



## Multimodal wrist-worn devices for seizure detection and advancing research: Focus on the Empatica wristbands

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### ABSTRACT

Wearable automated seizure detection devices offer a high potential to improve seizure management, through continuous ambulatory monitoring, accurate seizure counts, and real-time alerts for prompt intervention. More importantly, these devices can be a life-saving help for people with a higher risk of sudden unexpected death in epilepsy (SUDEP), especially in case of generalized tonic-clonic seizures (GTCS). The Embrace and E4 wristbands (Empatica) are the first commercially available multimodal wristbands that were designed to sense the physiological hallmarks of ongoing GTCS: while Embrace only embeds a machine learning-based detection algorithm, both E4 and Embrace devices are equipped with motion (accelerometers, ACC) and electrodermal activity (EDA) sensors and both the devices received medical clearance (E4 from EU CE, Embrace from EU CE and US FDA). The aim of this contribution is to provide updated evidence of the effectiveness of GTCS detection and monitoring relying on the combination of ACM and EDA sensors.

A machine learning algorithm able to recognize ACC and EDA signatures of GTCS-like events has been developed on E4 data, labeled using gold-standard video-EEG examined by epileptologists in clinical centers, and has undergone continuous improvement. While keeping an elevated sensitivity to GTCS (92–100%), algorithm improvements and growing data availability led to lower false alarm rate (FAR) from the initial 72 down to 0.2–1 false alarms per day, as showed by retrospective and prospective analyses in inpatient settings. Algorithm adjustment to better discriminate real-life physical activities from GTCS, has brought the initial FAR of 76 on outpatient real life settings, down to values comparable to best-case clinical settings (FAR < 0.5), with comparable sensitivity. Moreover, using multimodal sensing, it has been possible not only to detect GTCS but also to quantify seizure-induced autonomic dysfunction, based on automatic features of abnormal motion and EDA. The latter biosignal correlates with the duration of post-ictal generalized EEG suppression, a biomarker observed in 100% of monitored SUDEP cases.

### 1. Introduction

The continuous monitoring of epileptic seizures is an increasing aspiration. The gold standard for detecting seizures is video-electroencephalography (v-EEG), although it is impractical for long-term and real-life settings use. Seizure diaries represent the current standard in outpatient studies, but are unreliable, especially for counting seizures that cause loss of consciousness (Karoly et al., 2018), such as primary generalized tonic-clonic and focal to bilateral tonic-clonic (formerly known as secondarily generalized tonic-clonic). In this article, we label these two types as generalized tonic-clonic seizures (GTCS). Wearable

automated seizure detectors can potentially improve existing practice by providing continuous ambulatory monitoring and more accurate seizure counts (Zhao and Lhatoo, 2018). Of paramount importance, connected alert systems may prompt caregivers' intervention during or shortly after a seizure, which can reduce the risk of injuries and sudden unexpected death in epilepsy (SUDEP), particularly elevated after GTCS and when the patient is unattended, e.g., nighttime (Ryvlin et al., 2018; Watkins and Shankar, 2018).

Among non-EEG seizure-monitoring devices, systems combining multiple sensors hold the most promise for increasing sensitivity (Sens) while reducing false alarm rate (FAR) (van Westrhenen et al., 2018;

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Zhao and Lhatoo, 2018; Leijten, 2018). By tracking multiple biosignals, these systems may be useful to assess individual SUDEP risk (Ryvlin et al., 2018); the amplitude of electrodermal activity (EDA) surge accompanying GTCS has been shown to correlate to the duration of post-ictal generalized EEG suppression (PGES) (Poh et al., 2012a), a biomarker of SUDEP (Ryvlin et al., 2013). A rigorous validation of such devices is mandatory to allow their widespread adoption in outpatient settings (Leijten, 2018; Benicky and Ryvlin, 2018).

The Embrace and E4 wristbands (Empatica) are multimodal wearables with the unique capability to capture signs of ongoing GTCS by combining accelerometers (ACC) and EDA data (Boucsein, 2012). Starting from pioneering work at MIT and Boston Children's hospital (Poh et al., 2012b), Empatica developed the first machine learning-based seizure detector on ACC and EDA data acquired with E4, and subsequently transferred the technology to a stand-alone detection and alert system, the Embrace. Both devices received CE medical clearance from the European Union in 2016 (class IIa). Embrace received clearance by the US FDA in 2018 (Class II) for GTCS monitoring during periods of rest for adults and children aged 6 and up. This communication presents an updated summary of seizure detection and monitoring capability relying on EDA and ACC sensors.

## 2. Material and methods

### 2.1. E4 wristband

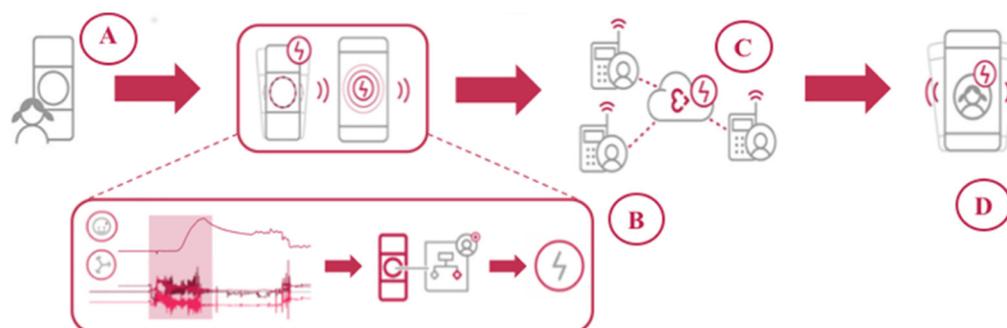
The Empatica E4 wristband embeds 3-axis ACC, EDA, photoplethysmography and temperature sensors ([www.empatica.com/en-eu/research/e4/](http://www.empatica.com/en-eu/research/e4/)). The device is intended for research and comes with a desktop application (E4 Manager) to transfer data to a cloud repository, a web application (Empatica Connect) to view and manage data, and mobile applications to stream, view, and process data in real-time on mobile devices.

### 2.2. Embrace wristband

The Embrace wristband embeds 3-axis ACC, EDA, temperature and gyroscope sensors ([www.empatica.com/en-eu/embrace2/](http://www.empatica.com/en-eu/embrace2/)). Unlike the E4, it runs an embedded machine learning-based GTCS detection algorithm. When a GTCS-like event is detected, the Embrace sends a message to the Alert app, which initiates calls and texts to summon designated caregivers (Fig. 1). A separate mobile application (Mate) automatically records physical activity levels and diary events (detected seizures) and makes it easy for the user to mark false alarms and add missed GTCS or other seizure types. Monthly reports of sleep, activity, and seizure patterns are provided online.

### 2.3. Development of the detection algorithm and performance measure

The detection algorithm uses machine learning artificial intelligence



[D]. The caregivers can be provided with the GPS location of the patient. The alert can be conveniently disabled by the wearer before it is transmitted to caregivers in case of false alarms.

detailed in previous publications (Onorati, Regalia et al., 2017). Briefly:

- 1 ACC and EDA data are processed to compute distinctive features.
- 2 Features and seizure labels are fed to a machine learning algorithm, which learns a decision rule discriminating GTCS from non-GTCS events.

The final, fixed detection algorithm trades off two metrics:

- 1 Maximizing the percentage of detected GTCS, i.e., sensitivity.
- 2 Minimizing the FAR. A reference upper limit for sufferable FAR is ~1–2, but individual tolerability and seizure frequency matter (Van de Vel et al., 2016).

## 3. Results

### 3.1. Inpatient performance evaluation

The detection algorithm has been trained on E4 data from epilepsy patients experiencing GTCS in Epilepsy Monitoring Units (EMUs), labelled by at least 2 qualified epileptologists using gold-standard v-EEG in level IV Epilepsy Centers. Initial retrospective analysis on 16 GTCS from 9 patients achieved Sens = 88% with FAR = 1 (Poh et al., 2012b). In the first attempt to improve performance, analysis on 20 GTCS from 9 patients showed Sens = 95%, with FAR = 2.02 using the original algorithm, and Sens = 95% with FAR = 0.48 for an improved version of the algorithm (Regalia et al., 2015). On bigger data sets (38 GTCS, 18 patients) the algorithm achieved Sens = 92% with FAR = 0.56 (Onorati et al., 2016a) and on 55 GTCS (69 patients, 22 with seizures) Sens = 94.55% with FAR = 0.2, with no false alarms during sleep (Onorati, Regalia et al., 2017).

An additional prospective EMU analysis with a “fixed and frozen” algorithm (undertaken for FDA clearance) on 40 GTC (135 patients, 22 with seizures) showed Sens = 100% with FAR = 0.42 (*unpublished*).

Fig. 2 (top) reports the evolution of the classifier on EMU data.

### 3.2. Outpatient performance evaluation

Much effort has been directed to improve performance in outpatient settings, where data labeling is provided by patient/caregivers' self-reports, and successively reviewed by experts blinded to the caregiver self-reports. Real-life seizure-like activities (e.g., hands clapping, teeth brushing) are the activities most frequently mistaken as GTCS. Testing the detector developed solely on clinical data for outpatients (55 GTCS, 36 patients, 10 with seizures) yielded Sens = 95% with FAR = 6.1. Adding outpatient data into the training set reduced the FAR to 2 (Onorati et al., 2016b). Additional algorithm improvements achieved Sens = 93% with FAR = 0.58 on 111 GTCS (27 outpatients, 14 with seizures) (Caborni et al., 2017).

Fig. 1. Embrace GTCS detection and alert system.

Scheme of Embrace generalized tonic-clonic seizure (GTCS) detection algorithm and alert system. A wristband embedding accelerometry (ACC) and electrodermal activity (EDA) sensors [A] uses machine learning to automatically detect an event based on signatures of ongoing GTCS [B] and sends an alert to a mobile App, which generates a call and text via a cloud-based system [C] directed at designated caregivers to prompt their intervention

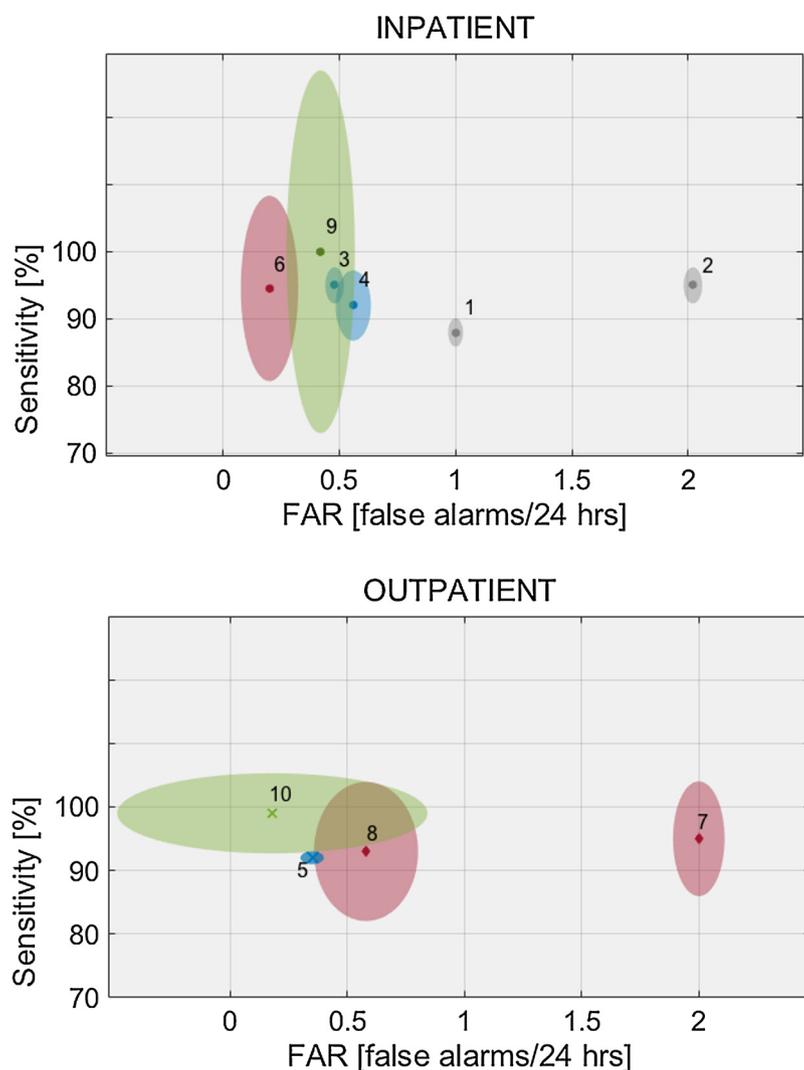


Fig. 2. Evolution of Empatica's GTCS detection algorithms performance.

Evolution of Empatica's GTCS detection algorithms performance in inpatient (top) and outpatient (bottom) settings. False alarm rate (FAR), i.e. number of false alerts on 24 h worn, are shown on the horizontal axes, while Sensitivity, i.e. the percentage of detected GTCS events, are shown on the vertical axes. The colored ellipses indicate the size of the testing set in terms of the total number of patients (vertical axes of the ellipse) and the number of seizures (horizontal axes of the ellipse). Ideally, larger the dataset, more reliable the relative performance. The detection algorithm evolution over time is indicated by the number superimposed on each point:

- [1]: first detection algorithm iteration on 7 patients (16 seizures) (Poh et al., 2012b)
  - [2]: first detection algorithm iteration on 9 patients (20 seizures) (Regalia et al., 2015);
  - [3], [4] and [5]: first (Regalia et al., 2015) and second (Onorati et al., 2016a) detection algorithm iteration tested in inpatient settings and in the first longitudinal outpatient study on one patient with 24 seizures (Picard et al., 2016), respectively;
  - [6]: second detection algorithm iteration tested on 69 inpatients (55 seizures) (Onorati, Regalia et al., 2017);
  - [7] and [8]: third detection algorithm iteration, in which real-life data are exploited in the training phase, tested on 36 patients (55 seizures) (Onorati et al., 2016b) and on 27 patients (111 seizures) (Caborni et al., 2017), respectively;
  - [9] and [10]: last detection algorithm iteration prospectively tested in inpatient settings on 135 patients (40 seizures) (unpublished) and outpatient settings on 3 patients (331 seizures) (Onorati et al., 2018), respectively;
- Legend: - circles, inpatients settings (EMUs); - diamonds, outpatient settings (real-life); - crosses, real-life longitudinal study.

### 3.3. Longitudinal analyses

A real-life longitudinal analysis was made on one patient affected by Dravet syndrome, monitored for 113 days. In this outpatient, 22 out of 24 convulsive seizures were detected (Sens = 92%), with FAR = 0.35 (Picard et al., 2016). Results from three users monitored for more than 1.5 years/each, with a total of 331 GTCS, achieved Sens = 99.4% with FAR = 0.18 (Onorati et al., 2018).

Fig. 2 (bottom) reports the evolution of the classifier on outpatient data. We note that the results above for both inpatients and outpatients improve upon those of devices that use only ACC (Appendix B).

### 3.4. Seizure characterization

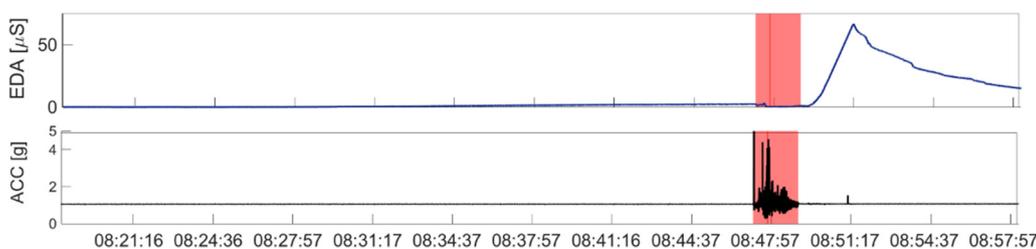
The combination of EDA and ACC is also valuable for objectively characterizing seizures. It has been possible to quantify autonomic dysfunction through the duration of abnormal motion retrieved from ACC sensors, shown to correlate with seizure duration by v-EEG, and through EDA surge evaluation (observed after more than 75% of focal to bilateral tonic-clonic seizures) (Onorati, Regalia et al., 2017). An unusually large EDA surge, consistent with prolonged PGES (Picard et al., 2017), was measured in the first case of a probable SUDEP monitored with Embrace, after the GTCS was detected and an alert was issued (Fig. 3). Despite the emergency call being promptly received by the caregiver, no caregiver was able to arrive before 15 min, at which point CPR failed to resuscitate the youth. The parents had never heard

of the possibility of SUDEP, despite having seen more than six neurologists.

## 4. Discussion and conclusions

Automated detection of GTCS with EDA and ACC wrist-worn sensors has proven effective, yielding high sensitivity (Sens > 92%) and bearable FAR (0.2–1). While the FAR during rest is favorably low, which is important for caregivers' peace of mind, and the sensitivity approaches 100%, which helps mitigate SUDEP risk, the current challenge is to further reduce false alarms during daily activities. Even though current rates in outpatients are promising, larger, prospective, home-based studies with long-term follow-up are needed to more reliably assess the alert/false alarm ratio and to demonstrate the added value of the device on patients' and caregivers' quality of life, as highlighted in a recent review (Van Westrhenen et al., 2018).

The tragic case of SUDEP recorded by Embrace (Picard et al., 2017) illustrates the importance of informing caregivers about both the possibility of SUDEP and the need of a prompt intervention. Thanks to its multimodal capability, Embrace may be also able to provide additional insights into mechanisms of SUDEP and its risk, for instance by informing not only of the occurrence of an alarm but also providing important characteristics of the ictal and postictal periods (Ryvlin et al., 2018). Moreover, multiple sensors open new research avenues, including possible detection of additional seizure types, algorithm personalization, and seizure forecasting.



**Fig. 3.** Electrodermal activity and motion signals related to a terminal seizure.

Continuous multimodal data measured by Embrace before, during, and ten minutes after a terminal seizure happened during sleep to a patient whose case has been reported in Neurology (Picard et al., 2017) to raise SUDEP awareness. Embrace detected and

alerted the caregivers to the event; however, the caregivers did not know about SUDEP and thus they were not aware that it was important to arrive within minutes. Top: Electrodermal activity (EDA), showing a significant surge upon the terminal seizure. Bottom: Physical movement derived from 3-axis accelerometers (ACC); the red highlighted region marks the time of convulsions. The thin vertical red line is when Embrace detected the seizure. Adapted from Picard et al., 2017 Neurology 89(6): 633–635.

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## Appendix A. - Tolerability and safety

The only known risks of using Empatica E4 and Embrace devices are rare cases of mild local skin irritation. All parts in contact with patients' skin passed tests showing conformity with ISO10993. Electrical safety tests performed in conformity with IEC60601-1 and electromagnetic compatibility tests performed in conformity with IEC60601-1-2 4<sup>th</sup> Edition, showed full compliance.

## Appendix B. – ACC-based wrist-worn detectors

Two other marketed-for-epilepsy wrist-worn detectors, neither FDA cleared, use ACC data to detect “shakes”. The Epi-Care Free/Mobile (Danish Care Technology, Sorø, Denmark) is a wristband (CE-mark, available in Europe only), with reported inpatient Sens = 90% with FAR = 0.2 (Beniczky et al., 2013), and outpatient Sens > = 90% (for 86% of patients) with FAR 0–12 (Meritam et al., 2018). The algorithm SmartWatch Inspyre (Smart Monitor, San Jose, California, USA) reports inpatient Sens = 31% (Patterson et al., 2015) and Sens = 92% (Velez et al., 2016), without disclosing FAR. Note that by allowing sensitivity to increase, FAR increases arbitrarily. Apart from FDA approval, the main differences between these devices and Embrace are that they employ only ACC and do not exploit robust machine learning to provide better Sens and FAR performance.

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