Research Paper

Nonlinear analysis of electroencephalogram at rest and during cognitive tasks in patients with schizophrenia

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Background: In spite of the large number of studies on schizophrenia, a full understanding of its core pathology still eludes us. The application of the nonlinear theory of electroencephalography (EEG) analysis provides an interesting tool to differentiate between physiologic conditions (e.g., resting state and mathematical task) and normal and pathologic brain activities. The aim of the present study was to investigate nonlinear EEG activity in patients with schizophrenia. **Methods:** We recorded 19-lead EEGs in patients with stable schizophrenia and healthy controls under 4 different conditions: eyes closed, eyes open, forward counting and backward counting. A nonlinear measure of complexity was calculated by means of correlation dimension (D2). **Results:** We included 17 patients and 17 controls in our analysis. Comparing the 2 populations, we observed greater D2 values in the patient group. In controls, increased D2 values were observed during active states (eyes open and the 2 cognitive tasks) compared with baseline conditions. This increase of brain complexity, which can be interpreted as an increase of information processing and integration, was not preserved in the patient population. **Limitations:** Patients with schizophrenia were taking antipsychotic medications, so the presence of medication effects cannot be excluded. **Conclusion:** Our results suggest that patients with schizophrenia present changes in brain activity compared with healthy controls, and this pathologic alteration can be successfully studied with nonlinear EEG analysis.

Introduction

The precise mechanisms underlying schizophrenia remain poorly understood, even though current pathophysiologic theories suggest that its core pathology is an abnormal functional integration of the neural system (disconnection hypothesis).[1] Numerous electroencephalographic (EEG) studies have been conducted to characterize the brain activity of patients with schizophrenia. Different nonspecific abnormalities have been reported, but it is generally agreed that no characteristic pattern is apparent on visual inspection of EEGs.[2,3] However, recent applications of the nonlinear theory of EEG have provided a new, potentially interesting research tool.[4] Nonlinear EEG patterns have been reported in different physiologic conditions, such as sleep,[5] and in pathologic states, such as epilepsy and dementia.[6–9] Nonlinear EEG patterns in patients with schizophrenia have also been described.[10,11] In 2006, Breakspear[12] suggested that the study of nonlinearity in the field of schizophrenia could be justified at a neurophysiologic level (the nonlinear dynamic properties of neural systems), at a clinical level (the dynamic nature and the fluctuations of symptoms) and from a conceptual point of view (psychotic symptoms as a failure of the stability of nonlinear brain systems).

One approach to apply nonlinear methods to the analysis of EEGs is to estimate the dimensional complexity of the signal through the correlation dimension (D2),[13] which can be defined as the number of independent variables necessary to describe the behaviour of a dynamic system.[14] The neurophysiologic meaning of D2 is not clear. However, since EEGs reflect cortical

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J Psychiatry Neurosci 2021;37(4):259-66.

Submitted Mar. 26, 2011; Revised Oct. 13, Nov. 17, 2011; Accepted Nov. 17, 2011.

DOI: 10.1503/jpn.110030

dynamics, D2 is often interpreted as a measure of complexity (or flexibility) of information processing, and it can be interpreted as an index of the integration of information in the brain. Nonlinear analysis of EEGs, namely D2 estimates, has proven to be very useful in comparing different physiologic states. A study conducted in young healthy volunteers demonstrated that the dimensional complexity of EEGs, as measured by D2, was greater while participants solved tasks of divergent (creative) rather than convergent thinking; in turn, the D2 values were greater during convergent thinking than mental relaxation.[15] Decreased D2 values have been detected in a variety of clinical and experimental conditions presenting grossly impaired information processing. Babloyantz and Destexhe[16] demonstrated low-dimensional dynamics in the EEG of a patient with Creutzfeldt–Jakob disease. Lower D2 values have been detected in healthy men in a state of total sleep deprivation,[17] and lower values have also been demonstrated in patients with epilepsy during an absence seizure.[18] Moreover, D2 has been extensively investigated in patients with Alzheimer disease,[7,19,20] and results have shown a decrease in values in the patient population, with a correlation between D2 and severity of dementia. These data suggest the possible use of this measure in the assessment of patients with Alzheimer disease, with improved accuracy of diagnosis.[9] Similarly, the possible usefulness of D2 values in a clinical setting has been supported by investigations in patients with Parkinson disease.[8,21]

Several studies have investigated D2 in patients with schizophrenia.[2,10,22,23] Some differences in EEG complexity between these patients and healthy controls have been reported, with contradictory findings likely owing to the wide variations in experimental conditions and sample selection.[24] However, to our knowledge, EEG patterns during resting and active conditions have not been compared yet, thus no information regarding the brain activity during different conditions is available.

Despite the widespread application of D2, limitations of nonlinear approaches to time series analysis have been recognized. In particular, there is the question of whether EEG time series contain nonlinear properties. To answer this question, control methods to test nonlinearity have been developed. One of the most popular methods is surrogate data testing.[25,26] Surrogate data are constructed to preserve the same linear properties (power spectrum/autocorrelation function) as the original time series but present different nonlinear dynamics. With this method, evidence of nonlinear dynamics has been detected in healthy participants[27] and in patients with epilepsy,[28] dementia and Parkinson disease.[29,30] However, for patients with schizophrenia, results in the field of EEG nonlinearity are still inconclusive.[11]

Taking these considerations into account, the aim of the present study was to investigate the dimensional complexity of EEG by means of D2 values in patients with schizophrenia. We sought to record 19-lead EEGs in a sample of patients with stable schizophrenia and healthy volunteers. An extensive protocol registration was developed, with a resting condition (eyes closed) and 3 active conditions (eyes open, counting forward and counting backward). We explored D2 changes from resting to active conditions. Furthermore, we investigated the presence of nonlinearity in EEG using a surrogate data technique.

Methods

Participants

We recruited patients with schizophrenia from the outpatient clinics at the Department of Neuroscience, Section of Psychiatry, and the Department of Mental Health ASL 1 Ospedale San Giovanni Battista, Turin, Italy. They all fulfilled formal *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)[31] criteria for schizophrenia. The diagnosis was confirmed by 2 expert clinicians using the Structured Clinical Interview for DSM-IV (SCID).[32] At the time of study entry, patients had been clinically stable for at least 6 months, as judged by the treating psychiatrist. This means that during this period, all patients could be treated as outpatients, treatment regimen was not modified, and there was no essential change in psychopathology. Patients were evaluated using a semistructured interview to assess demographic and clinical features. We collected data on age, sex, education, vocational functioning, age at onset of schizophrenia (report of first contact with a psychiatric service) and duration of illness. Participants were excluded if they had a current Axis I disorder other than schizophrenia (as determined with the SCID), a current or past comorbid diagnosis of an autism-spectrum disorder or another pervasive developmental disorder, a history of severe head injury (coma ≥ 48 h) or a diagnosis of a psychiatric disorder owing to a general medical condition. All patients were taking a second-generation antipsychotic at the time of assessment. We recruited a group of healthy matched controls without history of sustained head injury or other neurologic or psychiatric disorders. Controls were recruited from the community and from the local university.

Written informed consent was obtained from all participants after a complete description of the study. We determined whether patients with schizophrenia were capable of providing informed consent on the basis of the clinical interview and with the help of information obtained by the treating psychiatrist. The study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the ethics committee of our hospital (Comitato Etico Interaziendale A.O.U. San Giovanni Battista di Torino, A.O. C.T.O. Maria Adelaide di Torino).

Psychiatric and neuropsychologic assessment

We rated overall severity of illness using the Clinical Global Impression–Severity Scale (CGI-S),[33] and current levels of psychopathologic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), a rater-administered 30-item scale for measuring positive symptoms, negative symptoms and general psychopathology subscales.[36] The Global Assessment of Functioning (GAF) scale was used to quantify patients' psychologic, social and occupational/educational functioning.[35]

Neuropsychologic tests were administered by 1 trained psychologist who was unaware of participants' clinical characteristics or scores on the psychiatric rating scales. The battery was administered and scored on the day after the

psychiatric assessments. The total testing time was 1–2 hours per patient. No participants were familiar with the tests, and they all underwent a neuropsychologic battery assessing attention, verbal memory and executive functioning. To evaluate attentive functioning, we used the number of colours named in the conflicting card of the Stroop Test,[37] which is a specific index of the interference sensitivity and/or response inhibition. Moreover, we calculated the time measured in seconds of Part B minus Part A of the Trail Making Test (TMT)[38] to assess divided attention and set shifting. Verbal memory was assessed using the California Verbal Learning Test (CVLT),[34] and we recorded the total number of items correctly recalled over 5 learning trials (CVLT 1–5). To assess executive functioning, the number of achieved sorting categories of the Wisconsin Card Sorting Test (WCST) was used.[39]

Electroencephalogram recording

Participants sat in a comfortable chair, and EEG data were recorded using a 19-lead EEG (Galileo; EBNeuro S.p.A.). Nineteen electrodes were applied to the scalp in accordance with the 10–20 international system (Fz, F1, F2, F3, F4, F7, F8, C3, C4, Cz, P3, P4, Pz, T3, T4 T5, T6, O1, O2) with linked common ear reference. Impedance was less than 2 KΩ in each active lead. Data were collected and digitized at a sampling rate of 1024 Hz, with a low frequency filter of 3 Hz and a high frequency filter of 30 Hz in each channel. The EEG was recorded in 4 different conditions: a baseline period with eyes closed, an active period with eyes open and 2 cognitive task periods (counting forward and counting backward). Recordings started with 5 minutes with eyes closed followed by 4 minutes with eyes open, during which participants were asked to keep their eyes steady on an object positioned in front of them. After another 2 minutes with eyes closed, the 45 second cognitive tasks started: participants were asked to count forward in steps of 3 starting from 1 and, after another 2 minutes with eyes closed, they were asked to count backward in steps of 3 starting from 100. Recordings ended with 2 minutes with eyes closed (Fig. 1). All EEG scans were visually inspected offline by 3 independent raters to discard EEG artifacts, and 16-second epochs (16 384 data points) without artifacts were selected for each condition. Data from the T5 electrode were excluded from the analysis for technical problems evidenced in all the recordings during the data analysis.

Nonlinear and statistical analyses

To test the nonlinearity of the EEGs, we used the surrogate data method.[25,26] After the Fourier transform, the EEG phases were randomized and then the inverse Fourier transform was computed, returning to the time domain. Subsequently, we calculated the nonlinear measure (D2) on the surrogate data and compared it with the original values using z scores.[40] Only z scores greater than 1.96 ($p < 0.05$) were considered to be significant. We obtained D2 values with a specific program (Complexity v.2.0; Laxtha Inc.). The optimal values of embedding dimension and delay number were automatically set: we used an embedding dimension of 9 and time delays of 5–15 ms. Computation details are described in Appendix 1, available at cma.ca/jpn.

Four different regions were considered and designated as follows: frontal (average of Fp1, Fp2, F7, F3, Fz, F4, F8), central (average of C3, Cz, C4), temporal (average of T3, T4, T5, T6) and occipital (average of P3, Pz, P4, O1, O2). We performed a mixed analysis of variance (ANOVA) between groups using the Dunnet post hoc test for multiple comparisons.

Data are presented as means and standard deviations (SD), and we considered results to be significant at $p < 0.05$. The analysis was performed with Statistica, version 9, for Windows.

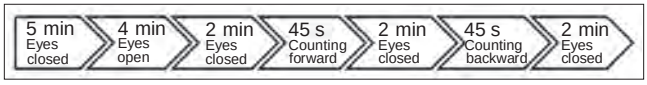

Fig. 1: Experimental protocol.

Results

We recruited 23 patients with schizophrenia for the study. Of these, 6 patients were excluded owing to unanalyzable EEG recording (EEG interference, muscular artifacts; $n = 2$), inability to follow the instructions of the experimental protocol ($n = 3$) and protocol interruption ($n = 1$). Data for 17 patients (10 men, 7 women, mean age 34.7 [SD 10.3] yr, mean education 12.1 [SD 3.2] yr) and 17 age- and sex-matched controls without history of psychiatric or neurologic disease (9 men, 8 women, mean age 36.5 [SD 13.9] yr, mean education 15.8 [SD 4.1] yr) were available for analysis. The demographic and clinical characteristics of participants are summarized in Table 1. All patients were right-handed, whereas 1 control was left-handed. Patients and controls did not differ in age ($t = –0.434$, $p = 0.67$) or sex ($\chi^2_1 = 0.000$,

Table 1: Demographic and clinical characteristics of patients with schizophrenia and healthy matched controls

Characteristic	Group; mean (SD)*	
	Patients	Controls
No.	17	17
Sex ratio, male:female	10:7	9:8
Age, yr	34.7 (10.3)	36.5 (13.9)
Education, yr	12.1 (3.2)	15.8 (4.1)
Psychiatric assessment		
Onset of schizophrenia, yr	24.5 (6.2)	—
Duration of illness, yr	9.8 (7.7)	—
CPZ equivalent, mg/d	212 (112)	—
CGI-S score	4.0 (0.8)	—
PANSS score	58.2 (19.4)	—
GAF score	65.3 (14.3)	—
Neuropsychological assessment		
Stroop CW, s	28.1 (6.9)	34.4 (9.8)
CVLT 1–5	44.4 (10.2)	66.2 (6.5)
WCST category score	5.8 (0.4)	6.0 (0.0)
TMT B–A, s	59.2 (21.9)	34.6 (25.1)

CGI-S = Clinical Global Impression–Severity Scale;[33] CPZ = chlorpromazine; CVLT 1-5 = California Verbal Learning Test over 5 learning trials;[34] GAF = Global Assessment of Functioning;[35] PANSS = Positive and Negative Syndrome Scale;[36] SD = standard deviation; Stroop CW = Stroop colour–word test;[37] TMT B-A = Trail Making Test;[38] WCST = Wisconsin Card Sorting Test.[39]
*Unless otherwise indicated.

$p > 0.99$) but a difference in education was observed, with a higher level in the control population ($t = –2.926$, $p = 0.006$; Table 1). However, the education level was not correlated with D2 variables in either group ($p > 0.09$ in all cases). The antipsychotic medications that patients were taking at the time of assessment are listed in Table 2.

We checked the accuracy of the cognitive task by assessing differences in right/wrong answers in the counting forward and counting backward conditions. No significant difference was found ($\chi^2_1 = 3.220$, $p = 0.07$ for forward counting and $\chi^2_1 = 1.275$, $p = 0.26$ for backward counting). Furthermore, no correlation was observed between medication (expressed in chlorpromazine [CPZ] equivalents) and D2 values ($r = –0.41$, $p = 0.09$ for the eyes closed condition; $r = –0.25$, $p = 0.33$ for the eyes open condition; $r = –0.38$, $p = 0.13$ for the counting forward condition; and $r = –0.28$, $p = 0.26$ for the counting backward condition).

The patient group showed a moderate severity of symptoms assessed by PANSS (mean 58.2 [SD 19.4] points) and CGI-S (mean 4.0 [SD 0.8] points). Moreover, the GAF results (mean 65.3 [SD 14.3] points) reflected an intermediate but significant level of functioning impairment. As far as the neuropsychologic assessment was concerned, controls performed better than patients on the CVLT (mean 66.2 [SD 6.5] points v. mean 44.4 [SD 10.2] points, $t = 7.08$, $p < 0.001$, Cohen $d = 2.55$), TMT B–A (mean 34.6 [SD 25.1] points v. mean 59.0 [SD 21.9] points, $t = –2.81$, $p = 0.009$, Cohen $d = 1.04$) and Stroop tests (mean 34.4 [SD 9.8] points v. mean 28.1 [SD 6.9] points, $t = 2.16$, $p = 0.040$, Cohen $d = 0.80$). The WCST results (controls: 6 categories; patients: 5.6 ± 0.4 categories) were similar for both groups.

Surrogate data

Globally, as revealed by the z scores, the original signals and the surrogate data differed in both groups in most conditions, suggesting the presence of nonlinear dynamics. In particular, in the control group the surrogate and the original D2 values differed in all conditions with the exception of frontal and central values for the counting forward condition. As for the patients, no differences were found in frontal, central and parietal values for the eyes closed condition or in frontal values for the eyes open condition. Accordingly, the above-listed conditions were excluded from the analysis and only the following 10 variables were considered: eyes closed (occipital), eyes open (central, parietal and occipital), counting forward (parietal and occipital) and counting backward (frontal, central, parietal and occipital).

Table 2: Antipsychotic medications taken by patients with schizophrenia enrolled in the study

Drug, active principle	No. patients	Daily dose; mean (range)* mg
Aripiprazole	4	21.2 (10–30)
Clozapine	1	100.0 (100)
Olanzapine	4	10.6 (2.5–20)
Paliperidone	1	12.0 (12)
Risperidone	6	3.3 (1.8–6)
Ziprasidone	1	120.0 (120)

*Unless only 1 patient was taking a particular medication.

Between-group analysis

The D2 values for each condition are reported in Table 3, Figure 2 and Figure 3 (individual electrodes) and in Table 4 (regions). A between-group analysis using a mixed ANOVA design was computed to investigate group differences. We observed a significant group effect ($F_{1,32} = 5.056$, $p = 0.031$; Fig. 4), with an increase of D2 values in the control group. Moreover, we observed a condition effect ($F_{9,288} = 1.401$, $p < 0.001$), with a

Table 3: Mean of correlation dimension values for each condition and group by individual electrodes

	Condition/task; mean (SD) value			
Group; electrode	Eyes closed	Eyes open	Counting forward	Counting backward
Controls				
Fp1	2.73 (0.48)	3.17 (0.55)	3.24 (0.74)	3.08 (0.59)
Fp2	2.75 (0.37)	7.00 (0.68)	3.32 (0.70)	2.86 (0.50)
F7	2.66 (0.55)	3.04 (0.66)	3.21 (0.84)	3.20 (0.58)
F3	2.68 (0.49)	3.02 (0.46)	3.17 (0.70)	3.13 (0.65)
Fz	2.67 (0.50)	2.92 (0.69)	2.97 (0.51)	2.92 (0.56)
F4	2.72 (0.49)	3.05 (0.67)	3.20 (0.63)	2.95 (0.47)
F8	2.72 (0.48)	3.03 (0.78)	3.16 (0.72)	2.91 (0.64)
T3	2.65 (0.53)	2.89 (0.72)	3.07 (0.63)	3.23 (0.68)
C3	2.60 (0.50)	2.90 (0.52)	3.18 (0.61)	3.20 (0.67)
Cz	2.59 (0.48)	2.83 (0.60)	3.06 (0.66)	3.01 (0.54)
C4	2.65 (0.46)	3.02 (0.62)	3.19 (0.66)	3.02 (0.58)
T4	2.47 (0.47)	3.11 (0.83)	3.02 (0.58)	3.07 (0.58)
P3	2.29 (0.51)	2.71 (0.64)	2.96 (0.78)	3.04 (0.68)
Pz	2.29 (0.51)	2.61 (0.63)	2.91 (0.79)	3.02 (0.71)
P4	2.26 (0.42)	2.73 (0.67)	2.86 (0.75)	2.91 (0.50)
T6	2.50 (0.76)	3.02 (1.13)	2.97 (1.12)	2.92 (0.64)
O1	2.12 (0.61)	2.71 (0.84)	2.55 (0.93)	2.66 (0.67)
O2	2.03 (0.51)	2.61 (0.68)	2.58 (0.82)	2.58 (0.43)
Global D2	2.52 (0.23)	2.92 (0.18)	3.03 (0.21)	2.98 (0.17)
Patients				
Fp1	3.18 (0.72)	3.11 (0.73)	3.23 (0.50)	3.25 (0.70)
Fp2	3.03 (0.51)	3.15 (0.72)	3.21 (0.51)	3.27 (0.54)
F7	3.09 (0.78)	3.09 (0.85)	3.23 (0.76)	2.97 (0.91)
F3	3.07 (0.53)	3.06 (0.77)	3.24 (0.48)	3.17 (0.62)
Fz	3.02 (0.60)	3.04 (0.64)	3.25 (0.52)	3.22 (0.69)
F4	3.04 (0.53)	3.04 (0.67)	3.19 (0.52)	3.14 (0.71)
F8	3.11 (0.75)	3.16 (0.81)	3.09 (0.81)	3.17 (0.90)
T3	3.00 (0.59)	3.05 (0.60)	3.12 (0.71)	3.20 (0.71)
C3	2.99 (0.40)	2.95 (0.69)	3.13 (0.53)	3.22 (0.75)
Cz	3.01 (0.47)	2.92 (0.63)	3.10 (0.50)	3.21 (0.66)
C4	2.88 (0.44)	2.91 (0.62)	2.96 (0.58)	3.20 (0.88)
T4	3.10 (0.58)	3.05 (0.78)	3.23 (0.73)	3.40 (0.85)
P3	2.66 (0.43)	2.89 (0.62)	2.99 (0.72)	3.05 (0.70)
Pz	2.62 (0.49)	2.75 (0.77)	3.01 (0.61)	3.01 (0.79)
P4	2.78 (0.46)	2.76 (0.66)	3.11 (0.63)	3.22 (0.76)
T6	3.02 (0.70)	2.77 (0.84)	2.97 (0.92)	2.68 (0.97)
O1	2.52 (0.56)	2.69 (0.85)	2.76 (0.53)	2.91 (0.83)
O2	2.81 (0.69)	2.68 (0.70)	2.80 (0.72)	3.04 (0.69)
Global D2	2.94 (0.19)	2.95 (0.16)	3.09 (0.15)	3.13 (0.16)

D2 = mean of correlation dimension; SD = standard deviation.

significant decrease of D2 values for the eyes closed compared with the active conditions (Fig. 5). To estimate the condition effect for each group, we performed the Dunnet post hoc test, comparing a single condition (reference) with all the others. We ran 2 separate tests, with the control or patient group values for

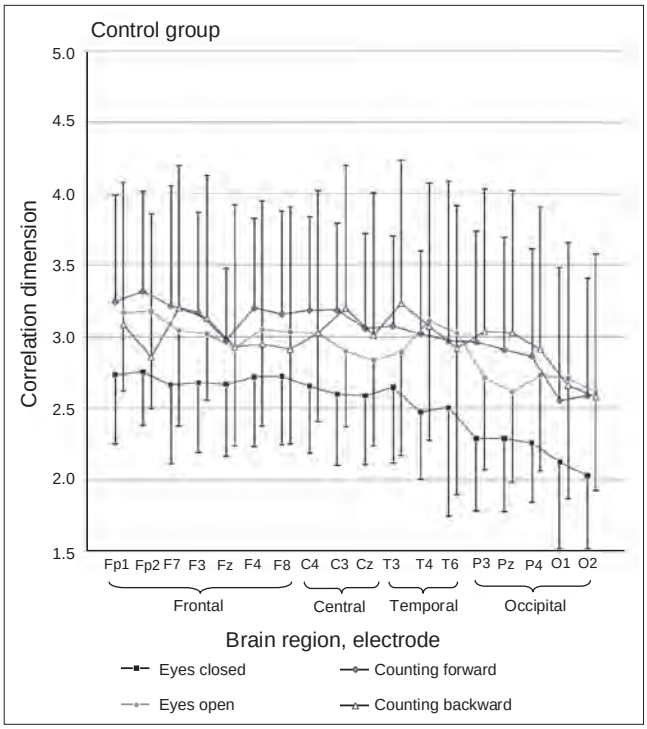

Fig. 2: Global mean of correlation dimension values for each channel and condition in the control group.

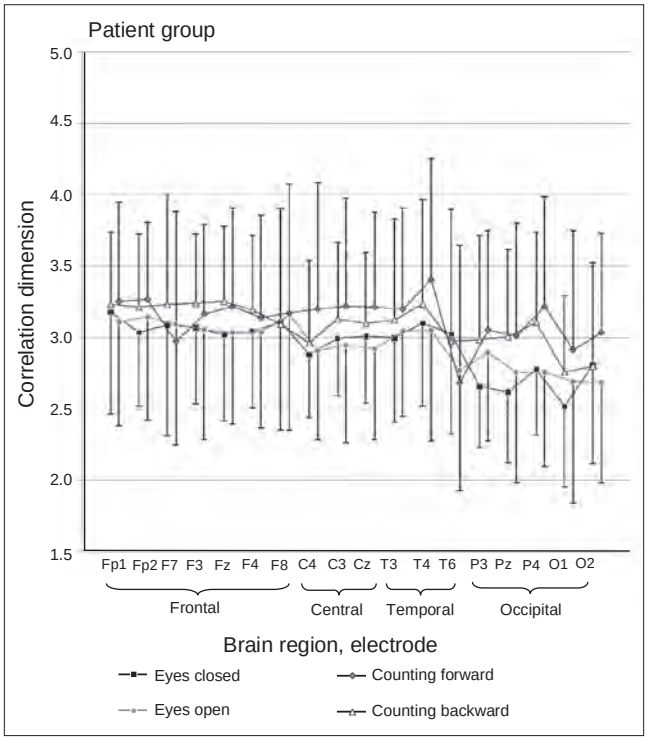

Fig. 3: Global mean of correlation dimension values for each channel and condition in the patient group.

Table 4: Mean of correlation dimension values for each condition and group by region

Group; region of electrodes	Condition/task; mean (SD) value			
	Eyes closed	Eyes open	Counting forward	Counting backward
Controls				
Frontal	2.70 (0.47)	3.06 (0.64)	3.18 (0.69)	3.01 (0.57)
Central	2.61 (0.47)	2.92 (0.57)	3.14 (0.62)	3.08 (0.62)
Temporal	2.54 (0.50)	3.01 (0.77)	3.02 (0.60)	3.07 (0.63)
Occipital	2.20 (0.51)	2.67 (0.68)	2.77 (0.81)	2.84 (0.62)
Patients				
Frontal	3.08 (0.63)	3.09 (0.73)	3.21 (0.59)	3.17 (0.72)
Central	2.96 (0.42)	2.93 (0.65)	3.06 (0.55)	3.21 (0.81)
Temporal	3.04 (0.58)	2.96 (0.68)	3.11 (0.71)	3.09 (0.78)
Occipital	2.68 (0.53)	2.76 (0.71)	2.93 (0.65)	3.05 (0.74)

SD = standard deviation.

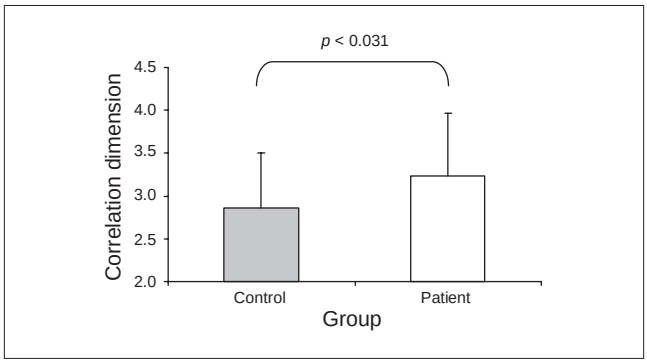

Fig. 4: Analysis of variance results for group effect. A significant increase of mean of correlation dimension values was observed in patients.

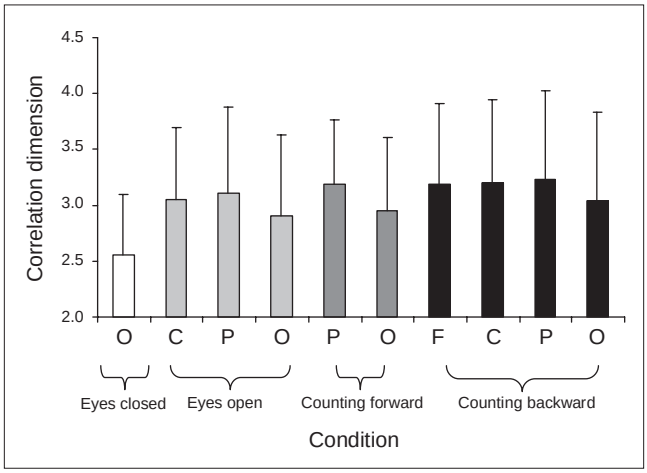

Fig. 5: Analysis of variance results for condition effect. A significant decrease of mean of correlation dimension values was observed in the eyes closed condition (occipital) compared with the active conditions. C = central; F = frontal; O = occipital; P = parietal.

the eyes closed condition as the reference. In the first test, a significant increase of D2 values was observed ($p = 0.035$ for all but 1 comparison, Fig. 6A), whereas in the second, an increase of D2 values was observed only in the comparison with controls for the eyes closed condition ($p = 0.035$, Fig. 6B).

Discussion

The primary aim of the present study was to investigate D2 in patients with schizophrenia. Recent studies have suggested that noninvasive EEG recordings can yield useful information on pathologic brain functioning. In particular, over the last few years, new nonlinear EEG analysis has been used to detect both pathologic and psychologic/physiologic changes that are not revealed by the use of conventional linear analysis. For example, several studies have reported that physiologic cognitive activities, such as mathematical tasks, induce an increase in D2 levels in healthy controls that is proportional to task complexity.[41,42] On the other hand, various studies have shown that patients with Alzheimer disease had significantly lower D2 values than age-matched healthy controls, indicating that the dynamic processes underlying EEG are less complex for patients with Alzheimer disease than for healthy controls.[19–21,29]

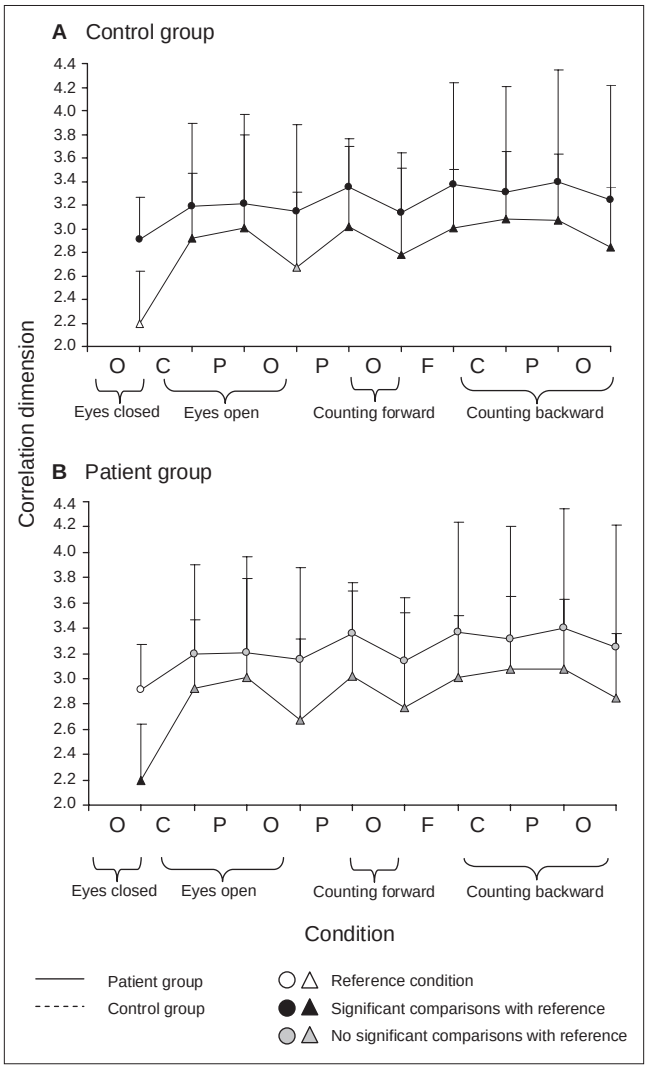

Fig. 6: Analysis of variance results, post hoc Dunnet test. In the (**A**) control group, eyes closed resulted in lower frontal values than the other conditions ($p < 0.03$), whereas in the (**B**) patient group, a significant increase of frontal values was observed only in the comparison with the same condition in the control group ($p = 0.03$). C = central; F = frontal; O = occipital; P = parietal.

In our study, we investigated patients with schizophrenia by using 2 experimental approaches: first, we assessed the effect of a cognitive task on brain dynamics and, second, we compared brain complexity of patients with schizophrenia and healthy controls. The main findings were as follows: first, brain activity was characterized by an increase of D2 values during active conditions (eyes open, counting forward and counting backward conditions) compared with baseline resting state (eyes closed condition) in healthy controls. This increase was not observed in patients with schizophrenia. Moreover, group comparison showed a global enhancement of D2 values in patients compared with controls. Furthermore, we tested the presence of nonlinear dynamics, confirming the prevalence of nonlinearity in the EEGs of healthy controls and patients with schizophrenia. This finding is in agreement with those of previous studies in which nonlinearity of EEGs in patients with schizophrenia was explored[11,43,44] and also with those of prior studies showing the presence of nonlinearity in the EEGs of patients with other diseases.[28–30]

To correctly interpret the results of the present study, the neurophysiologic meaning of D2 has to be discussed. As already mentioned, D2 can be interpreted as a measure of complexity (or flexibility) of information processing and as an index of information integration in the brain. This includes both the integration of the activity of functionally segregated neuronal groups and the integration of incoming stimuli with ongoing, spontaneous brain activity.[45] In this light, our results suggest that the increase of information processing and integration that occurred in healthy controls during active conditions and cognitive tasks is not preserved in patients with stable schizophrenia. Impaired information processing is a well-known phenomenon in populations with schizophrenia. Recently, deficits in information processing have been proposed to constitute the endophenotype of schizophrenia. It has been suggested that a breakdown in the processes that regulate the inflow of information from the environment is a core feature of the disease.[46] Successful processing of sensory inputs requires the ability to inhibit intrinsic responses to redundant or irrelevant inputs and, reciprocally, to facilitate responses to deviant, novel or salient stimuli. So our result of global increase of brain complexity in the patient group could be explained by this impairment of inhibitory processes.

The present results are difficult to compare with those of some studies of patients with schizophrenia owing to differences in experimental conditions, the algorithm chosen to calculate D2,[11] sample selection[47] and lack of control for surrogate data testing. Whereas a number of studies recruited newly onset, medication-naive and active symptomatic patients with schizophrenia,[2,23,48,49] others explored EEG

complexity in relatively chronic and less symptomatic patients who were taking medications.[10,50,51] In our study, the inclusion criteria were symptom stability for 6 months and pharmacologic treatment with antipsychotic medications. Different studies have addressed the question of whether schizophrenia can be characterized by specific changes in dynamic complexity, but the results appear to be contradictory. Koukkou and colleagues[22] found greater D2 values in patients with first-episode schizophrenia than in controls under resting-state and cognitive-task conditions on EEGs of temporoparietal regions. Elbert and colleagues[2] reported a higher dynamic complexity during the resting state in patients with schizophrenia in the frontal regions; however, in contrast to Koukkou and colleagues,[22] they found a lower dimension at central electrode locations in patients compared with healthy controls. Jeong and colleagues[10] found lower D2 values in the left inferior frontal and anterior temporal regions in the EEGs of patients with schizophrenia compared with controls in waking states. Finally, Kirsch and colleagues[23] showed that the dimensional complexity was lower in healthy controls than in patients with schizophrenia during complex cognitive tasks. It can be argued that the whole pattern of chaotic dynamics and the topographic distribution of dimensional changes cannot be properly investigated considering the EEG complexity at a limited number of electrodes. Moreover, schizophrenia is a heterogeneous disease, thus a clear and rigorous sample selection is necessary.

Our study had some strengths that should be emphasized. First, the patients included in our study were evaluated using established comprehensive tools for the assessment of psychiatric symptoms and neurocognitive functioning. Second, we investigated D2 using an extensive experimental protocol, which allowed us not only to study D2 changes in patients with schizophrenia compared with healthy controls, but also to explore the effect of cognitive activities on physiologic and pathologic brain dynamics. Third, we tested the presence of nonlinearity of our data. Moreover, a recording with an 19-lead EEG allowed us to investigate a more complete pattern of chaotic brain dynamics than studies conducted with a limited number of electrodes (1–16 electrodes in the studies by Elbert and colleagues,[2] Jeong and colleagues,[10] Koukkou and colleagues[22] and Kirsch and colleagues[23]).

Limitations

Some limitations of the present study should be acknowledged. First, we studied a relatively small sample. Second, all patients with schizophrenia were being treated with antipsychotic medications, with a mean of 212 (SD 112) CPZ equivalent doses. Although there was no correlation between D2 and antipsychotic treatment, consistent with findings of Itil and colleagues,[52] who also reported no effect of medication on EEG activities in patients with schizophrenia, we cannot completely exclude the presence of medication effects. It is tempting to speculate that the observed patterns in patients with schizophrenia might be related to the psychotic processes. However, future studies, preferably conducted in larger patient samples, comparing treated and untreated patients have to be conducted to exclude a possible medication effect.

Conclusion

On the whole, the results of our study suggested that the D2 increase observed in healthy controls when switching from resting to active states, including cognitive tasks, was not preserved in a sample of patients with stable schizophrenia. Moreover, a general increase of brain complexity was observed in the patients with schizophrenia. Those results could be interpreted as an indicator of the information processing deficits that occur in these patients. From a methodologic point of view, our findings suggest that D2 analysis can be used to enrich the set of approaches to analyze EEGs in individuals with pathologic conditions.

Competing interests: None declared.

Contributors: A. Pollo, F. Benedetti and P. Rocca designed the study. E. Carlino, M. Sigaudo, T. Mongini, F. Castagna and S. Vighetti acquired the data. E. Carlino and M. Sigaudo analyzed the data. E. Carlino, M. Sigaudo and A. Pollo wrote the article. F. Benedetti, T. Mongini, F. Castagna, S. Vighetti and P. Rocca reviewed the article. All authors approved its publication.

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