Wearable devices for seizure detection: state of the art and future perspective

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Outline:

- Why do we need seizure detection using wearable devices?
- How do we know they work?
- Validated devices
- ILAE-IFCN Clinical Practice Guideline

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Why do we need automated seizure detection?

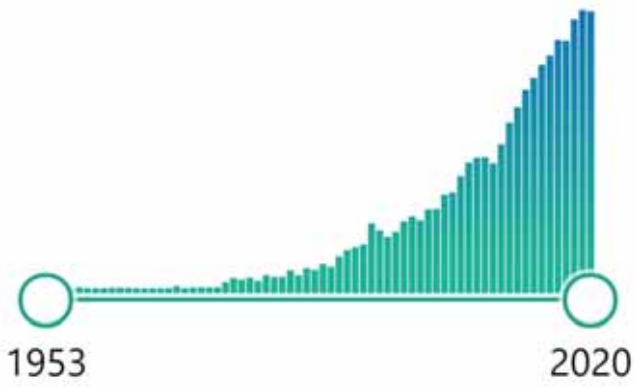
- Intervention and prevention:
  - Seizures lead to injuries;
  - GTCS = major risk factor for SUDEP.
  - Closed loop systems (trigger on-demand therapy).
- The unpredictable nature of seizure-occurrence: distressing & disabling for patients / caregivers → social isolation & decreased QOL.
- 47-63% of seizures: unrecognized by patients →

  Therapeutic decisions / drug-trials: unreliable data.
- Unreported seizures:
  - Daytime: 32%; Nocturnal: 85% not reported
  - CPS: 73%; sGTCS: 42% *(Hoppe et al. 2007)*
- Large patient-survey studies: need for wearable seizure monitoring – also outside the hospitals!

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- Many published papers!
  - Seizure detection: 11388
  - Using wearables: 194
- Do they **REALLY** work?
- What is the level of evidence for these devices?



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Accepted: 30 October 2017
DOI: 10.1111/epi.14049

SUPPLEMENT ARTICLE

Epilepsia

Standards for testing and clinical validation of seizure detection devices

Sándor Beniczky[1] | Philippe Ryvlin[2,3]

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Key features	Design
Subjects	Simulated data or healthy subjects → Low number of patients with seizures → High number of patients with seizures
Recordings	Conventional method → Dedicated device
	Discontinuous → Continuous
	Single center → Multicenter
	Retrospective → Prospective
Analysis & alarms	Training & testing using the dataset → Predefined algorithm and cutoff values
	Offline (after the recording) → Real time (simultaneous with the recording)
	Not blinded → Blinded
Reference standard	None → Information from patient and caregiver → Video or Video-EEG recordings

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Study design	Phase 0	1	2	3	4
Subjects					
Simulation/ healthy subjects	+	±	–	–	–
Number of patients with seizures	–	≥1	≥10	≥20	≥50
Number of seizures	–	≥1	≥15	≥30	≥75
Recordings					
Conventional methods	±	±	–	–	–
Dedicated device	±	±	+	+	+
Continuous	±	±	±	+	+
Multicenter	±	±	±	+	na
Offline/retrospective	+	+	+	–	–
Analysis & alarms					
Training & testing using the dataset	+	+	+	–	–
Predefined algorithm and cutoff values	–	–	–	+	+
Real time	–	–	–	+	+
Blinded	–	–	–	+	+
Reference standard					
Video or video-EEG recordings	±	+	+	+	±
Information from patient and caregivers	±	–	–	–	±

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Received: 29 September 2020 | Revised: 23 December 2020 | Accepted: 23 December 2020
DOI: 10.1111/epi.16818

Epilepsia

SPECIAL REPORT

Automated seizure detection using wearable devices: A clinical practice guideline of the International League Against Epilepsy and the International Federation of Clinical Neurophysiology

Sándor Beniczky[1,2] | Samuel Wiebe[3] | Jesper Jeppesen[4] | William O. Tatum[5] | Milan Brazdil[6,7] | Yuping Wang[8] | Susan T. Herman[9] | Philippe Ryvlin[10]

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ILAE-IFCN Clinical Practice Guideline

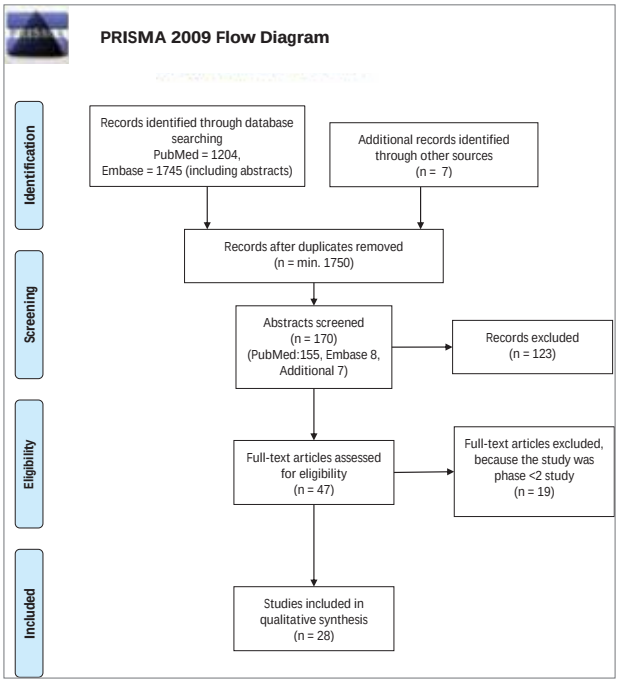
- Working group appointed by the two societies
- ILAE methodology for guideline development (PRISMA → GRADE)
- Public comments (ILAE homepage for 2 months)
- Reviewed by the International Bureau for Epilepsy
- Endorsed by both societies (ILAE & IFCN)

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Evaluation of evidence

- Search in PubMed & EMBASE
- Until October 16th 2019
- Validation studies, phase 2-4



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Automated seizure detection wearables: Validation studies

- **GTCS (including FBTCS)**
  - Phase-3: 3 studies (accelerometer, sEMG, multimodal); phase-4: 2 studies
  - Sensitivity: 90-96%
  - FAR: 0.2-0.7/24-hrs. (0.03/night)

- **Other seizure-types (non-convulsive)**
  - Only phase-2 studies
  - Sensitivity: over 90%
  - FAR: 1-500/24-hrs.
  - Promising results with wearable EEG, ECG (HRV)

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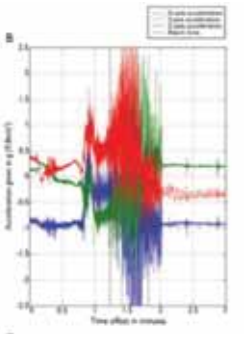
Accelerometry: EpiCare

Study design: Phase 3

- Multicenter
- Prospective, blinded
- Real-time analysis
- Pre-defined cut-off & algorithm
- 73 patients (39 GTCS in 20 patients)
- Gold standard: epilepsy monitoring unit

Results:

- Sensitivity: 90%
- Mean latency: 55 seconds
- False alarm rate: 0.2 per day





Beniczky S, et al. *Epilepsia* **2013;59:53–60**

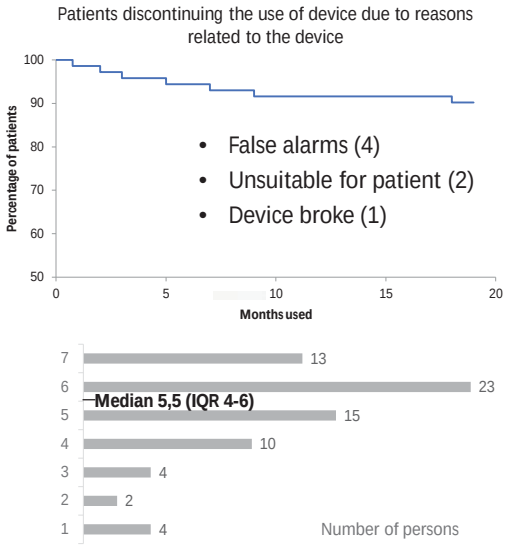
Accelerometry: EpiCare

Study design: Phase 4

- In-field study: 15-item questionnaire
- Modified after IBM´s Post-Study System-Usability Questionnaire
- 71 patients who have been using EpiCare

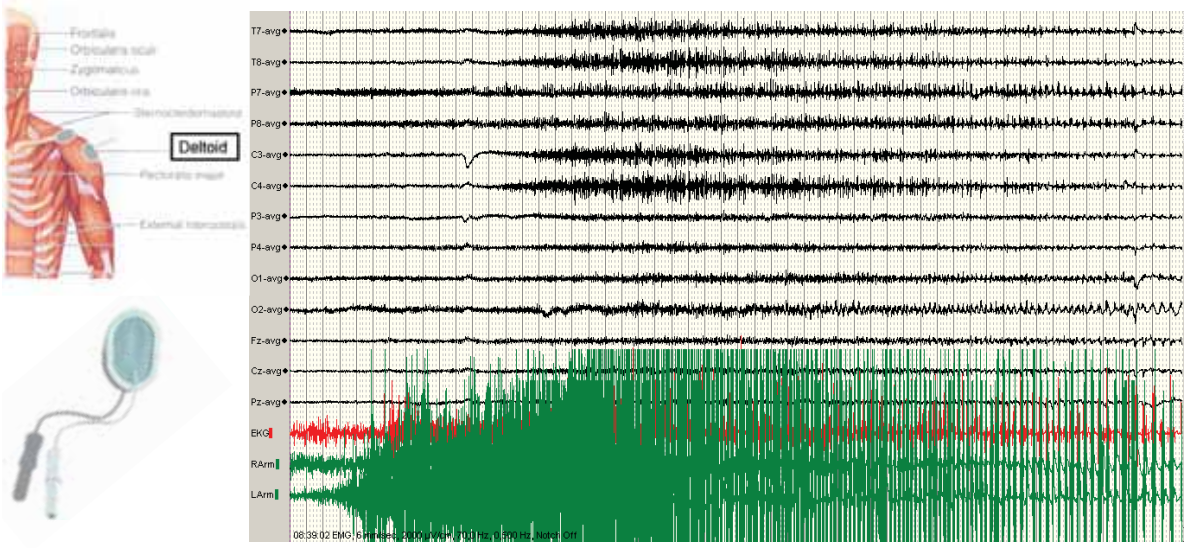
Results:

- Stopped using it due to reasons related to the device: 7 patients
- Usage: median 15 months (24 days - 6 years)
- Performance: similar to Phase 3
- Influenced logs in seizure-diary: 55%
- Decreased seizure-related injuries: 40%



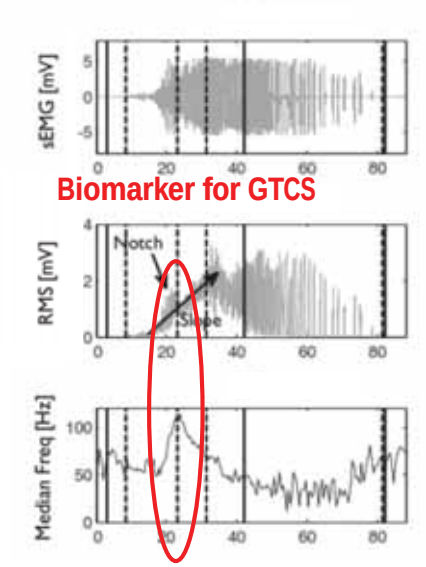
Meritam P, et al. Epilepsia 2018; 59:48-52

Surface electromyography

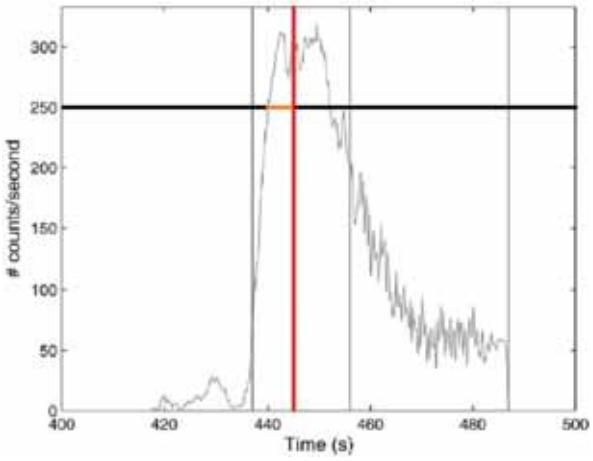


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Conradsen I, et al. *Epilepsy Res* 2013;104:84–93



Conradsen et al., IEEE Trans Biomed Eng. 2012

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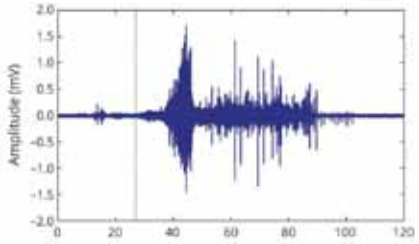
Surface-EMG: SeizureLink

Study design: Phase 3

- Multicenter
- Prospective, blinded
- Real-time analysis; pre-defined cut-off
- 71 patients (32 GTCS in 20 patients)
- Gold standard: epilepsy monitoring unit

Results:

- Sensitivity: 94%
- Median latency: 9 seconds
- False alarm rate: 0.7 per 24 hours (0.01 per night)



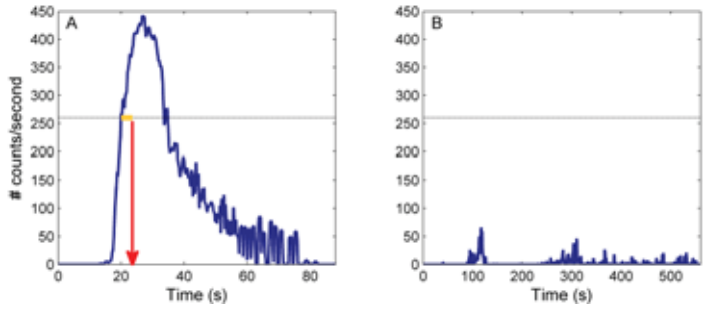


Beniczky S, et al. *Neurology* 2018; 90:e428-e434.

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Automated distinction between epileptic and non-epileptic convulsive seizures



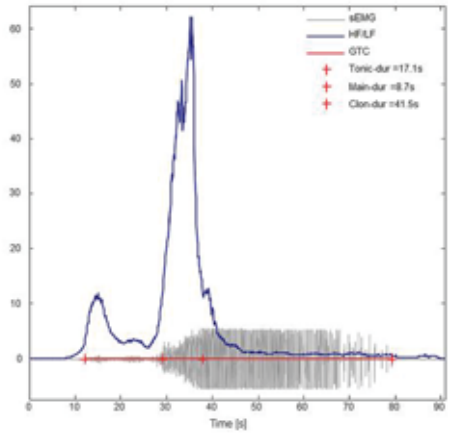
The sEMG-biomarker (algorithm)
distinguished GTCS from convulsive PNES with an overall accuracy of 95%

Beniczky S, et al. *Ann Neurol* 2015;77:348–351

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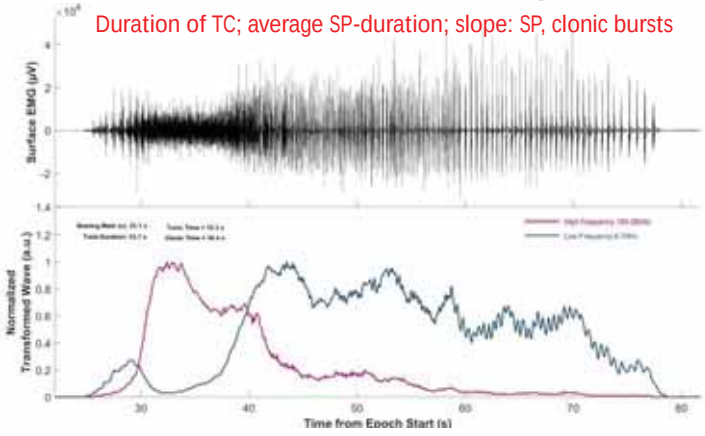
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Automatic measurement: duration of GTCS; T & C phase



Conradsen et al., Epilepsy Res. 2013

Duration of TC; average SP-duration; slope: SP, clonic bursts

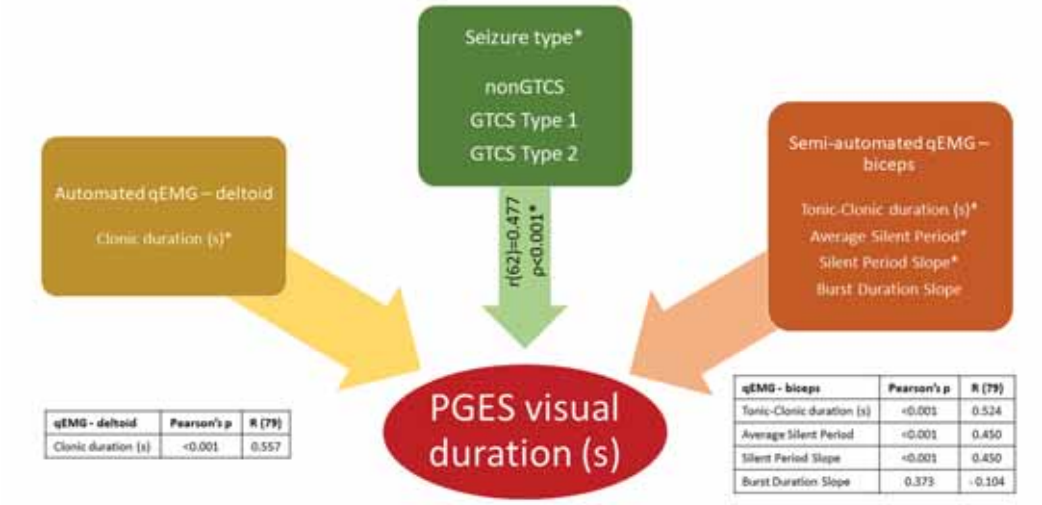


Cardenas et al., J Clin Neurophysiol. 2019

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Arbune et al., Neurology 2020



qEMG - deltoid	Pearson's p	R (79)
Clonic duration (s)	<0.001	0.557

qEMG - biceps	Pearson's p	R (79)
Tonic-Clonic duration (s)	<0.001	0.524
Average Silent Period	<0.001	0.450
Silent Period Slope	<0.001	0.450
Burst Duration Slope	0.373	-0.104

ML: EMG-based algorithm for identification of long-PGES / Accuracy = 85%

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Accelerometry+HR: **Nightwatch - Limitation: only nocturnal**

Study design: Phase 3+4

- Multicenter
- Prospective, blinded
- Real-time analysis; pre-defined cut-off
- 28 patients (14 previously in the training group)
- Gold standard: video surveillance (nurse)

Results:

- Sensitivity:
  - 81% - GTCS
  - 77% - other major motor seizures
- False alarm rate: 0.03 per night



Arends J, et al. *Neurology* **2018; 91:e2010-e2019**

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Accelerometry+EDA: **Embrace**

Study design: Phase 2

- Multicenter
- Prospective recording
- Off-line analysis; no pre-defined cut-off
- Cross-validation
- 69 patients (22 with GTCS)
- Gold standard: epilepsy monitoring unit

Results:

- Sensitivity: 95%
- FAR: 0.2 / 24 hrs



Poh MZ, et al. *Epilepsia* 2012;53:e93–97;
Onorati F, et al. *Epilepsia* 2017;58:1870–1879

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How to detect non-motor seizures using non-invasive wearable devices?



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Compelling evidence for scalp electroencephalography



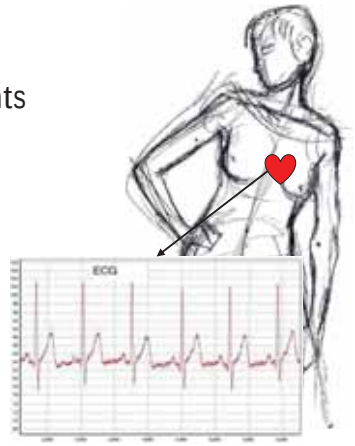
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Electrocardiogram / heart rate variability

- Changes in heart rate associated to seizures: 82% of patients
- Easy to measure
- Electrodes can be hidden under the clothes

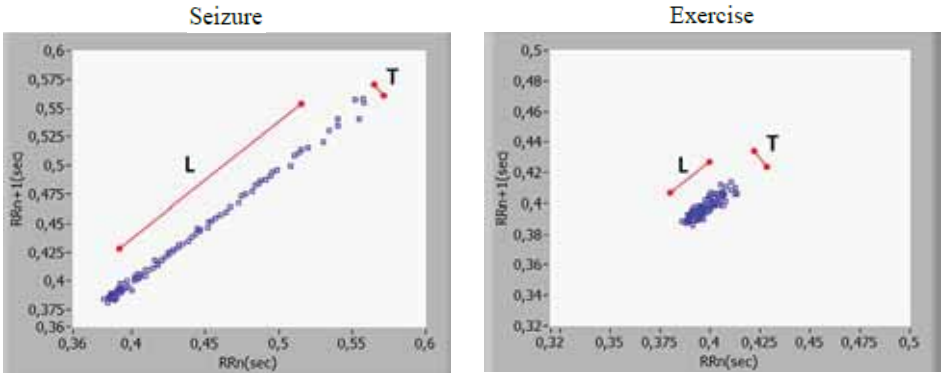
Jeppesen et al., Seizure 2014



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HRV-based seizure-detection: Modified CSI



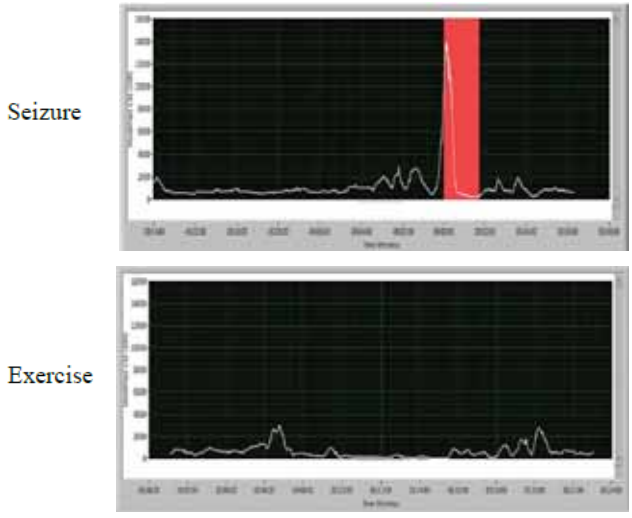
- CSI: L/T
- Modified CSI: L^2/T (calculated from 100 consecutive RRs)

Jeppesen et al., Seizure 2015

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HRV-based seizure-detection: Modified CSI-100



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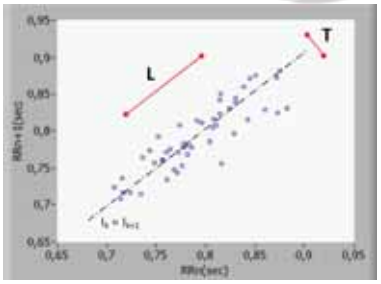
Surface-ECG / HRV: ePatch

Study design: Phase 2

- Multicenter; prospective recording; off-line analysis
- Training dataset: 100 pts (18 GTCS; others: NCS)
- Testing dataset: 39 pts – independent from the training set
- Gold standard: epilepsy monitoring unit
- Responders: predefined as ictal HR change >50bpm

Results: works in those with autonomic changes

- Training dataset
  - Responders: 53%
  - Sensitivity-NCS: 93%
  - Sensitivity-GTCS: 94%
  - FAR: 1 / 24 hrs
- Testing dataset
  - Responders: 57%
  - Sensitivity-NCS: 81%
  - Sensitivity-GTCS: 90%
  - FAR: 1 / 24 hrs





Jeppesen J, et al.

Epilepsia **2019 & Epilepsia 2020**

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HRV vs. GTCS & PGES

- GTCS - postictal
  - Increase in sympathetic activity (*CSI; LF/HF power; only GTCS*)
  - Decrease in parasympathetic activity (*HF power; RMSSD; also other motor sz.*)
  - Marked increase in HR-mean

- Prolonged PGES (>20 s)
  - Postictal: increase in HR-mean (sympathetic increase & parasympathetic decrease)
  - Preictal: decrease in HF power (parasympathetic decrease)

Arbune et al., Epilepsia 2020

Two relevant papers published after the guideline

Photoplethysmography: HR+oxygen saturation

Study design: Phase 3

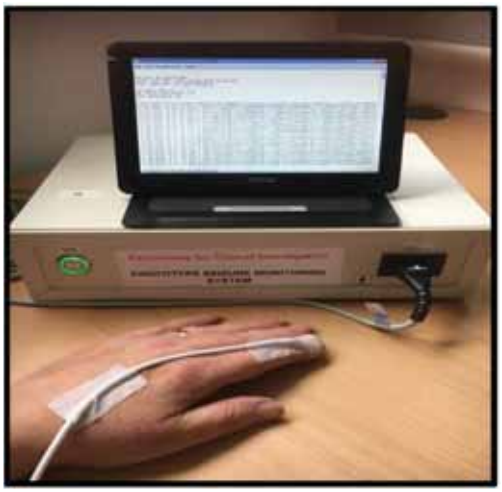
- Multicenter
- Prospective recording, real-time analysis
- 119 patients (77 seizures)
- Gold standard: epilepsy monitoring unit

Results:

- Sensitivity=87%
- FAR: 4.5 / 24 hrs.

Concerns:

- Not really a wearable. Mobility restricted
- Mainly the >25% HR-change makes the algorithm



Brotherstone, et al. *Seizure* **2020;82:109-117**

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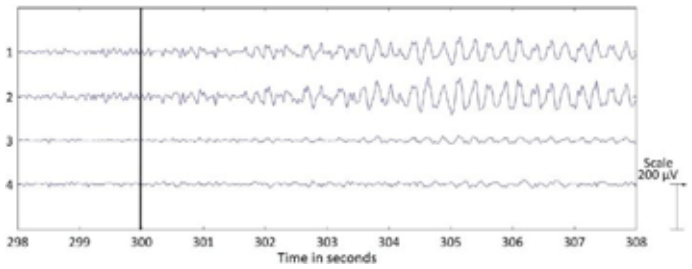
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Behind-the-ear EEG electrodes

- Phase-I study
  - Retrospective
  - Conventional electrodes and amplifier
  - Cross-validation
  - 54 patients - 42 with 182 seizures (mainly temporal lobe seizures with impaired awareness)
  - Patient-specific algorithm
- Sensitivity=63.4%; FAR=0.8/24h

(Vandecasteele et al. Epilepsia 2020; 61:766-775.)





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GRADE

Factor	Considerations	GTCS	Non-convulsive
Detection accuracy	Quality/ level of evidence	High	Moderate
Balance between desirable and undesirable effects	Do desirable effects (seizure detection) outweigh undesirable effects (false alarms, burden of usage)?	Yes	Uncertain
Values and preferences	Do patients, caregivers and healthcare personnel need wearable seizure detection devices?	Yes	Yes
Wise use of resources	Does currently available automated seizure detection provide input for meaningful outcome (prevention of injuries or SUDEP, objective seizure quantification) or increase in the quality of life?	Uncertain	No

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Recommendations for automated seizure detection using WD

The ILAE-IFCN Working Group

- **Recommends using clinically validated wearable devices for automated detection of GTCS (including FBTCS) when significant safety concerns exist, especially in unsupervised patients who do not share a bedroom, but where alarms can result in rapid intervention, within 5 minutes (weak / conditional recommendation).**
- **At present, does not recommend clinical use of the currently available wearable devices for seizure types other than GTCS and FBTCS, as more research and development are needed for this application (weak / conditional recommendation).**

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Need for further research & development:

- 1) To increase the performance of wearable devices and detection algorithms, especially for non-convulsive seizures.
- 2) To decrease the false alarm rate (even off-line), allowing objective documentation of seizure frequency.
- 3) To conduct properly designed clinical validation studies.
- 4) In-field (phase 4) studies are needed to demonstrate whether automated seizure detection leads to meaningful clinical outcomes, such as decreased morbidity and mortality associated with seizures, objective seizure quantification, improved quality of life.

Summary and take-home message

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Evidence for motor seizure (generalised tonic-clonic seizure)

- Phase 3 validation studies:
  - Accelerometry
  - Electromyography
  - Multimodal / accelerometry and heart rate





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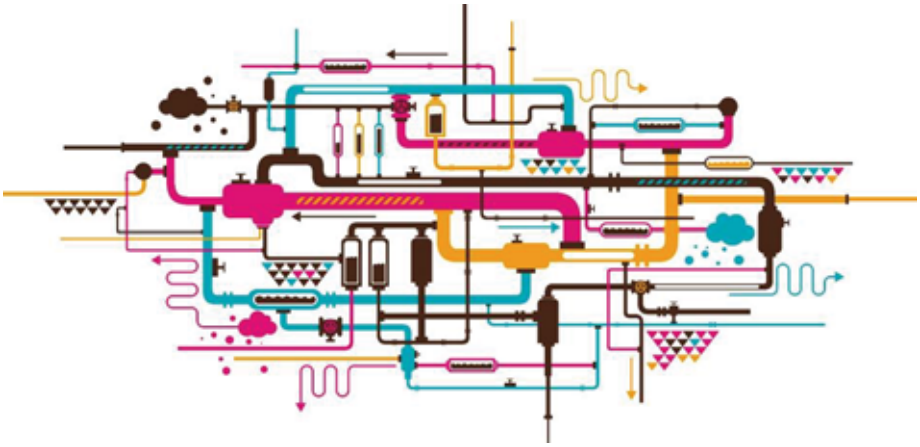
Promising results for focal non-convulsive seizure

- Phase 2 validation studies:
  - Electrocardiogram / heart rate variability / photoplethismography
- Phase 3 validation study:
  - Photoplethismography (HR+oxygen saturation)





Everything else is still in development



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