

When is something spikish an epileptiform spike ?

Sándor Beniczky

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 @SBeniczky

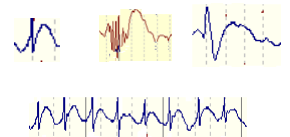
Disclosures

- Scientific consultant: Epihunter
- Speaker: Natus Neuro

Learning Objectives

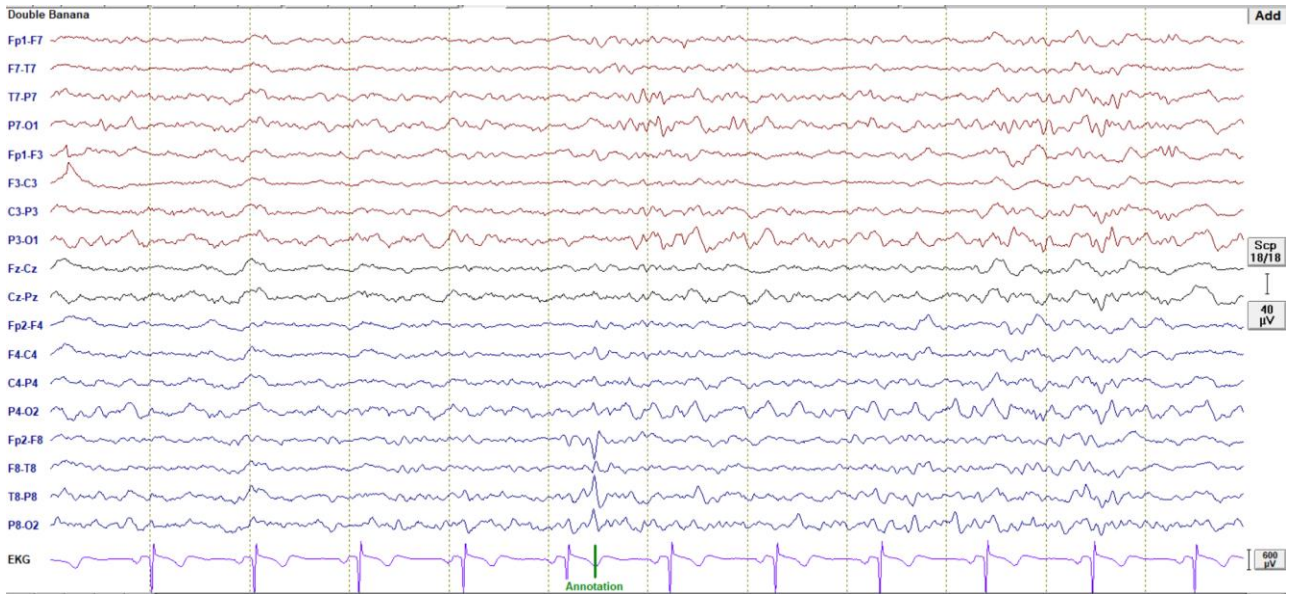
- To recognize the IFCN criteria for identifying IEDs.
- To distinguish between IEDs and non-epileptiform sharp transients applying the IFCN criteria.
- To explain the trade-off between sensitivity and specificity in clinical EEG reading

Interictal Epileptiform Discharges

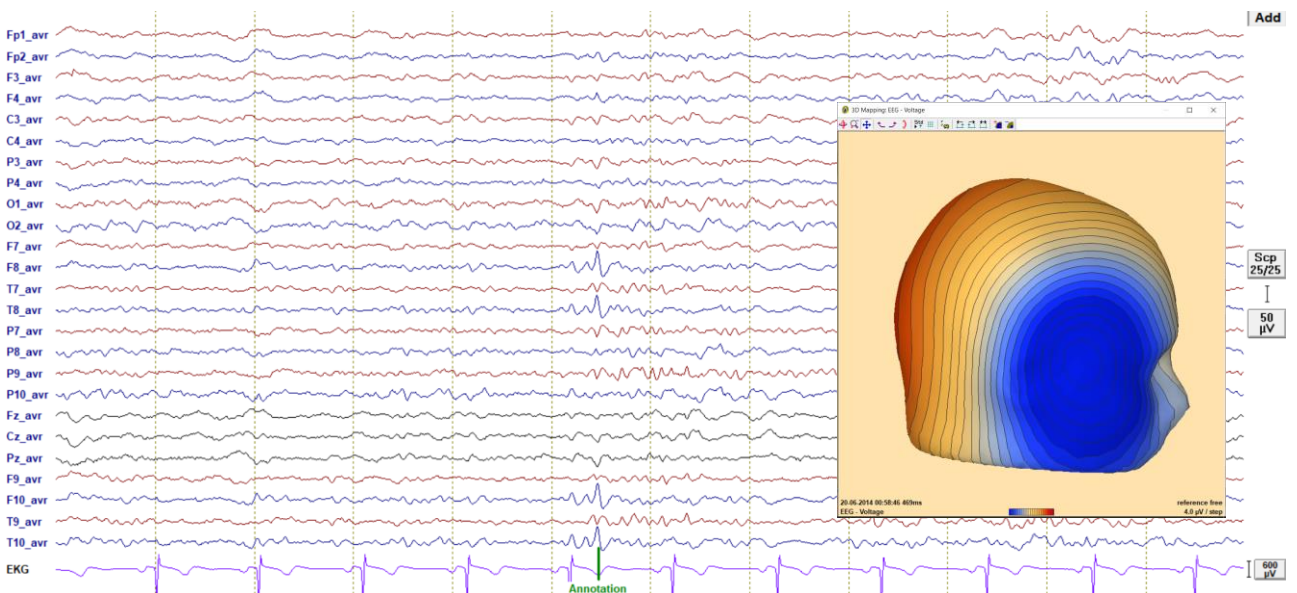


- The most well-documented EEG biomarker of epilepsy
- In skilled hands: diagnosis & classification of epilepsy
- However: it is also the most abused item in EEG

Is this an IED?



Is this an IED?



When is a spike a spike and who / what finds it?

- IEDs` role in epilepsy diagnosis
- IFCN` s operational criteria for IEDs
- Spotting IEDs in source space
- AI & hybrid systems

Epilepsy - diagnosis

ILAE OFFICIAL REPORT

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross,
 #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike
 Glynn, ¶¶Dale C. Hesdorffer, ###B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé,
 ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and
 ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014
 doi: 10.1111/epi.12550

- (1) At least two unprovoked (or reflex) seizures occurring >24 h apart
- (2) One unprovoked (or reflex) seizure and a probability of further seizures ≥ 60%
- (3) Diagnosis of an epilepsy syndrome.

Probability of further seizures after the first unprovoked seizure:

Children

- Normal EEG: ? %
- EEG=IED: ? %

Adults

- Normal EEG: ? %
- EEG=IED: ? %

Camfield et al, 1985; Shinnar et al, 1996; Stroink et al, 1998; Ramos Lizana et al, 2000
Donselaar et al 1992; Berg et al 2008; Wirrell et al, 2010; Su et al, 2013

Probability of further seizures after the first unprovoked seizure:

Children

- Normal EEG: 38%
- EEG=IED: ? %

Adults

- Normal EEG: 12%
- EEG=IED: ? %

Camfield et al, 1985; Shinnar et al, 1996; Stroink et al, 1998; Ramos Lizana et al, 2000
Donselaar et al 1992; Berg et al 2008; Wirrell et al, 2010; Su et al, 2013

Probability of further seizures after the first unprovoked seizure:

Children

- Normal EEG: 38%
- EEG=IED: 65%

Adults

- Normal EEG: 12%
- EEG=IED: 83%

Camfield et al, 1985; Shinnar et al, 1996; Stroink et al, 1998; Ramos Lizana et al, 2000
Donselaar et al 1992; Berg et al 2008; Wirrell et al, 2010; Su et al, 2013

Abusing spikes & EEG

- Over-reading EEG /IEDs: the most common source of misdiagnosing epilepsy
- 25%–30% of patients seen at epilepsy centers for drug-resistant seizures do not have epilepsy
- Detrimental consequences:
 - restrictions on driving
 - restrictions on career choices
 - unnecessary exposure to side effects of antiepileptic drugs
 - not treating the real condition of the patient.

WARNING:

The false-positive EEG report (over-reading) is potentially more harmful to the patient than the false negative report (under-reading)!



Causes of over-reading

- Lack of proper training
- "Trying too hard syndrome" (*Tatum & Benbadis*)
- Fetishizing phase reversal / big & spikey waveforms
- Too vague definition / lack of widely accepted operational criteria.

Operational definition of IEDs (spikes / polyspikes, sharp-waves)

Clinical Neurophysiology Practice 2 (2017) 170–185



Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

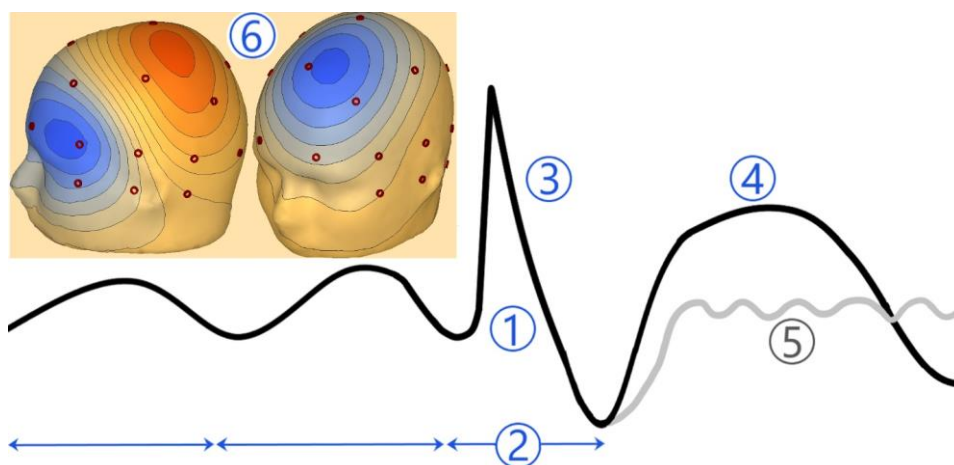
journal homepage: www.elsevier.com/locate/cnp



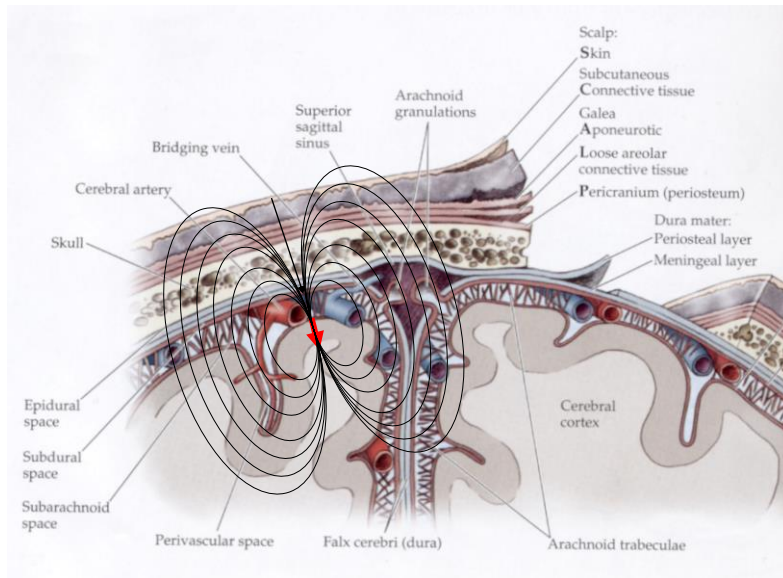
A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017

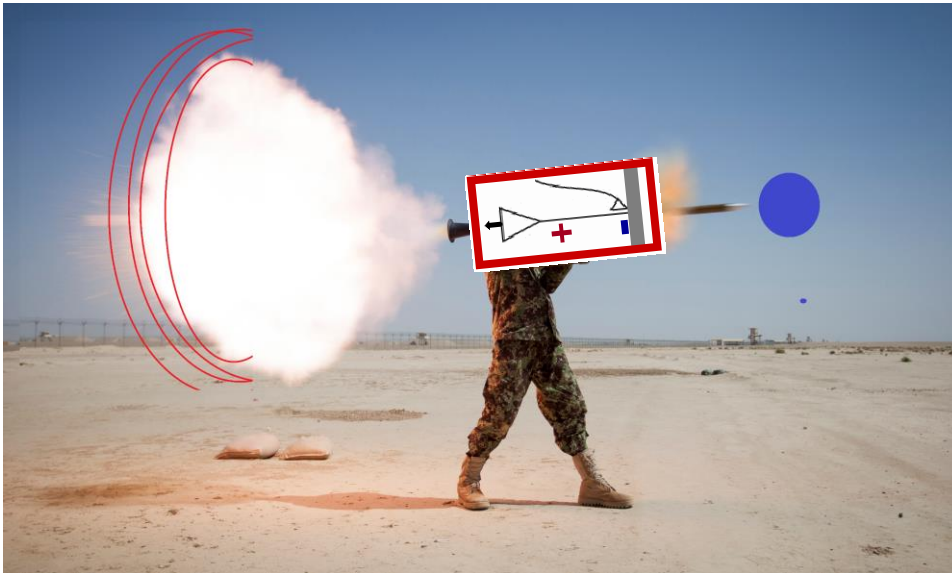


Nick Kane^{a,*}, Jayant Acharya^b, Sandor Beniczky^c, Luis Caboclo^d, Simon Finnigan^e, Peter W. Kaplan^b, Hiroshi Shibasaki^f, Ronit Pressler^a, Michel J.A.M. van Putten^g

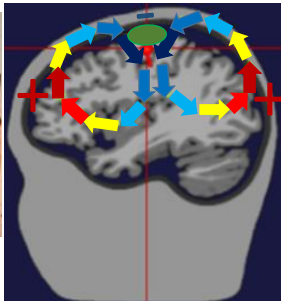


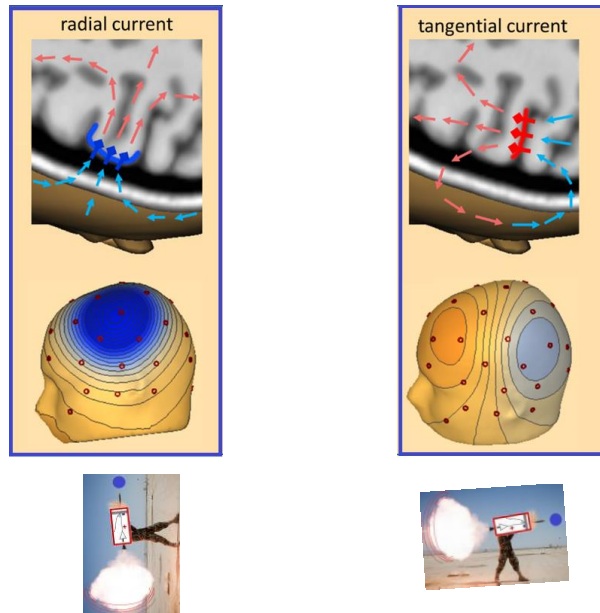
1. Di / tri-phasic waves with sharp / spiky morphology (pointed peak).
2. Different wave-duration than the ongoing background activity.
3. Asymmetry of the waveform.
4. The transient is followed by an associated slow after-wave.
5. The background activity surrounding IEDs is disrupted by the presence of the IEDs.
6. Distribution of the negative and positive potentials on the scalp suggests a source of the signal in the brain, corresponding to a radial, oblique or tangential orientation of the source. This is best assessed by inspecting voltage maps constructed using common-average reference.



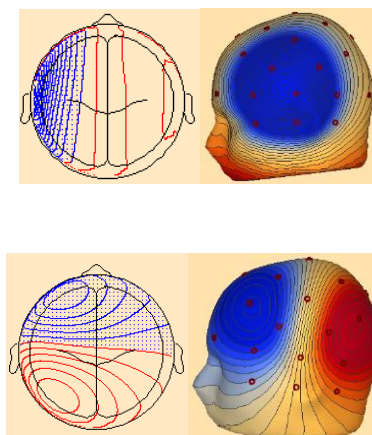


Signal generation:
Both negative and positive potentials on the scalp

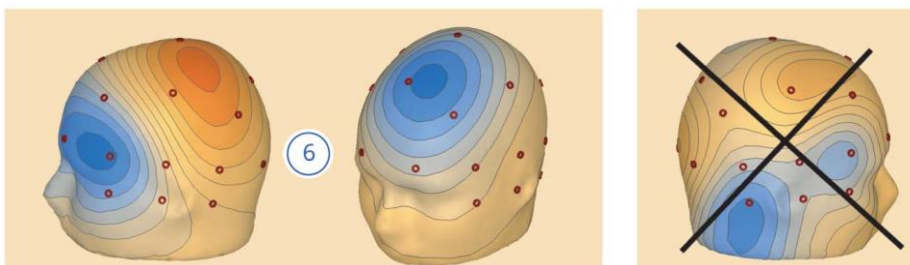
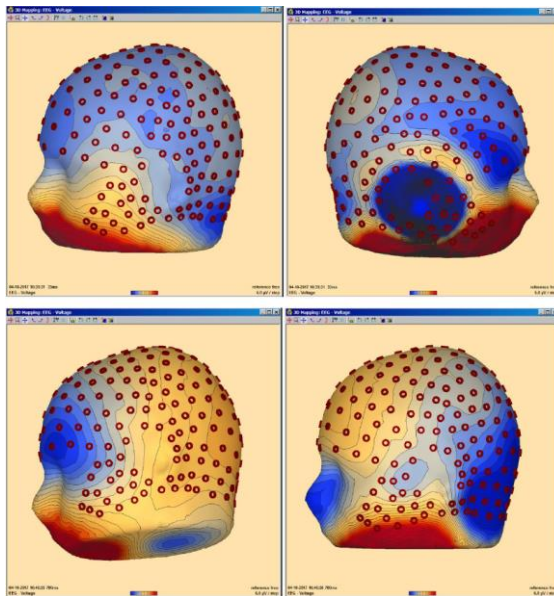


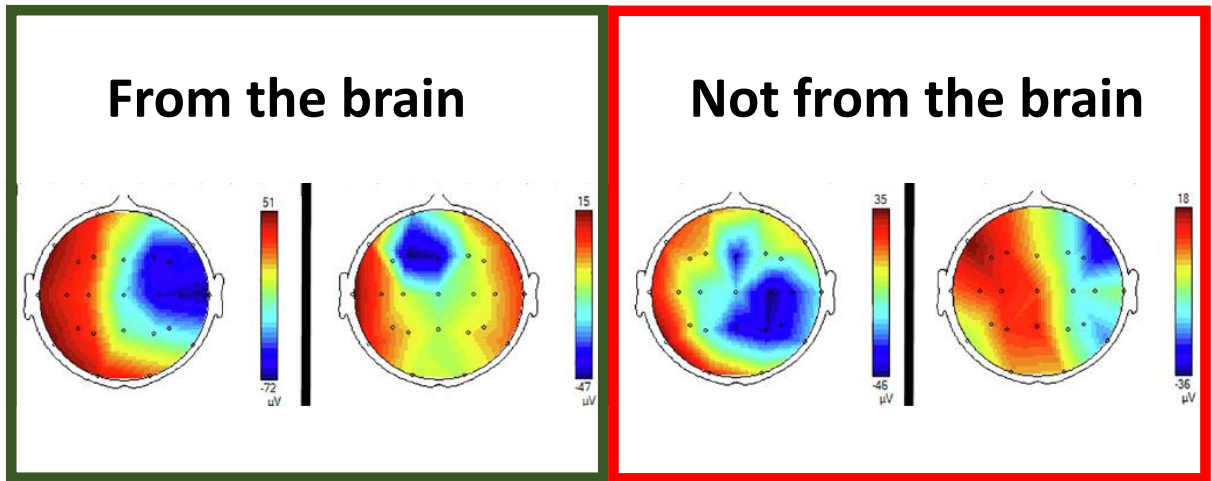


From the brain



Not from the brain





Does this work?

How many criteria need to be there?

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Criteria for defining interictal epileptiform discharges in EEG

A clinical validation study

Mustafa Aykut Kural, MD, Lene Duez, MD, PhD, Vibeke Sejer Hansen, MD, PhD, Pål G. Larsson, MD, DMSc, Stefan Rapp, MD, PhD, Reinhard Schulz, MD, Hatice Tankisi, MD, PhD, Richard Wennberg, MD, PhD, Bo M. Bibby, PhD, Michael Scherg, PhD, and Sándor Beniczky, MD, PhD

Neurology® 2020;94:e2139-e2147. doi:10.1212/WNL.0000000000009439

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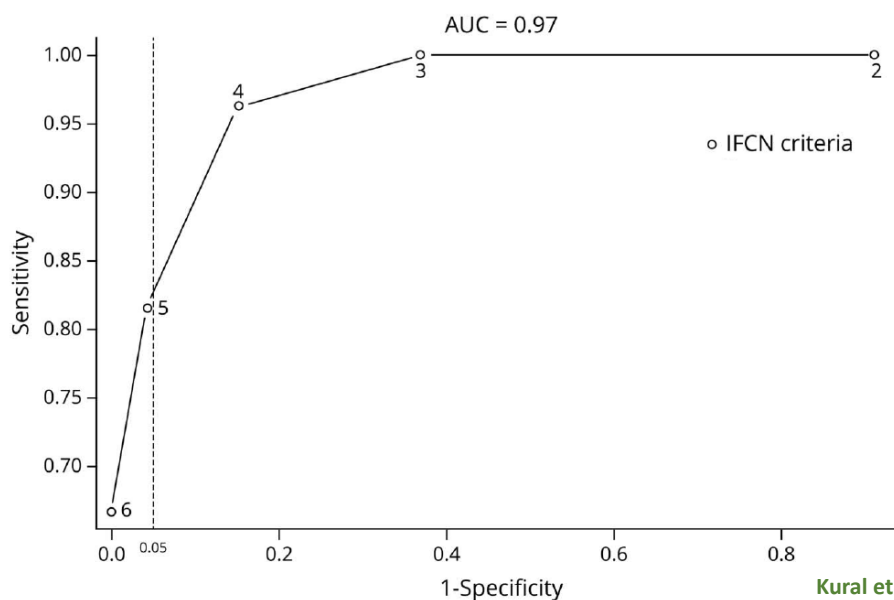
Epileptiform discharges:
Are we still defining them?

Page 862

Unequivocal gold standard:
Video-EEG recordings of the habitual
clinical episodes



Figure 3 Receiver operating characteristic (ROC) curve



Kural et al., *Neurology* 2020

Table 1 Sensitivity, specificity, accuracy, and IRA of the methods for identifying IEDs in sensor space and source space compared with expert scorings

Method	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)	AC1 (95% CI)
IFCN criteria in sensor space				
Cutoff (no. of fulfilled criteria)				
≥2	100 (93.40–100)	8.70 (2.42–20.79)	58 (47.71–67.80)	0.83 (0.76–0.88)
≥3	100 (93.40–100)	63.04 (47.55–76.79)	83 (74.18–89.77)	0.64 (0.53–0.74)
≥4	96.30 (87.25–99.55)	84.78 (71.13–93.66)	91 (83.60–95.80)	0.60 (0.53–0.69)
≥5	81.48 (68.57–90.75)	95.65 (85.16–99.47)	88 (79.98–93.64)	0.49 (0.38–0.60)
=6	66.67 (52.53–78.91)	100 (92.29–100)	82 (73.05–88.97)	0.60 (0.50–0.70)
Source space	85.19 (72.88–93.38)	95.65 (85.16–99.47)	90 (82.38–95.10)	0.59 (0.51–0.68)

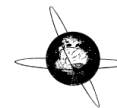
Abbreviations: AC1 = Gwet agreement coefficient; CI = confidence interval; IED = interictal epileptiform discharge; IFCN = International Federation of Clinical Neurophysiology; IRA = interrater agreement.

Is it just the number of criteria that matters?

Are all criteria equal?

or

Is there a specific combination of a few criteria that accurately identifies IEDs?



Optimized set of criteria for defining interictal epileptiform EEG discharges



Mustafa Aykut Kural^a, Hatice Tankisi^a, Lene Duez^a, Vibeke Sejer Hansen^a, Aparna Udipi^b, Richard Wennberg^c, Stefan Rampp^d, Pål G. Larsson^e, Reinhard Schulz^f, Sándor Beniczky^{a,g,h,*}

^aDepartment of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark

^bSection for Biostatistics, Department of Public Health, Aarhus University, Denmark

^cKrembil Brain Institute, Toronto Western Hospital, University of Toronto, Toronto, Canada

^dDepartment of Neurosurgery, University Hospital Erlangen, Germany and Department of Neurosurgery, University Hospital Halle (Saale), Germany

^eDepartment of Neurosurgery, Rikshospitalet, Oslo University Hospital, Oslo, Norway

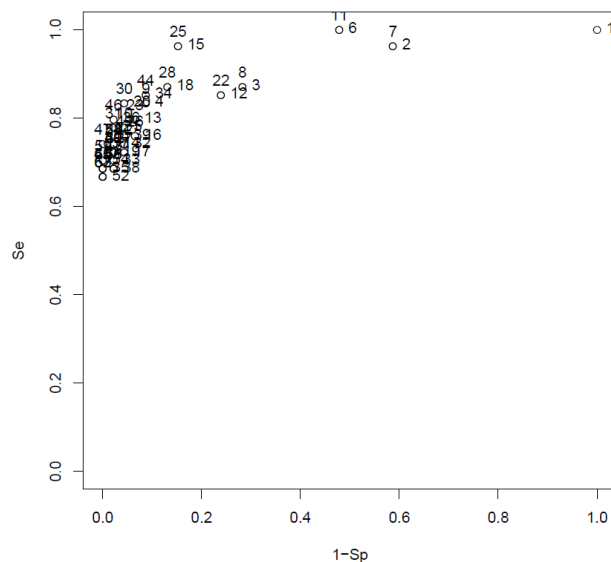
^fEpilepsy Center Bethel, Mara Hospital, Bielefeld, Germany

^gDepartment of Clinical Neurophysiology, Danish Epilepsy Centre, Dianalund, Denmark

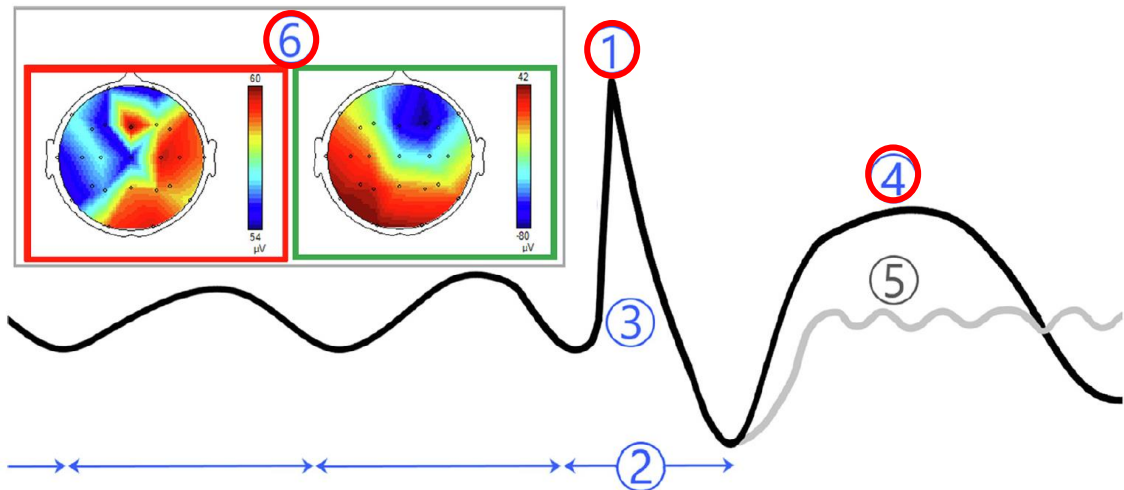
^hDepartment of Clinical Medicine, Aarhus University, Denmark



63 different combinations of the 6 criteria



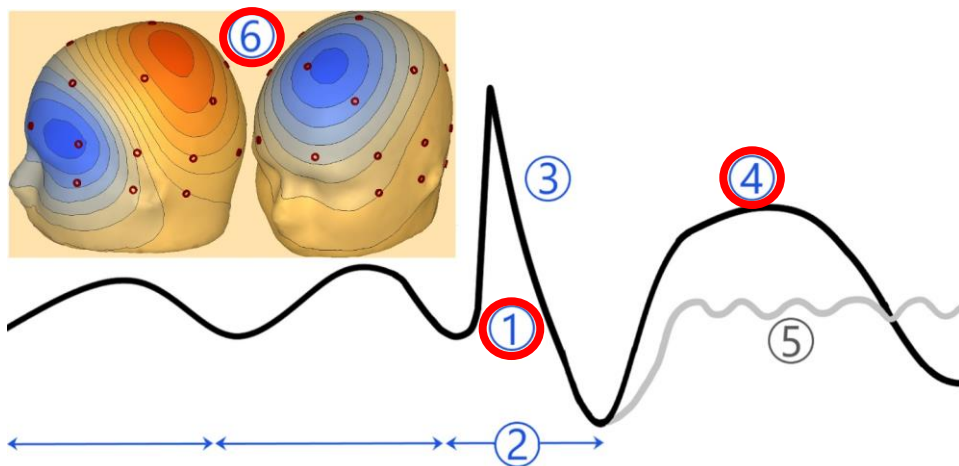
	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	Agreement coefficient
Subjective expert scoring				
Combinations of IFCN criteria	1-2-4-6			
	1-2-4			
	1-4-6			



1+4+6

or:

at least 5 of any criteria-combination



How many times do you need to spot a spike in a recording?



Clinical Neurophysiology

Available online 5 May 2021



The influence of the abundance and morphology of epileptiform discharges on diagnostic accuracy: How many spikes you need to spot in an EEG

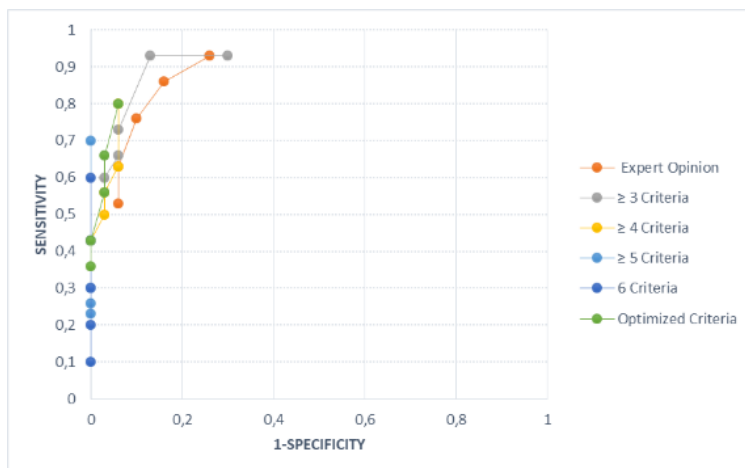
Mustafa Aykut Kural ^a, Erisela Qerama ^a, Birger Johnsen ^a, Steffen Fuchs ^a, Sándor Beniczky ^{a, b}  

<https://doi.org/10.1016/j.clinph.2021.03.045>



How many times do you need to spot a spike in a recording?

- IFCN criteria: a single discharge
- That is NOT the clinical scenario (20-30 minutes EEG recording)
- Less clear-cut spikes? Are they good enough if they occur many times?
 - Only few criteria present, but many discharges in the recording?
- 60 EEGs of 20 minutes: 30 epilepsy + 30 non-epileptic paroxysmal episodes
- 3 neurologists; majority consensus
- Gold standard = EMU



Sets of criteria	AUC
Expert Opinion (non-restricted)	0.897
≥ 3 IFCN Criteria	0.909
≥ 4 IFCN Criteria	0.869
≥ 5 IFCN Criteria	0.850
= 6 IFCN Criteria	0.715
Optimizing Criteria (#1-4-6)	0.883

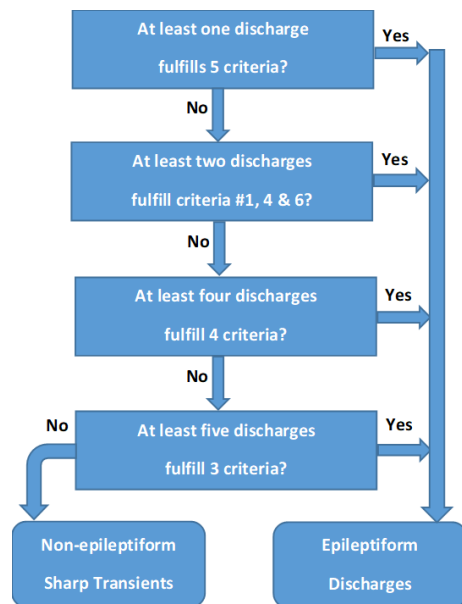
CRITERIA	Number of discharges	SENSITIVITY	SPECIFICITY	ACCURACY
Expert Opinion (non-restricted)	≥1	93.33%	73.33%	83.33%
	≥2	86.67%	83.33%	85.00%
	≥3	76.67%	90.00%	83.33%
	≥4	63.30%	93.33%	78.33%
	≥5	53.33%	93.33%	73.33%
≥3 IFCN criteria	≥1	93.33%	70.00%	81.67%
	≥2	93.33%	86.67%	90.00%
	≥3	73.33%	93.33%	83.33%
	≥4	66.67%	93.33%	80.00%
	≥5	60.00%	96.67%	78.33%
≥4 IFCN criteria	≥1	80.00%	93.33%	86.67%
	≥2	63.3%	93.33%	78.33%
	≥3	56.6%	93.33%	75.00%
	≥4	50.00%	96.67%	73.33%
	≥5	43.33%	96.67%	70.00%
≥5 IFCN criteria	≥1	70.00%	100.00%	85.00%
	≥2	43.33%	100.00%	71.67%
	≥3	30.00%	100.00%	65.00%
	≥4	26.67%	100.00%	63.33%
	≥5	23.33%	100.00%	61.67%
6 IFCN criteria	≥1	43.33%	100.00%	71.67%
	≥2	20.00%	100.00%	60.00%
	≥3	10.00%	100.00%	55.00%
	≥4	6.67%	100.00%	53.33%
	≥5	3.33%	100.00%	51.67%
Set of 3 Optimized Criteria	≥1	80.00%	93.33%	86.67%
	≥2	66.67%	96.67%	81.67%
	≥3	56.67%	96.67%	76.67%
	≥4	43.33%	100.00%	71.67%
	≥5	36.67%	100.00%	68.33%

Combination of Criteria-sets	Sensitivity	Specificity	Accuracy
1 IED fulfilling 5-criteria OR 2 IEDs fulfilling the Optimized Criteria	73.33%	96.67%	85.00%
1 IED fulfilling 5-criteria OR 4 IEDs fulfilling 4 criteria	70.00%	96.67%	83.33%
1 IED fulfilling 5-criteria OR 5 IEDs fulfilling 3-criteria	76.67%	96.67%	86.67%
1 IED fulfilling 5-criteria OR 2 IEDs fulfilling Optimized Criteria OR 4 IEDs fulfilling 4-criteria OR 5 IEDs 3-criteria	80.00%	96.67%	88.33%

How many criteria need to be there in a routine EEG?

To achieve a specificity >95%
(avoid over-reading)

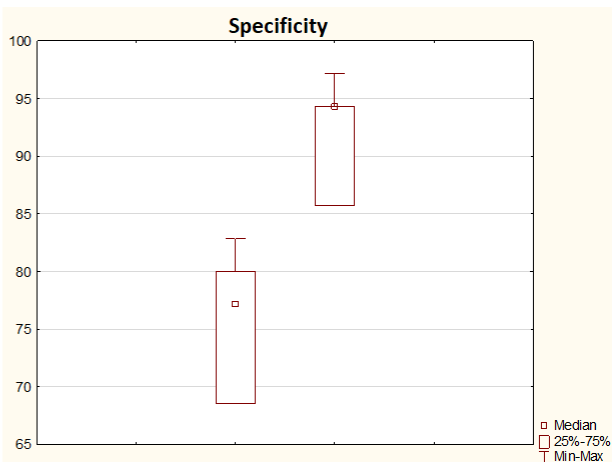
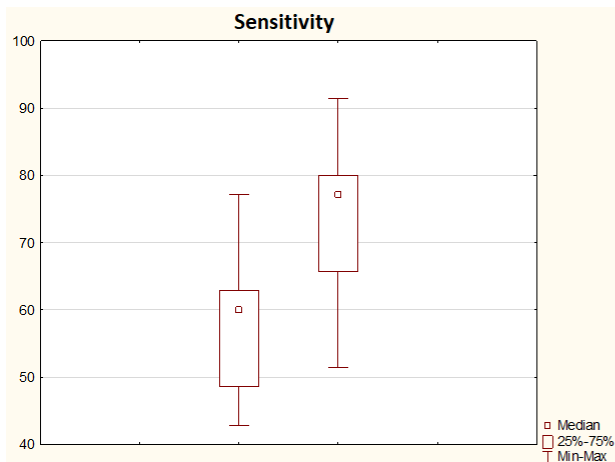
- ≥ 5 criteria: one is enough
- Criteria 1-4-6: \geq twice
- 4 criteria (any): ≥ 4 times
- 3 criteria (any): ≥ 5 times



Kural et al., Clinical Neurophysiology 2020

You can learn it!

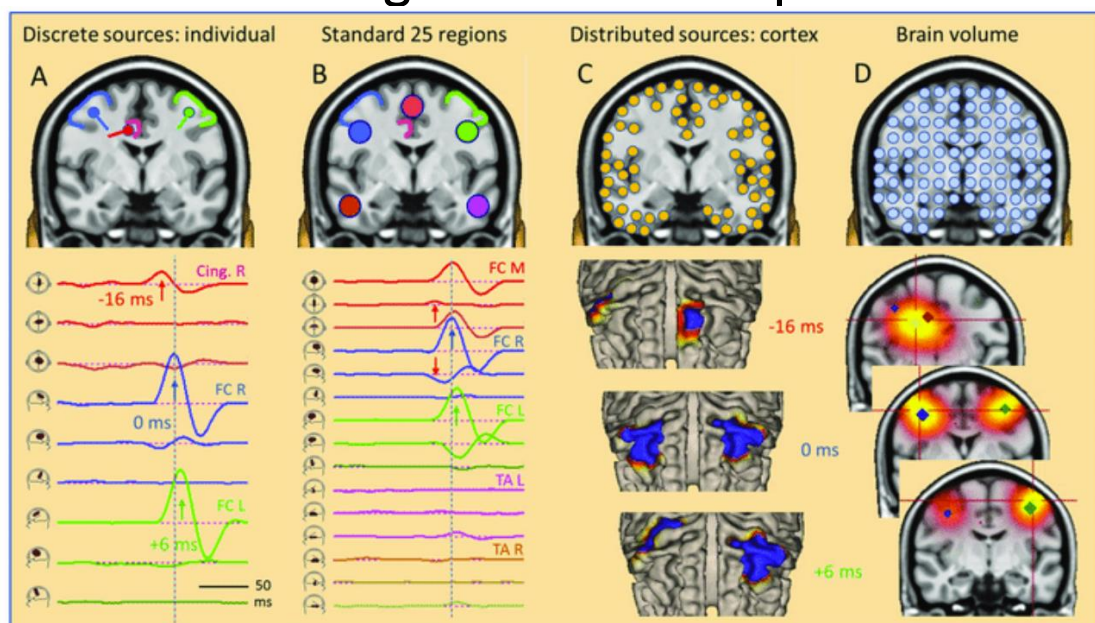
Seven trainees: before / after this teaching session



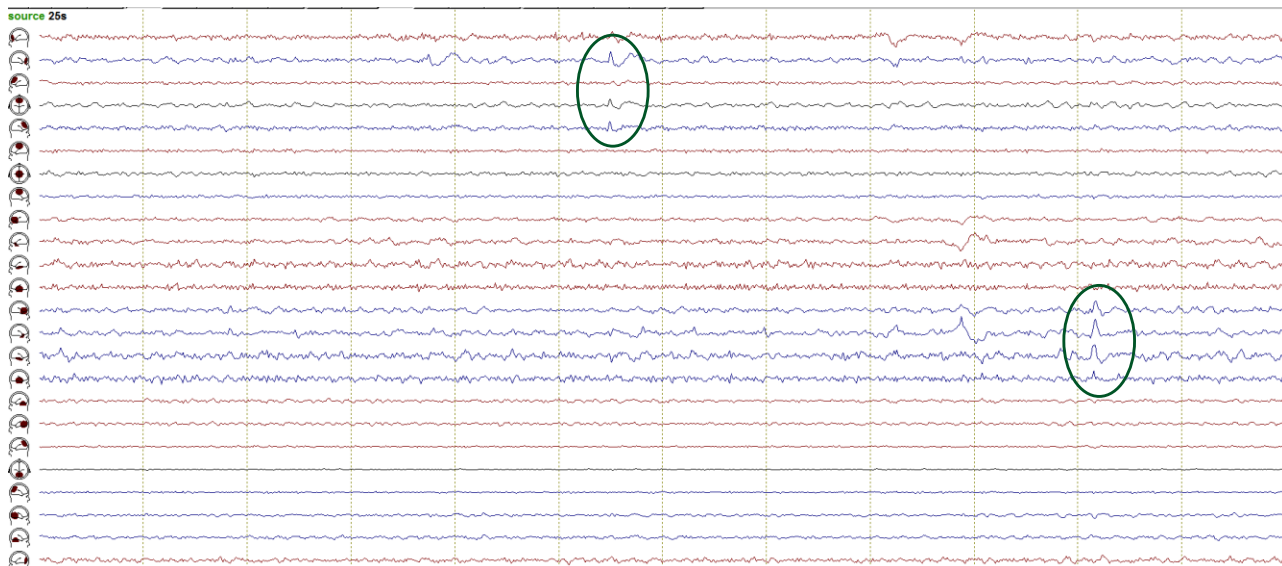
IRA: fair ($k=0.31$) \rightarrow high-moderate ($k=0.56$)

Kural et al., *Epileptic Disorders* 2021

Reading EEG in source space



EDs – in source space



EDs – in source space

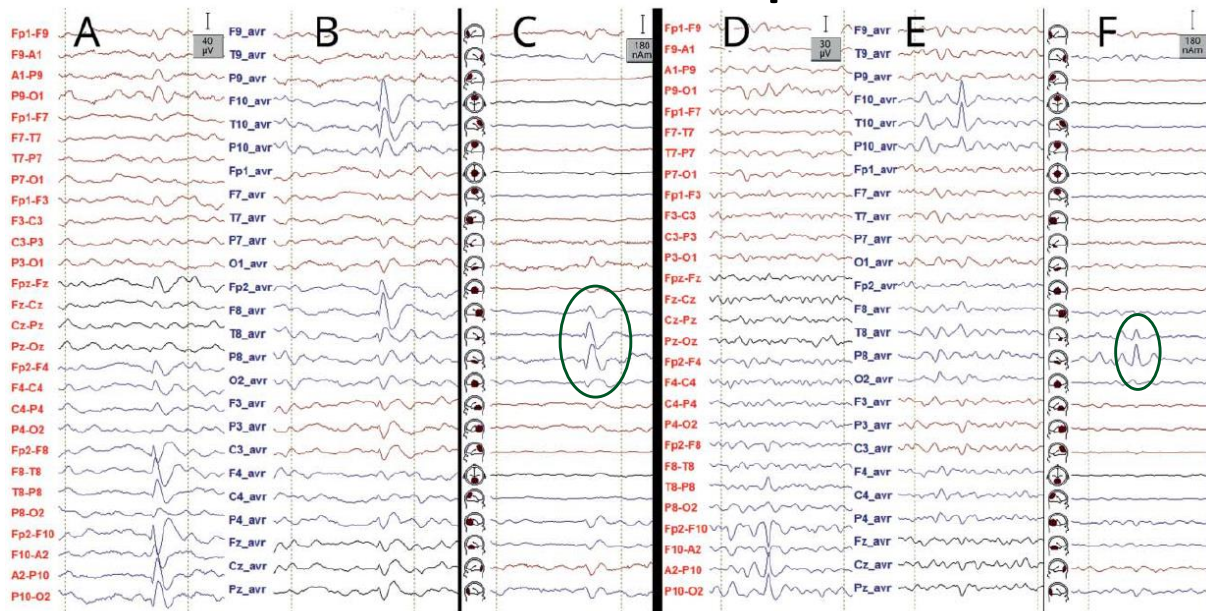


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Abbreviations: AC1 = Gwet agreement coefficient; CI = confidence interval; IED = interictal epileptiform discharge; IFCN = International Federation of Clinical Neurophysiology; IRA = interrater agreement.

Who / what finds the spikes?

- Algorithms & artificial intelligence

vs.

- Human experts



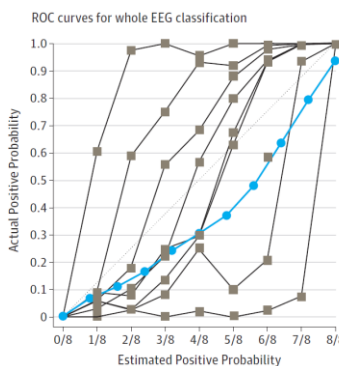
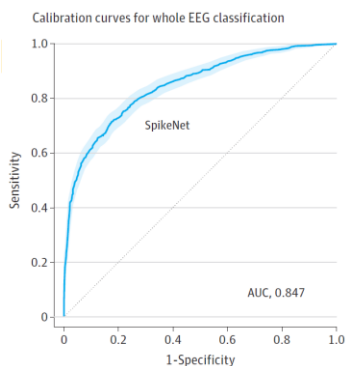
Research

JAMA Neurol. doi:10.1001/jamaneurol.2019.3485
Published online October 21, 2019.

JAMA Neurology | Brief Report

Development of Expert-Level Automated Detection of Epileptiform Discharges During Electroencephalogram Interpretation

Jin Jing, PhD; Haoqi Sun, PhD; Jennifer A. Kim, MD, PhD; Aline Herlopian, MD; Ioannis Karakis, MD, PhD; Marcus Ng, MD; Jonathan J. Halford, MD; Douglas Maus, MD, PhD; Fonda Chan, MD; Marjan Dolatshahi, MD; Carlos Muniz, MD; Catherine Chu, MD; Valeria Sacca, PhD; Jay Pathmanathan, MD; Wendong Ge, PhD; Justin Dauwels, PhD; Alice Lam, MD, PhD; Andrew J. Cole, MD; Sydney S. Cash, MD, PhD; M. Brandon Westover, MD, PhD



Clinical Neurophysiology 131 (2020) 1174–1179

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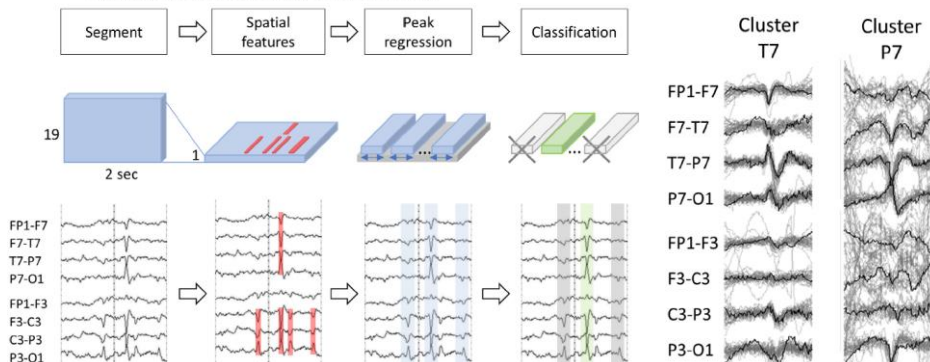
Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

An artificial intelligence-based EEG algorithm for detection of epileptiform EEG discharges: Validation against the diagnostic gold standard

Franz Fürbass^a, Mustafa Aykut Kural^b, Gerhard Critsch^a, Manfred Hartmann^a, Tilmann Kluge^a, Sándor Beniczky^{b,c,*}

^aCenter for Health & Bioresources, AIT Austrian Institute of Technology GmbH, Vienna, Austria
^bDepartment of Clinical Neurophysiology, Aarhus University Hospital and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
^cDepartment of Clinical Neurophysiology, Danish Epilepsy Centre, Dianalund, Denmark



Challenges & possible solutions

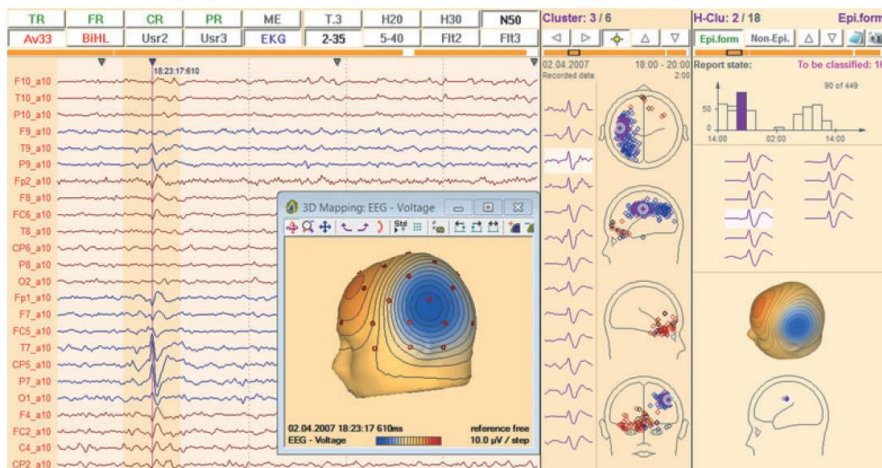
- Algorithms: at high sensitivity – too low specificity.
- Hybrid systems
 - Algorithms: scans the whole EEG → high sensitivity
 - Algorithm: groups detections into clusters → save time for evaluation
 - Human expert: reviews the clusters → high specificity

Epilepsia, 53(7):1196–1204, 2012
doi: 10.1111/j.1528-1167.2012.03503.x

FULL-LENGTH ORIGINAL RESEARCH

Fast evaluation of interictal spikes in long-term EEG by hyper-clustering

*Michael Scherg, *Nicole Ille, *Dieter Weckesser, *Arndt Ebert, *Andrea Ostendorf, ‡Tobias Boppel, †Susanne Schubert, ¶Pål G. Larsson, #Oliver Henning, and †**Thomas Bast



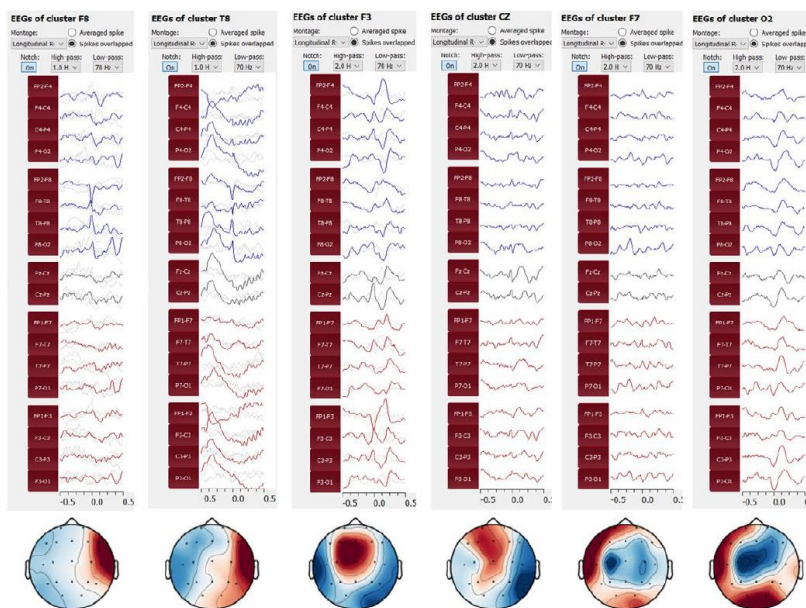
91% of the visually identified spikes

Accurate identification of EEG recordings with interictal epileptiform discharges using a hybrid approach: Artificial intelligence supervised by human experts

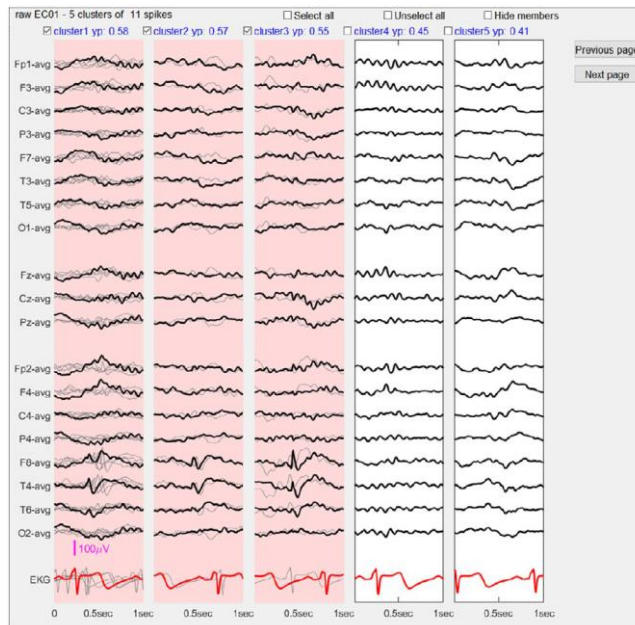
Mustafa Aykut Kural^{1,2,3} | Jin Jing⁴ | Franz Fürbass⁵ | Hannes Perko⁵ |
Erisela Qerama^{2,3} | Birger Johnsen^{2,3} | Steffen Fuchs² | M. Brandon Westover⁴ |
Sándor Beniczky^{1,2,3}

- Head-to-head comparison of 3 AI spike-detectors: 20 min. routine-EEG
- Diagnostic gold standard: habitual seizures recorded in LTM
- Fully automated
- Hybrid: evaluation of the clustered spikes , by experts using IFCN criteria

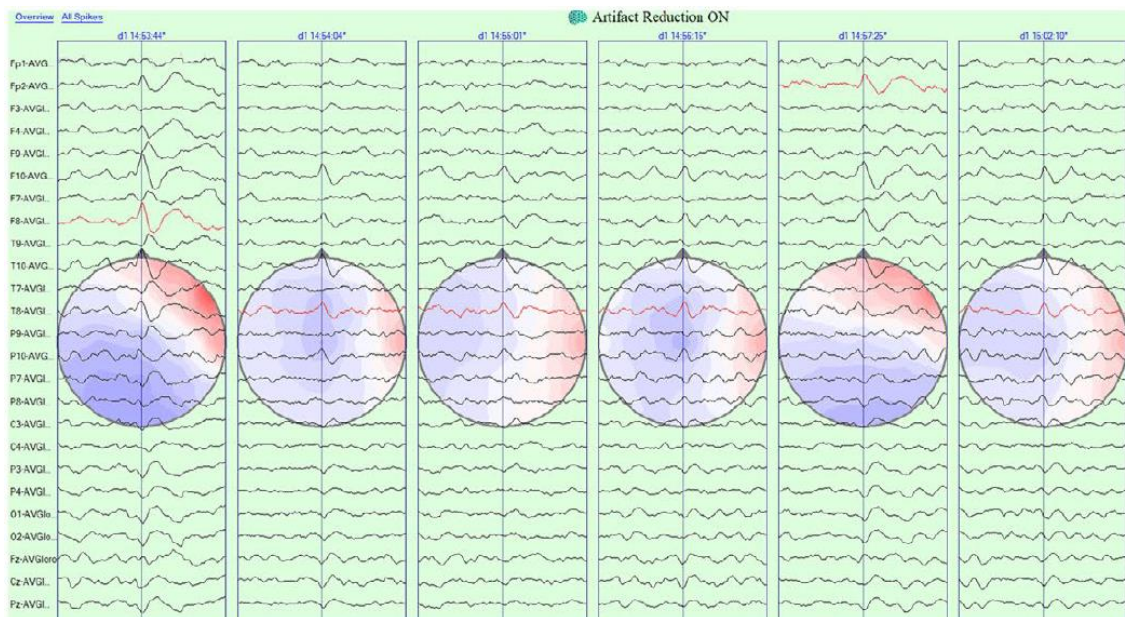
Encevis

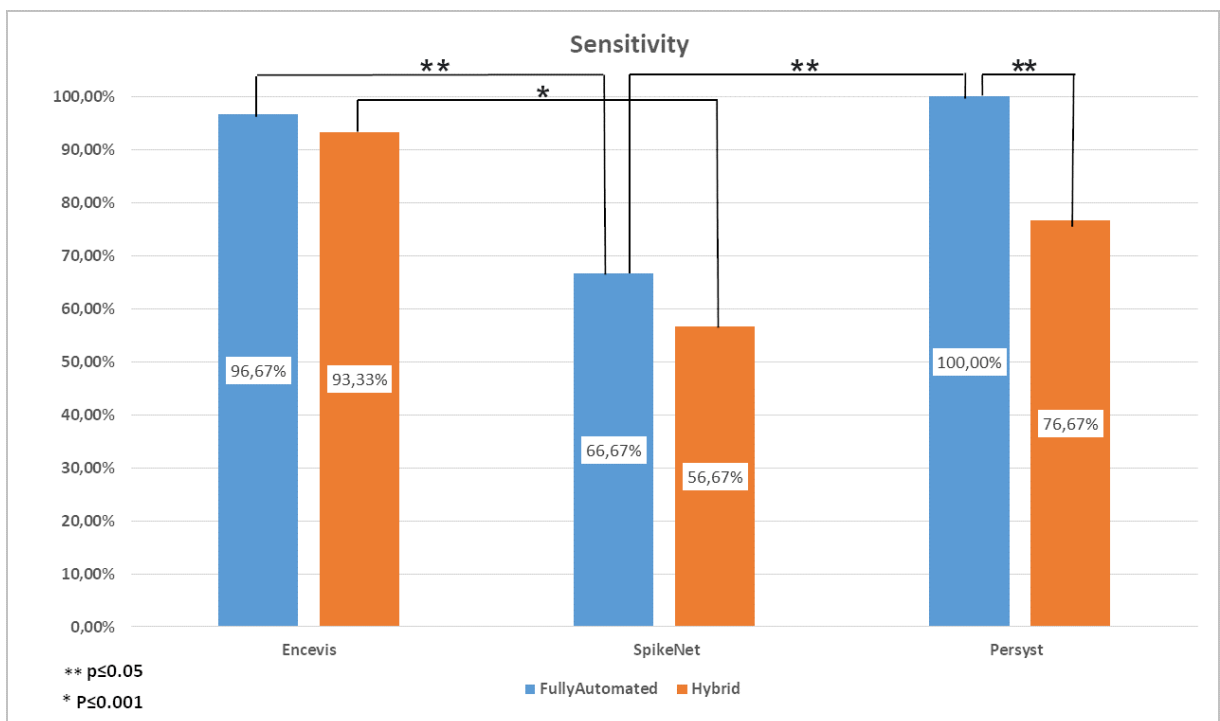
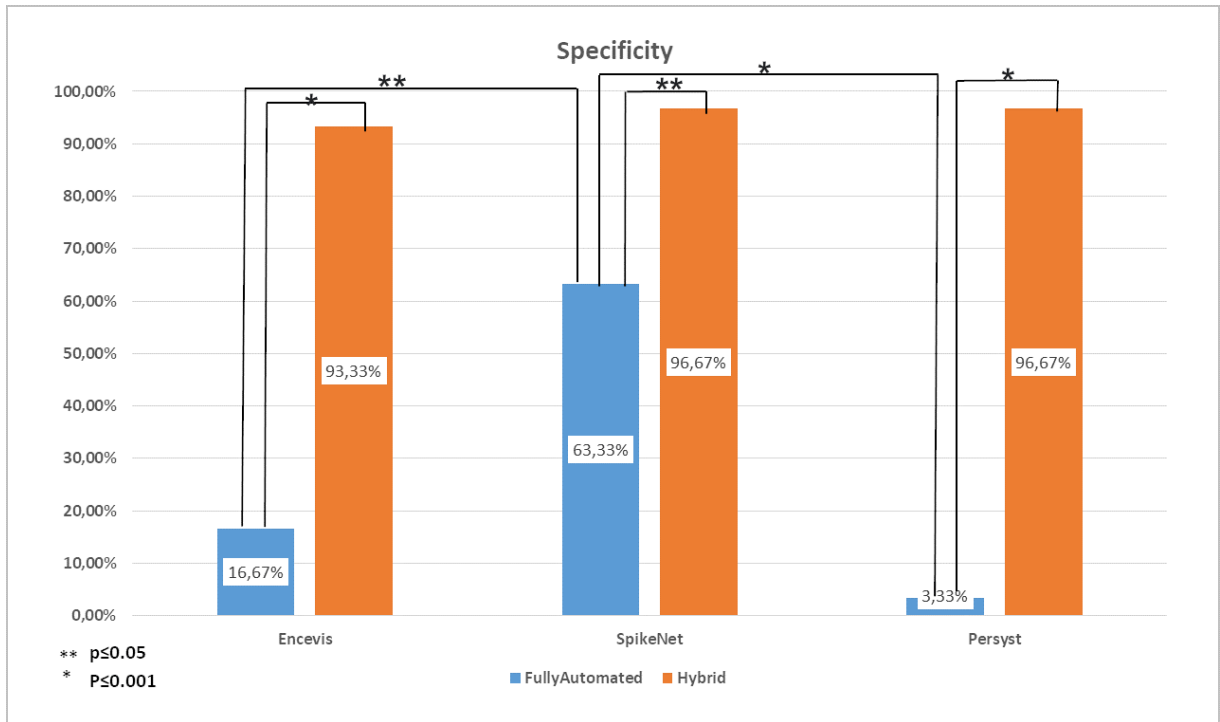


Spikenet



Persyst



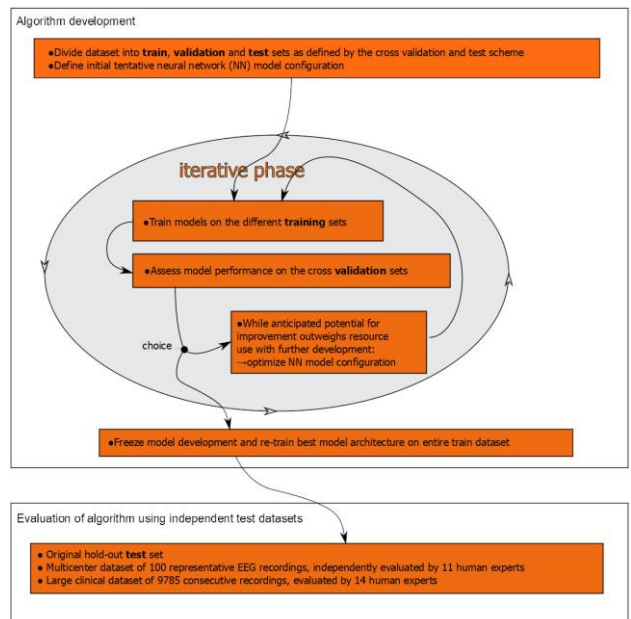


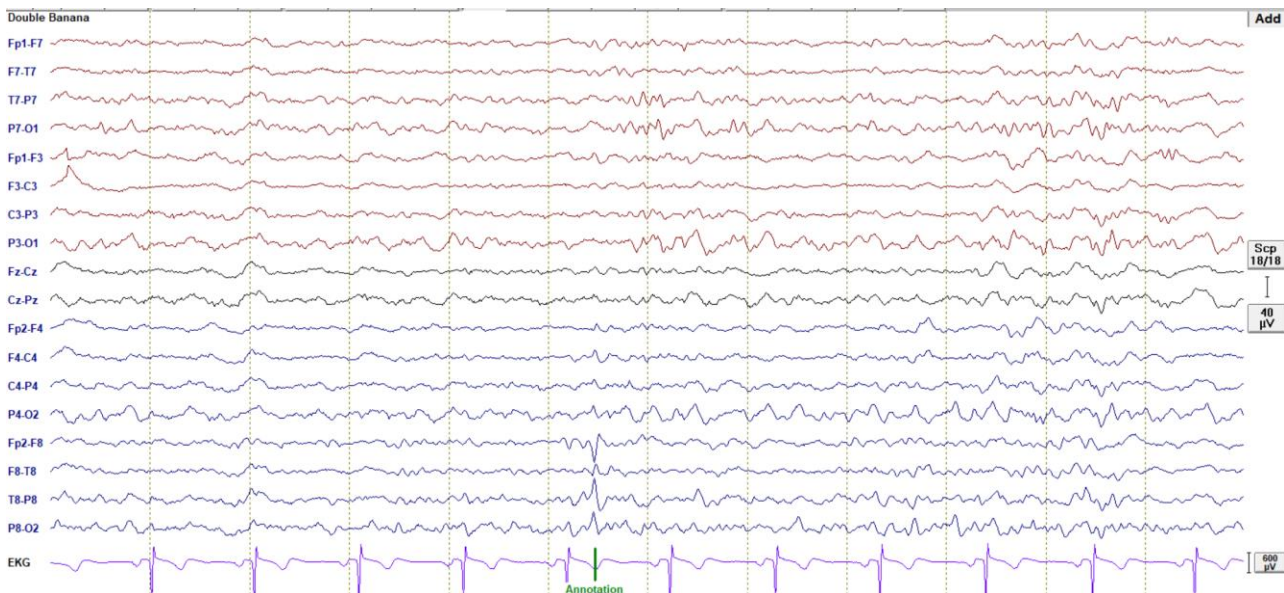
Reduced time-consumption!

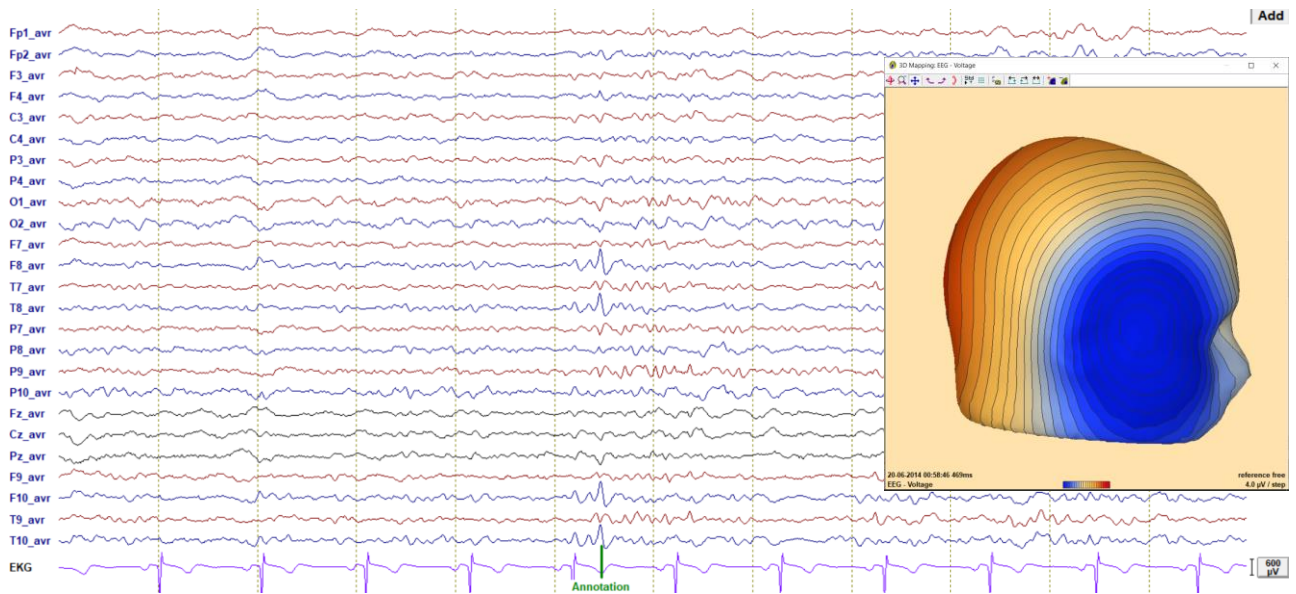
- by 26% – 91% using the hybrid approach
- $p < 0.001$

Fully automated EEG reading: routine clinical EEGs

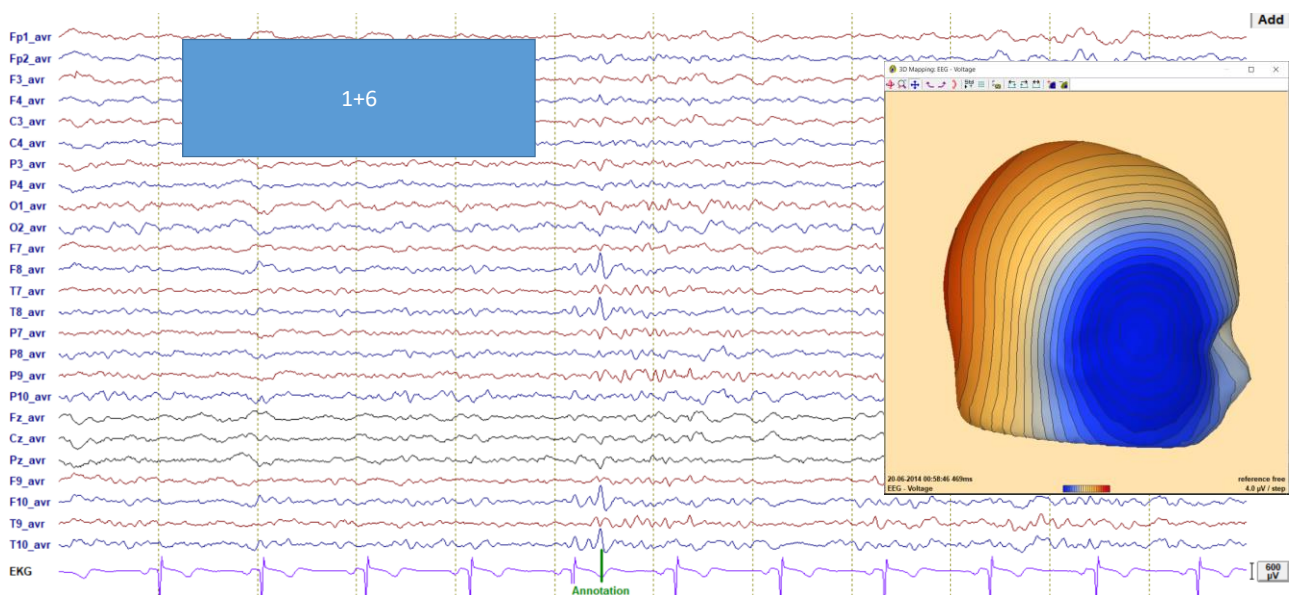
- AI (CNN) – autoSCORE
- Development:
 - 30k EEGs – highly annotated in SCORE
- Clinical Validation
 - Independent dataset: 10k EEGs
- Output:
 - Normal
 - Abnormal:
 - Epileptiform-Focal
 - Epileptiform-Generalized
 - Slowing-Diffuse
 - Slowing-Focal

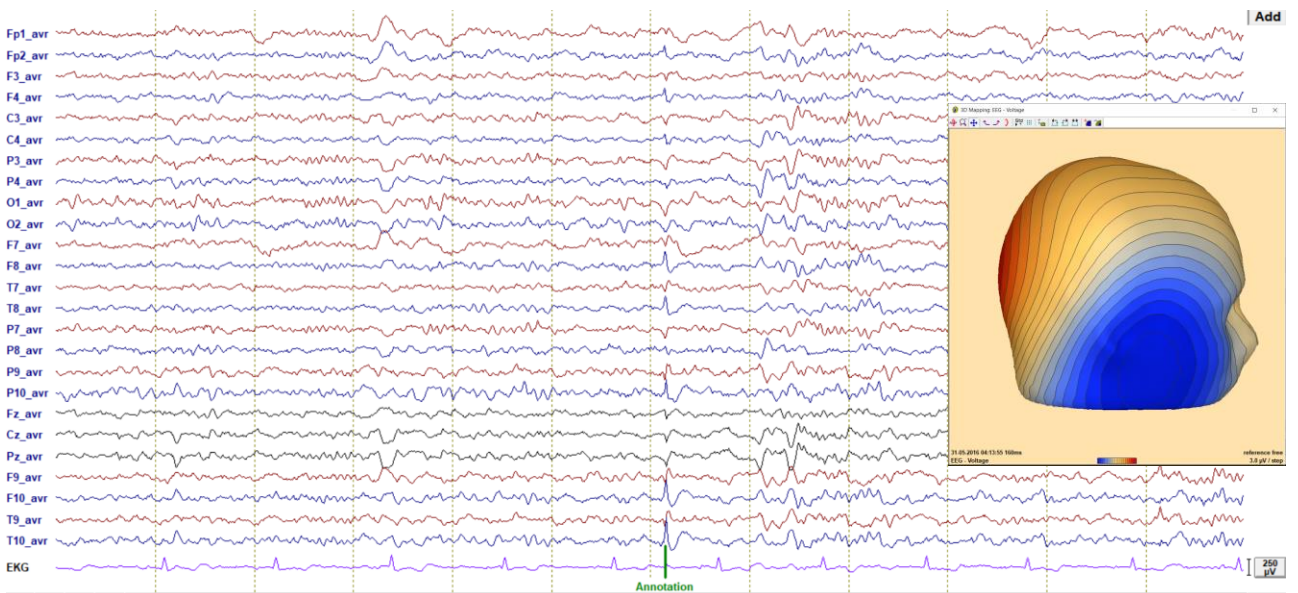
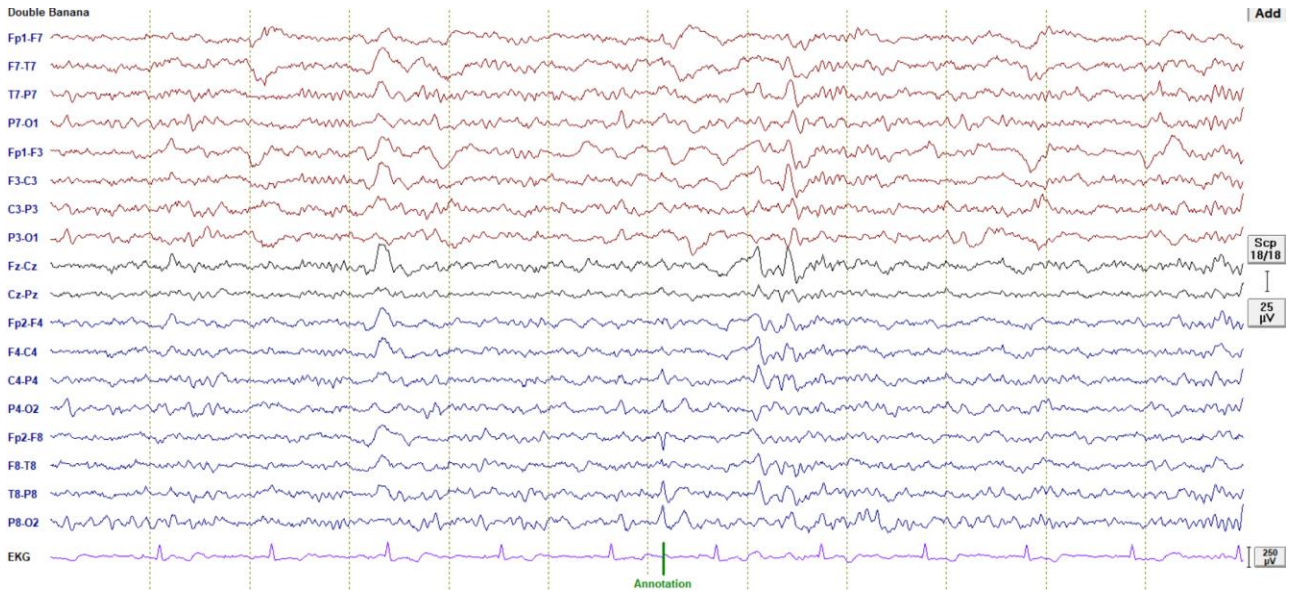




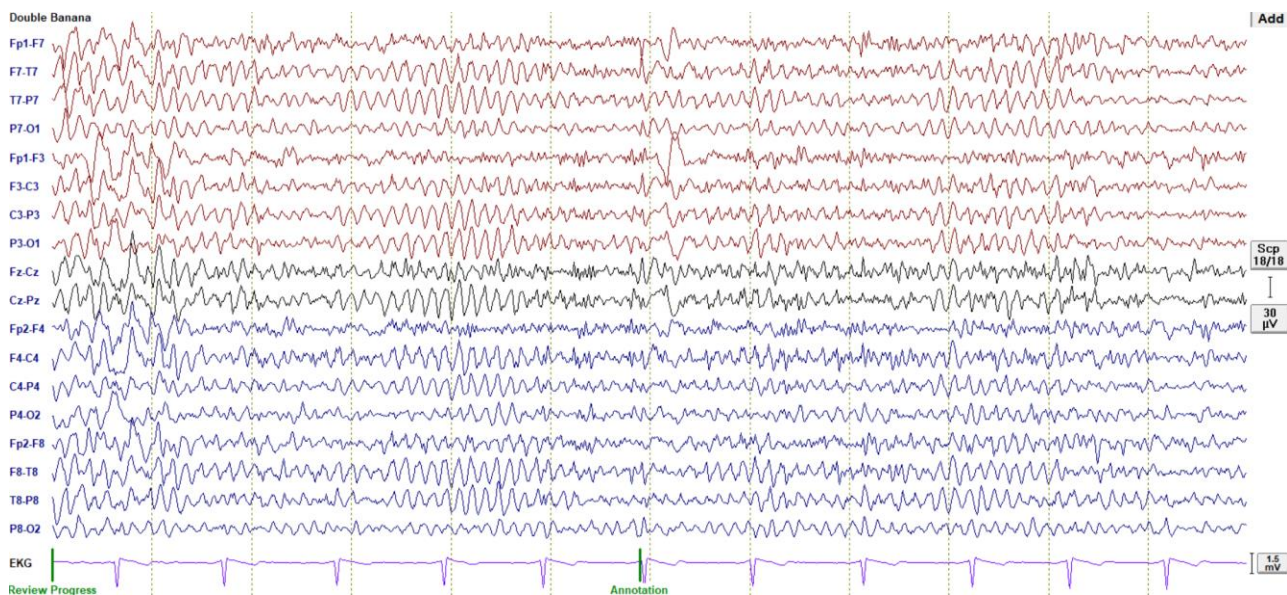
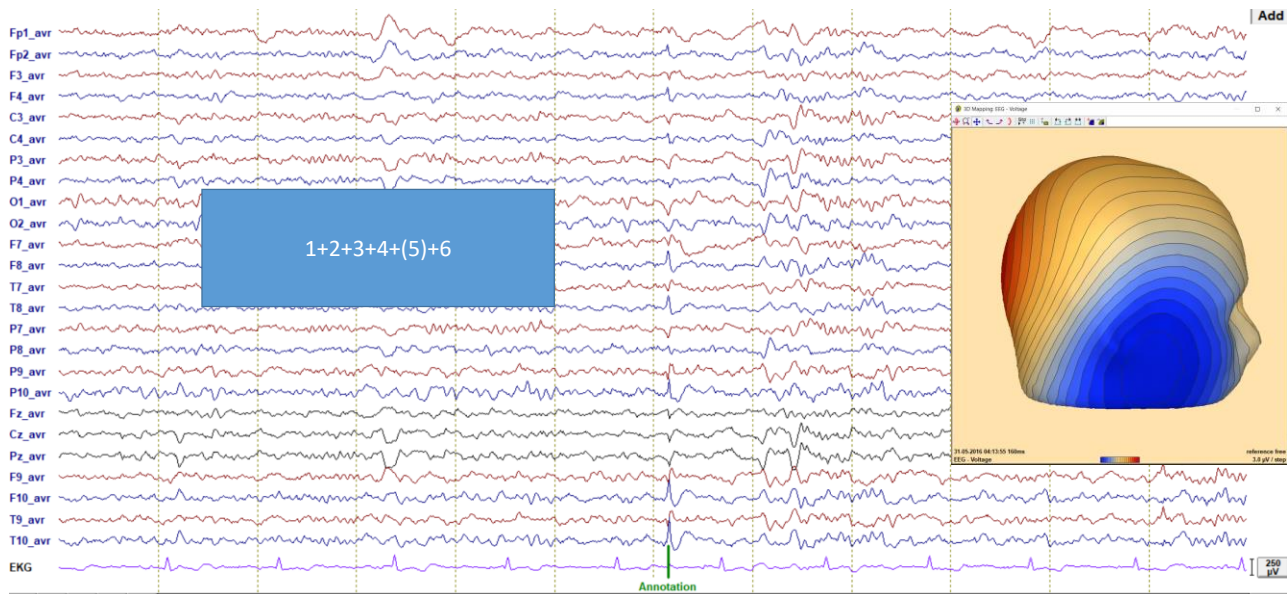


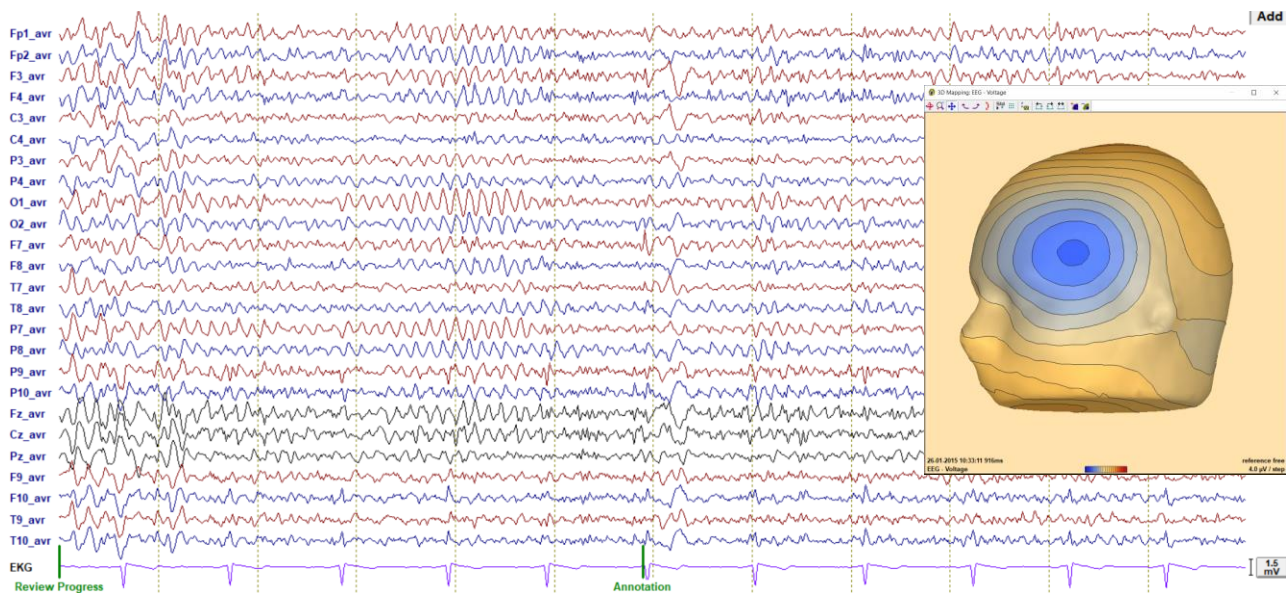
Normal sharp transient!



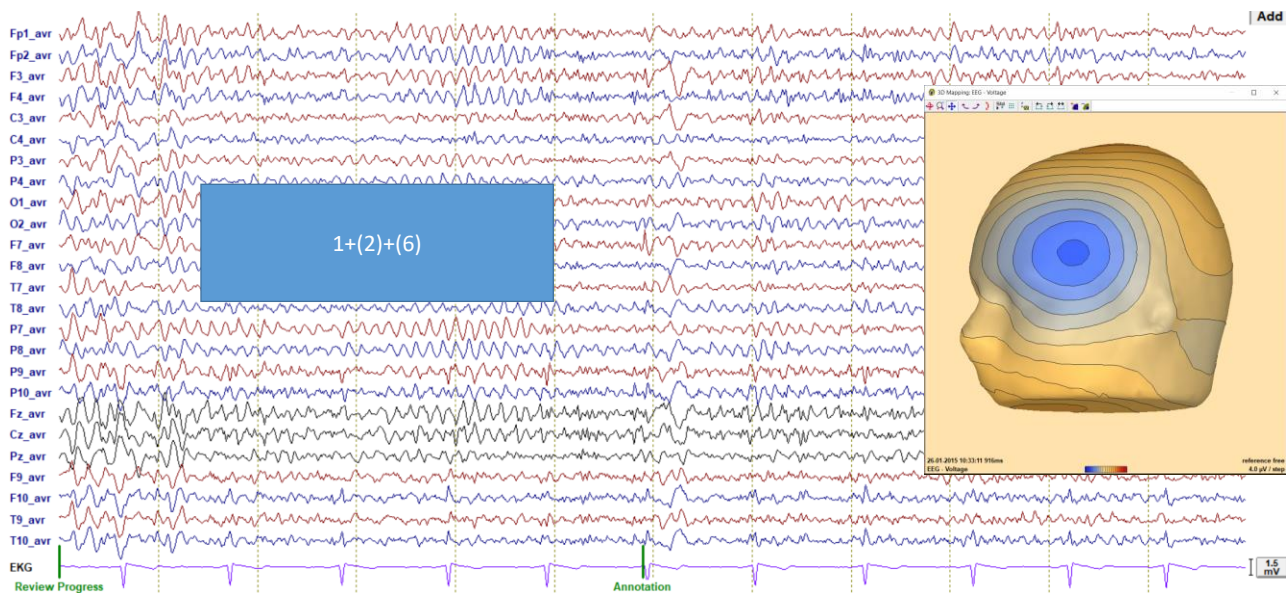


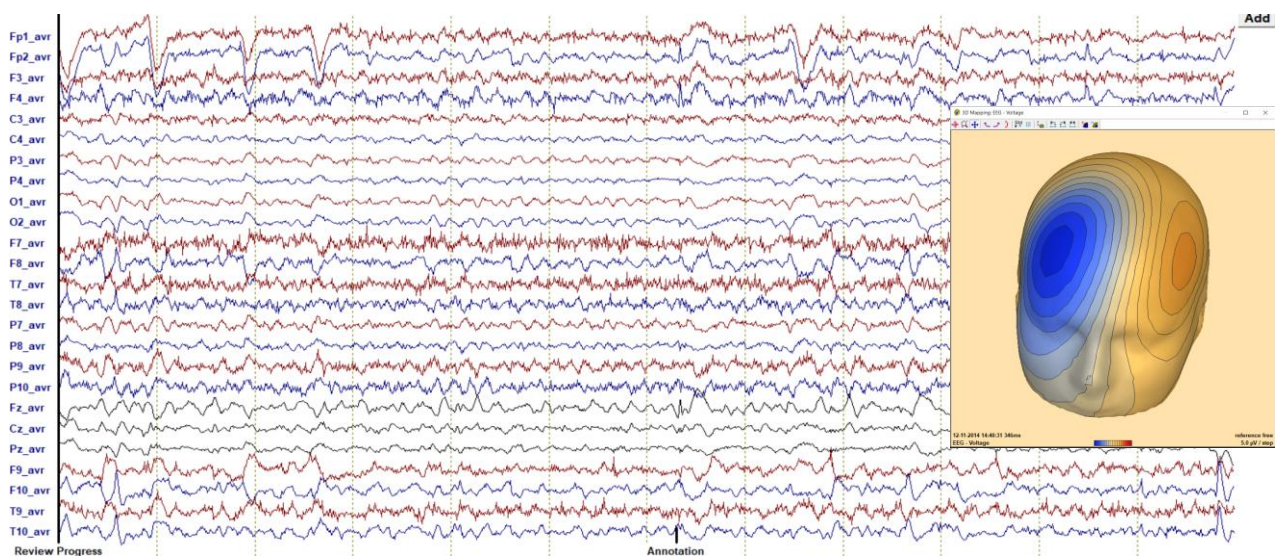
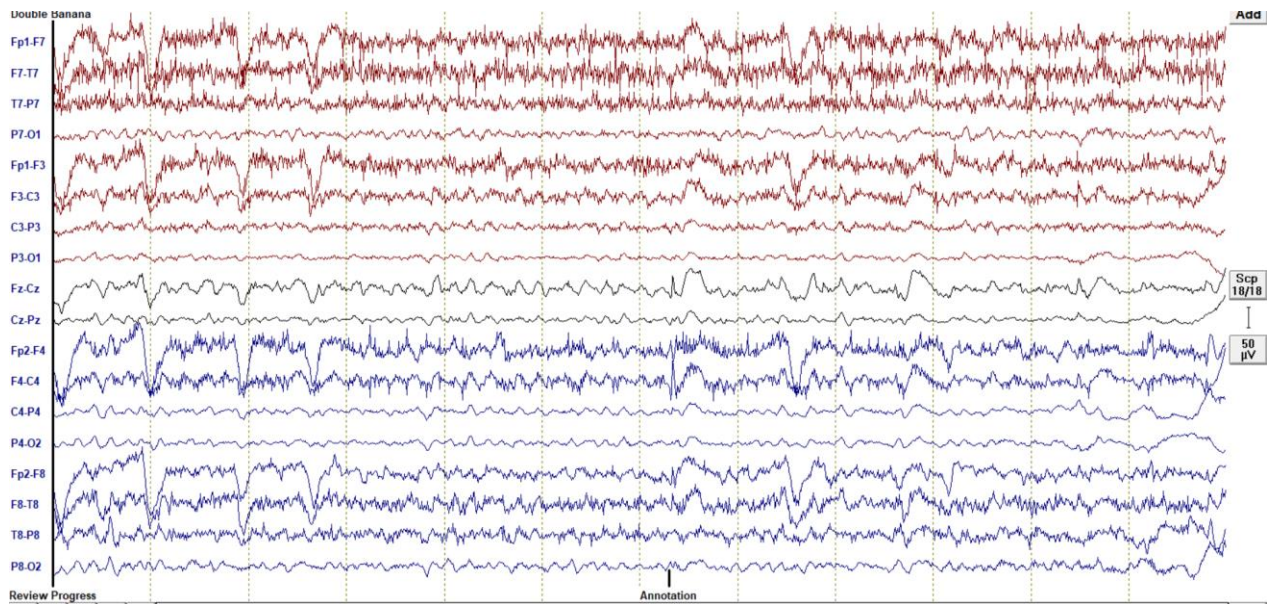
IED



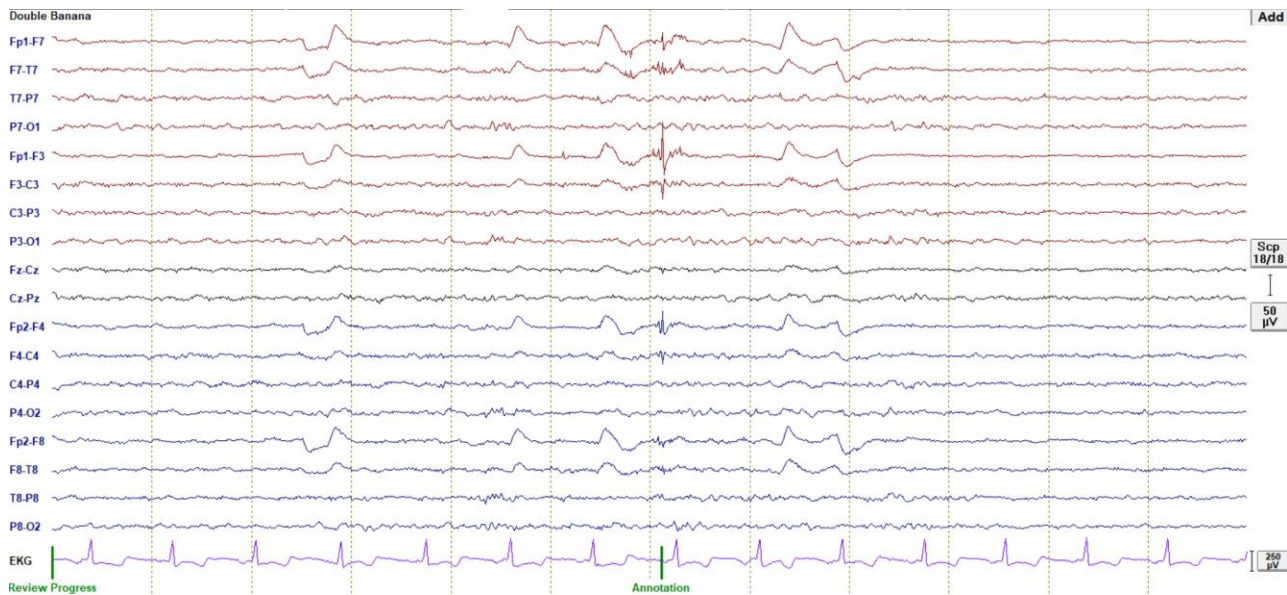
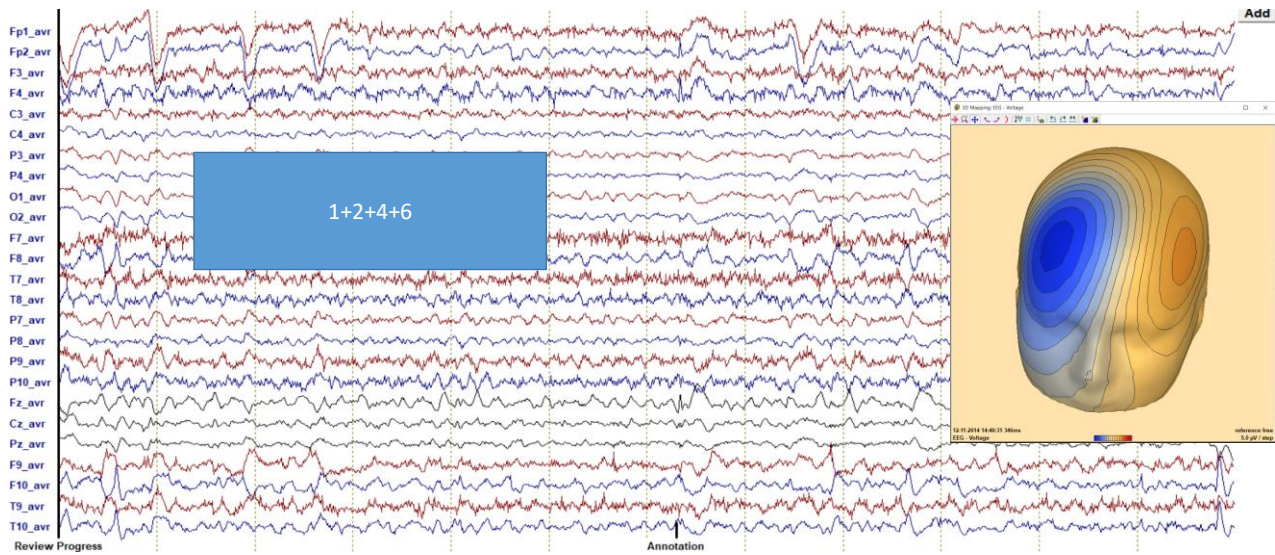


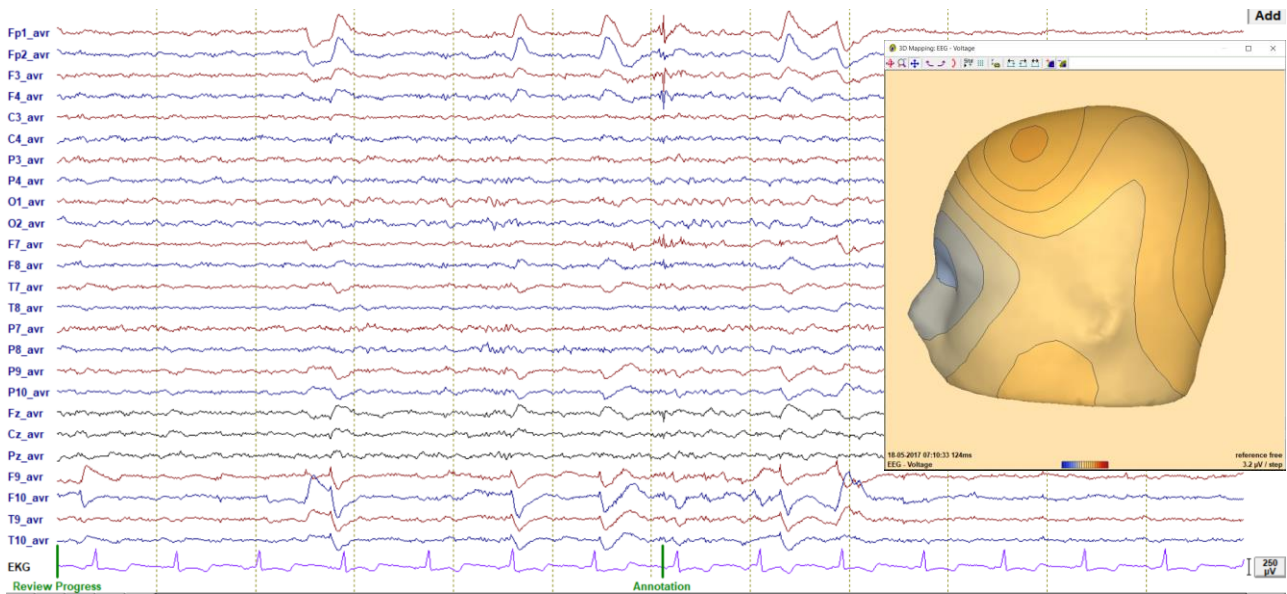
Normal sharp transient



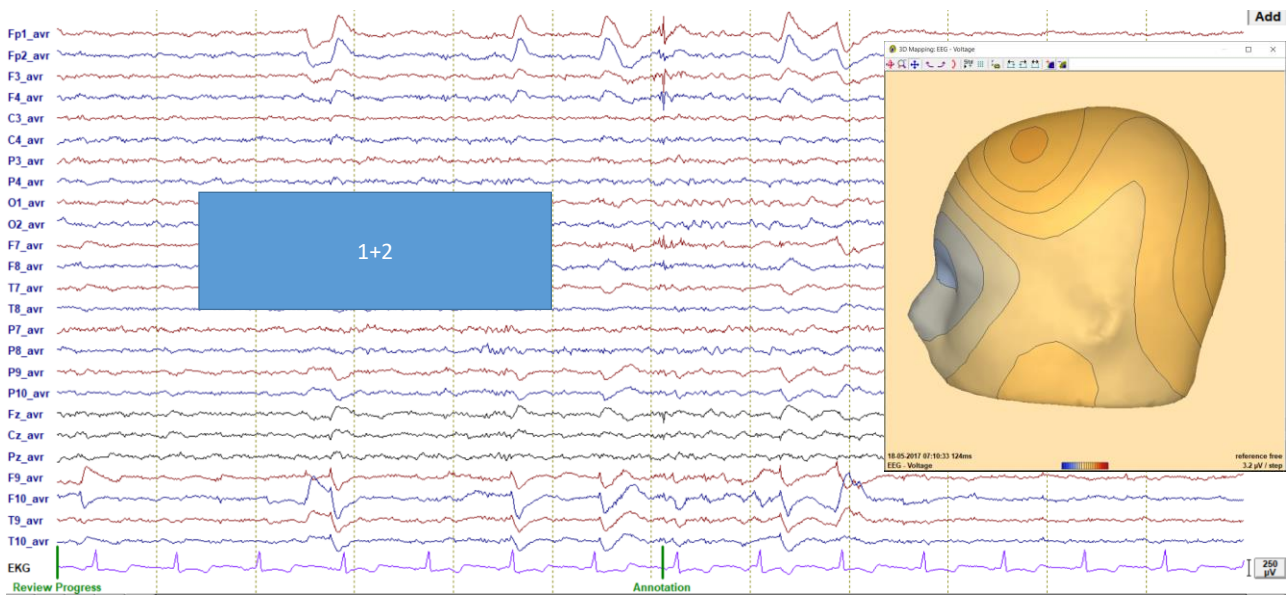


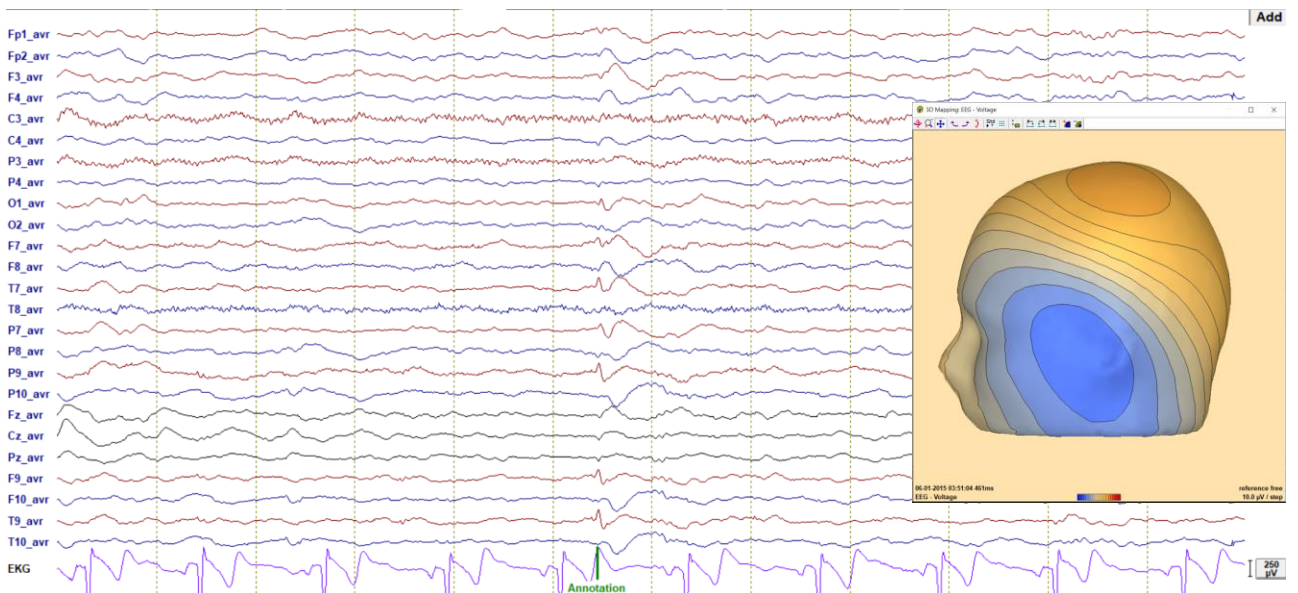
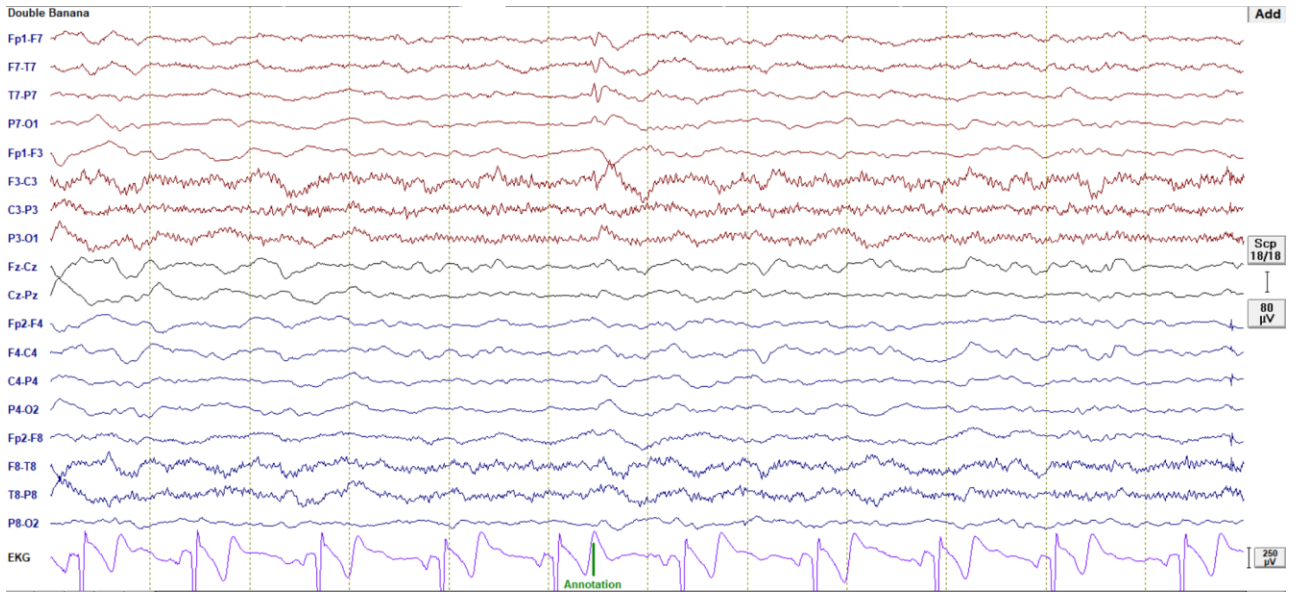
IED





Artifact





IED

