Brief Communication

Linear and non-linear EEG analyses before and after psychosis in patients with epilepsy

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Abstract

To investigate the linearity and nonlinearity of EEGs before and after psychosis in patients with epilepsy, continuous EEGs before and after psychosis of five patients who developed epileptic psychosis were examined. The continuous EEGs of eight patients without psychosis were used as controls. EEGs were analyzed by Fourier transform for the frequency bands of delta, theta, alpha, and beta as linear indices and by Sample entropy (SampEn) as a nonlinear index. Significant changes were seen in SampEn before vs after psychosis at bilateral frontal and frontal-anterior temporal regions. Significant differences in SampEn between the before psychosis group and the control group were found at the right frontal and frontal-anterior temporal regions. In patients with epilepsy, SampEn may not only decrease in the right frontal and frontal-anterior temporal regions before psychosis, but it may also increase in the frontal and frontal-temporal regions during psychosis. EEG complexity may be useful to investigate the pathophysiological association between epilepsy and psychosis.

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Introduction

The prevalence of psychosis in patients with epilepsy is approximately 5.6%, about 8 times that in the normal population [1]. Psychosis develops 14.4 years after onset of epilepsy [2], and one of the risk factors for psychosis is a higher seizure frequency [3].

An electroencephalogram (EEG) is a useful tool for research in epilepsy [4, 5]. The methods for investigating EEG as discrete signals include linear and nonlinear approaches. The class of linear systems is defined by the principle of superposition. If $y_1[n]$ and $y_2[n]$ are the responses of a system when $x_1[n]$ and $x_2[n]$ are the respective inputs, then the system is linear. The two properties comprise the principle of superposition; the first property is the additive property, and the second is the homogeneity or the scaling property, stated as $T\{ax_1[n]+bx_2[n]\}=aT\{x_1[n]\}+bT\{x_2[n]\}$ for arbitrary constants a and b . Linear analysis includes Fourier transform and wavelet transform [6]. None of the above properties apply to a nonlinear system. The nonlinear dynamic system has been developed using differential equations in the active field of mathematical research called ‘deterministic chaos’. The signal can display chaotic behavior; that is, the behavior can become unpredictable for relatively long periods and may be an expression of chaotic behavior [7]. Entropy, as it relates to nonlinear dynamical systems, is the rate of information production. Methods for estimating the entropy of a system represented by a time series are not, however, well suited to analysis of short and noisy data sets encountered in cardiovascular and other biological studies. Pincus introduced approximate entropy (ApEn), a set of measures of

system complexity closely related to entropy, which is easily applied to clinical cardiovascular and other time series. ApEn statistics, however, lead to inconsistent results. First, ApEn is heavily dependent on the record length and is uniformly lower than expected for short records. Second, it lacks relative consistency. Richman and Moorman [8] developed a new and related complexity measure, sample entropy (SampEn). SampEn agreed with theory much more closely than ApEn over a broad range of conditions. The improved accuracy of SampEn statistics should make them useful in the study of experimental clinical biological time series.

Therefore, in this study, assuming that persistent psychotic symptoms in patients with epilepsy are reflected in the EEG, continuous EEG sets of patients with epileptic psychosis were examined and compared before and after psychosis by linear and nonlinear EEG analyses.

Materials and Methods

Subjects

Of the 260 patients visiting our department between August 2017 and June 2018, seven who developed interictal psychosis fulfilled ICD10 code F068, without intellectual disability, alcohol dependence, or neurodegenerative disease [9]. Of these seven, one had no EEG before onset, and one was excluded due to the diagnosis of drug-induced psychosis. EEGs were examined several times at different intervals at Nagoya City University Hospital and were divided into a group before psychosis and a group after psychosis (Table 1). Three of the five patients had been prescribed levetiracetam (LEV) before psychosis

Table 1. Demographic and clinical data of the psychosis and control groups.

	Patients with psychosis (n=5)	Patients without psychosis (n=8)
Male/female	2/3	4/4
Age at onset of epilepsy (y) * ¹	8.8 (14.2)	15.5 (3.8)
Birth asphyxia	0/5	1/8
Febrile convulsion	2/5	2/8
Focal epilepsy	5/5	8/8
Age at onset of psychosis (y) * ¹	35.0 (16.5)	
Age at first EEG (y)* ^{1,2}	30.8 (17.1)	31.9 (11.4)
Age at final EEG (y)* ^{1,2}	36.2 (16.5)	37.5 (13.6)
Number of EEGs before psychosis* ³	10	16
Number of EEGs after psychosis* ⁴	15	13
Analyzed EEG segments (sec/recording) * ¹	92.0 (42.6)	60.3(17.2)
EEG focus right/left	2/3	3/2* ⁵
Number of AEDs* ⁶		
LEV	0 (3)	0 (6)
CBZ	4 (3)	5 (4)
PHT	1 (1)	4(2)
PB	1 (1)	0 (0)
GBP	1 (0)	0 (0)
VPA	0 (1)	2 (1)
PRM	0 (0)	1 (0)
ZNS	0 (0)	3 (1)
TPM	0 (0)	3 (2)
LTG	0 (0)	1 (2)
CLB	0 (1)	2 (1)
Seizure type* ⁷		
Cognitive	0	1
Emotional	1	0
Automatisms	1	2
Behavioral arrest	0	2
Hyperkinetic	2	0
Clonic	1	0
Focal to bilateral tonic clonic	4	5
Seizure frequency* ⁷		
None	1	1
Week	1	1
Month	3	3
Year	3	3

*¹ Data are expressed as mean (SD). *² Age at the first EEG analyzed and at the final EEG analyzed with the criteria in the methods section. *³ In the control group, the number of EEGs before LEV. *⁴ In the control group, the number of EEGs after LEV. *⁵ n = 3, unknown. *⁶ The number of AEDs in the before (after) psychosis group and control before LEV (after LEV) group. *⁷ Multiple answers. LEV, levetiracetam; CBZ, carbamazepine; PHT, phenytoin; PB, phenobarbital; GBP, gabapentin; VPA, valproate; PRM, primidone; ZNS, zonisamide; TPM, topiramate; LTG, lamotrigine; CLB, clobazam

(median duration: 23 months). Two patients were on monotherapy; phenytoin (PHT) in one and carbamazepine (CBZ) in the other. For this reason, a control group comprising eight patients, six on LEV and two on either PHT or CBZ monotherapy, was selected among the 260 patients, using the same exclusion criteria as the psychosis group. They were not diagnosed with any psychiatric disorder. EEGs of the control group were divided into those without LEV (control before LEV group) and those with LEV (control after LEV group) (Table 1). The psychotic symptoms and seizure types and frequencies were confirmed retrospectively from the medical charts. Four patients were diagnosed with schizophrenia, and one was diagnosed with a brief psychotic disorder (DSM-5) [10]. All patients had their first episode of psychosis. The symptoms of the patients with psychosis were auditory hallucinations and persecutory delusions. The epilepsy syndrome classification and seizure classification 2017 were used [11, 12].

EEG analysis

EEGs were recorded at a sampling frequency of 500 Hz and a time constant of 0.1 with a 60-Hz low-pass filter by the international 10-20 method with reference electrodes on both earlobes. EEG recording was performed in a shielded room at a constant temperature. The selection criteria for the continuous EEGs were as follows. (1) The seizure frequency at the time of EEG recording was unchanged before and after psychosis or LEV, because achieving a seizure-free state after psychosis or LEV would affect EEG complexity. If a seizure-free state was achieved

before psychosis or LEV, then a seizure-free state was also required at the time of EEG recording after psychosis or LEV. Seizure-free was defined as being seizure-free for at least one year at the time of EEG recording. (2) The psychotic symptoms in the psychosis group persisted despite antipsychotic treatment at the time of all EEG recordings. (3) The resting eye-closed and awake EEG showed no paroxysmal abnormalities including epileptic discharges and no motion or muscle artifacts. Consecutive EEGs satisfying these criteria were used for the linear and nonlinear analyses. At least 10-second fragments of each EEG were selected by a certified physician of the Japanese Society of Clinical Neurophysiology, confirming that there was no artifact contamination by unipolar montage. The selected EEG strips were then analyzed offline with a 16-lead longitudinal bipolar montage (1. Fp1-F7, 2. F7-T3, 3. T3-T5, 4. Fp1-F3, 5. F3-C3, 6. C3-P5, 7. P5-O1, 8. Fz-Cz, 9. Cz-Pz, 10. Fp2-F4, 11. F4-C4, 12. C4-P4, 13. P4-O2, 14. Fp2-F8, 15. F8-T4, 16. T4-T6). Each 16-lead EEG was standardized. EEG power values, performed as a linear analysis, were calculated by short time Fourier transform for each frequency band: delta (<4 Hz), theta (4-7 Hz), alpha (8-13 Hz), and beta (14-30 Hz) with 512 non-overlapped points using the Hamming window. Sample entropy (SampEn), performed as a nonlinear analysis, was calculated using the Physionet open source algorithm [13, 14]. A lower value of SampEn indicates greater self-similarity and regularity and lower complexity in the time series. The parameters of SampEn (N, m, r) were set at $r = 0.2$ and $m = 2$. N was at least 5000 points per EEG frag-

ment. The details of the calculation of SampEn are shown in the Supporting information (Appendix). This research was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the Ethics Committee of the Nagoya City University Medical School Ethics Committee, and written informed consent was obtained from each patient.

Statistical analysis

The within-group analyses (before vs after) for the psychosis and control groups were conducted using the Wilcoxon rank-sum test, because the Wilcoxon signed-rank test requires the same number of samples before and after. Significance was defined as $p < 0.0003$ ($= 0.05/16/5/2$; Bonferroni correction). When significant regions were found in the within-group analysis, each region was examined by between-group comparison (psychosis vs control) using the Wilcoxon rank-sum test.

Results

Demographic and clinical data of each group

The demographic and clinical data of the patients are shown in Table 1. Brain MRI and blood biochemical examinations showed no particular findings.

Comparison of before ($n = 10$) vs after psychosis ($n = 15$) groups

When EEGs recorded before and after psychosis were compared, significant differences were observed at bilateral frontal and frontal-anterior temporal and right frontal-central

regions (1. Fp1-F7, 4. Fp1-F3, 10. Fp2-F4, 11. F4-C4, 14. Fp2-F8) (Figure 1 and Table 2). Power spectrum analysis detected no region with significant difference at all frequencies (Table 2).

Comparison of control before LEV ($n = 16$) vs after LEV ($n = 13$) groups

SampEn and power spectrum analysis detected no significant difference in the comparisons between before and after LEV control groups.

Comparison of psychosis vs control groups

The five regions with significant differences before and after psychosis were compared among four groups as follows: before and after psychosis groups vs. control before and after LEV groups [significant difference set at $p < 0.003$ ($= 0.05/5/4$; Bonferroni correction)]. In the before psychosis group vs control before LEV group comparison, the right frontal-anterior temporal region (14. Fp2-F8) and frontal region (10. Fp2-F4) were significantly different ($p < 0.0001$ and $p = 0.002$, respectively). In the before psychosis group vs control after LEV group comparison, the right frontal-anterior temporal region (14. Fp2-F8) and frontal region (10. Fp2-F4) were significantly different ($p = 0.001$ and $p = 0.002$, respectively). In the after psychosis group vs control before or after LEV group comparison, there was no significant difference.

Discussion

Higher SampEn has been reported to be a result of seizure control [5, 15] and acute-phase schizophrenia [16]. Since patients in

Table 2. Comparisons of the average (standard deviation) SampEn and EEG power values (μV^2) in each frequency domain (alpha, beta, theta, and delta bands) between the before and after psychosis groups

EEG region	SampEn			Alpha			Theta			Delta			Beta		
	Before	After	P value	Before	After	P value	Before	After	P value	Before	After	P value	Before	After	P value
1.Fp1-F7	0.50(0.08)	0.84(0.12)	<0.0001 ¹	0.69(0.10)	0.68(0.22)	0.24	0.67(0.16)	0.65(0.16)	0.98	0.64(0.19)	0.63(0.12)	0.98	0.05(0.03)	0.09(0.05)	0.02
2.F7-T3	0.54(0.10)	0.69(0.14)	0.02	0.68(0.15)	0.64(0.16)	0.58	0.64(0.13)	0.62(0.16)	0.84	0.64(0.16)	0.62(0.15)	0.98	0.07(0.02)	0.08(0.04)	0.70
3.T3-T5	0.61(0.19)	0.68(0.19)	0.42	0.68(0.12)	0.59(0.12)	0.17	0.64(0.09)	0.69(0.14)	0.25	0.61(0.14)	0.72(0.12)	0.04	0.08(0.05)	0.10(0.05)	0.25
4.Fp1-F3	0.63(0.11)	0.95(0.13)	<0.0001 ¹	0.64(0.11)	0.63(0.16)	0.88	0.63(0.12)	0.68(0.19)	0.70	0.64(0.13)	0.69(0.13)	0.58	0.09(0.03)	0.11(0.07)	0.75
5.F3-C3	0.59(0.10)	0.76(0.14)	0.002	0.66(0.11)	0.64(0.10)	0.79	0.67(0.17)	0.66(0.13)	0.99	0.65(0.14)	0.66(0.14)	0.93	0.11(0.03)	0.13(0.05)	0.25
6.C3-P5	0.52(0.08)	0.61(0.09)	0.03	0.71(0.10)	0.61(0.13)	0.19	0.69(0.16)	0.70(0.17)	0.46	0.62(0.13)	0.69(0.13)	0.02	0.09(0.05)	0.13(0.06)	0.10
7.P5-O1	0.50(0.08)	0.53(0.09)	0.36	0.70(0.13)	0.57(0.15)	0.04	0.69(0.12)	0.64(0.16)	0.14	0.68(0.13)	0.67(0.17)	0.84	0.10(0.06)	0.09(0.05)	0.84
8.Fz-Cz	0.55(0.14)	0.67(0.11)	0.04	0.71(0.15)	0.62(0.18)	0.21	0.70(0.14)	0.63(0.17)	0.31	0.62(0.12)	0.66(0.17)	0.33	0.11(0.06)	0.13(0.07)	0.46
9.Cz-Pz	0.52(0.09)	0.61(0.11)	0.06	0.63(0.16)	0.61(0.17)	0.98	0.68(0.17)	0.66(0.12)	0.54	0.65(0.15)	0.67(0.11)	0.66	0.09(0.04)	0.11(0.05)	0.40
10.Fp2-F4	0.60(0.10)	0.97(0.18)	<0.0001 ¹	0.65(0.12)	0.67(0.09)	0.50	0.57(0.12)	0.68(0.18)	0.17	0.58(0.12)	0.69(0.17)	0.10	0.09(0.05)	0.13(0.08)	0.15
11.F4-C4	0.57(0.10)	0.85(0.18)	0.0003 ¹	0.66(0.09)	0.63(0.21)	0.88	0.69(0.24)	0.62(0.19)	0.98	0.66(0.18)	0.67(0.25)	0.66	0.11(0.05)	0.14(0.06)	0.25
12.C4-P4	0.49(0.10)	0.64(0.11)	0.003	0.64(0.20)	0.60(0.11)	0.66	0.69(0.18)	0.62(0.13)	0.50	0.67(0.14)	0.65(0.13)	0.70	0.08(0.04)	0.11(0.07)	0.28
13.P4-O2	0.46(0.09)	0.53(0.09)	0.17	0.65(0.09)	0.58(0.21)	0.33	0.66(0.14)	0.68(0.18)	0.75	0.68(0.15)	0.67(0.10)	0.75	0.07(0.06)	0.09(0.08)	0.50
14.Fp2-F8	0.45(0.14)	0.84(0.14)	<0.0001 ¹	0.70(0.23)	0.72(0.14)	0.31	0.66(0.15)	0.63(0.13)	0.75	0.63(0.11)	0.62(0.10)	0.75	0.05(0.04)	0.09(0.06)	0.05
15.F8-T4	0.46(0.12)	0.71(0.14)	0.0008	0.67(0.21)	0.62(0.21)	0.98	0.62(0.12)	0.58(0.16)	0.58	0.61(0.11)	0.62(0.14)	0.66	0.05(0.02)	0.08(0.05)	0.07
16.T4-T6	0.49(0.20)	0.62(0.14)	0.04	0.67(0.10)	0.62(0.13)	0.40	0.65(0.13)	0.62(0.13)	0.50	0.66(0.16)	0.60(0.12)	0.33	0.06(0.03)	0.08(0.05)	0.14

¹ * indicates significant difference ($p < 0.0003$, Bonferroni correction).

Figure 1. Sample entropy of the psychosis and control groups.

*indicates a significant difference ($p < 0.001$) between before and after psychosis groups.

†indicates a significant difference ($p < 0.003$) between before psychosis group and control before LEV group.

‡indicates a significant difference ($p < 0.003$) between before psychosis group and control after LEV group.

The X axis indicates the number of EEG montages described in the Methods section.

The Y axis indicates averaged SampEn.

the psychosis group (except one patient who was seizure-free) had uncontrolled seizures, the higher complexity during psychosis at the bilateral frontal and frontal-anterior temporal regions corresponds to the acute-phase psychotic symptoms in the present study, indicating the resulting aberrant limbic activity and impaired frontal control [17, 18]. On the other hand, the lower complexity at the right frontal and frontal-anterior temporal regions before psychosis may indicate the prodromal phase of psychosis. The present results could show the prodromal phase by means of SampEn approximately 4.2 years before the onset of psychosis, while epileptic psychosis took about 14.4 years to develop after the on-

set of epilepsy [2]. Two patients in the psychosis group were treated with psychotropic in the prodromal phase for symptoms of insomnia and anxiety. Thus, at which point the prodromal phase starts needs further investigation.

The multiscale entropy of schizophrenia at scale factor = 1, which was the same as SampEn, showed no significant difference from healthy controls [16], and the present results of the comparison between the after-psychosis group vs control group also showed no significant difference.

The EEG focus was on the right side in two of the five cases in the present study, and the relationship between the right-sided lower

complexity before psychosis and the EEG focus is unclear.

Three of the five patients in the psychosis group were prescribed LEV. Regarding the risk of psychosis associated with a specific AED, the AED was only one of the factors alongside individual factors directly related to the patient and the specific epileptic disorder [18], and not the only determinant of psychosis in patients with epilepsy [19]. Thus, the association with the effects due to LEV remains unclear from the present results.

There were some limitations in this retrospective study. First, the number of cases of interictal psychosis was small. Second, the severity of psychosis was not identified, and third, the AEDs were not consistent for all patient. Fourth, strict application of Bonferroni correction may miss the other significant regions, which represents type 2 error in this study.

SampEn in the resting state EEG of patients with drug-resistant epilepsy may decrease in the right frontal and frontal-anterior temporal regions during the prodromal phase before psychosis and may increase in the bilateral frontal and frontal-anterior temporal regions during psychosis.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Appendix

Calculation of Sample Entropy (SampEn)

For a time series of N points, $\{u(j): 1 \leq j \leq N\}$ forms the $N-m+1$ vectors $x_m(i)$ for $\{i | 1 \leq i \leq N-m+1\}$, where $x_m(i) = \{u(i+k): 0 \leq k \leq m-1\}$ is the vector of m data points from $u(i)$ to $u(i+m-1)$. $B_i^m(r)$ was defined as $(N-m+1)^{-1}$ times the number of vectors $x_m(j)$ within r of $x_m(i)$, where j ranges from 1 to $N-m$, and $j \neq i$ to exclude self-matches. Then $B^m(r) = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} B_i^m(r)$. Similarly $A_i^m(r)$ was defined as $(N-m+1)^{-1}$ times the number of vectors $x_{m+1}(j)$ within r of $x_{m+1}(i)$, where j ranges from 1 to $N-m$ ($j \neq i$), and set $A^m(r) = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} A_i^m(r)$. $B^m(r)$ is then the probability that two sequences will match for m points, where $A^m(r)$ is the probability that two sequences will match for $m+1$ points. Then the parameter $\text{SampEn}(m, r, N) = \lim_{N \rightarrow \infty} \{-\ln[A^m(r)/B^m(r)]\}$, which is estimated by the statistic $\text{SampEn}(m, r, N) = -\ln[A^m(r)/B^m(r)]$. Where there is no confusion about the parameter r and the length m of the template vector, $B = \{[(N-m+1)(N-m)]/2\} B^m(r)$ and $A = \{[(N-m+1)(N-m)]/2\} A^m(r)$, so that B is the total number of template matches of length m and A is the total number of forward matches of length $m+1$. So $\text{SampEn}(m, r, N)$ can be expressed as $-\ln(A/B)$ (Richman and Moorman, 2000). A lower value of SampEn indicates more self-similarity and regularity in the time series.

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