensive research has been performed and is ongoing to enable better quality and efficacy of EEG analyses for patients.

Hardware considerations include improving data capture by

EEG electrodes along with increasing electrode placement accuracy, while limiting tissue damage and decay of the electrodes for longer durations of use. Software considerations include better automated detection of seizures, artifact reduction, quantitative analyses and other aspects including higher quality and volume of data storage.

Intracranial EEG (IEEG) involves recording EEG from within the brain tissue using surface or implanted depth electrodes to better delineate the seizure network to determine the best choice of treatment. Video EEG (VEEG) includes continuous EEG monitoring with video surveillance to capture seizures to determine physical attributes associated with them and is performed in inpatient and ICU settings. Ambulatory (AEEG) and implanted EEG involves electrodes placed over or under the scalp to capture chronic EEG recordings to study patient. Seizure forecasting involves the use of techniques, including artificial intelligence (AI), to predict the probability and timing of future seizures in patients. Neurostimulators include electrical devices that are implanted within the body to help with diagnosis and treatment of epilepsy and include vagal nerve stimulation (VNS), responsive neurostimulation (RNS) and deep brain stimulation (DBS). Our paper seeks to highlight the various aspects and targets for these techniques and compare some of their capabilities to ensure correct choice and complementary usage to improve the value of EEG in patient care and research. EEG has also been studied for its utility in other conditions like dementia, psychiatric disorders, etc. as a research and support tool. We describe current capabilities as well as explore opportunities to improve various aspects of EEG, thus expanding the scope of EEG use within epilepsy and other conditions.

Methods

Our paper focuses on engineering aspects of EEG to identify targets for improvement in EEG capture and analyses to improve patient care and research capabilities. PubMed was used as the initial source of our research analyses. We used the relevant keywords and search terms and looked for high impact studies or papers that drew significant attention or detailed insightful opportunities or advancements in the field of EEG capture and related diagnostics. Papers of interest were identified as high impact based on their significance of findings, quality of research, citation scores and overall relevance to our line of investigation and the field of neurodiagnostics as a whole. We focused our efforts on identifying technical papers and studies that sought to improve the engineering technology behind EEG as a whole to showcase hardware related capabilities and future opportunities for EEG technology. We targeted studies and papers detailing EEG capture, signals analysis and AI, along with neurostimulation and non-epilepsy conditions, based on their relevance and utility in the field of neurodiagnostics. VNS and DBS do not use EEG technology for their diagnostic and therapeutic algorithms, and we accordingly did not focus on them in our neurostimulation section, as it was outside

the scope of this paper. We aimed to discuss EEG use for clinical care and research in various non-epilepsy conditions in our final section but realize that the list is too vast and our description, while exhaustive, is not complete by any means. Research papers and studies were selected based on their significance and relevance to the field, along with their innovation and impact on daily use in clinical care and research. Citation scores were not the only factors used in selection of papers or studies of interest. We did not perform any statistical analyses of our own as we were focused on the innovation, utility and opportunities afforded by various technologies. We, however, did pay significant attention to the statistical methods employed in the various studies used in our papers of interest to show the strength of their findings. The statements about future directions include insight from the papers we believed to be relevant, along with our personal opinions as well.

Discussion

Scalp EEG / routine EEGS

Scalp or Routine EEG involves placing electrodes on the outside of the head, over the scalp, to record electrical activity from the brain. It remains the preliminary and most basic investigation to look for the presence of abnormalities to confirm a diagnosis of epilepsy. Routine EEGs are generally performed for 20-30 minutes and show a diagnostic yield of 60% for detected abnormalities on a single study [2]. This can rise to a 92% detection rate after 4 consecutive studies [2]. Maneuvers like prolonging duration of study up to 40-60 minutes, sleep deprivation, photic stimulation and hyperventilation, in addition to early performance of the study within 48-72 hours of seizure occurrence, are all used to improve the diagnostic accuracy and yield of scalp EEGs [3].

While video EEG (VEEG) does have higher diagnostic yield than routine scalp EEGs; the cost, availability and disruptions to patients' lives by VEEG, makes scalp EEG an easier and more commonly performed option [3]. Ease of performance, low cost, ease of interpretation by most neurologists, short duration, and relatively good diagnostic yield with specificity make scalp EEG an excellent first option for initial evaluation and triage of patients with suspected epilepsy. Shorter duration of study makes it a great option for investigating seizures in patients with cognitive impairment or dementia, due to difficulties with prolonged monitoring and inability to maintain good electrode placement for longer durations.

Routine EEGs are of great value in research studies that require multiple studies to be performed in a consecutive manner with intervals of days or weeks due to their ease of performance and limited utilization of resources. Combining them with EEG analyses enables insightful utilization in research and allows researchers to study the effects of interventions on EEG. These principles have been used to study consecutive routine EEGs with advanced electrographic analyses in patients treated

with medications like cannabidiol to determine effects of treatment and identify better candidates for these treatments [4]. Similar studies have been conducted to measure the effects of anti-seizure medications (ASMs) on the EEG to develop digital biomarkers to enable better analyses of treatment responsiveness [5]. Some studies have shown that routine EEGs performed with limited electrode montages have significant utility in diagnosing recurrent seizures (status epilepticus) in inpatient and emergent settings. This finding is of great value as it would greatly save time, cost and manpower, in addition to limiting the need and use of VEEG on an emergent basis to confirm the presence of ongoing seizures [6].

Routine EEGs are often performed in the setting of brain death to confirm the diagnosis and enable transplantation and other terminal life decisions [7]. These routine EEGs are often performed in a specific manner and involve fewer electrodes and specific electrographic requirements to meet criteria supporting brain death. While newer ancillary tests like cerebral perfusion scans are now performed at many centers, the utility of Routine EEGs in brain death exams cannot be discounted entirely [7]. Routine EEGs are also of great value in neonatal and pediatric settings, but with limited utility due to the challenges of interpretation of pediatric EEG and the need to be read by highly trained neurologists [8,9]. Despite this, they continue to hold great value in the pediatric EEG world.

Routine EEGs thus have excellent utility in overall diagnosis for epilepsy but are showing increasing importance as research tools and are expected to become more commonly used for research analyses, especially in conjunction with quantitative EEG analyses and computational methods such as artifact reduction (described ahead). The use of routine EEGs with modifications like fewer electrodes or variable placement of electrodes also multiplies their use manifold, with some of these principles inspiring the development of bedside portable EEG devices and ambulatory technologies, and offering use in conditions like intraoperative monitoring of cerebral activity (described ahead). We expect that portable EEG devices will be used more frequently in emergent and ICU settings, especially during overnight evaluations, to minimize the need for EEG technologists to remain in the hospital and enable rapid and simple bedside evaluation to rule out ongoing seizures in comatose and critically ill patients.

Video EEG (VEEG) in the epilepsy monitoring units (EMU) and intensive care units (ICU)

VEEG remains the gold standard of epilepsy diagnostics due to its ability to capture events and seizures with associated electrographic and clinical changes [10]. VEEG is usually able to capture the event of interest within 48-72 hours in 85-87% of patient evaluations and achieve the required diagnostic goals [10,11]. Capturing an event on VEEG enables the treating neurologist to determine the type of seizure, location of seizure onset and spread zones, potential choice of medication, eligibility and need for surgical or other treatments, along

with correctly understanding the clinical changes that occur with a seizure. Prolonged duration of VEEG automatically improves diagnostic yield in comparison to routine EEGs due to higher chances of event capture and makes it a superior test [3]. Patients can be monitored in near natural situations which helps the physician simulate a real-world environment in many cases and also offer additional provocations like sleep deprivation, photic stimulation, hyperventilation and the use of seizure provoking medications to increase the probability of capturing a seizure [10].

The addition of video to EEG has greatly enhanced its diagnostic utility and capabilities in epilepsy management [3]. Video monitoring enables the physician to capture obvious clinical seizures or physical manifestations of seizures which confirm the diagnosis, assist with localization and lateralization of the seizure onset zone and identify other signs of the seizure that would have otherwise been unrecognized. Differentiating between epileptic and nonepileptic seizures without video can sometimes be very challenging and lateralization can be made easier with the use of video rather than eyewitness accounts to increase accuracy – 55% vs 21% based on some studies [12]. Frontal lobe seizures are very challenging to diagnose and localize or lateralize and can often remain poorly detected on EEG or mistaken for nonepileptic spells, with improved chances of diagnosis only due to the use of video [13]. Semiological features like aphasia or nose rubbing can be greatly effective in localization and lateralization on video EEG and greatly improve diagnostic accuracy [14,15]. Video use in VEEG greatly enhances diagnostic accuracy in identifying different seizure types from different parts of the brain and is often reflected in greater diagnostic accuracy seen with higher levels of experience in more practiced neurologists and epileptologists, compared to trainees and junior doctors [16]. We also note higher diagnostic accuracy for more clinically obvious seizures like convulsions over dyscognitive or more subtle seizures [16]. EMUs now add muscle activity monitors to enable better confirmation of convulsive seizures and aid in the diagnostics of muscular conditions like myoclonus that can mimic seizures – a development that greatly reflects on the engineering improvements that enable better studies of muscle movements to improve diagnostic accuracy in the EMU [17,18].

Seizures are often associated with cardiorespiratory dysfunction that can be life threatening and elevates the risks associated with VEEG monitoring. The most common cause of death in epilepsy patients, with an incidence of 2.2 per 1000 patients, is sudden unexplained death in epilepsy - SUDEP [19]. Postulated mechanisms include cardiac arrhythmias, central apnea, neurogenic induced pulmonary edema, and asphyxia. Clinical evidence of ictal or postictal apneas and cardiac arrhythmias is supportive of these hypotheses [20].

The most common cardiac consequence of seizures is sinus tachycardia, seen in up to 80% of seizures [21]. Many different cardiac patterns have been described as ictal and postictal

arrhythmias and contribute to varying degrees of morbidity and mortality. Rare deaths have been reported in EMUs due to ictal arrhythmias causing recorded SUDEP on VEEG [21]. The reason for lowered incidence of cases of SUDEP in EMUs has been due to the use of continuous telemetry with cardiac and pulse oximetry monitoring, along with the presence of resuscitative equipment in EMUs to enable rapid response to treat such events. Lessons learnt from cardiac monitoring in such patients have been extrapolated to enable better detection of fatal arrhythmic events during seizures and improve prediction and response times, and to also develop newer technologies to better monitor patients being evaluated for seizures in ambulatory settings (described ahead).

Neonatal ICU EEG monitoring is challenging due to the difficulties in maintaining electrode placement and bypassing the artifacts produced by multimodal monitoring on EEG in children. Many hardware and EEG software-based improvements have been adapted from adult VEEG monitoring to enable precise and accurate VEEG monitoring in neonates and children, reflecting the scope and opportunities for bioengineering to expand EEG access to this previously technically challenging group of patients [9]. These advancements have greatly improved abilities for EEG capture in pediatric patients resulting in improved outcomes in seizure diagnostics and treatments over the years [9].

Future advances are expected to include greater support from AI and automated seizure detections. Some studies have already tried to convert relevant power spectra in EEG into sound waves to enable rapid recognition of seizures at the bedside by non-neurologists to enable ease of seizure identification in critical care settings when time is of the essence in recognizing seizures and neurologists may not always be available at the bedside to enable rapid seizure identification [22]. Similar innovations are expected to improve the utility of VEEG and increase their yield at the bedside along with cost-saving and resource-saving improvements in technology.

Hardware related improvements in EEG capture

EEG remains the same technique it was when first described at inception. Changing from paper to digital EEG is often felt to be the first leap in improving hardware capabilities for EEG, resulting in spatial compression and lessening physical demands for EEG storage. That being said, various electromechanical and chemical techniques have been employed to improve quality and diagnostic yield of EEG over the years. These techniques have shown the efficiency of bioengineering at developing better materials and electromechanical interfaces to enable better quality EEG detection.

EEG capture involves the use of surface electrodes with or without conducting gels on the skin to enable signal capture. Long term use of pre-gelled electrodes is hindered by many

concerns, including bulkiness, skin irritation, along with poor robustness from gel dehydration [23]. While short term EEG recordings may show good efficacy with the use of gels (**Figure 1**), longer term monitoring involves dealing with complications related to the effects of perspiration, movement, electrode decay and has driven experts towards developing dry electrodes that are more resistant to long-term electrode placement [23,24]. These conductive and conformatory dry electrodes achieve low impedance and remove the need for conductive gel.

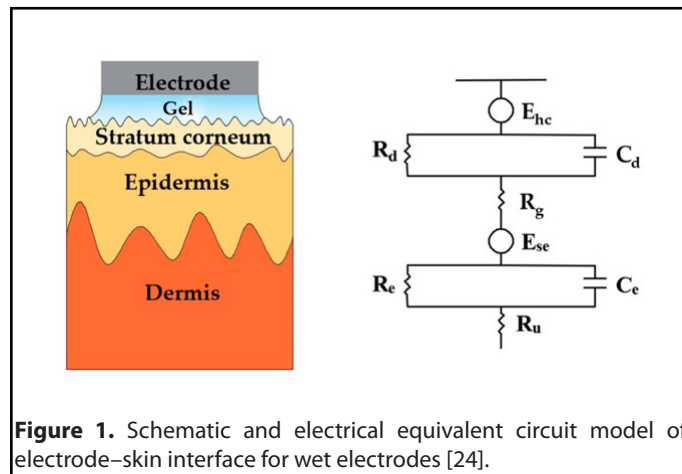
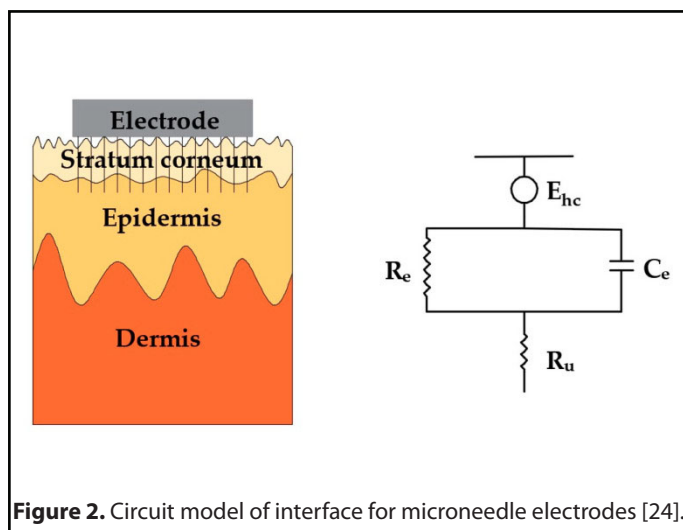


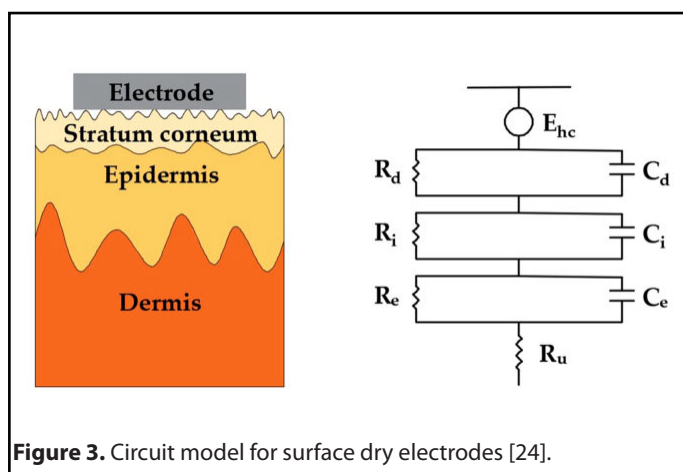
Figure 1. Schematic and electrical equivalent circuit model of electrode-skin interface for wet electrodes [24].

The use of such electrodes improves compatibility and enables long-term skin contact. They allow for efficient and unobtrusive monitoring of brain activity and can also be used for other types of biomonitoring (heart, muscle, etc.). These dry electrodes also operate with lower tensile strain and reduce the probability of skin irritation and breakdown/injury. Some newer electrodes have 3-dimensional conductive arrays enabling removal of extra contacts on the skin, expediting vertical connections, and achieving better density for multilayer devices, as compared to conventional electrodes with one-sided presence of conducting materials [23]. Fabrication methods for such electrodes are simple, economical, and scalable.

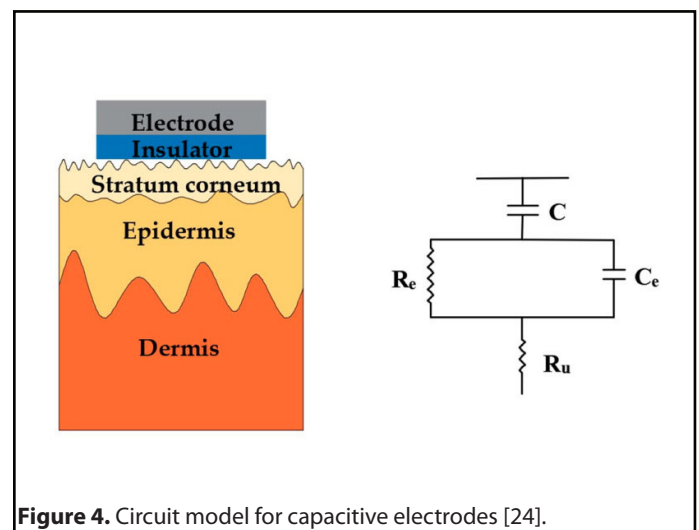
Dry electrodes can be divided into invasive microneedle, surface, and capacitive electrodes [25]. Invasive microelectrode needle electrodes have attracted great interest in EEG monitoring due to their excellent properties including penetration sans skin preparation, negligible skin trauma, low impedance, simplicity of operation, and great selectivity [24]. They are currently made out of silicon, metal or polymers. Each of these materials come with their share of challenges and benefits [24]. Skin penetration multiplies the probability of infection, and the length of microneedles should be enough to pierce skin without breaking it or causing severe pain, which limits the uses of microneedle-based electrodes (**Figure 2**). Microneedles are usually made of stiff material like silicon and metals, making them more susceptible to motion artifacts. These challenges raise significant obstacles to their regular use.



Surface dry electrodes are noninvasive with close skin contact. There are no conductive gels between the electrode and the skin surface, unlike commonly used wet electrodes. Motion does not reduce their contact significantly. They are made using carbon-based materials, polymers or even metals. They are the most studied dry electrodes due to their simple manufacturing and measuring processes (**Figure 3**). They achieve good skin contact without penetration, ensuring noninvasiveness, but motion artifact remains a major limitation. Adhesives to maintain adhesion or nanostructure patches with mechanical interlocking or nanopillars or 3D anatomies inspired by natural sources have been suggested and show promise. These adhesives lose grip on wet skin or skin exposed to flowing water. Nanopillar patches achieve excellent adhesion from mechanical interlocking, inspired by natural structures in frogs [26].



The modus operandi of capacitive electrodes is quite different from the other types. It equates to a capacitor coupled on the skin, does not need close skin contact, with improvement in comfort. Sweat does not affect them. Noise and motion artifacts are frequent due to high impedance and instability of the electrode-skin junction, as compared to common wet electrodes (**Figure 4**).



Bioengineering thus has an important role to play in the development and improvement of good quality electrodes to expand use and improve signal analyses and also reduce effects of prolonged electrode placement. Continued progress is ongoing and imperative to meet the increasing demand for better quality and accuracy of EEG acquisition and signal monitoring. Similar engineering principles also apply to invasive or implanted intracranial EEG electrodes and neuromodulation devices and are discussed further ahead in this paper. The above section lucidly highlights many important steps that engineers and scientists have made in achieving progress in developing better EEG electrodes to improve quality and ease of data acquisition. These different electrodes have been used in research settings with satisfactory outcomes and researchers are optimistic about expanding their use into clinical care to enable better quality and longer duration of EEG capture. These improved capabilities of EEG electrodes are expected to increase diagnostic yield and improve treatment related outcomes in patients.

Quantitative EEG analyses and seizure forecasting

While the previous section highlighted some of the advancements made in advancement of EEG related hardware to improve diagnostic capabilities, this section briefly goes into the software related advancements that have been engineered for improving the efficacy and accuracy of EEG.

Quantitative EEG (QEEG) involves applying digital signal analysis to recordings to enable automation of diagnostics and reveal patterns unseen by the human eye [27]. Decades of research have suggested that EEG analyses can unsheathe hidden differences between recordings of patients with epilepsy and non-epileptic subjects in terms of connectivity, signal predictability and complexity, spectral power and chaoticity [28]. Evident applications involve automation, along with scientific detailing and locating interictal epileptiform events or discharges and seizures, thus improving diagnostics and surgical management. Some fields

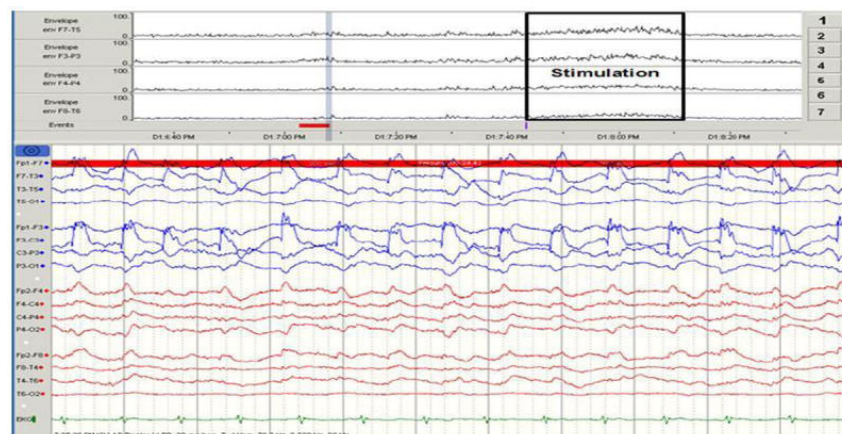


Figure 5. An example of the variable utility of QEEG for seizures in the ICU – inconsistent seizure detection of the same program for 2 different types of seizure events [94].

of interest within QEEG involve seizure prediction, pharmacoe-EEG, treatment monitoring, evaluation of cognition, and neurofeedback. Chief limitations include low reliability and insufficient generalizability of measures, as well as the need for customization of analyses to individual patients (**Figure 5**). Another major limitation towards clinical inclusion of QEEG analyses is also that training is excluded from standard curricula for many clinical neurophysiologists [27].

Automation or assistance in the detection of epileptiform spikes / discharges and seizures remains the main use of QEEG. Many studies have shown that the performance of QEEG based automated detection software (like Persyst) is non-inferior to visual inspection by a trained expert in the identification of spikes/discharges and greatly assists with diagnosis of epilepsy and saving time and effort in EEG review, along with aiding untrained care providers to identify abnormalities on EEG [29,30]. The data is mixed, however, when it comes to the use of QEEG to detect seizures in the EMU and ICU settings. One study conclusively showed that, in ICU settings, automated seizure capture had high rates of both false negatives and false positives that did not favor its use as an alarm in standard practice. The seizure detection rate was only about 50% while only 60% of QEEG identified seizures were actual epileptic events. Persyst shows maximum value in triaging of low-risk EEGs. This research stated that (Class II evidence) automated detection showed poor accuracy in identifying EEGs with seizures [31]. Other studies have shown non-inferior performance of Persyst software in seizure detection in prolonged EEG as compared to human interpreters and supported its use in EMU/ICU settings [32]. The presence of different seizure types results in variable rates of detection by QEEG software using different types of spectrograms to identify different seizure types; such as asymmetry spectrogram for detecting focal seizures, FFT

spectrogram for detecting secondarily generalized seizures, and seizure detection trend for generalized onset seizures [33]. Moreover, the rise of newer terminologies and conditions like the ictal-interictal continuum and nonconvulsive seizures has resulted in redefining parameters and definitions for seizures with a resultant change in detection sensitivity and accuracy as well. QEEG analyses in different frequency bands has helped improve understanding and diagnosis of focal epileptic onset zones and networks [34,35].

Quantitative analysis of the EEG in order to document the effect of drugs on electric activity of the brain is known as pharmacoe-EEG. Pharmacoe-EEG is non-invasive, risk free, cheap and commonly used. The EEG evaluates response to the initiated therapy, for example, is there a change in the burden of interictal discharges [36]. Pharmacoe EEG remains unpopular due to multiple reasons such as, poor use of the EEG as a biomarker, variance of EEG changes across different drugs, absence of standard operating procedures, high inter-individual variability for EEG as a whole, and large storage and processing requirements needed for EEG recording [37]. Studying epileptiform activity and event-related potentials was included in the realm of pharmacoe-EEG, but frequency analysis is of most importance. Frequency responses, correlation with side effects and prognostication of response to treatment were all studied with pharmacoe-EEG with limited correlation which made it a less attractive option over the years, despite having extensive attempts in the past to study older generation ASMs and understand their use [37]. There has been increasing interest of late in the use of pharmacoe-EEG to study the frequency band effects of drugs like cannabidiol and even perform higher quality and intensity graph network analyses to understand the effects of cannabidiol on epileptic and associated cognitive networks (**Figure 6**) [4,38].

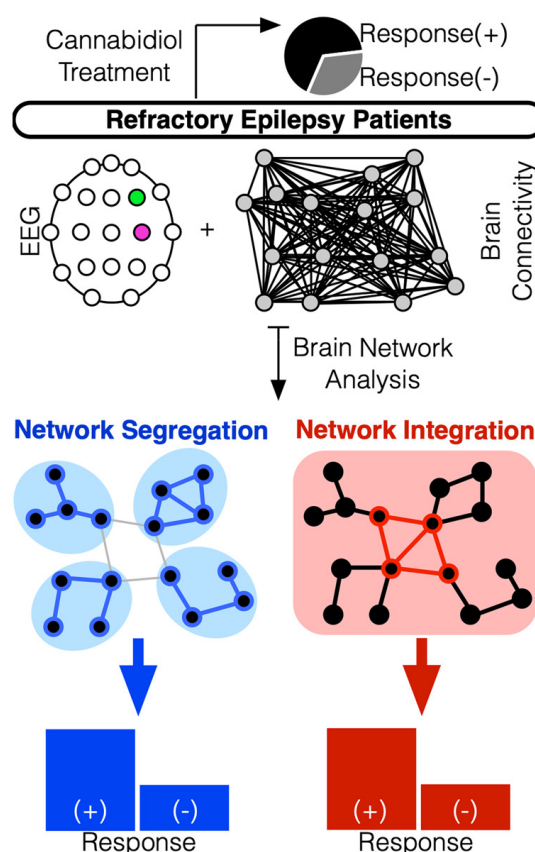


Figure 6. An overview of EEG connectivity analyses using QEEG and graph network analyses to study the effects of cannabidiol therapy on the EEG networks in patients with refractory epilepsy [4].

Performing QEEG analyses requires extensive skills and signal component analyses and recognition of patterns that are variable across patients and may need customization across different seizure types, indications and treatment settings. Many experts have thus begun to work with artificial intelligence (AI) and deep learning programs to develop and improve newer and more effective approaches to the use of QEEG and improve its efficacy and accuracy, along with offering assistance/automation to human EEG readers and researchers [39,40]. AI has not yet achieved levels of accuracy that would support its regular use in clinical practice, but it is felt to be a matter of time before that benchmark is achieved [40].

While QEEG remains a useful tool with research and clinical applications, many experts have focused on developing biomarkers and algorithms to enable better prevention and prompt treatment by enabling better prediction of seizures. Seizure prediction and forecasting involve predicting the timing of the next seizure and estimating the probability of having a seizure at a given time. The unpredictability of seizures worsens fear and anxiety in epileptics, limiting participation in day-to-day activities, and is a great source of epilepsy related morbidity.

Great steps have been made in the field of seizure forecasting, consisting of improvements in algorithms due to use of machine learning along with using non-EEG-based markers of seizure susceptibility, like physiological biomarkers, behavioral differences, environmental triggers, and cyclic ictal patterns. Research studying periodicities in individuals and their patterns of seizures has established that >90% of people have circadian seizure rhythm, and lots of them also experience cycles lasting many days, weeks, or longer time periods. Additional predictors for seizure susceptibility include changes in stress levels, heart rates, and quality of sleep, with all of these being able to be captured extensively over long periods of time. Applications of forecasting devices include, but are not limited to, improved quality of life in epileptics, adjustment of treatment plans and medication titration, optimizing surgical evaluations, and narrowing the required scope of scientific research [41].

Seizures are thought to arise from an identifiable pre-ictal state. Identifying this pre-ictal state would enable the monitoring physician or researcher to predict the occurrence of a seizure prior to it happening and help them devise appropriate measures of prevention and intervention. Seizure prediction looks for predictive EEG features or pre-ictal

biomarkers that can be captured using machine learning and related algorithms. These algorithms offer the likelihood of impending seizures and warn patients accordingly.

Multiple studies have been performed on intracranial EEG data gathered by the implanted Neurovista device and this data has been subjected to crowdsourced AI algorithms to identify markers of seizure prediction. Many algorithms have shown seizure predictive capabilities much higher than chance, especially with the use of modified and improved algorithms and addition of other parameters like circadian monitoring [42-44]. Bioengineering advances have helped us utilize digital markers, wearables, and biosensors to get data for future seizure-forecasting algorithms. This represents a great step forward, given that current predictive models are based on intracranial EEG analyses. Multimodal data including the coupling of EEG with non-EEG measures would likely advance the efficacy of seizure-forecasting algorithms. These non-EEG measures could include a host of biological and chemical measurements [45]. Customization and tailoring of seizure-forecasting algorithms to the needs of individual patients is necessary [45].

AI and machine learning are expected to revolutionize the field of epilepsy management and EEG interpretation. Advanced and robust machine learning models are being developed to analyze EEG features and improve and expedite diagnosis of abnormal EEG. These AI models are quite accurate and are expected to become standard of care and assist the clinician and researcher. While they may never completely replace humans, they will greatly assist us with diagnostics and seizure management and improve diagnostics of EEG as a whole. Better models are needed for seizure and spike detection in IEEG models, but it is only a matter of time before they are created. Ethical concerns about the accuracy and extrapolation skills of AI algorithms trained on smaller datasets with limited samples persist and these concerns are bound to be mitigated over time with use of larger datasets

and improved algorithms. The use of AI and machine learning in assisting the clinician in the inpatient and outpatient setting has also been explored and described, and while quite interesting, is beyond the scope of this EEG focused paper. Needless to say, the future of AI and machine learning in epilepsy and EEG diagnostics and management remains quite bright [46-48].

Ambulatory EEG and other monitoring devices

While the previous section discussed the use of various devices and wearables for biosignal collection and seizure forecasting, much work has also gone into making EEG technology portable and wearable. Ambulatory EEG (AEEG) devices offer easy, portable, digital EEG recording that can be performed with or without video. AEEG technology is similar to routine and VEEG but is also compact and wearable. AEEG technology is quite compatible with digital recording, signal processing, along with visual display. AEEG has several potential clinical indications, including, (1) distinguishing epileptic and nonepileptic events, (2) prolonged interictal EEG sampling, (3) classifying patients' seizures and syndromes, (4) determining seizure frequency and duration, (5) identifying non-hospital seizure triggers, and (6) adjustment of antiseizure medications [49].

AEEG has shown great utility in capturing and diagnosing events to confirm or exclude epilepsy, especially in the event of a non-diagnostic routine EEG. Its popularity skyrocketed during the pandemic due to the need for prolonged EEG monitoring and the convenience it offered in comparison to conventional VEEG [50]. This was extremely useful at a time when EMUs in hospitals were closed due to pandemic related restrictions. AEEG with video establishes diagnostic data in 80-85% of monitored patients with excellent event capture seen [50]. Home AEEG recording for up to 48 hours has a very high probability of capturing events and aiding in diagnoses related to epilepsy [51]. AEEG has inspired advancements in

Table 1. Multiple non-EEG parameters used to develop seizure detection devices. An asterisk indicates those recorded by patient diary, others possibly captured through smartphone, biosensors, or through sweat collection [45].		
• Mood* • Cortisol • Orexin • Patient self-prediction* • Electrical dermal activity • Heart rate • Temperature/weather • Respiration • Sleep cycle changes (sleep/wake staging) • Sleep quality	• Stress* • Fatigue* • Irritability* • Sex hormones • pH (brain) • Time of day* • Antiepileptic drug levels • Blood oxygen • Inflammatory markers • Glucose • External environment	• Compliance • Illness* • Food/alcohol intake • Orientation (cognitive) • Gait • Finer movements • Ketones • Speech • Body Temperature

developing other portable EEG devices to enable easier, faster, cheaper and less technical access to rapid EEG acquisition in inpatient and outpatient settings for patients [50]. Many AEEG recordings also offer capture of other parameters like heart rate, oxygenation, muscle movements and sleep monitoring which greatly increases the utility and yield of AEEG, while spike and seizure detection software are also often present with AEEG technology to enable better diagnostics and record review. It has shown great utility in resource limited countries and settings with some studies reporting a diagnostic yield of 86% and impact on clinical decision making in 60% of patients [52]. Patients with intellectual disabilities, autism, etc. have a high incidence of epilepsy and refractory epilepsy and often experience challenges with conventional EMU monitoring due to agitation in unfamiliar surroundings and the absence of continuous family presence. AEEG has shown great utility in evaluating such patients in the comfort of their homes or long-term facilities and increasing diagnostic ability to confirm or exclude seizures in them [53].

AEEG has inspired researchers to develop long-term implanted electrodes that can be left in place for weeks to months for chronic EEG recording to increase the probability of capturing seizures, especially in patients with infrequent seizures. Subscalp EEG consists of implanting electrodes with minimal invasiveness under the scalp and capturing long-term EEG recordings for weeks-months to enable good seizure capture. This technology is of great value in capturing seizures in patients with multiple seizure types or multifocal seizure onsets, patients with long intervals between seizures, and patients with suspected sleep disorders where the EEG is of interest.

Subscalp EEG is able to bypass the limitations of intracranial EEG in being able to be recorded for much longer and in recording data from the patient during natural activity in their usual surroundings. This technology has been developed and used in dogs and humans to confirm safety and feasibility of long-term recording and the results of these studies have been quite promising in confirming these features [54]. Subscalp EEG does have some limitations like poor detection of seizures from deeper structures in the brain and effects of artifacts. However, there are benefits to being able to detect seizures from most parts of the brain and in combining such recording devices with seizure detectors to provide warning systems to patients. These properties have been used to develop a variety of subscalp EEG devices to enable chronic EEG recordings [55]. Other devices have been developed to record EEG from nasal or ear electrodes with varying degrees of efficacy – ear electrodes show good capacity at capturing temporal onset seizures but are poor at capturing seizures from deeper structures, which limits their use [56]. Ear or nasal devices also have limited recording time as compared to implanted subscalp EEG electrodes. Even so, we expect to see such devices become more common and add to the multiple options available in the armamentarium of the clinician and researcher.

AEEG has also inspired the development of a portable EEG headband device, Ceribell. Ceribell is placed over the head to capture EEG data for short periods of time only and has been used quite easily to great effect. This device can easily be placed on the heads of patients in inpatient or ICU settings by providers with minimal neurological training to rapidly detect seizures. Studies have shown that Ceribell is easy to use, accurate and saves time with resources and costs, and limits need for EEG technologists in ICU and inpatient settings to recognize seizures [57]. This enables easier and faster recognition and treatment for recurrent seizures.

While EEG is often considered the gold standard of seizure identification and diagnosis for epilepsy, there is a growing interest in developing non-EEG based devices that can capture biomechanical data and facilitate recognition of seizures in non-hospital settings. There is great value for such devices to monitor patients at home, especially for parents of children with epilepsy. These devices capture tonic-clonic convulsions well but have limited accuracy in capturing other seizure semiologies. Even so, there is high value in identifying tonic-clonic seizures at the earliest to enable prompt treatment and reduce their known higher rates of morbidity and potential mortality from SUDEP.

Empatica Embrace (Boston, MA), a wrist worn smart watch, uses accelerometry and electrodermal activity to capture the subject's motion and operates with a continuous Bluetooth connection to the subject's smartphone, where a phone application transfers data and event detections to online cloud servers and releases caregiver alerts for seizures [58]. This device has shown high utility in detecting tonic-clonic seizures in patients and in helping caregivers monitor them without video.

The second device, Brain Sentinel SPEAC (San Antonio, TX) is fixed adhesively to the subject's bicep and uses electromyography/EMG to recognize tonic-clonic convulsions. This device also has an online cloud platform and can issue caregiver alerts too [59]. Most current commercial smartwatches possess accelerometric and photoplethysmography sensing devices, which show utility in tracking seizures, and many smartwatch and smartphone applications have been designed for this reason [60].

There are many other devices being developed that track and monitor a host of biosignals ranging from breathing to heart rate to sleep to sweat based secretions and can be combined with web databases or data repositories to enable storage and access for patients, families, clinicians and researchers [61]. It is expected that such wearables will constitute an important means of monitoring for patients and their families, especially in situations where EEG monitoring may be challenging to obtain or perform. Bioengineering advancements would greatly enhance the efficacy and utility of such devices and advance the field as a whole.

Intracranial EEG and electrocorticography (ECOG) with related surgical advancements

Intracranial EEG (IEEG) represents the most sophisticated form of EEG recording. It consists of placing subdural electrodes on the surface of the brain (ECoG) or stereotactically placed depth electrodes into the matter of the brain (SEEG), to record EEG data and enable better understanding of seizure networks. It forms an essential investigation for refractory epilepsy patients to determine the nature of their seizure networks, eloquent and non-resectable cortex, targets for epilepsy surgery or neurostimulation and brain mapping. To ensure long-term consistent recordings, newer and innovative intracortical microelectrodes are being manufactured for decreasing the neuro-inflammatory response. This newer approach stems from better understanding of the multi-dimensional role of inflammation in disrupting biologic and non-biologic segments of the neural interface circuit. To counter neuro-inflammation and increase recording quality, the field is progressing from conventional inorganic materials towards mechanisms that either minimize the microelectrode footprint or that include options like compliant materials, bioactive molecules, conducting polymers or nanomaterials. And yet, the immune-privileged cerebral cortex introduces further complexity compared to other biomedical applications that defy complete comprehension with current techniques [62].

SEEG is relatively newer than subdural grids and represents a different approach to IEEG evaluation of seizure networks. Pioneered by Talairach and Bancaud, SEEG has evolved over the years and is now the preferred technique to perform intracranial EEG, due to lower rates of morbidity and ease of customization for individual patients, as compared to subdural grids and strips. Studies from various centers have shown many advantages of SEEG over subdural strips or grids with some of the more prominent studies showing faster surgical time of implantation, greater number of electrode contacts implanted, lower frequency of hemorrhagic and infectious complications, lower dosage of operative narcotics for pain management, and better surgical seizure outcomes in patients, especially in patients without well-defined brain lesions [63]. While the outcomes may be difficult to compare, due to the diverse nature of both procedures; the other benefits of SEEG are myriad and proven and make it a very attractive option and showcase improvements in bioengineering to develop such technologies.

Conventional grids or strips have often been used in patients with obvious lesions, especially with cortical locations, and are most convenient in patients with single or discrete lesions within a single lobe due to ease of placing grids or strips in them and minimizing the risks of surgical morbidity. SEEG has greatly expanded the scope of IEEG to include patients with previously non-targetable lesions due to greater utility and ease of implantation. Bilateral cerebral exploratory studies, subcortical anatomical lesions like nodular heterotopias

or other multilobar or widespread pathologies like polymicrogyrias are perfect examples for exploration with stereotactic EEG, as many of these conditions are incompletely or inconclusively analyzed with the use of conventional subdural grids and strips, often yielding falsely localizing information on seizure zones as well [64]. Numerous studies have shown the utility of SEEG in such patients to enable exploratory implantations. Many centers also perform 2 stage IEEG surgeries where they perform SEEG and subdural grids or strips in succession to identify the seizure network and narrow it down or perform brain mapping and cortical stimulation to determine the appropriate interventions for the patient. While well-designed studies are lacking, anecdotal evidence has suggested that this combination of techniques in succession is a very effective and innovative way of evaluating patients safely and accurately. SEEG and subdural grids can also be combined to study some complex patients and there have been cases reported of this being used to great effect [65].

SEEG is of great value in epilepsy surgical evaluation due to its ability to achieve accurate localization and anatomical reconstruction in combination with radiological imaging and software techniques, and achieve precise and excellent surgical planning for treatment. Robotic surgical assistants (ROSA) implant these electrodes within fine margins and minimal error, highly increasing the efficacy and accuracy of lead placement and have revolutionized ECoG analyses of surgical evaluations. The margins of error between desired and actual targets are minimized to 0.85–3 mm, thus raising locational and diagnostic accuracy [66].

Bleeding complications are common due to proximity of vascular structures to the surgical zone. Three-dimensional reconstructions and excellent presurgical planning limit surgical contact with vasculature and result in severely reducing blood loss and negative surgical outcomes [67]. Grey and white matter injuries from surgery often causes cognitive deficits. Diffusion Tractography Imaging (DTI) pinpoints the locations of these regions and limits damage due to accurate presurgical localization, thus minimizing risks of injury and resultant damage. The use of DTI based mapping to avoid the Meyer's loop of the optic radiation pathways to maintain unhindered visual fields in temporal lobe resections is one example [68]. Reconstructive techniques highly increase the ability to localize seizure onset zones and spread nodes, particularly in pathologies like bottom-of-sulcus dysplasias, which are perfectly localized to enable pinpoint intervention and maximize positive surgical outcomes.

Reconstruction uses presurgical and postsurgical scans. Presurgical MRI scans act as a baseline on which postsurgical CT scans with electrodes are overlapped to achieve accurate positioning of electrodes with respect to brain structures. This is performed using software such as Freesurfer or 3-dimensional (3D) Slicer. Newer software additionally permits inclusion of brain mapping studies or cortical stimulation procedures to improve surgical results in these patients. These

reconstructions compile a 3D map that offers convenient identification of seizure onset zones along with relevant overlap or margins between the seizure onset or spread zones and eloquent cortex. These techniques are used nationwide across multiple centers, with the caveat that there does not exist a single standardized approach across various centers [69].

SEEG has shown great utility in surgical epilepsy due to its ability to be combined with and improve targeting for procedures like laser ablation. Laser ablation has shown great utility against targets like mesial temporal lobes along with others like heterotopias or tuberous sclerosis nodules or tubers to great effect, in addition to also being performed to complete corpus callosotomies - all of which are now performed quite effectively with SEEG guidance and targeting [70-73]. Using SEEG in combination with laser ablation and reconstructive techniques has thus greatly expanded its scope in the field of surgical epilepsy and been a major engineering and scientific innovation. While grids or strips remain the technique of choice for brain mapping and localization of eloquent cortex, SEEG has shown increasing utility and is often used for surgical margin localization in many cases, especially if extremely fine margins are not needed. We expect that the diagnostic accuracy of SEEG will continue to improve over the years to match, and possibly exceed that of grids or strips [74].

SEEG has also helped achieve good targeting of brain structures to achieve precise placement of targeting electrodes for responsive neurostimulators and deep brain stimulators – discussed in the next section. SEEG and IEEG as a whole represent a great field of neuroengineering that has developed quite nicely and continues to grow due to the innovative fusion of EEG analyses, engineering hardware and software developments with concomitant improvements

in radiology along with advancements in neurosurgical techniques. Some epilepsy centers now perform electrical ablation of seizure network nodes at the bedside for epilepsy treatment, once confirmed using bedside cortical mapping and stimulation; a technique that is likely to become increasingly popular in future to enable faster and innovative treatment of epilepsy networks by neurophysiologists in EMU or ICU settings for patients with SEEG implants. Improved SEEG based mapping is likely to offer better cortical stimulation and cerebral function mapping in EMUs/ICUs; a development that is bound to reduce the need and the incidence for operating room based awake language mapping of cerebral functions in patients. This would be a welcome change for the field as a whole since awake language mapping is very challenging and the accuracy and safety of the procedure is often questioned by experts [75].

EEG in responsive neurostimulation (RNS)

Neurostimulators represent the latest technologies on offer for the treatment of refractory epilepsy. Vagal Nerve stimulation (VNS), responsive neurostimulation (RNS) and deep brain stimulation (DBS) represent the main modalities available in the field of neurostimulation. VNS is fairly noninvasive and does not rely on EEG monitoring for the adjustment of therapy, although some researchers are attempting to produce a closed loop, EEG responsive VNS. DBS is an open loop system that also produces pulse electrical therapy targeting the anterior nucleus of thalamus or other implanted targets. However, it also does not use EEG to record responses and adjust therapies.

The RNS System (NeuroPace, CA, USA) has the distinction of being the first device on the market to offer closed-loop responsive brain stimulation (**Figure 7**). Closed-loop

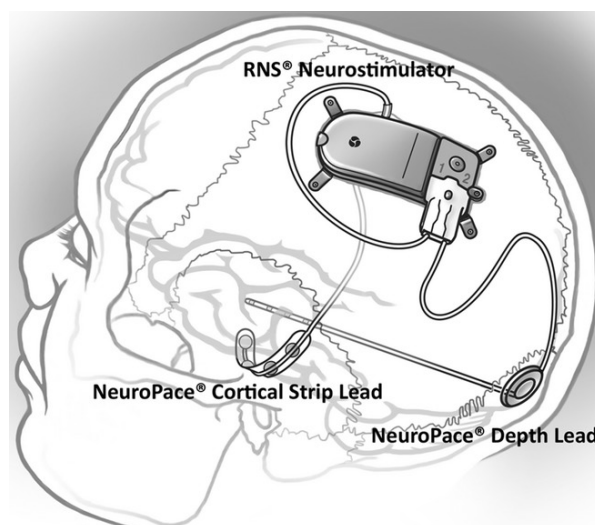


Figure 7. An overview of the NeuroPace RNS device and its major components – stimulator with battery and 2 intracranial electrodes – depth and strip electrode [95].

stimulation, also known as on-demand or responsive stimulation, is an innovative neurostimulation approach that represents a significant advancement over traditional open-loop neurostimulation. Closed-loop systems dynamically adjust stimulation based on real-time feedback from the patient's brain activity. This feedback is usually obtained through continuous ECoG monitoring [76].

The RNS system consists of an implanted neurostimulator within the skull compartment with non-stop ECoG recording through one or two depth and/or subdural cortical strip leads that are placed at the desired target. Detection of predetermined abnormal ECoG activity results in delivery of brief pulses of electrical stimulation to the target through the implanted leads from the stimulator.

The treating physician modifies detection and stimulation settings wirelessly using a programmer that communicates directly with the stimulator via a radiofrequency link. The neurostimulator stores ECoG data about the abnormal EEG and stimulations and treatments. The treating physician can also train the stimulator to store segments of the ECoG activity of specific predetermined events like, before and after detection of abnormal electrographic activity, responsive stimulation, a magnet swipe (suggesting a patient-marked clinical event) or according to specific time of day.

The PDMS (Patient Data Management System) is an online database that contains information uploaded from the device and programmer (**Figure 8**). The physician may access and review the patient's data from the PDMS at any time on any device with a web browser. The detection algorithms of the neurostimulator are optimized to perform real-time ECoG pattern detection (for seizures or spikes, etc).

The use of RNS and chronic ECoG has greatly revolutionized the management of refractory epilepsy and the use of IEEG for decision making. Patients that were not surgical epilepsy candidates in the past, were now able to achieve significant seizure reductions for different types of seizures (73-93%),

achieve prolonged seizure free periods (6 months – many years) and objective improvements in quality-of-life measures (QOLIE-89, etc) [77]. There was a lowering in death rates (SUDEP) and improvements in depression measures seen with the use of RNS [77].

Surgical management of epilepsy has greatly changed with the use of RNS and associated chronic ECoG. Previously untouchable regions like eloquent motor, visual or language cortices can all now be targeted and treated with RNS systems to enable significant palliation and improvements in seizure burden. Bitemporal epilepsy has undergone a dramatic change in management due to the use of RNS [78]. Previously poor surgical bitemporal epilepsy candidates have now had a rapid improvement in available options for treatment. RNS with chronic ECoG has enabled treating physicians to capture bitemporal seizures over months to establish unilateral predominance, lateralization of seizure burden, establish seizure spread patterns and rhythmic cycles of repetition [78]. Patients in whom such information was obtained were then able to have unilateral temporal lobectomies with or without continued neurostimulation to achieve significantly improved seizure outcomes [78]. The inability to perform laser ablations with RNS implants due to the risk of heat induced device damage is a minor shortcoming and is expected to improve in successive generations of the device in future. Better technology and higher device stability are expected in future versions of the device to limit the possible risks of heat induced damage from ablation and enable concurrent use of both these treatments. Laser ablation has also shown great utility in epilepsy treatment due to its ability to offer punch biopsies immediately prior to the ablation to permit histopathological confirmation of brain abnormalities to support the pathological causes of epilepsy. These findings have helped achieve better electrical, anatomical and electrical correlation in seizure networks.

The diagnostics of bitemporal epilepsy have changed as well due to RNS ECoG. Patients with presumed unilateral or unilateral predominant temporal lobe epilepsy have been

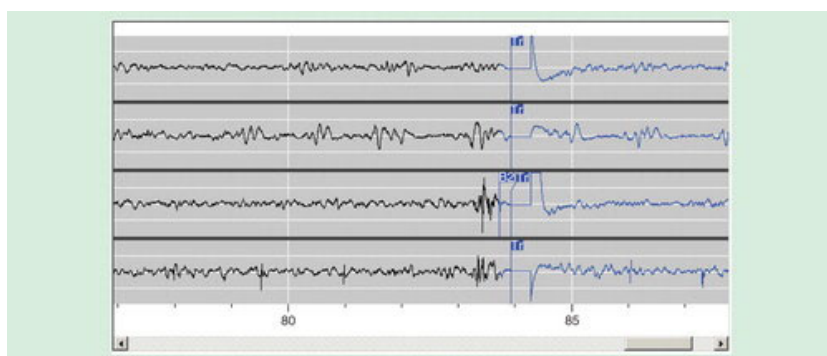


Figure 8. Example of an ECoG seen on PDMS. Following the initial detection, the EEG is displayed in blue [96].

found to have seizure arise from the opposite side, on average about 42 days after their usual lateralization of seizure onset; a finding that was not conceivably possible to detect on regular EMU monitoring, even with SEEG, due to the limited duration of ECoG sampling for a few days to a couple of weeks only [79]. Many patients with presumed bitemporal epilepsy were found to have high unilateral predominance, a finding which greatly increased their chances of achieving seizure control or freedom with epilepsy surgery [79]. RNS ECoG has enabled physicians to determine lateralization ratios in patients with up to 90% confidence in most bitemporal epilepsy cases to permit successful unilateral temporal lobe surgery and achieve excellent postsurgical outcomes after just 8-9 months of RNS monitoring [80]. Most centers accept a seizure lateralization ratio of 60% onset from one side as being adequate to qualify for temporal lateralization and targeting for surgery; although higher numbers are more likely to be associated with better surgical outcomes [80].

The battery life of the RNS device was 2.5-4.2 years in the past but with the use of newer battery devices, this can increase up to 8 years, according to the device manuals and NeuroPace company data. This increase in battery life greatly enhances the capabilities of the device and reduces the number of replacement surgeries necessary for battery changes over the lifetime of the device. It is hoped that future versions of the battery will provide greater periods of ECoG capture without replacement. The device has limited ECoG storage and newer data often overlaps and replaces older data, if not stored onto the PDMS by then.

Future engineering updates are expected to increase device storage capabilities and enhance transmission to PDMS. Wireless transmission over longer distances, remote programming of the device and implantation of more than 2-4 electrodes with greater ECoG capture and increased number of EEG channels are felt to be some of the available avenues for improvement of the device capability in future. The use of AI, to improve seizure detection and assist treating physicians to determine the best diagnostic and treatment algorithms for patients, is of great interest and is currently under development. The ability to perform MRI with an RNS implant in place is a newer development that has added to the utility of the device and expended use to a greater number of epilepsy patients. For example, patients with benign brain tumors and refractory epilepsy can now have the RNS implants with the knowledge that MRI compatibility of the device will not preclude repeated brain imaging for surveillance of the tumors. There is increasing interest in implanting RNS for generalized and multifocal epilepsies such as Lennox Gastaut Syndrome and posterior cortical epilepsies targeting currently infrequent and presumed nodal points for such syndromes, like the thalamic nuclei (dorsomedial, centromedian, pulvinar) [81]. Future directions would include the placement of RNS targeting in currently unorthodox locations to exploit network properties of unusual epilepsy syndromes and render them more amenable to neuromodulation therapy to improve

patient outcomes. NeuroPace is currently conducting a trial (Nautilus study) to determine the efficacy of RNS implantation for generalized epilepsy syndromes. This trial will greatly expand the use of RNS in epilepsy and offer this therapy to an increased number of refractory epilepsy patients that are currently ineligible for it based on current guidelines.

While VNS and DBS have not been discussed in this section since they do not rely on EEG based data for intervention, it must be mentioned that future versions of these devices may not have this limitation. Future directions for VNS include greater battery life, minimal effects on the recurrent laryngeal nerve and voice functions, remote device programming, cloud storage and computational capabilities along with the use of AI and machine learning algorithms. VNS may be able to offer its own version of closed loop therapy by using tachycardia from its cardiac monitoring system as a surrogate marker for epileptic seizures; a finding of increasing interest in epilepsy patients. Some VNS manufacturers work with seizure tracking applications to enable better correlation of patient care and use of VNS and anti-seizure medications (Epsy seizure tracking app with Livanova). There is increasing interest in the combining of VNS with RNS and their cumulative positive effects on the seizure networks in epileptic patients. Some research has already been performed in this regard and future directions would involve greater use of both devices simultaneously to benefit complex epilepsy patients [82].

There is increasing interest in the use of DBS to treat epilepsy syndromes. The anterior nucleus of thalamus is the FDA approved target for DBS implantation for the treatment of refractory focal epilepsy. However, newer targets like the centromedian and dorsomedial nuclei or the pulvinar are also being studied as future targets for posterior cortical or generalized epilepsy syndromes [83]. Future directions would also include having newer generations of the DBS device record EEG continuously to enable closed loop responses. Remote programming, greater battery life, EEG storage, cloud computation and AI capabilities are also features that are expected to embellish DBS technology in future.

Non epilepsy conditions and other opportunities in EEG

EEG has a premier role in the diagnosis and management of epilepsy. However, scientists and researchers have long attempted to utilize EEG to gain insight into other conditions as well due to its non-invasive nature and ease of performance and availability along with the presence of EEG abnormalities seen in a variety of neurological conditions.

Dementia is a common condition with increasing prevalence and multiple studies have shown high incidences of epilepsy in dementia patients, making EEG a valuable tool for evaluation and diagnosis of dementia [84,85]. The incidence of epilepsy varies across different types of dementia and Alzheimer's associated dementia appears to have better response to anti-seizure medications. However, these findings have not held up

very well across all studies [85]. QEEG analyses of various EEG spectra have not shown clinically relevant differences amongst various subgroups of dementia patients despite the presence or absence of epilepsy [85]. QEEG remains a tool of interest in the evaluation of dementias, even if only as a research tool at this time with limited clinical utility in the real world.

Parkinson's disease (PD) remains the second most common neurodegenerative condition worldwide, after a diagnosis of dementia. Motor symptoms form the predominant syndrome in Parkinson's disease and are often severe towards the latter stages of the disease. Early detection of Parkinson's disease would greatly aid in the diagnostic process and enable earlier treatment and prolongation in maintenance of quality of life. Researchers have studied various biomarkers to enable earlier diagnosis of Parkinson's and allied disorders, and EEG has been discussed as one of the pre-eminent candidates for this purpose. QEEG analyses have shown promise in this regard.

Changes in cortical and thalamic electrical coupling were captured as excessive EEG beta coherence in Parkinson's disease patients and showed direct correlation with UPDRS scores and captured dopamine transporter activity, supporting the utility of EEG coherence to act as an effective measure of disease severity in patients [86]. Sleep disturbances are indeed extremely common in PD, being often the earliest manifestation of the disease and thus representing the most likely candidate for helping in predicting its onset. Polysomnography (PSG) is the gold standard method to study sleep and its disorders. PSG with high-density electroencephalography (hdEEG-PSG) montage are nowadays frequently used to investigate sleep. These systems allow deeper investigation of sleep characteristics to confirm early diagnoses of sleep disorders and PD to expedite earlier treatment, modification of therapy and better outcomes [87]. EEG however does remain a research modality rather than a regularly used clinical tool for diagnosis and treatment of PD.

Psychiatry is a sister discipline to neurology and is often felt to be the other side of the coin, as far as brain disorders are considered. The utility of EEG in psychiatry has never been well established and yet, researchers have spent a long time trying to understand psychiatric disorders using EEG based markers. QEEG biomarkers of depression have been described by multiple experts but lack the specificity, sensitivity and accuracy necessary for routine clinical use [88]. QEEG analyses in children with ADHD have shown promise in differentiating the different subtypes of ADHD and improving our understanding of this condition; a finding that gives hope for the use of EEG for clinical evaluation of ADHD patients in the near future [89]. Neurofeedback consists of a therapy based on interactions between humans and computers that teaches subjects to train voluntarily and modify various functional biomarkers that are associated with a certain mental disorder. QEEG analyses have shown promise in the use of neurofeedback and researchers are optimistic regarding its use on a regular clinical basis [90]. QEEG analyses in combination with imaging like functional

MRI (fMRI) have shown great promise as research tools to study and improve treatment response predictions in various psychiatric disorders, with great potential for regular clinical use, especially in conjunction with AI and machine learning processes [91]. While the above list of applications of EEG in psychiatry is by no means exhaustive, it does offer a glimpse into the various potential means by which the EEG and QEEG analyses may achieve efficacious and innovative use in the realm of diagnosis and treatment of mental health disorders.

QEEG analyses have been developed to diagnose cervical myelopathy in conjunction with AI algorithms [92]. The use of QEEG with VEEG monitoring for the early detection and treatment of cerebral vasospasm from intracranial or subarachnoid hemorrhage is well known [93]. In combination with transcranial Doppler (TCD), QEEG is able to achieve excellent efficacy in the early diagnosis of vasospasm from subarachnoid hemorrhage and expedite treatment and improve outcomes in ICU patients [93].

The above conditions highlight the broad applicability of EEG in the diagnosis and management of various conditions besides epilepsy. It is expected that the combination of QEEG with multi-modality monitoring of patient parameters will greatly enhance patient care and associated outcomes in ICUs and similar settings.

Conclusions

EEG is thus a versatile technique that has expanded sufficiently from its humble origins in the 1920s to now become the cornerstone of management of simple and complex aspects of epilepsy and other neurological disorders as well. It shows great adaptability in its use for diagnosis in routine outpatient settings along with complex patient evaluations in the ICU settings, in addition to combination with AI and QEEG analyses in a variety of settings including presurgical evaluation, chronic and ambulatory monitoring and diagnosis and management of various non-epilepsy related neurological and psychiatric disorders. It is a testament to human ingenuity and scientific innovation that EEG technology has improved on multiple frontiers due to advancements in mechanical, electrical and technical components of EEG. Bioengineering advancements in EEG continue to drive the field forward and greatly increase the utility of EEG as an excellent diagnostic and research modality and important component of human biosignal monitoring. These advancements would result in lower costs, greater availability and accessibility to technology, ease of use for the common man and family practitioner, and significantly more frequent adaptation in the field of research to greatly increase EEG use.

QEEG, AI and machine learning algorithms are expected to improve automated detections and offer greater support for the interpreting physician in the management of seizures. Advancements in surgical technique are expected to improve localization of seizure networks due to more

accurate placement of EEG electrodes resulting in improved surgical outcomes. Newer technologies like laser ablations are expected to improve in accuracy and permit better and less invasive approaches to treatment of seizures, especially in conjunction with finely tuned and accurate intracranial EEG recordings. Neurostimulation as a whole is expected to advance exponentially due to significant improvements in technology, device design, material science, EEG signal capture and analysis, use of AI and machine learning algorithms for seizure identification and forecasting, and concomitant use of surgical techniques for high quality localization and treatment. EEG and seizure diagnostics are expected to significantly improve with the ever-expanding use of AEEG, implanted subdural EEG electrodes, other chronic EEG recording devices, and the use of other biosignal capturing devices and wearable technologies. Other neurological conditions like dementias and Parkinson's disease would also benefit from EEG related advancements and related improvements in clinical and research care. All these aforementioned advances would greatly contribute to more efficient and cost reducing approaches to the diagnostics and management of seizures, resulting in greater resource utilization within health systems for patient treatment rather than extraneous purposes. The implications of EEG advancement are profound and offer insights and lessons that permit extrapolation to other biosignals analyses to develop and improve the field as a whole. It is only through such innovative and forward thinking that the field of electrodiagnostic medicine and neurotechnology can advance as a whole for the benefit of mankind.

Acknowledgements

The author wishes to thank Abenaya Muralidharan, PhD for her critical review and valuable insight into this paper.

Author Contributions

The corresponding author was involved in the conception, critical design, scientific and literature review, writing, editing, submission of this paper and agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, are appropriately investigated, resolved, and documented in the literature.

Financial and Scientific Disclosures

There was no funding support involved in this study. This paper was published in conformity with accepted scientific and ethical guidelines for research publication. The author has no relevant conflicts of interest or other financial or scientific disclosures to make.

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