Wearable devices to detect epileptic seizures: lessons from the SeizeIT trials

Prof dr Wim Van Paesschen

UZ Leuven

Disclosures

- Wim Van Paesschen is the principal investigator of the SeizeIT2 trial, which is an academic trial, of which the University Hospitals Leuven are the sponsor
- No commercial interests in UCB Pharma or Byteflies

SeizeIT trials

CORE TEAM



Gergely Vertes, MBA
Solution accelerator lead
UCB



Hans Danneels, PhD
CEO & co-founder
Byteflies



Wim Van Paesschen, MD PhD
Head of Epilepsy Research
UZ Leuven



Hans De Clercq, PhD
CTO & co-founder
Byteflies



Bori Hunyadi, PhD
Postdoctoral Researcher
KU Leuven



Steven Vandeput, PhD
Innovation manager
KU Leuven

- Aim: develop a wearable device to detect epileptic seizures
- SeizeIT1: IMEC-Icon: 2016-18
  - Standard video-EEG equipment
- SeizeIT2: EIT Health: 2019-2022
  - Sensor-Dot

Mobile health and digital biomarkers

- The application of sensors, mobile apps, social media and location-tracking technology to obtain data pertinent to wellness and disease diagnosis, prevention and management
- Seize-IT: application of mobile health and digital biomarkers in epilepsy



Sim I. Mobile Devices and Health. N Engl J Med. 2019 Sep 5;381(10):956-968

Why do we need wearables to detect seizures ?

- Seizure under-reporting
  - Management of the individual patient
    - Incorrect adjustment of anti-epileptic medication
    - Granting permission to drive a car to patients who are not seizure-free
  - Clinical trials
    - Decrease of the statistical power of associated clinical trials
- Prevention of sudden unexpected death in epilepsy (SUDEP)
- Seizure prediction/forecasting

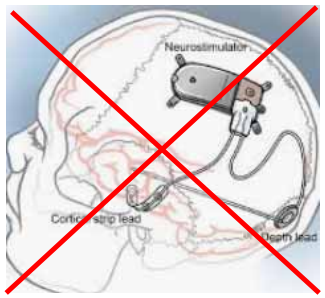
Elger CE and Hoppe C, Lancet neurology 2018;17:279-88

Wearables for automated seizure registration: patients's wants and needs

Variable		%
Ready to use automated seizure registration		94%
Ready for appointments with neurologist for device control		97%
Preference for devices which are removable at any time		91%
Ready to carry removable device		98%
	Wristband	90%
	Hat/cap	16%
Ready to use patch electrodes		47%
	Chest	98%
	Face	16%
Ready to get device implanted into the brain		16%
Seizure prediction is (very) important		76%
Device can generate emergency calls		58%
Device can document seizures		46%

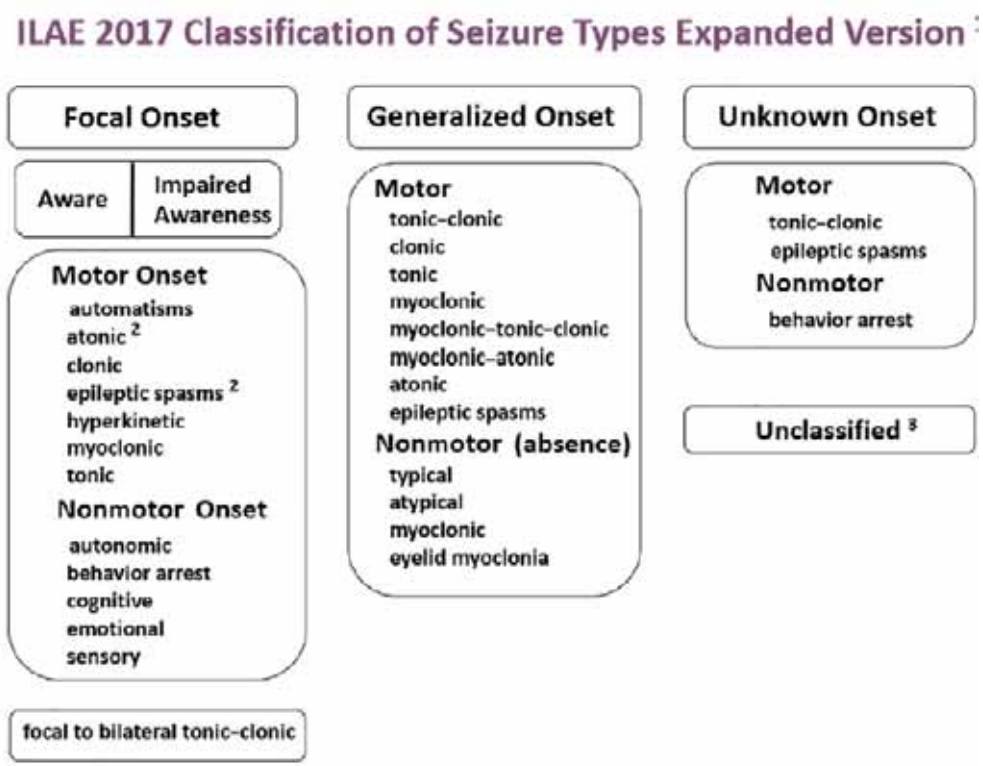






Hoppe C et al. Novel techniques for automated seizure registration: Patients' wants and needs. Epilepsy Behav. 2015 Nov;52(Pt A):1-7

Seizure classification



Scheffer IE et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-521.

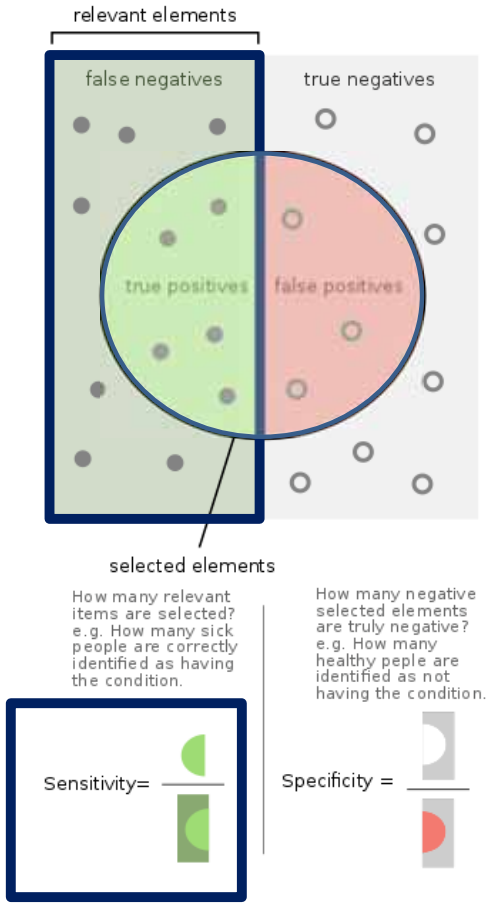
	FOCAL					GENERALIZED					
	simple				complex	absence	tonic-clonic	myoclonic	clonic	tonic	atonic
	temporal lobe	frontal lobe	parietal lobe	occipital lobe							
impairement of conscousness					yes	brief	yes				
motor aura		hyperkinetic behavior, clonic movements			diverse		muscle rigidity, convulsions	sporadic jerking movements	repetitive jerking movements	muscle stiffness rigidity	loss of muscle tone
sensory aura	olfactory hallucinations	sensory hallucinations	sensory hallucinations: paraesthesiae, painful sensations, numbness, somatic illusions	visual illusions and hallucinations							
psychic aura	anxiety, déjà vu										
autonomic aura	**tachycardia, bradycardia, hyperventilation, sweating,** sialiorhea, rising epigastric sensation										
ictal EEG changes	**ictal EEG changes in ~30%**				**ictal EEG changes in 40-60%**	**generalized spike and wave discharges in 100%**	**generalized ictal discharges in 100%**	**generalized ictal discharges (often also muscle artifact)**	**generalized ictal discharges**	**paroxysmal fast activity in 100%**	

Digital biomarkers

- SeizeIT1: EEG and ECG
- SeizeIT2: EEG, ECG, motion and EMG

F1-score

- Sensitivity = True positives/ (True positives + False negatives)
- Positive predictive value (PPV) = True positives/ (True positives + False positives)
- F1-score = 2x (Sensitivity x PPV)/ (Sensitivity + PPV)
  - Values: 0 to 1
  - Enables comparison between devices



Kurada et al. Seizure 2019; 66: 61-69

	Generalized tonic-clonic seizures		e types
Seizure forecasting/prediction			
Online detection of seizures with alarm function	√		
Offline seizure detection/seizure logging			

	Tonic clonic seizures
	ACM- and EMG-based devices (Epicare, Nightwatch, Epilert)
Sensitivity	89%
Positive predictive value	55%
F1-score	0.68

Verdru J, Van Paesschen W. Wearable seizure detection devices in refractory epilepsy. Acta Neurol Belg. 2020 Dec;120(6):1271-1281.

SeizeIT1: Comparison between Scalp EEG and Behind-the-Ear EEG for Development of a Wearable Seizure Detection System for Patients with Focal Epilepsy

- N=12 patients with focal seizures with ictal EEG changes on scalp EEG
- Visual recogniton of seizures on behind-the-ear EEG is possible
- Automatic seizure detection based on support vector machine (SVM) showed comparable seizure detection performance
  - scalp EEG: median sensitivity of 100% and a false detection rate of 1.14 per hour
  - behind-the-ear: median sensitivity of 94.5% and a false detection rate of 0.52 per hour.

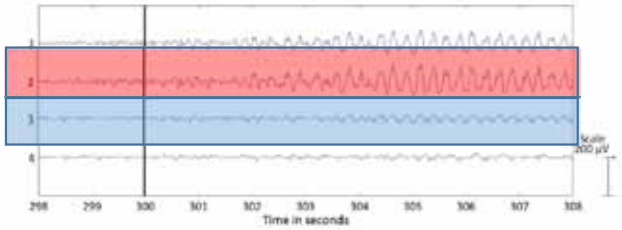


FIGURE 2 Left temporal lobe seizure recorded with behind-the-ear electroencephalographic (EEG) setup. The four bipolar EEG channels are shown over a period of 10 seconds: (1) crosshead 1, (2) crosshead 2, (3) unilateral left, (4) unilateral right. The bipolar EEG channels were filtered with a bandpass filter (1-25 Hz). The black horizontal line at 300 seconds depicts the seizure onset

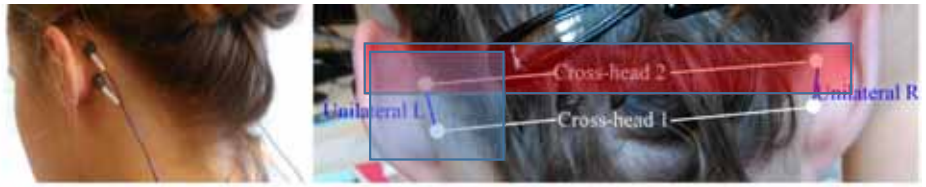


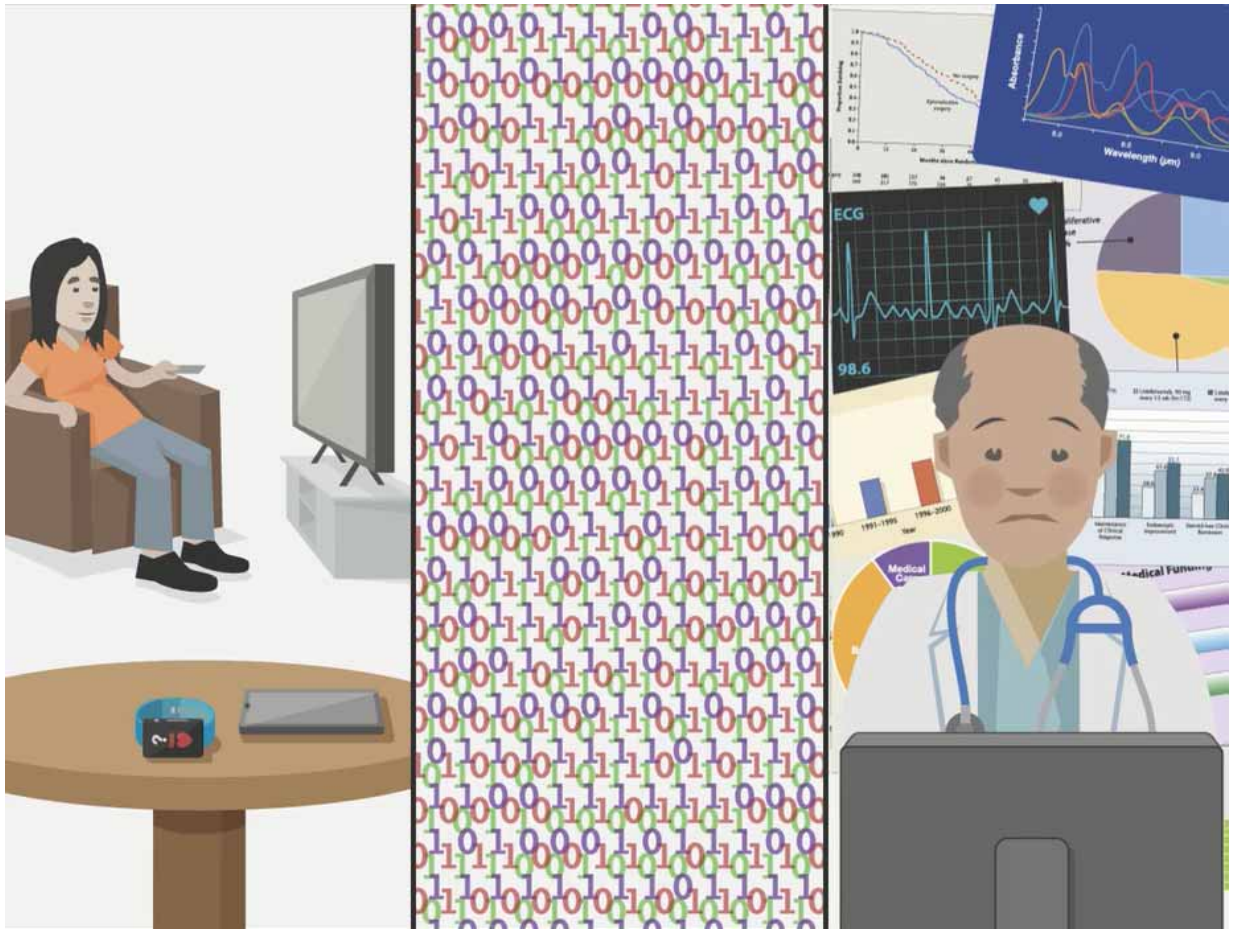
FIGURE 1 Behind-the-ear electroencephalographic setup. Left panel shows extra behind-the-ear electrodes glued to the skin. Right panel shows bipolar channel derivations. Reproduced with permission from Gu et al[14]

Gu Y, Cleeren E, Dan J, Claes K, Van Paesschen W, Van Huffel S, Hunyadi B. Comparison between Scalp EEG and Behind-the-Ear EEG for Development of a Wearable Seizure Detection System for Patients with Focal Epilepsy. Sensors (Basel). 2017 Dec 23;18(1).

Multimodal focal epileptic seizure detection based on ECG and behind-the-ear EEG (SeizeIT1)



Kaat Vandecasteele



Sim I. Mobile Devices and Health. N Engl J Med. 2019 Sep 5;381(10):956-968

Byteflies

Byteflies sensor dot: multimodal wearable



The smallest multimodal device on the market

- EEG
- ECG
- EMG
- Motion

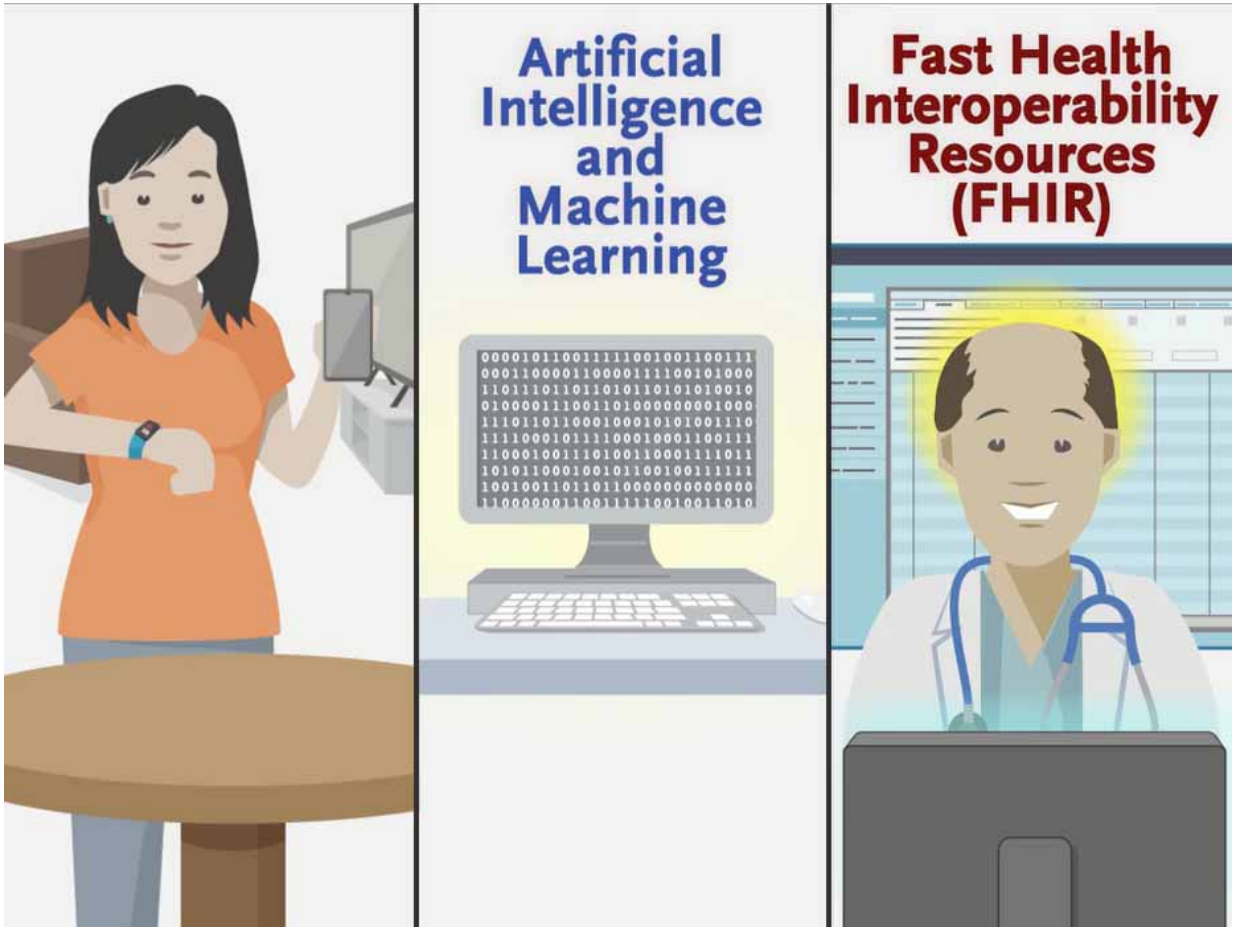












Sensor-Dot is a medical device

Neurologist knows epilepsy syndrome and advises Sensor-Dot set-up

Sensor-Dot data are read offline, reduced in size by AI-algorithms, which have a high sensitivity

Neurologists review seizure data, and discard false-positive detections

Data storage in electronic health records

Sim I. Mobile Devices and Health. N Engl J Med. 2019 Sep 5;381(10):956-968

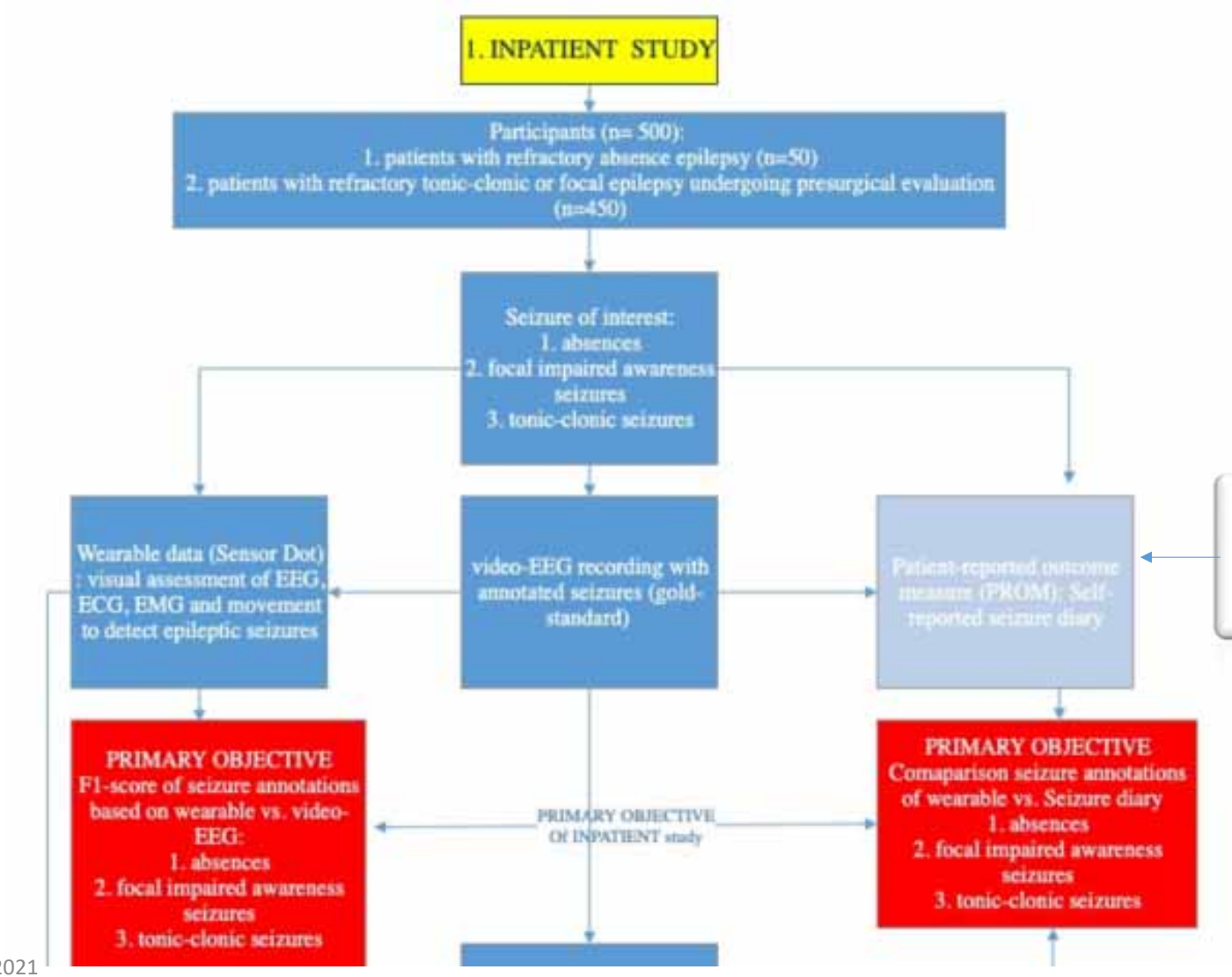
SeizeIT study 2 (EIT Health): An academic multicenter study to examine clinical scenarios for long-term monitoring of epileptic seizures with a wearable biopotential technology

- Recruitment starte DELAYED 2020
- Target: 500 patients
- Objectives:
  - Sensor-Dot detection of
    - Typical absence seizures,
    - Focal impaired awareness seizures,
    - Tonic-clonic seizures
  - Development of automatic seizure detection algorithms
- Measures
  - Hospital video-EEG (gold standard)
  - Sensor-Dot measurements
  - Patient seizure diary



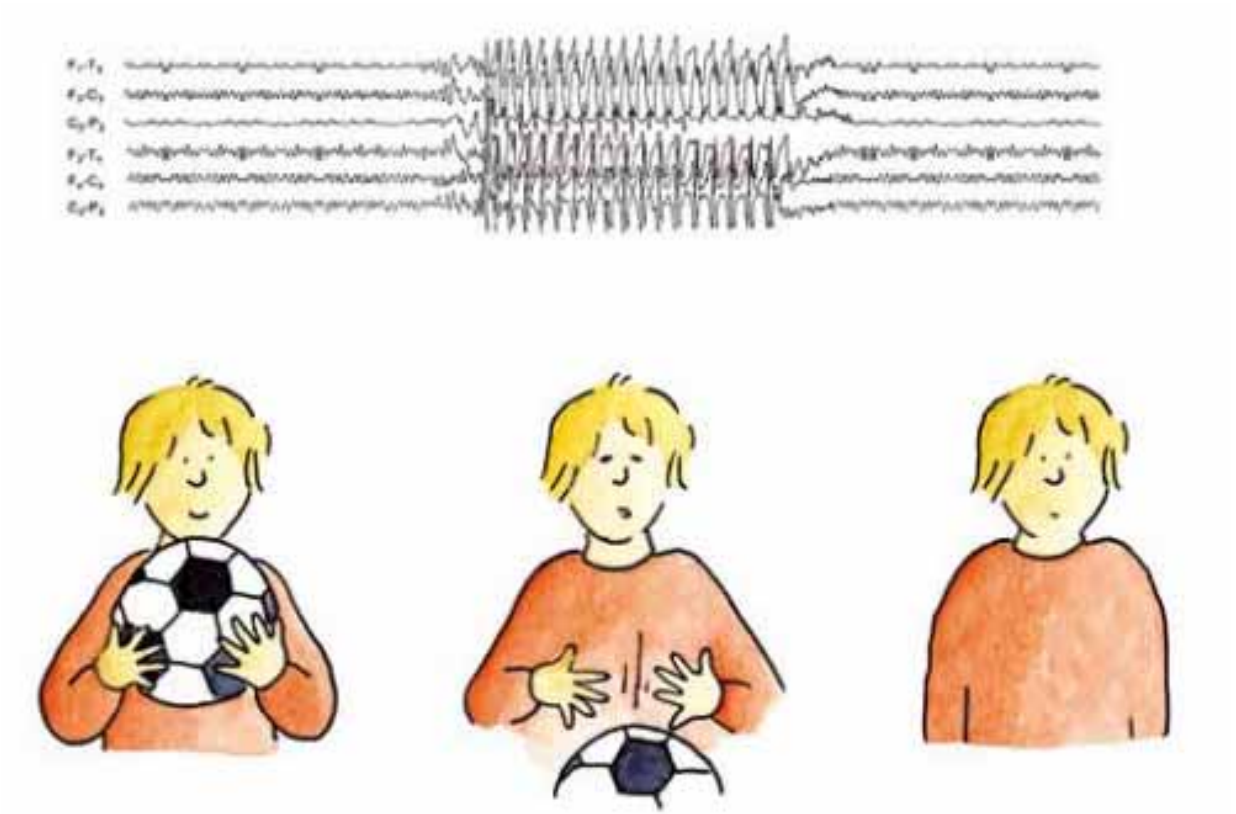
eit Health

Funded by the European Union


1. INPATIENT STUDY
Participants (n= 500):
1. patients with refractory absence epilepsy (n=50)
2. patients with refractory tonic-clonic or focal epilepsy undergoing presurgical evaluation (n=450)
Seizure of interest:
1. absences
2. focal impaired awareness seizures
3. tonic-clonic seizures
Wearable data (Sensor Dot) : visual assessment of EEG, ECG, EMG and movement to detect epileptic seizures
video-EEG recording with annotated seizures (gold-standard)
Patient-reported outcome measure (PROM): Self-reported seizure diary
PRIMARY OBJECTIVE
F1-score of seizure annotations based on wearable vs. video-EEG:
1. absences
2. focal impaired awareness seizures
3. tonic-clonic seizures
PRIMARY OBJECTIVE Of INPATIENT study
PRIMARY OBJECTIVE
Comaparison seizure annotations of wearable vs. Seizure diary
1. absences
2. focal impaired awareness seizures
3. tonic-clonic seizures


h
Helpilepsy

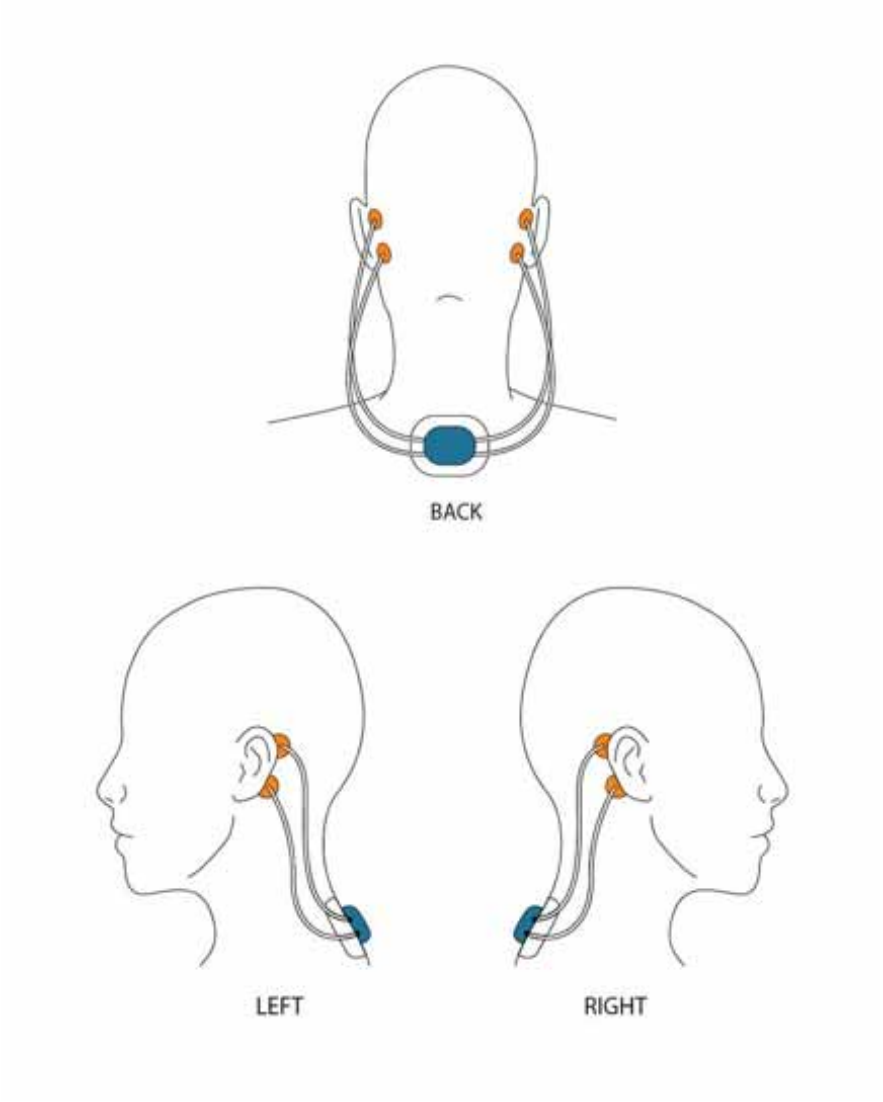
Typical absences



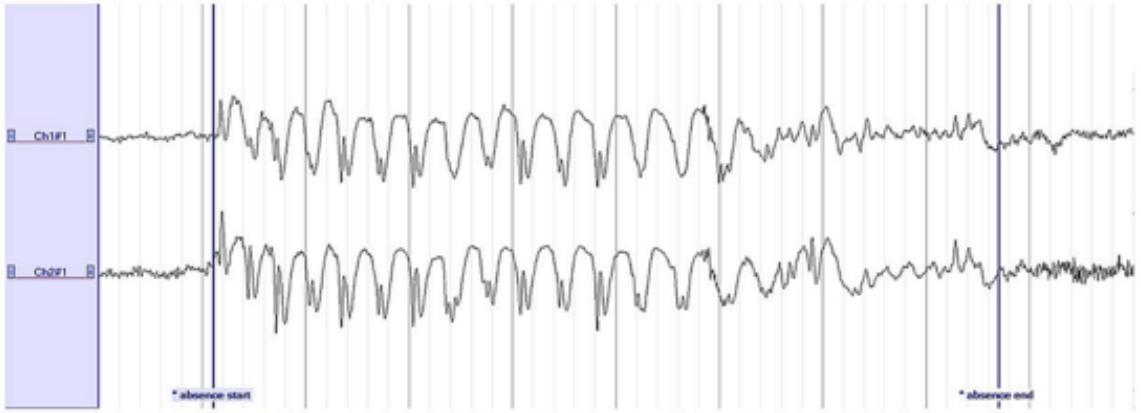
https://assets.uzleuven.be/files/2019-12/epilepsie.pdf

In-hospital typical absence study

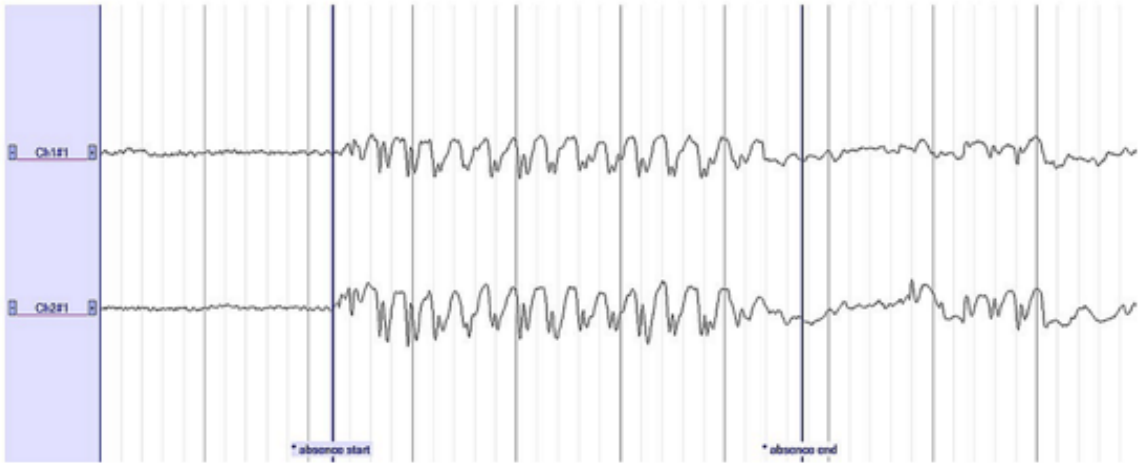
- N= 12
- Median age: 20 years (9-50)
- Gender: 7 women, 5 men
- Median age at epilepsy onset: 9 years (6-22)
- Epilepsy syndrome
  - Juvenile absence epilepsy: n=8
  - Childhood absence epilepsy: n=2
  - Juvenile myoclonic epilepsy: n=2
- Absences: defined as 3 Hz spike and wave discharge lasting ≥ 3 seconds: n= 283


BACK
LEFT
RIGHT

A


Ch1#1
Ch2#1
* absence start
* absence end

B


Ch-1#1
Ch-2#1
* absence start
* absence end

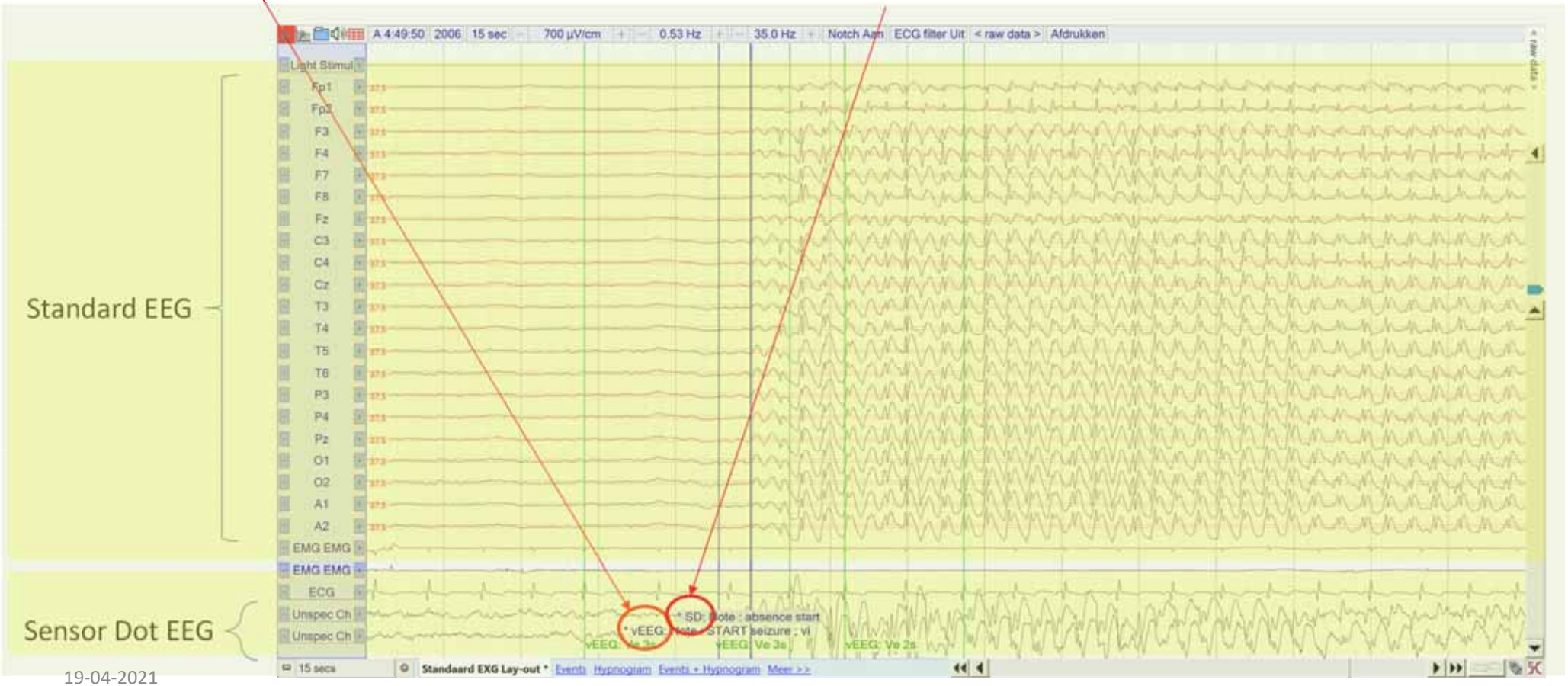
WVP(1

Absence, i.e. discharge of
3 Hz spike and wave lasting >3 seconds

1. Annotation of standard EEG

2. Blinded annotation of Sensor-Dot EEG (5 neurologists)

3. Merging of two EEG files and
Determination of
- Sensitivity
- Positive predictive value
- F1 score



Slide 22

WVP(1 Wim Van Paesschen (NEUROLOGIE); 2/12/2020

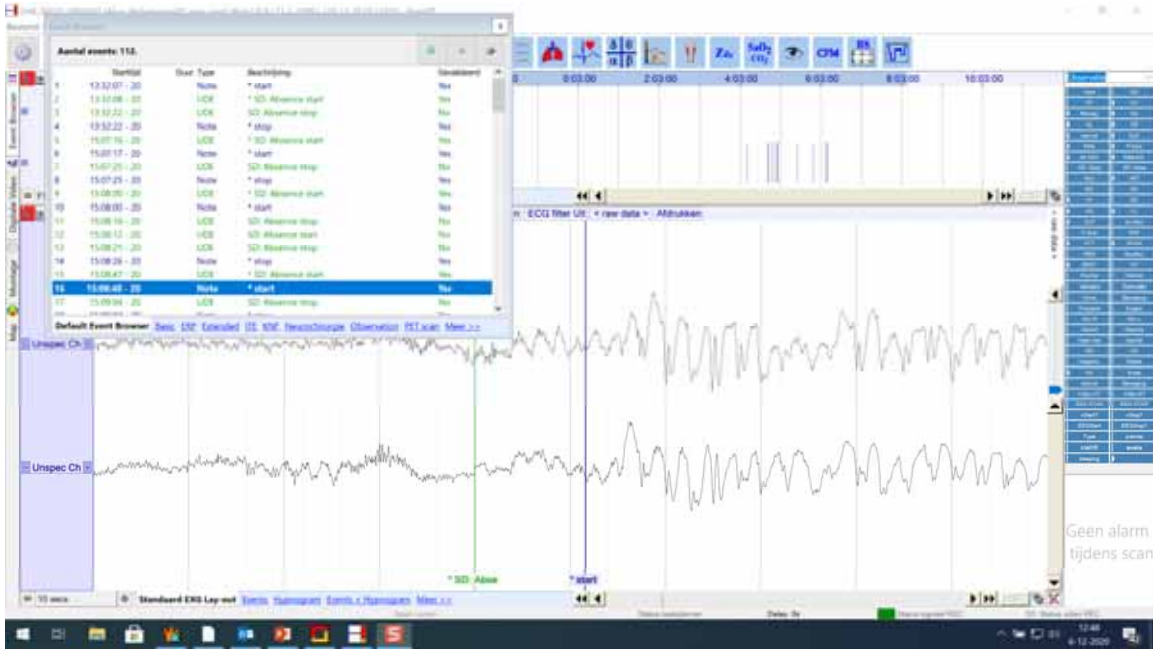


Primary outcome measures for in-hospital typical absence study

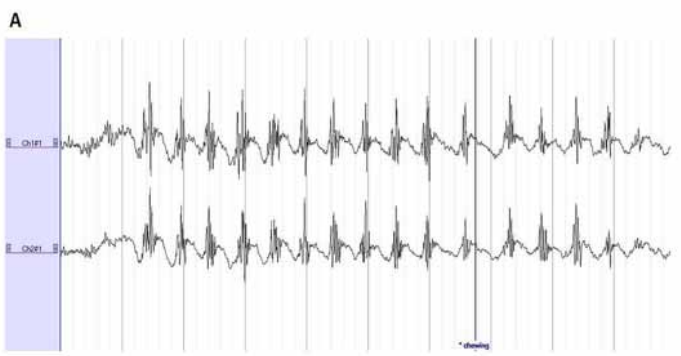
	Typical absences	
	Sensor-Dot EEG	Seizure diary
Sensitivity	83%	8%
Positive predictive value	89%	100%
F1-score	0.87	0.15

Lauren Swinnen et al, manuscript submitted to Epilepsia

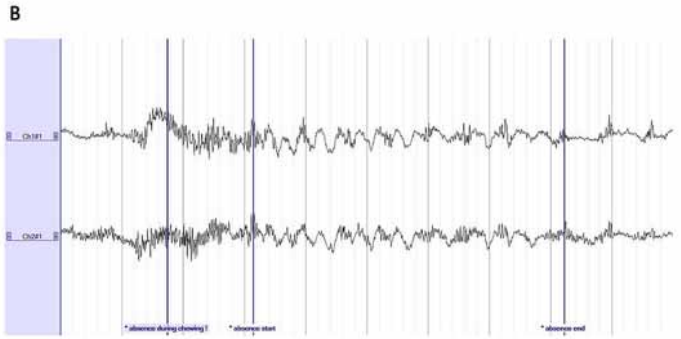
Personalised automated absence seizure detection algorithm



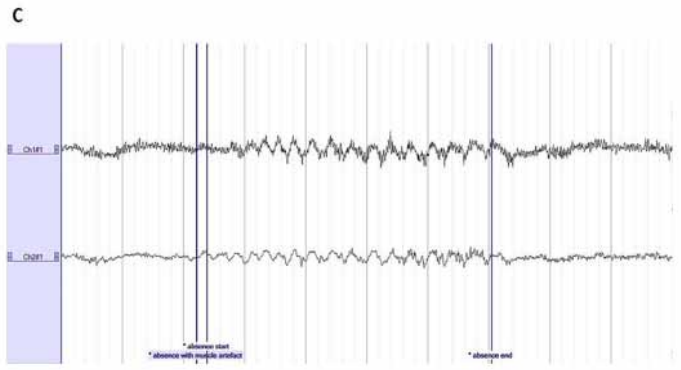
- Time to read 24 hour Sensor-Dot EEG: 1-2 hours
- Patient-specific algorithm to automatically detect absences with sensitivity of > 98%
- Time to read 24 hour Sensor-Dot EEG: median 6 minutes (range: 1-20)



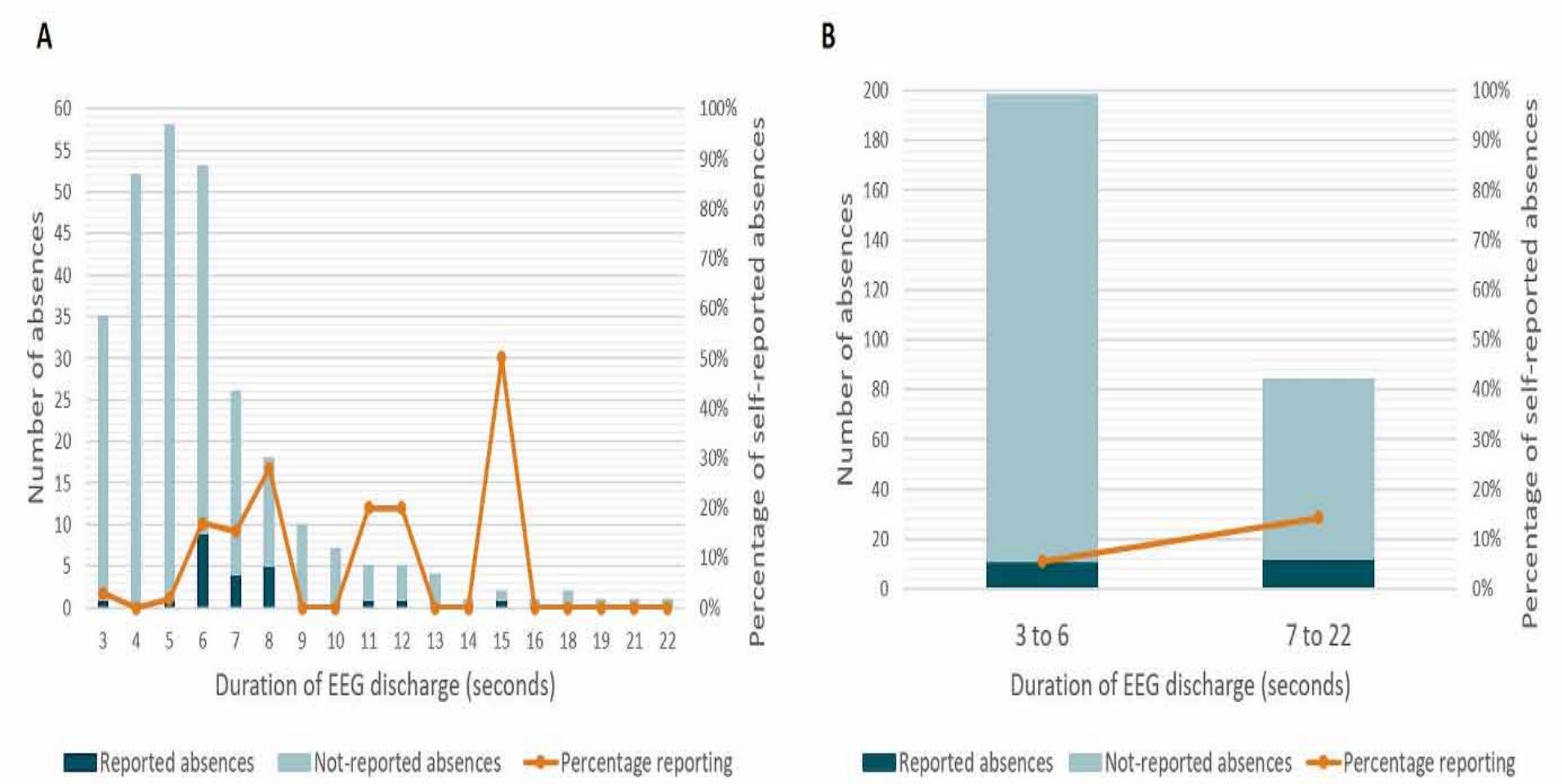
Chewing artefact



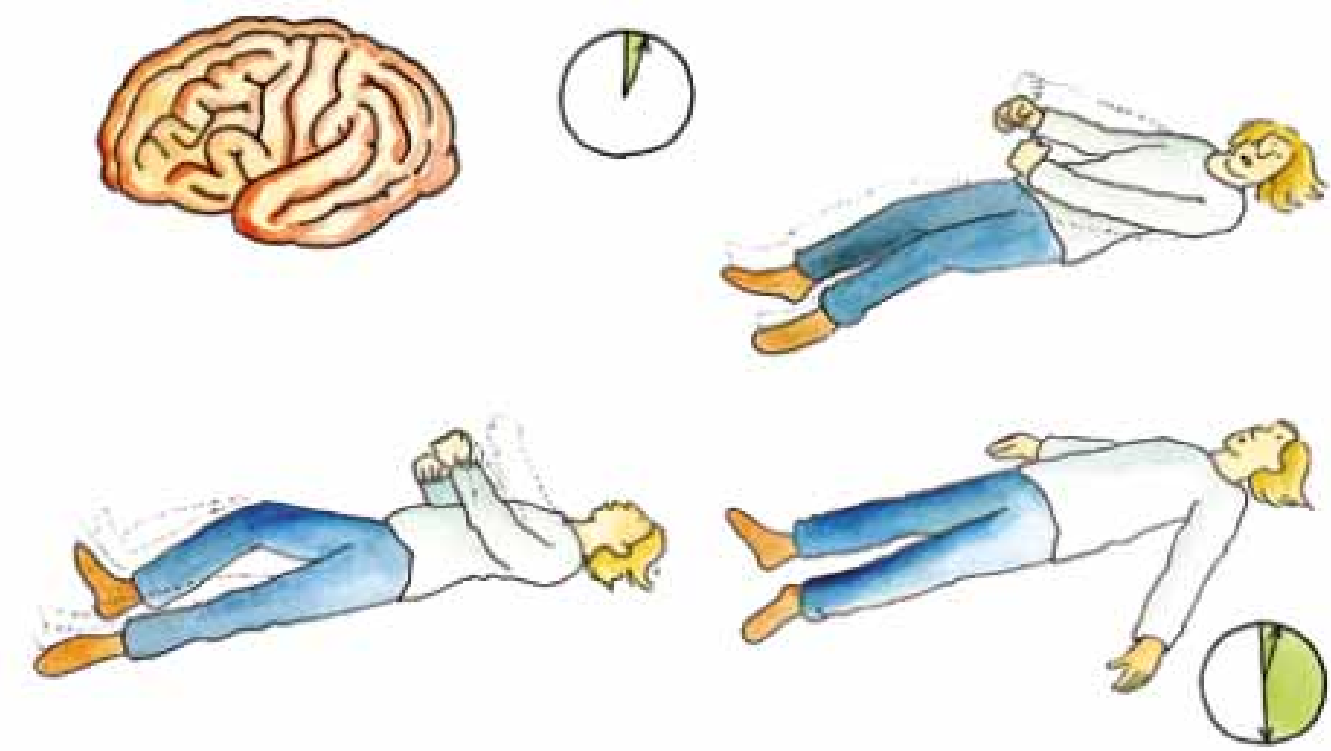
Absence seizure and chewing artefact



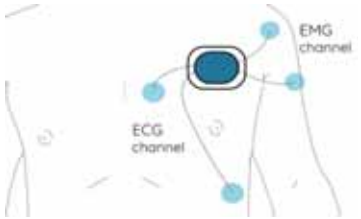
Absence seizure and muscle artefact


A
Number of absences
Percentage of self-reported absences
Duration of EEG discharge (seconds)
Reported absences
Not-reported absences
Percentage reporting
B
Number of absences
Percentage of self-reported absences
3 to 6
7 to 22
Duration of EEG discharge (seconds)
Reported absences
Not-reported absences
Percentage reporting

Tonic-clonic seizures



https://assets.uzleuven.be/files/2019-12/epilepsie.pdf



Focal to bilateral tonic-clonic seizure

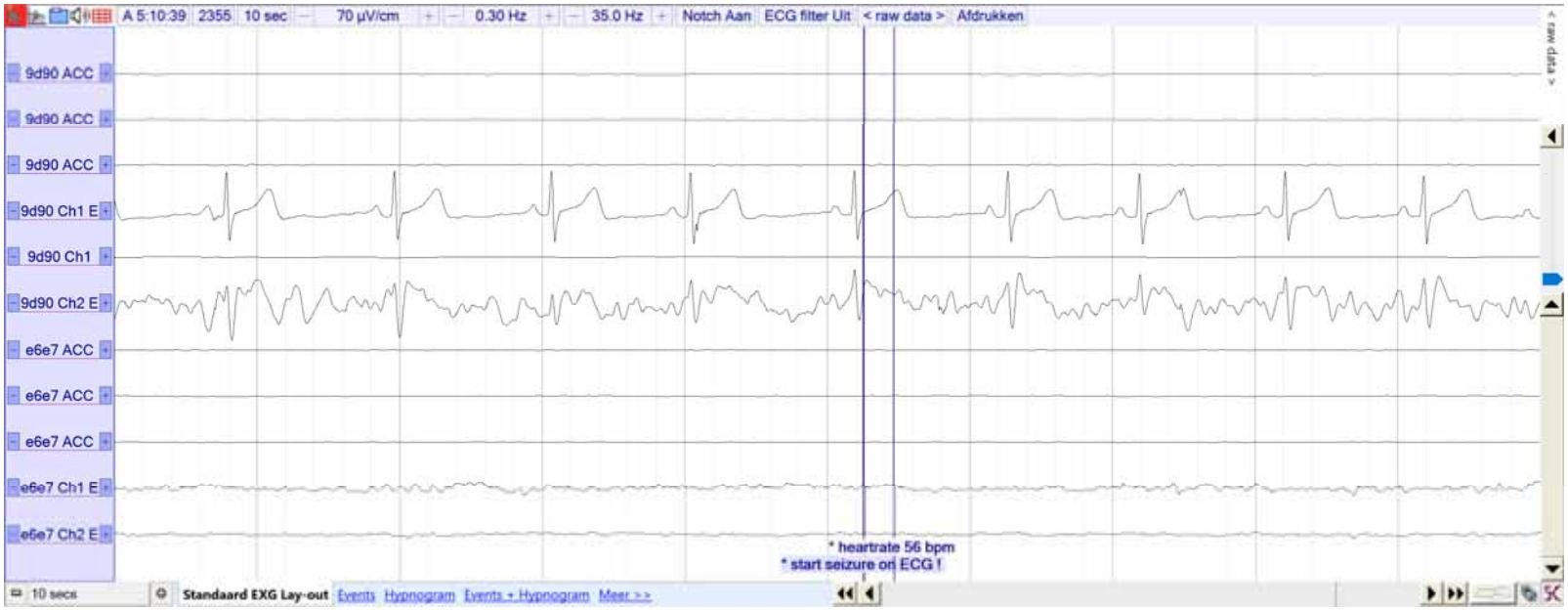
Accelerometer of Sensor Dot 1

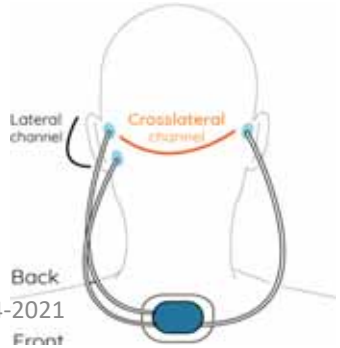
ECG

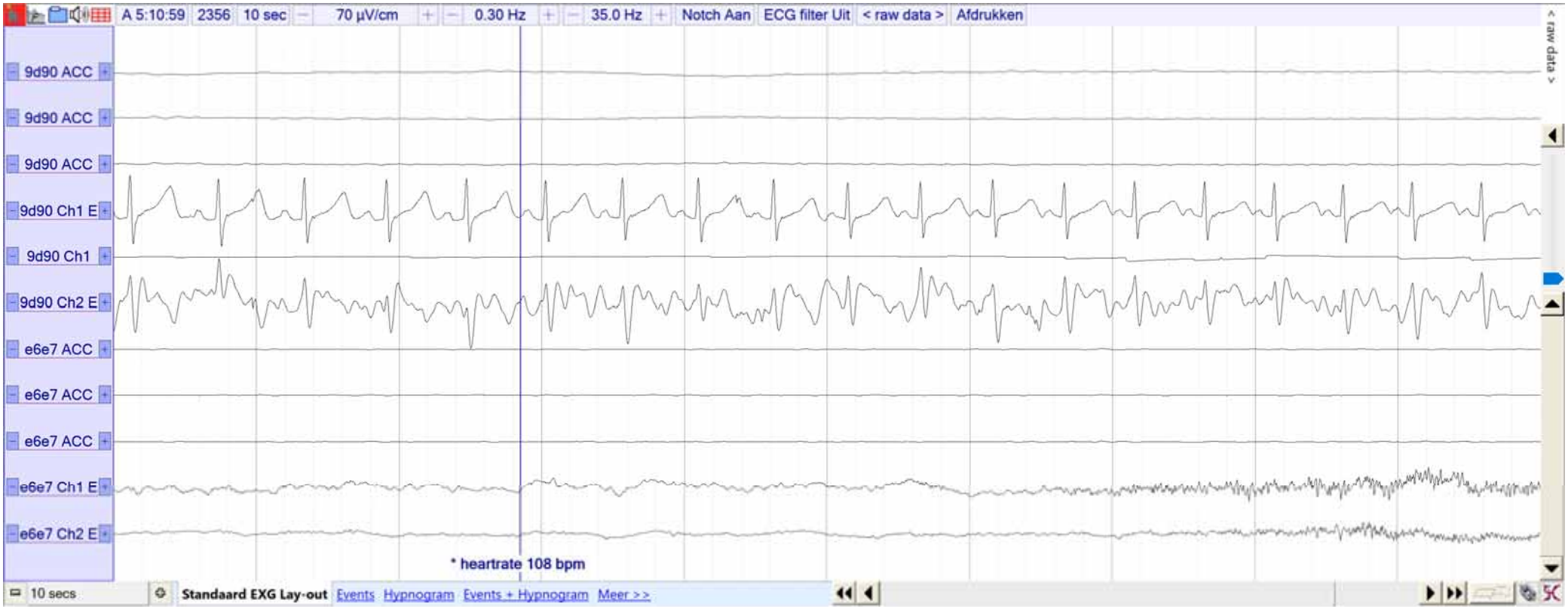
EMG L deltoid

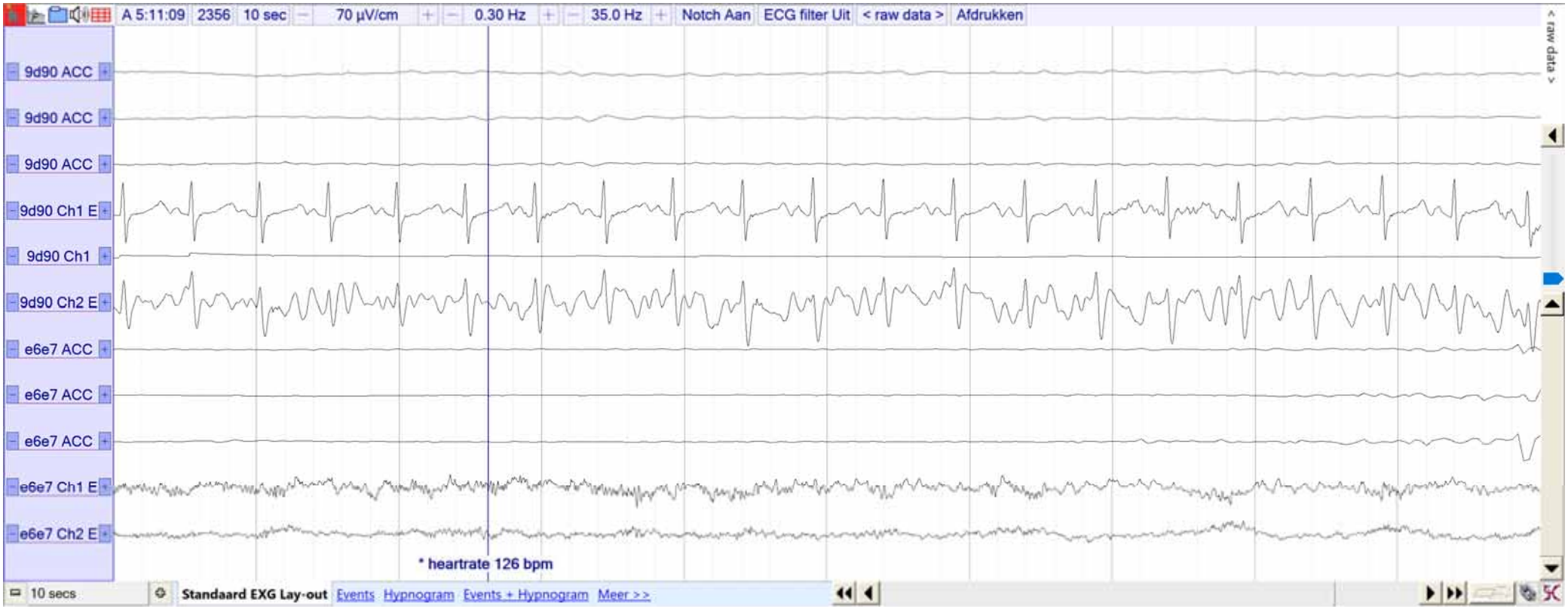
Accelerometer of Sensor Dot 2

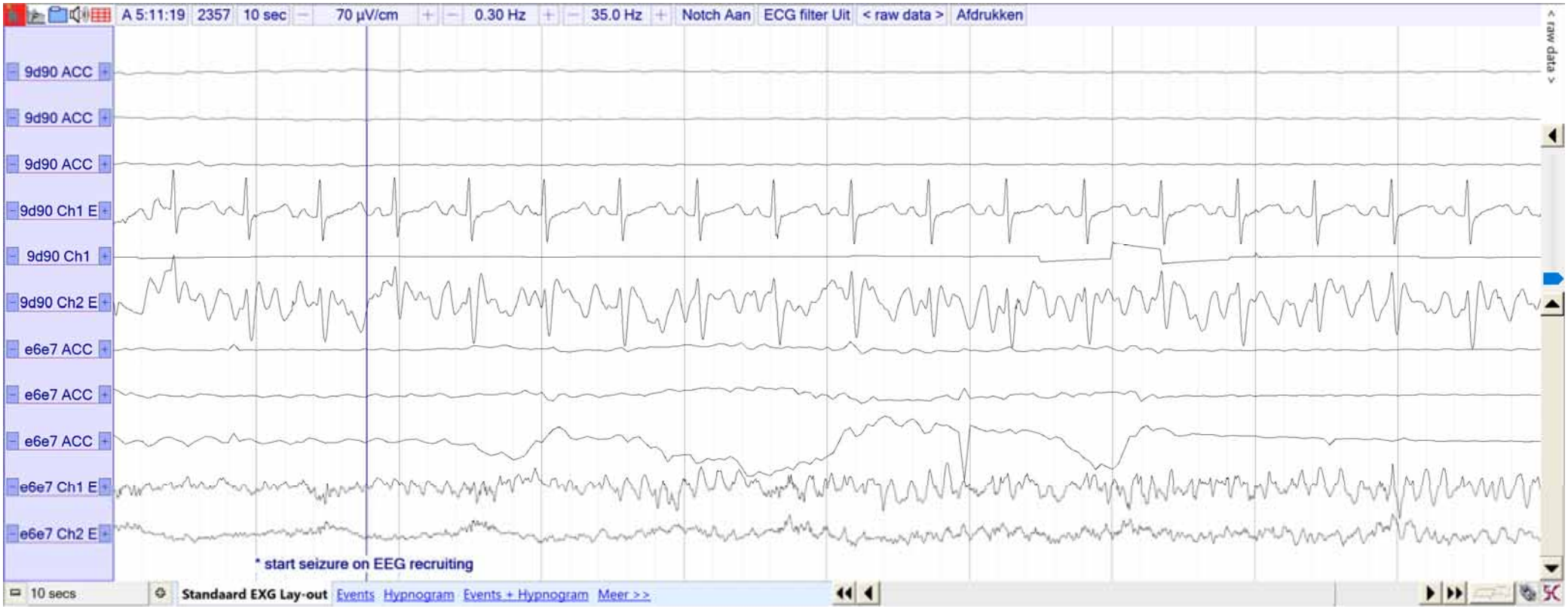
EEG Sensor Dot

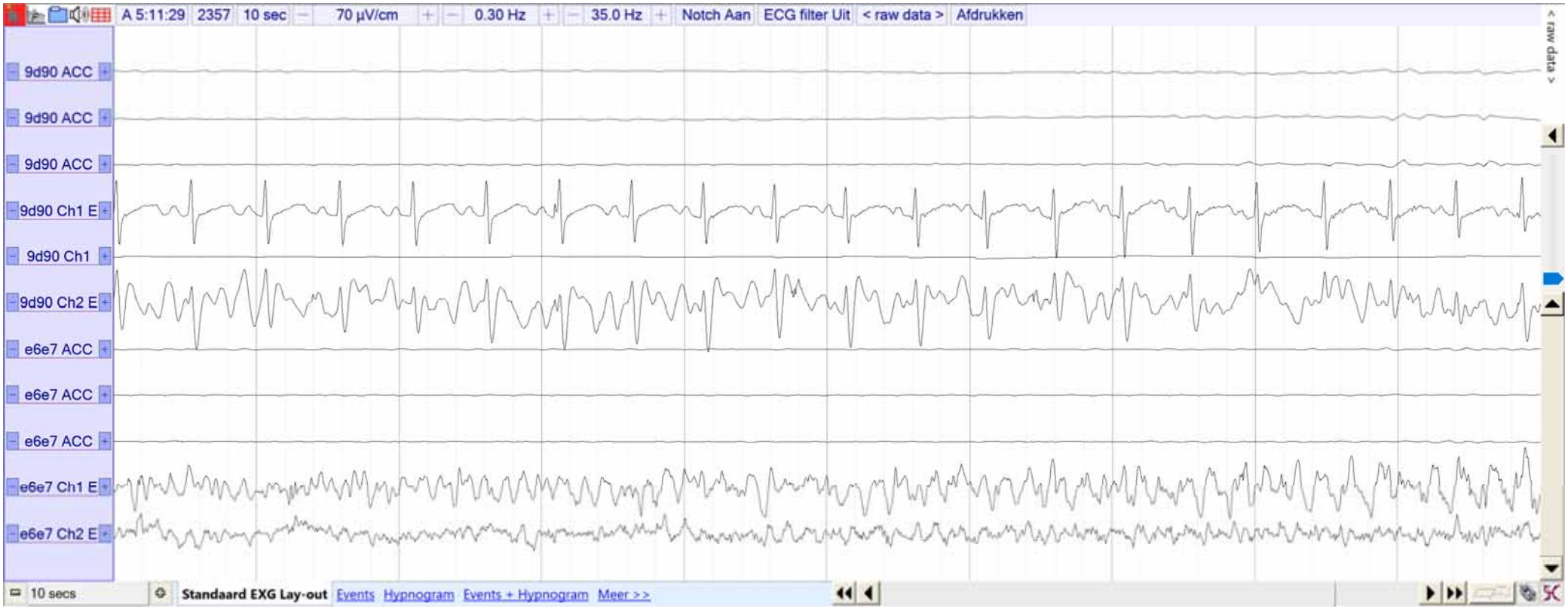


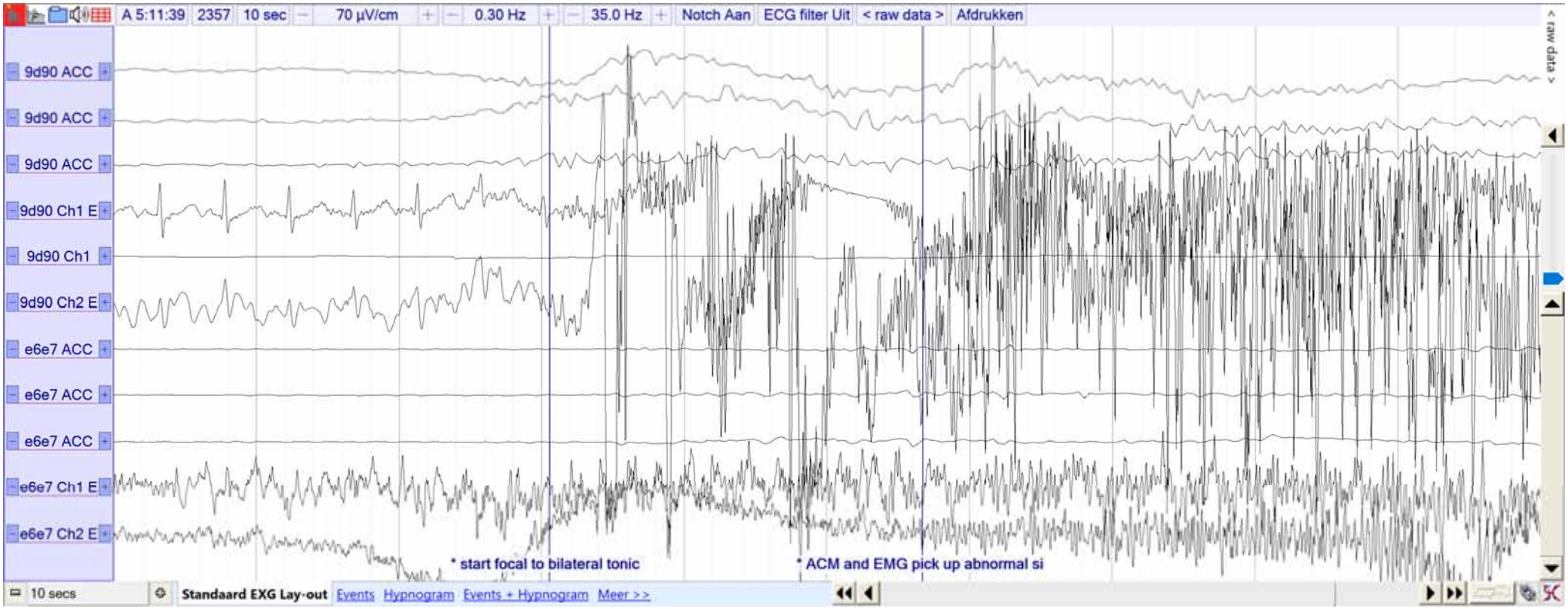


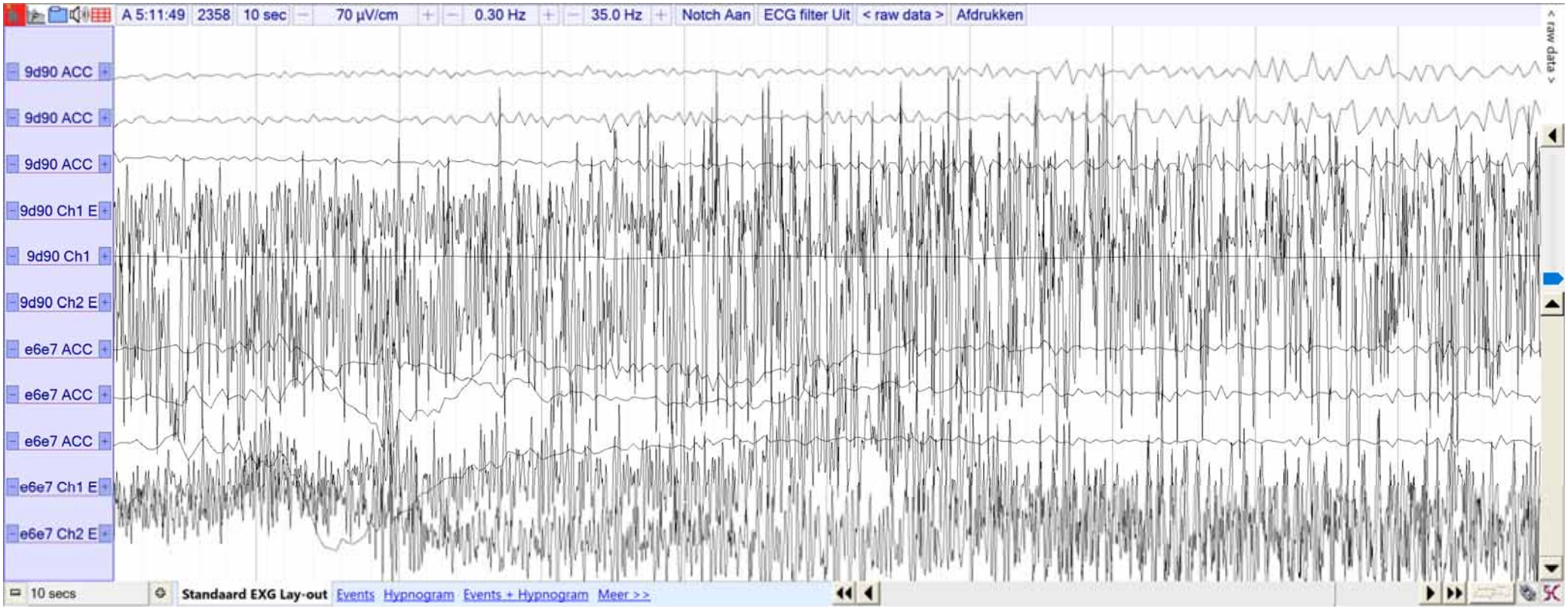

A 5:10:59
2356
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
* heartrate 108 bpm
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>

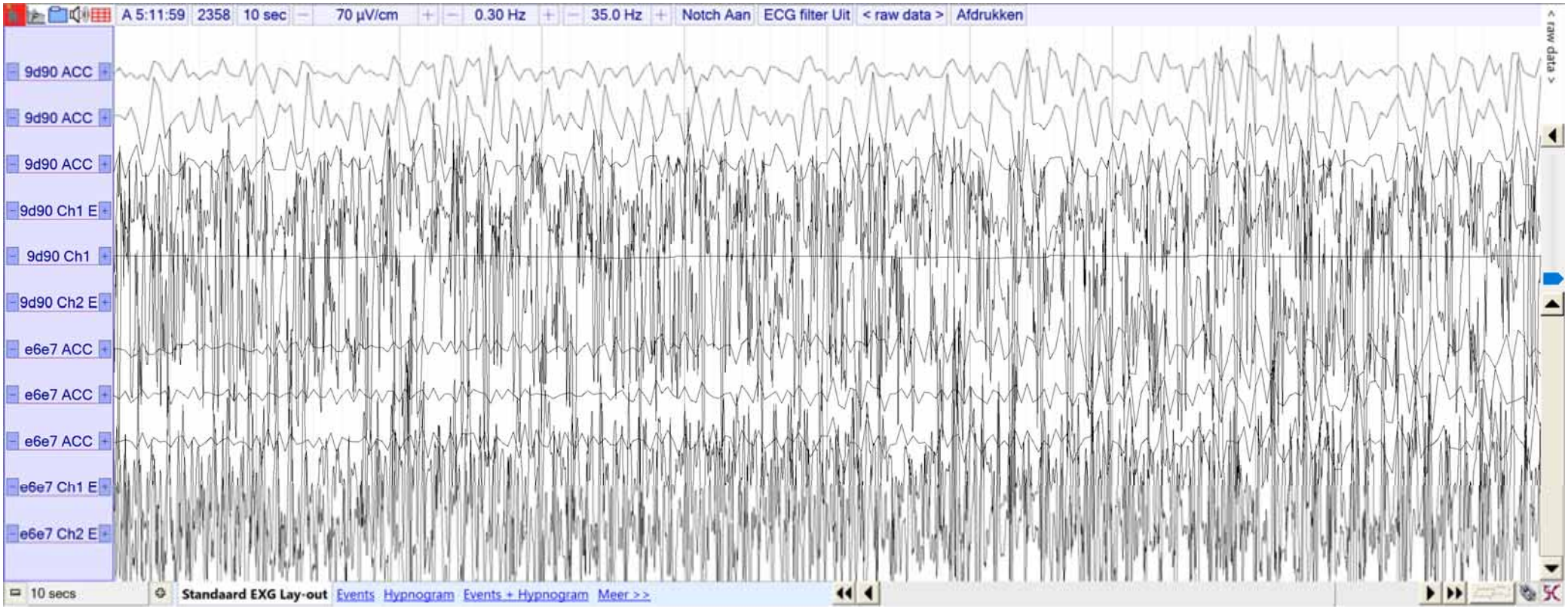

A 5:11:09
2356
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
* heartrate 126 bpm
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>

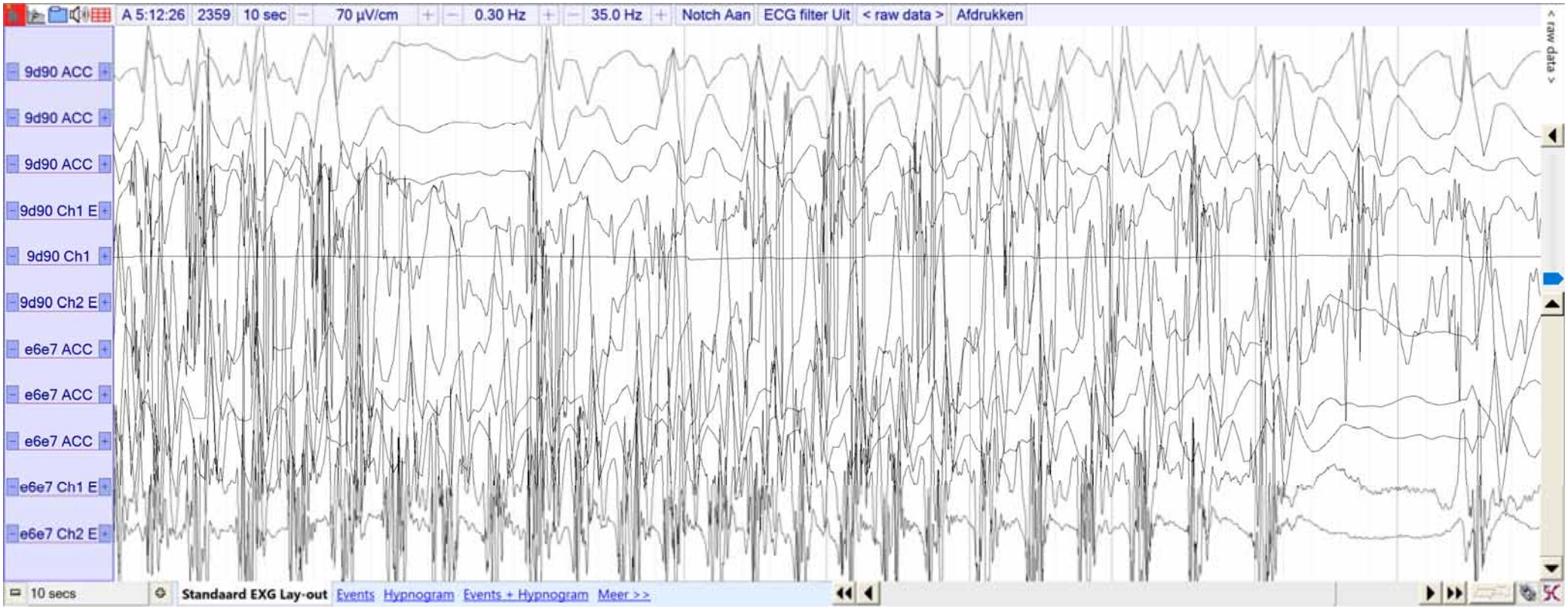

A 5:11:19
2357
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
* start seizure on EEG recruiting
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>

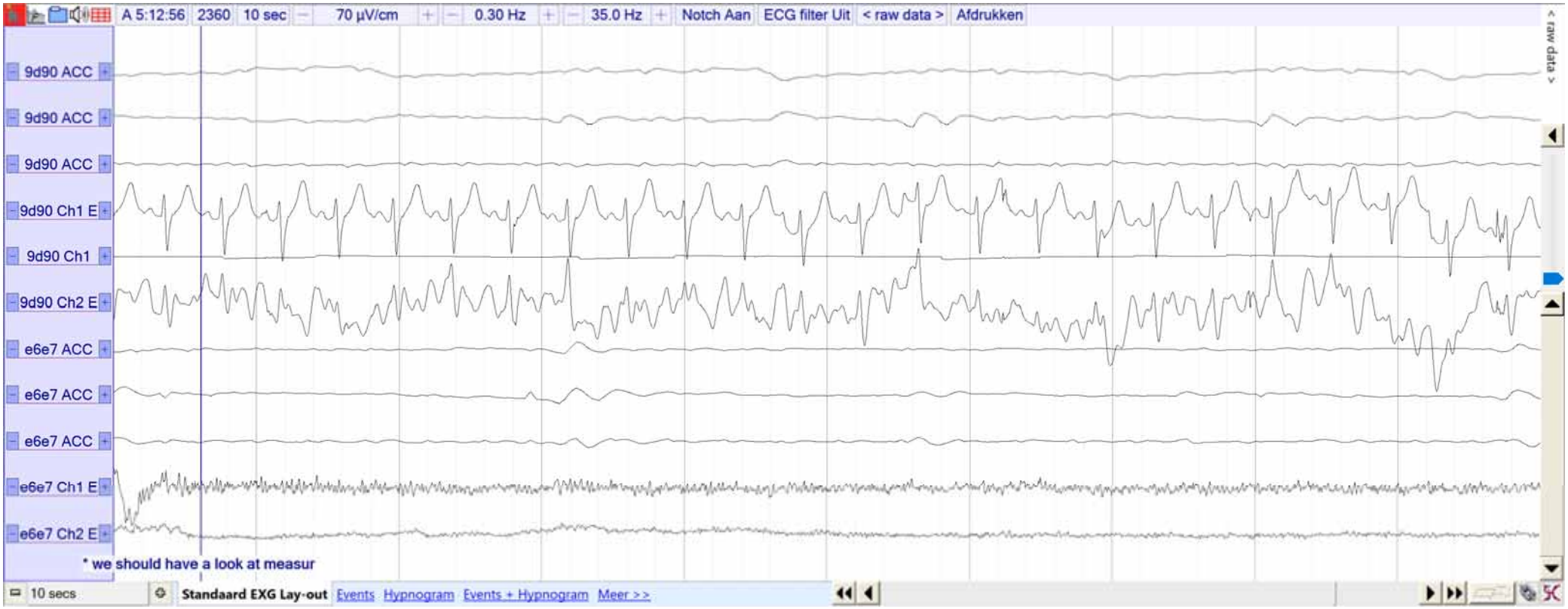

A 5:11:29
2357
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>


A 5:11:39
2357
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
* start focal to bilateral tonic
* ACM and EMG pick up abnormal si
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>


A 5:11:49
2358
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>


A 5:11:59
2358
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>


A 5:12:26
2359
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>


A 5:12:56
2360
10 sec
70 µV/cm
0.30 Hz
35.0 Hz
Notch Aan
ECG filter Uit
< raw data >
Afdrukken
9d90 ACC
9d90 ACC
9d90 ACC
9d90 Ch1 E
9d90 Ch1
9d90 Ch2 E
e6e7 ACC
e6e7 ACC
e6e7 ACC
e6e7 Ch1 E
e6e7 Ch2 E
* we should have a look at measur
10 secs
Standaard EXG Lay-out
Events
Hypnogram
Events + Hypnogram
Meer >>

Multimodal detection of tonic-clonic seizures

- With a multimodal wearable (ACM, EMG, EEG and ECG) , we aim to improve sensitivity, positive predictive value and F1 score.

	Tonic clonic seizures
	ACM- and EMG-based devices (Epicare, Nightwatch, Epilert)
Sensitivity	89%
Positive predictive value	55%
F1-score	0.68

Conclusion: SeizeIT trials

- SeizeIT trials: designed to develop and validate a multimodal, discrete wearable to detect
  - typical absences
  - focal impaired awareness seizures
  - tonic-clonic seizures
- Byteflies Sensor-Dot
- Each seizure type needs
  - a different registration strategy
  - a personalized artificial intelligence-based automated seizure detection algorithm
- Medical device: important role for neurologist
  - Selection of biosignals to measure and measurement set-up
  - Review of automated seizure detections
- Integration in daily clinical practice and patient management
- Cost-benifit analysis to obtain reimbursement

Acknowledgement


Gergely Vértes


Elisabeth Heremans


Kaat Vandecasteele


Jonathan Dan


Miguel Bhagubai


Thomas De Cooman


Jingwei Zhang


Alexander Bertrand


Maarten De Vos


Sabine Van Huffel


Victoria Broux


Evy Cleeren


Lauren Swinnen


Astrid Devulder


Jaiver Macea


Wim Van Paesschen