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EEG correlates of quality of life and associations with seizure without awareness and depression in patients with epilepsy

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Abstract

Aims: Quality of life (QOL) is an important issue for not only patients with epilepsy but also physicians. Depression has a large impact on QOL. Nonlinear electroencephalogram (EEG) analysis using machine learning (ML) has the potential to improve the accuracy of the diagnosis of epilepsy. Therefore, in this study, we examined EEG nonlinearity, EEG correlates of QOL in patients with epilepsy, and the accuracy of EEG for the interval from seizure without awareness (SA–) and for depression, using ML.

Methods: The Side Effects and Life Satisfaction (SEALS) inventory was used to assess QOL, and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was used as a screening tool for depression on the date of the EEG recording. EEG with wavelet denoising (WD), the Savitzky–Golay filter, and non-denoising were created in combination with low- and high-pass filters. These EEG sets were adopted for phase space reconstruction methods. Using a generalized linear mixed-effects model for SEALS, sample entropy as a measurement of regularity, SA–, seizure with awareness, and depression were examined.

Results: WD and non-denoising EEG sets in the bilateral posterior temporal-occipital, centro-parietal, parieto-occipital, and Fz–Cz of the 10–20 method were associated with SEALS and demonstrated nonlinearity, and the moderate effects of classification for the interval elapsed from SA– and for depression. When the intervals from SA– were added, the effects of the EEG classification for depression increased.

Conclusion: These findings suggest that EEG regions associated with QOL showing nonlinearity are useful for classifying SA– and depression.

KEYWORDS
depression, EEG, epilepsy, nonlinear, phase reconstruction, QOL

1 | INTRODUCTION

Epilepsy is a neurological disorder characterized by the unpredictable occurrence of seizures. In most patients, seizures are controlled using antiepileptic drugs (AEDs). Despite treatment with AEDs, some patients still experience uncontrolled seizures. Patients with epilepsy whose seizures are either controlled or uncontrolled tend to be under psychological distress and carry a social burden,[1] which affects their quality of life (QOL).

Therefore, QOL is an important issue for not only patients with epilepsy but also physicians.[2,3] Depression is a common comorbidity

reported to occur in more than 30% of community-based epilepsy cases and has a large impact on QOL.[4,5] The Side Effects and Life Satisfaction (SEALS) inventory has been reported to provide information on QOL that is complementary to the Quality of Life in Epilepsy Inventory-31-P (QOLIE-31-P).[6,7] Among various QOL instruments, SEALS has been reported as being useful in selected situations for patients with epilepsy.[8] We previously suggested that using both SEALS and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), a screening tool for depression, may be useful for detecting various aspects of QOL in the clinical setting.[9,10]

Electroencephalogram (EEG), which measures brain function, has been clinically used for the diagnosis of epilepsy by means of visual inspection.[11] Recently, nonlinear methods using EEG have been reported for the diagnosis of epilepsy or for seizure prediction using machine learning (ML).[12,13] We are interested in the recent progress in the diagnosis of epilepsy using nonlinear EEG analysis. Therefore, in this study, we examined EEG nonlinearity, EEG correlates of QOL in patients with epilepsy using nonlinear EEG analysis, and the accuracy of EEG as a measure of regularity with regard to the frequency of epileptic seizure without awareness (SA–) and depression, using ML methods.

2 | METHODS

From January to August 2019, a total of 251 patients with epilepsy (age > 18 years) who visited the outpatient clinic at Nagoya City University Hospital were examined. The inclusion criterion was being able to complete the SEALS and NDDI-E on the day of or within a 1-week period immediately preceding an EEG. SEALS, which was originally developed to measure the side effects of treatment with AEDs, provides information on QOL that is complementary to that obtained by the QOLIE-31-P. In particular, it has been reported that SEALS provides information on the cognitive and psychosocial impacts of treatment with AEDs and epilepsy itself.[7,14] The NDDI-E and SEALS do not include items representing epilepsy or treatment with AEDs; therefore, patients are likely to respond without being primed to judge whether seizures or treatment with AEDs caused their troubles.[14] SEALS is therefore considered to be an appropriate alternative to QOL. The exclusion criteria were comorbidities such as schizophrenia, anxiety disorder, alcohol or drug dependence, migraines, neurodegenerative disease, cerebrovascular disease, brain tumors, psychogenic non-epileptic seizure, history of epilepsy surgery, and intellectual disability. After exclusion, 63 patients with epilepsy were eligible for this study. Brain magnetic resonance imaging (MRI) showed no obvious demonstrable abnormalities in any of the patients. On the date of the EEG, the patients who had more than one seizure per year were classified into the following groups: (1) SA–: focal impaired awareness seizure (FIAS), focal to bilateral tonic–clonic seizure (FBTCS), and generalized tonic–clonic seizure (GTCS); and (2) seizure with awareness (SA+): focal awareness seizure (FAS) and myoclonic seizure. Patients who did not have any seizures for at least 1 year prior to the date of the EEG were classified as (3) seizure-free (SF). Furthermore, seizure frequency was classified into categories of either more than once per week, more than once per month, or more than once per year. Number of AEDs, diagnosis (focal vs generalized), age, age at onset, and sex were also confirmed by the patients and their families using a chart review. The interval (months) between the last seizure and the date of the EEG was calculated. For patients in the SA– and SA+ groups, the SA– interval was prioritized; for example, if a myoclonic seizure occurred in the past 2 months and a GTCS in the past 3 months, the interval was calculated as 3 months, and the patient was classified into the SA– group. For patients with both FBTCS and FIAS, the FBTCS interval was prioritized; for example, if an FIAS occurred in the past 3 months and an FBTCS in the past 6 months, the interval was calculated as 6 months. The reasoning behind this was based on reports that patients with FBTCS and FIAS show cognitive and psychomotor dysfunction, and those with FBTCS are worse than those with FIAS.[15–17] EEG laterality was classified as left, right, and unknown. Major depression (depression) was suspected with an NDDI-E score of >16, and was diagnosed by a psychiatrist through a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[9,18] The International League Against Epilepsy classification of epilepsies and operational classification of seizure types were also used.[19,20]

2.1 | EEG examinations

EEGs were recorded at a sampling frequency of 500 Hz and a time constant of 0.3 seconds with a 120-Hz low-pass filter using the international 10–20 system with reference electrodes on both earlobes. All EEGs were recorded in a shielded room at a constant temperature using a Nihon Kohden EEG device (Nihon Kohden). Before selecting the EEG data, one of the authors (HA), who is a physician certified by the Japanese Society of Clinical Neurophysiology, interpreted the whole EEG and confirmed the background alpha rhythm when the participants rested with their eyes closed. Then, five sets of 3-second EEG fragments with no overlap while resting with the eyes closed and awake EEG with no paroxysmal abnormalities including epileptic discharges, or no non-paroxysmal abnormalities, and without contamination from the effects of alternating current interference, body motion artifacts, adhesive failure of the electrodes, or baseline fluctuations, were selected by unipolar montage.[21] We considered that a 3-second EEG strip would satisfy the requirements of both fewer artifacts by visual inspection and a minimum number of data points for nonlinear analysis. The selected EEG strips were then analyzed using an 18-lead longitudinal bipolar montage: Fp1–F7, F7–T3, T3–T5, T5–O1, Fp1–F3, F3–C3, C3–P3, P3–O1, Fz–Cz, Cz–Pz, Fp2–F4, F4–C4, C4–P4, P4–O2, Fp2–F8, F8–T4, T4–T6, and T6–O2.

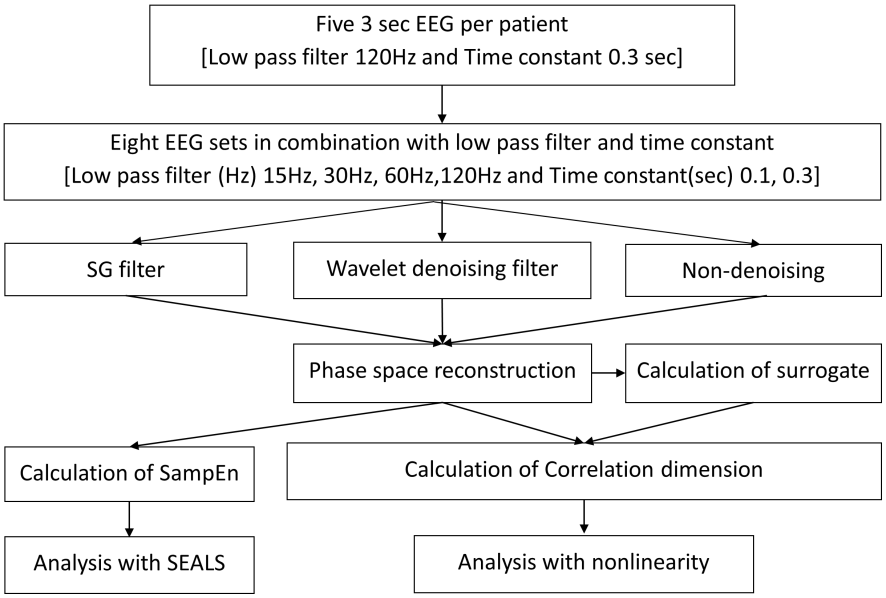

FIGURE 1 Flow diagram of the electroencephalogram calculation and analysis. SampEn, sample entropy; SG, Savitzky–Golay

2.2 | Filter adaptation

Low-pass (15, 30, 60, and 120 Hz) and high-pass filters (1.60 Hz [time constant (TC): 0.1 seconds] and 0.53 Hz [TC: 0.3 seconds]), which were built into the Nihon Kohden EEG device, were used in combination. Low- and high-pass filters are typically used to cancel the effects of the above-mentioned artifacts. In the present study, these filters were used on an exploratory basis to examine their effects on the nonlinear EEG analysis. After selecting five 3-second EEG sets filtered with low- and high-pass filters, a Savitzky–Golay (SG) filter (legible fourth-order and 27-frame length) and a wavelet denoising (WD) filter with the sym4 wavelet of the MATLAB function were used as the smoothing filter.[22] Thus, three sets of EEGs (SG, WD, and non-denoising) per patient were created.

2.3 | Phase space reconstruction

In the theory of dynamical systems, an EEG time series is a phase space object and a non-deterministic system. The concept of the state of a system is useful and applicable for EEG time series. The attractor in a system of EEG is periodic motion: a limit cycle. The full-phase space dynamics of a limit cycle are reconstructed from the measurement of a single EEG time series using the attractor reconstruction technique.[23–26] Therefore, in the present study, the phase space reconstruction for each 3-second EEG in each EEG region was calculated using the embedding dimension, which is estimated using the false nearest neighbor algorithm,[27] and the delayed time, which is estimated using average mutual information.[28] MATLAB functions were used to calculate the embedding dimension and delayed time.

2.4 | Examination of nonlinearity

EEGs show nonlinearity and weak stationarity.[29,30] To investigate EEG nonlinearity in the present study, the correlation dimension (CD) was calculated with the embedding dimension and the delayed time using the Grassberger–Procaccia algorithm,[31] which quantifies the number of the dimension of the attractor. The CD is frequently used to determine the index as nonlinearity.[29,32] At the same time, surrogate data using 3-second EEGs were produced using the amplitude-adjusted Fourier transform (AAFT) method. As a result, the surrogates showed the approximate power spectrum for the original EEG and a Gaussian distribution.[33] Nonlinearity was examined by comparing the average CD of the original EEG and surrogates of all patients. The surrogates produced using the AAFT method do not contain the same time dependence of the running mean and variance as the stationarity of the original data.[34] Therefore, a rejection of the null hypothesis indicates nonlinearity, and the possibility of non-stationarity cannot be ruled out.

2.5 | Entropy as a measure of regularity

Entropy involves the rate of information and is a concept that addresses system randomness and predictability, with greater entropy being associated with more randomness and less system order.[35] Pincus[35] developed approximate entropy (ApEn) as a quantification of regularity via Kolmogorov entropy. Lower ApEn reflects a high degree of regularity. Richman et al[36] reported that ApEn algorithms have two biases, dependent record length and relative inconsistency, and subsequently developed sample entropy (SampEn), which improved these biases. A lower SampEn

value indicates more regularity and self-similarity. SampEn values are largely independent of record length and display relative consistency. In this study, SampEn was used as a measure of regularity.

2.6 | Relationship with SampEn and SEALS

After the phase space reconstruction, SampEn was calculated to investigate the relationship with SEALS. SampEn was calculated using the Physionet open source algorithm.[36–38] Before calculating SampEn, each EEG was standardized. SampEn parameters (N, m, r) were set at $r = 0.2$ and $m = 2$. N was 1500 points per 3-second EEG. Five sets of each lead of 3-second EEGs per patient were averaged. Then, a linear mixed-effects model was used to investigate the effects of SampEn on SEALS as the response variable. The fixed effects were SampEn, SA–, SA+, and depression. SampEn in each EEG lead in Section 2.1 were inserted separately as the fixed effect. The random effects were age, age at onset, sex, number of AEDs, diagnosis, EEG laterality, NDDI-E, and the interval. We determined the EEG regions with both nonlinearity and the effects of SEALS as those that correlated with SEALS. The effects of SampEn on SA– and depression were then examined using ML. A flow diagram of the EEG calculation and analysis is shown in Figure 1.

2.7 | Machine learning (ML)

In this study, an ML approach was used to detect the effects of SampEn on SA– and depression. We randomly selected half of the data as training data and the other half as test data without

TABLE 1 Demographic and epilepsy-related data (n = 63)

	SA– (n = 24)	SA+ (n = 11)	SF (n = 28)
Age (y)	49.7 (21.4)	37.8 (9.4)	46.4 (15.2)
Male/female	16/8	4/7	11/17
Age at onset (y)	26.3 (18.8)	16.8 (12.5)	20.8 (20.0)
NDDI-E	13.7 (5.4)	13.4 (4.1)	11.5 (4.6)
Number of AEDs	2.3 (1.3)*	1.9 (1.5)	1.0 (0.7)*
Laterality: left/right/unknown	6/8/10	6/1/4	8/5/15
Interval (months) (median) (range: 0–657)	2*	1**	110*,**
SEALS total score	44.1 (13.9)*	41.2 (12.3)	33.3 (19.4)*
Cognition	39.4 (20.9)	32.5 (19.8)	26.7 (25.9)
Dysphoria	48.7 (16.9)	53.0 (12.2)	45.7 (12.9)
Temper	41.9 (29.8)	35.0 (19.8)	26.6 (24.0)
Tiredness	46.0 (18.2)	43.0 (18.3)	34.1 (25.0)
Worry	53.9 (26.5)	58.7 (25.3)	42.2 (30.0)
Focal epilepsy (n = 56)	23	8	25
FBTCS[a]	0/6[b]/1[b]/1	0/0/0/0	12/0/0/0
FIAS[a]	0/12/4/1	0/0/0/0	12/0/0/0
FAS[a]	1/4/4/5	0/2/4/2	1/0/0/0
Generalized epilepsy (n = 7)	1[c]	3	3[d]
GTCS[a]	0/1/0/0		3/0/0/0
MS[a]	0/0/1/0	0/1/0/2	1/0/0/0

Abbreviations: AEDs, antiepileptic drugs; FAS, focal awareness seizure; FBTCS, focal to bilateral tonic–clonic seizure; FIAS, focal impaired awareness seizure; GTCS, generalized tonic–clonic seizure; Interval, from the last seizure to the date of the EEG; MS, myoclonic seizure; NDDI-E, Neurological Disorders Depression Inventory for Epilepsy; SA–, seizure without awareness; SA+, seizure with awareness; SEALS, Side Effects and Life Satisfaction Inventory; SF, seizure-free.

[a]Indicates none/more than once per year/more than once per month/more than once per week.

[b]Indicates that two patients had both uncontrolled FBTCS and FIAS more than once per year and month, respectively.

[c]Indicates that one patient had both uncontrolled GTCS and MS.

[d]Indicates that one patient had both controlled GTCS and MS. The Kruskal–Wallis test was conducted to compare the demographic data between seizure groups. Multiple comparisons were adjusted with the Bonferroni correction; P-values were set at $<0.05/3 = 0.02$ to indicate significance. * and ** indicate $P < 0.02$ as the statistically significant difference between each group. Age, age at onset, NDDI-E, number of AEDs, and SEALS show the average (standard deviation), respectively.

stratification or cross-validation. A decision tree (split criterion: Gini's diversity index, the maximal number of decision splits: 100), linear discriminant analysis, logistic regression analysis, and a linear support vector machine (SVM) were selected exploratorily.[39–42] Then, the accuracy, area under curve (AUC), sensitivity, and specificity were calculated, respectively. Each method was repeated 20000 times and the mean and standard deviation were calculated.

2.8 | Statistical analysis

Significance in the statistical tests was set at $P<0.05$ and adjusted for multiple comparisons using the Bonferroni correction. Statistical inference for nonlinearity was conducted using the Wilcoxon rank-sum test. Multiple comparisons using the linear mixed-effects model for SampEn on SEALS were adjusted using the false discovery rate (FDR = 0.05), with the adjusted *P*-value to indicate significance set at <0.05.[43] All analyses were carried out in MATLAB R2020a (MathWorks). This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and approved by the Ethics Committee of the Nagoya City University Medical School. Written, informed consent was obtained from all patients.

3 | RESULTS

The participants' demographic and epilepsy-related variables are shown in Table 1. One patient answered the SEALS and NDDI-E 2 days before the EEG. The other patients answered the SEALS and NDDI-E on the date of the EEG. Fifteen patients had depression across all groups. The demographic data of the patients with

TABLE 2 Results of SampEn, embedding dimension, delayed time, and correlation dimension for each filtering method

Filtering methods	SampEn (SD)	Embedding dimension (SD)	Delayed time (SD)	$CD_{original}$ (SD)	$CD_{surrogate}$ (SD)	*P*-value
N15-1	0.37 (0.08)	3.01 (0.02)	6.42 (0.73)	2.78 (0.33)	2.83 (0.28)	**0.001**
N15-3	0.37 (0.08)	3.00 (0.01)	7.42 (1.14)	2.73 (0.31)	2.77 (0.27)	0.012
N30-1	0.54 (0.13)	3.13 (0.10)	5.59 (0.39)	2.95 (0.41)	3.02 (0.45)	0.012
N30-3	0.45 (0.13)	3.07 (0.05)	6.43 (0.96)	2.86 (0.38)	2.92 (0.37)	0.023
N60-1	0.72 (0.19)	3.27 (0.16)	5.35 (0.35)	3.15 (0.55)	3.20 (0.57)	0.306
N60-3	0.61 (0.19)	3.18 (0.11)	6.08 (0.83)	3.04 (0.50)	3.09 (0.53)	0.122
N120-1	1.03 (0.25)	3.45 (0.23)	5.56 (0.23)	3.40 (0.69)	3.43 (0.73)	0.558
N120-3	0.91 (0.26)	3.35 (0.13)	6.20 (0.69)	3.24 (0.62)	3.32 (0.65)	0.030
S15-1	0.35 (0.07)	3.00 (0.01)	6.51 (0.77)	2.79 (0.32)	2.81 (0.27)	0.193
S15-3	0.28 (0.07)	3.00 (0.00)	7.46 (1.15)	2.72 (0.31)	2.75 (0.26)	0.042
S30-1	0.45 (0.09)	3.06 (0.05)	5.80 (0.43)	2.91 (0.38)	2.90 (0.33)	0.961
S30-3	0.37 (0.09)	3.04 (0.04)	6.63 (1.03)	2.81 (0.34)	2.83 (0.32)	0.049
S60-1	0.49 (0.11)	3.11 (0.07)	5.72 (0.37)	2.94 (0.40)	2.95 (0.40)	0.988
S60-3	0.41 (0.11)	3.06 (0.05)	6.45 (0.98)	2.86 (0.37)	2.88 (0.35)	0.250
S120-1	0.52 (0.12)	3.10 (0.09)	5.66 (0.33)	2.95 (0.42)	2.98 (0.41)	0.138
S120-3	0.43 (0.12)	3.07 (0.05)	6.38 (0.95)	2.87 (0.37)	2.89 (0.36)	0.268
W15-1	0.37 (0.08)	3.01 (0.02)	6.42 (0.73)	2.78 (0.31)	2.82 (0.27)	0.003
W15-3	0.30 (0.07)	3.00 (0.01)	7.42 (1.14)	2.72 (0.30)	2.77 (0.26)	**0.0004**
W30-1	0.54 (0.13)	3.12 (0.09)	5.61 (0.40)	2.96 (0.42)	3.01 (0.45)	0.022
W30-3	0.44 (0.13)	3.07 (0.06)	6.43 (0.97)	2.88 (0.37)	2.92 (0.40)	0.083
W60-1	0.70 (0.18)	3.29 (0.17)	5.36 (0.33)	3.15 (0.56)	3.22 (0.59)	0.093
W60-3	0.59 (0.18)	3.18 (0.11)	6.13 (0.86)	3.03 (0.47)	3.07 (0.52)	0.329
W120-1	0.81 (0.21)	3.38 (0.22)	5.44 (0.33)	3.24 (0.59)	3.32 (0.64)	0.062
W120-3	0.70 (0.22)	3.27 (0.13)	6.16 (0.81)	3.12 (0.53)	3.21 (0.61)	0.008

Note: $CD_{original}$ was calculated using the embedding dimension and the delayed time with the Grassberger–Procaccia algorithm. The embedding dimension and delayed time were calculated with 3-s EEG strips and averaged for all patients. The surrogate of each data set was calculated using the amplitude-adjusted Fourier transform method, and then the $CD_{surrogate}$ was calculated with surrogate data sets similarly to $CD_{original}$. *P*-values indicate the results of the Wilcoxon rank-sum test compared between $CD_{original}$ vs $CD_{surrogate}$, and statistical significance at $P<0.002 = 0.05/24$ with the Bonferroni correction for multiple comparisons (BOLD).

N, no smoothing filters; S, Savitzky–Golay filter; W, wavelet denoising filter, 15, 30, 60, 120; low-pass filter (Hz), respectively, 1,3; 0.1 and 0.3 time constant (s), respectively. SampEn, sample entropy; CD, correlation dimension; SD, standard deviation.

depression are shown in Table S1. The proportions of AEDs were as follows: carbamazepine 27%, levetiracetam 23.8%, lamotrigine 19%, valproate 19%, phenytoin 15.9%, clonazepam 9.5%, clobazam 9.5%, phenobarbital 11.1%, lacosamide 7.9%, perampanel 6.3%, topiramate 3.2%, primidone 3.2%, and zonisamide 3.2%.

3.1 | Examination of the nonlinearity

EEGs with a WD filter with low-pass filter (15 Hz) and high-pass filter (0.3-second TC; W15-3) and a non-smoothing filter with low-pass filter (15 Hz) and high-pass filter (0.1-second TC; N15-1) showed nonlinearity (Table 2). No significant nonlinearity pattern was seen using the SG filter. Table 3 shows SampEn for all electrodes in N15-1 and W15-3.

3.2 | EEG regions of SampEn associated with SEALS

Table 4 shows the EEG regions of SampEn that were significantly associated with SEALS. The EEG regions showing nonlinearity (seven EEG regions: T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, and T6–O2) for N15-1 and W15-3 were identical. In all analyses with the linear mixed-effects model, the significant results indicated higher SEALS (worse QOL), lower SampEn (higher regularity), the existence of SA–, and depression (Tables S2–S5). Analysis of variance between seven EEG regions in N15–1 and W15–3 showed no significant differences (sum of squares [SS]: 0.011, degrees of freedom (*df*): 6, mean square (MS): 0.0018, *F* value: 0.47, and $P = 0.83$ in N15-1; SS: 0.035, dif: 6, MS: 0.0058, *F* value: 1.38, and $P = 0.22$ in W15-3). Post hoc analysis of SampEn with the Wilcoxon rank-sum test showed that in the seven EEG regions of N15-1, SA– (0.36 [0.05] of average [SD]) vs non-SA– (0.40 [0.05]) ($P = 0.05$) and FBTCS and GTCS (0.36 [0.04]) vs FIAS (0.37 [0.06]) ($P = 0.47$) were nonsignificant, and in the seven EEG regions of W15-3, SA– (0.32 [0.05]) vs non-SA– (0.40 [0.06]) ($P = 0.04$) and FBTCS and GTCS (0.31 [0.04]) vs FIAS (0.33 [0.05]) ($P = 0.31$) were nonsignificant. No significant differences were found between depression (0.38 [0.07]) vs non-depression (0.38[0.06]) in the seven EEG regions in N15-1 ($P = 1.0$) and depression (0.34 [0.08]) vs non-depression (0.34 [0.06]) in the seven EEG regions in W15-3 ($P = 0.84$). *P*-values were significant at $P < 0.05/6$ with the Bonferroni correction in the multiple comparisons.

3.3 | Accuracy, AUC, sensitivity, and specificity of SampEn in SA– And depression

In the classification of SA–, the effects of linear SVM, tree, linear discriminant, and logistic regression in W15-3 were all superior to those in N15-1, and those excluding tree in W15-3 showed a moderate AUC, low sensitivity, and high specificity (Table 5). In the classification of depression, the effects of linear SVM, linear discriminant, and logistic regression, excluding tree, in W15-3 were the same as those in N15-1 (moderate). The effects of linear discriminant showed a moderate AUC and high specificity (Table 6). When the interval from seizure was added, the effects of linear SVM and linear discriminant increased the accuracy, AUC, and specificity in both N15-1 and W15-3 (Table 7).

TABLE 3 Mean (standard deviation) sample entropy (SampEn) of all bipolar electrodes in N15-1 and W15-3

	N15-1	W15-3
Fp1–F7	0.29 (0.08)	0.17 (0.07)
F7–T3	0.34 (0.10)	0.23 (0.09)
T3–T5	0.39 (0.08)	0.33 (0.07)
T5–O1	0.38 (0.06)	0.34 (0.06)
Fp1–F3	0.35 (0.09)	0.23 (0.08)
F3–C3	0.40 (0.08)	0.33 (0.08)
C3–P3	0.39 (0.06)	0.34 (0.07)
P3–O1	0.38 (0.05)	0.35 (0.06)
Fz–Cz	0.38 (0.08)	0.32 (0.08)
Cz–Pz	0.40 (0.07)	0.35 (0.08)
Fp2–F4	0.36 (0.10)	0.23 (0.09)
F4–C4	0.41 (0.08)	0.33 (0.09)
C4–P4	0.39 (0.06)	0.34 (0.07)
P4–O2	0.38 (0.05)	0.35 (0.06)
Fp2–F8	0.32 (0.10)	0.20 (0.08)
F8–T4	0.35 (0.10)	0.25 (0.10)
T4–T6	0.38 (0.06)	0.33 (0.07)
T6–O2	0.38 (0.06)	0.34 (0.06)

N15-1 indicates SampEn with no smoothing filters, 15-Hz low-pass filter, and 0.1-s time constant. W15-3 indicates SampEn with wavelet denoising filter, 15-Hz low-pass filter, and 0.3-s time constant.

4 | DISCUSSION

To our knowledge, no EEG correlates of QOL in patients with epilepsy have been reported. Here, we examined SEALS as an alternative to QOL and used SampEn as a measure of regularity. We identified EEG correlates of QOL in the bilateral posterior temporal-occipital, centro-parietal, parieto-occipital, and Fz–Cz regions (seven EEG regions). Furthermore, ML showed that SampEn moderately classified both SA– that occurred within or after 1 year and the index episode of depression in the seven EEG regions of N15-1 and W15-3.

Cao et al[44] reported that beta band coherence differentiated normal vs generalized epilepsy with more than 90% accuracy using 4-second EEG, and Fz–Cz was the same bipolar electrode used for our results. Psychogenic non-epileptic seizure (PNES) with epilepsy vs no PNES with epilepsy was diagnosed with lower accuracy (73%) compared with normal vs generalized epilepsy. They considered that the diagnosis of PNES was affected by epilepsy in both groups. This

TABLE 4 EEG regions associated with SEALS

Filtering methods	EEG regions associated with SEALS
N15-1	**T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, T6–O2**
N15-3	T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, T6–O2
N30-1	Fz–Cz
N30-3	C3–P3, Fz–Cz, Cz–Pz, P4–O2, T6–O2
N60-1	No EEG regions
N60-3	No EEG regions
N120-1	No EEG regions
N120-3	No EEG regions
S15-1	T3–T5, T5–O1, C3–P3, P3–O1, C4–P4, P4–O2, T4–T6, T6–O2
S15-3	T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, T4–T6, T6–O2
S30-1	Fz–Cz, P4–O2, T6–O2
S30-3	T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, T6–O2
S60-1	Fz–Cz, P4–O2, T6–O2
S60-3	C3–P3, Fz–Cz, C4–P4, P4–O2, T6–O2
S120-1	Fz–Cz, P4–O2, T6–O2
S120-3	C3–P3, Fz–Cz, Cz–Pz, P4–O2, T6–O2
W15-1	T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, T6–O2
W15-3	**T5–O1, C3–P3, P3–O1, Fz–Cz, C4–P4, P4–O2, T6–O2**
W30-1	Fz–Cz, P4–O2
W30-3	C3–P3, Fz–Cz, Cz–Pz, P4–O2, T6–O2
W60-1	Fz–Cz
W60-3	No EEG regions
W120-1	No EEG regions
W120-3	No EEG regions

Note: EEG sets indicating nonlinearity were N15-1 and W15-3 (BOLD). The seven EEG regions showing nonlinearity for N15-1 and W15-3 were identical.

N; no smoothing filters, S; Savitzky–Golay filter, W; wavelet denoising filter, 15, 30, 60, 120; low-pass filter (Hz), respectively, 1,3; 0.1 and 0.3 time constant (s), respectively.

point of view is the same as our study comparing the presence or absence of seizure in patients with epilepsy.

Varatharajah et al[45] reported that alpha wave analysis differentiated normal vs focal epilepsy with an AUC of 0.83, and bilateral F–C and T–C were partially the same as our results. Movahed et al[46] reported that nonlinear and wavelet analysis of alpha waves differentiated normal vs depression using radial basis function SVM with 87% specificity, which is close to our results. Boylan et al[4] reported that depression in patients with epilepsy was not associated with seizure frequency per se, but we demonstrated that a better classification for depression could be obtained when the months elapsed from SA– were added as a predictable variable, indicating that the months from SA– to the date of the EEG affects the EEG classification of depression in patients with epilepsy. However, in temporal lobe epilepsy, depression seems to be associated with a different pattern of brain change compared with major depression in neuroimaging studies.[47] Our EEG analysis method was different from that used in the above reports. Furthermore, to our knowledge, no studies have been conducted on EEG diagnosis of epilepsy and depression using the bipolar EEG electrodes associated with QOL. Interestingly, the electrodes associated with the diagnosis of epilepsy and depression in previous studies were partially the same as those used for our results. The high specificity in epilepsy and depression found in this study could be clinically useful for auxiliary diagnoses. Furthermore, what causes differences in EEG nonlinear dynamics in the presence or absence of epilepsy needs to be investigated in a future study.

Regarding the statistical analysis for multiple comparisons, this exploratory study investigated the association between SEALS and SampEn. As the statistical method for multiple comparisons (24 filtered EEGs with 18 bipolar electrodes; total of 432 comparisons), we used the FDR[42] as opposed to the Bonferroni correction. The statistical power was 0.37 when the FDR was 0.05 and $P<0.05$. However, when the Bonferroni correction is used with $P = 0.05/432$ and FDR = 0.05, the statistical power is 0.18 (Figures S1 and S2, Tables S6 and S7). Therefore, in this study, it was appropriate to use the FDR, the power for which was superior to that by the Bonferroni correction.

This study had several limitations. First, the sample size of each seizure group was relatively small. Thus, only the classification of SA–, not the diagnosis of epilepsy syndrome, was examined in this

TABLE 5 Results of machine learning to classify seizure without awareness

EEG region	Method	Accuracy	AUC	Sensitivity	Specificity
N15-1	Linear SVM	64.3 (7.3)	0.65 (0.08)	0.29 (0.18)	0.84 (0.15)
	Tree	58.8 (9.7)	0.56 (0.10)	0.42 (0.19)	0.68 (0.03)
	Linear discriminant	64.4 (7.6)	0.66 (0.08)	0.41 (0.17)	0.78 (0.13)
	Logistic regression	62.9 (6.7)	0.65 (0.08)	0.04 (0.07)	0.99 (0.02)
W15-3	Linear SVM	67.0 (7.1)	0.70 (0.08)	0.35 (0.20)	0.85 (0.14)
	Tree	60.2 (9.5)	0.57 (0.09)	0.42 (0.19)	0.70 (0.17)
	Linear discriminant	67.7 (7.7)	0.71 (0.09)	0.46 (0.18)	0.79 (0.13)
	Logistic regression	63.1 (6.9)	0.72 (0.10)	0.04 (0.07)	0.99 (0.02)

Note: N15-1 indicates SampEn with no smoothing filters, 15-Hz low-pass filter, and 0.1-s time constant. W15-3 indicates SampEn with wavelet denoising filter, 15-Hz low-pass filter, and 0.3-s time constant. Accuracy = (TP + TN)/(TP + FP + TN + FN), Sensitivity = TP/(TP + FN), Specificity = TN/(TN + FP). TP, TN, FP, and FN are the true positive, true negative, false positive, and false negative, respectively. All results are expressed as mean (standard deviation).

TABLE 6 Results of machine learning to classify depression

EEG region	Method	Accuracy	AUC	Sensitivity	Specificity
N15-1	Linear SVM	75.2 (6.2)	0.69 (0.10)	0.16 (0.19)	0.93 (0.07)
	Tree	66.5 (10.4)	0.52 (0.11)	0.22 (0.19)	0.80 (0.14)
	Linear discriminant	77.3 (6.6)	0.73 (0.09)	0.46 (0.20)	0.86 (0.08)
	Logistic regression	77.3 (6.4)	0.66 (0.11)	0.19 (0.21)	0.96 (0.05)
W15-3	Linear SVM	74.7 (6.5)	0.69 (0.10)	0.14 (0.18)	0.93 (0.08)
	Tree	69.0 (10.7)	0.55 (0.11)	0.29 (0.22)	0.81 (0.14)
	Linear discriminant	74.3 (7.1)	0.73 (0.09)	0.37 (0.21)	0.85 (0.09)
	Logistic regression	76.5 (6.1)	0.67 (0.12)	0.18 (0.19)	0.96 (0.05)

Note: N15-1 indicates SampEn with no smoothing filters, 15-Hz low-pass filter, and 0.1-s time constant. W15-3 indicates SampEn with wavelet denoising filter, 15-Hz low-pass filter, and 0.3-s time constant. Accuracy = (TP + TN)/(TP + FP + TN + FN), Sensitivity = TP/(TP + FN), Specificity = TN/(TN + FP). TP, TN, FP, and FN are the true positive, true negative, false positive, and false negative, respectively. All results are expressed as mean (standard deviation).

TABLE 7 Results of machine learning to classify depression when the interval is added as a prediction variable

EEG region	Method	Accuracy	AUC	Sensitivity	Specificity
N15-1	Linear SVM	76.0 (5.8)	0.74 (0.10)	0.05 (0.12)	0.98 (0.06)
	Tree	66.4 (10.2)	0.52 (0.11)	0.22 (0.19)	0.80 (0.13)
	Linear discriminant	79.6 (6.7)	0.77 (0.09)	0.51 (0.18)	0.88 (0.07)
	Logistic regression	77.2 (6.4)	0.57 (0.11)	0.09 (0.18)	0.99 (0.03)
W15-3	Linear SVM	75.8 (6.0)	0.73 (0.10)	0.03 (0.11)	098 (0.06)
	Tree	66.5 (10.3)	0.52 (0.11)	0.23 (0.19)	0.80 (0.14)
	Linear discriminant	77.0 (7.2)	0.78 (0.09)	0.46 (0.22)	0.86 (0.09)
	Logistic regression	77.5 (6.5)	0.57 (0.12)	0.09 (0.17)	0.99 (0.03)

Note: N15-1 indicates SampEn with no smoothing filters, 15-Hz low-pass filter, and 0.1-s time constant. W15-3 indicates SampEn with wavelet denoising filter, 15-Hz low-pass filter, and 0.3-s time constant. Accuracy = (TP + TN)/(TP + FP + TN + FN), Sensitivity = TP/(TP + FN), Specificity = TN/(TN + FP). TP, TN, FP, and FN are the true positive, true negative, false positive, and false negative, respectively. All results are expressed as mean (standard deviation).

study. Second, the diagnosis of epilepsy in this study was set as generalized vs focal because the focal diagnosis was difficult owing to the unknown EEG focality of some patients. Third, the analyses of EEG data using many electrodes are usually combined with principal component analysis for feature extraction. However, interpreting the results regarding the effects of the dimensionality reduction is difficult for clinical applications because of the loss of information on the electrodes. Our identification of the seven EEG regions based on the international 10–20 method is likely to be applicable to further clinical studies. Fourth, this study demonstrated that the denoising,

filtered, and phase space reconstruction methods in EEG studies are challenges to explore the nature of the limit cycle. Fifth, this observational study used a cross-sectional design in a continuous patient series. Thus, a validation study is needed for the classification of SA– using complexity measurements in the seven EEG regions compared with healthy controls.

5 | CONCLUSION

Nonlinear EEG analysis using the denoising, filtered, and phase space reconstruction methods demonstrated moderate classification with emergence within 1 year of seizure without awareness and depression in brain regions associated with SEALS as an alternative to QOL in the bilateral posterior temporal-occipital, centro-parietal, parieto-occipital, and Fz–Cz regions. However, further validation studies for the classification of seizure without awareness and depression in the identified brain regions are needed. In clinical settings, our results could be expected to be used as an auxiliary tool for patients with epilepsy.

AUTHORS CONTRIBUTIONS

HA designed the study, wrote the protocol, and managed the data acquisition. All authors critically reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest and received no financial support.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

INFORMED CONSENT

Written, informed consent was obtained from all participants.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEW BOARD

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.

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REFERENCES

1. Beghi E. Addressing the burden of epilepsy: many unmet needs. Pharmacol Res. 2016;107:79–84.
2. Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. Epilepsia. 1997;38(3):353–62.
3. Kubota H, Awaya Y. Assessment of health-related quality of life and influencing factors using QOLIE-31 in Japanese patients with epilepsy. Epilepsy Behav. 2010;18(4):381–7.
4. Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology. 2004;62(2):258–61.
5. Ettinger A, Reed M, Cramer J. Depression and comorbidity in community-based patients with epilepsy or asthma. Neurology. 2004;63(6):1008–14.
6. Cramer JA, Van Hammée G, Group NS. Maintenance of improvement in health-related quality of life during long-term treatment with levetiracetam. Epilepsy Behav. 2003;4(2):118–23.
7. El Hasnaoui A, Crespel A, Daures JP, Baldy-Moulinier M, Picot MC. Psychometric validation of the French version of the side-effects and life satisfaction inventory (SEALS) in epileptic patients: comparison with the QOLIE-31 inventory and a generic quality of life questionnaire. Epileptic Disord. 2005;7(2):103–13.
8. Leone MA, Beghi E, Righini C, Apolone G, Mosconi P. Epilepsy and quality of life in adults: a review of instruments. Epilepsy Res. 2005;66(1–3):23–44.
9. Tadokoro Y, Oshima T, Fukuchi T, Kanner AM, Kanemoto K. Screening for major depressive episodes in Japanese patients with epilepsy: validation and translation of the Japanese version of neurological disorders depression inventory for epilepsy (NDDI-E). Epilepsy Behav. 2012;25(1):18–22.
10. Azuma H, Akechi T. Effects of psychosocial functioning, depression, seizure frequency, and employment on quality of life in patients with epilepsy. Epilepsy Behav. 2014;41:18–20.
11. Tatum WO, Rubboli G, Kaplan PW, Mirsatari SM, Radhakrishnan K, Gloss D, et al. Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. Clin Neurophysiol. 2018;129(5):1056–82.
12. Elger CE, Widman G, Andrzejak R, Arnhold J, David P, Lehnertz K. Nonlinear EEG analysis and its potential role in epileptology. Epilepsia. 2000;41(Suppl 3):S34–8.
13. Schmidt H, Woldman W, Goodfellow M, Chowdhury FA, Koutroumanidis M, Jewell S, et al. A computational biomarker of idiopathic generalized epilepsy from resting state EEG. Epilepsia. 2016;57(10):e200–4.
14. Kugoh T. Quality of life research in adults with epilepsy in Japan. Clin Ther 1998;20 Suppl A:A48-57; discussion A8-60.
15. Prevey ML, Delaney RC, Cramer JA, Mattson RH. Complex partial and secondarily generalized seizure patients: cognitive functioning prior to treatment with antiepileptic medication. VA epilepsy cooperative study 264 group. Epilepsy Res. 1998;30(1):1–9.
16. Pulliainen V, Kuikka P, Jokelainen M. Motor and cognitive functions in newly diagnosed adult seizure patients before antiepileptic medication. Acta Neurol Scand. 2000;101(2):73–8.
17. Mathon B, Bordes A, Amelot A, Carpentier A, Méré M, Dupont S, et al. Evaluation of psychomotor functions in patients with drug-resistant epilepsy. Epilepsy Behav. 2020;106:106985.
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: Cambridge University Press; 2013.
19. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international

league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–30.
20. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.
21. Azuma H, Nagata H, Akechi T. Linear and non-linear EEG analyses before and after psychosis in patients with epilepsy. Epilepsy Seizure. 2019;11(1):20–9.
22. Kawala-Sterniuk A, Podpora M, Pelc M, Blaszczyszyn M, Gorzelanczyk EJ, Martinek R, et al. Comparison of smoothing filters in analysis of EEG data for the medical diagnostics purposes. Sensors. 2020;20(3):807. doi:10.3390/s20030807
23. Kantz H, Schreiber T. Nonlinear time series analysis. Cambridge: Cambridge University Press; 2004.
24. Packard NH, Crutchfield JP, Farmer JD, Shaw RS. Geometry from a time series. Phys Rev Lett. 1980;45(9):712–6.
25. Strogatz SH. Nonlinear dynamics and chaos: with applications to physics, biology, chemistry, and engineering. Boca Raton: Addison-Wesley; 1994.
26. Takens F. Detecting strange attractors in turbulence. Berlin, Heidelberg: Springer Berlin Heidelberg; 1981.
27. Rhodes C, Morari M. False-nearest-neighbors algorithm and noise-corrupted time series. Phys Rev E. 1997;55(5):6162–70.
28. Kliková B, Raidl A, editors. Reconstruction of phase space of dynamical systems using method of time delay. Proceedings of the 20th Annual Conference of Doctoral Students-WDS; 2011.
29. Andrzejak RG, Lehnertz K, Mormann F, Rieke C, David P, Elger CE. Indications of nonlinear deterministic and finite-dimensional structures in time series of brain electrical activity: dependence on recording region and brain state. Phys Rev E Stat Nonlin Soft Matter Phys. 2001;64(6 Pt 1):061907.
30. Thuraisingham RA. Examining nonlinearity using complexity and entropy. Chaos. 2019;29(6):063109.
31. Grassberger P, Procaccia I. Measuring the strangeness of strange attractors. In: Hunt BR, Li T-Y, Kennedy JA, Nusse HE, editors. The theory of chaotic attractors. New York, NY: Springer New York; 2004. p. 170–89.
32. Rombouts SARB, Keunen RWM, Stam CJ. Investigation of nonlinear structure in multichannel EEG. Phys Lett A. 1995;202(5):352–8.
33. Theiler J, Eubank S, Longtin A, Galdrikian B, Doyne FJ. Testing for nonlinearity in time series: the method of surrogate data. Phys D Nonlinear Phenom. 1992;58(1):77–94.
34. Schreiber T, Schmitz A. Surrogate time series. Phys D Nonlinear Phenom. 2000;142(3):346–82.
35. Pincus SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify? Am J Physiol. 1994;266(4 Pt 2):1643–56.
36. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol. 2000;278(6):H2039–49.
37. Goldberger AL, Amaral LAN, Glass L, Hausdorff JM, Ivanov PC, Mark RG, et al. PhysioBank, PhysioToolkit, and PhysioNet. Circulation. 2000;101(23):e215–20.
38. Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. Am J Physiol Regulat Integr Comp Physiol. 2002;283(3):R789–97.
39. Breiman L, Friedman J, Stone CJ, Olshen RA. Classification and regression trees. New York: Taylor & Francis; 1984.
40. Guo Y, Hastie T, Tibshirani R. Regularized linear discriminant analysis and its application in microarrays. Biostatistics. 2007;8(1):86–100.
41. McCullagh P, Nelder JA. Generalized linear models. London: Springer US; 1983.
42. Platt J. Probabilistic outputs for support vector machines and comparisons to regularized likelihood methods. Adv Large Margin Classifiers. 1999;10(3):61–74.
43. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B Methodol. 1995;57(1):289–300.
44. Cao J, Grajcar K, Shan X, Zhao Y, Zou J, Chen L, et al. Using interictal seizure-free EEG data to recognise patients with epilepsy based on machine learning of brain functional connectivity. Biomed Signal Process Control. 2021;67:102554.
45. Varatharajah Y, Berry B, Joseph B, Balzekas I, Pal Attia T, Kremen V, et al. Characterizing the electrophysiological abnormalities in visually reviewed normal EEGs of drug-resistant focal epilepsy patients. Brain Commun. 2021;3(2):fcab102.
46. Movahed RA, Jahromi GP, Shahyad S, Meftahi GH. A major depressive disorder classification framework based on EEG signals using statistical, spectral, wavelet, functional connectivity, and nonlinear analysis. J Neurosci Methods. 2021;358:109209. https://doi.org/10.1016/j.jneumeth
47. Elkommos S, Mula M. A systematic review of neuroimaging studies of depression in adults with epilepsy. Epilepsy Behav. 2021;115:107695.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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