Scuola Superiore di Neurologia

CORSO RESIDENZIALE SIN

Update su diagnosi e monitoraggio delle epilessie

Genova, 24 - 25 febbraio 2015

Accademia Nazionale di Medicina - Via M. Piaggio 17/6 - Genova

10.45-11.30 Predizione EEG delle crisi epilettiche
U. AGUGLIA, *Cantanzaro*

Predizione crisi: definizioni

Previsione, Predizione, Anticipazione: sinonimi

Identificazione precoce (di esordio delle crisi): algoritmi che identificano l'inizio della crisi (**non è predizione**)

Predizione crisi: potenziali utilità

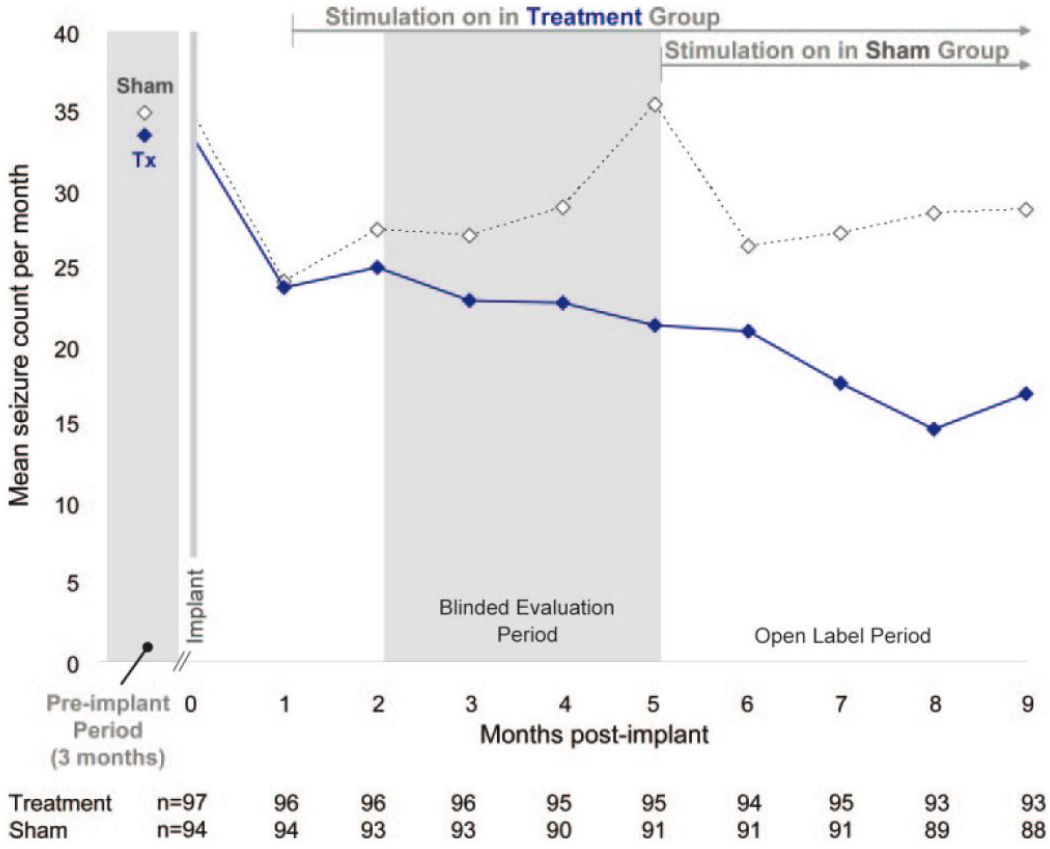
1. Cliniche:
   a. prevenzione incidenti, disagi, ecc..
   b. supporto diagnostico (monitoraggi video-EEG, SPECT/PET critica, ecc..)

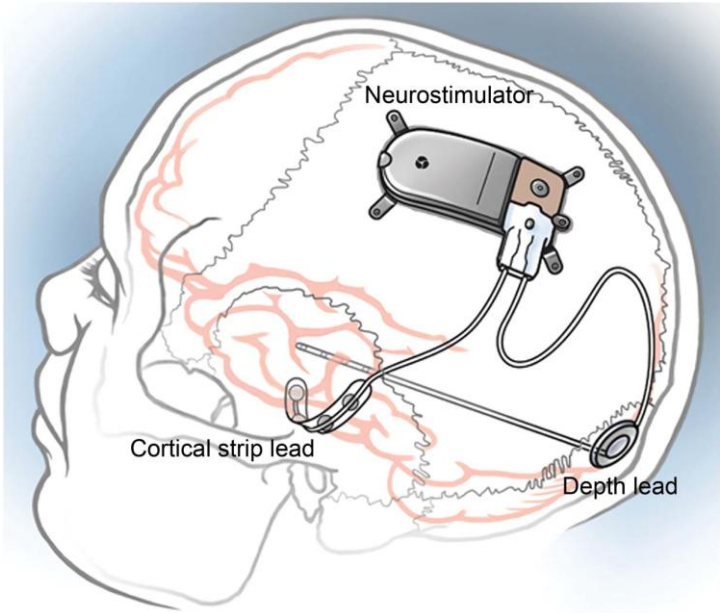
2. Terapeutiche:
   a. profilassi farmacologica immediata
   b. interventi sul focus (stimolazione elettrica, ecc..)

Responsive cortical stimulation for the treatment of medically intractable partial epilepsy

Neurology® 2011; 77:1295-1304

Martha J. Morrell, MD
On behalf of the RNS System in Epilepsy Study Group





Neurology® 2015;84:1-8

Long-term seizure reduction: Long-Term Treatment Study (n = 230 enrolled, ongoing)

	No.[a]	Median % reduction (1st quartile, 3rd quartile)	Responder rate (95% confidence interval)[b]
Year 5			
Months 60–62	172	65.5 (23.2, 91.2)	61.0 (53.6–68.0)
Months 63–65	161	60.7 (21.4, 91.6)	60.9 (53.2–68.1)
Months 66–68	142	62.4 (25.0, 92.2)	59.9 (51.6–67.6)
Months 69–71	117	48.1 (14.8, 86.2)	49.6 (40.7–58.5)
Year 6			
Months 72–74	115	65.7 (30.6, 87.1)	59.1 (50.0–67.7)

Predizione crisi

E’ vero che alcuni pazienti riescono a predire l’insorgenza delle loro crisi ?

Hungarian multicentre epidemiologic study of the warning and initial symptoms (prodrome, aura) of epileptic seizures

Seizure 1997; **6**: 361–368

P. RAJNA*, B. CLEMENS†, E. CSIBRI*, E. DOBOS‡, A. GEREGELY§, M. GOTTSCHAL¶, I. GYÖRGY‖, Á. HORVÁTH**, F. HORVÁTH††, L. MEZÖFI‡‡, I. VELKEY§§, J. VERES* & E. WAGNER¶¶

562 pazienti
studio basato su questionario compilato da un operatore

50% del pazienti avrebbe
sintomi di allarme o sintomi iniziali di crisi
(in alcuni o quasi tutti gli eventi)

Aure o “anticipazioni” ?

Seizure anticipation by patients with focal and generalized epilepsy: A multicentre assessment of premonitory symptoms

Andreas Schulze-Bonhage [a,*], Christoph Kurth [b], Astrid Carius [a], Bernhard J. Steinhoff [b], Thomas Mayer [c]

Epilepsy Research 70 (2006) 83–88

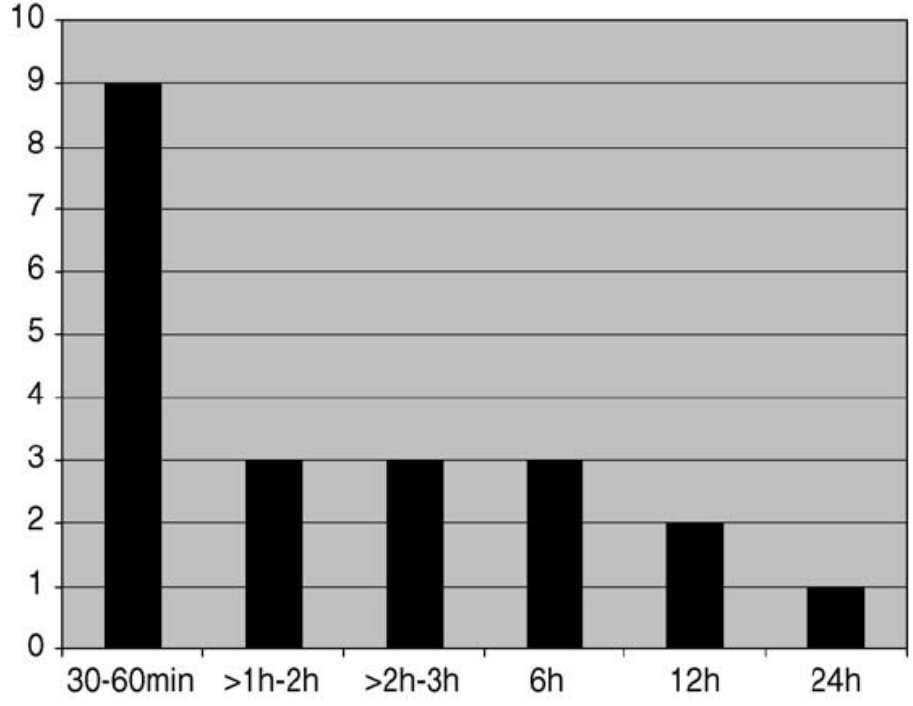


Fig. 1. Number of patients with a given estimated time interval of premonitory symptoms preceding a subsequent seizure. Three additional patients indicated "several hours" before a seizure, which does not allow for representation in this graph.

400 pazienti
Questionario auto-somministrato
Aure escluse

6% dei pazienti riferisce di anticipare le crisi

Type of premonitory symptoms reported by several patients, and respective number of reports

Premonitory symptom	Number of patients reporting the symptom
Restlessness	10
Headache	6
Malaise	5
Nausea	2
Impaired concentration	2
Dizziness	2
Tiredness	2

Seizure anticipation: Are neurophenomenological approaches able to detect preictal symptoms?

Patients with partial epilepsy feeling an aura (n=9) frequently experienced prodromes (n=6).

Claire Petitmengin [a,b,*], Michel Baulac [c,d], Vincent Navarro [c,e]

Epilepsy & Behavior 9 (2006) 298–306

Facilitating factors, prodromes, and auras

Patient	Facilitating factors	Prodrome	Aura (simple partial seizure)
1	Fatigue, sleep deprivation	No (the seizure cancels what happens before)	Feeling of absurdity, tachypsychia, sudden reminiscences, epigastric oppression
2	Intermittent photic stimulation	Distress, feeling of loss, irritation provoked by various stimuli	Déjà vu, warm feeling, breathing difficulty
3	Anxiousness, annoyance, fatigue	Fatigue, feeling of head compression since the awakening, buzzing in the ears, lower limb weakness, vertigo, and distress	*Daytime seizures* (infrequent): right hand anesthesia (or right nasal paresthesia), anxious, right upper limb elevation, then tonic posture of the four limbs and falls without loss of consciousness *Nocturnal seizures* (frequent: each night): tonic posture of the four limbs starting from the right upper limb
4	Cold (and cold drinking), rapid movement of the head	Feeling of fragility, fatigue, troubled by noise, bad mood (according to his wife); these symptoms sometimes occurred 24 hours before the seizure	Dizziness, cold feeling in the lower limb, fear of dying as a "earthquake"; rarely, thoracic oppression, then complex partial seizure
5	Fatigue, stress, onset of menses	Feeling of ill-being, weakness, lack of energy and vitality, clumsiness; aching, troubled by noise and light, concentration difficulty, elocution difficulty, headache; these symptoms sometimes occurred 24 hours before the seizure	Feeling of going out, of losing control of her body, tachycardia, warm feeling, aphasia then loss of consciousness, and frequent secondary generalization
6	Stress, relaxing period, alcohol	No	Ascending epigastric warm feeling, dizziness, then complex partial seizure
7	Fatigue, alcohol, sleep deprivation	Distress since the awakening	Right hand paresthesia, then modification of hearing perception, then complex partial seizure
8	Stress, fatigue, noise, video game, emotion	Weakness, fatigue, and fragility since the awakening	Feeling of flash or explosion in the head, tachycardia, distress, then complex partial seizure
9	Fatigue, alcohol, sleep deprivation, period of stress or of decreasing stress	No	Ascending epigastric feeling, then sometimes déjà vécu, or dreamy state, nausea, then complex partial seizure

Prodromal symptoms in epileptic patients: Clinical characterization of the pre-ictal phase

Seizure 18 (2009) 246–250

Alejandro Scaramelli *, Patricia Braga, Andrea Avellanal, Alicia Bogacz, Claudia Camejo, Isabel Rega, Tamara Messano, Beatriz Arciere

100 adult patients (randomly selected)

Semi-structured interviews
Auras excluded

Premonitory symptoms: **39%** of patients.

Type of PS	*N*
Behavioral changes	13
Cognitive disturbances	11
Anxiety and mood changes	9
Fatigue	7
Sleep disturbances	7
Dysthermia	6
Speech disturbances	4
Voiding changes	4
Gastrointestinal symptoms	3
Headache	2
Changes in appetite	2
Paresthesias	1
Pain (other than headache)	1
Other	5
Total	75

Can patients with epilepsy predict their seizures?

NEUROLOGY 2007;68:262–266

"prospective seizure diary study"

Sheryl R. Haut, MD; Charles B. Hall, PhD; Aaron J. LeValley, MA; and Richard B. Lipton, MD

Table 1 *Demographic characteristics of predictors and nonpredictors*

	Predictors	Nonpredictors	Total	*p*
No.	12	59	71	
Age, median, y	32.1	41.3	41.1	0.026
Male/female	4/8	22/37	26/45	NS
Epilepsy localization				NS
Temporal	8	24	32	
Frontal	2	4	6	
Extratemporal other	1	9	10	
Nonlocalizable	1	22	23	
Median years of education	14.5	14.0	14.0	NS
Mean seizure rate/month	5.5	2.25	2.9	0.003
Median seizure rate/month	5.9	1.3	2.0	0.005

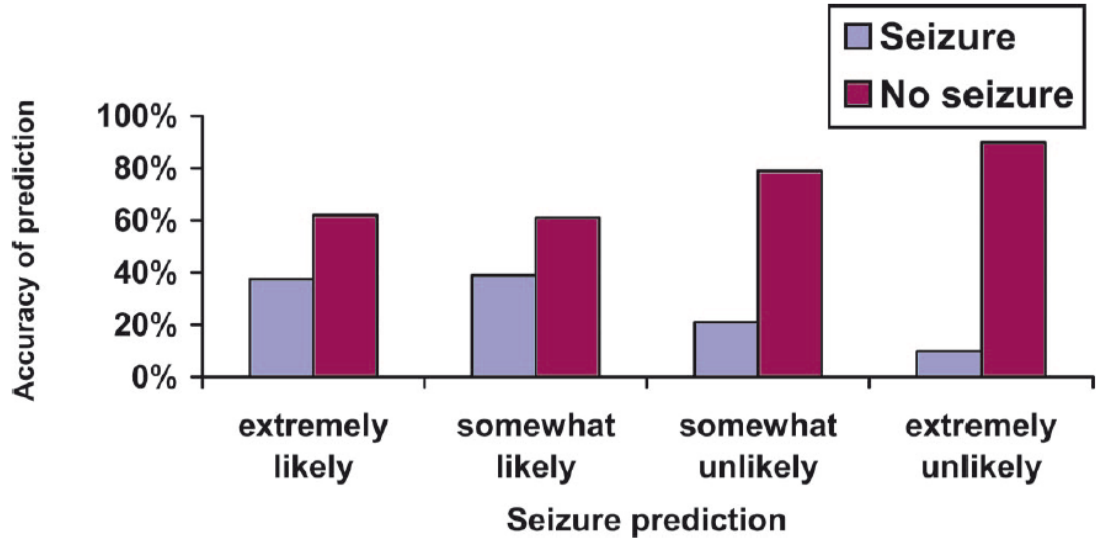


Figure 3. Accuracy of seizure predictors. Positive predictive and negative predictive values for the subgroup (n = 12) of subjects demonstrating significant seizure prediction. Values are adjusted for within-person correlation.

A positive prediction of seizures was associated with a twofold increased risk of seizure (Cochran-Mantel-Haenszel OR 2.25). Overall, the specificity of positive prediction was 83.2% while the sensitivity was 31.9%.

Biases dello studio Haut el al, 2007

1) Bias di selezione dei 134 pazienti (scelti in modo non casuale da una popolazione ben definita)

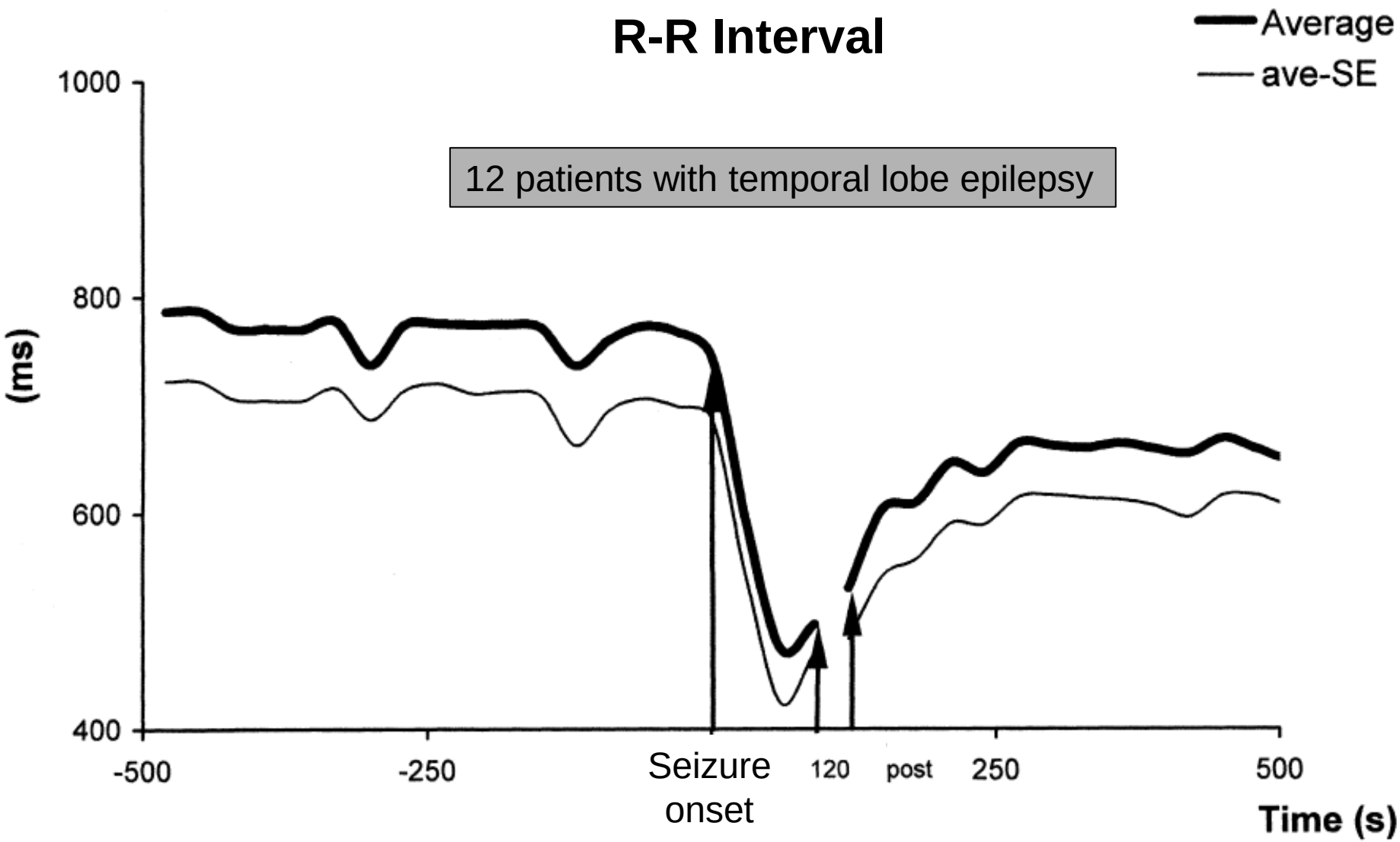
2) Bias da “non risposta” (pazienti incapaci di predire non inviano il questionario e quindi il risultato ottenuto è sbilanciato in favore dei pazienti “predittori”)

3) Bias da “risposta compiacente” (alcuni pazienti potrebbero aver risposto sintomi predittivi per compiacere lo sperimentatore)

Time-frequency mapping of R–R interval during complex partial seizures of temporal lobe origin

Vera Novak [a,*], Andrew L. Reeves [a], Peter Novak [a], Phillip A. Low [b], Frank W. Sharbrough [b]

Journal of the Autonomic Nervous System 77 (1999) 195–202

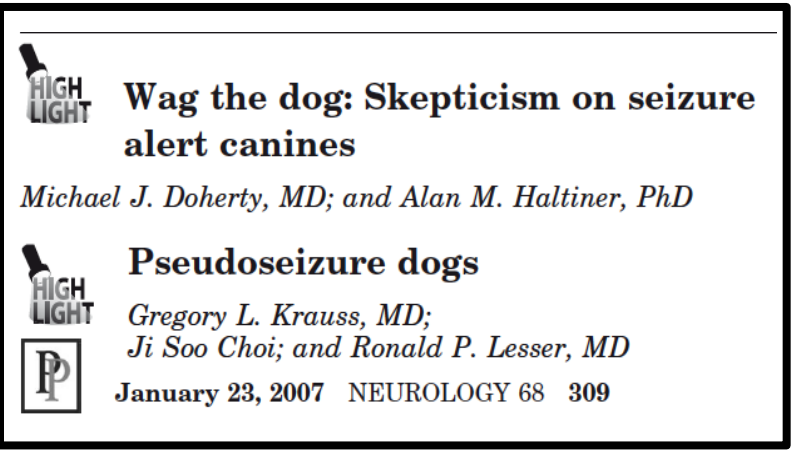


Can seizure-alert dogs predict seizures?

Stephen W. Brown[a], Laura H. Goldstein[b,*]

Epilepsy Research (2011) 97, 236–242

Anecdotal reports of pet dogs spontaneously anticipating human epileptic seizures.



HIGH LIGHT

Wag the dog: Skepticism on seizure alert canines

Michael J. Doherty, MD; and Alan M. Haltiner, PhD

HIGH LIGHT

Pseudoseizure dogs

Gregory L. Krauss, MD;
Ji Soo Choi; and Ronald P. Lesser, MD

January 23, 2007 NEUROLOGY 68 **309**

Recent sceptical reports of **non-epileptic seizures** in some people with SADs have cast doubt on dogs' ability to anticipate **true** epileptic seizures.

Whether the seizures are epileptic or non-epileptic, it is speculated that SADs probably alert to **subtle pre-ictal human behaviour changes**, but may also be sensitive **to heart rate or olfactory cues.**

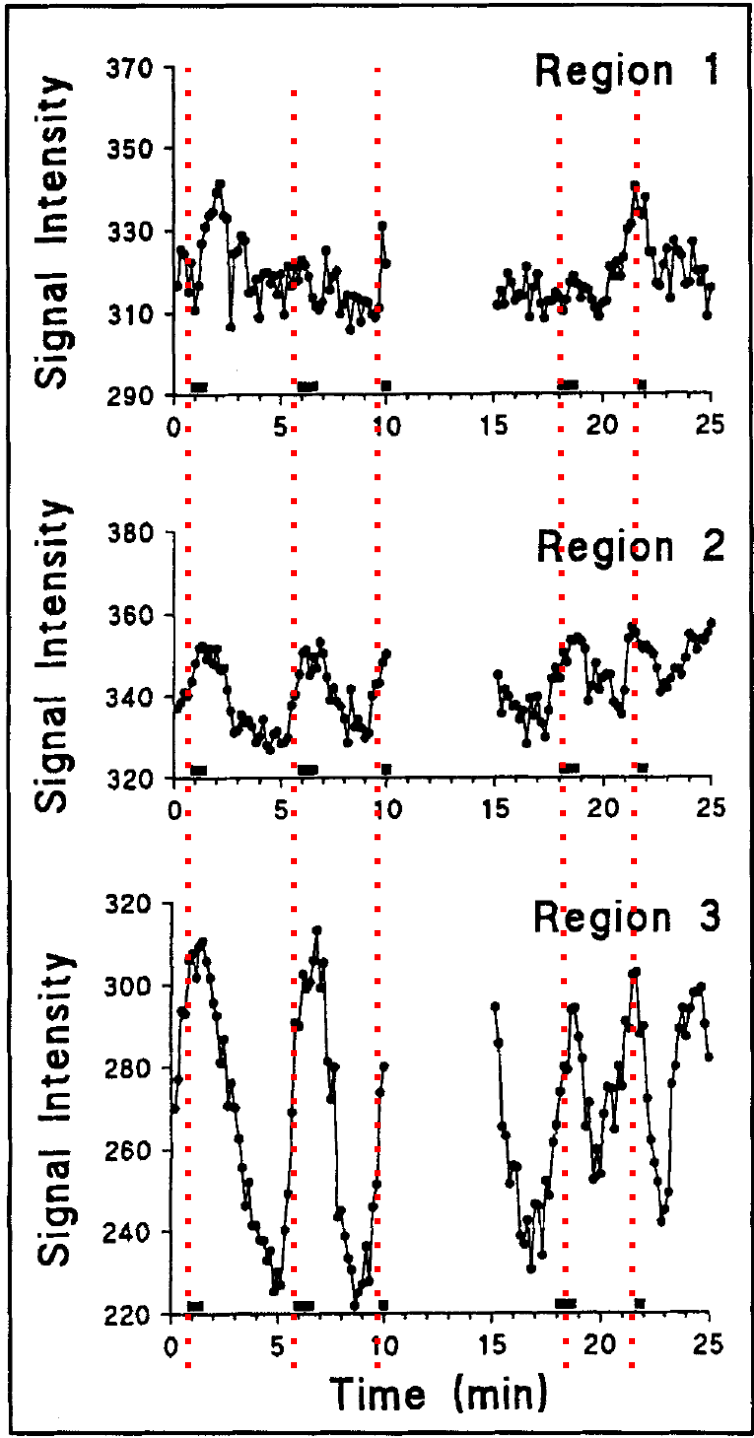
No rigorous data exist as to whether seizure prediction by seizure-alert-dog is better than chance, and what false positive and negative prediction rates might be

Functional magnetic resonance imaging of focal seizures

G.D. Jackson, FRACP; A. Connelly, PhD; J.H. Cross, MRCP;
I. Gordon, FRCR; and D.G. Gadian, DPhil

NEUROLOGY 1994;44:850-856

4-year-old boy
with Rasmussen's encephalitis
of right hemisphere

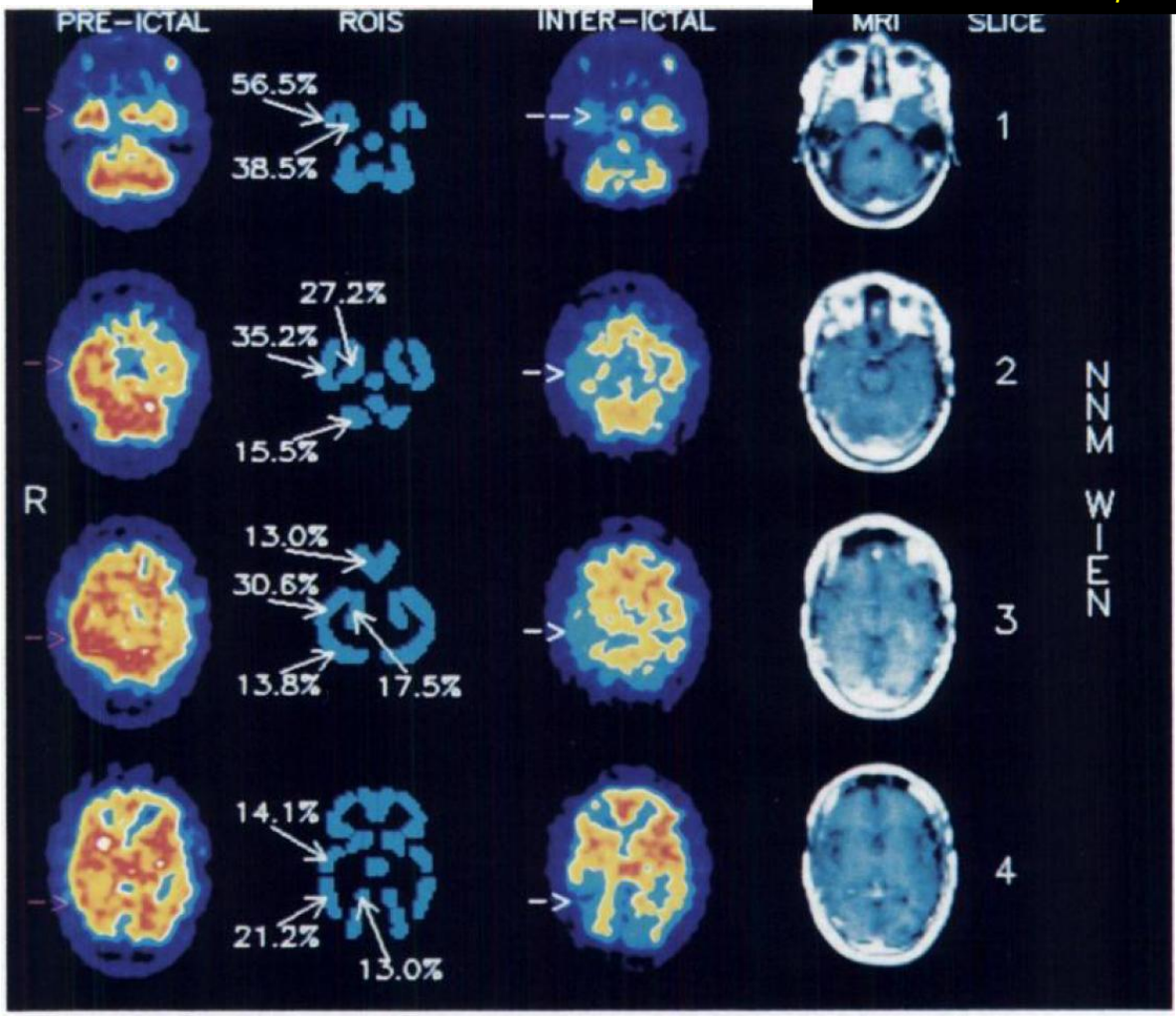


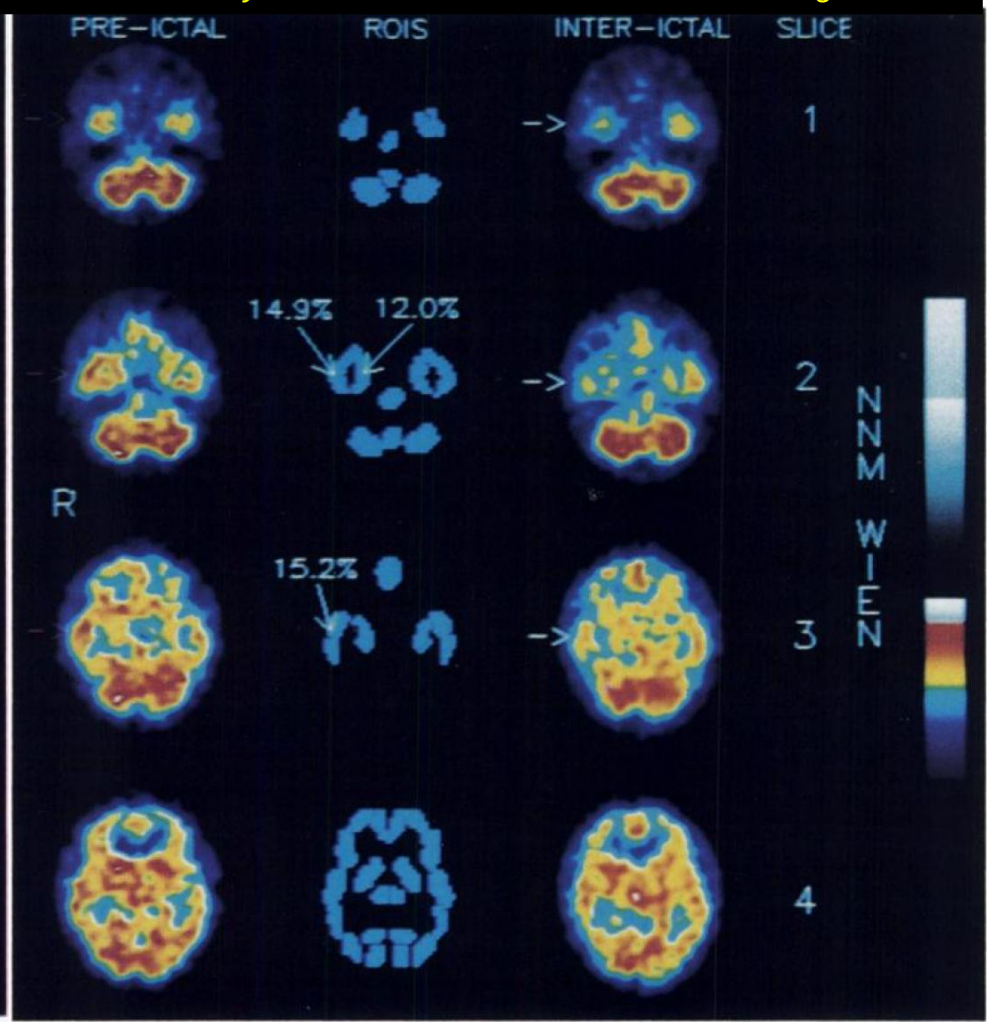
Preictal SPECT in Temporal Lobe Epilepsy: Regional Cerebral Blood Flow Is Increased Prior to Electroencephalography-Seizure Onset

J Nucl Med 1998; 39:978–982

Christoph Baumgartner, Wolfgang Serles, Fritz Leutmezer, Ekaterina Pataraia, Susanne Aull, Thomas Czech, Uwe Pietrzyk, Alessandro Relic and Ivo Podreka

SPECT scans were performed fortuitously under continuous video-EEG monitoring control



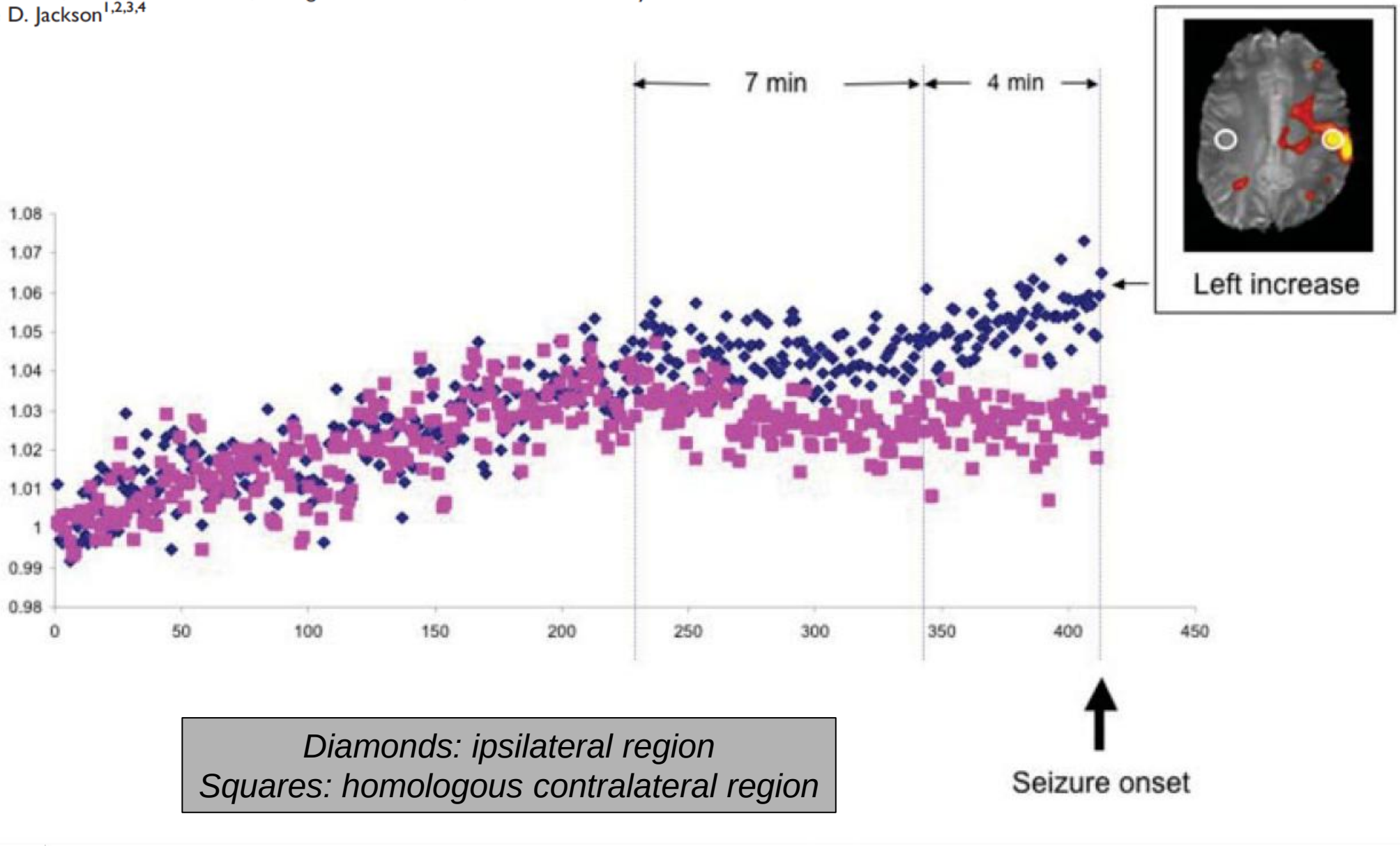


doi:10.1093/brain/awh533 *Brain* (2005), **128**, 1811–1817

Functional MRI of the pre-ictal state

Paolo Federico,[1,2,5] David F. Abbott,[1,2] Regula S. Briellmann,[1,2] A. Simon Harvey[1,2,4] and Graeme D. Jackson[1,2,3,4]

Patient 1 with **left central cortical dysplasia** had typical seizure in the scanner while BOLD fMRI images were acquired



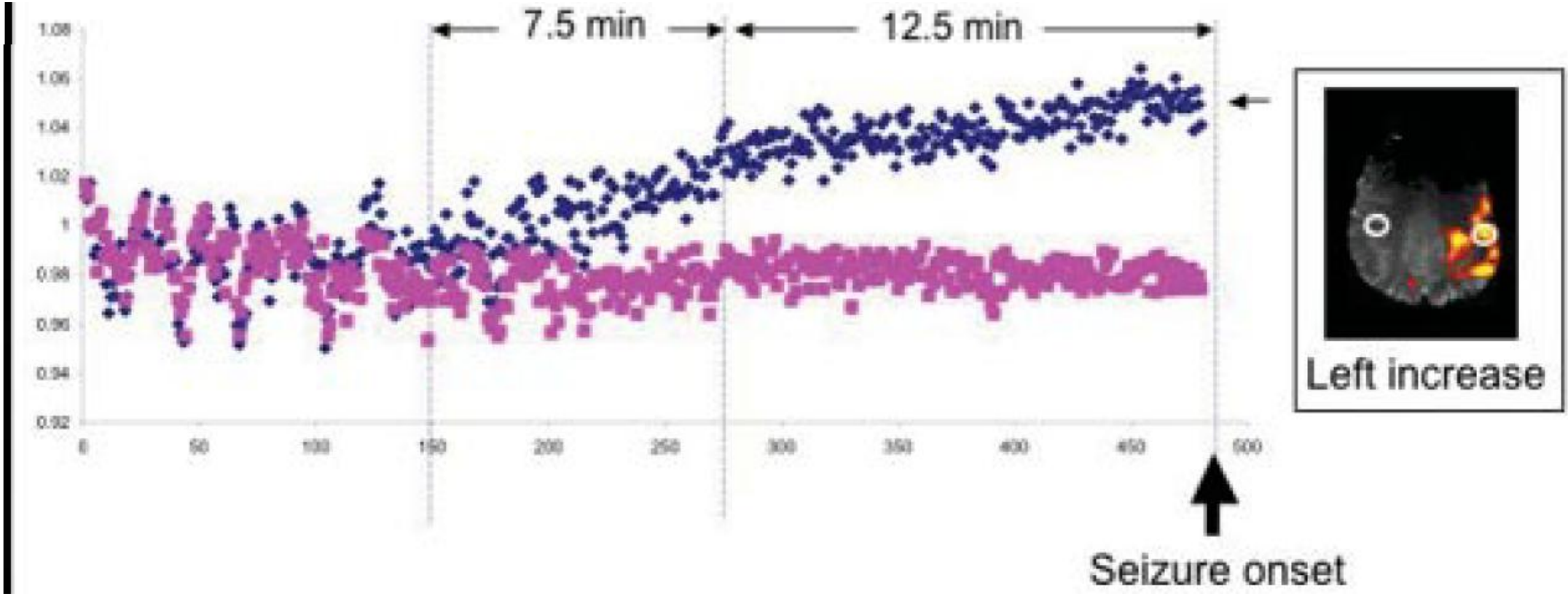
Diamonds: ipsilateral region
Squares: homologous contralateral region

doi:10.1093/brain/awh533 *Brain* (2005), **128**, 1811–1817

Functional MRI of the pre-ictal state

Paolo Federico,[1,2,5] David F. Abbott,[1,2] Regula S. Briellmann,[1,2] A. Simon Harvey[1,2,4] and Graeme D. Jackson[1,2,3,4]

Patient 2 with **right frontal cortical dysplasia** had typical partial seizure in the scanner while BOLD fMRI images were acquired



Diamonds: ipsilateral region
Squares: homologous contralateral region

Imaging e fase precritica

Aumento del metabolismo nell'emisfero:

1) **<u>omolaterale</u>** al focus: *attivazione* zona epilettogena.

2) **<u>controlaterale</u>** al focus:
   a. area coinvolta in *genesi* crisi ?
   b. area coinvolta in *inibizione* crisi ?

PREDIZIONE CRISI

Evidenze cliniche:

Probabilmente possibile in alcuni pazienti

Evidenze strumentali:

Convincente disautonomia in alcuni pazienti

Contradditorie modifiche del metabolismo

PREDIZIONE CRISI

e l' EEG ?

Analisi tradizionale: EEG intercritico
Frequenze delle punte intercritiche

Aumentata: Gastaut, 1954

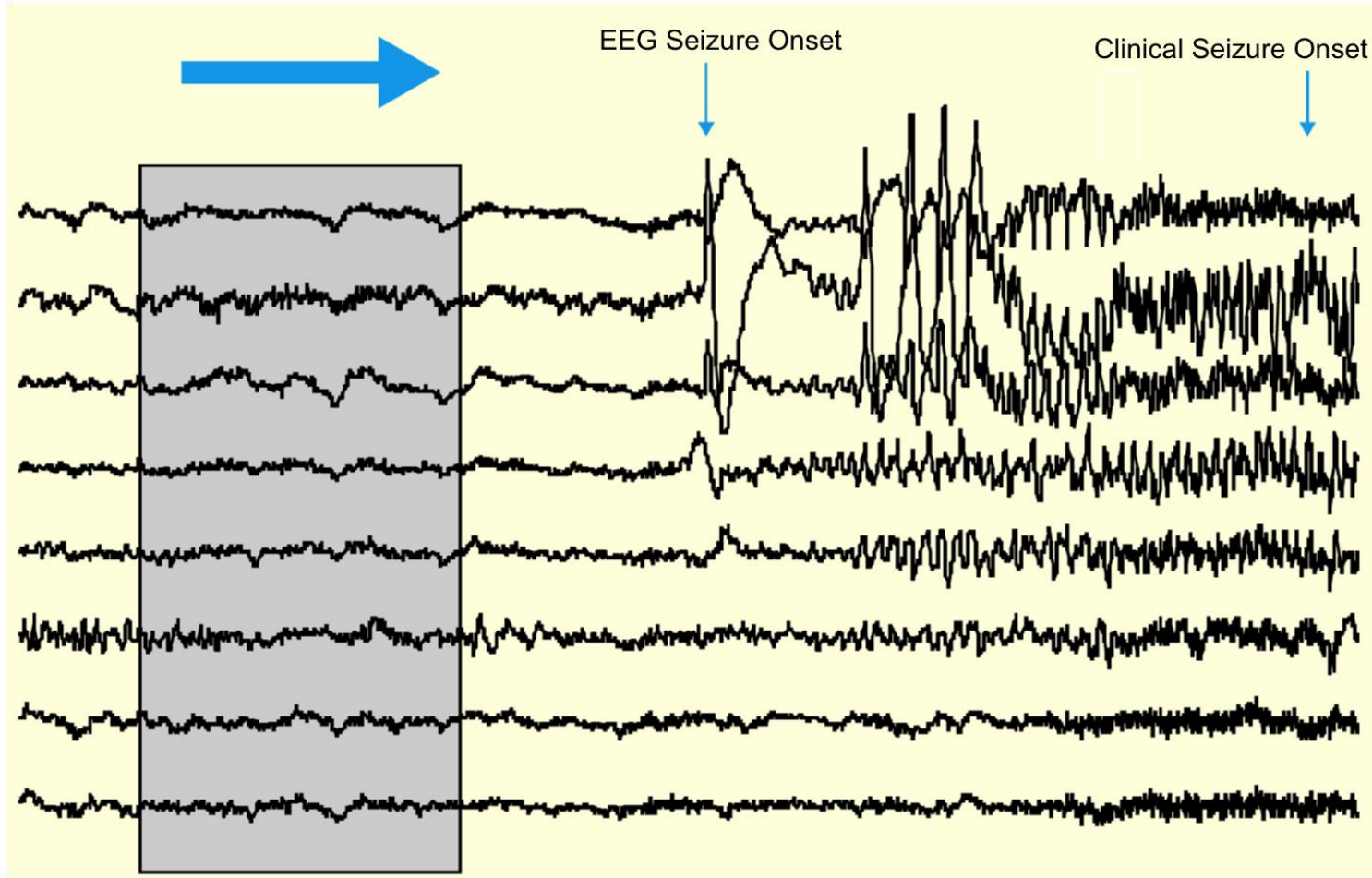
Ridotta: Wiser, 1989

Invariata: Lieb et al, 1978;
Gotman and Marciani, 1985;
Katz et al., 1991

Predizione di cosa ?

Crisi clinica,
Infraclinica,
o entrambe ?

Predizione di cosa ?



Inizio crisi EEG o Clinica ?

(Modificato da: Litt and Echauz, Lancet of Neurology; 2002)

Quale tracciato ?

Intracranico: alto rapporto segnale/rumore; alta definizione spaziale (inclusa zona epilettogena); non artefatti; utile per closed-loop devices (es. stimolazione precritica del focus).

Extracranico: non invasivo, esplora l'intero scalp (registra anche da zone distanti dal focolaio)

Tracciato ideale per testare il sistema:

protratto (alcuni giorni) e con molte crisi fra loro ben distanziate (ore).

Electroencephalography and Clinical Neurophysiology, 1975, 39 431–436

SOCIETY PROCEEDINGS

WESTERN EEG SOCIETY

Seattle, Washington, February 13–15, 1975

24. Epileptic seizure prediction. — S. S. Viglione and G. O Walsh (Los Angles, Calif.).

In a cooperative effort with the Departments of Neurology at UCLA and UCSF, the McDonnell Douglas Astronautics Company is conducting a program to validate the concept of predicting major motor seizure onset through an automated analysis of the EEG from the epileptic subject Ten epileptics, who are subject to generalized seizures, are being hospitalized and 5–6 seizure (and associated preseizure) recordings obtained from each subject Continuous monitoring of two channels (C_4, O_2, C_3, O_1) of the subject's EEG is provided through the use of a biotelemetry system Additionally the subjects are monitored on a video tape system during their waking hours

The EEG data is categorized into two sets (1) preseizure activity, *i e*, EEG recorded 20–30 min prior to the seizure, and (2) baseline activity, *i e*, no seizure activity that day The analog tapes are then digitized and automatically screened for artifacts Subsequent computer processing involves a spectral analysis of the EEG and then the application of a pattern recognition analytic procedure to the spectral data in each contiguous 15 sec inderval of the two classes of EEG data Results of the computer analysis of these data and the design simulation of the seizure warning system will be presented

This program is funded through the Office of Research Grants and Demonstrations, Social and Rehabilitation Services, Department of Health, Education and Welfare (HEW) Mr J Traub is the HEW Project Monitor

Misure caratterizzanti l’ EEG
Tipo di calcolo

Lineare: fenomeni fisici sprovvisti di distorsioni, turbolenze e fenomeni caotici in generale. Anche i fenomeni più complessi (EEG) possono essere studiati "approssimando il sistema" con un modello lineare.
Esempi: analisi spettrale, coerenza lineare.

Non lineare: fenomeni fisici complessi provvisti di distorsioni, turbolenze e fenomeni caotici in generale, che evolvono in modo apparentemente inatteso e non proporzionale (come nei circuiti neuronali).
Esempi: STLmax, indiceT, dimensione di correlazione, entropia.

Misure caratterizzanti l' EEG
Tipo di analisi

Univariata: calcolata su 1 canale EEG

Bivariata: calcolata su 2 canali EEG

Multivariata: calcolata su $\geq$ 2 canali EEG

$$\mathrm{Energy}(t,w) = \frac{1}{w} \cdot \sum_{i=t-w}^{i=t} s(i)^2$$

$$E[n] = \frac{1}{N} \sum_{i=(n-1)N}^{nN}$$

$$\mathrm{AE}(q) = \frac{1}{100} \sum_{t=1}^{t=q} \mathrm{Energy}(t,w)$$

$$\mathrm{ANE} = \frac{1}{N} \sum_{n=1+(k-1)(N-D)}^{k(N-D)+D} \mathrm{NE}_w[n]$$

$$\frac{\frac{1}{2}\left(uu_{-1} - \Lambda_1 - \Lambda_1 uu\right)}{1 - \Lambda_1 uu} = \left(u_n, \ldots, a_2, a_1\right) = d'$$

$$Q_m = 60(60+2)\sum_{k=1}^{m} (60-k)^{-1} r_k^2$$

$$L_i^t = \left\{\mathrm{STL\,max}_i^t, \mathrm{STL\,max}_i^{t+1}, \ldots, \mathrm{STL\,max}_i^{t+59}\right\}$$
$$L_j^t = \left\{\mathrm{STL\,max}_j^t, \mathrm{STL\,max}_j^{t+1}, \ldots, \mathrm{STL\,max}_j^{t+59}\right\}.$$

Then $D_{ij}^t = L_i^t - L_j^t = \{d_{ij}^t, d_{ij}^{t+1}, \ldots, d_{ij}^{t+59}\}$ with $\{d_{ij}^{t'}\} = \{\mathrm{STL\,max}_i^{t'} - \mathrm{STL\,max}_j^{t'}\}$ and $t' \in [t, t+59]$. The pair-T statistic at time t, between electrode sites i and j, is then estimated by

$$T_{ij}^t = \frac{\left|\overline{D}_{ij}^t\right|}{\frac{\hat{\sigma}_d}{\sqrt{60}}} \qquad W = \frac{\left(\sum_{i=1}^n a_i x_i\right)^2}{\sum_{i=1}^n \left(x_i - \bar{x}\right)^2}$$

Characterizing measures of the EEG

Univariate linear measures

Statistical moments
Spectral band power
Spectral edge frequency
Accumulated energy
Characteristics of the autocorrelation function
Hjorth parameters
Autoregressive modelling

Univariate non-linear measures

Measures based on the correlation sum
Correlation dimension
Correlation density
Correlation entropy
Marginal predictability
Dynamical similarity index
State space dissimilarity measures
Largest Lyapunov exponent
Local flow Δ*
Algorithmic complexity
Surrogate time series and surrogate correction
Loss of recurrence

Bivariate linear measures

Maximum linear cross-correlation
Linear coherence

Bivariate non-linear measures

Non-linear interdependence
Dynamical entrainment
Measures for phase synchronization

(Mormann et al.; Brain, 2007)

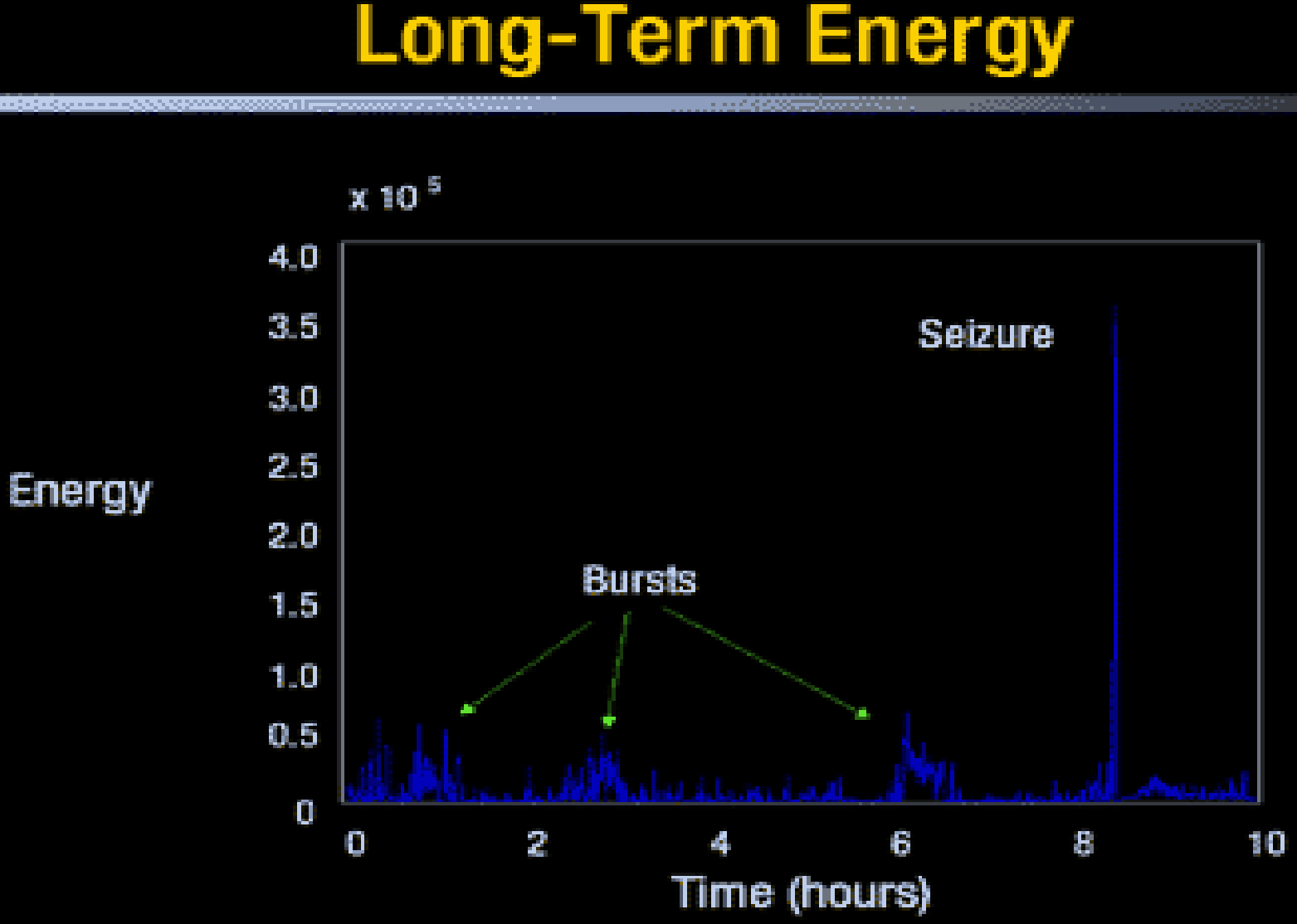
Misure caratterizzanti l' EEG
Metodo di analisi

"A finestre mobili"

Finestre temporali predefinite (da 10 a 40 sec)

e consecutive ⟶ profilo temporale

Esempio di analisi lineare



Esempio di analisi non lineare

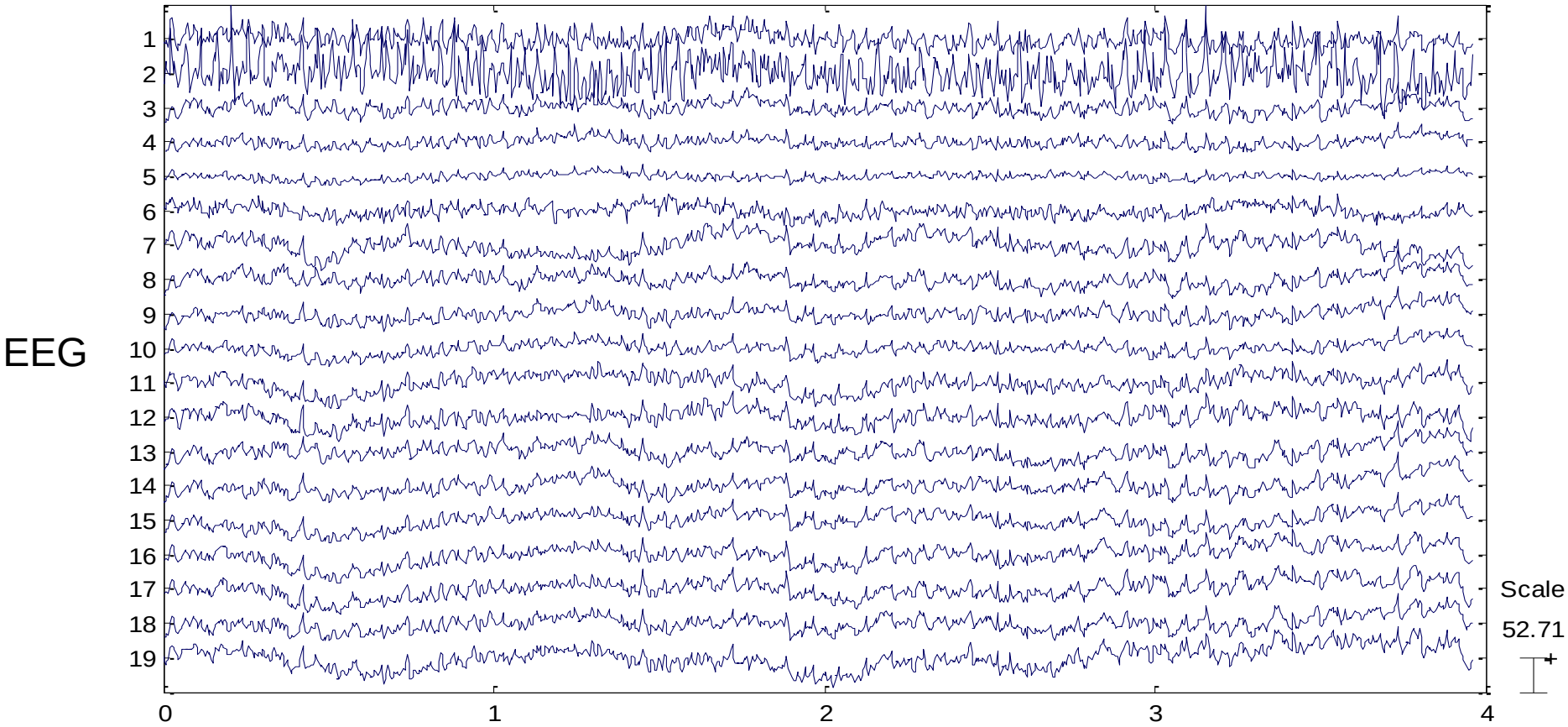
Massimo Esponente di Lyapunov

- Il ***massimo Esponente di Lyapunov*** rappresenta un indice della caoticità di un ***sistema non lineare***: è una misura di quanto il sistema sia "ordinato". ***STLmax*** è la sua versione ottimizzata per i segnali EEG.

- Analizzando EEG intracranici di pazienti affetti da epilessia del lobo temporale, si è osservato che il sistema transita da una condizione di "minore ordine" ad una di "maggiore ordine" con l' avvicinarsi della crisi.

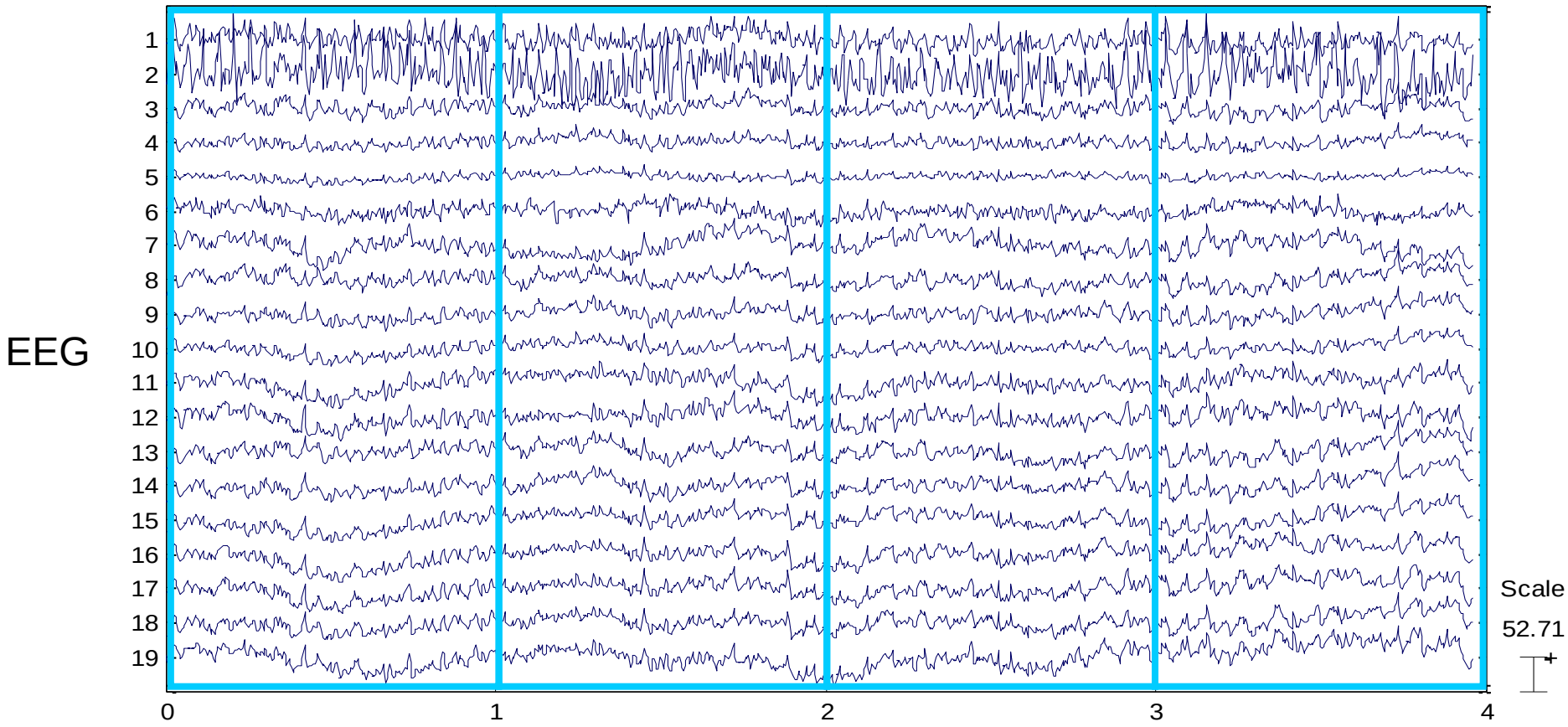
Costruzione dell' indice di Lyapunov

Si parte dal tracciato EEG



Costruzione dell' indice di Lyapunov

Si partiziona i tracciato in finestre:

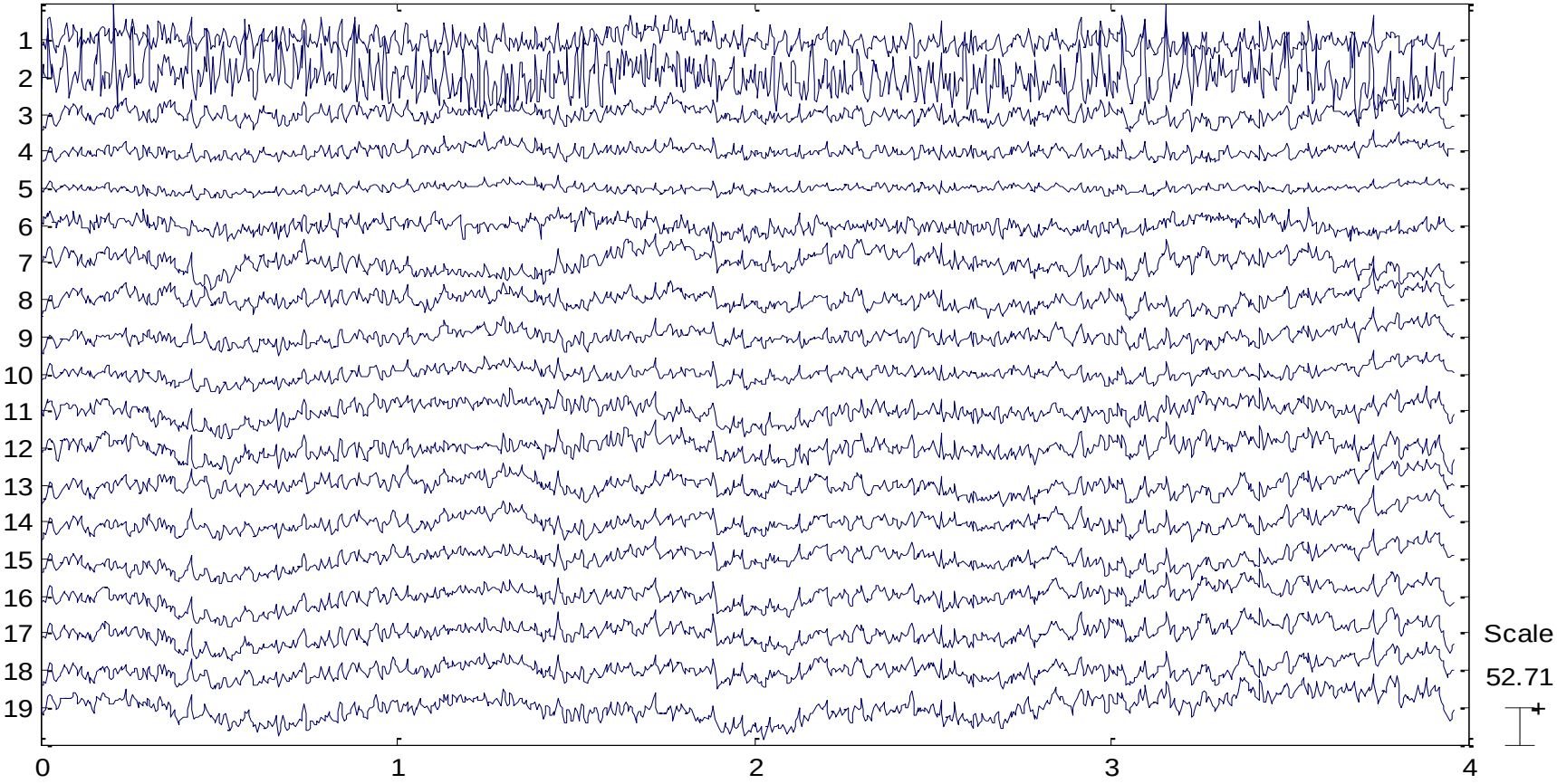


Per ogni finestra, si estrae un valore *STLmax* da ciascun elettrodo

Costruzione dell’ indice di Lyapunov

Si ottiene così un nuovo tracciato contenente i valori di STLmax invece dei valori di potenziale elettrico.

STLmax



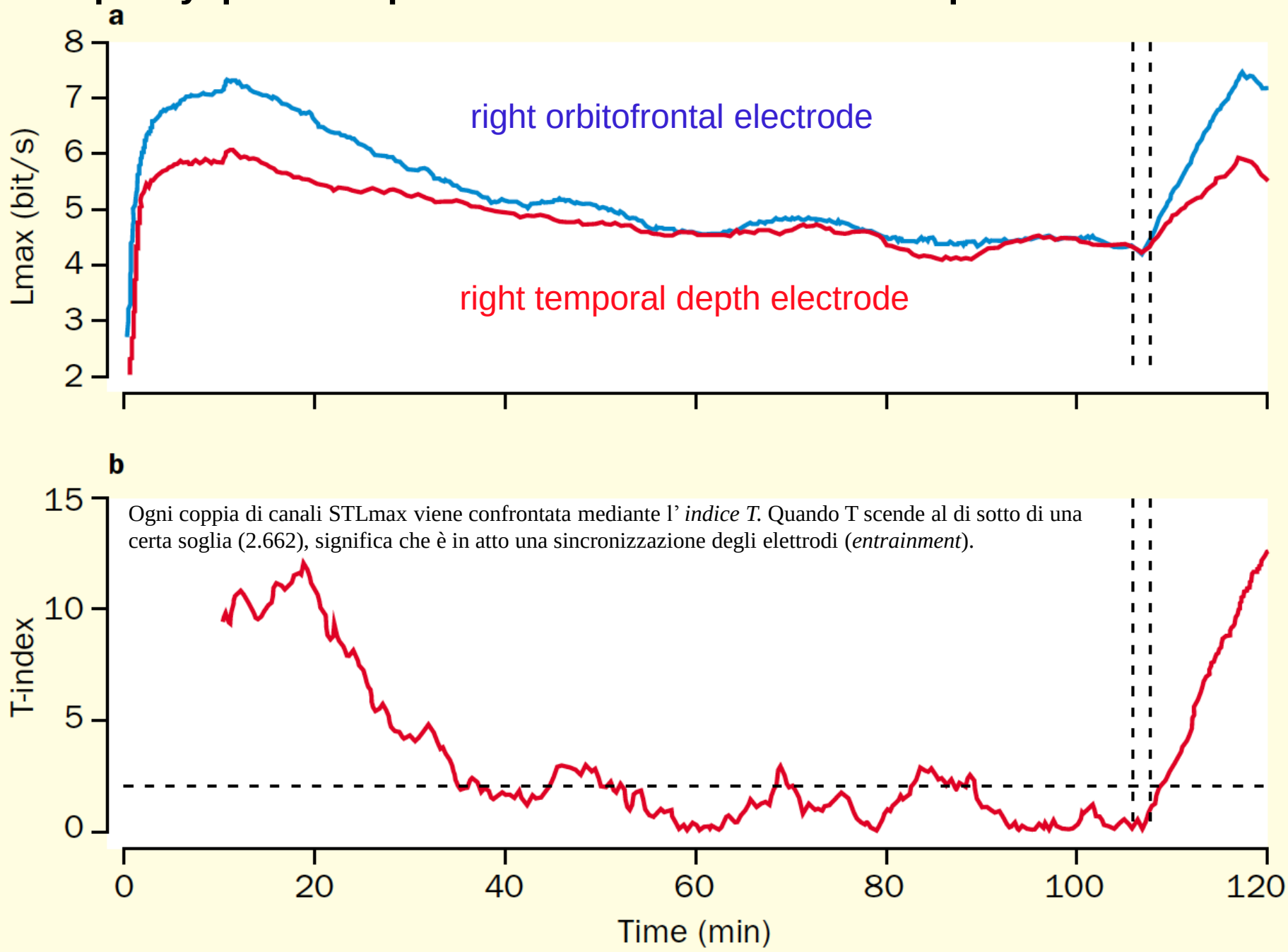
Principal Lyapunov exponents and T-index in seizure prediction

Prediction of epileptic seizures

Review

Brian Litt and Javier Echauz

Lancet Neurology 2002; **1**: 22–30



Esempio di analisi non lineare

Permutation entropy

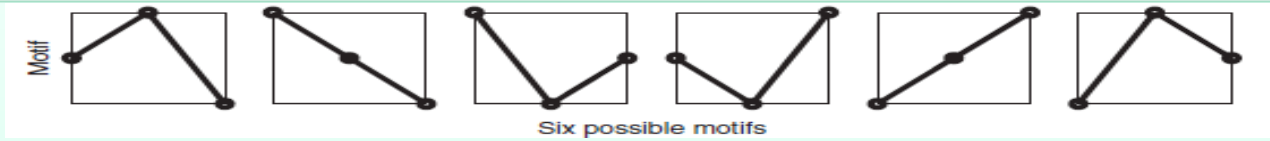
ENTROPIA = misura di irregolarità (disordine) del segnale EEG

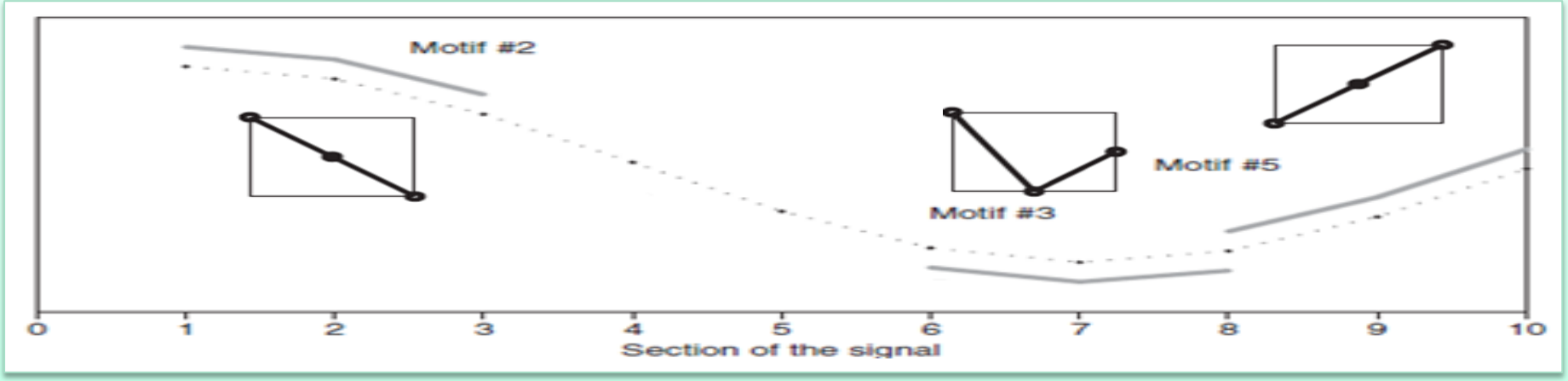
Permutation Entropy (PE) è un metodo veloce e robusto per estrarre informazioni da una serie temporale con **tecnica ordinale**.

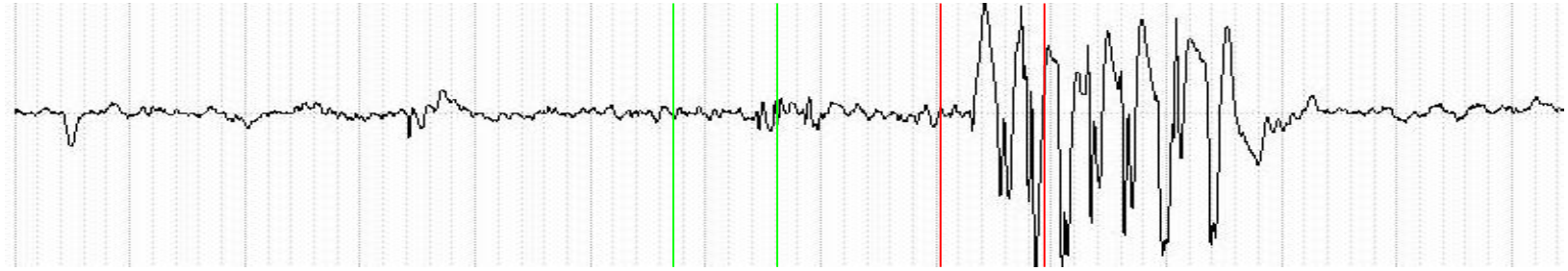
Onde EEG = serie di punti nel tempo

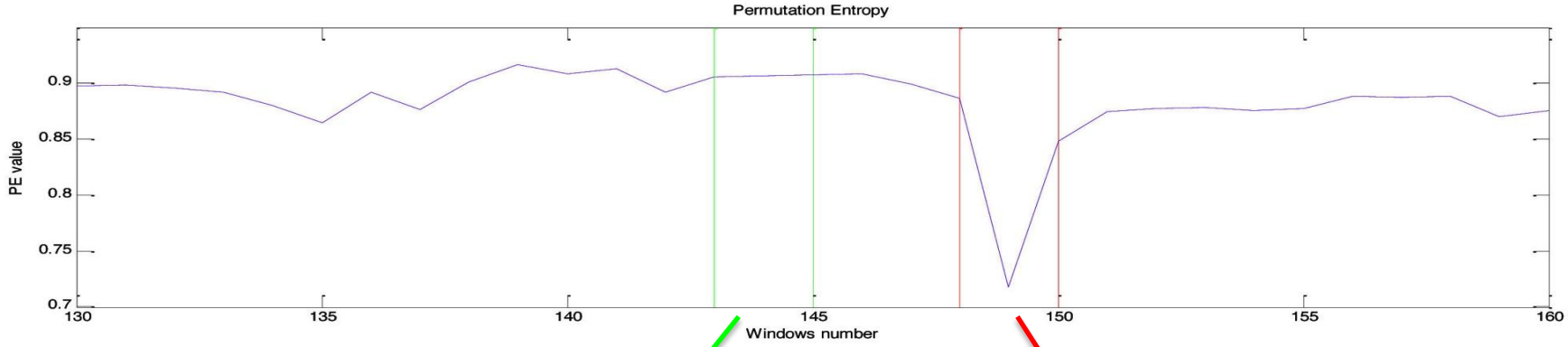
Tecnica ordinale: considera l'ordine dei punti (campioni) nella distribuzione del segnale (sequenza della **posizione** dei punti) nel tempo

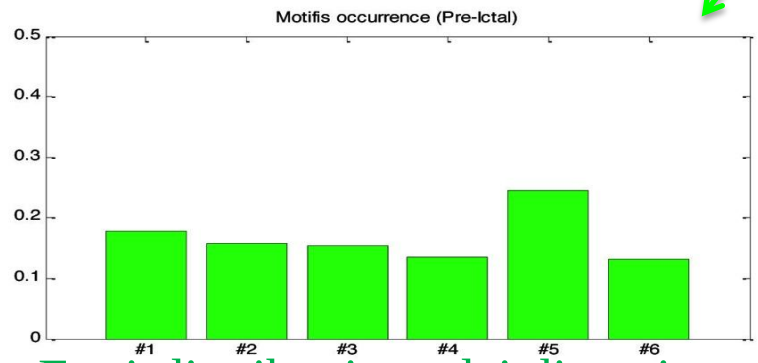
Le onde EEG sono scomposte in differenti "motivi", ognuno costituito da 3 (o più) punti equidistanti.





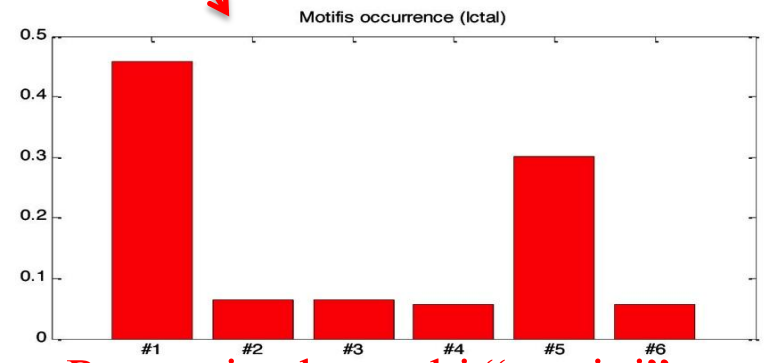






Equi-distribuzione dei diversi "motivi"

Alto valore di PE



Presenti solo pochi "motivi"

Basso valore di PE

Predizione crisi: disegni di studio

Statistico: compara le medie di una (o più) variabili (o misure caratterizzanti) fra fasi intercritiche e (presunte) fasi pre-critiche. Struttura temporale non considerata. (Utile in studi preliminari, per studiare potenziali variabili predittive).

Algoritmico: analizza l'andamento temporale di una (o più) variabili (o misure caratterizzanti). Identifica "soglie di allarme" (veri o falsi allarmi).

Predizione crisi: **Performances**

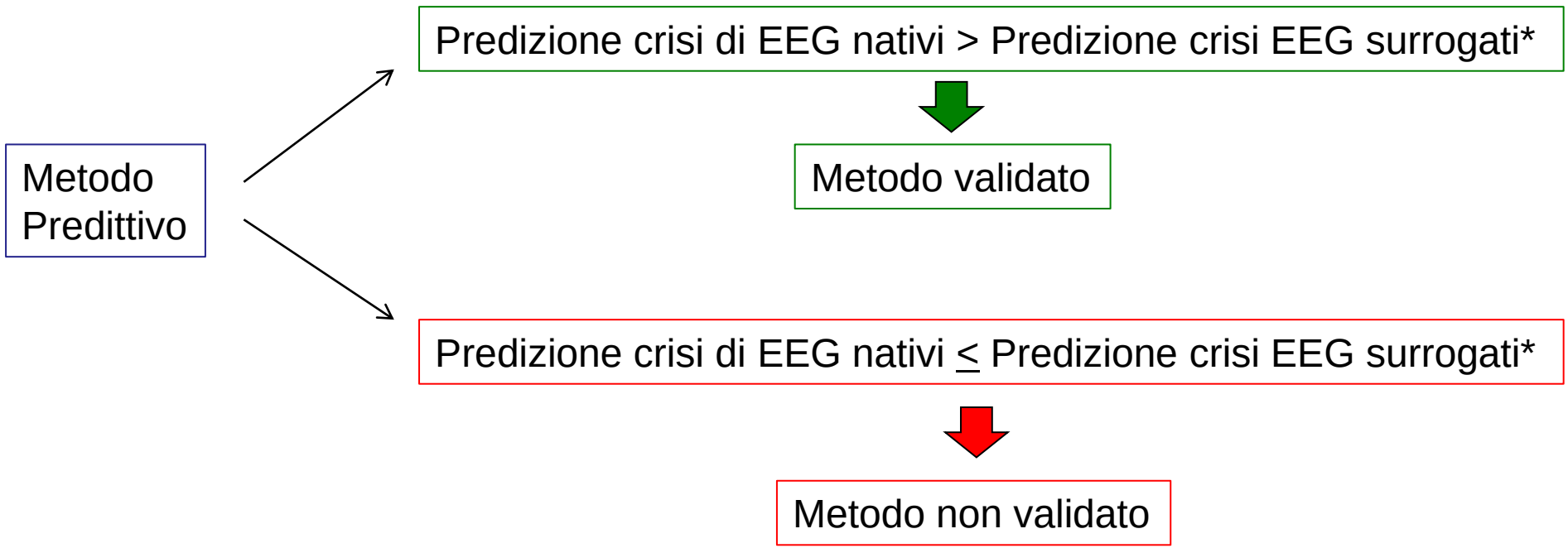
Sensibilità: rapporto fra crisi segnalate/crisi totali in un arco temporale definito.

Specificità: false predizioni/periodo intercritico in un arco temporale definito; oppure: periodo di falso allarme/periodo intercritico in un arco temporale definito

Predizione crisi: **Performances** con EEG surrogati*

<u>Ipotesi nulla</u>

"il metodo non è superiore al caso nell'identificare la fase pre-critica".



* Composto da inizi artificiali di crisi, generati da "rimescolamento" casuale di intervalli intercritici originali

doi:10.1093/brain/awl241 Brain (2007), 130, 314–333

REVIEW ARTICLE

Seizure prediction: the long and winding road

Table 1 Studies on seizure prediction and their relevant characteristics (see text)

Authors	Year	Type of epilepsy	Type of EEG	Characterizing measure	Patients	Seizures	Total EEG (h)	Inter-ictal controls (h)	Type of analysis	In-sample parameter optimization	Retrospective best channel selection	Prospective	Assumed pre-ictal period (min)	Sensitivity (%)	False-positive rate (FP/h)	Mean prediction time (min)	Statistical validation of performance
Lehnertz and Elger	1998	MTLE	iEEG	Correlation dimension	16	16	21	16.9	Statistical	Yes	Yes	No	30	94	0	12	No
Martinerie *et al.*	1998	MTLE	iEEG	Correlation density	11	19	13	0	Algorithmic	No	Yes	No	20	89	n.a.	3	No
Le Van Quyen *et al.*	1999	MTLE	iEEG	Similarity index	13	23	15	0	Algorithmic	No	Yes	No	20	83	n.a.	6	No
Le Van Quyen *et al.*	2000	MTLE	iEEG	Similarity index	9	17	11	0	Algorithmic	No	Yes	No	20	94	n.a.	4	No
Mormann *et al.*	2000	MTLE	iEEG	Phase synchronization	2	3	4	1.8	Proof of principle	No	Yes	No	n.s.	100	0	n.s.	No
Cerf *et al.*	2000	Focal	iEEG	Lerner density	7	9	n.s.	1.8	Statistical	Yes	Yes	No	60	100	0	n.s.	No
Hively *et al.*	2000	Focal	sEEG	Dissimilarity measures	n.s.	20	40	0	Algorithmic	Yes	No	No	262.5	100	n.a.	52	No
Le Van Quyen *et al.*	2001*a*	TLE	sEEG	Similarity index	23	26	26–35	0	Algorithmic	No	Yes	No	60	96	n.a.	7	No
Iasemidis *et al.*	2001	TLE	iEEG	Dynamical entrainment	5	58	266	53.9	Statistical	Yes	Yes	No	Variable	91	n.s.	49	No
Litt *et al.*	2001	MTLE	iEEG	Accumulated energy	5	30	>312	50	Statistical	Yes	No	No	180	90	0.12	19	No
Le Van Quyen *et al.*	2001*b*	Neocortical	iEEG	Phase synchronization	8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	No	n.s.	77	n.s.	Several min	No
Lehnertz *et al.*	2001	Focal	iEEG	Correlation dimension	59	95	>145	>115	Algorithmic	Yes	Yes	No	n.s.	47	0	19	No
Protopopescu *et al.*	2001	Focal	sEEG	Dissimilarity measure	41	46	261	73.9	Algorithmic	Yes	Yes	No	60	95	0	n.s.	No
Jerger *et al.*	2001	Children	iEEG	Seven different measures	4	12	1	0	Algorithmic	Yes	Yes	No	3	100	n.a.	2	No
Navarro *et al.*	2002	Neocortical	s+iEEG	Similarity index	11	41	53–142	12–60[c]	Algorithmic	No	Yes	No	90	83	0.31[c]	8	No
Schindler *et al.*	2002	Focal	sEEG + FO	Simulated neuronal cells	7	15	144	n.s.	Algorithmic	Yes	No	No	Variable	100	n.s.	83	No
Mormann *et al.*	2003*a*	MTLE	iEEG	Synchronization/correlation	10	14	31	15	Algorithmic	Yes	No	No	240	86	0	86/102[h]	Yes
Mormann *et al.*	2003*b*	Focal	iEEG	Phase synchronization	18	32	117	49	Algorithmic	Yes	No	No	240	81	0	4–221	No
De Clercq *et al.*	2003	MTLE	sEEG	Similarity index	12	n.s.	n.s.	0	Algorithmic	No	Yes	No	60	0	n.a.	–	No
Niederhauser *et al.*	2003	Focal	iEEG	Sign periodogram transf.	5[a]	31	336	335	Algorithmic	Yes	Yes	No	2	94	0.08[f]	5–80 s	No
Chávez *et al.*	2003	Neocortical	iEEG	Phase synchronization	2	6	22	9	Proof of principle	Yes	Yes	No	90	n.s.	n.s.	>>30	No
Hively and Protopopescu	2003	Focal	sEEG	Dissimilarity measure	41	46	261	73.9	Algorithmic	Yes	No	No	60	88	0.02	35	No
D'Alessandro *et al.*	2003	MTLE	iEEG	Feature selection	4	46	n.s.	160	Algorithmic	Yes	Yes	No[d]	10	63	0.28	3	No
Iasemidis *et al.*	2003	TLE	iEEG	Dynamical entrainment	5	28[b]	214	n.s.	Algorithmic	No	No	Yes	180	83	0.17[f]	100	No
Winterhalder *et al.*	2003	Focal	iEEG	Similarity index	21	88	588	509	Algorithmic	Yes	Yes	No	30[e]	42	0.15	n.s.	No
Aschenbrenner *et al.*	2003	Focal	iEEG	Correlation dimension	21	88	588	509	Algorithmic	Yes	Yes	No	50[e]	34	0.10	n.s.	No
Van Drongelen *et al.*	2003	Children	s+iEEG	Kolmogorov entropy	5	5	5	0	Algorithmic	Yes	No	No	60	60	n.a.	21	No
Li *et al.*	2003	MTLE	sEEG	Marginal predictability	8	24	37	13.3	Statistical	No	No	No	60	n.s.	n.s.	n.s.	No
Drury *et al.*	2003	MTLE	sEEG	Marginal predictability	14	44	59	14.7	Statistical	No	No	No	60	n.s.	n.s.	30	No
Maiwald *et al.*	2004	Focal	iEEG	Accumulated energy	21	88	588	509	Algorithmic	Yes	Yes	No	32[e]	30	0.15	n.s.	No
Gigola *et al.*	2004	Focal	iEEG	Accumulated energy	4	13	26	10.5	Statistical	Yes	n.s.	No	70	92	0	n.s.	No
D'Alessandro *et al.*	2005	MTLE	iEEG	Feature selection	2	19[b]	177	140	Algorithmic	No	No	Yes	10	100/13[g]	1.10/0.71[g]	2/n.s.[g]	No
Esteller *et al.*	2005	MTLE	iEEG	Accumulated energy	4	42	294	>168	Algorithmic	Yes	Yes	No[d]	180[e]	71	0.11[f]	85	No
Harrison *et al.*	2005*a*	MTLE	iEEG	Accumulated energy	5	51	311	<92	Statistical	No	No	No	60	0	–	–	No
Iasemidis *et al.*	2005	MTLE	iEEG	Dynamical entrainment	2	11[b]	41	>8	Algorithmic	No	No	Yes	120	82	0.15[f]	78	No
Jouny *et al.*	2005	MTLE	iEEG	Complexity/synchrony	2	25	177	n.s.	Statistical	No	No	No	60	0	–	–	No
Le Van Quyen *et al.*	2005	MTLE	iEEG	Phase synchronization	5	52	305	25–120	Algorithmic	Yes	No	No[d]	Variable	69	n.s	187	No
Mormann *et al.*	2005	MTLE	iEEG	30 different measures	5	51	311	>107	Statistical	Yes	Yes	No	5–240[e]	n.s.	n.s.	–	Yes
Kalitzin *et al.*	2005	TLE	iEEG	Phase clustering	3	20	>75	n.s.	Statistical	Yes	Yes	No	–	n.s.	n.s.	–	No
Navarro *et al.*	2005	Focal	iEEG	Similarity index	13	129	227	0	Algorithmic	No	Yes	No	120	64	n.a.	>13	No
Chaovalitwongse *et al.*	2005	TLE	iEEG	Dynamical entrainment	10	64[b]	597	>404	Algorithmic	No	No	Yes	180	69	0.15[f]	72	Yes[i]
Harrison *et al.*	2005*b*	Focal	iEEG	Correlation dimension	20	960	2347	n.s.	Statistical	Yes	No	No	90/15[e]	0	–	–	No
Schelter *et al.*	2006	MTLE	iEEG	Phase synchronization	4	20	112	96	Statistical	No	Yes	No	40[e]	70	0.15	n.s.	Yes

Predizione crisi: Problemi e Limitazioni

Variabilità intra-individuale (vigilanza, terapia, stato cognitivo, ecc)

Variabilità interindividuale (sede, estensione, connessioni, tipo di focus)

Scelta dei parametri (uno o più ? lineari e/o non lineari ?)

Scelta degli elettrodi (solo dalla zona epilettogena ?)

Variabili di confondimento o "rumore":

Ambiente

Paziente (attività muscolari, movimenti, ecc..)

Possibile soluzione

Ottimizzazione intra-campione

(***training*** di un algoritmo predittivo con parametri selezionati)

Variabilità intra-individuale

Scelta dei parametri

Elevata performance su QUEL campione

Scarsa performance su ALTRI campioni

Variabilità interindividuale

LA SVOLTA: RETI NEURALI ARTIFICIALI

Modelli matematici che riproducono l'interconnessione tra costrutti matematici che imitano le proprietà dei neuroni.

Risolvono problemi molto complessi (intelligenza artificiale)

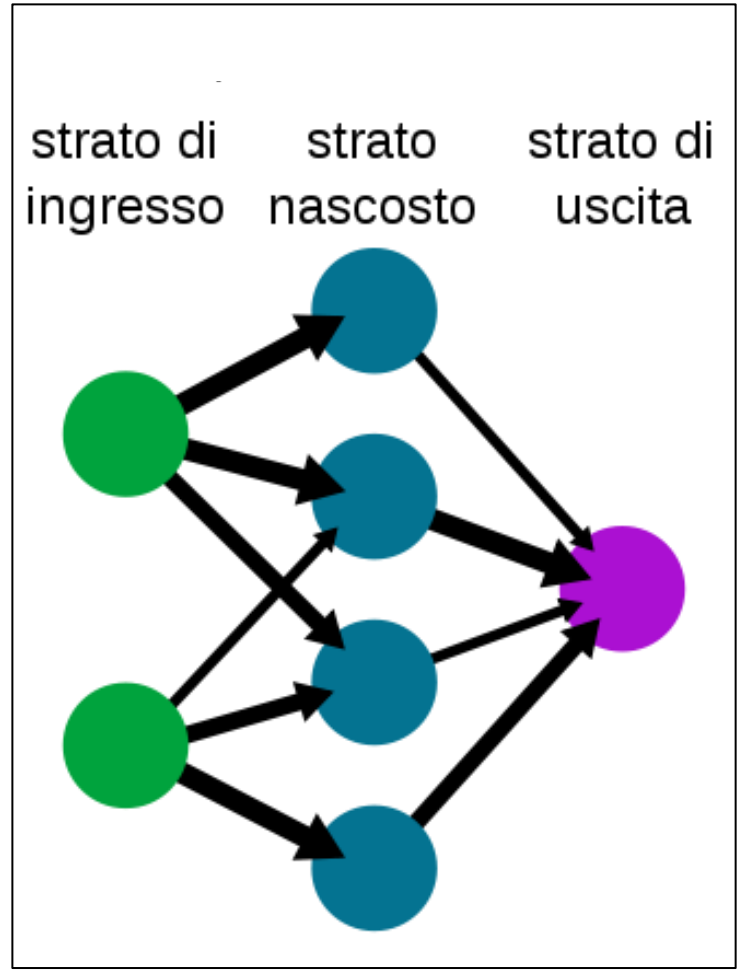
Possono essere realizzate (*digital signal processing)* sia con softwares (molto precisi) che con chips dedicati (meno precisi, ***ma impiantabili***)

SUPPORT VECTOR MACHINE (CLASSIFICATORE)

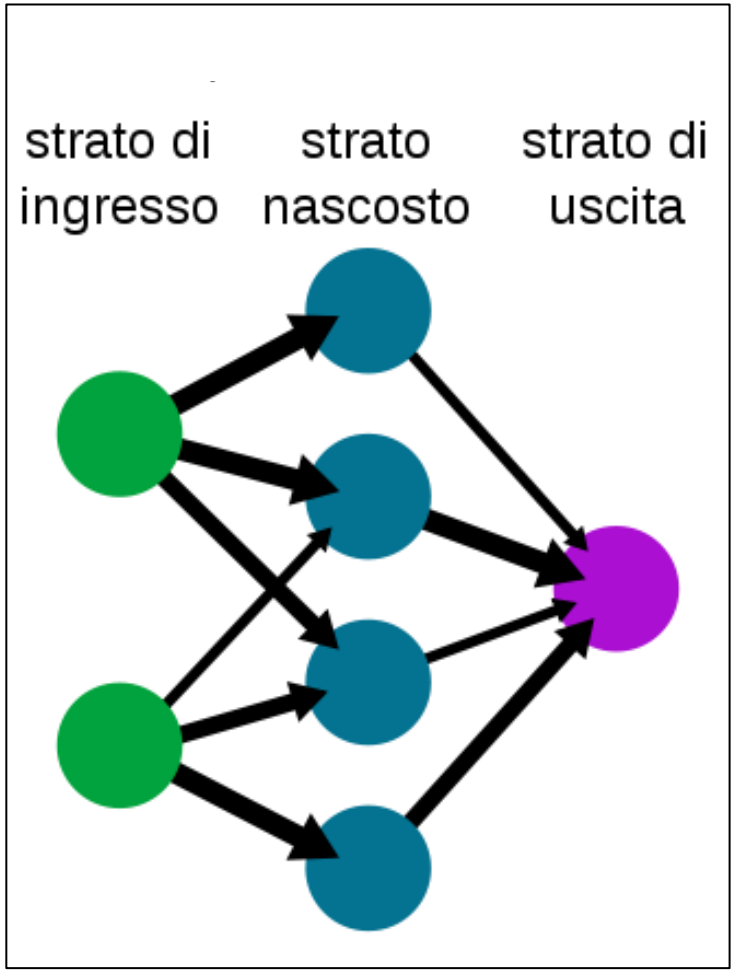
Modello matematico costruito per fare previsioni sullo 'stato' futuro di un fenomeno o di un sistema.

Formato “a strati”

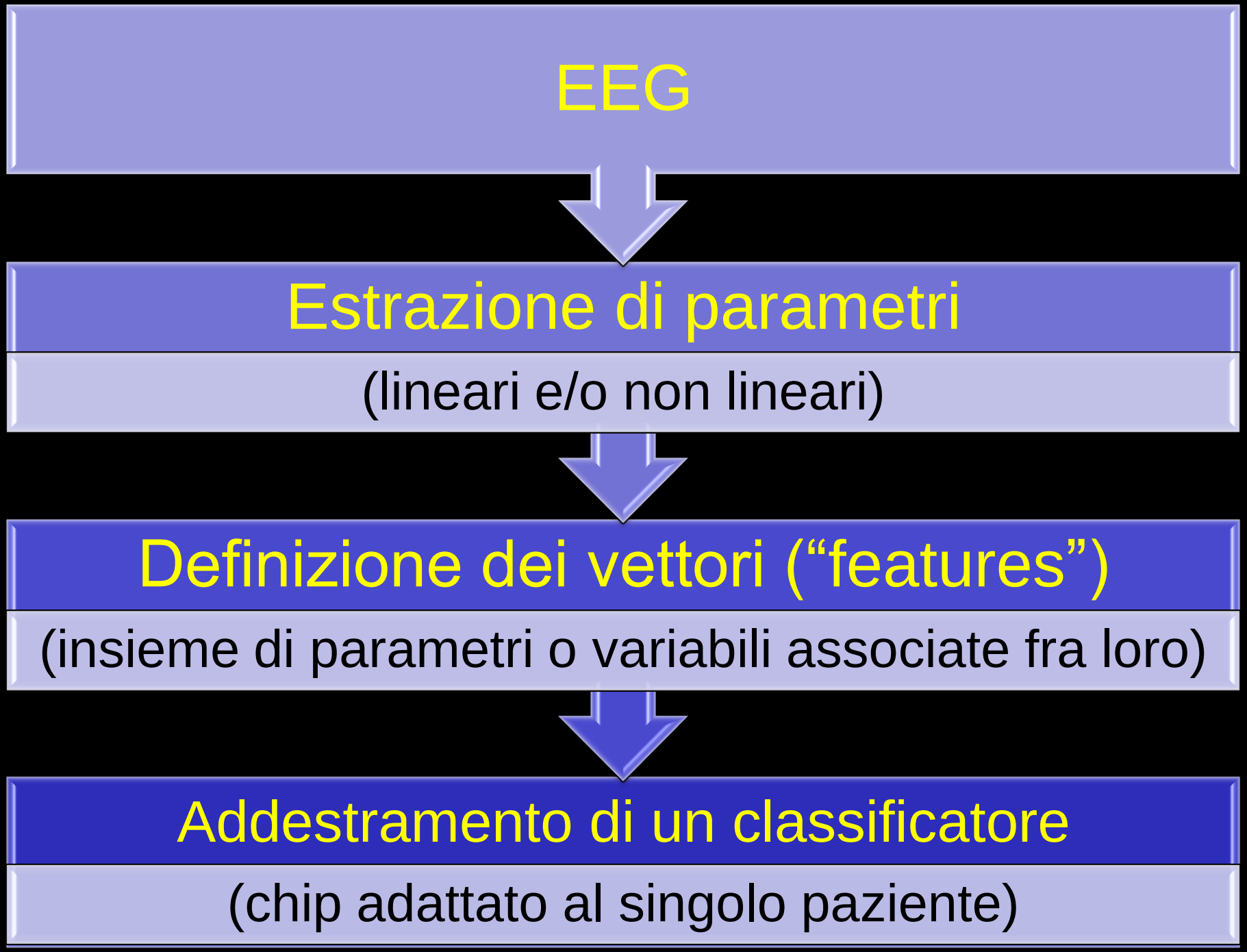
Riceve input (“vettori”), li elabora e restituisce (output) la *probabile evoluzione* di un fenomeno o di un sistema



SUPPORT VECTOR MACHINE (CLASSIFICATORE)



L’ affidabilità dell’ output dipende dalla qualità e dalla quantità degli input (**apprendimento** con training).


EEG
Estrazione di parametri
(lineari e/o non lineari)
Definizione dei vettori (“features”)
(insieme di parametri o variabili associate fra loro)
Addestramento di un classificatore
(chip adattato al singolo paziente)

Seizure prediction with spectral power of EEG using cost-sensitive support vector machines

*Yun Park, *Lan Luo, *Keshab K. Parhi, and †Theoden Netoff

Epilepsia, 52(10):1761–1770, 2011

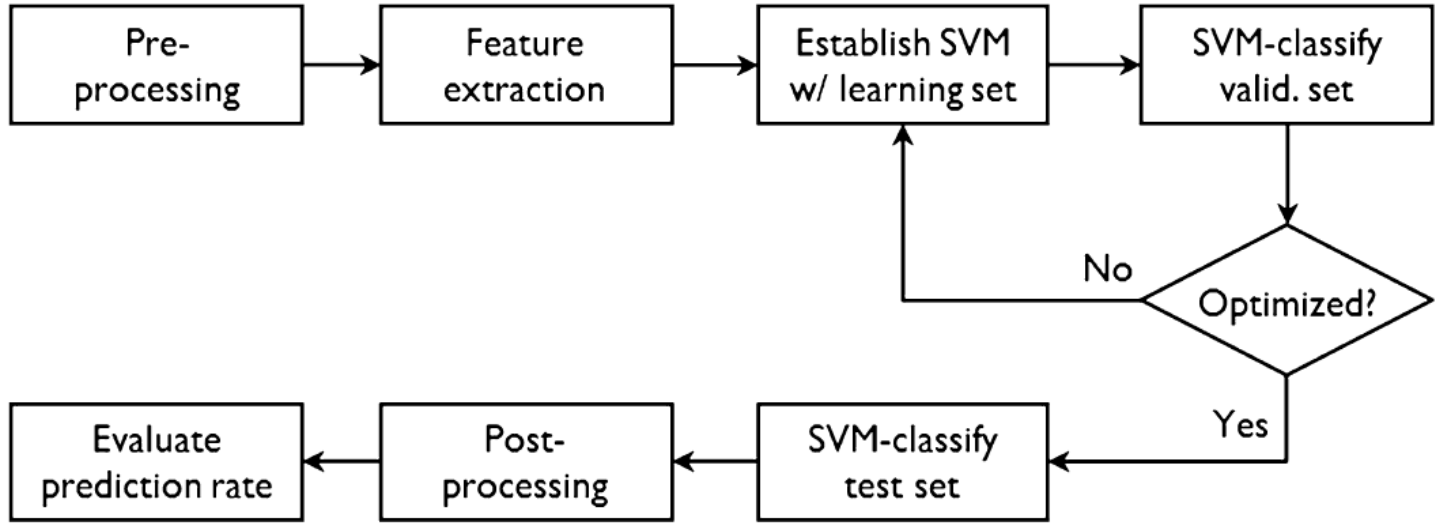
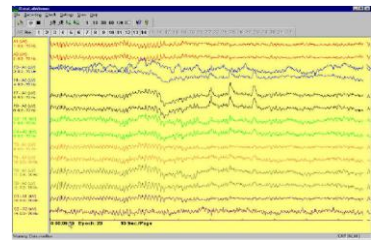
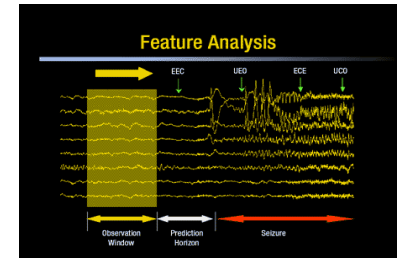


Figure 2.
Outline of the proposed seizure prediction algorithm.

Seizure Detection/Prediction System

Multichannel

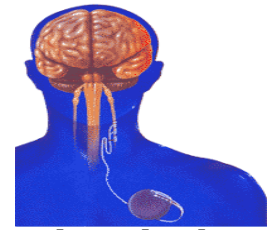


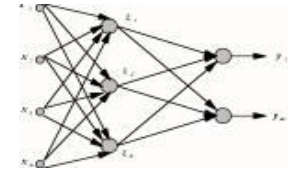


Feature Extraction

Data Acquisition

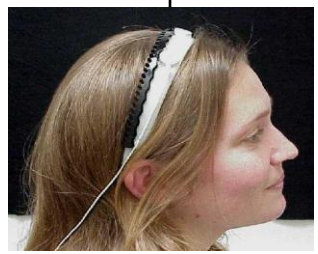
Interface Technology





Pattern Recognition

Stimulation
Drug delivery.



User

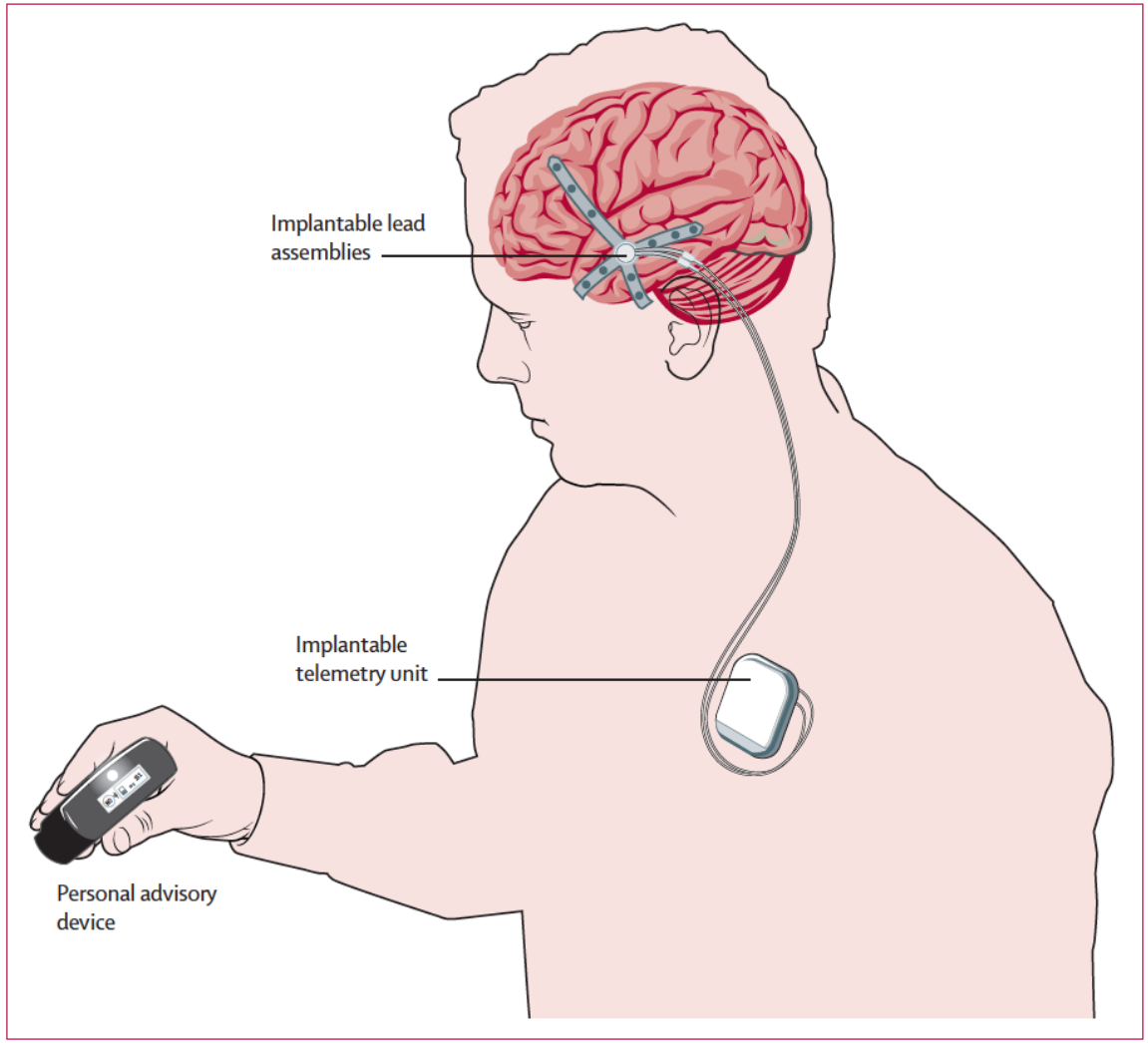
Alert

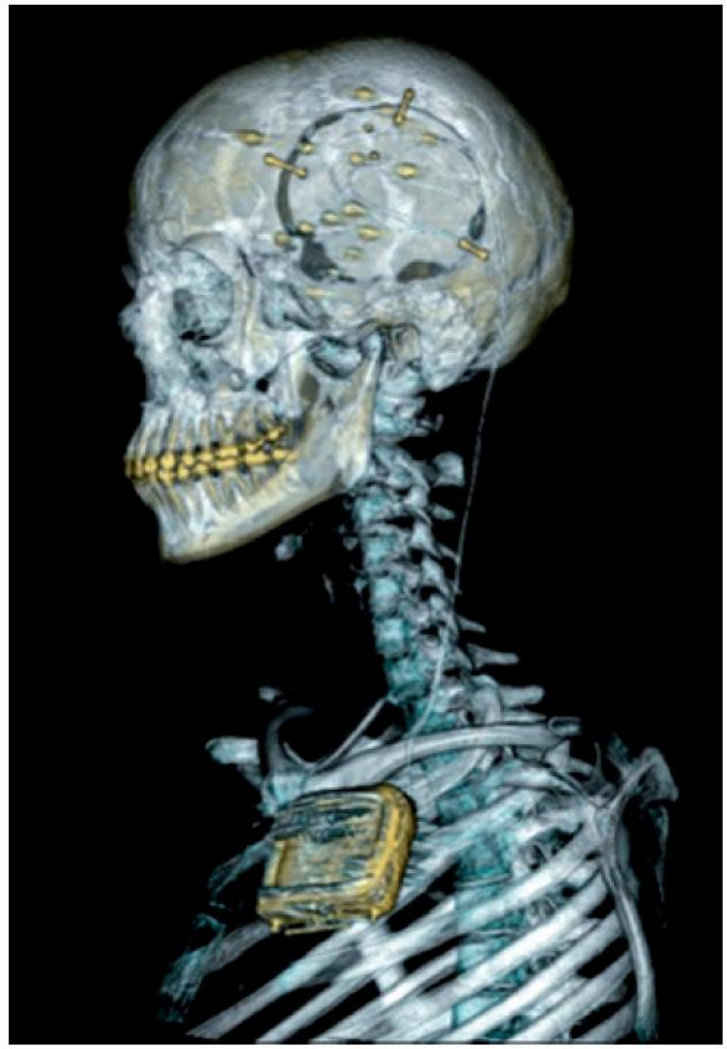
Initiate a Variety of Therapies

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

Lancet Neurol 2013; 12: 563–71

Mark J Cook, Terence J O'Brien, Samuel F Berkovic, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D'Souza, Raju Yerra, John Archer, Lucas Litewka, Sean Hosking, Paul Lightfoot, Vanessa Ruedebusch, W Douglas Sheffield, David Snyder, Kent Leyde, David Himes



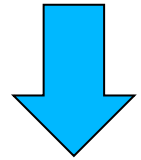


The statistics of a practical seizure warning system

J. Neural Eng. **5** (2008) 392–401

David E Snyder[1], Javier Echauz[2,4], David B Grimes[1] and Brian Litt[3,4]

TESTING



90 % Sensitivity for true positives

100% Negative predictive value for true negatives

Outputs of:

high likelihood seizures:	43% of times
moderate likelihood seizures:	39% of times
low likelihood seizures:	17% of times

The statistics of a practical seizure warning system

J. Neural Eng. 5 (2008) 392–401

David E Snyder[1], Javier Echauz[2,4], David B Grimes[1] and Brian Litt[3,4]

Filtering

- Collection of digital filtering from 8 to 128 Hz (Notch included)

Extraction

- 5” window spectral analysis:
  - *Average energy*
  - *Teager-Kaiser energy*

Classification (Patient-specific algorithm for seizure prediction)

- likelihood Outputs:
  - *High*
  - *Moderate*
  - *Low*
  - *Uncertain*

Personal advisory device

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

Lancet Neurol 2013; 12: 563–71

Mark J Cook, Terence J O'Brien, Samuel F Berkovic, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D'Souza, Raju Yerra, John Archer, Lucas Litewka, Sean Hosking, Paul Lightfoot, Vanessa Ruedebusch, W Douglas Sheffield, David Snyder, Kent Leyde, David Himes

	Age (years)	Sex	Age at diagnosis (years)	Antiepileptic drugs	Epileptogenic zone	Previous resection
Patient 1	26	Male	4	Clonazepam, levetiracetam, lamotrigine, valproate	Parietal-temporal	No
Patient 2	44	Male	12	Lacosamide, lamotrigine, oxcarbazepine, valproate	Occipitoparietal	No
Patient 3	22	Female	16	Carbamazepine, lamotrigine, phenytoin	Parietal-temporal	Yes
Patient 4	61	Male	48	Carbamazepine, lacosamide, lamotrigine, topiramate, phenytoin	Parietal-temporal	No
Patient 5	20	Female	1	Clonazepam , lamotrigine, oxcarbazepine, topiramate	Frontotemporal	Yes
Patient 6	62	Male	37	None	Temporal	No
Patient 7	52	Male	26	Carbamazepine, clonazepam, levetiracetam	Frontotemporal	No
Patient 8*	48	Male	20	Carbamazepine, levetiracetam	Frontotemporal	Yes
Patient 9	51	Female	10	Carbamazepine	Occipitoparietal	No
Patient 10	50	Female	15	Levetiracetam, oxcarbazepine, zonisamide	Frontotemporal	Yes
Patient 11	53	Female	15	Lacosamide, phenytoin, perampanel	Frontotemporal	No
Patient 12	43	Male	20	Lamotrigine, lacosamide, phenytoin, retigabine	Temporal	No
Patient 13	50	Male	20	Carbamazepine, clonazepam, levitiracetam, lacosamide	Temporal	Yes
Patient 14	49	Female	4	Clonazepam, oxcarbazepine	Parietal-temporal	No
Patient 15	36	Male	5	Carbamazepine, lacosamide, perampanel, topiramate	Temporal	Yes

Drugs were used throughout the study, with variations according to clinical parameters (ie, toxic effects).*Patient 8 had previous vagus nerve stimulation.

***Table 1*: Demographics of patients at baseline**

15 Patients

- Data collection phase (cross validation estimate)

15 Patients

- Generation of a patient-specific algorithm for seizure prediction

15 Patients

- Test performance of algorithm
- [**sensitivity** of red (high risk) and blue (low risk) leds]

11 Patients

- Advisory Phase (prospective **performance** at 4 months)

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

Lancet Neurol 2013; 12: 563–71

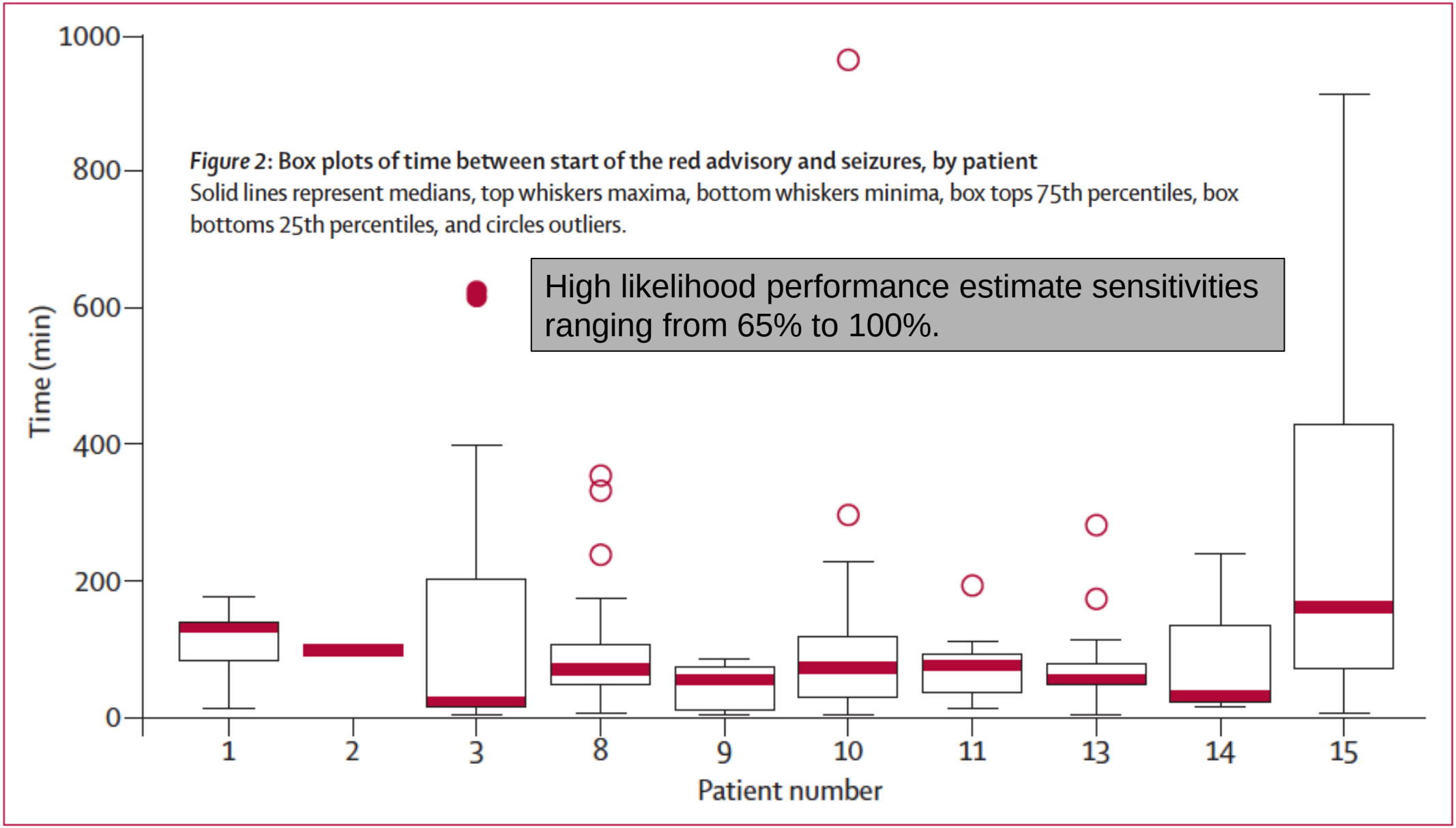


***Figure 2*: Box plots of time between start of the red advisory and seizures, by patient**
Solid lines represent medians, top whiskers maxima, bottom whiskers minima, box tops 75th percentiles, box bottoms 25th percentiles, and circles outliers.

High likelihood performance estimate sensitivities ranging from 65% to 100%.

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

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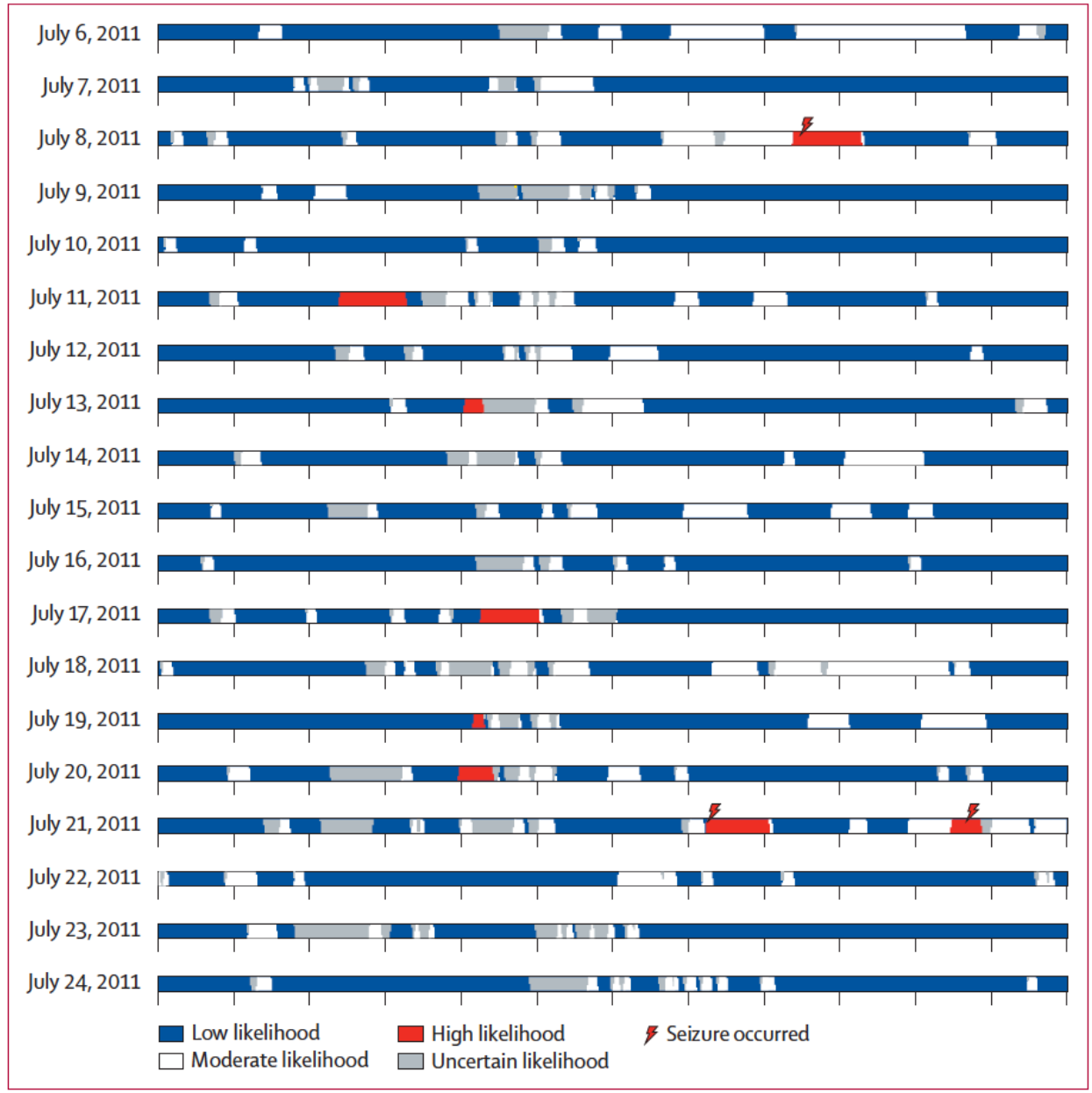

***Figure* 3: Excerpt from patient 2's advisory timeline**

Each horizontal row represents a day broken into 2 h periods. Within each line, pixel columns are 2·3 min in duration and are broken down vertically into 13·8 s pixels. During periods of uncertain likelihood, the algorithm could not provide advisories because of data loss. From top to bottom, left to right, warning times for seizures were 14·9 min, 6·3 min, and 29·7 min.

Patient 2:
100% specificity
(advisory phase)

Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study

Lancet Neurol 2013; 12: 563–71

Mark J Cook, Terence J O'Brien, Samuel F Berkovic, Michael Murphy, Andrew Morokoff, Gavin Fabinyi, Wendyl D'Souza, Raju Yerra, John Archer, Lucas Litewka, Sean Hosking, Paul Lightfoot, Vanessa Ruedebusch, W Douglas Sheffield, David Snyder, Kent Leyde, David Himes

	Adverse events		Serious adverse events	
	4 months after implantation	12 months after implantation	4 months after implantation	12 months after implantation
Device migration	1	..	1	..
Device-related infection	..	1	..	1
Reaction at site of medical device	1	1	..	1
Postoperative nausea	1	..	..	..
Postoperative vomiting	1	..	..	..
Procedural headache	5	..	..	..
Procedural pain	1	..	..	..
Seroma	1	..	1	..

Adverse events total includes serious adverse events. For the primary endpoint, we followed up adverse events for 4 months after implantation of the device (12 months for secondary endpoints). No further device-related adverse events were noted before study termination; five of the 12 remaining (when the study was terminated) implanted patients reached the endpoint of 24 months after implantation.

***Table 2*: Device-related adverse events and serious adverse events**

CONCLUSIONE

La predizione EEG con dispositivi intracranici durante l’ attività quotidiana dei pazienti è possibile ed affidabile, anche se perfettibile.

Ma è utile ?