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ORIGINAL RESEARCH

Non-stationarity of EEG during wakefulness and anaesthesia: advantages of EEG permutation entropy monitoring

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Abstract Monitors evaluating the electroencephalogram (EEG) to determine depth of anaesthesia use spectral analysis approaches for analysis windows up to 61.5 s as well as additional smoothing algorithms. Stationary EEG is required to reliably apply the index algorithms. Because of rapid physiological changes, artefacts, etc., the EEG may not always fulfil this requirement. EEG analysis using permutation entropy (PeEn) may overcome this issue, since PeEn can also be applied to practically nonstationary EEG. One objective was to determine the duration of EEG sequences that can be considered stationary at different anaesthetic levels. The second, more important objective was to test the reliability of PeEn to reflect the anaesthetic levels for short EEG segments. EEG was recorded from 15 volunteers undergoing sevoflurane and propofol anaesthesia at different anaesthetic levels and for each group 10 data sets were included. EEG stationarity was evaluated for EEG sample lengths from 4 to 116 s for each level. PeEn was calculated for these sequences using different parameter settings and analysis windows from 2 to 60 s. During wakefulness EEG can only be considered stationary for sequences up to 12 s. With increasing anaesthetic level the probability and duration of stationary EEG increases. PeEn is able to reliably separate consciousness from unconsciousness for EEG segments as short as 2 s. Especially during wakefulness a conflict between stationary EEG sequence durations and methods used for monitoring may exist. PeEn does not require stationarity and functions for EEG sequences as short as 2 s. These promising results seem to support the application of non-linear parameters, such as PeEn, to depth of anaesthesia monitoring.

Keywords Anaesthesia · EEG · Nonlinear signal analysis · Signal stationarity · Depth of anaesthesia monitoring

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1 Introduction

Monitoring of the hypnotic component of anaesthesia using the electroencephalogram has become an established method to assess "depth of anaesthesia". This task may be performed by different analytical methods. Commercially available monitors mainly use spectral analyses such as the bispectrum or spectral entropy [1, 2]. The application of these frequency-based methods requires stationarity of the EEG over the analysis period [3]. Since EEG is the result of highly complex cortical activity originating from different sources, the EEG signal in most instances does not fulfil the requirement of stationarity, especially not in circumstances of longer analysis periods [1]. Generally, EEG is a non-stationary signal, though it can contain stationary episodes. The most widely used depth of anaesthesia monitor, the bispectral index BIS (Covidien, Mansfield, MA, USA) uses EEG segments up to 61.5 s for index calculation [1]. The spectral entropy integrated in the Entropy Module (GE Healthcare, Helsinki, Finland) also analyses EEG periods of up to 60 s for index calculation. The non-linear parameter permutation entropy (PeEn) [4] has also proved to be suitable for depth of anaesthesia

monitoring [5, 6]. As an advantage of PeEn, it does only require very weak stationarity [4] of the underlying signal. The first objective of the presented analysis was to determine the duration of EEG sequences that can be considered stationary at different anaesthetic levels of sevoflurane and propofol in order to reveal possible conflicts between EEG segment length used for index calculation and duration of stationarity signal episodes. After determination of the length of stationary sequences at different anaesthetic levels, the second objective was to test the reliability of PeEn to reflect the anaesthetic levels for EEG segments shorter than the stationarity threshold. Efforts were made to determine the lower EEG sequence time limit for reliable separation between consciousness and unconsciousness.

2 Methods

2.1 Study design

The experiments were based on the study conducted and published by Horn et al. [7]. In brief, after approval from the ethics committee of the Technische Universität München, Munich, Germany, EEG was recorded in fifteen male volunteers (18–35 years, ASA-status I). Electrodes were placed at the forehead [AT1, Fz (reference) and Fpz (ground), according to the international 10–20 system]. All volunteers received both, sevoflurane and propofol mono-anaesthesia on 2 different days following a cross-over design. Details can be found in the article by Horn et al. [7]. EEG was recorded at five distinct and stable levels of sevoflurane or propofol anaesthesia. These levels represented the states awake, loss of consciousness (LOC), burst suppression and two intermediate levels inter1 and inter2. Anaesthesia was either induced with propofol (effect-site target concentration: 1.0 μg/ml) or sevoflurane (end-expiratory target concentration: 0.5 vol %). Drug concentrations were increased in a stepwise manner (propofol: target-controlled infusion (TCI): 0.1 μg/ml; sevoflurane end-expired concentration: 0.1 vol %) until the test subjects failed to respond to the verbal command "squeeze my hand". This event was denoted as LOC. Anaesthetic concentrations were subsequently increased until the EEG showed burst suppression patterns. Drug concentrations required to reach the intermediate levels were derived by dividing the difference between the anaesthetic's concentration at LOC and burst suppression into three equal intervals. The study protocol is displayed in Fig. 1. During the course of anaesthesia, each targeted level was maintained for 15 min. EEG was recorded during the last 2 min of the stable levels at a sampling rate of 1 kHz, filtered with a band-pass (0.5–400 Hz) and stored on a personal computer. Only EEG sequences that did not show EEG

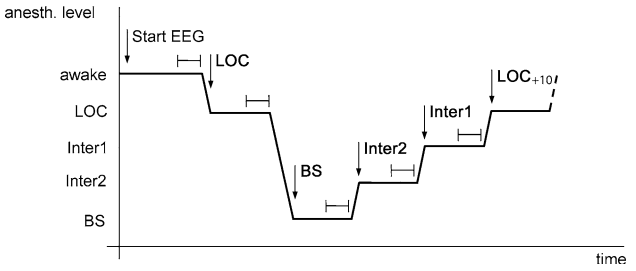

Fig. 1 Study design: Each anaesthetic level was maintained for 15 min. A 100 s EEG sequence was extracted at the end of each stable level

potentials exceeding 250 μV or amplitude differences of more than 140 μV/ms were used for further analyses. This led to an n of ten for the sevoflurane as well as for the propofol group. Because periods of burst suppression EEG are innately non-stationary due to the transitions from burst intervals to suppression episodes [1], they were excluded during the analysis process. The extracted sequences were used for "weak", i.e., evaluating the time behaviour of the root mean square RMS value only, stationarity analysis. In order to avoid high frequent influences, for instance electromyographic (muscle) activity which may be particularly contaminate the EEG γ-band ($f > 30$ Hz), a digital Butterworth low pass filter with cut-off frequency of 30 Hz was used before parameter calculation followed by a down sampling to $fs = 200$ Hz. The filtering was performed using LabView 6i (National Instruments, Austin, TX, USA). Stationarity analysis was additionally performed for the EEG segments after filtering to the bandwidths 0.8–32 Hz (Entropy Module, SE) and 11–20 Hz (BIS, one component in the relative β-ratio) in order to reflect frequency ranges used for index calculation by the monitors.

2.2 Stationarity analysis

Weak stationarity analysis was performed using LabView 6i as described by Bendat and Piersol [8]. Signals were considered non-stationary if they showed time varying RMS. Therefore, the selected sequences were divided in non-overlapping EEG samples and RMS was calculated over each of these segments leading to a series of RMS values: RMS (1), RMS (2),.., RMS (i), …. A reversal r is counted every time RMS (i) < RMS (j) for all i < j. The total number of detected reversals is denoted A. The maximum possible number of reversals is $r = r(r-1)/2$. If the EEG sequence does not show a trend, i.e., is stationary, r should be close to $r = r(r-1)/4$.

Shortest EEG sample length was 10 s and segment length was consecutively increased by 2 s steps, up to 116 s. For each 2 s block within the sample a RMS value was obtained. The block length of 2 s was chosen to ensure

that also the slow delta frequency band with frequencies down to 0.5 Hz are included. The obtained RMS values of each 2 s sample were used for the reverse arrangement test as a criterion for weak stationarity.

Z-score was calculated according to Beck et al. [9] using equation

$$z = \frac{A - \left[\frac{N(N-1)}{4}\right]}{\sqrt{\frac{2N^3+3N^2-5N}{72}}}.$$

A represents the number of reverse arrangements in the samples, and N is the total number of samples in the sequence. Significance level to reject the null hypothesis that there is no underlying trend and the analysed sequence is stationary, was set to $p < 0.05$, i.e., a z-score of $|z| < 1.96$.

2.3 Permutation entropy

PeEn is an ordinal measure of signal complexity and well established in the evaluation of anaesthetic effects on the EEG [5, 6]. In the applied PeEn algorithm the signal (i.e., EEG) is converted into a sequence of permutation patterns of ranks of $m = 5$ ("embedding dimension") data points and the probability of each permutation is used to calculate an entropy value according to the Shannon entropy. A permutation pattern is formed by coding the EEG amplitudes of m data points to their ranks within the EEG segment of length m. For example an EEG segment of $m = 3$ (EEG(t1) = 50 μV, EEG(t2) = 75 μV, EEG(t3) = 30 μV) is coded to the pattern 1-2-0, the highest EEG amplitude value in the pattern is set to the highest rank. A detailed explanation can be found elsewhere [4, 5]. PeEn as an ordinal method can be applied to almost non-stationary signal sequences. Calculation of PeEn was carried out using LabView 6i.

2.4 Statistical analyses

Prediction probability P_K [10] can be performed without any knowledge about particular parameter threshold values which renders the test more independent from specific test data. It has been established in anaesthesia as a statistical method to asses the capability of a parameter to distinguish between different anaesthetic levels. The aim of the test is to quantify the association between the (clinically) observed anaesthetic levels and the parameter values. In contrast to other statistical tests, non parametric P_K is independent from scale units and assumptions on underlying distributions. For dichotomous paradigms P_K is equal to the area under the receiver operating curve (AUC) and can be calculated as follows: Let $x = (x_1, x_2, \ldots, x_n)$ be the vector of obtained parameter values and $y = (y_1, y_2, \ldots, y_n)$ the corresponding observed anaesthetic level, in our case $y_i \in \{0\ (\text{unconscious}),\ 1\ (\text{conscious})\}$. P_K differs three cases, (A) the probability p_c, that a pair (x_i, x_j) $(i, j \in \{1, \ldots, n\},\ i \neq j)$ of arbitrary drawn parameter values is in concordance with the anaesthetic level (y_i, y_j), i.e. $y_i > y_j \Rightarrow x_i > x_j$, (B) the probability p_d that it is in discordance, i.e. $y_i > y_j \Rightarrow x_i < x_j$ and (C) the probability p_t that a parameter value is assigned to more than one anaesthetic level, i.e. $y_i \neq y_j \Rightarrow x_i = x_j$. Then $P_K = \frac{2 \cdot p_c + p_t}{2 \cdot (p_c + p_d + p_t)}$, where a value of 1 gives a completely concordant relation between x and y, $P_K = 0$ implies completely discordant relation and $P_K = 0.5$ means that there is no relation between x and y. To estimate the uncertainness of the realization of the test statistic 95 % percentile bootstrap confidence intervals were applied (PK-Tool [11]).

In the present analysis the ability of PeEn to separate consciousness (baseline) from unconsciousness (LOC) using different analysis periods (T = 2, 4… 60 s) was evaluated Further, P_K analysis was used to detect possible differences between effects of sevoflurane and propofol on PeEn. PeEn values obtained for one regimen at one anaesthetic level and one EEG window length were pooled. From this pool ten PeEn values were randomly extracted from the sevoflurane as well as from the propofol group. Additionally power spectral density PSD was calculated from the EEG raw data using Welch's method with MATLAB R2012a (The MathWorks, Natick, MA, USA) to detect changes in the EEG spectrum.

Further, Mann–Whitney U test was used to evaluate differences on stationarity induced by the different anaesthetics, i.e., sevoflurane and propofol.

3 Results

In EEG sequences recorded during consciousness the probability of a recorded sequence to be stationary decreases with the length of the segments in all analysed frequency ranges. The exact values for the states "awake" and propofol or sevoflurane induced LOC are presented in Table 1. The EEG stationarity during LOC is strongly influenced by the anaesthetic used whereas at levels "inter1" and "inter2" the probability of a stationary sequence are always above 90 % independent of the drug used and the analysed EEG segment length.

Nonetheless, different effects of either drug on the stationarity issue can be observed at LOC. For example significantly different probabilities for stationary sequences of pooled EEG sequences from 32 to 60 s taken from either the propofol-induced or sevoflurane-induced LOC could be

Table 1 Probabilites of stationary sequences for different EEG frequency bands at levels "awake" and propofol or sevoflurane-induced LOC

Frequency range (Hz)	Anaesthetic level	Probability of stationary sequences			
		10–20 s	22–30 s	32–60 s	62–120 s
0.5–30	Awake	0.93 (0.03)	0.86 (0.03)	0.85 (0.06)	0.78 (0.10)
	LOC (propofol)	0.91 (0.05)	0.89 (0.03)	0.83 (0.04)	0.91 (0.07)
	LOC (sevoflurane)	0.87 (0.07)	0.80 (0.04)	0.74 (0.09)	0.83 (0.11)
0.8–32	Awake	0.94 (0.04)	0.91 (0.03)	0.87 (0.06)	0.80 (0.11)
	LOC (propofol)	0.91 (0.04)	0.88 (0.05)	0.82 (0.05)	0.87 (0.08)
	LOC (sevoflurane)	0.90 (0.07)	0.80 (0.03)	0.76 (0.08)	0.82 (0.12)
11–20	Awake	0.91 (0.04)	0.92 (0.04)	0.90 (0.07)	0.85 (0.09)
	LOC (propofol)	0.89 (0.05)	0.91 (0.06)	0.89 (0.06)	0.74 (0.15)
	LOC (sevoflurane)	0.88 (0.08)	0.78 (0.07)	0.78 (0.10)	0.83 (0.08)

The probability of stationary sequences decreases for with EEG segment length. The probability of stationary sequences is smaller at LOC than at wakefulness. The probability also depends on the anaesthetic used

observed in all analyzed frequency ranges. The Mann–Whitney U test showed a significant higher probability of stationary sequences in the propofol group than in the sevoflurane group (threshold $p < 0.05$). In the 0.5–30 Hz range, probability of stationary sequences was 83.1 ± 3.6 % (mean ± standard deviation) for propofol and 73.9 ± 8.7 % for sevoflurane ($p = 0.001$). Further, probabilities were 81.9 ± 4.5 % (propofol) and 76.1 ± 8.1 % (sevoflurane, $p = 0.013$) in the 0.8–32 Hz range and 88.6 ± 5.7 % (propofol) and 77.9 ± 10.0 % (sevoflurane, $p = 0.003$) in the 11–20 Hz range.

3.1 Performance of PeEn for short EEG segments

PeEn values derived with a parameter order of $m = 5$ as recommended in the literature [4] were used to analyse EEG segments of different length. PeEn values were obtained from EEG recorded at baseline (awake), LOC, inter1 and inter2 for EEG sequences of 2, 10 and 30 s in length. Figure 2 presents the single PeEn values for a randomly chosen sevoflurane and propofol experiment as well as box plots displaying the overall performance in the sevoflurane and propofol group.

According to results in Fig. 2, PeEn provides a separation of consciousness from unconscious conditions which is mainly independent from the analysis period. These findings are confirmed by a P_K analysis, which was performed to assess the ability of PeEn to distinguish between consciousness and unconscious states (combined LOC, inter1 and inter2) for EEG sequences of different length. The results are presented in Table 2.

In order to reveal substance specific differences, PSD of the raw EEG traces was calculated for both anaesthetics and the results are displayed in Fig. 3. In both groups, slow frequencies in the δ-range (1–4 Hz) are activated with the anaesthetic and a secondary peak can be observed at frequencies in the α- (8–12 Hz) and θ-range (4–8 Hz) at levels LOC, inter1, and inter2. For sevoflurane, the peak occurs at slower frequencies at inter1 and 2 compared to propofol. These drug specific effects impact PeEn. At inter1 and inter2 significantly different PeEn values between sevoflurane and propofol were obtained for all EEG segment lengths. The corresponding P_K values and confidence intervals are presented in Table 3.

4 Discussion

Our results show an increasing probability of EEG stationarity with increasing levels of anaesthesia. In addition, this stationary is maintained over longer sequences of the EEG. For patients awake, EEG stationarity is maintained for sequences up to 12 s. The probability of stationarity decreases with longer EEG sequences. The width of EEG analysis windows for BIS and Entropy Module is up to 60 s [1, 2]. In fully conscious patients, only 2/3 to 3/4 of EEG sequences between 50 and 60 s in length can be considered stationary. Cohen and Sances as well as Kawabata reported that EEG sequences up to 25 s can be regarded stationary in humans awake [3, 12]. The presented results confirm these findings. EEG sequences of 20 s in length are stationary with a probability of approximately 90 %. At deeper anaesthetic levels inter1 and inter2, the probability of stationarity of an EEG sequence increases. Hence, the most critical states with respect to non-stationary of EEG sequences are wakefulness and LOC. At this level the probability of stationary sequences was also dependent on the anaesthetic used. The EEG was stationary more often for propofol. EEG recordings derived from subjects awake are often distorted by artefacts such as EMG or eye blinks. These distracting factors are mainly absent during anaesthesia. Further, during consciousness, there is a higher

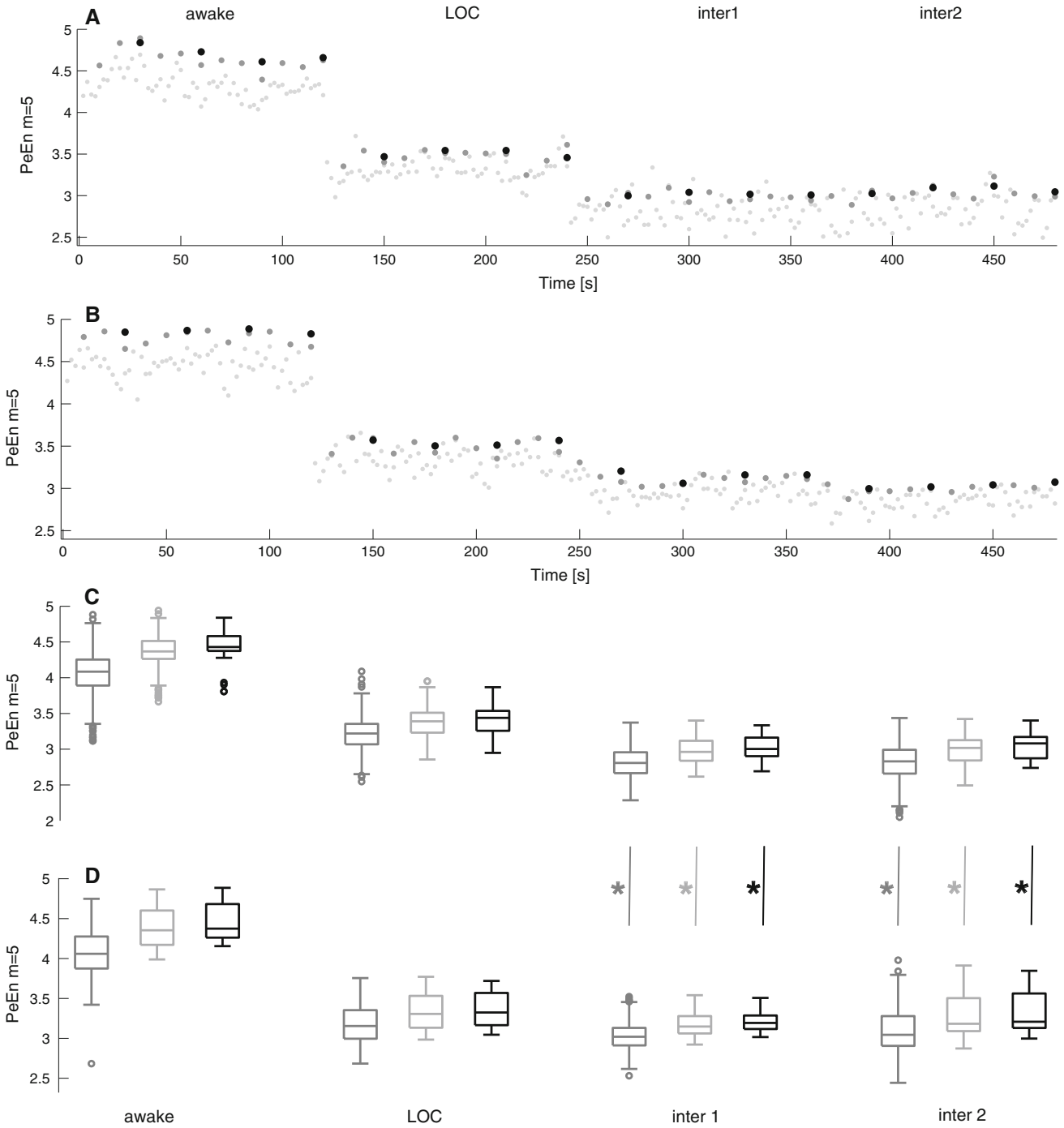

Fig. 2 Representative course from an exemplary volunteer of PeEn calculated from EEG segments of different length (*black circle* 30 s, *dark grey circle* 10 s, *light grey circle* 2 s) at anaesthetic levels awake, LOC, inter1 and inter2 induced by sevoflurane (**a**) or propofol (**b**). The absolute values of PeEn may differ for different segment lengths within one anaesthetic level but a very good separation between parameter values from "awake" EEG and anaesthetic levels can be observed. The *box plots* represent the PeEn distribution (*black*: EEG segment length 30 s, *dark grey*: 10 s, *light grey*: 2 s) over all volunteers and all anaesthetic levels induced with sevoflurane (**c**) or propofol (**d**). The *horizontal bar* in *each box* represents the median. *Upper* and *lower box* limit represent the 25th and 75th percentiles (q_1 and q_3). Maximum whisker span is from $q_3 + 1.5(q_3-q_1)$ to $q_1-1.5(q_3-q_1)$. Parameter values outside the interval are considered outliers

degree of information processing throughout the cortex—the generator of the EEG—intracortically and corticocortically. With anaesthesia, cortical high frequency activity, related to information transfer and processing dilutes [13] causing the EEG to be stationary over longer time segments. These findings suggest that only short EEG

Table 2 P_K values and corresponding confidence intervals for the PeEn analyses ($m = 5$) of EEG segments of different length

EEG segment length	P_K(CI)				
	2 s	4 s	10 s	30 s	60 s
Propofol	0.98 (0.92–1)	1	1	1	1
Sevoflurane	0.99 (0.97–1)	1	0.99 (0.95–1)	0.99 (0.96–1)	0.99 (0.94–1)
Combined	0.98 (0.95–1)	0.99 (0.98–1)	0.98 (0.95–1)	0.98 (0.95–1)	0.97 (0.94–1)

The P_K values evaluate the performance of PeEn to separate between the state awake and the anaesthetic levels (LOC, inter1, inter2). For the single anaesthetics and the combined analysis, P_K values are very close to 1, i.e. PeEn performs adequately in distinguishing the state awake from anaesthetic levels

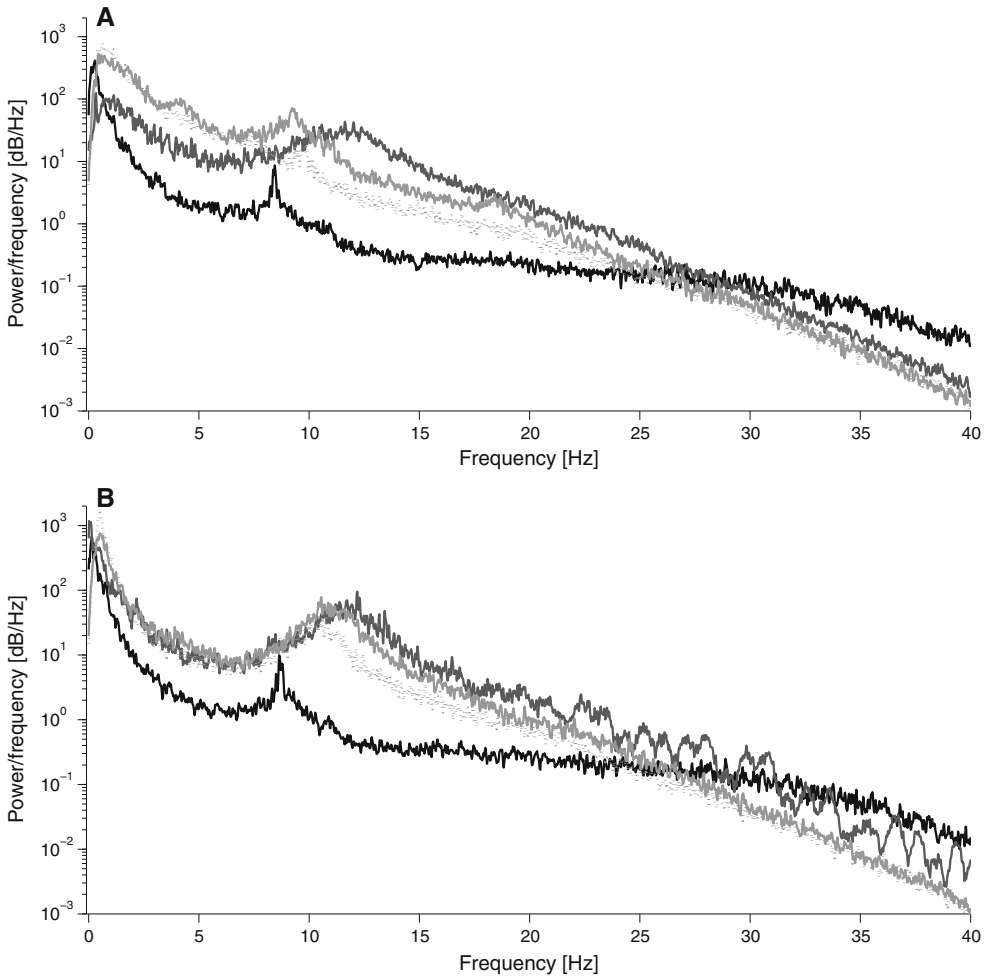

Fig. 3 Averaged power spectra for the sevoflurane (**a**) and propofol (**b**) analyses for the anaesthetic levels "awake" (*black*), LOC (*dark grey*), inter1 (*grey, solid*), and inter2 (*grey, dotted*). In the sevoflurane group peak frequencies in the alpha and theta band are shifted left compared to the propofol group

sequences up to 25 s should by used for an analysis which requires stationary signals. But these short sequences may conflict with the analysis windows of BIS and Entropy Module algorithms, both methods which require stationarity.

PeEn seems well suited to monitor anaesthesia. It has been shown to be a useful method to evaluate the anaesthetic level and to distinguish between consciousness and unconsciousness [5, 6]. The present investigation completes results from a previous study showing that the ordinal measure separates both states without inclusion of the EEG high frequency γ-band and mostly independent from a selected order m [5]. Exclusion of the EEG γ-band may focus more on cortical activity rather than surrogate muscle activity. Furthermore, independence from order m improves the parameters robustness with respect to changing neural dynamics. The possibility to analyse non-stationary data allows application of PeEn with less limitations than they pertain for spectral approaches. Results show that PeEn is capable to distinguish consciousness

Table 3 P_K values and confidence intervals (CI) indicate different effects of propofol and sevoflurane on PeEn at the different anaesthetic levels

EEG segment length	P_K (CI)		
	2 s	10 s	30 s
LOC	0.45 (0.20–0.71)	0.45 (0.19–0.71)	0.46 (0.21–0.74)
inter1	**0.78 (0.56–0.97)**	**0.81 (0.59–0.97)**	**0.81 (0.59–0.98)**
inter2	**0.78 (0.55–0.95)**	**0.80 (0.58–0.96)**	**0.80 (0.57–0.96)**

If the CI does not contain 0.50 a significant different PeEn values were observed with sevoflurane than with propofol. At inter1 and inter2 significant differences could be detected for all EEG segment lengths (printed in bold)

from unconsciousness for EEG segments as short as 2 s. This is superior to reported time delays of sometimes more than 1 min for available EEG monitors like BIS, Entropy Module and other devices [14–16]. The ability to generate valid results for such short EEG segments makes the measure mostly independent from the signal stationarity issue. A short delay of the depth of anaesthesia index is particularly important for detecting wakefulness. Conscious episodes of 30 s or more increase the risk of recall [17, 18] and therefore long delays may not be able to prevent this phenomenon. The derived results of the stationarity analysis question the performance of spectral parameters during consciousness and sedation. The finding that PeEn does even work for short EEG sequences overcoming the stationarity issue supports the application of this parameter to depth of anaesthesia monitoring. An additional finding is the drug dependence for both, stationarity analysis and PeEn calculation. Although P_K values and hence performance of the parameter seem similar, the applied drugs alter the EEG in different ways. Sevoflurane causes a left shift of peak frequencies in the α- and θ- frequency range leading to different PeEn values. These observations support the view that a unitary method to evaluate anaesthetic levels may not be the best choice. Drug specific properties should be taken into consideration.

4.1 Limitations

The data set that was used for the experiments was derived from a volunteer study. The test subjects did not receive opioids or muscle relaxants. The observed effects are solely caused by the anaesthetic but EMG may influence the EEG recordings since there is a wide overlap of the EEG and EMG frequency spectra. This leads a possible limitation that observed effects may be not only due to anaesthetic induced changes in EEG activity but also due to modifications of EMG activity. The study setup only contained EEG recordings from frontal positions hence the influence of recording positions on the parameter performance could not be evaluated and is subject for further studies.

Other possible limitations to be considered may be the performance of PeEn to distinguish different anaesthetic levels. Separation between consciousness and unconscious states by PeEn is very good, but different levels of anaesthesia may not reliably be differentiated. Other parameters like approximate entropy may be better suited to fulfil this task [5]. Further, the experiments revealed drug dependence, i.e., different performances for sevoflurane and propofol.

PeEn seems to perform reliably in separating consciousness from unconsciousness for EEG sequences as short as 2 s. Commercial EEG monitors using spectral approaches calculate their index from EEG segments up to 60 s in length. This leads to the increased risk that these monitors have to deal with non-stationary episodes possibly influencing index calculation by sudden changes in the spectrum, e.g. due to artefacts. This may lead to longer calculation times, since it takes longer to "collect" valid data or increased risk of invalid or no index values to display, because of poor signal quality. With the use of very short EEG segments PeEn seems to be able to display valid indexes very fast if the signal is of good quality and come back to valid indexes very quickly, if artefacts were detected and valid PeEn calculation was not possible.

To sum up, the results point out that there may be a conflict between the length of EEG windows used for depth of anaesthesia monitoring with spectral approaches and a possible non-stationarity of these EEG sequences. PeEn, being an ordinal measure, does not require stationarity and performs reliably for EEG sequences as short as 2 s. These promising results support the application of non-linear parameters, such as PeEn, to depth of anaesthesia monitoring.

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