Variability, Regularity, and Complexity of Time Series Generated by Schizophrenic Patients and Control Subjects

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***Abstract*—We analyzed time series generated by 20 schizophrenic patients and 20 sex- and age-matched control subjects using three nonlinear methods of time series analysis as test statistics: central tendency measure (CTM) from the scatter plots of first differences of data, approximate entropy (ApEn), and Lempel-Ziv (LZ) complexity. We divided our data into a training set (10 patients and 10 control subjects) and a test set (10 patients and 10 control subjects). The training set was used for algorithm development and optimum threshold selection. Each method was assessed prospectively using the test dataset. We obtained 80% sensitivity and 90% specificity with LZ complexity, 90% sensitivity, and 60% specificity with ApEn, and 70% sensitivity and 70% specificity with CTM. Our results indicate that there exist differences in the ability to generate random time series between schizophrenic subjects and controls, as estimated by the CTM, ApEn, and LZ. This finding agrees with most previous results showing that schizophrenic patients are characterized by less complex neurobehavioral and neuropsychologic measurements.**

***Index Terms*—Approximate entropy, central tendency measure, Lempel-Ziv complexity, random rhythms, schizophrenia.**

I. Introduction

SCHIZOPHRENIA is a severe mental illness that often shows a variety of symptoms affecting thought, language, perception, and behavior. Increasing attention to cognitive disorders in schizophrenic patients is also being observed. The most consistent finding appears to be verbal memory impairment [1]. Although clinical, neuropsychological, neurophysiological and neuroimaging approaches have contributed to a better understanding of the illness, a more precise knowledge of the underlying mechanisms is still necessary.

In the last two decades, nonlinear methods have been applied to biological functions in order to analyze psychiatric disorders including schizophrenia. For example, some authors [2]–[4] studied electroencephalogram (EEG) signals of schizophrenic patients and control subjects with nonlinear methods of time series analysis. Their results showed differences in the dynamic processes underlying the EEG signal between schizophrenic patients and control subjects. In order to assess the working hypothesis that schizophrenia might be viewed as a dynamical disease, other authors examined the long-term dynamics of 14 patients [5]. In this study, the data consisted of daily rating of psychopathology observed for 200 or more consecutive days for each subject, and results were based on two nonlinear forecasting approaches combined with the surrogate data method to enable statistical testing. The results of the classification of dynamics showed evidence that a large proportion of schizophrenic psychoses showed nonlinear time courses [5]. In an interesting and little-known test named the random number generation [6], subjects were asked to choose several times a number from one to ten. Numbers had to lack a generative rule, that is, to be as random as possible. The authors found that schizophrenic patients tended more to repetition, and therefore performed worse than normal subjects. Other authors [7] have carried out a simple choice task consisting in predicting 500 random right or left appearances of a stimulus, in order to obtain binary response in patients with schizophrenia and control subjects. Applying mutual and cross-mutual information they found that the response sequences generated by patients exhibited a higher degree of interdependency than those of control subjects. Structural brain changes [8] and rhythmic finger oscillations in schizophrenic patients [9] have also been studied using nonlinear methods. In addition, some authors [10], [11] developed computer programs to study random generation behaviors. Finally, schizophrenia may be seen as a dynamical disease due to the abnormal spatial or temporal dynamics of the overall system [12].

Focusing on a particular feature, the ability to create random rhythms, the objective of our study is to analyze the cognitive performance of patients with schizophrenia, and compare it with the cognitive performance of healthy subjects. We developed a new cognitive test with the objective of measuring the subjects' capacity of developing random rhythms: the test of random rhythm generation (ARG), which was presented in [13] and [14] and has been registered at the University of Valladolid, Spain. A random rhythm of blows, without an evident rule for its generation, appears to be an irregular process. This task hypothetically requires a certain level of mental ability. Consequently, generation of random rhythms must be understood as a "normal" performance. On the contrary, a stable rhythm, formed

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by a regular sequence of blows, has a rule for its generation that should be easy to find. The latter is associated more with a loss of mental ability and therefore must be considered as a "pathological" performance. In order to prove that individual's ability to create random sequences is associated with a high neuropsychological performance, we have assessed this ability in schizophrenic patients by means of the ARG.

Assessment of repetition of rhythms is included in other neuropsychological batteries, as the Luria battery and the Neurological Evaluation Scale [15]. Indeed, the "rhythm tapping test" of the previous Scale consists in asking the subject to reproduce exactly the series of taps heard while keeping the eyes closed. In the present study, we apply three nonlinear methods as test statistics to analyze time series generated by 20 schizophrenic patients and 20 sex- and age-matched control subjects, divided in a training set and a test set. These methods are the following:

- computation of the central tendency measure (CTM) from scatter plots of first differences of the data;
- the approximate entropy (ApEn);
- the Lempel-Ziv (LZ) complexity.

II. Subjects

Twenty patients with schizophrenia and twenty sex- and age-matched control subjects were tested. The patients, 15 (75%) men and 5 (25%) women with a mean age of 30.8 ± 7.4 years, were diagnosed according to DSM-IV criteria [16]. They were recruited from the Department of Psychiatry at the University Hospital of Valladolid, Spain. Inclusion criteria were: 1) age between 16 and 55 years; 2) history of prior hospital admission(s); 3) no psychotic episodes during the last year; 4) no mental retardation or other cerebral disorders. All patients of the schizophrenic group (SG) were living at home and on ambulatory treatment, 15 were receiving neuroleptics, mainly middle doses of haloperidol or risperidone. Neuroleptic treatment during the last month was converted into equivalents of chlorpromazine; the mean daily dose was 192.5 ± 205.7 mg/day. Twelve patients suffered from paranoid schizophrenia (60%), six were residual schizophrenics (30%), and two patients had an undifferentiated type (10%).

In addition, a control group (CG) of 20 sex- and age-matched subjects lacking past or present psychiatric history was tested. They were all healthy volunteers with good disposition to take part in the study. There were 15 men (75%) and 5 women (25%) with a mean age of 30.8 ± 7.4 years. All the patients and control subjects had right-hand dominance. Informed consent was obtained from all subjects.

In the SG, psychopathological assessment at the time of performing the ARG was carried out by means of the positive and negative syndrome scale (PANSS) [17] and the Frankfurt Complaint Questionnaire [Frankfurter Beschwerde-fragebogen (FBF)] in its third version [18]. The same experienced psychiatrist, who was blind to the results and analysis performed with the ARG test carried out all the clinical assessments. While the PANSS objectively collects positive and negative symptoms, the FBF aims at subjectively perceived deficiency symptoms, also called "basic symptoms." A certain degree of patients' cooperation is necessary to fulfill the FBF and perform the ARG, what is usually achieved within a few days of hospitalization. Psychopathologic symptoms at this phase were assessed by means of the PANSS. Patients were receiving neuroleptic treatment, which was converted into equivalents of chlorpromazine. In summary, the average type of patient is a man of 30.8 years old, suffering from a paranoid schizophrenia during the last 11.3 years. His psychopathological picture includes positive, negative and basic symptoms (see scores in PANSS-P, PANSS-N, and FBF). He was receiving 192.5 mg/day of chlorpromazine.

We divided our data into a training set and a test set. The training set was used to develop the algorithm (i.e., to choose the radius in the CTM method, m and r in ApEn) and to select the optimum thresholds for each method. The final algorithm was then applied without further alteration to the data from the test set. In the training set, we included 10 patients (3 women and 7 men) and 10 sex- and age-matched control subjects with a mean age of 31.5 ± 9.9 years, while in the test set there were 10 patients (2 women and 8 men) and 10 sex- and age-matched control subjects with a mean age of 30.0 ± 4.9 years. In both the training and the test set, six patients suffered from paranoid schizophrenia (60%), three were residual schizophrenics (30%), and one had an undifferentiated type (10%). Results obtained in the psychopathological scales and sociodemographic data divided in training set and test set are summarized in Table I.

III. Methods

A. Test of Random Rhythm Generation (ARG)

This study is aimed at analyzing time series generated by schizophrenic patients and healthy subjects. To generate these time series, the subject is asked to press the space bar of the computer as irregularly as possible [13], [14]. If possible, the test is performed in an ordinary examination room, the computer being placed at a side of the table. A natural light projected on the computer was preferred. Interruptions during the exploration or pressure of time must be avoided. The doctor in charge holds a short interview with the patient in order to check his/her present mental state as well as the level of motivation and cooperation to perform the test. If the interviewer judges them satisfactory, the patients must sit in front of the computer and be able to perfectly see the screen. The interviewer first asks which hand he/she normally uses and checks that the patient is able to press comfortably the space bar with his/her dominant hand. Then the following instruction is given: "This is a simple test with a computer. You must press this key – and shows the space bar – with a finger at a rhythm as irregular as possible during some time, until the screen indicates the end of the task. First, you are going to see an example." The computer shows an example, consisting of a square of 4×4 cm, which appears and disappears in the screen at an irregular rhythm. The presence of the square in the screen is accompanied by a beep. The interviewer repeats that this was only an example and that he/she must try to do it as irregular as possible. The subject performs now a sequence consisting of a sequence of blows. Once the patient has completed 128 blows, the program stops and asks about a second sequence. The interviewer inquires the patient

TABLE I
SOCIODEMOGRAPHIC DATA AND RESULTS OBTAINED IN THE PSYCHOPATHOLOGICAL SCALES WITH THE SCHIZOPHRENIC GROUP DIVIDED IN A TRAINING SET AND A TEST SET

TRAINING SET										
No.	Sex	Age	Age at onset	Duration in years	Diagnosis DSM-IV	PANSS-P	PANSS-N	PANSS-C	PANSS-G	FBF
1	F	33	16	17	295.60	10	18	-8	35	23
2	F	36	30	6	295.30	26	24	2	39	91
3	M	31	20	11	295.30	19	12	7	27	65
4	F	54	29	25	295.60	23	23	0	42	58
5	M	32	17	15	295.30	13	28	-15	30	17
6	M	16	13	3	295.30	23	27	-4	52	25
7	M	35	16	19	295.30	31	11	20	43	49
8	M	28	22	6	295.60	10	28	18	41	17
9	M	27	19	8	295.90	18	16	2	41	83
10	M	23	22	1	295.30	15	22	-7	37	56
Mean value		31.5 ± 9.9	20.4 ± 5.6	11.1 ± 7.7		18.8 ± 7.0	20.9 ± 6.3	1.5 ± 11.1	38.7 ± 7.0	48.4 ± 27.1
TEST SET										
No.	Sex	Age	Age at onset	Duration in years	Diagnosis DSM-IV	PANSS-P	PANSS-N	PANSS-C	PANSS-G	FBF
11	M	28	15	13	295.60	16	16	0	32	28
12	M	39	19	20	295.60	10	18	-8	35	84
13	M	23	22	1	295.30	13	16	-3	33	90
14	M	26	20	6	295.30	19	19	0	34	65
15	M	34	21	13	295.60	28	25	3	46	59
16	F	32	25	7	295.30	9	16	-7	31	31
17	F	31	18	13	295.90	16	27	-11	33	n.v.
18	M	34	16	18	295.30	9	20	-11	36	50
19	M	27	15	12	295.30	10	17	-7	33	56
20	M	26	21	5	295.30	17	20	-3	37	53
Mean value		30 ± 4.9	19.2 ± 3.3	10.8 ± 5.9		14.7 ± 5.9	19.4 ± 3.8	-4.7 ± 4.8	35 ± 4.3	57.3 ± 20.8

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; PANSS = Positive And Negative Syndrome Scale; PANSS-P = PANSS Positive scale; PANSS-N = PANSS Negative scale; PANSS-C = PANSS Composed scale; PANSS-G = PANSS General scale; FBF = Frankfurter Beschwerde-fragebogen (Frankfurt Complaint Questionnaire); n.v. = not valuable

how difficult he/she has found the task and checks if the subject has understood the task to perform. Usually, only one trial is necessary; then the last sequence is proposed to be analyzed. The sequence points are the time intervals between blows in milliseconds. Thus, the nth data point represents the time interval between the nth and the $(n+1)$th blow.

One of the key points in this and similar tests is the optimum length of time series. We dealt with it in a previous paper [13]. We needed long series to achieve a good estimation with several methods, but if the series were too long, results could be wrong because generating long random series is a very hard and tiring task. We analyzed time series of several lengths (1024, 512, 256, 128, 64) and found that series longer than 128 points were more regular at the end than at the beginning. This suggests that results might be distorted due to subjects' tiredness, affecting both patients and controls. Therefore, we decided to use series of 128 points.

In the next subsections, we explain the applied methods to analyze the time series generated by the patients and controls.

B. Central Tendency Measure (CTM)

We can produce graphs using scatter plots of differences of the data

$$[x(n+2)-x(n+1)] \text{ vs. } [x(n+1)-x(n)]. \quad (1)$$

Scatter plots of first differences centered around the origin are useful in modeling biological systems such as hemodynamics and heart rate variability, and represent the degree of theoretical chaos [19]. With this approach, rather than defining a time series as chaotic or not chaotic, the degree of variability or chaos is evaluated.

We use the CTM with scatter plots of first differences of the data. The CTM is computed by selecting a circular region of radius ρ around the origin, counting the number of points that fall within the radius, and dividing by the total number of points. Given N data points from a time series, $N-2$ would be the total number of points in the scatter plot. Then, the CTM can be computed as [20]

$$\mathrm{CTM} = \frac{\sum_{i=1}^{N-2} \delta(d_i)}{N-2} \quad (2)$$

where

$$\delta(d_i) = \begin{cases} 1, & \text{if } \left[(x(i+2)-x(i+1))^2+(x(i+1)-x(i))^2\right]^{1/2} < \rho \\ 0, & \text{otherwise} \end{cases}. \quad (3)$$

The radius is chosen depending upon the character of the data. We have developed a new method to select the radius. First, we compute the CTM with several radii of the time series generated

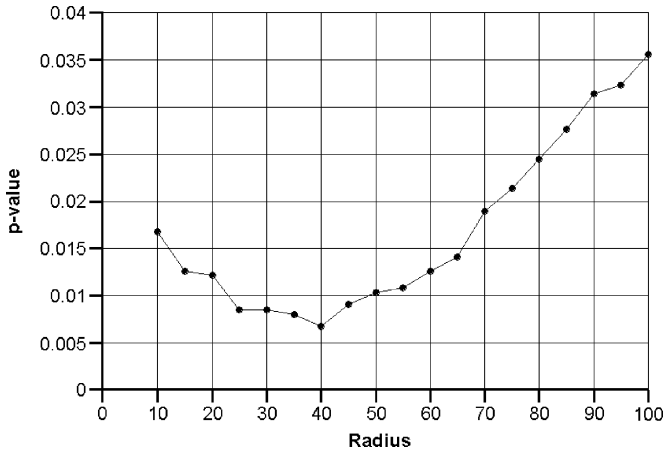

Fig. 1. Student's t-test p-values obtained with the different CTM computations from the time series generated by 10 schizophrenic patients and 10 sex- and age-matched control subjects in the training set using several radii ρ.

by 10 schizophrenic patients and 10 sex- and age-matched control subjects from the training set. Then, we apply the Student's t-test to calculate which of the radii in the training set achieves the most significant differences between time series generated by schizophrenic and control subjects. The result of this process is shown in Fig. 1. We noticed that we could select the radius from a large set of radii in which the differences between the CTM values of the time series generated by both groups are significant ($p < 0.01$). The best radius was estimated at $\rho = 40$ ($p = 0.006$).

C. Approximate Entropy (ApEn)

Approximate entropy (ApEn) is a family of statistics introduced as a quantification of regularity in the data without any *a priori* knowledge about the system generating them. Pincus first proposed it in 1991 [21], initially motivated by applications to short and noisy data sets. ApEn has been mainly used in the analysis of heart rate variability [22], endocrine hormone release pulsatility [23], in the characterization of postoperative ventricular dysfunction [24] and the impact of pulsatility on the ensemble orderliness of neurohormone secretion [25]. It has also been applied to extract features from electroencephalogram (EEG) and respiratory recordings of a patient during Cheyne-Stokes respiration [26], to predict epileptic seizures from EEG time series [27] and to quantify the depth of anesthesia [28].

ApEn is scale invariant and model independent, evaluates both dominant and subordinant patterns in data, and discriminates series for which clear feature recognition is difficult. Notably it detects changes in underlying episodic behavior not reflected in peak occurrences or amplitudes [29]. It is nearly unaffected by low level noise, it is also robust to meaningful information with a reasonable number of data points and is finite for both stochastic and deterministic processes [28]. ApEn assigns a nonnegative number to a time series, with larger values corresponding to more complexity or irregularity in the data. It has two user-specified parameters: a run length m and a tolerance window r. Briefly, ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on subsequent incremental comparisons. It is important to consider $ApEn(m, r)$ – or $\mathrm{ApEn}(m, r, N)$, where N is the number of points of the time series – as a *family* of characterizing measures: comparisons between time series can only be made with the same values of m and r [30].

Formally, given N data points from a time series $\{x(n)\} = x(1), x(2), \ldots, x(N)$, to compute ApEn, one should follow these steps [30].

1) Form m-vectors $X(1), \ldots, X(N-m+1)$ defined by: $X(i) = [x(i), x(i+1), \ldots, x(i+m-1)], i = 1, \ldots, N-m+1$. These vectors represent m consecutive x values, commencing with the ith point.
2) Define the distance between $X(i)$ and $X(j)$, $d[X(i), X(j)]$, as the maximum absolute difference between their respective scalar components, i.e., the maximum norm

$$d[X(i), X(j)] = \max_{k=1,2,\ldots,m} |x(i+k-1) - x(j+k-1)|. \quad (4)$$

3) For a given $X(i)$, count the number of j ($j = 1, \ldots, N-m+1$, $j \neq i$) so that $d[X(i), X(j)] \leq r$, denoted as $N^m(i)$. Then, for $i = 1, \ldots, N-m+1$

$$C_r^m(i) = \frac{N^m(i)}{(N-m+1)}. \quad (5)$$

$C_r^m(i)$ measures, within a tolerance r, the frequency of patterns similar to a given one of window length m.
4) Compute the natural logarithm of each $C_r^m(i)$, and average it over i

$$\phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_r^m(i). \quad (6)$$

5) Increase the dimension to $m+1$. Repeat steps 1) to 4) and find $C_r^{m+1}(i)$ and $\phi^{m+1}(r)$.
6) We define ApEn by

$$ApEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r). \quad (7)$$

As suggested by Pincus [30], for the study discussed in this paper ApEn is estimated using the widely established parameter values of $m = 1$, $m = 2$, and $r = 0.1$, 0.15, 0.2, and 0.25 times the standard deviation (SD) of the original data sequence $\{x(n)\}$. Normalizing r in this manner gives ApEn a translation and scale invariance, in that it remains unchanged under uniform process magnification, reduction, or constant shift to higher or lower values [30]. Several studies [21], [29], [31] have demonstrated that these input parameters produce good statistical reproducibility for ApEn with time series of length $N \geq 60$, as considered herein.

D. Lempel-Ziv (LZ) Complexity

The LZ complexity measure for sequences of finite length was suggested by Lempel and Ziv [32]. It is a nonparametric, simple-to-calculate measure of complexity in a one-dimensional signal that does not require long data segments to compute [33]. LZ complexity is related to the number of distinct substrings and the rate of their recurrence along the given

sequence [27]. It has been applied to study the brain function [34], brain information transmission [35], ECG dynamics [36], and epileptic seizures [27]. Others authors have used LZ complexity to detect ventricular tachycardia and fibrillation [33], to predict movement in anesthesia in animals [37], to estimate the depth of anesthesia [28], [38] and to quantify oscillations in uterine electromyography [39].

LZ complexity analysis is based on a coarse-graining of the measurements, so before calculating the complexity measure $c(n)$, the signal must be transformed into a finite symbol sequence. In this study, the simplest way is selected to convert time series values ($x(i)$, $i = 1,2,\ldots,N$) into a sequence of characters (zero and one). The mean value is estimated as a threshold T_d. By comparison with the threshold, the signal data are converted into a 0–1 sequence $P = s(1), s(2), \ldots, s(n)$: if $x(i) < T_d$, $s(i) = 0$, otherwise $s(i) = 1$ [38]. Previous studies [27], [34]–[37] show that 0–1 conversion is enough to study the dynamic complexity of a system. The sequence P is scanned from left to right and the complexity counter $c(n)$ is increased by one unit every time a new subsequence of consecutive characters is encountered. The complexity measure can be estimated using the following algorithm [28], [33], [38].

1) Let S and Q denote two subsequences of P and SQ be the concatenation of S and Q, while sequence $SQ\pi$ is derived from SQ after its last character is deleted (π means the operation to delete the last character in the sequence). Let $v(SQ\pi)$ denote the vocabulary of all different subsequences of $SQ\pi$. At the beginning, $c(n) = 1$, $S = s(1)$, $Q = s(2)$, therefore, $SQ\pi = s(1)$.
2) In general, $S = s(1), s(2), \ldots, s(r)$, $Q = s(r+1)$, then $SQ\pi = s(1), s(2), \ldots, s(r)$; if Q belongs to $v(SQ\pi)$, then Q is a subsequence of $SQ\pi$, not a new sequence.
3) Renew Q to be $s(r+1), s(r+2)$ and judge if Q belongs to $v(SQ\pi)$ or not.
4) Repeat the previous steps until Q does not belong to $v(SQ\pi)$. Now $Q = s(r+1), s(r+2), \ldots, s(r+i)$ is not a subsequence of $SQ\pi = s(1), s(2), \ldots, s(r+i-1)$, so increase $c(n)$ by one.
5) Thereafter, S is renewed to be $S = s(1), s(2), \ldots, s(r+i)$, and $Q = s(r+i+1)$.

These procedures have to be repeated until Q is the last character. At this time the number of different subsequences in P – the measure of complexity – is $c(n)$.

In order to obtain a complexity measure which is independent of the sequence length, $c(n)$ should be normalized. If the length of the sequence is n and the number of different symbols in the symbol set is α, it has been proved [32] that the upper bound of $c(n)$ is given by

$$c(n) < \frac{n}{(1-\varepsilon_n)\log_\alpha(n)} \tag{8}$$

where ε_n is a small quantity and $\varepsilon_n \to 0$ ($n \to \infty$). In general, $n/\log_\alpha(n)$ is the upper bound of $c(n)$, where the base of the logarithm is α, i.e.,

$$\lim_{n\to\infty} c(n) = b(n) \equiv \frac{n}{\log_\alpha(n)}. \tag{9}$$

For a 0–1 sequence, $\alpha = 2$, therefore

$$b(n) \equiv \frac{n}{\log_2(n)} \tag{10}$$

and $c(n)$ can be normalized via $b(n)$

$$C(n) = \frac{c(n)}{b(n)}. \tag{11}$$

$C(n)$ reflects the arising rate of new patterns along with the sequence.

IV. Results

We present the results obtained with each of the methods on the training set and the test set. The training set was used for algorithm development (i.e., to choose the radius in the CTM method, m and r in ApEn) and optimum threshold selection. Each of the methods was validated prospectively using the test set.

A. Training Set

1) Central Tendency Measure (CTM): Scatter plots of first differences of the data for all the time series generated by schizophrenic patients and control subjects have been calculated. Fig. 2 shows the scatter plot corresponding to the time series generated by a schizophrenic patient, whereas the plot corresponding to the time series generated by a control subject is illustrated in Fig. 3. Points in the time series generated by patients have a higher tendency to be located in the center, as we can notice in Fig. 2. This is reflected by higher CTM values.

In the computations of CTM, the selected radius has a high dependency. A radius equal to 40 ($\rho = 40$) has been chosen to achieve the most significant differences in the t-test ($p = 0.006$) with the time series generated by 10 schizophrenic patients and 10 sex- and age-matched control subjects from the training set. The CTM values in the CG time series are 0.22 ± 0.18. They are lower than the values of SG time series (mean value: 0.62 ± 0.37).

2) Approximate Entropy (ApEn): $\mathrm{ApEn}(m, r, N)$ has to be seen as a family of characterizing measures, where N is the number of points in our time series ($N = 128$). As suggested by Pincus [30], we used $m = 1$ and $m = 2$ and four different values of r: 0.1, 0.15, 0.2, and 0.25 times the standard deviation (SD) of the data. In Table II, we show the mean ApEn values calculated from the time series generated in the training set with different values of m and r. The best results according to the Student's t-test are obtained with $m = 1$ and $r = 0.25$ times the SD of the data. $ApEn(m = 1, r = 0.25, 128)$ measures the logarithmic frequency with which blocks of length $m = 1$ that are close together remain close together for blocks augmented by one position (i.e., $m = 2$). Larger values of ApEn imply substantial fluctuation, or irregularity, in the time series [30]. Thus, the smaller ApEn values in the time series generated by the schizophrenic patients imply stronger regularity, or persistence, than in the sequences generated by control subjects.

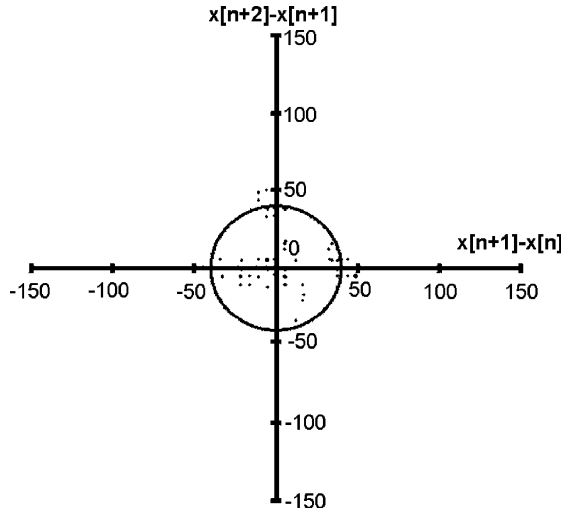

Fig. 2. Scatter plot of first differences of the time series generated by a schizophrenic patient using a circle of radius $\rho = 40$.

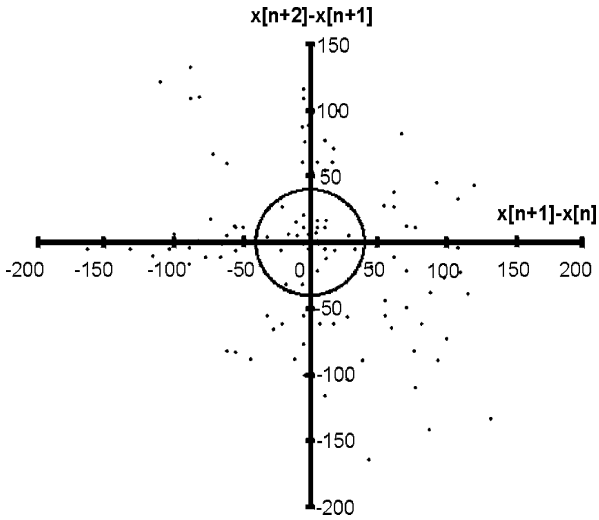

Fig. 3. Scatter plot of first differences of the time series generated by a control subject using a circle of radius $\rho = 40$.

TABLE II
AVERAGE $\mathrm{ApEn}(m, r)$ VALUES ESTIMATED FROM TIME SERIES GENERATED BY 10 SCHIZOPHRENIC GROUP (SG) AND 10 CONTROL GROUP (CG) OF THE TRAINING SET USING $m = 1$ AND $m = 2$, AND DIFFERENT VALUES OF r: 0.1, 0.15, 0.2, 0.25 OF THE SD

		ApEn(m,r)	*ApEn(m,r)*	*t-test*	
m	***r***	***CG***	***SG***	$F_{2,38}$	***p-value***
1	0.1SD	1.65 ± 0.11	1.31 ± 0.28	13.09	0.000196
1	0.15SD	1.71 ± 0.12	1.28 ± 0.34	13.94	0.001519
1	0.2SD	1.66 ± 0.12	1.21 ± 0.36	14.32	0.00136
1	0.25SD	1.58 ± 0.13	1.07 ± 0.37	16.63	0.00071
2	0.1SD	0.75 ± 0.12	0.55 ± 0.29	4.54	$p > 0.01$
2	0.15SD	0.74 ± 0.17	0.59 ± 0.17	4.56	$p > 0.01$
2	0.2SD	0.76 ± 0.18	0.75 ± 0.18	0.026	$p > 0.01$
2	0.25SD	0.89 ± 0.05	0.75 ± 0.21	4.10	$p > 0.01$

3) Lempel-Ziv (LZ) Complexity: The average value of LZ is higher in time series generated by the CG from the training set. Mean values were 1.03 ± 0.08 in the CG and 0.76 ± 0.27 in the SG. The differences between both groups are statistically significant ($p = 0.0055$, t-test). These results suggest that the complexity (in the sense of number of new subsequences or distinct patterns contained in the time series) in time series generated by schizophrenic patients is lower.

TABLE III
RESULTS ON DIFFERENT METHODS FROM TIME SERIES GENERATED BY 10 SG AND 10 CONTROL GROUP (CG) OF TEST SET USING THE OPTIMUM PARAMETERS (ρ, m, r) AND OPTIMUM THRESHOLDS OBTAINED FROM TIME SERIES IN THE TRAINING SET

	CG	*SG*	*SEN.* (%)	*SPE.* (%)	*ACC.* (%)
CTM (ρ=40)	0.39 ± 0.31	0.73 ± 0.31	70	70	70
ApEn (*m*=1, *r*=0.25*SD*)	1.47 ± 0.19	1.17 ± 0.33	90	60	75
LZ	0.99 ± 0.29	0.82 ± 0.24	80	90	85

SEN.: Sensitivity = TP/(TP+FN); *SPE.*: Specificity = TN/(TN+FP); *ACC.*: Accuracy = (TP + TN)/(TP+FN+TP+FP), where TP = true positive, FN = false negative, TN = true negative and FP = false positive.

4) Optimum Threshold: We selected the optimum threshold from the training set of the three applied methods by means of sensitivity, specificity and accuracy. We used a radius equal to 40 in the CTM, $m = 1$ and $r = 0.25$ times the SD of the time series in the ApEn estimation, and two symbols (0–1) with LZ complexity. We selected different thresholds or cutoff points (CTM, ApEn, or LZ values) and calculated the sensitivity/specificity pair for each one of them. Sensitivity – the true positive rate – is the proportion of schizophrenic patients recognized by each method, whereas specificity – the true negative rate – represents the percentage of healthy subjects recognized. Accuracy is a related measure that quantifies the number of subjects correctly classified. The optimum threshold corresponds to the cutoff point in which the highest accuracy (minimal false negative and false positive results) is obtained.

In CTM, the optimum threshold is obtained at 0.27 with a sensitivity of 90% and specificity of 60% (accuracy: 75%), while in ApEn an optimum threshold of 1.43 is selected with 90% sensitivity and 90% specificity (accuracy: 90%). Finally, we estimate the best threshold at 0.94 in LZ complexity with 80% sensitivity and 90% specificity (accuracy: 85%).

B. Test Set

Table III summarizes the results from the time series generated by 10 schizophrenic patients and 10 control subjects of the test set. We used the parameters chosen from the study of the training set time series: a radius equal to 40 in CTM, $m = 1$ and $r = 0.25$ times the SD of the time series in ApEn. Moreover, we computed sensitivity and specificity in the test set with the optimum thresholds obtained with the training set. We can notice that the highest sensitivity (90%) is obtained with ApEn, whereas specificity (90%) improved with LZ complexity. The best accuracy (85%) is obtained with LZ.

V. DISCUSSION

Our findings applying CTM show a diminished variability in the times series generated by schizophrenic patients in both the training and the test sets (reflected by the fact that points in the time series generated by them have a higher tendency to be located in the center of the scatter plots). Although patients tend

to press the space bar more frequently, the differences in the mean time between blows, the SD and the coefficient of variability of the time series between both groups were not significant ($p > 0.01$). Thus, it seems that CTM reflects differences in the time series that could not be detected with more conventional statistical methods. According to ApEn results, we can state that the rate of new pattern generation in the time series generated by SG is lower than in those corresponding to CG, a fact also suggested by their lower LZ complexity values. Thus, all results show that schizophrenic patients tend to generate more regular and rhythmic series than control subjects.

We hypothesize that creating a more random rhythm requires a higher cognitive effort than creating a more regular rhythm. Therefore, our results suggest that schizophrenic patients have a reduced ability to generate random series when compared with controls. This fact agrees with findings showing that schizophrenic patients are characterized by less complex neurobehavioral and neurophysiologic measurements than control subjects:

1) in a test of random number generation, consisting in choosing several times a number between 1 and 10 without any generative rule, schizophrenics tended more to repetition and therefore performed worse than normal subjects [6];
2) when performing a listening task they showed a high degree of semantic recurrence in hallucinated "voices" [40];
3) a decreased dimension complexity was found in the EEG of schizophrenic patients compared to controls [3], [41]; and
4) the EEGs dimensionality during sleep stages II and REM was reduced in schizophrenia [42].

However, these consistent results, which our data also confirm, differ from a finding described by Paulus *et al.* [43]–[45] when subjects were asked to predict 500 random right or left appearances of a stimulus. A basic behavioral dysregulation occurs in a single test session, consisting in both high predictable and high unpredictable response sequences.

Several objections can be raised against the time series analysis and the ARG test. The first objection that merits consideration relates to the use of nonlinear methods in our study. With CTM, rather than defining a time series as chaotic or not chaotic, the degree of variability is evaluated [19]. ApEn was constructed by Pincus [21] to provide a widely applicable, statistically valid formula that will distinguish data sets by a measure of regularity. It can potentially distinguish a wide variety of systems: low-dimensional deterministic, periodic and multiply periodic, high-dimensional chaotic, stochastic and mixed (stochastic and deterministic) systems [21]. Moreover, one important feature of LZ complexity is model-independence. Only those differences between activity patterns that make a difference to the underlying system itself are considered, no matter whether the system is dominated by deterministic chaos or a stochastic process [38]. In our study, the time series may not be simply generated by a purely deterministic or stochastic process, but rather by some combination of both. While applying LZ complexity to the sequences we are not testing for a particular model form, but attempting to distinguish among the time series generated by schizophrenic patients and control subjects on the basis of complexity in the sense of number of new subsequences or distinct patterns contained in the time series. Due to model-independence and wide applicability, rather than trying to find a certain dynamical model for the time series, we have treated CTM, ApEn, and LZ complexity as test statistics.

Secondly, due to the usual subjects' tiredness in performing the task we had to analyze short time series. It could be argued that ApEn and LZ complexity are data demanding measures. Several studies [21], [29], [31] show that the selected ApEn input parameters values m and r produce good statistical reproducibility with time series of length $N \geq 60$, as considered herein. LZ complexity is a simple measure that does not require long data segments to compute [33], although the analyzed time series might be short.

The third objection which might be considered is if the patient correctly understands the instruction "press this key with a finger at a rhythm as irregular as possible." To assure this, the computer gives an example; also, the subject has the possibility of making several trials, and the interviewer must check that the subject understands the task to perform. However, the moment of assessment should be carefully selected; the doctor in charge of the patient should check his/her present mental state.

The fourth drawback is whether the patient is motivated to perform the test or not. This question arises when applying most cognitive tests, symptom questionnaires and psychosocial therapies in schizophrenic patients. It is again the doctor in charge who must check the degree of motivation and cooperation. The interviewer also tries to enhance them by presenting the test in an attractive way. Our experience shows that the test is generally very well accepted by patients, and that the instruction "This is a simple test with a computer" helps to minimize any possible patients' fear or mistrust at the beginning.

The final objection which might be discussed is the possible influence of neuroleptic medication in the performance of the ARG. Once the neuroleptic treatment was converted into equivalents of chlorpromazine, we obtained that patients of this study were receiving 192.5 ± 205.7 mg/day. Therefore, neuroleptic treatment could effectively account for at least some part of the results. We certainly believe that the task to perform—generate random sequences—is not only of a motor nature, but also includes a high component of executive functions, particularly cognitive flexibility: to get the best results, the subject has to use different strategies and plan exactly when he/she is pressing the space bar. Although ideally patients should be without neuroleptic medication in these kinds of studies, this is almost a utopia in such a severe disease, at least in our ordinary work. On the other hand, we have preferred to study a sample of patients meeting DSM-IV criteria for diagnosis of schizophrenia. This requires a minimum illness period of 6 months and the presence of social/work dysfunction. However, this interesting point about the possible influence of medication requires further investigation and is one of the research lines we are dealing with. A second research line is the possible correlation of these nonlinear methods with disorders of higher level cognitive functions, such as working-memory deficits, gating disorders or cognitive dysmetria, as suggested in [45].

To avoid the optimization of all parameters involved (method/measure parameters and threshold) on the whole data record, we divided our data into a training set (10 patients and 10 control subjects) and a test set (10 patients and 10 control subjects). The training set was used to choose the parameters in each method and to select the optimum thresholds. The final algorithm was then applied to the data from the test set. However, further work is now required to test the potential value of our methodology with a larger data set.

VI. Conclusion

In this paper, we have hypothesized that the generation of random rhythms, that is, irregular sequences lacking an evident rule for its generation, requires a certain level of mental ability and must be understood as a "normal" performance. On the contrary, regular and rhythmic sequences are hypothetically associated with a loss of mental ability and consequently must be considered as a "pathological" performance.

We developed a new cognitive instrument, which measures the subject's capacity to generate random rhythms: the ARG. It was observed that schizophrenic patients could not generate time series as random as control subjects. This fact agrees with findings showing that schizophrenic patients are characterized by less complex neurobehavioral and neurophysiologic measurements.

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