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Electroencephalographic Order Pattern Analysis for the Separation of Consciousness and Unconsciousness

An Analysis of Approximate Entropy, Permutation Entropy, Recurrence Rate, and Phase Coupling of Order Recurrence Plots

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Background: **Nonlinear electroencephalographic parameters, *e.g.*, approximate entropy, have been suggested as measures of the hypnotic component of anesthesia. Compared with linear methods, they may detect additional information and quantify the irregularity of a dynamical system. High dimensionality of a signal and disturbances may affect these parameters and change their ability to distinguish consciousness from unconsciousness. Methods of order pattern analysis, in this investigation represented by permutation entropy, recurrence rate, and phase coupling of order recurrence plots, are suitable for any type of time series, whether deterministic or noisy. They may provide a better estimation of the hypnotic component of anesthesia than other nonlinear parameters.**

Methods: **The current analysis is based on electroencephalographic data from two similar clinical studies in adult patients undergoing general anesthesia with sevoflurane or propofol. The study period was from induction until patients followed command after surgery, including a reduction of the hypnotic agent after tracheal intubation until patients followed command. Prediction probability was calculated to assess the parameter's ability to separate consciousness from unconsciousness at the transition between both states.**

Results: **Parameters of order pattern analysis provide a prediction probability of maximal 0.85 (training study) and 0.78 (evaluation study) with frequencies from 0 to 30 Hz, and maximal 0.87 (training study) and 0.83 (evaluation study) including frequencies up to 70 Hz, both higher than 0.77 (approximate entropy).**

Conclusions: **Parameters of the nonlinear method order pattern analysis separate consciousness from unconsciousness and are grossly independent of high-frequency components of the electroencephalogram.**

ELECTROENCEPHALOGRAM-BASED monitors have obtained increasing interest as a supplement to standard anesthesia monitoring with the aim of reducing the risk of awareness. The electroencephalogram is based on the electrical activity of the brain, which is picked up by scalp electrodes. Electroencephalographic signals can be understood as a superposition of postsynaptic potentials mainly generated in layer V of the cerebral cortex, an ultrahigh-dimensional dynamical system.[1] The main objective of electroencephalogram-based parameters is a reduction of the complex electroencephalographic pattern to a single value that is associated with the anesthetic drug effect and clinical patient status, *e.g.*, consciousness and unconsciousness.[2]

Different methods have been applied to electroencephalographic signal analysis.[1,3] Parameters based on the frequency spectrum reflect only linear signal properties, where median frequency[3] and spectral edge frequency[3] are well-known examples and have been recently improved by the introduction of weighted spectral median frequency.[4] It has been shown that a restriction of the classic electroencephalographic frequency band (0–30 Hz) using a high-pass filter at 8 Hz and an attenuation of high spectral amplitudes results in a parameter that separates consciousness from unconsciousness.[4] This approach reflects only linear properties of the electroencephalogram and omits frequencies below 8 Hz, which may limit parameter performance over the entire range of anesthesia.

Nonlinear electroencephalographic parameters, *e.g.*, correlation dimension[5,6] and Lempel Ziv complexity,[7] as well as entropies[8] such as approximate entropy (ApEn),[9,10] may emphasize some additional characteristics of the electroencephalogram that are related to nonlinear systems or may be used to model the electrical activity of the brain.[1,8,11] A main problem of most complexity measures such as correlation dimension in analysis of the electroencephalogram is that some requirements for the signal quality are not met, so reliable estimates may not be obtained.[1,12] For example, most such parameters require a sufficient number of data points for calculation, which are not available because the electroencephalogram may not be stationary for time periods longer than a few seconds. ApEn was designed to overcome these restrictions to some extent,[10] and therefore it is included in the current analysis. It has been shown that ApEn can be used to indicate deepening of anesthesia until electroencephalographic burst suppression.[10,13,14] Permutation entropy (PeEn)[15] is a recently introduced method for analyzing time series in general, *i.e.*, without constraints to their generation process. Therefore, PeEn should be adequate to analyze

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electroencephalographic signals that are high dimensional and superposed with artifacts, even if the signal length is limited.[16,17] Both recurrence rate and phase coupling of order recurrence plots (ORR and OPC)[18] can be considered as similar to PeEn. The parameters ApEn, PeEn, ORR, and OPC are assessed using electroencephalographic data at the transition from consciousness to unconsciousness (or *vice versa*). For parameter calculation, different high cutoff frequencies were considered. This indicates how much a parameter may depend on the presence of high-frequency components ($>$ 30 Hz) to distinguish consciousness from unconsciousness. Inclusion of high frequencies bears the risk that such components do not only reflect the electrical cortical activity, but are influenced or generated by the electromyogram, affecting the detection of potential awareness.

A central question is whether the application of nonlinear methods to the analysis of electroencephalographic signals yields information that cannot be obtained by conventional measures. A comparison of both approaches seems to be adequate, but only if the involved electroencephalographic parameters have been carefully adapted to the signal properties.

The aim of this study was to determine which characteristics of selected nonlinear parameters show greatest association with consciousness *versus* unconsciousness. Responsiveness to command was used as a conservative measure of consciousness identifying patients who may soon become capable of formulating recall.[2] Data immediately before and after loss and return of consciousness from two previously studied cohorts were used for parameter calculation, one for parameter development and the other for parameter evaluation.

Materials and Methods

Protocol Design and Data Collection

Data from two clinical studies with similar clinical design were used for the current analysis and were denoted as study A and study B. Both studies were approved by the ethics committee of the Technische Universität München, Faculty of Medicine, Munich, Germany. In each of the studies, 40 consenting adult patients undergoing general anesthesia were enrolled,[2,19] and the study period was from induction of anesthesia until patients followed command after surgery and included a reduction of the hypnotic agent after tracheal intubation until patients followed command. Patients with contraindications to the study drugs, with a history of psychiatric or neurologic disease, drug abuse, or medication known to affect the central nervous system, pregnancy, or indication for rapid-sequence induction were excluded from the study. In study A, patients were randomly assigned to an anesthetic regimen with remifentanil (minimum infusion rate 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and sevoflurane (20 patients) or remifentanil and propofol (20 patients).[2,19] In study B, the sevoflurane and propofol groups were divided into two subgroups with either "low" infusion rate of remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or "high" infusion rate (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$).[2,19] Without premedication, remifentanil infusion was started *via* a cannula in the cubital vein. In 30-s intervals, patients were asked to squeeze the investigator's hand. A response was verified by an immediate repetition of the command that also required a response. This prevents a misinterpretation of involuntary movement as a response. Anesthesia was slowly induced with sevoflurane inhalation or propofol injection (0.7 mg/kg, followed by 20 mg every 30 s). The first time when the patient did not squeeze the investigator's hand to command was labeled as loss of consciousness 1. Additional propofol or sevoflurane was given to increase depth of anesthesia, a tourniquet was used to occlude the circulation of the right forearm for 5 min to maintain the ability to move the hand to command, and then succinylcholine (1.0 mg/kg) was given (Tunstall isolated forearm technique).[20] After intubation, sevoflurane or propofol was stopped until patients followed command (return of consciousness 1). Thereafter, sevoflurane (5 vol%) or propofol (20-mg boluses) was readministered to induce anesthesia again. The time when patients stopped responding to command again was defined as loss of consciousness 2, and requests to squeeze the hand were stopped. Anesthetic drugs were administered according to clinical practice, and surgery was performed. At the end of surgery, requests to squeeze the hand were recommenced, and sevoflurane, propofol, and remifentanil were discontinued. Return of consciousness 2 was observed at the first verified response to command. Recovered from anesthesia, patients were asked for signs of recall in the recovery room. This interview[21] was repeated within 48 h in the ward. Standard monitoring parameters were measured with a Datex AS/3 (Datex-Ohmeda Division Instrumentation Corp., Helsinki, Finland) compact anesthesia monitor. For data transfer and storage, a personal computer with NeuMonD (Department of Anesthesiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany) was used. NeuMonD is a software program developed by members of the research group allowing the recording of monitoring data and the electronic storage of events and comments during the study.[22] In addition to standard monitoring, the electroencephalogram and auditory evoked potentials were measured (study A). Two-channel electroencephalographic signals at electrode positions AT1, M2, Fpz (reference), and F7 (ground) were recorded on a second personal computer with synchronized system time. This auditory evoked potential/electroencephalographic device has been designed specifically for intraoperative use and has been described previously.[23] Electroencephalogram and concomitant trigger information of auditory evoked potentials were stored with a sampling rate of f_s = 1,000 Hz and 12-bit amplitude resolution. In study B, the electroencephalogram was recorded using the Aspect A-1000 electroencephalographic monitor (BIS® version 3.3; Aspect Medical Systems Inc., Newton, MA). A two-channel referential electroencephalogram was obtained from ZipPrep Ag/AgCl electrodes in positions AT1, AT2, Fz (reference), and Fp1 (ground, electrode positions according to the international 10-20 system). The high pass was set at 0.25 Hz, and the notch filter (50 Hz) was enabled. The electroencephalogram was continuously digitized at 256 Hz per channel and simultaneously recorded with standard monitoring parameters. For data analysis in both studies, a time window duration of T = 10 s was used.

Signal processing and statistical analysis were performed using LabVIEW 6.0 (National Instruments, Austin, TX), MATLAB 6.0 release 12 (The MathWorks, Inc., Natick, MA), and R 2.4.0 (R Foundation for Statistical Computing, Vienna, Austria) on personal computers with Windows XP (Microsoft Corporation, Redmond, WA).

Approximate Entropy

In 1991, Pincus *et al.* proposed ApEn, which is related to Kolmogorov Sinai entropy and quantifies the irregularity in a signal.[9,10] Although "long" signals containing as many data points as possible are beneficial to analyze high-dimensional dynamical systems, this requirement cannot be fulfilled in the case of the electroencephalogram, *e.g.*, because of nonstationarity. ApEn should overcome this problem and allows a computation on the basis of signals with moderate length.[10,24] It gives a predictability of current amplitude values based on the knowledge of n previous signal amplitudes, *i.e.*, n is the length of compared runs of data (embedding dimension). The calculation of ApEn is based on a distance function applied to pairs of subvectors of length n, where a noise filter defines the tolerance r that will discern "close" and "not close" subvectors of length n. It has been shown that n and r are in a way dependent on the available signal length N, where $N > 10^n$ is recommended.[9,10] In the current investigation, ApEn is computed using n between 2 and 15 (n of 2 and 3 is recommended),[10] providing subvectors with a time span between 10 and 75 ms. A tolerance of $r = 0.2 \times$ SD of the analyzed electroencephalographic signal is chosen for parameter calculation. A time span of 10 s and f_s = 200 Hz implies a signal length of N = 2,000. Furthermore, parameter calculation is performed using the complete electroencephalographic frequency band from 0.5 Hz, with different high cutoff frequencies f_{high} from 30 to 70 Hz, *i.e.*, with or without the gamma band of the electroencephalogram. To avoid influences of the electromyogram (muscle activity), a high cutoff frequency of 30 Hz is of particular interest in the analysis (classic electroencephalographic frequency band).

In nonlinear signal analysis methods, as represented by ApEn, PeEn, OPC, and ORR, the embedding dimension n is basically intended as one component to determine low-dimensional dynamics of the generating system. It may lead to information about the time evolution of the system state, especially whether a dynamical system shows determinism or is random. Unfortunately, a reliable estimation of n is limited in the case of the electroencephalogram, because the signal is suspected to be ultrahigh-dimensional and may show characteristics similar to noise.[25,26] Even if the methods provide favorable results at specific values of the embedding dimension, conclusions regarding determinism and dimensionality of the electroencephalogram must be drawn with caution. Nevertheless, in the current analysis, varying the embedding dimension n should indicate how much a parameter is sensitive to a specific value of n. Robustness may be advantageous because of the mostly unknown generating dynamics of the brain and because of a shift in predominant frequencies of the electroencephalogram with changing levels of anesthesia.

Permutation Entropy

Permutation entropy was introduced by Bandt *et al.*[15] in 2002. Similarly to ApEn, PeEn is a measure of the irregularity of signals, and it is based on a comparison of the neighboring order of signal values. It has been shown that PeEn is mainly unaffected by signal disturbances, and it can be used to analyze time series generated by high-dimensional systems with low stationarity. Similar to ApEn, PeEn analyzes consecutive subvectors of constant length n (embedding dimension) in the analyzed signal interval. The order of samples in every subvector according to their amplitudes is computed and defines permutations of order n. The parameter value is given by the entropy of the distribution of the obtained permutations and quantifies the monotone behavior of adjacent signal amplitudes. Therefore, PeEn remains independent of absolute amplitude values. A calculation example of PeEn is shown in figure 1. In the current analysis, the dimension n varies between 2 and 15 (n between 3 and 7 is recommended),[15] with a sampling rate corresponding to the frequency f_s of 200 Hz, so that analyzed subvectors include a time span between 10 and 75 ms. If $n!$ is high compared with the number of available samples in the signal, there is a bias in the calculation of PeEn, because the $n!$ possible permutations appear with unequal probabilities.[15] Different settings of the high cutoff frequency f_{high} (as for ApEn) and the embedding dimension n may change the capability of PeEn to separate consciousness from unconsciousness.

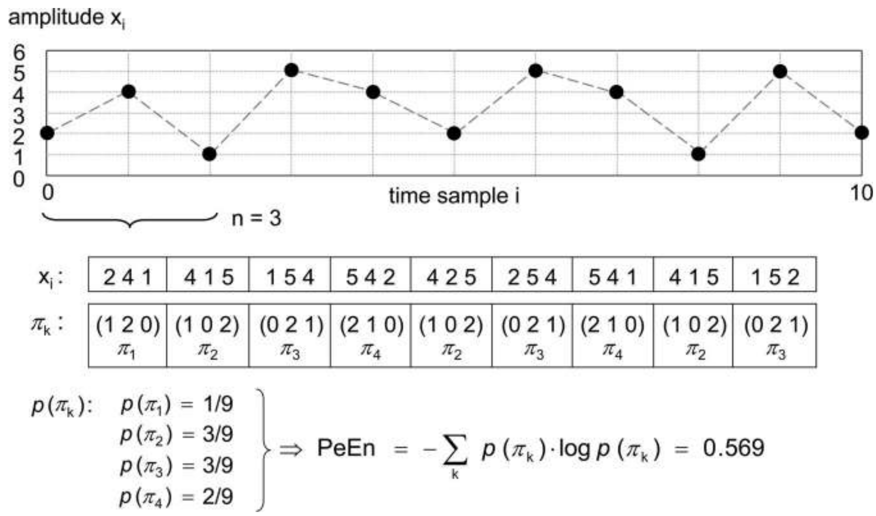

Fig. 1. Exemplary time series with a calculation scheme for the parameter permutation entropy (PeEn) on the basis of an embedding dimension $n = 3$. In a first step, consecutive subvectors of the length n containing amplitude values are extracted from the time series (signal). Second, a ranking of the amplitudes for every obtained subvector is defined. They are called permutations π_k (of order n), because the rankings always consist of the numbers 0 (lowest amplitude value), 1, and 2 (highest amplitude value). Equal amplitude values within a subvector can be changed by the addition of a small random perturbation. This is justified because the amplitude distribution of the electroencephalogram is basically continuous, such that equalities are assumed to be rare. In a third step, the probability $P(\pi_k)$ for the occurrence of every obtained permutation π_k is calculated, defining a probability distribution of the permutations. In a last step, PeEn is obtained as the Shannon entropy of the resulting probability distribution of π_k. It quantifies the amount of different amplitude rankings π_k of length n, where a minimum value of 0 is obtained if only one ranking type occurs, and a maximum is obtained if all rankings are of equal probability.

Order Recurrence Rate and Order Phase Coupling

Recurrence plots detect dependencies in a dynamical system, *i.e.*, coupling properties at different time points of a time series or in multivariate data.[27] Related to the idea of PeEn, recurrence plots can be adapted in the language of order pattern analysis that may improve the robustness against amplitude distortions, as proposed by Groth.[18] Two measures in the context of order recurrence plots are applied in this investigation.

First, the ORR[18] is a measure of statistical similarities in time series, where the similarity is defined by comparing the order of amplitudes in two shifted subvectors of length n (dimension) with respect to a fixed time lag of τ. For these purposes, ORR computes the number of similar pairs of subvectors in the signal. Similarity is defined as 1 when the order of both subvectors is equal; otherwise it is 0. Figure 2 shows the calculation scheme of ORR based on an exemplary time series. In the current analysis, ORR is analyzed on the basis of a frequency range and embedding dimension n as described for the parameter ApEn. For $\tau > 4$, the ability to separate consciousness from unconsciousness decreases. In the anal-

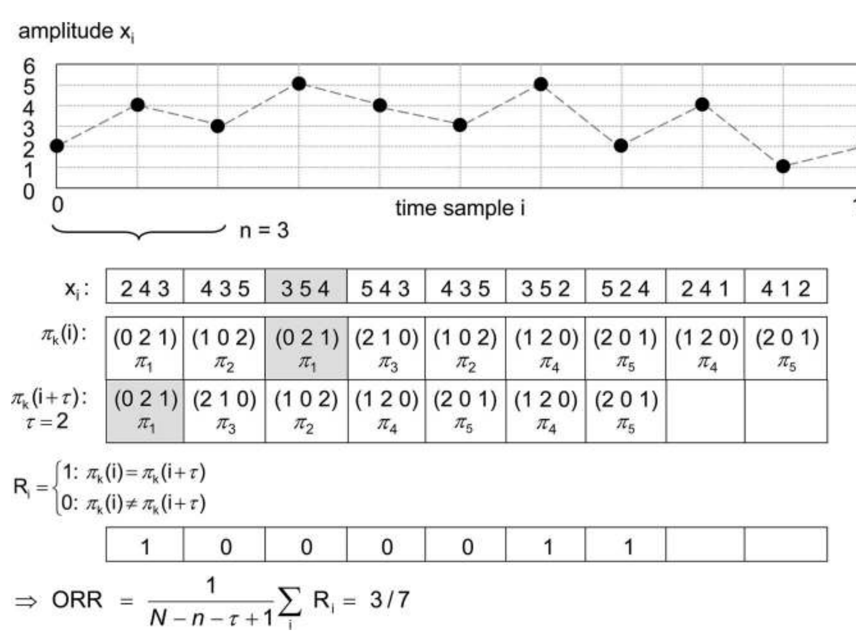

Fig. 2. Exemplary time series with a calculation scheme for the parameter order recurrence rate (ORR) on the basis of an embedding dimension $n = 3$ and a time lag $\tau = 2$. As for calculation of permutation entropy, in the first three steps amplitude values for every subvector of length n are ranked, resulting in permutations $\pi_k(i)$ at every sample i. In a next step, permutations $\pi_k(i)$ are shifted over a time span of τ samples preceding the current sample i (*e.g.*, filled areas). Both current permutations and shifted permutations at samples i are compared, leading to R_i. The comparisons result in 1 if both permutations are equal, and otherwise result in 0. ORR is the sum of the R_i over the signal length and indicates dependencies of signal order with time lag τ. A normalization with respect to the signal length (N samples) leads to comparable parameter values for variable N.

ysis, τ between 1 and 10, *i.e.*, a time lag of 5–50 ms between each pair of subvectors, is considered (see Results). The time lag τ may indicate time related coupling effects in a signal generated by a (low-dimensional) dynamical system.[25,26]

Second, the OPC[18] quantifies the degree of coupling over the time lag τ. It is defined as the Shannon entropy of a normalized ORR over τ, where the time lag τ varies from 1 to a fixed upper bound. Therefore, OPC is related to the calculation of ORR as shown in figure 2. In the current analysis, the frequency range and n are applied as described for the parameter ApEn, and for the upper bound of τ, values from 3 to 10 are used, which allows calculation in an acceptable time frame.

Notice that the above is only a rough description of the mathematically sophisticated parameters ORR and OPC: PeEn, ORR, and OPC reflect similar properties when applied to electroencephalographic signals. Therefore, the main focus is on PeEn, a very understandable and expedient method for electroencephalographic analysis.

Parameter Assessment and Statistical Analysis

Parameter settings for the high cutoff frequency f_{high} and embedding dimension n for the parameters ApEn, PeEn, ORR, and OPC are varied to identify settings that indicate changes from consciousness to unconsciousness (or *vice versa*). This approach will indicate whether the parameters are dependent on signal information with frequencies above the classic electroencephalographic frequency band (f_{high} = 30 Hz) and may therefore include electromyographic information to detect consciousness.

Parameter calculation is based on a set of electroencephalographic signals (samples) of T = 10 s duration directly before or after the transition between consciousness and unconsciousness. Study A and study B each involved 40 patients.[2,4,19] Two signals were analyzed at each of the following clinical events: loss of consciousness 1 and 2 and return of consciousness 1 and 2. Therefore, a maximum of 320 signals was available from each study, A and B (see Protocol Design and Data Collection). The signals are entirely derived from either a phase of consciousness or a phase of unconsciousness. Automatic artifact detection was used to exclude signals of constant amplitude ("flat" line) or values exceeding the measuring range of 250 μV. For study A (development study), 279 signals (133 assigned to consciousness and 146 assigned to unconsciousness) were used for analysis, and for study B (evaluation study), 278 signals (125 assigned to consciousness and 153 assigned to unconsciousness) were used for analysis.

Results from prediction probability (P_K)[28] were used to identify suitable settings for the parameters ApEn, PeEn, ORR, and OPC. Data from study A were used to optimize parameter settings for the upper frequency limit. P_K was calculated for a frequency range of up to (1) 30 Hz, (2) 49 Hz, and (3) 70 Hz. For verification, identified settings were applied to data from study B to calculate P_K for the separation of consciousness from unconsciousness for ApEn, PeEn, ORR, and OPC.

Bootstrap confidence intervals[29] (1,000 resamples, significance level of 95%, Bonferroni correction for the comparison of four P_K test statistics)[30] were used to identify significant differences of P_K values of selected parameters taken from study B.

Results

Results of Study A (Development Study)

Figure 3 shows P_K values for the electroencephalographic parameters ApEn, PeEn, ORR, and OPC on the basis of electroencephalographic data from study A, where a P_K value results for every mapped embedding dimension (n = 2, 3, . . ., 15) and high cutoff frequency (f_{high} = 30, 31, . . ., 70 Hz).

P_K of ApEn (fig. 3A) depends on the choice of the high cutoff frequency f_{high}, *e.g.*, P_K values vary between 0.60 and 0.76 using the recommended[10] embedding dimension of n = 2. A maximum P_K value of 0.77 is obtained for the settings f_{high} = 70 Hz and n = 7.[10]

Order pattern analysis reaches a maximum P_K of 0.87 with settings as shown in table 1. Three groups of high cutoff frequencies are considered: (1) f_{high} = 30 Hz, (2) $f_{high} \leq$ 49 Hz, and (3) $f_{high} \leq$ 70 Hz. In contrast to ApEn with a maximum P_K for f_{high} = 70 Hz, PeEn, ORR, and OPC (figs. 3B–D) achieve maximal P_K values within group 2 with $f_{high} \leq$ 49 Hz. Furthermore, PeEn and ORR are grossly independent of the choice of the high cutoff frequency f_{high}, *e.g.*, P_K of PeEn remains "stable" between 0.84 and 0.87 for the recommended embedding dimension of n = 5.[15] Therefore, order pattern analysis may neither be sensitive nor depend on the presence of high-frequency components in the electroencephalographic signal. Furthermore, P_K of PeEn seems to remain stable if the embedding dimension n is shifted over a wide range between 3 and 12 (P_K between 0.81 and 0.87). The time lags τ = 2 for the parameter ORR and τ = 3 for OPC provide highest P_K for both parameters.

Exemplary Time Series

Figure 4 A shows exemplar time series of the parameters ApEn (n = 2)[10] and PeEn (n = 5)[15] based on the full "classic" electroencephalographic frequency range from 0.5 to 30 Hz. In figure 4B, the plots of ApEn (f_{high} = 70 Hz, n = 7) and PeEn (f_{high} = 42 Hz, n = 9) using the settings with highest P_K are shown, *i.e.*, including the electroencephalographic gamma band, which may contain electromyographic activity.

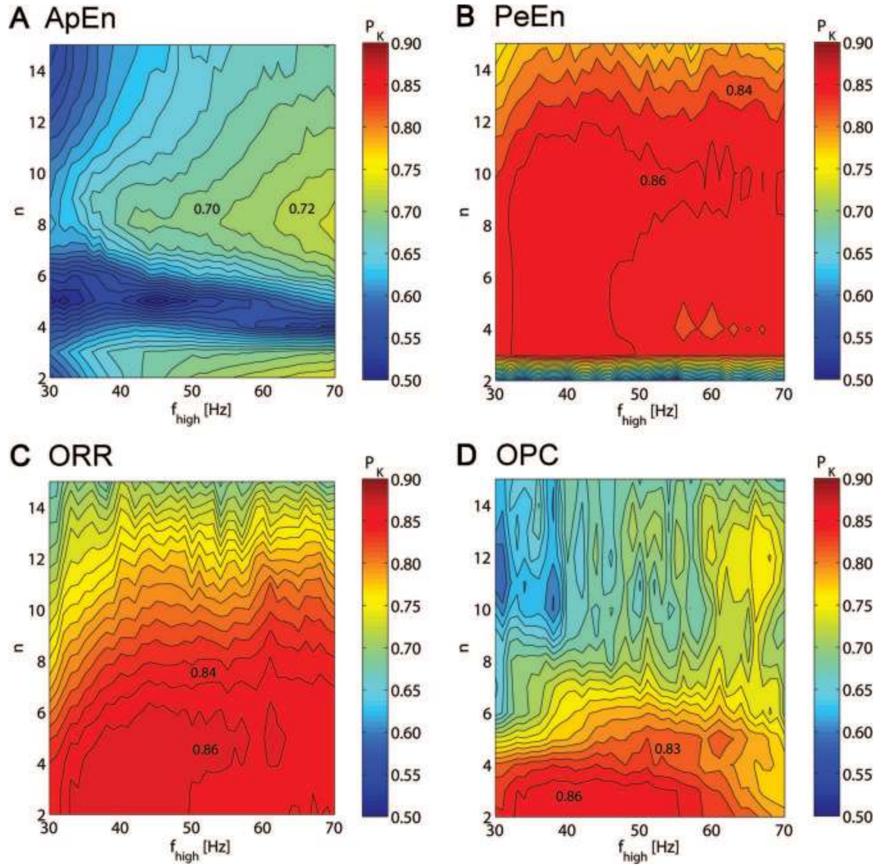

Fig. 3. Prediction probability (P_K) of approximate entropy (ApEn; *A*), permutation entropy (PeEn; *B*), order recurrence rate (ORR; *C*), and order phase coupling (OPC; *D*) based on data from study A (development study). P_K indicates the ability to separate consciousness and unconsciousness at the transition between both states. Parameter calculations include the entire frequency band above 0.5 Hz. For the high cutoff frequency f_{high}, settings between 30 and 70 Hz (x-axis) are considered, and for the embedding dimension n, settings between 2 and 15 (y-axis) are considered. ORR is computed using a time lag $\tau = 2$ leading to highest P_K, and OPC is computed at $\tau = 3$. The resulting P_K values of parameters with corresponding settings of f_{high} and n are plotted as *colors*, where the scaling of the P_K values is indicated by *gradient bars*. The P_K values are interpolated (bilinear interpolation), giving a continuous approximation of the discrete settings to obtain a better presentation. PeEn, ORR, and OPC achieve a maximum $P_K > 0.86$ with a high cutoff frequency below 50 Hz (*dark red area*), in contrast to ApEn, which is dependent on frequencies above 60 Hz to detect consciousness from unconsciousness with a $P_K > 0.72$. PeEn and ORR are grossly independent of f_{high}, *i.e.*, the color remains "stable" along the x-axis. In addition, P_K of PeEn remains unaffected by varying the settings of n between 3 and 12, which is expressed by a constant color scheme in direction of the y-axis. In contrast, P_K of ApEn seems to be sensitive to the settings of f_{high} and n.

Although P_K values of PeEn are mainly independent of f_{high}, the analysis of time series shows that the parameter values are more stable during wakefulness if high frequencies (above the classic electroencephalographic band) are included in the analysis. After loss of consciousness 1, PeEn and ApEn follow the hypnotic component of anesthesia. Before loss of consciousness 1, ApEn may be sensitive to signal disturbances, *e.g.*, generated by muscle artifacts.

Results of Study B (Validation Study)

Parameters with maximal P_K values based on data from study A were validated using electroencephalographic data from study B. The resulting P_K values are shown in table 1.

Order pattern measures PeEn and ORR lead to significantly higher P_K than ApEn for every group of high cutoff frequencies f_{high}, *i.e.*, (1) $f_{high} = 30$ Hz, (2) $f_{high} \leq 49$ Hz, and (3) $f_{high} \leq 70$ Hz. P_K values of parameters based on a high cutoff frequency of $f_{high} = 30$ Hz are not significantly different from the P_K of parameters including frequencies above 30 Hz.

Discussion

Electroencephalogram-based monitoring of the hypnotic component of anesthesia should reliably indicate the level of consciousness and may reduce the risk of awareness in a patient population at high risk.[31] Analysis of the electroencephalogram requires mathematical techniques that reflect information of cortical activity of the brain, which can be seen as an ultrahigh-dimensional nonlinear dynamical system.[1] Such techniques should be as independent as possible from additional sources that may be superposed on the electroencephalogram, such as muscle activity.

Table 1. Prediction Probability Values for Different Settings of the Electroencephalographic Parameters

f_{high}	Parameter	P_K Study A	P_K Study B
30 Hz (group 1)	ApEn (n = 8)	0.66 (0.58–0.74)*	0.61 (0.52–0.69)†
	PeEn (n = 7)	0.85 (0.79–0.91)	0.78 (0.72–0.85)
	ORR (n = 2, τ = 2)	0.85 (0.79–0.90)	0.78 (0.72–0.85)
	OPC (n = 2, τ = 3)	0.85 (0.78–0.90)	0.77 (0.69–0.84)
≤ 49 Hz (group 2)	ApEn (f_{high} = 44 Hz, n = 8)	0.74 (0.65–0.81)†	0.61 (0.50–0.70)*
	PeEn (f_{high} = 42 Hz, n = 9)	0.87 (0.82–0.92)	0.82 (0.75–0.89)
	ORR (f_{high} = 39 Hz, n = 2, τ = 2)	0.87 (0.82–0.92)	0.83 (0.76–0.89)
	OPC (f_{high} = 47 Hz, n = 2, τ = 3)	0.87 (0.81–0.92)	0.81 (0.73–0.87)
≤ 70 Hz (group 3)	ApEn (f_{high} = 70 Hz, n = 7)	0.77 (0.68–0.84)	0.64 (0.55–0.73)†
	PeEn (f_{high} = 42 Hz, n = 9)	0.87 (0.82–0.92)	0.82 (0.75–0.89)
	ORR (f_{high} = 39, n = 2, τ = 2)	0.87 (0.82–0.92)	0.83 (0.76–0.89)
	OPC (f_{high} = 47, n = 2, τ = 3)	0.87 (0.81–0.92)	0.81 (0.73–0.87)

Prediction probability (P_K) values of approximate entropy (ApEn), permutation entropy (PeEn), recurrence rate of order patterns (ORR), and phase coupling of order patterns (OPC) computed from data from study A (maximal P_K values with respect to the specified high cutoff frequencies f_{high} of groups 1, 2, and 3) and study B (P_K values at specified settings) including 95% bootstrap confidence intervals with Bonferroni correction for each group of high cutoff frequency. Disjoint bootstrap confidence intervals indicate significant differences of P_K in groups 1, 2, and 3.

* ApEn significantly different from PeEn, ORR, and OPC. † ApEn significantly different from PeEn and ORR.

n = embedding dimension; τ = time lag.

In a traditional approach, harmonic analysis of the electroencephalogram is used. This may lead to acceptable results for the separation of consciousness from unconsciousness. A recently developed electroencephalographic parameter that follows these criteria is the weighted spectral median frequency.[3,4,32] Nevertheless, nonlinear measures may provide additional information about the signal.[7,8,10,15,33] The electroencephalographic parameters ApEn, PeEn, ORR, and OPC are such nonlinear methods. Each of these parameters has different requirements for the analyzed signal. ApEn analyzes differences of amplitudes, whereas PeEn, ORR, and OPC are based on the analysis of order patterns and analyze order of amplitudes— entirely independent of signal values. This can be advantageous if signals are highly nonstationary and superposed with noise,[15] as is the case with the intraoperatively recorded electroencephalogram. For example, fluctuations in electrode impedance may not essentially affect parameters of order pattern analysis. Previous studies have shown that PeEn, ORR, and OPC are robust against signal artifacts,[15,18] making the parameters suitable for electroencephalographic monitoring of anesthesia. In the current analysis, parameters were calculated from the electroencephalogram

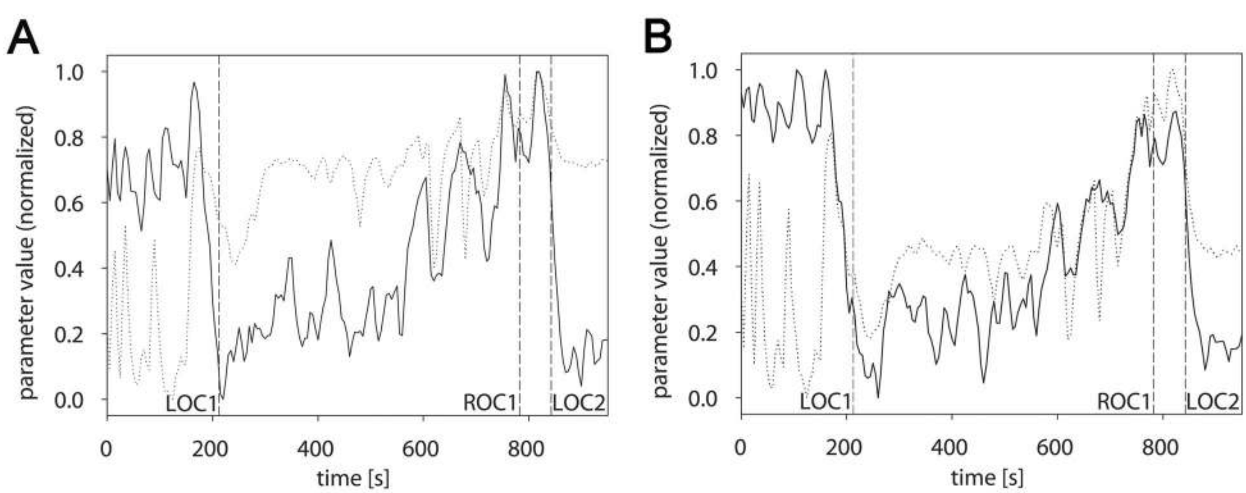

Fig. 4. Parameter time series during induction of anesthesia in a randomly selected patient (propofol) from study A. Parameters approximate entropy (with n = 2; *dotted line*) and permutation entropy (with n = 5; *solid line*) including a frequency range from 0.5 Hz to 30 Hz (*A*), and approximate entropy (with f_{high} = 70 Hz, n = 7; *dotted line*) and permutation entropy (with f_{high} = 42 Hz, n = 9; *solid line*) including the electroencephalographic gamma band (*B*). Parameter values are normalized to the interval (0,1). The *dashed lines* indicate changes of the level of consciousness: loss of consciousness at induction (LOC1: 215 s) and return of consciousness after intubation (ROC1: 785 s), followed by second loss of consciousness (LOC2: 845 s). Permutation entropy indicates the state of consciousness better than approximate entropy. The inclusion of high-frequency components may lead to more stability during wakefulness. Parameter calculation was performed in time steps of 5 s using a signal 10 s in duration (overlapping factor 2).

immediately before and after loss and return of consciousness, to assess their performance at a critical point, the transition between consciousness and unconsciousness. For the current analysis, consciousness was defined as responsiveness to command. This approach identifies intact short-term (working) memory, a memory of small capacity that holds a small amount of information in an active, available state for approximately 20 s and must not be confused with long-term memory (recall). Patients with intact short-term memory will not necessary remember that they were conscious. Nevertheless, intact short-term memory provides the basis for conscious perception and subsequent recall, *i.e.*, avoidance of intact short-term memory will prevent memory and recall.

For both study A and study B, patients were randomly assigned to receive either total intravenous anesthesia or a combination of opioid and volatile anesthetic. This was performed to include both anesthetic regimens equally into the data set for parameter development (study A) and validation (study B) and to avoid overfitting of a parameter to a specific anesthetic regimen.

The application of different settings for parameter configuration shows that order pattern analysis—as represented by the electroencephalographic parameters PeEn, ORR, and OPC—separates consciousness from unconsciousness better than ApEn. On the basis of data from study B (evaluation study), prediction probability analysis of PeEn, ORR, and OPC results in $P_K = 0.78$ if a high cutoff frequency f_{high} of 30 Hz is applied, and $P_K = 0.83$ with a maximal high cutoff frequency f_{high} of 70 Hz.

These results are similar to the P_K values of the spectral parameter weighted spectral median frequency, using the same studies as for the current analysis ($P_K = 0.82$ using data from study A, $P_K = 0.79$ using data from study B with f_{high} of 30 Hz and $P_K = 0.82$ with f_{high} of 49 Hz).[4] Therefore, one may speculate that nonlinear measures do not identify additional crucial information leading to significantly better separation of consciousness and unconsciousness. This may be in part due to signal distortions in the measurement chain of the electroencephalogram. On the other hand, anesthesia-induced unconsciousness may not only be due to cortical effects of anesthesia, but also reflect subcortical mechanisms—which may or may not be detected by changes of cortical electrical activity. In contrast to the presented nonlinear parameters, weighted spectral median frequency considers signal frequencies above 8 Hz only,[4] and this may cause a drawback of the parameter performance during deeper levels of anesthesia. With increasing levels of anesthesia, the electroencephalogram does not only show more regularity, but frequencies are also decreased. Therefore, the inclusion of frequencies in the delta and theta bands, *i.e.*, below 8 Hz, may be essential.

On the basis of a similar data set from study A, a multiparametric indicator of consciousness from the electroencephalographic parameters weighted spectral median frequency and ApEn and on two wavelet coefficients of auditory evoked potentials was developed previously.[2] This indicator reached a P_K of 0.87, which is similar to $P_K = 0.85$ ($f_{high} = 30$ Hz) and $P_K = 0.87$ ($f_{high} = 49$ Hz) as obtained for PeEn, ORR, and OPC. Whereas P_K values are similar, the basis of these values is different. The multiparametric indicator includes information from the auditory evoked potential, which reflects not only a cortical but also a subcortical neuronal pathway. Therefore, it may reflect not only cortical but also subcortical effects of anesthetics. Although this approach may be helpful, because it includes monitoring of important effect sites of anesthesia, it adds requirements and may complicate consciousness monitoring. First, the auditory pathway of patients must be grossly intact, *i.e.*, deafness or severe hardness of hearing may limit the value of anesthesia monitoring. Second, additional equipment is required to produce repeated auditory stimuli. This may increase cost and limit acceptance by the clinical user. This potential drawback may be overcome by the use of nonevoked, spontaneous electrical activity of the brain, the electroencephalogram. With the tested methods of signal analysis, comparable P_K values were obtained. This underlines the potential of the new order pattern analysis in a practical application for electroencephalogram-based monitoring.

Furthermore, parameters of order pattern analysis are largely independent of the upper frequency limit f_{high}, *i.e.*, the classic electroencephalographic frequency band up to 30 Hz contains sufficient information to separate consciousness from unconsciousness. This may be an advantage because inclusion of frequencies above 30 Hz, *i.e.*, analysis of the gamma band, bears the risk that the resulting index does not primarily reflect activity of the main target organ of anesthesia, the brain. In particular, if electrodes are positioned on the forehead, gamma activity is overlapped by electromyogram of the frontal muscle. Therefore, such a parameter may also be a surrogate measure (muscle activity) of the hypnotic component of anesthesia. As a consequence, a patient who is fully awake during neuromuscular block may not be detected as "awake" if no electromyogram is detected.[34]

In addition, P_K of PeEn is independent not only of f_{high} but also of its embedding dimension (fig. 3B). This may indicate that the parameter is robust against more or less unknown underlying characteristics of electroencephalographic signals, and therefore PeEn represents a "state-of-the-art" electroencephalographic parameter to distinguish consciousness from unconsciousness during general anesthesia. Nevertheless, it is unknown to which degree the electroencephalogram contains low-dimensional dynamics,[25,26] and therefore a conclusion about determinism and dimensionality of the electroencephalogram should not be drawn, even if an "optimal" embedding dimension for a specific nonlinear parameter was found.

The current investigation shows that nonlinear measures of the regularity of an electroencephalographic signal are not equally useful for the separation of consciousness from unconsciousness. It is important to which degree such a parameter is influenced by different sources of interference, high dimensionality, and nonstationarity of the signal. Order pattern analysis seems to be a beneficial approach. It leads to parameters that are largely independent of settings (*e.g.*, high cutoff frequency and embedding dimension) and perform equally well on both training and evaluation data sets for separation of consciousness from unconsciousness.

Although ApEn is less adequate to separate consciousness from unconsciousness, it shows a monotone relation between parameter values and anesthetic concentration in phases of increasing anesthetic concentrations until electroencephalographic burst suppression.[10,13,14]

The challenging selection of data immediately before and after loss and return of consciousness leads to analysis periods that are very close both in time and in drug concentration but are characterized by a different clinical patient status. Consideration of four transitions between consciousness and unconsciousness per patient includes evaluation of intraindividual parameter stability in P_K statistics and completes interindividual assessment. In principle, the analysis of repeated measurements from a single patient may induce nonindependent data. In the current analysis, no statistical compensation for possibly dependent data was performed, because measurements from identical clinical states were from distinct time points. In addition, this approach keeps statistical results comparable with those of previous investigations.[2,4] The results support the applicability of order pattern analysis in electroencephalographic monitoring in anesthesia. In the next step, analysis of order patterns must be performed not only for the two states, consciousness and unconsciousness, but for the entire range from light sedation to general anesthesia. It remains to be examined whether ApEn and order pattern analysis, in particular PeEn, can be combined into an indicator of depth of anesthesia.

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