Increased determinism in brain electrical activity occurs in association with multiple sclerosis

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Objective: Increased determinism (decreased complexity) of brain electrical activity has been associated with some brain diseases. Our objective was to determine whether a similar association occurred for multiple sclerosis (MS).

Methods: Ten subjects with a relapsing–remitting course of MS who were in remission were studied; the controls were age- and gender-matched clinically normal subjects. Recurrence plots were calculated using representative electroencephalogram (EEG) epochs (1–7 seconds) from six derivations; the plots were quantified using the nonlinear variables percent recurrence (%R) and percent determinism (%D). The results were averaged over all derivations for each participant, and the means were compared between the groups. As a linear control procedure the groups were also compared using spectral analysis.

Results: The mean $\pm$ SD of %R for the MS subjects was $6.6 \pm 1.3\%$, compared with $5.1 \pm 1.3\%$ in the normal group ($P=0.017$), indicating that brain activity in the subjects with MS was less complex, as hypothesized. The groups were not distinguishable using %D or spectral analysis.

Discussion: Taken together with our earlier report that %R could be used to discriminate between MS and normal subjects based on the ability to exhibit evoked potentials, the evidence suggests that complexity analysis of the EEG has potential for development as a diagnostic test for MS.

Keywords: Complexity, Multiple sclerosis, Nonlinear modeling, Phase space, Recurrence plot, Recurrence quantification analysis

Introduction

Multiple sclerosis (MS) has commonly been regarded as an immune-mediated disease of the human central nervous system, but recent reports revealed significant gray-matter involvement, indicating that MS affects the whole brain.[1] Cognitive activity, which is mediated by temporal–spatial electrical interactions among brain networks, is also a process that emerges at the organ level.[2] In principle, analysis of the electroencephalogram (EEG) could provide the basis of a functional method for detecting organ-level changes in brain activity associated with MS, even before disease-related changes were detectable by imaging of brain structure.

Traditional electrophysiological methods such as time averaging or spectral analysis were designed to evaluate specific neural pathways. These methods are not well suited for studying brain electrical states occurring during cognitive processing, because brain states change profoundly from moment to moment under the influence of nonlinear dynamical laws.[3] Methods developed to study nonlinear physical systems are potentially useful for extracting information encoded in the EEG but not recognized using traditional methods.[4] Recurrence quantification analysis (RQA) is a particularly promising approach.[5,6] It has been used to describe sleep levels,[7] predict the onset of an epileptic seizure,[8,9] infer the existence of previously unrecognized human sensory capability,[5] quantify the depth of anesthesia,[10] and analyze functional magnetic resonance images of the brain.[11]

Using RQA, we previously demonstrated an association between MS and changes in the onset evoked potential triggered by magnetic stimuli.[12] Here, we were interested in the possibility of an association between baseline EEG and the presence of MS. We compared EEGs from subjects having MS with EEGs from clinically normal age- and gender-matched subjects to ascertain whether baseline brain activity could be statistically distinguished between the two groups.

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Methods

Subjects

Subjects with MS were recruited from an outpatient neurology clinic. Inclusion criteria were: definite MS[13] with a relapsing–remitting course, but in remission; expanded disability status scale score $\leqslant 3.0$;[14] absence of acute relapses and intravenous corticosteroid treatment for at least 60 days before inclusion in the study; no changes of expanded disability status scale score for at least 3 months prior to inclusion in the study; no other neurological disease. The criteria resulted in the identification of 10 subjects who volunteered to participate in the study, all of whom were females. Their average age was 33 years (range 18–52 years), and all were being treated with beta-interferons or glatiramer acetate. The subjects in the control group were recruited from the general population; the group consisted of 10 gender- and age-matched females who had no medical complaints (average age 34 years, range 24–53 years). Written informed consent was obtained from each participant. The institutional review board at the Louisiana State University Health Sciences Center approved all experimental procedures.

EEG measurements

EEGs were recorded continuously for 10 minutes from O_1, O_2, C_3, C_4, P_3, and P_4 (international 10–20 system) referenced to linked ears, using gold-plated electrodes attached to the scalp with conductive paste; electrode impedances were less than 10 kΩ. During recording of the EEG the subjects sat in a darkened room on a comfortable chair with their eyes closed. The signals were amplified (Nihon Kohden, Irvine, CA), analog-filtered to pass 0.5–35 Hz, sampled at 300 Hz using a 12-bit analog-to-digital converter (National Instruments, Austin, TX), and analyzed offline.

Representative artifact-free epochs were selected randomly from each signal, digitally filtered between 0.5 and 35 Hz, and then analyzed using RQA and spectral analysis. The process was repeated for epoch lengths of 1–7 seconds in steps of 1 second to evaluate the role of epoch length. The overall results did not depend on epoch length; consequently, the results obtained using 2-second epochs are presented here.

Recurrence quantification analysis

Our approach was based on the theory that the EEG signal is an instantaneous sum of axonally and electrotonically propagating contributions from numerous neuronal networks, each of which exhibits intra- and inter-network interactions.[15] By hypothesis, some networks were affected by the presence of disease resulting in dynamical changes in their contributions to the signal recorded on the scalp; we used RQA to detect the putative changes.

Each of the selected 2-second epochs was embedded in a five-dimensional phase space with a time delay of 5 points (17 milliseconds).[16] The embedding parameters were arrived at empirically, because there was no evidence that the methods used in connection with the analysis of nonlinear mathematical equations[17] were applicable to the EEG. The parameters were initially determined on the basis of modeling studies in which fully deterministic linear and nonlinear signals (signals generated by mathematical equations) having the same power spectrum as the EEG were added to baseline EEGs, and the ability of RQA to detect the added signals was studied as a function of the embedding parameters.[18] The optimal conditions thus identified were employed in stimulus–response studies involving animal and human subjects and shown to be effective for detecting stimulus-induced changes in the EEG.[5,12]

A recurrence plot was produced for each epoch by plotting a point in two-dimensions at the location addressed by (i,j), whenever the ith and jth state vectors were near.[19] Two states were defined as near, if they were within 15% of the maximum Euclidean distance between any two states. The plots were quantified using the RQA variables percent recurrence (%R) and percent determinism (%D).[20] RQA can be used to quantify any kind of determinism in a signal, whether linear or nonlinear; the method does not require that the signal be stationary.[6] %R was defined as the number of points in the plot divided by the total number of point locations (places where a point could have been placed); the variable expresses the amount of law-governed activity in a signal in the sense that higher values are interpreted to mean more determinism (less noise). %D was defined as the percentage of points in the plot that formed diagonal lines (defined as $\geqslant 20$ adjacent points, on the basis of preliminary studies). Adjacent diagonal points in a recurrence plot correspond to successive states of the system in phase space; successive states are assumed to have occurred as the result of a deterministic law. In this sense, therefore, %D is also a measure of the amount of the law-governed activity in a signal. Although the two variables are formally related (only a recurrent point can count towards %D), for statistical purposes we treated them as equally relevant and mutually independent variables (see below). Other recurrence variables have been defined[20] but were not employed here, because their use provided no benefit beyond that realized using %R and %D. RQA variables are only relative measures of determinism, because their numerical values depend on the choices of embedding and other parameters.

For each subject the mean values of %R and %D from each derivation (50 epochs/signal) were computed

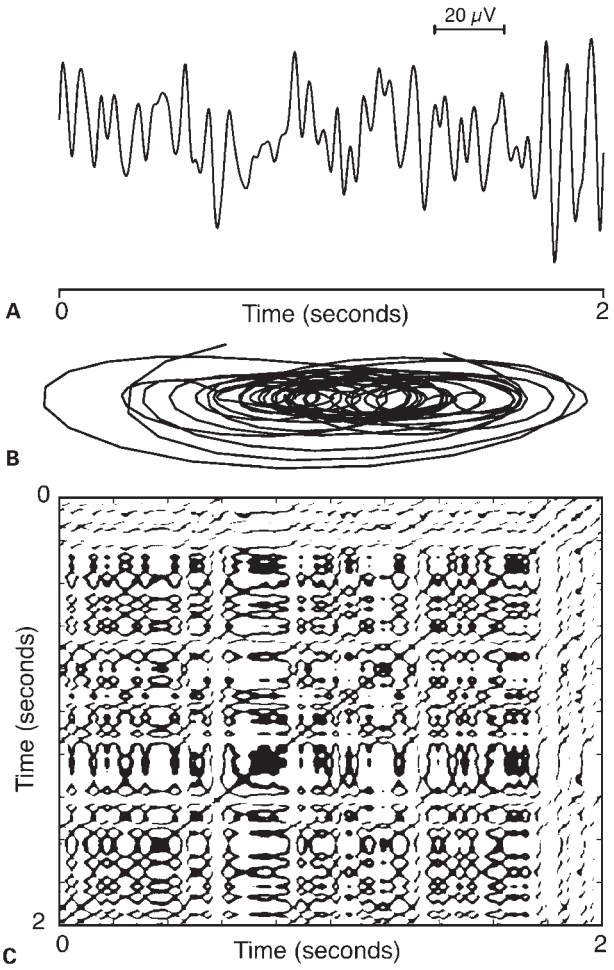

Figure 1 RQA analyses of a representative EEG. (A) Two-second EEG epoch. (B) Two-dimensional projections from the trajectory of the system in phase space. (C) Recurrence plot for the system. %R=5.8%; %D=41.2%.

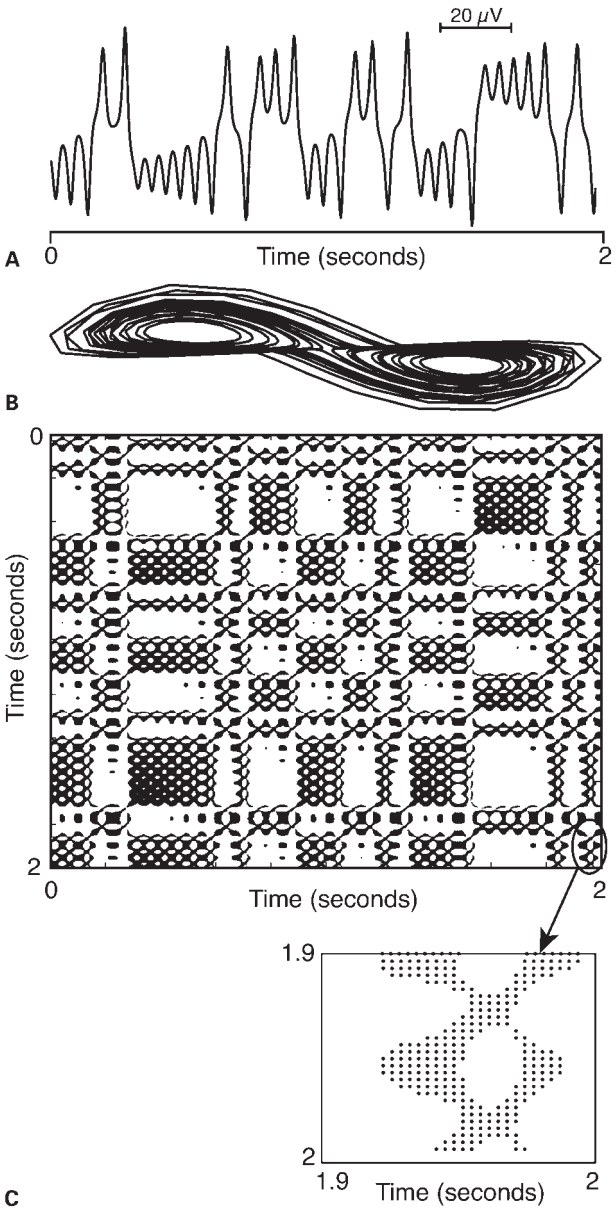

Figure 2 RQA analyses of a representative Lorenz solution. (A) Two-second epochs from a solution. (B) Two-dimensional projection from the trajectory of the system in phase space. (C) Recurrence plot for the system. The basic point structure of a plot is shown in the expanded-scale insert. %R=7.7%; %D=49.7%.

and averaged across all six derivations to form the grand means, which were used in the planned comparisons. The MS and control groups were compared using the Mann–Whitney *U* test at a significance level of $P<0.025$, because we planned to conclude that the groups differed if a statistical difference was found using either %R or %D (Bonferroni procedure).

As a control procedure, the data were also analyzed by spectral analysis. The relative power in 0.5–7, 8–12, 13–20, and 21–35 Hz was computed for each epoch and the grand means were formed and compared between groups at $P=0.0125$ (Bonferroni).

Modeling

To help provide an intuitive basis for understanding the ability of recurrence plots to reveal the presence of deterministic activity, we computed plots for solutions of the Lorenz equations at a time scale that resulted in signals having power spectra similar to those of EEGs.[21] The Lorenz equations (originally developed to explain atmospheric processes in terms of a particular model) are a completely law-governed noiseless unitary system (no interacting subsystems); consequently, every recurrent point in a plot from a Lorenz solution is so by necessity. A solution consists of a time-dependent signal that represents a particular variable, temperature for example. It can be shown that the effect of all atmospheric variables considered in the model can be extracted from any given solution.

Results

Although the EEGs were nonperiodic (Fig. 1A), they contained law-governed activity as evidenced by their phase-space appearance, which typically was a recognizable trajectory rather than a random distribution of points (Fig. 1B). The corresponding recurrence plots similarly revealed patterns (Fig. 1C), further indicating that the trajectory was at least

partially deterministic. Mathematically, certain signals from the Lorenz equations also appeared irregular in time (Fig. 2A), but exhibited more pronounced patterns in phase space (Fig. 2B) and in the corresponding recurrence plots (Fig. 2C).

For each subject, recurrence plots were computed for fifty 2-second EEG epochs from each of six derivations, quantified using %R and %D, and the individual values were averaged to form a mean that characterized the subject's EEG (Table 1). The grand mean $\pm$ SD of %R for the subjects with MS was $6.6 \pm 1.3\%$, compared with $5.1 \pm 1.3\%$ in the normal group ($P=0.017$). The corresponding grand-mean values for %D were $40.5 \pm 4.9\%$ and $35.2 \pm 6.6\%$ ($P=0.089$).

Similar results for %R and %D were found using epoch lengths of 1 second and 3–7 seconds in steps of 1 second, indicating that the ability of the analysis to discriminate between groups did not depend on the length of the epoch chosen for analysis (data not presented).

Spectral analysis yielded no evidence of intergroup differences in power in any of the frequency bands studied (Table 2).

Discussion

We used RQA to explore whether the tendency of brain electrical activity to follow unknown, but certain laws was altered in subjects with MS. The potential advantage of RQA was its ability to detect determinism (law-governed activity) in a signal, even when the signal appeared random when viewed in the time domain (Fig. 2). Previously reported links between increased determinism (in our method, higher values of %R, %D, or both) and disease included increased regularity of EEGs in subjects with Alzheimer's disease,[22,23] more rigid postural instability in subjects with Parkinson's disease,[24] and increased determinism during the seizure-onset period in subjects with epilepsy.[9] We therefore expected an increase in one or both of the recurrence variables.

On average, %R was greater ($P=0.017$) in subjects with MS (Table 1). The groups did not differ significantly using %D, indicating that, for unknown reasons, not all RQA variables are sensitive to the presence of the disease. No evidence of an intergroup difference was found by comparing the relative power in the standard frequency bands (Table 2); this result supported an interpretation that the effect on %R stemmed from a difference in the amount of nonlinear determinism.

There is general agreement that the various RQA variables each capture something unique about the dynamical activity of the system, but exactly what these differences might be is unknown at both the theoretical and empirical levels for all biological signals. Consequently, rationalizing observations of intergroup differences are possible, but predicting which RQA variable will be optimally sensitive to the effect of the factor of interest (here, MS), or why, is presently not possible.

In sum, the implication from previous reports that brain electrical activity associated with disease states exhibited more deterministic dynamical patterns also includes subjects with MS, as ascertained using %R (Table 1). Taken together with the absence of an effect when a linear analytical method was used (Table 2), the results suggest (but do not prove) that the dynamical determinism associated with MS was nonlinear.

To provide an initial estimate of the reliability of RQA for diagnosing MS, we used the midpoints of the distributions of the individual mean values of %R and %D to evaluate sensitivity and specificity (%R=5.8%, %D=37.5%). Only two subjects had a %R lower than the midpoint (MS1 and MS8), indicating two false-negative results, and two controls had values above the midpoint (N4 and N6), indicating two false-positive results. Thus the sensitivity and specificity were each 80%, which is a promising result considering the preliminary nature of the study. The results were essentially the same, when the midpoint between the means of the %D values of the two groups was chosen as the basis of the decision regarding diagnosis. These reliability

Table 1 Evaluation of electroencephalograms using recurrence quantification analysis

Subject	%R	%D	Subject	%R	%D
MS1	5.4	34.7	N1	4.6	34.9
MS2	6.6	45.9	N2	3.9	28.0
MS3	8.7	43.3	N3	4.9	34.8
MS4	5.8	41.9	N4	7.6	47.0
MS5	8.1	46.2	N5	3.9	33.0
MS6	6.2	34.3	N6	7.3	41.2
MS7	8.0	43.5	N7	4.8	37.0
MS8	4.7	33.6	N8	4.1	24.0
MS9	6.2	43.6	N9	5.7	39.7
MS10	6.3	37.9	N10	4.4	32.3
	*6.6 $\pm$ 1.3	**40.5 $\pm$ 4.9		5.1 $\pm$ 1.3	35.2 $\pm$ 6.6

Note: Percent recurrence (%R) and percent determinism (%D) in the electroencephalograms of 10 subjects with multiple sclerosis (MS1–MS10) and 10 normal control subjects (N1–N10). Mean $\pm$ SD for O, C, and *P* derivations. *$P=0.017$ compared with controls. ** $P=0.089$ compared with controls.

Table 2 Evaluation of electroencephalograms using spectral analysis

	0.5–7 Hz	8–12 Hz	13–20 Hz	21–35 Hz
Multiple sclerosis	50.4 $\pm$ 19.7	29.4 $\pm$ 20.3	11.6 $\pm$ 6.3	4.4 $\pm$ 2.2
Controls	60.3 $\pm$ 15.6	26.0 $\pm$ 13.7	7.1 $\pm$ 3.5	3.3 $\pm$ 2.2
P	0.140	0.639	0.095	0.339

Note: Relative power in four frequency intervals compared between 10 subjects with multiple sclerosis and 10 clinically normal subjects. Mean $\pm$ SD for O, C, and *P* derivations.

observations presently have only limited value, because increased recurrence correlates with brain disease in general, not specifically with MS. Nevertheless, the results suggest the possibility that either or both RQA variables could be developed for practical use. For example, baseline %R and %D might be used with measurements of evoked potentials to form a discriminant metric to confirm a diagnosis of MS.[12]

Lack of a mechanistic relationship between RQA variables and the relevant physiological change is a drawback to the use of RQA. For example, the diagnosis of osteoporosis is based on a measurement of bone mineral density, and the link between decreased mineral density and increased risk for bone fracture is intuitively obvious. In contrast, RQA provides a measure of the self-organizing tendency of the brain in which the development of abnormal activity (disease) is reflected in an increase of order (decrease of complexity), not in a change of an intrinsic structural property like mineral density. Although complexity measures are not traditional physiological variables, they hold considerable promise for use as the basis of a functional test for MS that can be validated empirically, independently of the validity of any reference model.

References

1 Minagar A. Gray matter involvement in multiple sclerosis: a new window into pathogenesis. J Neuroimaging. 2003;13:291–2.
2 Gazzaniga MS. The new cognitive neurosciences. Cambridge: MIT Press; 2000.
3 Rubinov M, Sporns O, van Leeuwen C, Breakspear M. Symbiotic relationship between brain structure and dynamics. BMC Neurosci. 2009;10:55.
4 Pritchard WS, Duke DW. Measuring chaos in the brain: a tutorial review of nonlinear dynamical EEG analysis. Int J Neurosci. 1992;67:31–80.
5 Carrubba S, Frilot C, Chesson AL Jr, Marino AA. Evidence of a nonlinear human magnetic sense. Neuroscience. 2007;144:356–67.
6 Zbilut JP, Webber CL Jr. Recurrence quantification analysis. In: Akay M, editor. Wiley encyclopedia of biomedical engineering. Hoboken: John Wiley & Sons; 2006. p. 2979–86.
7 Song IH, Lee DS, Kim SI. Recurrence quantification analysis of sleep electroencephalogram in sleep apnea syndrome in humans. Neurosci Lett. 2004;366:148–53.
8 Ouyang G, Li X, Dang C, Richards DA. Using recurrence plot for determinism analysis of EEG recordings in genetic absence epilepsy rats. Clin Neurophysiol. 2008;119:1747–55.
9 Schindler K, Gast H, Stieglitz L, Stibal A, Hauf M, Wiest R, *et al*. Forbidden ordinal patterns of periictal intracranial EEG indicate deterministic dynamics in human epileptic seizures. Epilepsia. 2011;52:1771–80.
10 Li X, Sleigh JW, Voss LJ, Ouyang G. Measure of the electroencephalographic effects of sevoflurane using recurrence dynamics. Neurosci Lett. 2007;424:47–50.
11 Bianciardi M, Sirabella P, Hagberg GE, Giuliani A, Zbilut JP, Colosimo A. Model-free analysis of brain fMRI data by recurrence quantification. NeuroImage. 2007;37:489–503.
12 Carrubba S, Minagar A, Gonzalez-Toledo E, Chesson AL Jr, Frilot II C, Marino AA. Multiple sclerosis impairs ability to detect abrupt appearance of a subliminal stimulus. Neurol Res. 2010;32:297–302.
13 McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121–7.
14 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444–52.
15 Ioannides AA. Dynamic functional connectivity. Curr Opin Neurobiol. 2007;17:161–70.
16 Jeong J, Chae J-H, Kim SY, Han S-H. Nonlinear dynamic analysis of the EEG in patients with Alzheimer's disease and vascular dementia. J Clin Neurophysiol. 2001;18:58–67.
17 Abarbanel HD. Nonlinear systems. In: Trigg GL, editor. Encyclopedia of applied physics. New York: VCH Publishers; 1994. p. 417–39.
18 Carrubba S, Frilot C, Chesson A, Marino A. Detection of nonlinear event-related potentials. J Neurosci Meth. 2006;157:39–47.
19 Eckmann J-P, Kamphorst SO, Ruelle D. Recurrence plots of dynamical systems. Europhysics Lett. 1987;4:973–9.
20 Webber CL Jr, Zbilut JP. Dynamical assessment of physiological systems and states using recurrence plot strategies. J Appl Physiol. 1994;76:965–73.
21 Lorenz EN. Deterministic, nonperiodic flow. J Atmos Sci. 1963;20:130–41.
22 Hornero R, Abásolo D, Escudero J, Gómez C. Nonlinear analysis of electroencephalogram and magnetoencephalogram recordings in patients with Alzheimer's disease. Philos Transact A Math Phys Engl Sci. 2009;367:317–36.
23 Jeong J. EEG dynamics in patients with Alzheimer's disease. Clin Neurophysiol 2004;115:1490–505.
24 Schmit JM, Riley MA, Dalvi A, Sahay A, Shear PK, Shockley KD, *et al*. Deterministic center of pressure patterns characterize postural instability in Parkinson's disease. Exp Brain Res. 2006;168:357–67.