Chapter 1

EEG Long-Term Dynamics to Measure Progress of Concurrent Patients in Drug-Resistant Childhood Syndromes

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Additional information is available at the end of the chapter

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Abstract

It is well known that in order to study the evolution of a drug-resistant epilepsy, it is necessary to practice a lot of Electroencephalographic signals (EEG) studies during the child's life. The number of EEG collected by parents during the child's life might easily range between 10 and 20, depending of the severity of the affection, age and neurologist's requirements. With all these data, natural questions posed by parents and physicians are as follows: (a) Which zone of the brain has been the most affected so far? (b) On which year was the child better? Naturally, the neurologist would wish to correlate these answers with the prescribed drugs history but responding objectively those questions is certainly not easy (or even impossible). However, both questions were already answered quantitatively in [1] where a very difficult case of Doose syndrome (DS) was investigated. In this work, we propose to go further answering an additional question frequently posed by parents and physicians which is as follows: (c) How bad is our child with respect to other with similar affections? Note that replying this question results also very difficult because this would imply to compare *sets* of *multiple, massive* EEG (one for every kid involved in the study). In addition, the possibility of answering this question also implies to compare medications/results among all the children in the investigation. What we propose here is to answer *quantitatively* question (c) by using our complexity measures and indices introduced here and the experience obtained in [1] with all this linked to medications. The question arises as follows: Why to use complexity, that is, entropy to characterize EEG information? Because it would be formidable to determine a mathematical model which could represent *in general, each case of DS or LGS*. This is not yet possible but after analyzing a set of *nonlinear models*, we concluded that it is more reliable to work with *nonlinear statistics* (entropies) to extract information from EEG in children epilepsy [1]. As a result of this, we offer here the multiscale entropy (MSE) index and the bivariate multiscale (BMSE) index to evaluate all channels of multiple EEG.

Keywords: simultaneous EEG dynamics, time series entropy, drug-resistant children epilepsy, epileptic encephalopathies

1. Introduction

Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure [3]. A syndrome is a group of signs and symptoms that, added together, suggest a particular medical condition. The International League Against Epilepsy (ILAE) defines an epileptic encephalopathy (EE) as the condition where the epileptic activity itself contributes to cognitive and behavioural impairments seen in severe epilepsy, beyond that expected from the underlying pathology alone [4, 5]. In addition, the ILAE Task Force has chosen the preferred term *drug resistant* to replace terms as *pharmacoresistant, intractable, refractory* because these would imply that there is no chance of remission, which is not necessarily the case [6–8]. Childhood epilepsy syndromes as Lennox-Gastaut (LGS) and Doose (DS) are typical examples of epileptic encephalopathies (EE). When these affections are drug resistant, finding reliable treatments becomes a challenge. Although some works in applied mathematics to epilepsy have been successfully conducted (see for instance [9] and references therein), papers which investigate quantitatively EEG in drug-resistant epileptic encephalopathies are practically null. Main attention has been devoted to adult affections as Alzheimer's disease, Creutzfeldt-Jakob disease, schizophrenia, Parkinson's disease and others [9–12]. About quantitative investigation of children epilepsy (see [1, 2]).

1.1. The Doose syndrome

Hermann Doose first described the features of a previously incompletely defined epilepsy syndrome characterized by very different seizures, consisting of jerks, drop attacks, or sometimes a jerk followed by a fall. Absence seizures can happen as well as the so-called generalized tonic-clonic seizures. The EEG may be initially normal, but development of the disease will exhibit patterns of generalized spike and wave activity, 4–7 rhythms/s and bursts. Photoparoxysmal reaction may be observed in the EEG as well. About 1–2% of all children epilepsy is confirmed by DS [7]. This illness affects children with an initial normal development which age ranges from 7 months to 6 years although early manifestations are typically exhibited from 2 to 5 years [13].

1.2. The Lennox-Gastaut syndrome (LGS)

Although precise definition of LGS is still controversial, it is accepted nowadays that three main features must be present in an LGS diagnosis: (a) slow spike wave activity in the EEG, (b) a wide variety of different kind of seizures (typically from sleep) and (c) intellectual

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impairment. A very special feature in LGS is the presence of tonic seizures during sleep, which are often overlooked. Typically, onset is between 3 and 8 years of age and LGS shows up with drop or atonic seizures, but as mentioned, a lot of other phenomena may exist as tonic seizures and atypical absence seizures. As a result of this, providing a differential diagnosis can be quite difficult, particularly at the onset before the development of typical characteristics. Structural and brain damages are frequently reported as main causes of LGS [7, 8, 13].

Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed [4]. In this work, we are interested in the preictal, ictal and postictal stages of a seizure.

1.3. Note about the subjects considered in this study

The present investigation is a pilot study of how mathematics can support neurologists in severe children epilepsy by means of entropy measures. We present a series of five cases of study; four patients with drug-resistant EE (one kid with a fuzzy transition from DS to LGS; two, confirmed LGS; and one with preponderant features of DS; see Section 2 for details). The fifth kid is neurologically normal, and his EEG collection was used merely as a comparison with the affected children. The EEG studies were recorded with sleep deprivation in the abnormal children, and the nonaffected one was awaken but relaxed developing several activities described in Section 2.5. We remark that finding a suitable (representative) population is quite difficult as a result of the rareness and conditions required in this research (see list below). All data were analyzed anonymously by paying attention only to the numerical information and medications. Artefacts were excluded by an expert neurophysiologist (**Figure 1**).

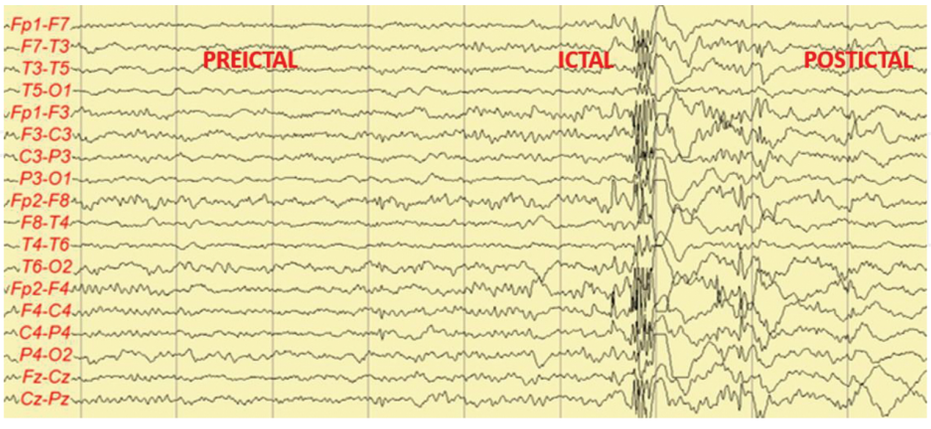

Figure 1. Stages of a seizure.

A question arises about EE: Why to work precisely with this type of affections? Because they have not been examined before (excluding [2] and [1]) and because this kind of epilepsy represents a challenge to deal with not only from a therapeutic viewpoint but also from a

mathematical perspective. In addition, parents' observations are taken into account here when they described the type of seizures and improvement (or worsening) of them. Their remarks helped physicians to construct the tables and information about medications given in this work. Since our work is a pilot study, we do not offer, at this moment, neither hypothesis testing results nor power analysis;however, the conclusions shown here will guide the design and implementation of a larger scale study [14]. Such work is already being developed; nevertheless, we remark that a study as ours is still lacking. With the intention of giving examples of papers which considered just a few subjects in similar studies, we would like to cite [15] (one patient), [16] (three patients), [17] (seven patients), and [18] (15 patients). In those references, the investigation is conducted in absence of epilepsy and autistic children; more common affections than long term-drug-resistantepileptic encephalopathies.

The patients were selected in order to satisfy the following requirements; that is, they had to:

1. Be children (their epilepsy is more time-varying than adult's).
2. Suffer a drug-resistant EE of the type DS or a LGS since a long time ago, that is about 10 years.
3. Be adhered to medical treatments.
4. Continue such medical treatment in the same hospital (in order to follow their evolution continuously).

It was a challenge to find the subjects which could fulfil all the above-mentioned conditions. Note that as more we require, as less children we can collect. It is noteworthy mention that in developing countries complying with medical treatments in public hospitals may imply a lot of third party complications as lacking of beds, very long waiting lists to be attended, shortage of medicines, etc., just to mention a few [1, 19]. In addition, when parents cannot see a real improvement in short term, they change the physician or the hospital. The worst case is when parents do not understand the gravity of the illness and they do not comply the medical treatment [19–21]. These facts complicate even more to collect the required candidates for our investigation.

1.4. Main anticonvulsants prescribed for our subjects

A list of abbreviations for the anticonvulsants prescribed for the patients is given next. Details about action mechanism, dosages, etc., can be consulted in [22–24].

1. IMI = imipramine,
2. PA = piracetam,
3. VPA+ = valproate sodium,
4. TPM = topiramate,
5. CLB = clobazam,
6. VPA = valproic acid,

7. LTG = lamotrigina,
8. LEV = levetiracetam,
9. ATX = atomoxetine,
10. ESM = ethosuximide,
11. PSE = prednisone,
12. MDZ = midazolam,
13. CZP = clonazepam,
14. ZNS = zonisamide,
15. CZP = clorazepate dipotassium,
16. PB = phenobarbital,
17. LCM = lacosamide
18. PRM = primidone,
19. Q10 = co-enzyme Q10 (not an anticonvulsant),
20. Star (*) means that an EEG was recorded in a given year that such record was used in this work,
21. Letters *a* and *b* mean first and second semester of a year, respectively,
22. √ and × mean a relative good and poor control of seizures, respectively,
23. NA means not applicable.

2. Subjects, EEG description and medication

The set of subjects is composed by four children. Children A and B were born in 2002, child C in 2000,child D in 2003 and child E in 2000. Child A was diagnosed with DS, but it seemed to evolve to LGS, although not all physicians are agreed [1]. Kid B has been diagnosed as LGS; child C as DS and child D as LGS. Kid E is considered normal (no seizures). Children A-D suffer a multifocal effect, but child A has a main source in the frontal lobe while kid B present seizures which seem to originate from the frontal and temporal lobes. On the other hand, all records were sleep-deprived EEG for all non-normal subjects. The databases were retrieved from different children hospitals where the EEG was recorded from scalp in 32 channel-Grass Technologies Clinical Systems [25] according to the international 10–20 standards with 7 mm, 50 μv calibration [26]. In our work, the electrodes are as follows: Fp1, F3, F7, T3, C5, T5, P3, O1, Fp2, F4, F8, T4, C4, T6, P4, O2, Fz, Cz and Pz. The sample frequency was 200 Hz corresponding to 5 ms of sample time. The electrode Oz was not considered. In the case of the healthy subject, the equipment employed is produced by g.Tech and the model is g.Nautilus, a

relatively new wireless biosignal acquisition system with possibility of having quality EEG recordings from 32/16/8 channels at 250–500 Hz of sampling frequency [27]. This device was very useful to record diverse activities in the normal kid. The version used is equipped with eight channels which are Fz, Cz, F3, Pz, P4, PO7, PO8 and Oz, and the sample frequency was 250 Hz, that is 4 ms of sample time. As known, these syndromes manifest very differently and that is why we offer our entropies perspective.

2.1. Patient A

A 12-year-old child was investigated in [1, 2], and her history is continued here. The onset of epilepsy in kid A was at 4 years with very short absence seizures. A few months later (when she became 5), seizures started as shivers and then they worsen as droop heads (See **Table 1**). A very wide spectrum of medications was tried without a clear success. Twenty anticonvulsants were used through all the child life and the worst season was at the beginning of 2014 when even 80 seizures a day were presented. The seizureslooked as shivers every 5 min and, as a consequence, the girl had to be admitted in the hospital emergency room but without any possibility of correcting this and deterioration started to be serious. The type of seizures was mainly drops, drop head and myoclonic. As a result of this, the child had to use a helmet and she had to interrupt her attendance to a special education school as well as psychomotor therapy. Some months were needed to admit this kid in the hospital in order to substitute clonazepam (CZP) byclobazam (CLB) because CZP had reached its highest dosage without positive results. This action ended up with about four months of relative success, but still several seizures were present. After many useless trials to improve her condition, parents took her child and left this hospital in order to let their kid to be treated in another institution where intravenous immune globulin (IVIG) was suggested as last resource (although with some doubts about success by some physicians).

Anticonvulsant	Year	Comments	Seizures	MSE	BMSE
IMI, PM	2006	First medicines consumed. Stopped suddenly	NA	NA	NA
VPA+, TPM, CLB, VPA	2007	Beginning of VPA+	NA	NA	NA
VPA, LTG, TPM, VPA+, CLB, LEV, ATX, ESM, PSE, MDZ	2008*	Pancreatitis. Beginning of ESM, LEV. ATX worsen seizures	√.	OK	OK
TPM, LEV, LTG, PSE, ESM, CZP, ZNS,	2009	ZNS useless. Retirement of ETS worsen seizures	NA	NA	NA
ZNS, ESM, CZP, LEV, CZP	2010*	CZP useless. Seizures worse	×	Bad	Bad
CZP, LEV, LTG, ESM, PB	2011*	PB useless	×	Bad	Bad
LCM, ESM, LEV, LTG, CZP	2012	LCM shows up.ETS retired again worsening seizures	NA	NA	NA
LCM, LEV, LTG, PRM, CZP, Q10, ESM	2013a*	Gastritis aggravate	√	OK	OK
LEV, ESM, LCM, LTG, CZP	2013b*	Idem.	√	OK	OK
LEV, ESM, LTG, CLB, *IVIG*	2014	LCM worsen seizures, CZP replaced by CLB	√	NA	NA
LEV, ESM, LTG, CLB, *IVIG*	2015	LCM retired, gastritis improved	√	NA	NA

Table 1. Anticonvulsants per year for patient A.

Nevertheless, it is remarkable how IVIG improved the life of this child which has received this treatment twice, one at the end of 2014 and another one by mid of 2015. She will repeat this by the end of 2015 (see [1] for disease details and its relation with other entropy measures). This information is an update of this case.

Although the disease process of this child starts in 2006, the EEG database encompasses only 2008, 2010, 2011, and 2013; missing years were not accessible for administrative purposes. The four EEG which compose the present database are referred to as EEG1, EEG2, EEG3, and EEG4, respectively. The entire set of the four EEG clearly shows typical features of DS although some clinical manifestations are not consistent with a typical DS (overlapping with LGS). This patient is a case of multifocal epilepsy which quickly spreads through all the brain. Apparently, the initial focus is the frontal lobe. Our results in [1] were in line with this.

Table 1 provides updated information about the main anticonvulsants prescribed for the kid during 2008–2015. In that table, the abbreviations used were already explained in Section 1.4. Details about those antiseizures can be reviewed in [8, 22–24, 28]. Note: The last two columns of **Tables 1** and **2** refer to the entropies described in this work which will be explained from Section 3 on.

Anticonvulsant	Year	Comments	Seizures	MSE	BMSE
VPA+	2007*	Onset of seizures, VPA+ prescribed	×	Bad	Bad
VPA+	2008	Seizures improve a bit	√	NA	NA
VPA+	2009	Seizures continue	×	NA	NA
VPA+	2010*	Seizures improve	√	OK	OK
VPA+	2011	VPA+ retired	√	NA	NA
VPA	2012*	Seizures starts to worsen	×	Bad	Bad
VPA, LTG	2013	Seizures improve, bad later	×	NA	NA
VPA, LTG	2014*	LTG prescribed, seizures improve	√	OK	OK

Table 2. Anticonvulsants per year for patient B.

2.2. Patient B

Kid B was diagnosed as LGS and started in 2007 with multifocal discharges with probable initial focus in the frontal and temporal lobes. The first medicine prescribed was VPA+ and continued until 2010. In 2011, this anticonvulsant was retired as a result of a relative improvement in his condition but seizures worsen and in 2012, and VPA was prescribed. LTG [28] was included to help in 2013 and 2014. More detailed information is missing (see **Table 2**). Notice the difference between the anticonvulsants needed by patient A and patient B. The available EEG was recorded in 2007, 2010, 2012 and 2014 and was named as EEG1-EEG4, respectively.

2.3. Patient C

This kid apparently suffers DS but (as in the case of child A) the border with LGS seems to be fuzzy. More information about child C is missing. We only could access the numerical database

which corresponds to four records: 2005, 2008, 2012 and 2014. The main anticonvulsant was VPA, LTG, LEV and CLB. This disease is also multifocal.

2.4. Patient D

This kid is a case of LGS. The set of EEG was collected from 2005 to 2014. Here, we only could access the numerical databases of 2005, 2009 and 2014 as well. The main antiepileptic drugs consumed were VPA, ESM and LEV. This patient seems to be the less affected as a result of being DS. The level of consciousness seems to bebetter in this kid as a result of being DS.

2.5. Subject E

Kid D is healthy and his EEG was used to compare how entropy contrasts with epileptic affections versus normality. The EEG was recorded while the kid developed diverse activities (A1-A4) during a total of 5 min (M1=minute 1 to M5=minute 5), (1 min each). These actions are resumed below where the letters mean: R is the resting, MA is the muscle activity, HM is the hearing music (lying down), T is the talking (lying down), D is the drawing (sat down), LD is the lying down, SD is the singing/dancing (slowly) and W is the walking slowly (**Table 3**).

A/t	M1	M2	M3	M4	M5
A1	R	R	R	R	R
A2	R	MA	HM	R	T
A3	R	D	LD	SD	R
A4	R	W	W	W	R

Table 3. Activities in a normal kid.

3. Methods: nonlinear models or nonlinear statistics?

There are two main streams in modelling of EEG: (a) nonlinear dynamical systems (chaos-based theory) and (b) stochastic models [9–11, 29]. Although there have been interesting reports about this, they have been focused on adults epilepsy and literature about children epilepsy is rather scanty [1, 2]. But even considering their relative success, the models provided cannot be general as a result of the highly nonlinear, time-varying (and sometimes stochastic) nature of EEG in (children and adults) epilepsy. We sketch next our investigation about how we concluded to apply nonlinear parameters rather than nonlinear models to investigate EEG in children epilepsy.

As it was just mentioned, there have been good results in some adults epilepsy (Creutzfeldt-Jacob disease, schizophrenia, Alzheimer's disease, etc.) modelled by chaotic dynamical systems [9–11]. That is why we focused on time series (TS) characteristics considering TS as a particular case of a stochastic process. Those basic characteristics are as follows: normality (in distributional sense), stationarity and linearity of the TS.

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3.1. Time series from EEG

A common consideration about EEG signals is that they are Gaussian and stationary. In this case, frequency analysis is a natural alternative [30]. If this were not the case, there also exists the possibility of dealing with nonstationary signals in frequency domain [31]. Some serious adult's brain disorders such as Alzheimer's disease (AD), Creutzfeldt-Jacob disease (CJD), schizophrenia obey neither stationary nor Gaussianity restrictions [10, 12]. Without being very formal, the following characteristics were explored in our databases.

3.1.1. Normality

In order to have an idea about the shape of the probability distributions of each channel in the patients' database, a very simple algorithm to test normality was used and it concerns the well-known Q-Q plot [32]. Using standard MATLAB commands, this test was run for all the databases resulting that all channels tends to present a non-normal (non-Gaussian) distribution. Providing a detailed statistical study for this is out of the scope of this work but for the time being it suffices to say that normality is not satisfied. The tails of the distributions are distorted in many channels of all patients.

3.1.2. Stationarity

It is well known that a process is called stationary in mean and stationary in variance if such quantities remain constant through time. From the amplitude vs. time plots, it can be seen by qualitative inspection that all patients' EEG signals have no trend, that is they are stationary in mean. In addition, in order to confirm absence of trend, two simple nonparametric tests were done; the Bendat-Piersol run and trend tests [33, 34] which agreedwith such observation. Later, the autocorrelation function was plotted showing that each channel of the whole database of the patients is not covariance stationary. A *t* test was also developed on all data, being in line with this. Correlograms of all EEG channels showed that they do not behave randomly (figures not shown).

3.1.3. Linearity

First, the notion of linearity has been established. Linearity with respect to what? It is known in our days that most of physiological signals represented by time series are nonstationary [35] and nonlinear in general. In the scope of this work, we will consider that an EEG signal is linear if its Q-Q plot is a straight line, that is, the distribution of a given EEG channel coincides almost perfectly with a normal distribution. However, as explained above, most of the EEG zones (channels) showed a non-normal distribution. In this sense, the meaning of statistical non-normality and medical non-normality coincides (see more details about this in [1, 36]).

As a result of all this, it was decided that working with nonlinear statistics (entropy of TS) was more reliable and useful because they can be computed for any TS (see next section).

3.2. Complexity of signals as time series

Time series complexity or entropy measures how regular a sampled signal is. For instance, a sine wave (or any periodic signal) will exhibit a low value of entropy because such signal is very predictable. As known, this signal is characterized only by its amplitude and frequency parameters. However, consider now a white noise variable. Since it is characterized by its random nature, its complexity value will be high (with respect to the sine wave). Broadly speaking, a signal will be complex if its entropy value is bigger (or equal to) than 1. Nevertheless, it is also important to determine *when* such value is reached. In order to explain deeper this important idea which supports our results, the basics of entropy are shown next. Immediately later, a workout example is provided.

3.2.1. What does entropy measure and how?

In time series context, entropy is the rate of information production [37]. Pincus [37] developed the theory for a measure of regularity, the rate of generation of new information that can be applied to clinical data. This statistic was called *approximate entropy, ApEn*. It had as a goal to measure systems complexity (the terms complexity and entropy are used interchangeably [37–39]). This statistic has been evolving, and it has taken new names depending of the improvements: *sample entropy* [40], *multiscale entropy, MSE* [39], our version of MSE and our proposed *bivariate MSE* (BMSE) and some others [1]. A collection of four entropy measures was evaluated in [1] showing that MSE was the more convenient to be used in our databases.

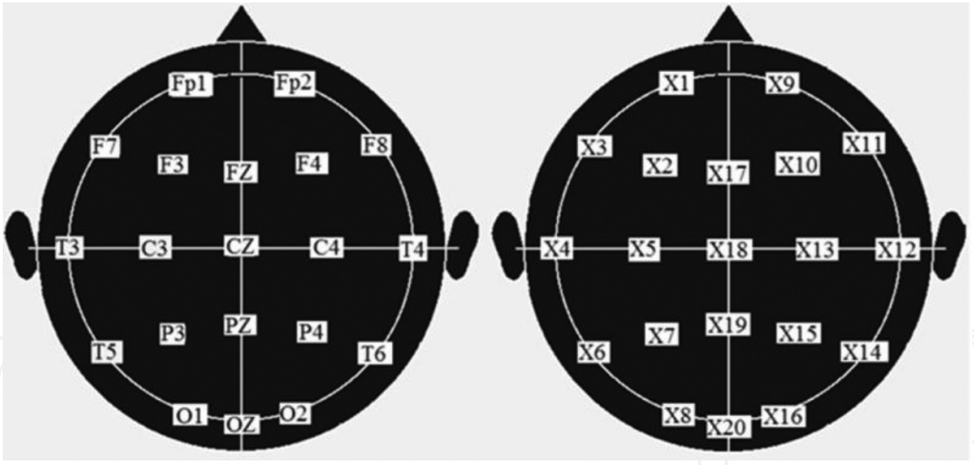
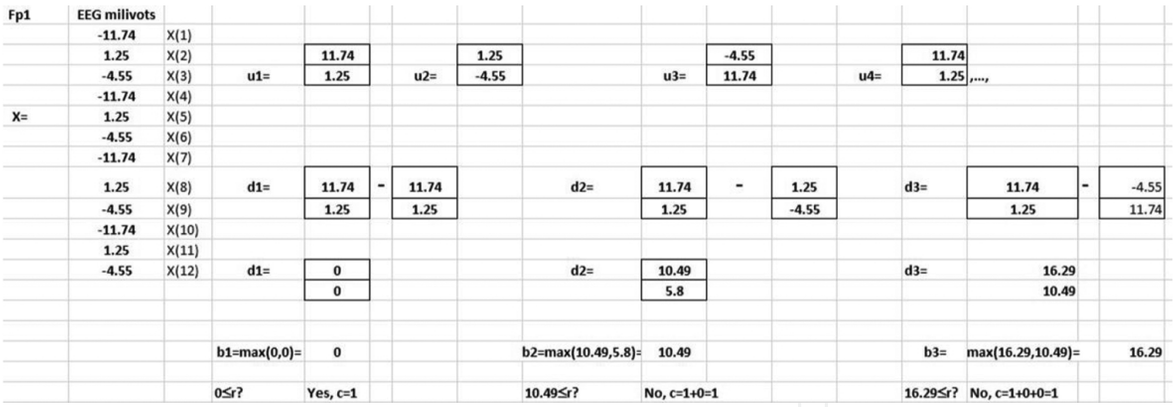


Figure 2. Schematic representation of the international standard 10–20 for electrodes placement and its corresponding nomenclature used in Algorithm 1 (see Section 3.2).

3.2.2. How to compute MSE?

Without loss of generality, before describing MSE, we would like to explain a generic algorithm to compute complexity, actually, ApEn. Later, we will comment how to modify this algorithm to determine MSE [1, 37, 39, 40]. For ease of exposition, this algorithm is explained for only one EEG channel:



Fp1	EEG milivots																	
	-11.74	X(1)																
	1.25	X(2)		11.74		1.25			-4.55			11.74						
	-4.55	X(3)	u1=	1.25	u2=	-4.55		u3=	11.74		u4=	1.25	,...,					
	-11.74	X(4)																
X=	1.25	X(5)																
	-4.55	X(6)																
	-11.74	X(7)																
	1.25	X(8)	d1=	11.74	-	11.74		d2=	11.74	-	1.25		d3=	11.74	-	-4.55		
	-4.55	X(9)		1.25		1.25			1.25		-4.55			1.25		11.74		
	-11.74	X(10)																
	1.25	X(11)																
	-4.55	X(12)	d1=	0				d2=	10.49				d3=	16.29				
				0					5.8					10.49				
			b1=max(0,0)=	0				b2=max(10.49,5.8)=	10.49				b3=	max(16.29,10.49)=		16.29		
			0≤r?	Yes, c=1				10.49≤r?	No, c=1+0=1				16.29≤r?	No, c=1+0+0=1				

Figure 3. Basic steps to compute entropy generically in a hypothetical channel Fp1. In this example, $r = 3$ and the number of subvectors u whose distance is smaller or equal than r is 17 of a total of 50 samples (partially shown here). The value c means *count*. This figure encompasses Steps 1–7 from Algorithm 1. From Steps 8–10, the resultant entropy will be 0(see Section 3.2.3).

Algorithm 1. MSE

1. Define a time series for a chosen EEG channel, say X_1 (if we consider 19 EEG channels, we will have 19 numerical sets; one for each zone of the brain in the EEG). So, X_1 will correspond to Fp1, $X_2$to F3 and so on (see **Figure 2**). Recall that each vector $X = [X(1)\ X(2)\ X(3)\ldots]$ (the EEG channel) consists of voltage amplitudes, that is numerical values.
2. For the given EEG channel, X_1, that is, Fp1 do the following (see **Figure 3**):
3. Construct a set of test vectors (from X) called u of length m. Typically, $m = 2$. So, the test vectors will be formed taking sets of $m = 2$ elements from X. Hence, $u_1 = [X(1)\ X(2)]$. This means that the first vector $u_1$will be constructed with the first to components of X, the voltage amplitudes of the corresponding EEG channel. So, $u_2 = [X(2)\ X(3)]$, $u_3 = [X(3)\ X(4)]$, until finishing the elements of X. Recall that the length ℓ of X, the EEG channel is determined by the EEG time t_{EEG} (in seconds) and the sample time, T. So, $\ell = t_{EEG}/T$.
4. From vectors u, compute a set of *distances* called d as follows: $d_1 = [X(1) - X(2)]$, $d_2 = [X(2) - X(3)]$, $d_3 = [X(3) - X(4)]$, until exhaust all the elements of X.
5. From vectors u, compute a set of *distances* called d as follows: $d_1 = \underbrace{[X(1) - X(2)]}_{\text{From } u_1}$, $d_2 = \underbrace{[X(2) - X(3)]}_{\text{From } u_2}$ $d_3 = \underbrace{[X(3) - X(4)]}_{\text{From } u_3}$, until exhaust all the elements of X.
6. Choose the maximum value b between two consecutive elements of d (with no attention to its sign): $b_1 = max\ (d_1,d_2)$, $b_2 = max\ (d_3,d_3,d_4)$, etc.
7. Define $r = 0.2\sigma(X)$, where σ is the standard deviation. If $b_1 \geq r$ then count it as valid, else not. The same for b_2, b_3, etc. Add the total number of valid values of all b's in c_1. Take the natural logarithm of $c_1$as $ln(c_1)$.
8. Go to Step 3 and repeat it to 7 redefining $u_1 = [X(2)\ X(3)]$, $u_2 = [X(3)\ X(4)]$, $u_3 = [X(4)\ X(5)]$ etc., until exhausting all the values of the EEG channel, X.

9. Add all the natural logarithms computed in Step 7 and divide them by the total length (in time samples) of the EEG channel, A. Call this number F_1.

10. Go to Step 3 and use $m + 1$ instead of m and repeat all until Step 9 but name the result of all this F_2. Define the *entropy* of the EEG channel as $F_1 - F_2$.

3.2.3. Worked out example

Assume that we want to analyze the complexity of a 50 samples long EEG signal given by X = …, 11.74,1.25, −4.55, 11.74, 1.25, −4.55, 11.74, 1.25, −4.55,…. (millivolts), $N = 51$. Assume that $m = 2$, $r = 3$. In this case, the sequence of subvectors u of length m (see Algorithm 1) is given by u_1 = [11.74 1.25], u_2 = [1.25 −4.55], u_3 = [−4.55 11.74], u_4 = [11.74 1.25]. Now, the distances are evaluated in such a way those vectors which satisfy the constraint $d = max(u_1,u_j) \leq r$ will be counted. Observe that $d_1 = (u_1,u_1) = 0$. (counted), $d_2(u_1,u_2) = max|11.74 - 1.25|, |1.25 - (-4.55)| = |11.74 - 1.25| = 10.49 > 3$ (not counted), where $|\ |$ means absolute value (taking positive numerical value). Similarly, $d_3(u_1,u_3) = 16.29 > 3$ (not counted either) and $d_4\ (u_1,u_4) = 0 < 3$ (counted). Continuing this process, we realize that vectors which satisfy $d(u_1,u_j) \leq 3$ are the following: u_1, u_2, u_4, u_7, … u_{49} (seventeen elements). Next, b_1 will be given by 17/50. Continuing this way, F_1 will be 0.334. Analogously for F_2=0.334 and the resulting entropy will be $F_1 - F_2 = 0$.

In this case, this periodic signal (or at least, the part considered here) is not complex. A complex signal has entropy values equal or above 1 [1]. In the case of Algorithm 1, we took continuous values of the EEG channel. If we repeat this process, downsampling a time series for τ = 2,3,4,

Fp1	EEG milivots		EEG milivots		EEG milivots		EEG milivots	
	-11.74		-11.74		-11.74		-11.74	
	1.25							
	-4.55		-4.55					
	-11.74				-11.74			
X=	1.25		1.25				1.25	
	-4.55							
	-11.74		-11.74		-11.74			
	1.25							
	-4.55		-4.55				-4.55	
	-11.74				-11.74			
	1.25		1.25					
	-4.55							
	:							
	τ=1		τ=2		τ=3		τ=4	
L=No. Of samples	12 samples		6 samples		4 samples		3 samples	,…,
	L		L/2		L/3		L/4	
	↓		↓		↓		↓	
	Algorithm 1		Algorithm 1		Algorithm 1		Algorithm 1	
	↓		↓		↓		↓	
	Entropy 1		*Entropy 2*		*Entropy 3*		*Entropy 4*	

Figure 4. Algorithm 1 in Section 3.2.2 calculates a first value of entropy for the original time series (numerical values of a given EEG channel) taking contiguous elements ($\tau = 1$). Forming subseries from the original one as shown above (i.e. by *downsampling*) and applying them again Algorithm 1 produce a collection of entropy *values* for each element of τ. Plotting τ vs. entropy produces an entropy plot (see Section 3.2.3 and **Figures 3**, **5**, and **6**).

τ_{max}, meaning that we take values of the EEG channel jumping in steps of 2,3,4… as just mentioned above, we will obtain a complexity plot in terms of τ the downsampling rate (see **Figure 4**).

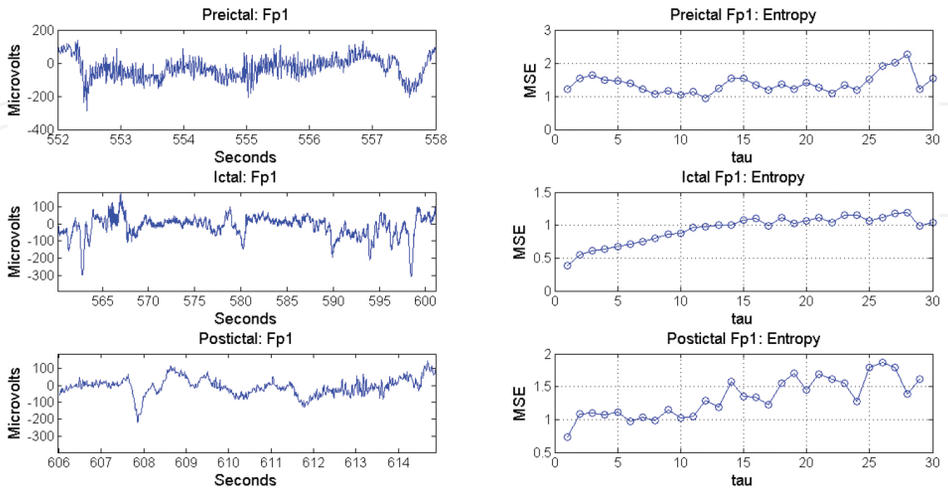


Figure 5. EEG stages and corresponding MSE plots for patient B. Note the entropy values above/below 1 (high/low complexity).

If we partition X in small subvectors and apply to them Algorithm 1, we obtain an entropy value referred to as *Multiscale Entropy* [1, 18, 39]. In this way, the latter algorithm permits to compute (and eventually) plot MSE curves for a time factor scale vector τ for a given period of time. This idea has been applied to a seizure in **Figure 5**, where each of its phases can be observed with their corresponding entropy (MSE) graphs.

3.2.4. Why high complexity implies MSE ≥ 1?

Consider a periodic (or quasi periodic) signal $y(t) = y(t + p)$, where p is the period. In this case, the number of elements which satisfy the distance threshold r is almost the same for vectors of length m and $m + 1$. This means that in Step 8 in Algorithm 1, the numerator and denominator of the logarithm of the ratio are almost equal to each other, and hence, we will take the logarithm of a quantity approximately equal to 1. Hence, its logarithm will be almost 0, a low value of complexity or entropy. In contrast, for an aperiodic signal, the result is the other way around and we will obtain high values of complexity(see [1] for details).

The ideas exposed above can be applied to a preictal-ictal-postictal event as shown in **Figure 5**. There, it is possible to compare the three stages of a seizure with respect to their complexity MSE curves. Such graphs were obtained by applying Algorithms 1 and 2 to patient B. Observe how during the preictal phase the complexity curve remains above MSE = 1 with some peaks; nevertheless, when the ictal stage comes, this complexity curvecomes down (below 1), and after some period, it improves finally by reaching values a little bit higher than 1. At the postictal phase, the complexity recovers going above 1 with some peaks which indicate no seizure activity.

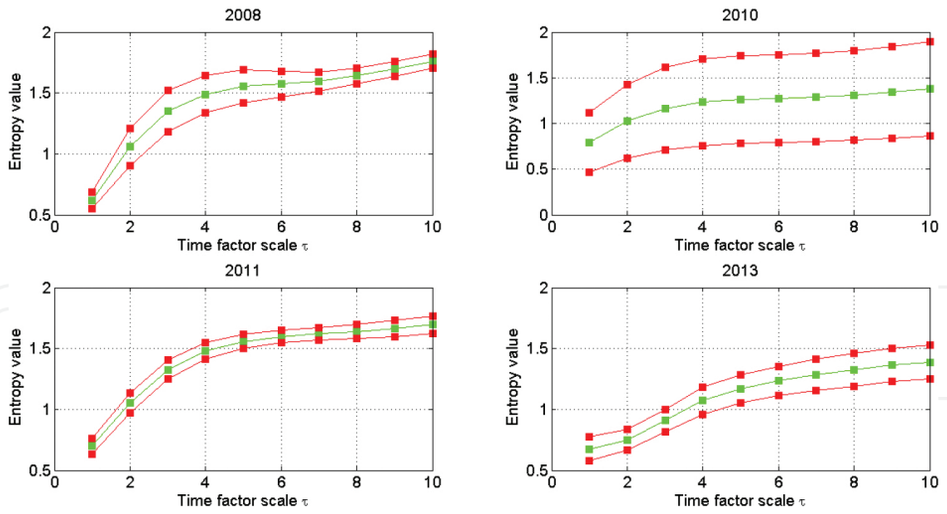


Figure 6. MSE plots averaging all channels per year for patient A. 2010 was the worst period. Observe the standard deviation curves especially wide with respect to the slightlybigger than one-average entropy plot (in the middle of the three curves). This indicates the presence of seizures as a preponderant behaviour in all channels in 2010 during a given period of EEG time (see also **Figure 4**).

This idea can be applied to all channels of a given EEG in order to obtain the average MSE plot for the year the EEG was recorded in. In **Figure 6**, the curves related to the average MSE (plus/minus one standard deviation) are shown for each year of the database of kid A. Notice how easy is to identify the worst year for this child (2010). This process was also applied to all years of the database to obtain an MSE average curve (plus/minus one standard deviation) for each *zone of the brain (channel)* allowing so to identify now the most affected zone (F3 in this patient). This process was applied to all our subjects' databases.

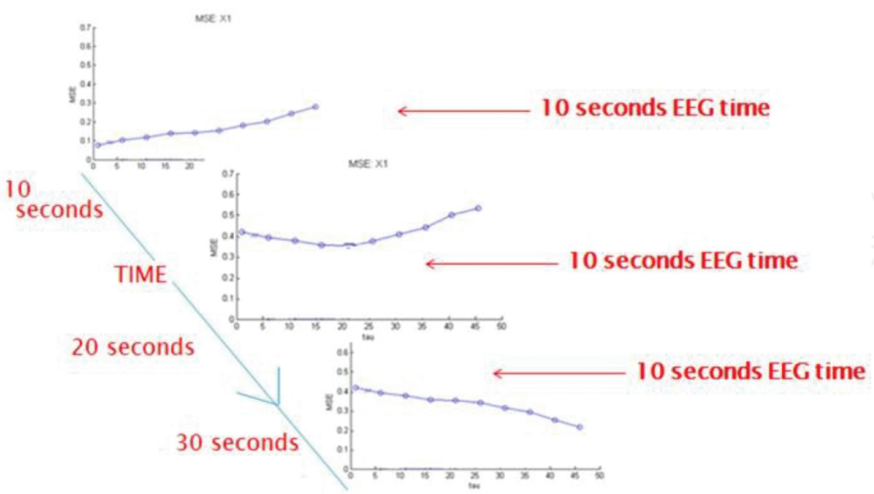


Figure 7. A single entropy plot is produced for a given period of EEG time. But partition this total EEG time in a collection of smaller periods would permit us to associate them a set of corresponding entropy plots (MSE) plots as shown here. Moreover, placing side-to-side dozens, hundreds or thousands of slices like these will form an entropy surface (see **Figure 8**).

It has been seen that we have obtained a single curve for a given period of EEG time. However, we can partition this EEG time in smaller periods in order to produce a single entropy plot for *each period*. So, we would obtain a collection of entropy plots as indicated in **Figure 7**.

Moreover, it is possible to put all these MSE curves together, side to side in order to construct an entropy *surface* (see **Figure 7**). This fact will define what we referred to as *Bivariate MSE*. These surfaces will allow us to make comparisons among several patients at the same time as it has been done in **Figure 9**. The surface can be formed with the following simplified version of an algorithm taken from [1]:

Algorithm 2. BMSE = MSE (t, τ)

1. Fix the EEG time to compute a set of MSE surfaces from.
2. Choose a number of MSE curves which will form BMSE (the complexity surface).
3. Divide the time given in Step 1 over the number of surfaces fixed in Step 2.
4. With Algorithm 1, compute a single MSE curve for each period of time defined in Step 3.
5. Plot all together the latter MSE curves. They will form a surface referred to as BMSE (bivariate MSE).

3.3. Complexity measures for MSE curves and BMSE surfaces

As mentioned above in Ref. [1], the complexity of signals was evaluated qualitatively, that is, those curves lying mainly above MSE = 1 or BMSE = 1 were classified as complex and those below 1 as noncomplex. A metric was missing, and we offer a simple one here. Such metric is referred to as *complexity index*, $\overline{MSE(\tau)}$, and is nothing but the mean of all the MSE values for each time factor scale τ in an MSE curve (see Algorithm 1), that is

$$\overline{MSE(\tau)} = \frac{1}{n}\sum_{i=1}^{n} MSE(\tau_i) \tag{1}$$

Moreover, the idea of a MSE curve (a bidimensional or 2D complexity plot) can be extended to a 3D one, a *complexity surface*. For this, we define $\overline{BMSE(t,\tau)}$ and compute a set of n_s $\overline{MSE(t,\tau)}$ curves (slices) which compound such surface (see Algorithm 2).

$$\overline{BMSE(t,\tau)} = \frac{1}{n_s}\sum_{i=1}^{n_s} \overline{MSE(\tau_i)} \tag{2}$$

A way to quantify the variation of MSE and BMSE is done via the standard deviation. Considering all the EEG database information about each patient, the algorithm, which permits to determine which kid was the most affected and on which zone of their brain, is (Algorithm 3) as follows:

Algorithm 3. $MSEZone_{Zone}$, $\sigma Zone_{Zone}$, $MSE_{Y\,ear}$, $\sigma_{Y\,ear}$

1. Define p, the number of patients, n_r the number of EEG for each patient and n_c the number of channels in each EEG record.
2. For all p, n_r and n_c, compute the average MSE, that is $\overline{MSE(t,i,j,k)}$
3. The most affected zone per patient will be determined by the *smallest MSE and its corresponding biggest standard deviation*.

In order to find *the year where the kids were most affected by their seizures*, we only need to change line 1 by n_y, where n_y is the year associated with each EEG. Hence, the new Step 3 follows. We remark that the EEG duration is implicit above. The number of samples per channel defines such time. As explained in Ref. [1] in order to extend the EEG time to much longer periods, we can use the BMSE and their surfaces. Fifteen minutes, half an hour or longer EEG durations can be compressed in BMSE surfaces. Once we have identified the worst zone/year of a patient, we plot its corresponding BMSE surface and obtain its BMSE index $\overline{BMSE(t,\tau)}$.

4. Results and discussion: which kid was healthier, when and on which region of the brain?

As an example, a period of 7 min was chosen as a duration of the EEG time to compute MSE and BMSE to know quantitatively which kid was healthiest and on which part of the brain. Notice that 7 min imply a lot of traditional EEG pages. Of course, this period can be much more longer. For all subjects, a set of entropy plots was generated. They are of two kinds: bidimensional (2D) MSE and three-dimensional (3D) MSE, that is BMSE [1]. MSE plots allowed us to determine the worst year/most affected area represented by a collection of EEG records. BMSE permits to create a 3D surface of the most affected channel in the worst year of the child.

4.1. Information from bidimensional MSE

4.1.1. Worst year/zone of brain for patient A

In [1] and [2], it was reported that 2010 was the worst year for this kid with F3 as the more discharging zone. This conclusion was obtained by scrutinizing the MSE mean and standard deviation curves (**Figure 6**). The MSE mean lies a little bit above 1, and the standard deviation curves are wider than in the other years. This means less complexity with higher variation in MSE as a result of more seizures with respect to the other years (**Figure 6**). The complexity indices were calculated for the four years to support the latter observations. In addition, the curves $\bar{\sigma}_+$ and $\bar{\sigma}_-$ were plotted for each EEGyear in **Figure 6**. There, the mean curve $\overline{BMSE(\tau)}$ lies between $\Delta = 2\bar{\sigma}(MSE(\tau)))$. So, the set of measures were as follows:

- $\overline{MSE}_{2008} = 1.8539, \bar{\sigma}_{2008} = 0.1481$

- $\overline{MSE}_{2010} = 1.3598, \bar{\sigma}_{2010} = 0.0185$(worst year)
- $\overline{MSE}_{2011} = 1.8329,\ \bar{\sigma}_{2011} = 0.2844$
- $\overline{MSE}_{2013} = 1.4802,\ \bar{\sigma}_{2013} = 0.4236$

The worst year combines the lowest value of MSE with the biggest variation $\bar{\sigma}$. More illustrations about the worst channel, years, zones of patient A can be found in [1, 2].

4.1.2. Worst year/zone of brain for patient B

Proceeding analogously as before, it was determined that 2007 was the worst year because the average MSE plot lies below 1 with wide standard deviation curves although 2014 showed a more complex mean curve with wider variation in the signals. This can be interpreted as having a relative good intellectual development, but accompanied of a continuous discharge state. See below the numerical values of the entropy index. It is remarkable how entropy makes comparable EEG studies per year/channel among several patients.

- $\overline{MSE}_{2007} = 0.7998, \bar{\sigma}_{2007} = 0.4993$ (worst year)
- $\overline{MSE}_{2010} = 1.1821, \bar{\sigma}_{2010} = 0.5658$
- $\overline{MSE}_{2012} = 0.8401, \bar{\sigma}_{2012} = 0.6392$
- $\overline{MSE}_{20147} = 1.2393, \bar{\sigma}_{2014} = 1.0104$

4.1.3. Worst year/zone of brain for patient C

Analogously as proceeded above, it was found that 2006 was the worst year and region T5 the one which suffers more discharges in this case. This kid is noteworthy as a result of his high average complexity. He was diagnosed with DS and recall that (in general) DS is less severe than LGS.

- $\overline{MSE}_{2005} = 1.4582, \bar{\sigma}_{2005} = 1.1140$
- $\overline{MSE}_{2008} = 1.1068, \bar{\sigma}_{2008} = 0.3415$ (worst year)
- $\overline{MSE}_{2012} = 1.3440, \bar{\sigma}_{2012} = 0.1153$
- $\overline{MSE}_{2014} = 1.7761, \bar{\sigma}_{2014} = 0.1447$

4.1.4. Worst year/zone of brain for patient D

Working as above, it was concluded that 2008 was the worst year with Fz the most affected area for this kid.

- $\overline{MSE}_{2005} = 1.1701, \bar{\sigma}_{2005} = 0.3131$

- $\overline{MSE}_{2009} = 1.0107, \bar{\sigma}_{2009} = 0.4101$ (worst year)
- $\overline{MSE}_{2014} = 1.3011, \bar{\sigma}_{2014} = 0.3805$

From the MSE indices, we conclude that the most affected patient among all was child B with the smallest $\overline{MSE(\tau)}$ and biggest $\sigma\left(\left(\overline{MSE(\tau)}\right)\right)$. Next, the MSE data will be used to generate the BMSE surfaces which will verify the latter conclusions for much longer EEG durations. See image 9.

4.2. Information from three-dimensional MSE: BMSE

A BMSE surface is illustrated in **Figure 8**, where 2.5 h (9000 s) have been compressed in a single image. The channel corresponds to Fp1, subject A, in 2013. Observe how the surface seems to be mounted on a constant plane equal to one. This means the main activity (red/orange tones) in child A tends to be normal. Notice also that there aretwo sinks (coloured in blue) at t = 5500 s and at t = 6700 s where episodes of seizures were present. Here, $\overline{BMSE} \approx 1.2$.

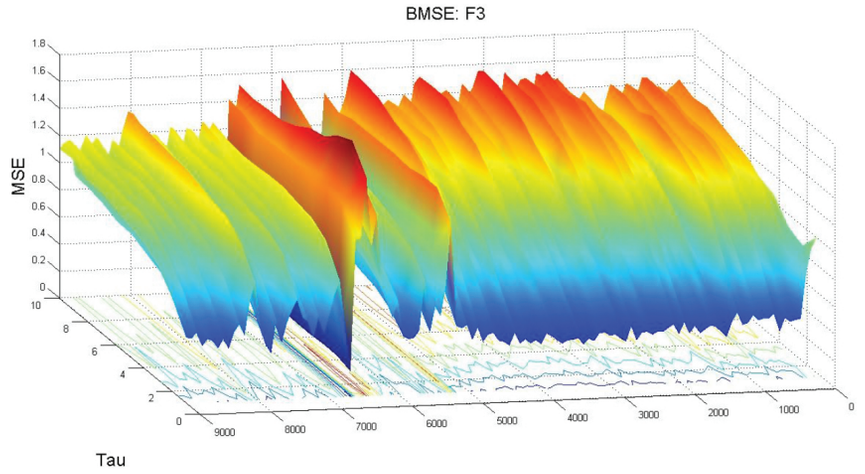


Figure 8. About 2.5Â h have been compressed in a single image for subject A, zone F3, in 2013. Blue sinks are seizures, and orange regions are high complexity regions. Note seizure/recovery times at t = 6000Â s and 7000Â s.

However, notice now that in **Figure 9**,we can compare the four patients' worst situation very easily instead of trying to compare among bunches of EEG. Moreover, the medication can be correlated with the MSE plots and BMSE surfaces as a useful support for the physician. Obviously, with all this, we do not try to replace the physician opinion, but to help it. In this sense, let us examine **Figure 9** where the BMSE surfaces have been plotted for the four subjects for the worst year and the most affected channel. Patient A exhibits a BMSE surface which lies mainly above 1 but with blue zones (low complexity) and a lot of ripples which are also coloured in orange/red meaning high complexity activity. This means that this patient suffers a constant discharging state but with a relative good consciousness and responsive state (note, however, the gash which appears at t≈ 125 s). Now, the BMSE of patient B tends to lies mainly below 1 (blue regions) with more pronounced peaks than patient A. This means that this subject

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suffer more acute seizures than patient A, and his consciousness is less active than patient's A. Subject's C BMSE surface lies mainly above 1 but observe the low and high complexity ripples during all the EEG record. Kids A and C are similar about consciousness state according to these graphs and to their affection. Now, let us examine child's D plot. This structure does not exhibit that many peaks as in cases A, B and C but rather tends to be flatter with low complexity. This means that the brain activity has slowed down (with respect to the other subjects) which could be the result of a relaxing mind state. Kid's E (normal one) graph lies mainly on 1 with a lot of high complexity ripples. Observe (and compare) child E with child A (which is closest to normality) and kids B, C and D where the lower part of the surfaces is quite close to small values of complexity.

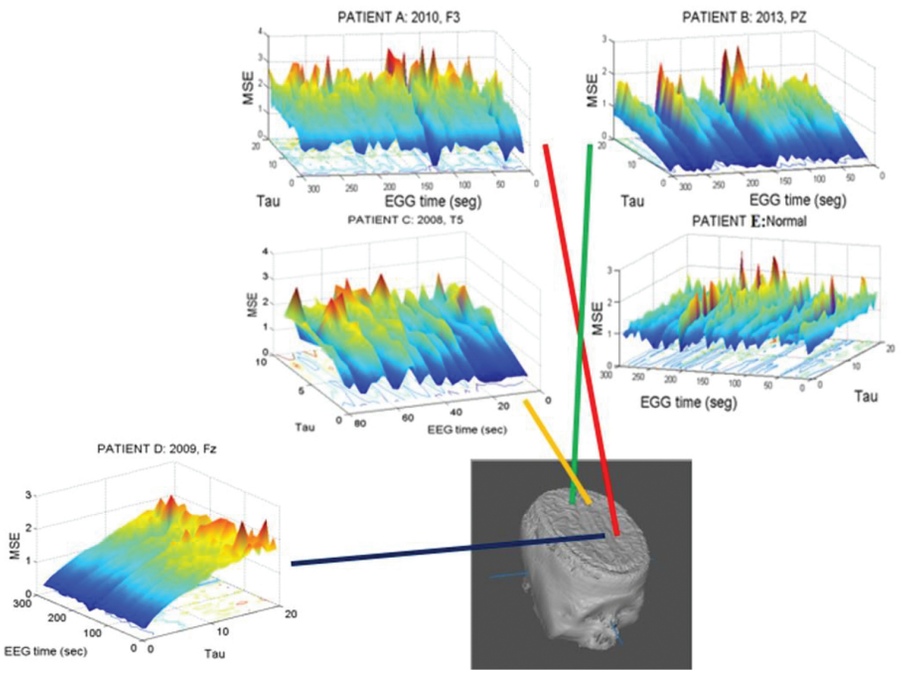

Figure 9. BMSE surfaces for the five subjects considering their worst year and zone of the brain. Note that it is easier to examine these surfaces than scrutinizing bunches of EEG in order to determine which subject was healthier and why. We remark that now all subjects are comparable to each other. Their corresponding BMSE indices are given in the text.

We remark that now all subjects are comparable to each other. Moreover, these facts are supported by the computation of $\overline{BMSE(t,\tau)}$ as follows:

- $\overline{BMSE(t,\tau)}_{A,F3,2010} = 1.6469, \bar{\sigma}_{A,F3,2010} = 0.3083$ (healthies patient)
- $\overline{BMSE(t,\tau)}_{B,PZ,2007} = 1.0469, \bar{\sigma}_{B,PZ,2013} = 0.5246$ (most affected kid)
- $\overline{BMSE(t,\tau)}_{C,T5,2008} = 1.2666, \bar{\sigma}_{C,T5,2008} = 0.0708$
- $\overline{BMSE(t,\tau)}_{D,Fz,2009} = 1.1140, \bar{\sigma}_{D,Fz,2009} = 0.0860$
- $\overline{BMSE(t,\tau)}_{E,C3,2015} = 1.7741, \bar{\sigma}_{D,C3,2015} = 0.3791$ (normal subject)

4.3. Conclusions: correlation with individual medication

Consider the medications of all the children in this study. Compare this resumed information with their corresponding complexity curves/indices. It is now visually easy to observe the effects of such drugs during treatments comparing all subjects at the same time. Our measures will allow neurologists to afford (objectively) the parents' questions established in the Abstract. We would like to recall that handling massive information to evaluate progress in a single patient is challenging, but objective comparisons among progress of different patients are practically impossible.

Declaration of conflicting interest

The authors declared no conflicts of interest with respect to the research, authorship and/or publication of this article.

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