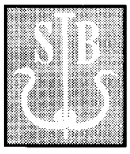

ORIGINAL ARTICLES

Depression as a Dynamical Disease

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Mathematical models are helpful in the understanding of diseases through the use of dynamical indicators. A previous study has shown that brain activity can be characterized by a decrease of dynamical complexity in depressive subjects. The present paper confirms and extends these conclusions through the use of recent methodological advances: first episode and recurrent patients strongly differ in their dynamical response to therapeutic interventions. These results emphasize the need for clinical follow-ups to avoid recurrence and the necessity of specific therapeutic intervention in the case of recurrent patients.

Key Words: Depression, dynamical systems, multichannel electroencephalogram, entropy, multivariate surrogate data, chaos

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Introduction

A number of studies provide a view of disease as a change in an intact physiological system operating within a range of control parameters leading to abnormal dynamics (Glass and Mackey 1979; Mackey and Milton 1987; Pool 1989; Schiff et al 1994). The onset of disease can be associated with changes from one dynamical regime to another (Mackey and Glass 1977). Such changes (called bifurcations) have been observed in neurology (Milton et al 1989) and particularly in epilepsy, which constitutes an illustration of obvious qualitative changes visible in macro potentials (Babloyantz and Destexhe 1986). In depression, altered biological rhythms, such as circadian rhythms (Wehr and Goodwin 1979; Wehr et al 1982) and cortisol secretion (Hollister et al 1980) have been observed, but traditional electroencephalographic approaches do not allow definition of specific modifications in brain dynamics.

We have started from the assumption that new nonlinear methods could provide insights into such psychopathological changes. Methods of neuronal and global brain dynamic characterization have been developed since the 1980s (for reviews see Pritchard and Duke 1992; Freeman 1992a; Elbert et al 1994), and the use of this framework in the study of mental disorders has been considered as promising (Freeman 1992b; Globus and Arpaia 1994; Redington and Reidbord 1992).

In early studies brain dynamics was quantified using correlation dimension as a dynamical indicator in neurological pathologies (e.g., Babloyantz and Destexhe 1986, 1988; Pijn et al 1991; Pritchard et al 1993) or in psychiatric diseases (Röschke and Aldenhoff 1993). Nevertheless it has been shown that this method has serious flaws when applied to spatially distributed systems such as the brain (Albano and Rapp 1993; Politi et al 1989; Lorenz

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Table 1. Mean Scores and Standard Deviations of the Groups of First-Episode (1st ep.) and Recurrent (Rec.) Patients for Hamilton Depressive Rating Scale (HDRS), Montgomery and Asberg Depressive Rating Scale (MADRS), Widlöcher's Depressive Retardation Scale (WRDS), and Tyrer's Anxiety Scale (TAS)

	N	Age (years)	Sex	HDRS	MADRS	WRDS	TAS
1st ep.							
D0	8	34.6	8 fem.	23 ± 2.3	28 ± 4.5	17 ± 6	16 ± 6.8
D21	6	35	6 fem.	6 ± 4	9 ± 2.6	8 ± 4.6	10 ± 6.3
Rec.							
D0	8	45.6	6 fem.	25 ± 4.4	31 ± 4.5	25 ± 3.2	18 ± 4.4
D21	7	46.2	6 fem.	6 ± 1.7	10 ± 2.6	9 ± 3.1	10 ± 5.9

D0 corresponds to the first recording and D21 to the second one. (*N*: group effective.)

1991). To avoid these drawbacks, in this study we adapt nonlinear forecasting methods (Casdagli 1989; Farmer and Sidorowich 1987; Sugihara and May 1990) to characterize multichannel electroencephalogram (EEG) recordings (Destexhe et al 1988). This method allows one to compute the entropy of brain dynamics, which quantifies its rate of loss of information (Wales 1991).

Signals generated by stochastic processes, however, can exhibit characteristics similar to those of natural nonlinear deterministic systems (Rapp et al 1993), leading to the difficulty of distinguishing between these two types of processes on the basis of empirical results. To deal with this problem, we have compared the prediction of EEG data to that of random surrogate data (Theiler et al 1992; Prichard and Theiler 1994). If the dynamical indices differ significantly between raw and surrogate data, then the hypothesis that the actual data correspond to linearly correlated noise can be rejected with a level of statistical confidence.

In a preliminary study (Nandrino et al 1994), we have shown that depressive patients possess a brain electrical activity that is more predictable than that of control subjects. After treatment, first-episode patients recover a level of predictability comparable to controls, whereas recurrent patients do not. In the present study, surrogate construction allows us to strengthen a reliable diagnosis of nonlinear processes in brain dynamics, and changes associated with recovery processes as a function of recurrence of depressive episodes are characterized using both linear and nonlinear indices.

Materials and Methods

Subjects

Two groups of eight right-handed inpatients have been selected according to the DSM-III-R criteria for major depressive episode. The duration of the episode was at least 1 month. Their minimum scores were: 19 in the Hamilton Depression Rating Scale (Hamilton 1960), and 22 in the Montgomery and Asberg Depressive Rating Scale (MADRS; Montgomery and Asberg 1979). The first group consisted of first-episode depressive patients free of antidepressant treatment and the second one of previously treated patients with recurrent depressive episodes. Hamilton Depression Rating Scales, MADRS, Tyrer Anxiety Scale (Tyrer et al 1984), and Wildlöcher Psychomotor Retardation Scale (Widlöcher 1983a) were performed both upon entrance, and when patients were discharged from the hospital about 3 weeks later (see Table 1 for group descriptions).

A control group of eight subjects, without any history of psychiatric illness, was matched for age (mean age: 36 years) and gender to the patients.

Treatment

Before the first recording session, recurrent patients were placed under a 3-day washout period of their previous treatment. During their stay in the hospital all patients were treated with drugs, no electroconvulsive therapy was used, and counseling was similar in each group. The first-episode patients were treated with clomipramine at a 150-mg daily dose during the whole stay. For three recurrent patients the treatment was similar to those of first-episode patients. In five cases, another tricyclic (fluoxetine) was added to clomipramine after an initial period of 10 days.

Task

Two tones of identical duration (150 msec) but of different frequencies (550 Hz and 1500 Hz) were randomly presented via earphones to the left or the right ear (random interstimulus interval from 1800 msec to 2300 msec). On average low and high tones were equiprobably distributed for each ear. Subjects were asked to respond as fast as possible to the tones by pressing a key with their right index finger for the low tones and with their left index finger for the high tones, independently of the stimulated

ear. This attention task was chosen in order to maximize the "mental load," which has been found to be crucial in differentiating mental illness from normality (e.g., Baribeau-Braun et al 1983; El Massioui and Lesèvre 1988).

EEG Recording

EEG was recorded from 12 derivations set on the scalp according to the 10-20 international electrode placement system (Fpz, Fz, Cz, Pz, F8, F4, F3, F7, C4, C3, P4, P3) and referred to the nose. Horizontal and vertical electro-oculograms (EOG) were simultaneously recorded in order to correct eye movements (Gratton et al 1983). The lower bandpass limit was 0.08 Hz for EEG and 0.02 Hz for EOG. Both upper bandpass limits were 30 Hz. The data were digitized on-line on 12 bits using a 250-Hz sampling rate (sample and nonhold device with interchannel sampling rate equal to 8 μsec). The signal was stored during the experiment on a hard disk of a PC 386-33 MHz, and then transferred onto the disk of a Micro-Vax for further processing.

Patients were recorded twice: upon their entrance to the hospital and when discharged, after antidepressant treatment and a minimal improvement on depressive scales of 50%. For the second recording session, six first-episode and seven recurrent patients out of the eight of the first session were recorded. The control subjects were also recorded twice with a 21-day interval.

Numerical Methods

NONLINEAR FORECASTING AND ENTROPY COMPUTATION. The detailed use of certain nonlinear methods (forecasting and entropy computation) in cerebral dynamics studies have been described elsewhere (Pezard et al 1994). Here, only the main steps are summarized (reconstruction of the trajectory, noise reduction, and quantification of the dynamics).

Reconstruction of the Trajectory. For each subject, three contiguous epochs of 32.8 sec (8192 samples) were analyzed. The records chosen for analysis were obtained after the subject had learned the task and had become comfortable with the recording environment. The trajectory of the system was reconstructed separately for each epoch (130 in total) in a 12-dimensional embedding space using the multichannel method (Destexhe et al 1988; Dvorak 1990; Pezard et al 1992), and the resulting dynamical measures obtained were averaged for each subject for each day of recording. Among the 45 individual daily averages (16 controls, 15 recurrent patients, and 14 first-episode patients), 40 were computed with three epochs, four were computed with two epochs, and one was computed with one epoch. The failure to compute all 45 averages with three epochs was due to artifacts in the original records.

For computational reasons, the set of recorded values was normalized and centered: for each channel the signal was shifted to zero mean and rescaled to unit variance.

Singular Value Decomposition. Singular value decomposition of the cross correlation matrix was computed, and those axes for which the variance was inferior to the noise level (10^{-2} in our case) were deleted. This reduction of the space dimension strongly decreases the computation time for the next steps, with no significant loss of information (Broomhead and King 1986; Albano et al 1988). In this reduced space, a k-d tree partition (Bentley 1975, 1979) was used to determine the nearest neighbor of each point to be used in the prediction method.

Starting from previous results (Morgera 1985), we have computed an index (Λ) to quantify the linear complexity of the correlation matrix, defined as follows:

$$\Lambda = -(\Sigma_i\ \nu_i \log(\nu_i))/\log n$$

where n is the number of channels ($n = 12$) and ν_i ($i = 1, ..., 12$) denotes the ith nonzero normalized eigenvalue. Λ varies from 0 for a one-dimensional distribution, to 1 for equidistributed white noise. It quantifies the shape of the distribution of the scatter of points within state space, and can be considered as a quantity analog to the "statistical entropy." This index is related to the one used previously by Palus et al (1991).

Computation of Predictability. The data set was divided into two equal parts. The first one, or learning set, was used to model the dynamics of the system, yielding a series of predictions. The second set, or test set, was used to evaluate the predicted values: the mean correlation coefficient ρ between the observed and the predicted series was computed for 1–10 time steps ahead (Sugihara and May 1990).

The first part of the curve of $\ln(1 - \rho)$ as a function of the prediction time (Tp) is linear for chaos, whereas it is not for Brownian motion (Tsonis and Elsner 1992). Wales (1991) has shown that for the linear part of the curve:

$$\ln(1 - \rho) = 2\ln(S_0/(2\sigma_x)) + 2KTp$$

where σ_x is the variance of the observed data. Two characteristic indices (K and S_0) can thus be computed using the regression line of the first three points of this curve. The information index, S_0, reflects the representativity of the learning set as compared to the test one and thus the stationarity of the dynamic. The Kolmogorov entropy, K, quantifies the rate of loss of information during the temporal evolution.

TEST FOR NONLINEARITY. Since dynamical methods may be biased by linearly correlated noise (Rapp et al

1993), the validity of dynamical indices should be tested by the comparison between the values computed on raw data and those computed on surrogate data with the same linear properties (power spectrum, autocorrelation function). Surrogate data are constructed from raw data by randomizing their phases in the Fourier domain (Theiler et al 1992). To have a reliable test against linear bias in the case of multivariate data, the surrogates have to preserve also the cross-correlation between the individual channels (Prichard and Theiler 1994). Such multivariable surrogates are used here to characterize multichannel EEG recordings.

More precisely, we have adopted the following procedure (Rapp et al 1994):

1. Assume a null hypothesis that the raw data are linearly correlated noise;
2. One or more dynamical measure M are obtained from the raw data; these shall be denoted here as M_{raw}. In our case, a set of five measures was used to test the null hypothesis (see below, step 6);
3. An ensemble of multi-surrogate data sets are constructed, in agreement with the null hypothesis defined in step 1, i.e., as linearly correlated noise. A total of 39 multi-surrogate data sets are used to ensure a level of confidence of .05 for the rejection of the null hypothesis (see step 5);
4. The same measure M, introduced in step 2, is calculated from the set of surrogates; its mean value is denoted here as $\langle M_{sur} \rangle$ and its standard deviation is denoted σ_{sur}.
5. An estimation of the difference between M_{raw} and $\langle M_{sur} \rangle$ is now obtained by means of the estimate S_M (Theiler et al 1992):

$$S_M = | M_{raw} - \langle M_{sur} \rangle | / \sigma_{sur}$$

Roughly, if $S_M \geq 2$, one can reject the null hypothesis for the measure M, with a confidence level of approximately $p \leq .05$. If the distribution of S_M is Gaussian, a probability value can be directly obtained (Larson 1982); however, we used a more robust empirical measure of the probability by the application of the Monte-Carlo probability (Barnard 1963; Hope 1968): P_m = [number of cases $M_{raw} \leq M_{sur}$]/(39 + 1) if $M_{raw} \geq \langle M_{sur} \rangle$, and P_m = [number of cases $M_{raw} \geq M_{sur}$]/(39 + 1) if $M_{raw} \leq \langle M_{sur} \rangle$. Under these conditions the null hypothesis is rejected if $P_m \leq 1/40$ (= .025) with the confidence level .05 for two-tailed test.

6. We have applied this procedure for the following five measures: the values of the correlation coefficient ρ for the first three prediction times (Tp = 4, 8, and 12 msec), K, and S_0 (see above, under Nonlinear Forecasting and Entropy Computation). Only when these five measures were significant did we accept the time series as truly nonlinear.

Table 2a. Percentage of Rejections of the Null Hypothesis for Each Group and Each Recording Session

	First recording	Second recording
Controls	12.5% (3/24)	33.3% (8/24)
First-episode patients	28.6% (6/21)	33.3% (6/18)
Recurrent patients	26.1% (6/23)	40.0% (8/20)

In parentheses, the number of rejections is given with the total number of windows studied.

Table 2b. Percentage of Windows Belonging to the Intervals Defined in Number of Sigmas by S_M for the Five Measures M Tested

M	$0 < S_M \leq 2$	$2 < S_M \leq 4$	$4 < S_M$
ρ (Tp = 4 msec)	65.4% (85)	16.9% (22)	17.7% (23)
ρ (Tp = 8 msec)	66.2% (86)	19.2% (25)	14.6% (19)
ρ (Tp = 12 msec)	67.7% (88)	19.2% (25)	13.1% (17)
K	71.5% (93)	13.8% (18)	14.6% (19)
S_0	66.2% (86)	16.2% (21)	17.7% (23)

The number of windows is given in parentheses. S_M = 2 corresponds approximately to the 5% significance threshold. ρ: correlation coefficient; Tp: prediction time; K: entropy; S_0: information index.

COMPARISON BETWEEN GROUPS. We have also compared the shape of the prediction curves between the subjects groups. An analysis of variance (ANOVA) has been performed using two intergroup factors: the subjects group (three modalities: controls, first-episode, and recurrent patients) and the recording sessions (two modalities: day 0 and day 21); the intragroup factor was the prediction time (Tp, 10 modalities). In the ANOVA calculations the sphericity (degree of covariance–matrix asymmetry) has been corrected by the Greenhouse–Geisser adjustment of degrees of freedom. Finally we have compared the values for K, S_0, and Λ between the subjects for each day of recording (Mann–Whitney U test) and between the two recording sessions (Wilcoxon matched pairs test).

Results

Comparison of Raw and Surrogate Data

The null hypothesis was formally rejected by the two-tailed test at the 95% level in 37 of the 130 windows (28%). This is considerably more than the expected number (5% or 6.5 windows) of rejections if the null hypothesis were true for all data sets. For each group, the rejection rate is similar (see Table 2a). Table 2b presents an average of the distance (index S_M in Numerical Methods) for the ensemble of five measures (defined in step 6 above) calculated for all 130 windows. For illustration,

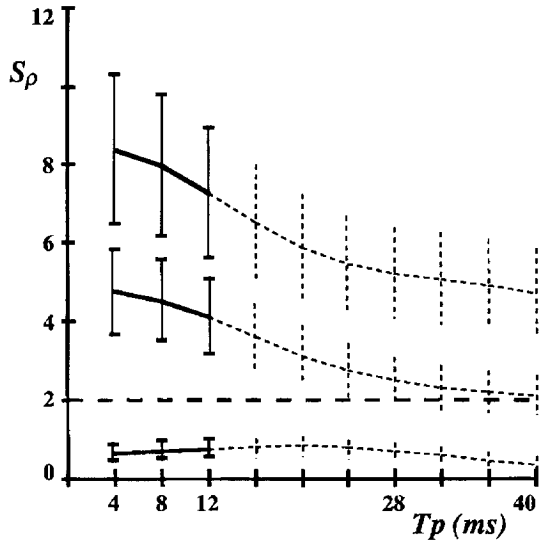

Figure 1. Values of S_ρ (= | ρ_{raw} − <ρ_{sur}> | σ_{sur}) and their error bars (Theiler et al 1992) as a function of prediction time (*Tp* in milliseconds) for the three recording epochs in one subject. The dotted lines, represent approximately the 5% level of confidence. The first three points (used to compute nonlinear indices) are distinguish from the rest of the curve, shown here for completeness.

Figure 1 shows an example of significant rejection of the null hypothesis for two out of three windows in one subject (recurrent patient, second recording session).

Clinical Results

Figure 2 shows the mean prediction curves for each group and for each of the two recording sessions. They are similar to those previously published (Nandrino et al 1994), confirming that this new data normalization does not alter the overall results. The ANOVA shows that the 10-step prediction time can be clearly differentiated whatever the group ($F_{1.95;\ 52.48} = 250.37$; $p < .001$). Table 3 summarizes the ANOVA results obtained when the significant interaction between groups and prediction time ($F_{2.69;\ 52.48} = 6.19$; $p = .002$) is decomposed. At day 0, the prediction curves do not differ between the two groups of depressed patients. Predictability in the case of depressed patients' brain dynamic is significantly higher than that of controls. At day 21, the first episode patients recover a level of prediction that can no longer be differentiated from the controls, whereas the recurrent patients' predictability remains above that of both first-episode patients and controls (note that the last comparison is slightly above the significance threshold).

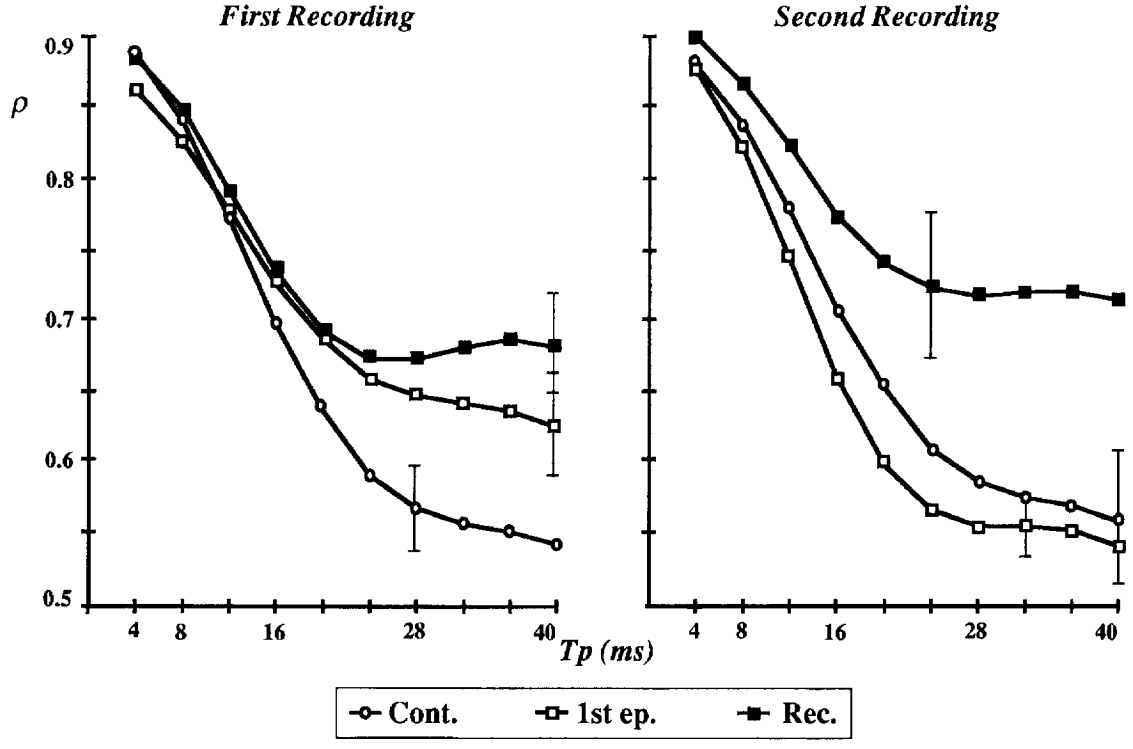

Figure 2. Mean prediction values for the two recording sessions and the three groups. Cont.: controls; 1st ep.: first-episode patients; Rec.: recurrent patients; ρ: correlation coefficent; Tp: prediction time in milliseconds. The vertical bars represent the largest standard errors.

Table 3. ANOVA Results of the Comparisons of the Prediction Curves for the Three Groups for the Two Recording Sessions

	First recording			Second recording		
	Cont./Rec.	Cont./1st ep.	Rec./1st ep.	Cont./Rec.	Cont./1st ep.	Rec./1st ep.
df	1.36; 19.07	1.43; 20.05	1.33; 18.64	1.28; 16.67	1.20; 14.36	1.43; 15.78
F	10.09	4.57	0.89	3.95	0.41	5.32
p	**0.003**	**0.033**	0.389	0.055	0.570	**0.025**

Cont.: controls; 1st ep.: first-episode patients; Rec.: recurrent patients; df: number of degrees of freedom.
Bold characters represent significant differences ($p < .05$).

Table 4 shows the values of Λ, K, and S_0, and Tables 5 and 6 give the results of the statistical tests of the different comparisons for these indices between groups and recording sessions.

LINEAR ANALYSIS. For the first recording session, the recurrent patients display a lower level of linear complexity than that of controls. No difference is observed either between first-episode patients and recurrent patients or between first-episode patients and controls. For the second recording session, the recurrent patients have a lower level of linear complexity that is significantly different from the two other groups. Controls and first-episode patients do not differ. Between the two recording sessions, no difference is found for each group. Nevertheless, one can note a tendency for the linear complexity to decrease in recurrent patients.

Table 4. Values of Linear (Λ) and Nonlinear (K and S_0) Indices for the Three Groups and the Two Recording Sessions

	Λ	K (sec^{-1})	S_0
Cont.			
D0	$0.52\ (3.4 \times 10^{-2})$	44.1 (2.7)	$0.40\ (1.4 \times 10^{-2})$
D21	$0.50\ (3.3 \times 10^{-2})$	39.0 (4.5)	$0.42\ (2.1 \times 10^{-2})$
1st Ep.			
D0	$0.52\ (4.2 \times 10^{-2})$	30.6 (5.9)	$0.47\ (2.6 \times 10^{-2})$
D21	$0.50\ (6.5 \times 10^{-2})$	49.1 (5.1)	$0.41\ (2.8 \times 10^{-2})$
Rec.			
D0	$0.40\ (4.3 \times 10^{-2})$	40.7 (5.0)	$0.40\ (3.2 \times 10^{-2})$
D21	$0.29\ (3.7 \times 10^{-2})$	35.5 (8.7)	$0.39\ (3.1 \times 10^{-2})$

Cont.: controls; 1st ep.: first-episode patients; Rec.: recurrent patients; D0: first recording session; D21: second recording session. Standard errors are given in the parentheses.

NONLINEAR ANALYSIS. For the first recording session, the first-episode group shows a lower level of entropy K and a higher level of S_0 than controls; however, these indices do not differ either between controls and recurrent patients or between the two groups of depressive patients. For the second recording session, K and S_0 do not differ between groups. Between the two recording sessions, entropy increases and S_0 decreases for the first-episode patients. No difference is found for these indices for the two other groups.

The main results of these linear and nonlinear characterizations (values of Λ and K) are visually depicted in Figure 3.

Discussion

Dynamical Analysis

The rejection of the null hypothesis in 28% of the studied windows establishes the presence of a nonlinear phenomenon underlying the global measurements taken from the

Table 5. Mann–Whitney U Test Results of the Comparisons Between Groups for the Two Recording Sessions for the Linear (Λ) and Nonlinear (K and S_0) Indices

	First recording			Second recording		
	Cont./Rec.	Cont./1st ep.	Rec./1st ep.	Cont./Rec.	Cont./1st ep.	Rec./1st ep.
Λ						
Z	−2.00	−0.26[a]	−1.58	−2.89	−0.52	−2.14
p	**0.046**	0.793	0.115	**0.004**	0.606	**0.032**
K						
Z	−0.21[a]	−2.00	−1.47[a]	−0.46	−1.03	−1
p	0.834	**0.046**	0.141	0.643	0.302	0.317
S_0						
Z	−0.21[a]	−2.10[a]	−1.21[a]	−0.58	−0.32[a]	−0.43
p	0.834	**0.035**	0.227	0.563	0.747	0.668

Cont.: controls; 1st ep.: first-episode patients; Rec.: recurrent patients.
[a] Z and p corrected for ties.
Bold characters represent significant differences ($p < .05$).

Table 6. Wilcoxon Matched Pairs Test Results of the Comparisons between Recording Sessions for the Three Groups for Linear (Λ) and Nonlinear (K and S_0) Indices

	Controls	1st-episode patients	Recurrent patients
Λ			
Z	−0.28	−0.74[a]	−1.69
p	0.779	0.462	0.091
K			
Z	−1.26	−2.20	−0.68
p	0.208	**0.028**	0.499
S_0			
Z	−1.54	−2.20	0
p	0.134	**0.028**	1

Bold characters represent significant differences ($p < .05$).
[a] Z and p corrected for ties.

patients' brains; however, these results cannot be taken as equivalent to the presence of stable low-dimensional chaos. Rather, we can only state that the possibility that chaos serves as a signature has not been ruled out.

The difficulty in establishing more precisely the nature of an underlying nonlinear process could be due to a number of interrelated methodological drawbacks. First, the reconstruction of the dynamic was realized in a 12-dimensional space, which may be too low to ensure the characterization of a higher dimensional dynamic (say dimension superior to 6). Second, the differentiation between chaos and noise in a spatially extended system has been shown to be difficult (Grassberger 1989; Mayer-Kress and Kaneko 1989). Thus, the indices computed with nonlinear methods such as the ones used here can be considered only as discriminating indices and not as specific characterization of nonlinear dynamics.

The linear and nonlinear indices used in this paper address two main characteristics of the trajectory once reconstructed: the linear index characterizes the shape of the scatter of reconstructed data points, while the nonlinear prediction characterizes the temporal evolution of their trajectory. Thus the linear index quantifies statistical properties of the embedded data, whereas the nonlinear indices quantify dynamical properties of brain activity. These two characterizations establish major differences in the temporal evolution of brain activity in first-episode and recurrent depressive patients.

In the first recording session, the two groups of depressive patients cannot be differentiated on the basis of either nonlinear or linear indices. Nevertheless, first-episode patients have a lower entropy and a higher S_0 than the controls. Within the first-episode group, a decrease of entropy and a decrease of stationarity in brain dynamics are observed during the depressive episode. These results suggest that the dynamical changes are unstable in first-episode patients. On the other hand, recurrent patients have a lower linear complexity than the controls. Thus the previous treatment or recurrence makes an important difference in the dynamical changes linked with the depressive episode. During the major depressive episode, when the patients are compared to the controls, recurrent patients are characterized by the statistical properties of the data, whereas the first-episode group is characterized by nonlinear dynamical indices.

One can speculate that in the case of depression, a low level of complexity in the brain dynamics is related to the reduction of cognitive production in the depressive behavior and ideation, described as ruminations and psychomotor retardation (Widlöcher 1983b).

Clinical Implications

Although their clinical improvements are similar, treatment-induced dynamical changes differ between the two groups of patients: 1) the entropy increases toward normality for the first-episode patients, but keeps its initial level in recurrent patients; and 2) the linear complexity differs between recurrent patients and the two other groups at day 21. These differences between electrophysiological and clinical indices may reflect different temporal scales between behavioral and physiological levels of recovery processes (Ashton et al 1988).

These results suggest that first-episode and recurrent patients are drastically different. Recurrence could be characterized by a specific inertia in the effect of the treatment inducing a different temporal scale of changes between the two groups. These differences in the response

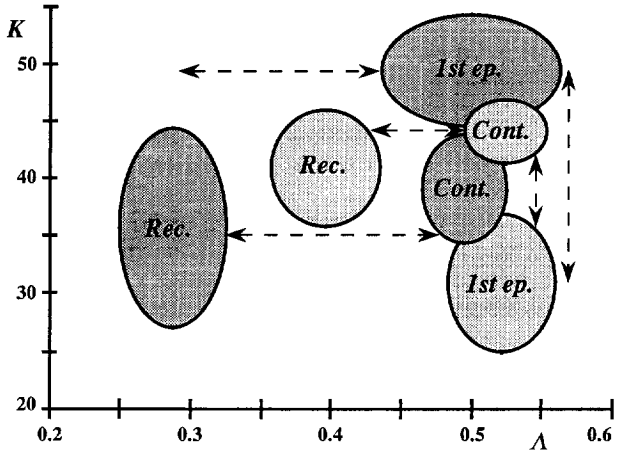

Figure 3. Schematic summary of the main results obtained with linear (Λ) and nonlinear (K) indices. Light gray corresponds to the first recording session and deep gray to the second one. Cont.: controls; 1st ep.: first-episode patients; Rec.: recurrent patients; K: entropy in sec^{-1}; Λ: linear index. The axis of the ellipses corresponds to the standard errors on abscissas, and ordinates. The dotted arrows represent the significant differences ($p \leq .05$) between groups and/or recording sessions.

to the treatment may be due either to differences between the subjects' histories (number of episodes, length of the disease, affective environment, etc.), or to specific interactions between dynamical state and pharmacological effects. No systematic link has been made so far between these different behaviors and clinical or pharmacological treatment. Only a longitudinal study could show whether or not recurrent patients keep their inertia induced by the long-lasting pathology; however, our results tend to show that recurrent patients display a characteristic signature of their global brain dynamics that is difficult to modify during drug treatment and hospitalization. It emphasizes the need for therapeutic follow-ups to avoid recurrence, and the necessity of finding new strategies to cause the recurrent patients' brain dynamics to be altered.

Conclusions

Changes in brain dynamics have been quantified in mental diseases with new quantitative tools. The results show that disease onset and recovery do not share the same characteristics between first-episode and recurrent patients. These differences could be used as prognostic indices if our results are confirmed in a larger population and longitudinal studies. This new insight in pathological states may be of great interest for clinicians to further investigate mental disorders. Furthermore the possibility of dealing with macroscopic dynamical indices that are close to the clinician experience could constitute a kind of "thermodynamic" approach in psychiatry, which is not merely metaphorical in nature but based on a prudent characterization of biological correlates.

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References

Albano AM, Rapp PE (1993): On the reliability of dynamical measures of EEG signals. In Jansen BH, Brandt ME (eds), *Nonlinear Dynamical Analysis of the EEG.* Singapore: World Scientific, pp 117–139.

Albano AM, Muench J, Schwartz C, Mees AI, Rapp PE (1988): Singular value decomposition and the Grassberger-Procaccia algorithm. *Phys Rev* A38:3017–3028.

Ashton H, Golding JF, Marsh VR, Thompson JW, Hassanyeh F, Tyrer SP (1988): Cortical evoked potentials and clinical rating scales as measures of depressive illness. *Psychol Med* 18:305–317.

Babloyantz A, Destexhe A (1986): Low-dimensional chaos in an instance of epilepsy. *Proc Natl Acad Sci USA* 83:3513–3517.

Babloyantz A, Destexhe A (1988): The Creutzfeldt-Jacob disease in the hierarchy of chaotic attractors. In Markus M, Müller S, Nicolis G (eds), *From Chemical to Biological Organization.* Berlin: Springer-Verlag, pp 307–316.

Baribeau-Braun J, Picton TW, Gosselin J-Y (1983): Schizophrenia: A neurophysiological evaluation of abnormal information processing. *Science* 219:874–876.

Barnard GA (1963): New methods of quality control. *J R Stat Soc* B25:255–258.

Bentley JH (1975): Multidimensional binary search trees used for associative searching. *Commun ACM* 18:509–517.

Bentley JH (1979): Multidimensional binary search trees in data base applications. *IEEE Trans Softw Eng* 5:333–340.

Broomhead DS, King GP (1986): Extracting qualitative dynamics from experimental data. *Physica* D20:217–236.

Casdagli M (1989): Nonlinear prediction of chaotic time series. *Physica* D35:335–356.

Destexhe A, Sepulchre JA, Babloyantz A (1988): A comparative study of the experimental quantification of deterministic chaos. *Phys Lett* A132:101–106.

Dvorak I (1990): Takens versus multichannel reconstruction in EEG correlation exponent estimates. *Phys Lett* A151:225–233.

Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N (1994): Chaos and physiology: Deterministic chaos in excitable cell assemblies. *Physiol Rev* 74:1–47.

El Massioui F, Lesèvre N (1988): Attention impairment and psychomotor retardation in depressed patients: An event-related study. *Electroencephalogr Clin Neurophysiol* 70:46–55.

Farmer JD, Sidorowich JJ (1987): Predicting chaotic time series. *Phys Rev Lett* 59:845–848.

Freeman WJ (1992a): Tutorial on neurobiology: From single neurons to brain chaos. *Int J Bifurcation Chaos* 2:451–482.

Freeman WJ (1992b): Chaos in psychiatry. *Biol Psychiatry* 31:1079–1081.

Glass L, Mackey MC (1979): Pathological conditions resulting from instabilities in physiological control systems. *Ann NY Acad Sci* 316:214–235.

Globus GG, Arpaia JP (1994): Psychiatry and the new dynamics. *Biol Psychiatry* 35:352–364.

Grassberger P (1989): Information content and predictability of lumped and distributed dynamical systems. *Physica Scripta* 40:346–353.

Gratton G, Coles MGH, Donchin E (1983): A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 55:468–484.

Hamilton MA (1960): Rating scale of depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Hollister LE, Davis KL, Davis BM (1980): Hormones in the treatment of psychiatric disorders. In Kreiger DT, Hughes JC (eds), *Neuroendocrinology.* Sunderland, MA: Sinauer, pp 167–175.

Hope ACA (1968): A simplified Monte-Carlo significance test procedure. *J R Stat Soc* B30:582–598.

Larson HJ (1982): *Introduction to Probability Theory and Inference.* New York: Wiley.

Lorenz EN (1991): Dimension of weather and climate attractors. *Nature* 353:241–244.

Mackey MC, Glass L (1977): Oscillation and chaos in physiological control systems. *Science* 197:287–289.

Mackey MC, Milton JG (1987): Dynamical diseases. *Ann NY Acad Sci* 504:16–32.

Mayer-Kress G, Kaneko K (1989): Spatiotemporal chaos and noise. *J Stat Phys* 54:1489–1508.

Milton JG, Longtin A, Beuter A, Mackey MC, Glass L (1989): Complex dynamics and bifurcations in neurology. *J Theor Biol* 138:129–147.

Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.

Morgera SD (1985): Information theoretic covariance complexity and its relation to pattern recognition. *IEEE Trans Systems Man Cybern* 15:608–619.

Nandrino J-L, Pezard L, Martinerie J, El Massioui F, Renault B, Jouvent R, Allilaire J-F, Widlöcher D (1994): Decrease of complexity in EEG as a symptom of depression. *Neuroreport* 5:528–530.

Palus M, Dvorak I, David I (1991): Remarks on spatial and temporal dynamics of EEG. In Dvorak I, Holden AV (eds), *Mathematical Approaches to Brain Functioning Diagnostics.* New York: Manchester University Press, pp 369–385.

Pezard L, Martinerie J, Breton F, Renault B (1992): Nonlinear forecasting and correlation dimension of brain dynamics: A multichannel study. *Proc 14th Ann Internat Conf IEEE-EMBS,* vol 3. Piscataway IEEE Inc. pp 979–981.

Pezard L, Martinerie J, Breton F, Bourzeix J-C, Renault B (1994): Nonlinear forecasting measurements of multichannel EEG dynamics. *Electroencephalogr, Clin Neurophysiol* 91: 383–391.

Pijn JP, Van Neerven J, Noest A, Lopes da Silva FH (1991): Chaos or noise in EEG signals: Dependence on state and brain state. *Electroencephalogr Clin Neurophysiol* 79:371–381.

Politi A, D'Alessandro G, Torcini A (1989): Fractal dimensions in coupled map lattices. In Abraham NB, Albano AM, Passamante A, Rapp PE (eds), *Measures of Complexity and Chaos.* New York: Plenum, pp 409–424.

Pool R (1989): Is it healthy to be chaotic? *Science* 243:604–607.

Prichard D, Theiler J (1994): Generating surrogate data for time series with several simultaneous measured variables. *Phys Rev Lett* 73:951–954.

Pritchard WS, Duke DW (1992): Measuring chaos in the brain: A tutorial review of nonlinear dynamical EEG analysis. *Int J Neurosci* 67:31–80.

Pritchard WS, Duke DW, Coburn KL, Moore NC, Tucker KA (1993): Altered EEG dynamical responsivity with Alzheimer's disease: Replication and extension. In Jansen BH, Brandt ME (eds), *Nonlinear Dynamical Analysis of the EEG.* Singapore: World Scientific, pp 165–168.

Rapp PE, Albano AM, Schmah TI, Farwell LA (1993): Filtered noise can mimic low dimensional chaotic attractors. *Phys Rev* 47E:2289–2297.

Rapp PE, Albano AM, Zimmerman ID, Jiménez-Montaño MA (1994): Phase-randomized surrogates can produce spurious identifications of non-random structure. *Phys Lett* A192:27–33.

Redington D, Reidbord S (1992): Chaotic dynamics in autonomic nervous system activity of a patient during psychotherapy. *Biol Psychiatry* 31:993–1007.

Röschke J, Aldenhoff JB (1993): Estimation of the dimensionality of sleep-EEG data in schizophrenics. *Eur Arch Psychiatry Clin Neurosci* 242:191–196.

Schiff SJ, Jerger K, Duong DH, Chang T, Spano ML, Ditto WL (1994): Controlling chaos in the brain. *Nature* 370:615–620.

Sugihara G, May RM (1990): Nonlinear forecasting as a way of distinguishing chaos from measurement error in time series. *Nature* 344:734–741.

Theiler J, Galdrikian B, Longtin A, Eubank S, Farmer JD (1992): Using surrogate data to detect nonlinearity in time series. In Casdagli M, Eubank S (eds), *Nonlinear Modeling and Forecasting.* Reading, MA: Addison-Wesley, pp 163–188.

Tsonis AA, Elsner JB (1992): Nonlinear prediction as a way of distinguishing chaos from random fractal sequences. *Nature* 358:217–220.

Tyrer P, Owen RT, Cicchetti DV (1984): The brief scale for anxiety: A subdivision of the comprehensive psychopathological rating scale. *J Neurol Neurosurg Psychiatry* 47:970–975.

Wales DJ (1991): Calculating the rate of loss of information from chaotic time series by forecasting. *Nature* 350:485–488.

Wehr TA, Goodwin FK (1979): Rapid cycling in manic-depressives induced by tricyclic antidepressants. *Arch Gen Psychiatry* 36:555–559.

Wehr TA, Goodwin FK, Wirz-Justice A, Craig C, Breitmeier J (1982): 48-hour sleep-wake cycles in manic-depressive illness: Naturalistic observations and sleep deprivation experiments. *Arch Gen Psychiatry* 39:559–565.

Widlöcher D (1983a): Psychomotor retardation: Clinical, theoretical and psychometric aspects. In Akiskal HS (ed), *The Psychiatric Clinics of North America.* Philadelphia: Saunders, pp 27–40.

Widlöcher D (1983b): Retardation: A basic emotional response? In Davis J, Mass J (eds), *The Affective Disorders.* Washington, DC: American Psychiatric Press.