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Getting Under the Skin of Seizure Monitoring: A Subcutaneous EEG Tool to Keep a Tally Over the Long Haul

Detecting Temporal Lobe Seizures in Ultra Long-Term Subcutaneous EEG Using Algorithm-Based Data Reduction

Remvig LS, Duun-Henriksen J, Fürbass F, Hartmann M, Viana PF, Kappel Overby AM, Weisdorf S, Richardson MP, Beniczky S, Kjaer TW. *Clin Neurophysiol*. 2022;142:86-93. doi:10.1016/j.clinph.2022.07.504. PMID: 35987094

Objective: Ultra long-term monitoring with subcutaneous EEG (sqEEG) offers objective outpatient recording of electrographic seizures as an alternative to self-reported epileptic seizure diaries. This methodology requires an algorithm-based automatic seizure detection to indicate periods of potential seizure activity to reduce the time spent on visual review. The objective of this study was to evaluate the performance of a sqEEG-based automatic seizure detection algorithm. Methods: A multicenter cohort of subjects using sqEEG were analyzed, including nine people with epilepsy (PWE) and 12 healthy subjects, recording a total of 965 days. The automatic seizure detections of a deep-neural-network algorithm were compared to annotations from three human experts. Results: Data reduction ratios were 99.6% in PWE and 99.9% in the control group. The cross-PWE sensitivity was 86% (median 80%, range 69-100% when PWE were evaluated individually), and the corresponding median false detection rate was 2.4 detections per 24 hours (range: 2.0-13.0). Conclusions: Our findings demonstrated that step one in a sqEEG-based semi-automatic seizure detection/review process can be performed with high sensitivity and clinically applicable specificity. Significance: Ultra long-term sqEEG bears the potential of improving objective seizure quantification.

Commentary

"If you can't measure it, you can't manage it" is a classical mantra in the corporate and medical world alike. In epilepsy that holds particularly true as seizure counts comprise the most important determinant of clinical decision-making. Yet, due to faulty perception, poor documentation volition or memory impairment, seizure reporting by the patients is representative of reality in approximately 50% of the cases, while seizure reporting by the caregivers does not improve the situation dramatically.[1] Inaccurate reporting may lead to overtreatment in cases where non epileptic spells are misinterpreted as seizures or undertreatment in cases where epileptic events are poorly recognized. Erroneous estimates of seizure control may affect decisions on eligibility to drive or return to school or work. The ramifications may extend beyond clinical practice, as inaccurate seizure counts have been also observed in clinical trials for epilepsy treatments.[2]

This unreliability of seizure self-report has fostered the development of numerous devices for long-term seizure detection.[3-5] Many of them use indirect biomarkers of ictal activity such as accelerometry, electrodermal activity, heart or respiratory rate monitoring, video and audio recordings, and combinations thereof.[5] While useful for convulsive seizures, they tend to fall short in spotting focal unaware seizures.[4,5] Thus, electroencephalography (EEG) remains the cornerstone of seizure monitoring.[1] Among the various EEG options, scalp EEG (eg, prolonged, home-based, EEG monitoring) constitutes the least invasive modality at the cost of low signal quality and poor sustainability for practical purposes. At the other end of the spectrum, intracranial EEG (eg, ambulatory electrocorticography through the responsive neurostimulator) offers high quality signal at the cost of low spatial resolution and invasiveness. To reconcile those priorities, subcutaneous EEG systems have been developed, where limited EEG channels are implanted with a minimally invasive procedure under the scalp to provide long-term recordings.[3] Yet, all these systems face the challenge of data management and analysis to bridge the abundance of the collected data with the need for their timely and accurate interpretation.

The current study[6] investigates the performance of an automatic seizure detection algorithm of sq-EEG (UNEEG Medical A/S, Denmark), a recently launched device with promising potential in recorded EEG signal quality,[7] seizure detection,[8] and forecasting.[9] An "epilepsy" dataset including 9 persons with temporal lobe epilepsy monitored with sq-EEG for 2 to 3 months each was compared to a "control" dataset of

12 healthy persons monitored in the same way for similar duration.[6] The implantation took place unilaterally and the monitoring included mostly nonconvulsive seizures. Three independent clinical experts were used as reviewers utilizing diverse methodology that included a combination of raw EEG analysis and automatically detected software, with and without data reduction utilization. Cross-validation of individual interpretations from each original reviewer was performed by the other reviewers to establish through majority a gold standard against which the automated algorithm could be evaluated. That algorithm utilized a deep neural network model previously trained on a different dataset. Kappa statistics were used to determine the degree of agreement between the patient diaries, the reviewer identified electrographic seizures, and the automated algorithm. The algorithm resulted in substantial data reduction both in the patient and the healthy controls group (approximately 2.2 hours of EEG review per patient per month of recording). The median cross-sensitivity for seizure detection in the patient group was 80% with a false detection rate of 2.4 detections per day. In the healthy control group, the median false detection rate was 0.91 detections per day. Comparison with subject logs demonstrated significant heterogeneity in the agreement between diary entries, electrographic seizures review, and automatic algorithm identifications.[6]

The strongest aspect of this study[6] is its prospect, that is, the use of an automated algorithm for seizure monitoring through a minimally invasive, long-term, subcutaneous EEG technology. Independent experienced reviewers were recruited to evaluate a previously validated through scalp EEG recordings algorithm in patients with epilepsy, utilizing a control group for comparison. Cross-reference with subjective seizure counts was performed. On the other hand, a limited sample of unilaterally but diversly implanted, purely temporal lobe, medication refractory epilepsy cases were tested. Inherent shortcomings of the device such as low channel count, poor brain coverage, and susceptibility to muscle artifact[7-9] were inevitably present. One patient with excessive interictal epileptiform activity was excluded from analysis introducing further selection bias.[6] Raw EEG data were not reviewed in their entirety by all reviewers and agreement by the secondary reviewers was evaluated only on the selections of the original reviewer.[6]

This thought-provoking study[6] raises several practical questions. Can this technology be used to accurately establish a diagnosis? Despite its promise, it is currently tested mostly on patients with drug-resistant temporal lobe epilepsy showing suboptimal inter-reviewer reliability, algorithmic detection sensitivity, and patient log agreement rate. Moreover, the high false detection rate in healthy controls casts doubt about its ability to reliably differentiate epileptic seizures from nonepileptic events. How about epilepsy classification and localization? Albeit not formally tested, its low spatial resolution would unlikely serve such purposes. A potential exception to this contention would be a scalp or intracranial EEG proven bitemporal epilepsy scenario where long-term lateralization of the greatest ictal burden is required to guide future treatments. Can it be used for seizure quantification to assess response to pharmacologic, dietary, and neuromodulatory treatment? In principle, possibly, though the high degree of heterogeneity detected in this study teaches us that one size does not fit all and that a custom-made algorithm adjustable to each patient's electrographic signature may be the way to go. Beyond seizures, can this technology be used to monitor interictal epileptiform activity in age-dependent (eg, childhood absence epilepsy) or state-dependent (eg, benign epilepsy with centrotemporal spikes or electrical status epilepticus in sleep) syndromes where longitudinal assessment of cortical irritability interictally may define clinical decisions on anti-seizure medications withdrawal or escalation? Beyond epilepsy, can it be used for longitudinal monitoring of physiologic functions toward identification of other dynamic neurological diseases (eg, sleep disorders or migraines) or brain computer interfaces for more static neurological conditions (eg, stroke, spinal cord injury, or amyotrophic lateral sclerosis)?[7] The answer to both those last questions is subject to study, but such proposition provisionally appears plausible.

In the grand scheme of things, getting under the skin of seizure monitoring through subcutaneous EEG recordings over the long haul holds great promise to shift away from subjective to objective tally keeping, but it has also ample room for refinement. It remains to be seen how this device compares to other EEG-based and non EEG-based platforms, both as a seizure detection but also as seizure prediction/warning tool. And how such information can impact not only clinical management but also individual and population analytics for research trials design and regulatory decrees on persons living with epilepsy. At the end of the day, the success of such emerging technologies will depend on their usability (ease of application, attractive appearance, low visibility, low intrusiveness) and acceptability (reliability, self-empowerment, data confidentiality and timely technical/clinical support) by the primary stakeholders, namely the patients and their caregivers.[4]

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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