



When is something spikish an epileptiform spike ?

Sándor Beniczky





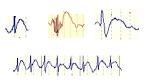
Disclosures

- Scientific consultant: Epihunter
- Speaker: Natus Neuro

Learning Objectives

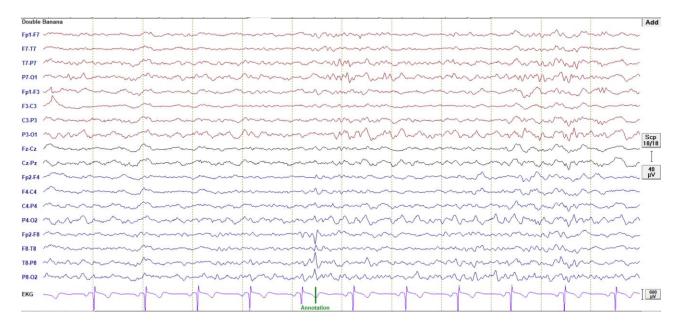
- To recognize the IFCN criteria for identifying IEDs.
- To distinguish between IEDs and non-epileptiform sharp transients applying the IFCN criteria.
- To explain the trade-off between sensitivity and specificity in clinical EEG reading

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?

Fp1_avr Fp2_avr Fp2_avr Fp2_avr Fp3_avr Fq3_avr Fq3_avr Fq3_avr Fq3_avr Fq4_v
F3_avr P Money B16-Mare F4_avr P Money B16-Mare G1_avr P Money B16-Mare P3_avr P Money B16-Mare P1_avr
F4_avr Image Ut a way C1_avr Image Ut a way C4_avr Image Ut a way C4_avr Image Ut a way C4_avr Image Ut a way C1_avr Image Ut a way C2_avr Image Ut a way C1_avr Image Ut a way C2_avr Image Ut a way F1_avr Image Ut a way F6_avr Image Ut a way
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P3_avr P4_ovr 00_ovr F7_ovr F8_avr
P4_avr 01_avr 02_avr F7_avr F8_avr
01_svr 02_svr FT_svr FB_svr
O2_avr
FT_SVT F8_SVT
F8_avr - Scop
T8 avr many har her her her her her her her her her he
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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 <u>epilepsy syndrome</u>.

Probability of further seizures after the first unprovoked seizure:

Children		Adults	
Normal EEG:	?%	• Normal EEG:	?%
• EEG=IED:	?%	• 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		Adults		
Normal EEG:	38%	Normal EEG:	12%	
• EEG=IED:	?%	• 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		Adults	Adults			
Normal EEG:	38%	Normal EEG:	12%			
• EEG=IED:	65%	• 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 <u>more harmful</u> 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.

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

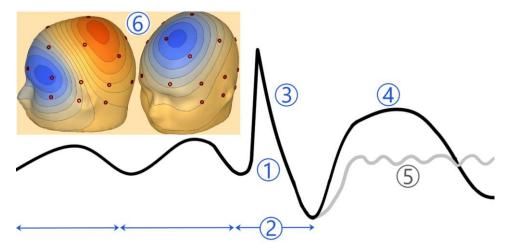
Clinical Neurophysiology Practice 2 (2017) 170-185



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

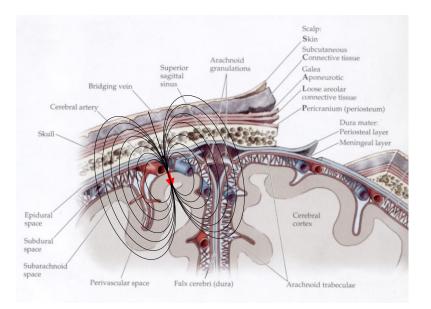


Nick Kane ^{a,*}, Jayant Acharya^b, Sandor Beniczky^c, Luis Caboclo^d, Simon Finnigan^e, Peter W. Kaplan^b, Hiroshi Shibasaki^f, Ronit Pressler^a, Michel J.A.M. van Putten^g

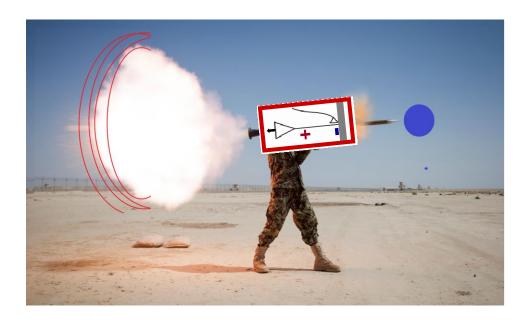


- 1. Di / tri-phasic waves with sharp / spiky morphology (pointed peak).
- 2. Different wave-duration than the ongoing background activity.
- 3. Asymmetry of the waveform.
- 4. The transient is followed by an associated slow after-wave.
- 5. The background activity surrounding EDs is disrupted by the presence of the EDs.

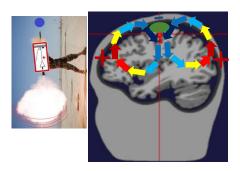
6. Distribution of the negative and positive potentials on the scalp suggests a source of the signal in the brain, corresponding to a radial, oblique or tangential orientation of the source. This is best assessed by inspecting voltage maps constructed using common-average reference.

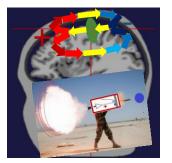


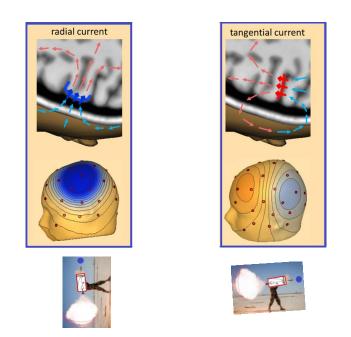




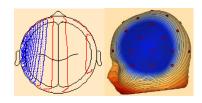
Signal generation: Both negative and positive potentials on the scalp

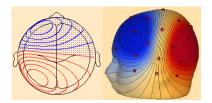




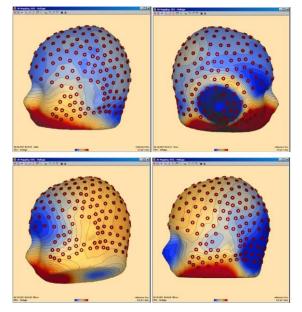


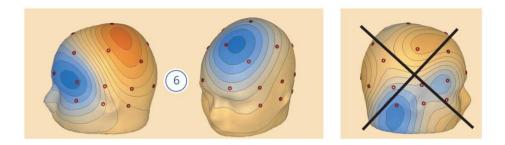
From the brain

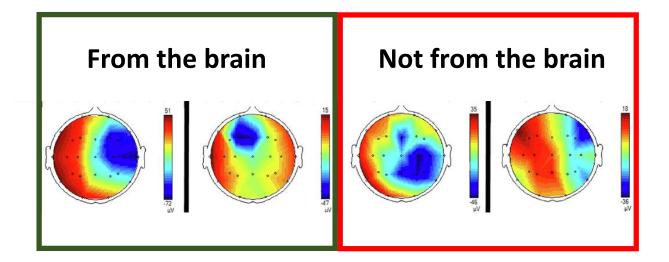




Not from the brain







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 Rampp, 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.00000000009439

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



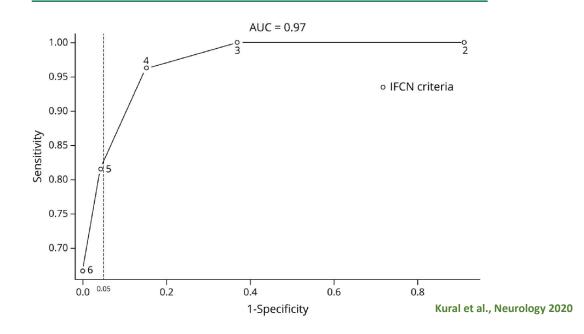
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Editorial Epileptiform discharges: Are we still defining them? Page 862

Figure 3 Receiver operating characteristic (ROC) curve



Method	Sensitivity % (95% Cl)	Specificity % (95% CI)	Accuracy % (95% CI)	AC1 (95% CI)
IFCN criteria in sensor space				
Cutoff (no. of fulfilled criteri	a)			
≥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 <mark>(</mark> 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

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

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? Clinical Neurophysiology 131 (2020) 2250-2254



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Clinical Neurophysiology



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

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 Udupi^b, Richard Wennberg^c, Stefan Rampp^d, Pål G. Larsson^e, Reinhard Schulz^f, Sándor Beniczky^{a,g,h,*}

^a Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark

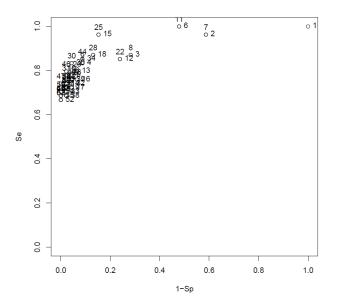
^e Department of Neurosurgery, Rikshospitalet, Oslo University Hospital, Oslo, Norway

⁸ Department of Clinical Neurophysiology, Danish Epilepsy Centre, Dianalund, Denmark ⁹ Separtment of Clinical Neurophysiology, Danish Epilepsy Centre, Dianalund, Denmark

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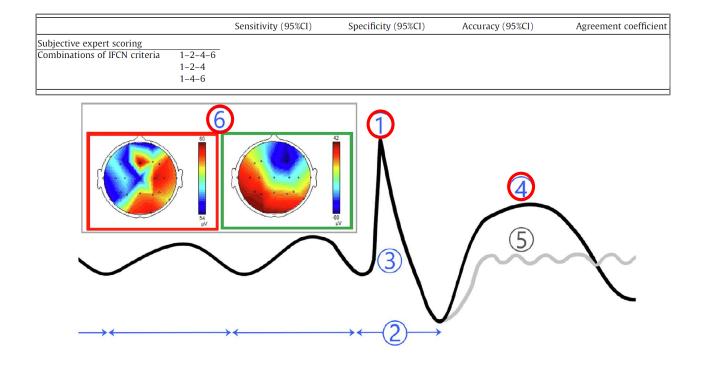


63 different combinations of the 6 criteria

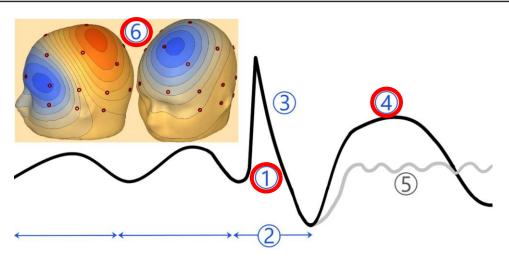


^b Section for Biostatistics, Department of Public Health, Aarhus University, Denmark

^c Krembil Brain Institute, Toronto Western Hospital, University of Toronto, Toronto, Canada
^d Department of Neurosurgery, University Hospital Erlangen, Cermany and Department of Neurosurgery, University Hospital Halle (Saale), Germany



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



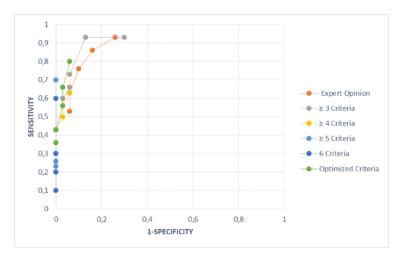
The influence of the abundance and morphology of epileptiform discharges on diagnostic accuracy: How many spikes you need to spot in an EEG

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

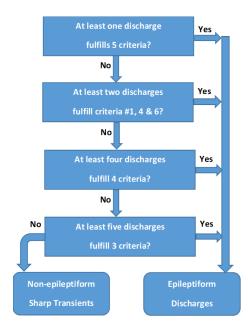
CRITERIA	Number of	SENSITIVITY	SPECIFICITY	ACCURACY
	discharges			
Expert	≥1	93.33%	73.33%	83.33%
Opinion	≥2	86.67%	83.33%	85.00%
(non-	≥3	76.67%	90.00%	83.33%
restricted)	≥4	63.30%	93.33%	78.33%
	≥5	53.33%	93.33%	73.33%
≥3 IFCN	≥1	93.33%	70.00%	81.67%
criteria	≥2	93.33%	86.67%	90.00%
	≥3	73.33%	93.33%	83.33%
	≥4	66.67%	93.33%	80.00%
	≥5	60.00%	96.67%	78.33%
≥4 IFCN	≥1	80.00%	93.33%	86.67%
criteria	≥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	≥1	70.00%	100.00%	85.00%
criteria	≥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	≥1	43.33%	100.00%	71.67%
criteria	≥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	≥1	80.00%	93.33%	86.67%
Optimized	≥2	66.67%	96.67%	81.67%
Criteria	≥3	56.67%	96.67%	76.67%
	≥4	43.33%	100.00%	71.67%
	≥5	36.67%	100.00%	68.33%

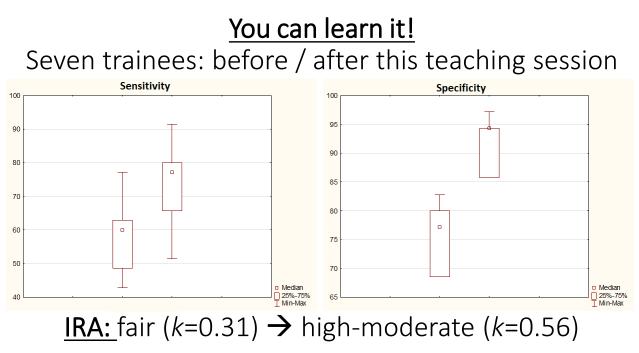
Combination of Criteria-sets	Sensitivity	Specificity	Accuracy
1 IED fulfilling 5-criteria OR 2 IEDs fulfilling the Optimized Criteria	73.33%	96.67%	85.00%
1 IED fulfilling 5-criteria OR 4 IEDs fulfilling 4 criteria	70.00%	96.67%	83.33%
1 IED fulfilling 5-criteria OR 5 IEDs fulfilling 3-criteria	76.67%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

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

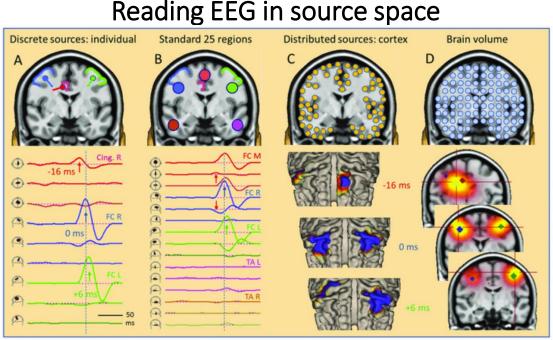
To achieve a specificity >95% (avoid over-reading)

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

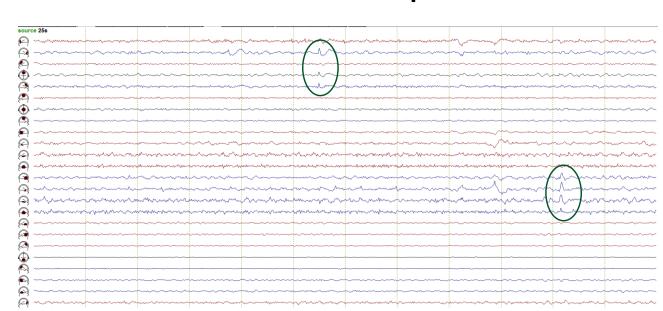




Kural et al., Epileptic Disorders 2021



Reading EEG in source space



EDs – in source space

EDs – in source space

Fp1-F9 America F9_avr Bernanda Commercia	1 Fp1-F9 1 - F9_avr
F9.A1 min PV T9_avr min P	
A1-P9 man P9_avr many man ()	- A1-P9
P9-01 1 F10_avr F10_avr	P9-01
Fp1-F7 T10_avr (Fp1-F7 mm T10_avr Mmm
FT.TT	F7-T7
17.P7 P10_avr 1	T7-P7 P10_avr_v/
P7-01 Fp1_avr	- P7-01
FD1-F3 man F7_avr	- Fp1-F3 v F7_avr MAN
F3-C3 manufin TT_avr	F3-C3 man TT_avr man D
C3P3 harris P7_avr man Quant	C3-P3 Amman P7_avr Amman @
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C2.P2	Cz-Pz
Pz.Oz	PZ-OZ month T8_avr month and Am
P8_avr V A Q month and	FD2-F4 mmm P8_avr mmmm Q.MMmm
Fp2.F4 O2_evr O	F4-C4 mmmmm 02_avr - Chammer -
	~ C4-P4 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
	and share the second
P4-02 P3_avr p3_avr fat	
Fp2-F8 C3_avr called and fa	
F8-T8 F4_avr f4_avr	F4_avr
T8-P8 C4_avr	TB-P8 C4_avr - C4_avr -
P8-02 P4_avr m P4_avr m	P8-02 PM P4 avr mmmmmm
Fp2-F10 Fz_avr	Fp2-F10 m Fr avr monther fr
F10-A2	FID-AZ
A2-P10 CZ_AVT CZ_AVT	A2-P10 - CZ_AVF - CZ_
P10-02 PZ_avr PZ_avr	P10-02 MM Pz_avr mm Pz_avr

compared with expert scorings					
Sensitivity % (95% Cl)	Specificity % (95% CI)	Accuracy % (95% Cl)	AC1 (95% CI)		
100 (93.40–100)	8.70 (2.42–20.79)	58 (47.71-67.80)	0.83 (0.76–0.88)		
100 (93.40–100)	63.04 (47.55–76.79)	83 (74.18–89.77)	0.64 (0.53-0.74)		
96.30 (87.25–99.55)	84.78 (71.13–93.66)	91 (83.60–95.80)	0.60 (0.53-0.69)		
81.48 (68.57–90.75)	95.65 (85.16–99.47)	88 (79.98–93.64)	0.49 (0.38-0.60)		
66.67 (52.53–78.91)	100 (92.29–100)	82 (73.05-88.97)	0.60 (0.50–0.70)		
85.19 (72.88–93.38)	95.65 (85.16–99.47)	90 (82.38–95.10)	0.59 (0.51–0.68)		
	Sensitivity % (95% Cl) 100 (93.40-100) 100 (93.40-100) 96.30 (87.25-99.55) 81.48 (68.57-90.75) 66.67 (52.53-78.91)	Sensitivity % (95% Cl) Specificity % (95% Cl) 100 (93.40-100) 8.70 (2.42-20.79) 100 (93.40-100) 63.04 (47.55-76.79) 96.30 (87.25-99.55) 84.78 (71.13-93.66) 81.48 (68.57-90.75) 95.65 (85.16-99.47) 66.67 (52.53-78.91) 100 (92.29-100)	Sensitivity % (95% Cl) Specificity % (95% Cl) Accuracy % (95% Cl) 100 (93.40-100) 8.70 (2.42-20.79) 58 (47.71-67.80) 100 (93.40-100) 63.04 (47.55-76.79) 83 (74.18-89.77) 96.30 (87.25-99.55) 84.78 (71.13-93.66) 91 (83.60-95.80) 81.48 (68.57-90.75) 95.65 (85.16-99.47) 88 (79.98-93.64) 66.67 (52.53-78.91) 100 (92.29-100) 82 (73.05-88.97)		

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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.

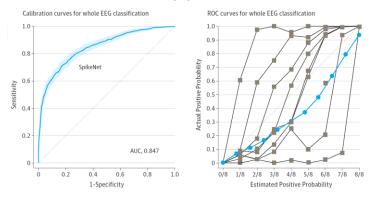
• Human experts



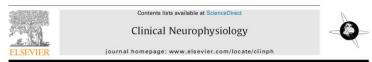
Research JAMA Neurol. doi:10.1001/jamaneurol.2019.3485 Published online October 21, 2019. JAMA Neurology | Brief Report

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

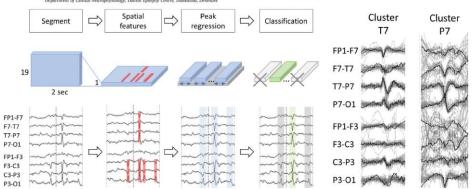


An artificial intelligence-based EEG algorithm for detection of epileptiform EEG discharges: Validation against the diagnostic gold standard



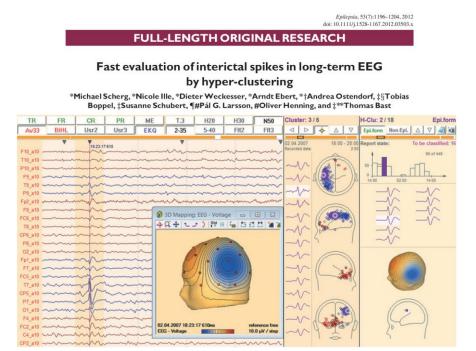
Franz Fürbass ^a, Mustafa Aykut Kural ^b, Gerhard Gritsch ^a, Manfred Hartmann ^a, Tilmann Kluge ^a, Sándor Beniczky $^{\rm bC,\bullet}$

^a Center for Health & Bioresources, AIT Austrian Institute of Technology GmbH, Vienna, Austria ^b Department of Chinical Neurophysiology, Anthus University Hospital and Department of Chinical Medicine, Aarhus University, Aarhus, Denmark ^b Department of Chinical Neurophysiology, Dunith Effetory Center, Diamaland, Denmark



Challenges & possible solutions

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



91% of the visually identified spikes

Received: 10 January 2022	Revised: 17 February 2022	Accepted: 17 February 2022
DOI: 10.1111/epi.17206		

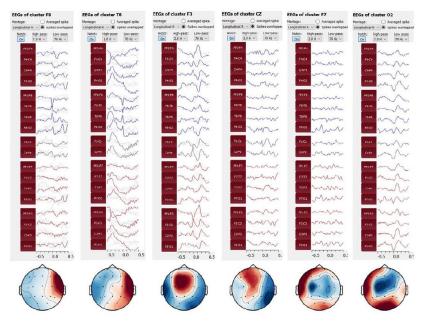
RESEARCH ARTICLE

Epilepsia

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

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- 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 exerts using IFCN criteria

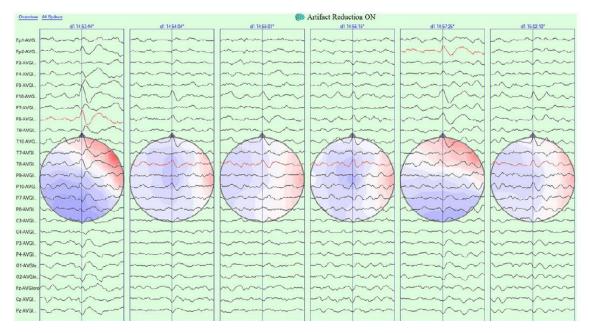


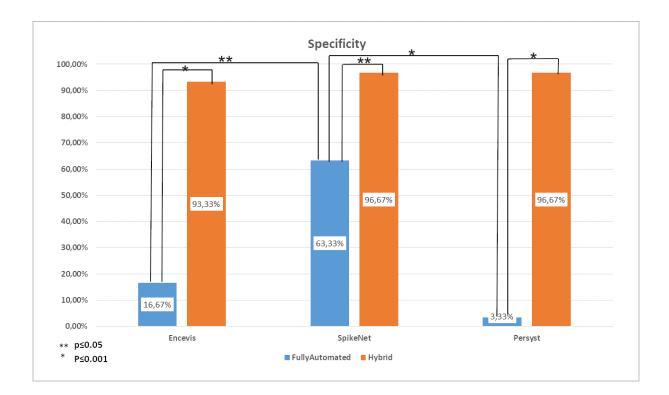
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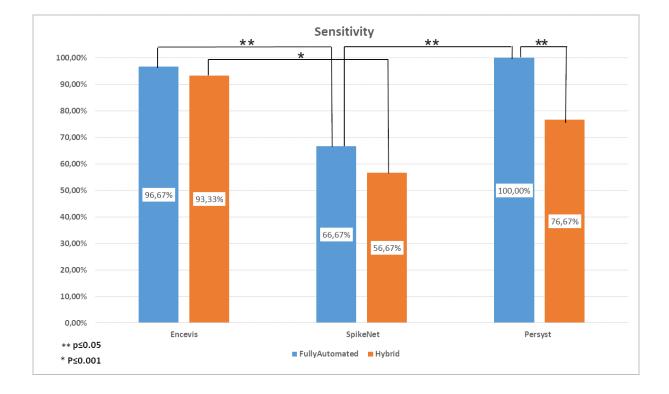
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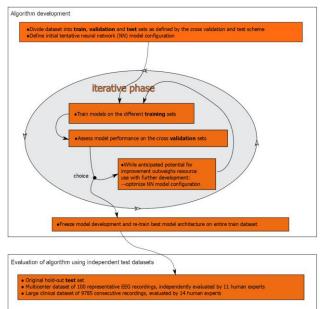


Reduced time-consumption!

- 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



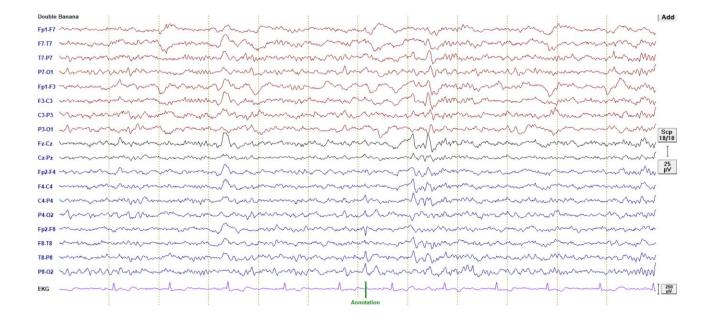


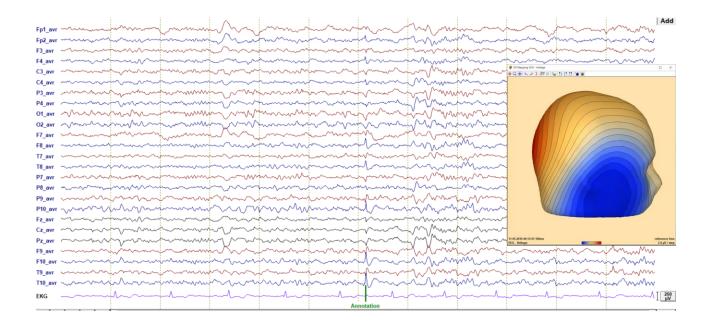




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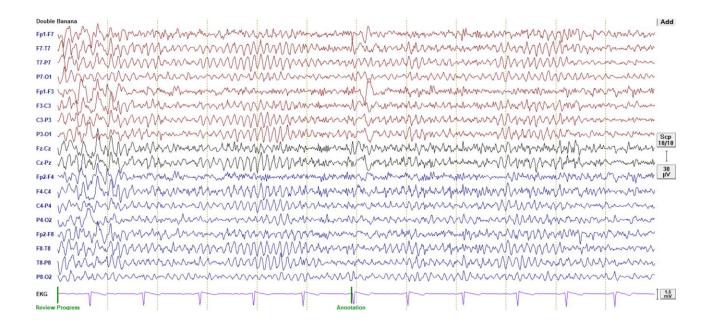
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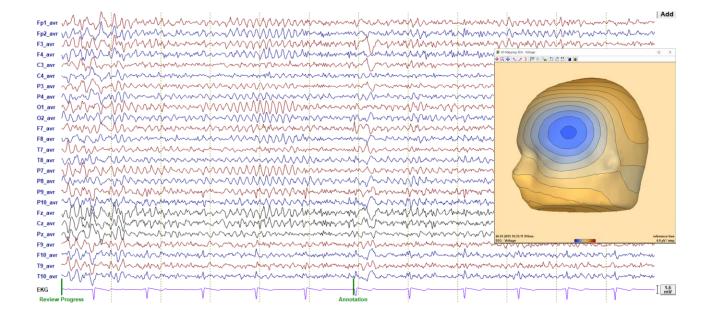




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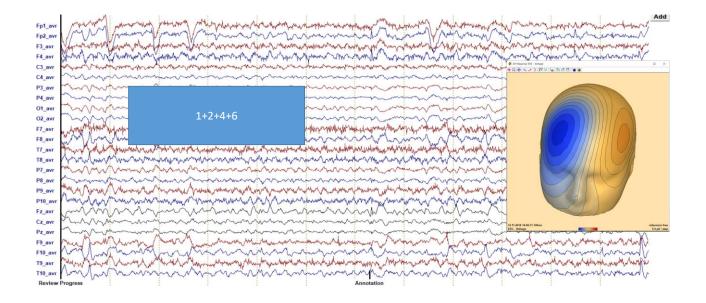
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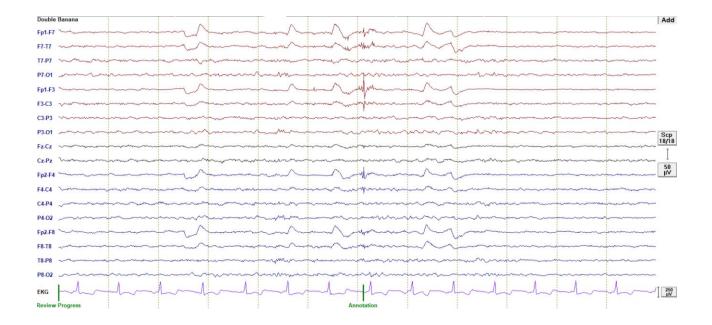
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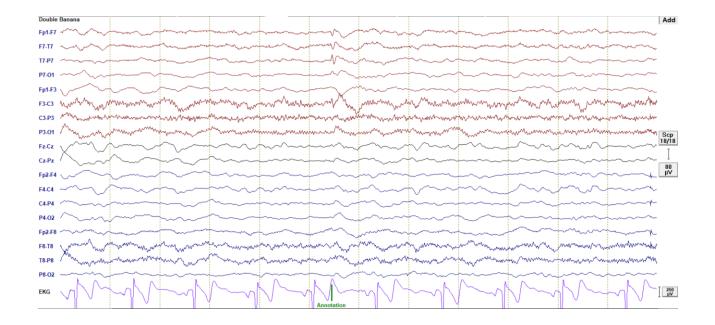


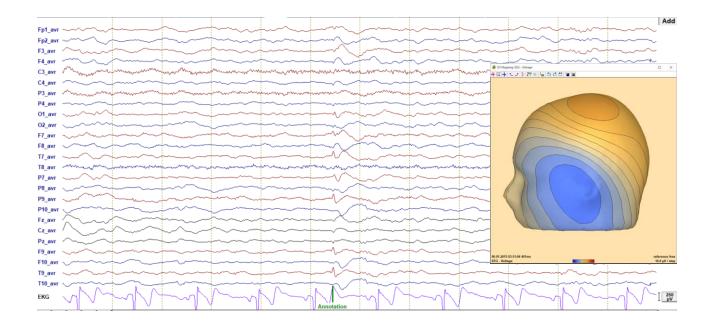




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