Nonlinear Analysis of Time Series Generated by Schizophrenic Patients

Measuring the Capacity to Develop a Random Rhythm as a Test for Estimating Cognitive-Motor Dysfunction

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Schizophrenia is a severe mental disorder that appears in approximately 1% of the general population. According to the diagnostic criteria of the American Psychiatric Association [1], patients show some characteristic symptoms including delusions (for example, thinking that there is a conspiracy against them), hallucinations (hearing insulting voices), or disorganized speech. A central characteristic of schizophrenia can be conceptualized as a failure to put thoughts and perceptions into their proper relationships. Although usually measured by means of interviews and cognitive tasks, another possibility to precociously recognize schizophrenic patients is the study of their cognitive performance, including memory, abstract thinking, and language skills [2]. Many tests have been applied to this end.

Recently, methods from chaos theory have been applied to biological functions in order to analyze schizophrenia. For example, some authors [3, 4] have studied the EEG signals comparing schizophrenic patients and control subjects by means of nonlinear analysis, and finding that the chaotic attractors had different correlation dimensions. In a curious and little-known test (random-number generation [5]) subjects were asked to choose a number from one to 10 several times. Subjects were told to select these numbers as randomly as possible. It was found that schizophrenic patients tended more to repetition, and therefore performed worse than normal subjects. Other studies [6] consisted of a simple choice task (the prediction of 500 random right or left appearances of a stimulus) in order to obtain a binary response. Results, obtained by using methods from chaos theory, showed that the response sequences generated by schizophrenic patients exhibited a higher degree of interdependency than those of control subjects.

Focusing on a particular feature, the ability to create random rhythms, our study is aimed at the analysis of cognitive performance in patients with schizophrenia, comparing them with normal subjects. We have developed a new cognitive test using methods from nonlinear dynamical systems theory, with the objective of measuring the subject's capacity of developing a random rhythm.

Methods and Materials

Twenty patients with schizophrenia and 20 age-matched control subjects were tested. The patients, 16 men and four women with a mean age of 30.75 ± 7.64 years, were diagnosed according to DSM-IV criteria [1]. They were recruited from the Department of Psychiatry at the University Hospital of Valladolid, Spain. At the time of the study, all patients were living at home and following ambulatory treatment. All were receiving neuroleptics, mainly middle doses of haloperidol or risperidone. Twelve patients suffered from paranoid schizophrenia, six were residual schizophrenics, and two patients had an undifferentiated type. Control subjects lacking past or present psychiatric history included 13 men and seven women, whose mean age was 30.7 ± 7.4.

As mentioned above, this study aimed to analyze time series generated by schizophrenic patients and control subjects. For generating these time series, the subject was asked to press the space key of the computer as irregularly as possible, until the screen showed the end of the exercise. Once the subject is placed under

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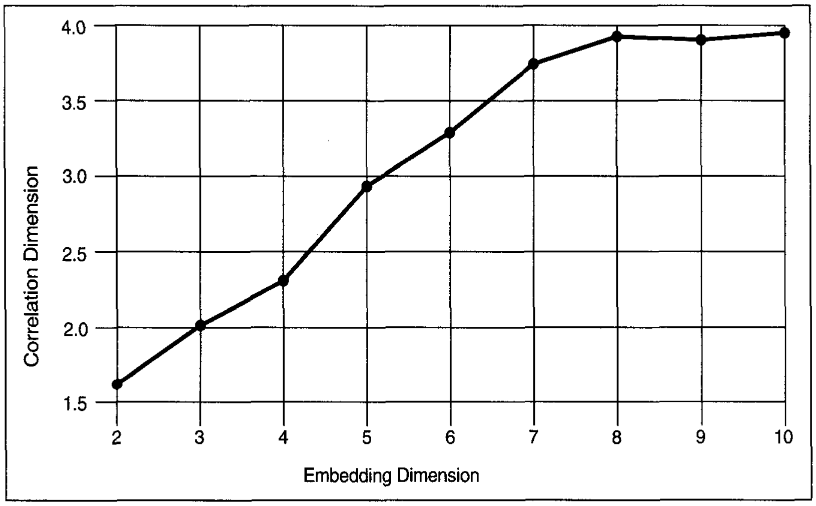
the same standard conditions as in a previous contact, the computer shows first an example of the required sort of rhythms. Following the instructions given, the subject must then generate two series of 128 strokes. Then, only a third series is recorded for assessment, once it has been determined that the subject understands the task to be performed.

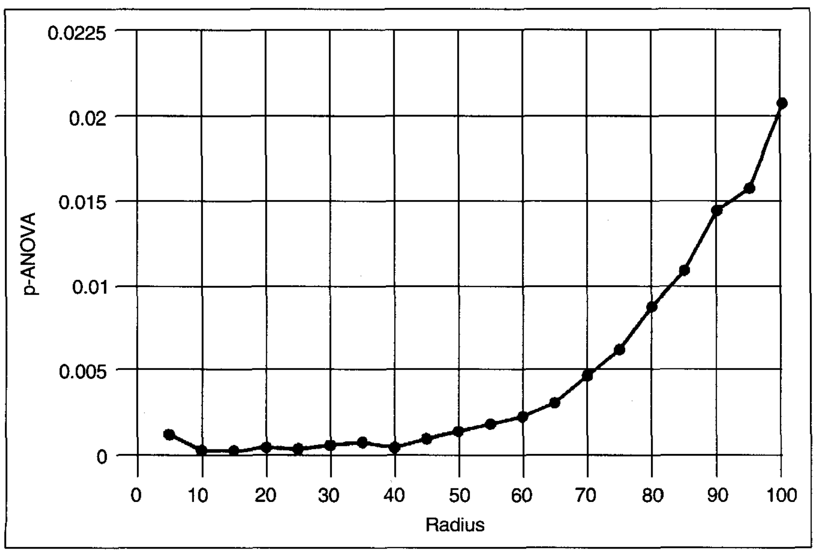
In this work, the first study was to find the optimum length of the time series. We need a long series to achieve a good estimation of the correlation dimension, but if the series were too long the results could be wrong, because generating a long random series is a very hard and tiring task. We analyzed time series of several lengths (1024, 512, 256, 128, 64), arriving at the conclusion that series longer than 128 points were more regular at the end than at the beginning. The results would be wrong because of control subjects and patients tiring. So, we decided to use series of 128 points. Because of these relatively short series, we followed the advice of some authors [7-9] to estimate the correlation dimension with small data sets.

The time series generated by 20 schizophrenic patients and 20 age-matched control subjects were analyzed by means of two methods from the nonlinear dynamical system theory. These were the correlation dimension of the chaotic attractor reconstructed from the time series, and the estimation of central tendency measure (CTM) of the second-order difference plots, which we explain in the following sections.

The concept of phase space is central to the analysis of nonlinear dynamics.



1. Correlation dimension vs. embedding dimension of a time series generated by a control subject.



2. Value of the p-ANOVA calculated in the differences of the CTM computations of the time series generated by 20 schizophrenic patients and 20 age-matched control subjects with several radii r.

Correlation Dimension (D_2)

The 1D time-series data generated by schizophrenic patients and control subjects were transformed into multidimensional phase-space plots. The concept of phase space is central to the analysis of nonlinear dynamics. In a hypothetical system governed by n variables, the phase space is n-dimensional. Each state of the system corresponds to a point in phase space whose n coordinates are the values assumed by the governing variables for this specific state. If the system is observed for a period of time, the sequence of points in phase space forms a trajectory. This trajectory fills a subspace of the phase space, called the system's attractor.

One of the important mathematical quantities characterizing an attractor is its correlation dimension. For example, in the case of steady-state behavior, the correlation dimension of the attractor is zero; in the case of periodic behavior, the correlation dimension of the attractor is one; and in chaotic states, the dimension usually takes on noninteger values. The larger the correlation dimension of the attractor, the more complicated the behavior of the nonlinear system. The correlation dimension is thus a measure of the complexity of the process being investigated and characterizes the distribution of points in the phase space.

The reconstruction of the attractor in the phase space was carried out through the technique of delay maps [10]. The coordinates of a point $X(n)$ in the phase space are the parameters of a state model of the reconstructed time series at time n.

It is important that the reconstruction be embedded in a space of sufficiently large dimension to completely represent the dynamics.

The attractor is reconstructed by the succession of these points $X(n)$ in the phase space. The vectors $X(n)$ in a multidimensional phase space are constructed by time-delayed values of the time series, which determine the coordinates of the phase-space plot:

$$X(n) = \{x(n), x(n+T), x(n+2T), \ldots, x(n+(m-1)T)\} \quad (1)$$

where $X(n)$ is one point of the trajectory in the phase space at time n, $x(n+iT)$ are the coordinates in the phase space corresponding to the time-delayed values of the time series, T is the time delay between the points of the time series considered, and m is the embedding dimension.

The reconstruction of the attractor with time-delay coordinates is not an automatic process, especially with small data sets [7-9]. The choice of an appropriate delay T and embedding dimension m are important for the success of the reconstruction.

Several suggestions can be found in the literature regarding the determination of the best time delay T; for example, the evaluation of the first zero of the autocorrelation function [10] and the first minimum of the mutual information [11, 12]. Other researchers [13, 14] sometimes adjust T until the results seem satisfactory. This procedure could introduce biases, but the invariant quantities computed from reconstructed attractors are often not too sensitive to T. Because of the features of our synthesized time series, we used the latter method. After trying various time-delay values ($T = 1, 2, 5, 10, 15, 20, 25, 30$ and 40), we found that results in the estimation of the correlation dimension were very similar, except with time delays greater than 20. In this case, results were not very reliable because there were not adequate conditions to estimate the correlation dimension [15, 16]. Thus, we did not employ delays greater than 20. Finally, we decided to use $T = 1$ because the results were very similar to using other delays, and in this way we reconstructed the attractor with the largest possible number of points.

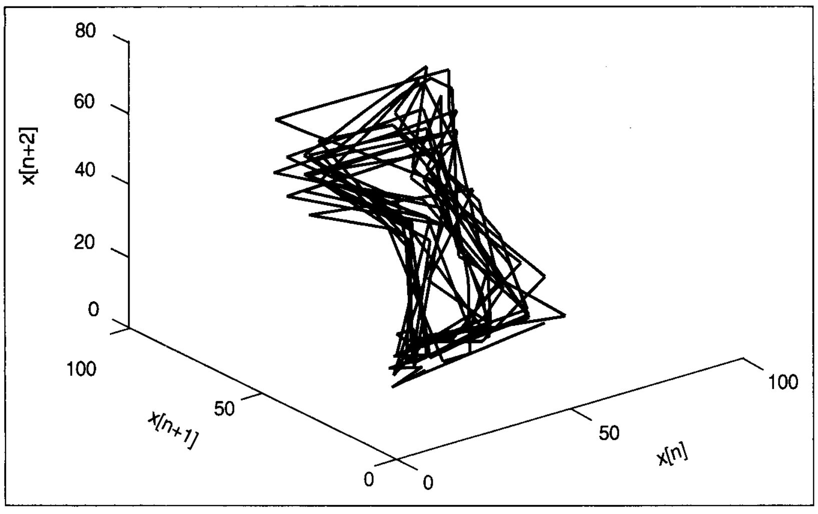
In reconstructing from an arbitrary experimental time series of unknown dynamics, the dimensionality of the attractor is unknown. It is important that the reconstruction be embedded in a space of sufficiently large dimension to completely represent the dynamics. Takens [17] suggested that it is sufficient for the embedding dimension (m) to be larger than the correlation dimension (D_2) according to the relation $m \geq 2 \cdot D_2 + 1$. However, other authors [18] have shown that the calculation of the correlation dimension does not require that m be large enough to verify $m \geq 2 \cdot D_2 + 1$; they showed that it is often sufficient for the embedding dimension to be larger than the attractor dimension ($m > D_2$). Therefore, the stringent Takens [17] condition may not be required for dimension calculation.

Nevertheless, the dimensionality of the attractor is usually unknown for experimental data and, therefore, the required embedding dimension is also unknown. Fortunately, there is a procedure that yields both quantities simultaneously. The process, first proposed by Grassberger and Procaccia [15, 16], is as follows: we reconstruct the attractor in a low-dimensional space and calculate its apparent correlation dimension. The dimension of the embedding space is now increased by 1; the attractor is then reconstructed in this new space and its correlation dimension is recalculated. The process is continued until a limiting value of the correlation dimension is reached. It is better not to use an embedding space of a dimensionality higher than the one required to produce a limiting value of D_2, because the undesirable effects of experimental noise become more pronounced for embeddings of higher dimension. We carried out this process with the time series generated by schizophrenic patients and control subjects [19]. In Fig. 1, this process is shown with a time series generated by a control subject (con-1), where an embedding dimension of order 8 was sufficient.

The correlation dimension was performed using the Grassberger and Procaccia [16, 17] method. In this procedure, the correlation dimension (D_2) is based on determining the relative number of pairs of points in the phase-space set that are separated by a distance less than r. It is computed from:

$$D_2 = \lim_{r \to 0} \frac{\log[C(N,r)]}{\log(r)} \quad (2)$$

where the correlation integral $C(N,r)$ is defined by:



3. Attractor of the time series generated by a schizophrenic patient.

$$C(N,r) = \frac{1}{N\cdot(N-1)} \sum_{i,j=1,i\neq j}^{N} \theta(r - \|X(i) - X(j)\|) \quad (3)$$

where $X(i)$, $X(j)$ are the points of the trajectory in the phase space, N is the number of data points in the phase space, the distance r is a radius around each reference point $X(i)$, $\|X(i) - X(j)\|$ is the Euclidean distance between vectors $X(i)$ and $X(j)$, and $H(x)$ is the Heavyside function, defined as 1 if $x > 0$ and 0 if $x \leq 0$. The summation in Eq. (3) counts the number of pairs of vectors $X(i)$ and $X(j)$ for which the distance $\|X(i) - X(j)\|$ is less than r. For small values of r, $C(N,r) \approx r^{D_2}$. Then, one plots $C(N,r)$ versus r on a log-log scale, and the correlation dimension is given by the slope of this curve over a selected range of r. During this procedure, it should be considered that a data length of $N > 10^{D_2/2}$ is necessary for a sufficient correlation-dimension estimation [7].

Central Tendency Measure (CTM)

Chaotic equations are sometimes used to generate graphs, which are known as Poincaré plots. We can produce graphs using the second-order difference plots:

$$(x_{n=2} - x_{n+1}) \text{ versus } (x_{n=1} - x_n). \quad (4)$$

Second-order difference plots centered around the origin represent the rate of variability. They represent the degree of theoretical chaos [20, 21] and are useful in modeling biological systems such as hemodynamic and heart-rate variability.

We used the CTM parameter to quantify the degree of variability in the second-order difference plots. The CTM is computed by selecting a circular region of radius r around the origin, counting the number of points that fall within the circle, and dividing by the total number of points. Let N be the total number of points, and r the radius of central area. Then [20]:

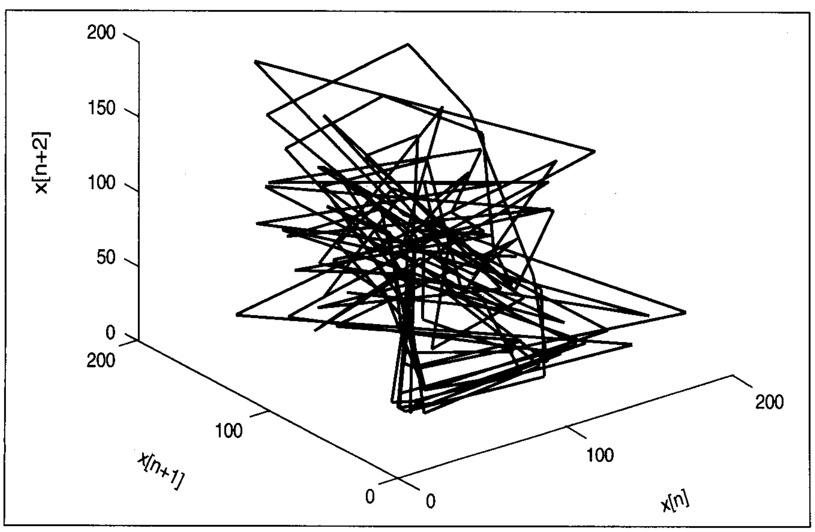
$$\text{CTM} = \frac{\sum_{i=1}^{N-2} \delta(d_i)}{N-2} \quad (5)$$

Where

$$\delta(d_i) = \begin{cases} 1 & \text{if } \; [(x_{i+2} - x_{i+1})^2 + (x_{i+1} - x_i)^2]^{1/2} < r \\ 0 & \text{otherwise} \end{cases} \quad (6)$$

The radius is chosen depending upon the character of the data. We developed a new method to select the radius. First, we computed the CTM using several different radii. Then, we applied an ANOVA test to calculate which of the radii achieved the more significant differences between time series generated by schizophrenic and control subjects. The result of this process is shown in Fig. 2.

In Fig. 2, we notice that there is a large range that could be used to select the radius. For radii lower than 80, we obtained $p < 0.01$, which indicates significant differences between the time series generated by both groups. The best range of the radii is between $10 \leq r \leq 40$, where a p-value lower than 0.001 is achieved.



4. Attractor of the time series generated by a control subject.

All results show that schizophrenic patients tend to generate more regular and rhythmic series than control subjects.

Results

At this point, we present examples of chaotic dynamic attractors in a 3D plot, estimation of the correlation dimensions of the times series generated by schizophrenic patients and normal persons, and samples of second-order difference plots with computations of the CTM parameter.

Attractors and Correlation Dimension

Figure 3 shows the reconstructed attractor of the time series generated by a patient with schizophrenia. The reconstructed attractor of the time series generated by a control subject is shown in Fig. 4. We present these attractors in a 3D plot. It must be noted that a sufficient phase-space reconstruction of our series needs an embedding dimension greater than three. Unfortunately, these embedding dimensions cannot be shown graphically. It has been necessary for visualization to reduce the dimension of the embedding space, but the correlation dimensions were evaluated using the correct embedding dimension. Nevertheless, these 3D phase-space plots can give a preliminary impression of the differences in structure between the schizophrenic patients series and those of control subjects. We calculated all control subjects and patients attractors, and observed that patient attractors seem to be more regular. Thus, the control-subject attractors showed a greater complexity than those of schizophrenic patients.

The multidimensional chaotic attractors were quantitatively characterized by the estimation of correlation dimension, which represents a measurement of the

Creating a more random rhythm requires a higher cognitive effort than creating a more regular rhythm.

system complexity. After calculating the correlation dimension of time series generated by 20 schizophrenic patients and 20 age-matched control subjects, a significant difference ($F_{1,38}$ = 15.66, p-ANOVA = 0.00032) in correlation dimension was observed for the time series generated by schizophrenic patients (mean 2.78 ± 0.65 SD) compared with that of control subjects (mean 3.69 ± 0.41 SD).

Second-Order Difference Plots and CTM

Figure 5 shows the second-order difference plot of the time series generated by a schizophrenic patient, whose chaotic dynamic attractor was illustrated in Fig. 3. The second-order difference plot of the time series generated by a control subject, whose chaotic dynamic attractor was presented in Fig. 4, is shown in Fig. 6. In the second-order difference plots, we observed that points in the time series generated by patients had a higher tendency to be located in the center, so their CTM values were going to be higher.

In the computations of the CTM parameter, we realized that the values had a high dependency of the radius used. To avoid this effect, we computed the mean CTM values in the best range, which was between radius 10 and 40, as shown in Fig. 2.

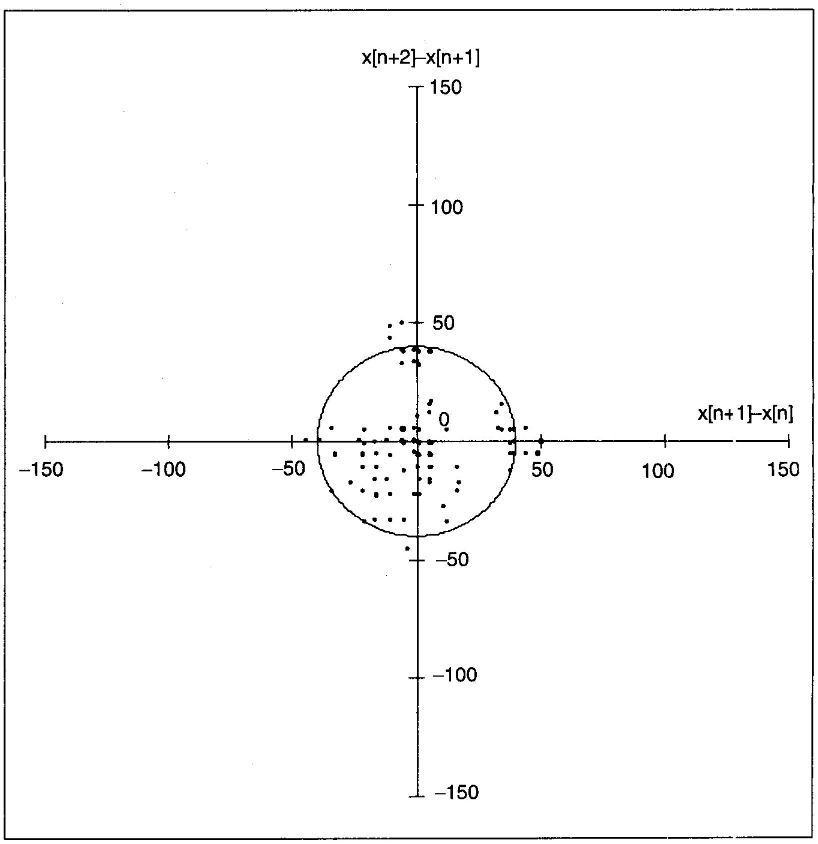
The CTM values in the range of radius $10 \le r \le 40$ were lower in the time series generated by the control subjects (a mean value of 0.18 ± 0.03 SD) compared with the CTM values of the time series generated by the schizophrenic patients (a mean of 0.52 ± 0.11 SD). These results show that the degree of variability of the time series generated by the control subjects is higher. Thus, schizophrenic patients generated more regular and rhythmic series than control subjects. There was a significant difference with the ANOVA procedure ($F_{1,38}$ = 17.01, p = 0.00019) between the groups.

Discussion

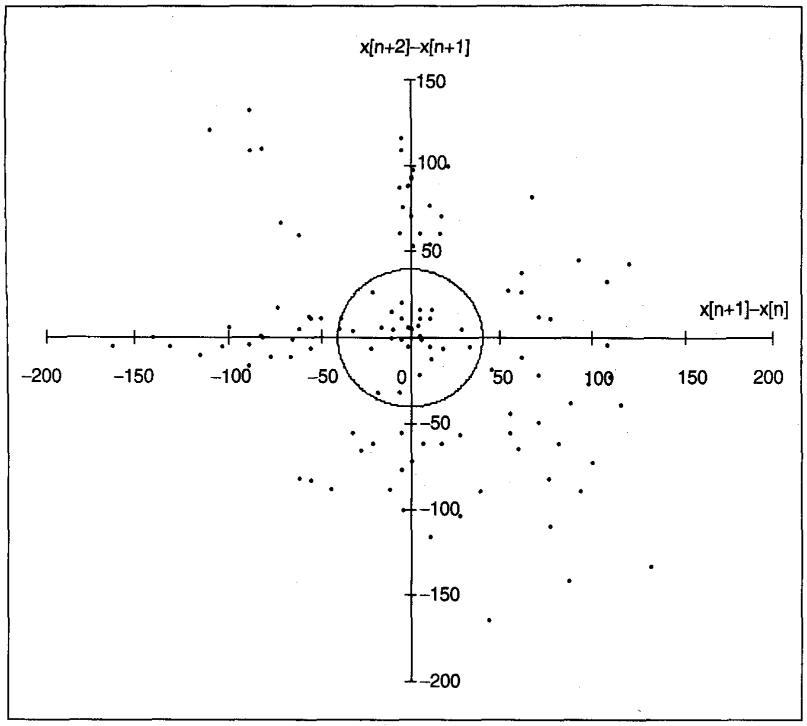
The correlation dimension is lower for the time series generated by schizophrenic patients compared to control subjects. The parameter (D_2) dimension can be viewed as a measure of system complexity. Our findings, therefore, indicate a diminished complexity in the times series generated by schizophrenic patients. According to the results with the CTM parameter, which quantifies the degree of variability, we can state that time series generated by schizophrenic patients had less variability. 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 show a reduction of complexity and variability in the inability to generate random series. These results are in agreement with findings that schizophrenic patients are characterized by less complex neurobehavioral measurements than normal subjects [3-6].

However, some remarks must be made in the interpretation of these data. We analyzed short time series, which makes it difficult to compute a correct estimation of the correlation dimension. So, we followed the advice given by some authors [7-9] in calculating the correlation dimension with small data sets. Our conclusions are thus based on analysis of variance (ANOVA) comparing clinical and control samples, and not on the absolute values of the correlation dimension. Another consideration is the possibility that past or current therapies could affect performance in the time series generated by schizophrenic patients. In fact, none of the patients had been treated with electroconvulsivant therapy before, but all of them were receiving neuroleptics at the time of the study, mainly middle doses



5. Second-order difference plot of the time series generated by a schizophrenic patient with a circle of radius r = 40.



6. Second-order difference plot of the time series generated by a control subject with a circle of radius $r = 40$.

of haloperidol or risperidone. Patient medication is undoubtedly an extended methodological difficulty in studies concerning cognitive performance of schizophrenic patients.

In spite of the above-mentioned aspects, we suggest that this easy test, when applied in conjunction with the nonlinear analysis, may be useful for the estimation of the cognitive-motor dysfunction in schizophrenic patients, usually diagnosed by clinical-evolutive criteria.

Conclusions

We analyzed time series generated by 20 schizophrenic patients and 20 age-matched control subjects by using methods from nonlinear dynamical system theory. We represented the chaotic dynamic attractors and the second-order difference plots of the time series, and we calculated the correlation dimension and the CTM parameter. Results showed that time series generated by schizophrenic patients had a lower complexity and variability than time series generated by control subjects with significant differences (p-ANOVA < 0.001) between the groups. We conclude that this easy test with this kind of analysis could be a complementary tool to help physicians in the estimation of cognitive-motor dysfunction in schizophrenic patients.

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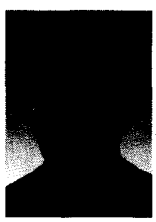

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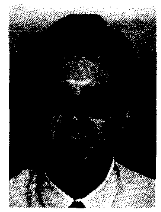

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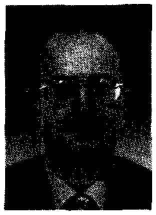

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