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Correlation between the EEG monitors BIS and State entropy and their performance in differentiate consciousness and unconsciousness - an EEG Reanalysis

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1 Introduction

1.1 Anesthesia and intraoperative awareness

Anesthesia means the absence of sensation and consciousness as induced by various anesthetic medications. It can be separated into distinct components: muscle relaxation, sedation-hypnosis (defined as loss of consciousness), amnesia, analgesia, control of vital signs and ablation of autonomic reflexes[1].

The depth of anaesthesia is planned to allow the surgical procedure to be performed without the patient experiencing pain, moving, or having any recall of the procedure. The desirable aim of anesthesia is a fast and smooth induction with an adequate depth of anesthesia during surgery, a fast recovery and little risk of side-effects. An inadequate depth of anesthesia might come along with episodes of intraoperative awareness which can occur in every anesthetic procedure or surgery.[2]

The 2006 Practice Advisory of the ASA Task Force on Intraoperative awareness defines that "intraoperative awareness occurs when a patient becomes conscious during a procedure performed under general anaesthesia and subsequently has recall of these events".[3] But it is necessary to differentiate intraoperative awareness from postoperative recall, because intraoperative awareness does not necessarily consolidate memories.

According to Jones[4] intraoperative awareness can be classified in 4 different levels. In level 4 no awareness occurs as this is the actual aim of anesthesia.

- Level 1: Intraoperative awareness with explicit memory
- Level 2: Intraoperative awareness with implicit memory
- Level 3: Intraoperative awareness without memory
- Level 4: No awareness

Both explicit (conscious) and implicit (unconscious) memory may have enduring effects for patients. Adults who experience intra-operative awareness can develop disturbing long-lasting after-effects, such as daytime anxiety, sleep disturbances, nightmares, flashbacks and, in the worst case, post-traumatic stress disorder (PTSD).[5]

In a study from Sandin et al. 2000[6], 11785 patients were asked about memory of intraoperative awareness after surgery in general anesthesia using a standardized

interview. After leaving the recovery room the patients were interviewed. This interview was repeated on day 1-3 after surgery and on day 7-14. 0.18% of the patients who received muscle relaxants had memory of intraoperative awareness, whereas only 0.1% of patients who had not received muscle relaxant had memory of intraoperative awareness.

As a result, the use of relaxant during surgery increases the risk of intraoperative awareness compared to patients without muscle paralysis.

1.2 Source of brain waves and electroencephalogram

The human brain contains more than 100 billions of neurons and most of them are able to communicate with many other neurons. Electrical activity is created through this communication process, termed signaling which results in the EEG. To transmit information the neuron must generate an electrical current, a so-called action potential. Generation of an action potential requires an electrical or chemical stimulus which changes the ion flow into the cell.[7]

The electrical current that flows into and out of the cell is carried by ions, both positively charged (cations) and negatively charged (anions). Cations move in the direction of the electrical current whereas anions move in the opposite direction. The polarity of the resting membrane is changed by the ionic flow which results in a more negative (hyperpolarization) or less negative membrane potential (depolarization)[7].

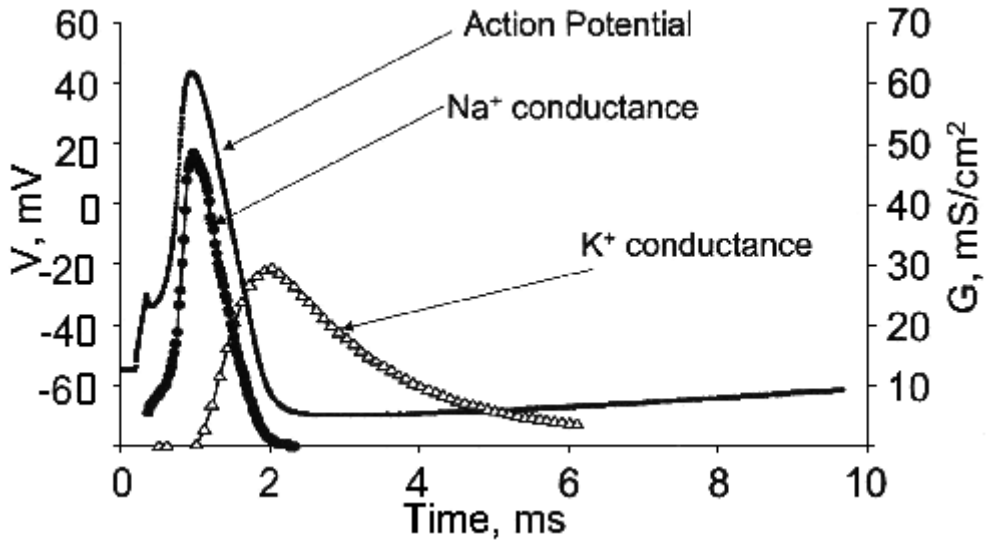

Figure 1 from Bezanilla 2006 [8]: Openings of channels during the action potentialDuring the action potential, the membrane voltage goes from its resting value of about -70 mV (negative inside) to about +30 mV in less than 1 ms and returns to its resting value within a few milliseconds (Figure 1)[8]. When the membrane potential reaches a threshold (-55 to -60 mV) the voltage-gated Na+ channels open rapidly. The influx of Na+ leads to a more positive interior of the cell whereas the K+ concentration which normally is higher inside the cell decreases[7]. This ionic shift leads to a change of the electrical membrane potential. Along the cell membrane an electrical potential gradient is caused which again leads to the formation of an electrical dipole surrounding the whole cell. This dipole can be measured from the surface of the head if there is a sum of several synchrone dipoles. For the EEG performance only the vertical pyramide cells in the cortex are relevant[9].

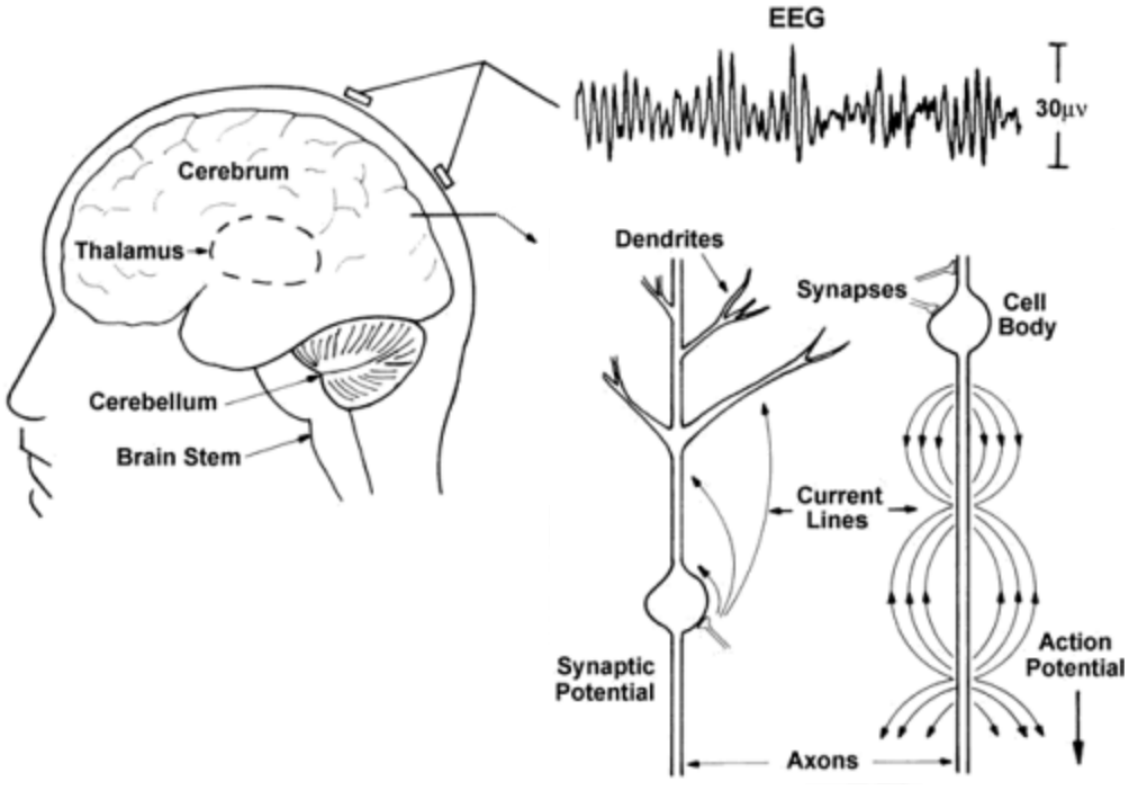

Figure 2, modified from Nunez 2006, Electric fields of the brain[10]: Generation of EEG

The recorded EEG is a time series of potential changes generated in the cortex. In the recorded EEG, the changing voltage between the electrodes is plotted against time. A wave-like line is generated which amplitude expresses the voltage in mcV (Figure 1: Opening of channels during action potential). These oscillations can be classified in different frequency bands as alpha, beta, theta, delta and gamma waves (Figure 3)[11].

EEG can be measured on the scalp using electrodes. They are usually located and defined according to the International 10 – 20 System[12]. This system ensures that the denotation of electrodes is consistent across laboratories and hospitals.

EEG waveforms are generally classified according to their frequency, amplitude, and shape, as well as the site on the scalp at which they are recorded[13],[9].

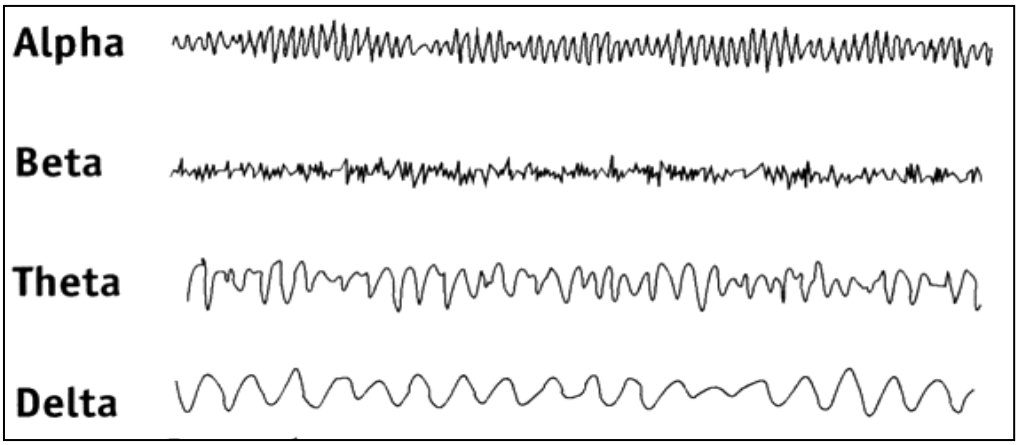

Figure 3: Simplified classification of EEG waves[9]

Alpha activity is mostly associated with relaxation, closed eyes or attentional demands and disappears normally with attention (mental arithmetic, stress, opening eyes). Beta activity is common in emotional and cognitive processes and is attended by a small amplitude in the EEG. Drugs, such as barbiturates and benzodiazepines, augment beta waves. Theta and delta waves are known collectively as slow waves and are mostly seen at sleep (Table 1)[9]. Gamma waves the frequency range approximately 30–100 Hz. Gamma rhythms are thought to represent binding of different populations of neurons together into a network for the purpose of carrying out a certain cognitive or motor function[13].

Cerebral signals observed on the scalp ranging from 0 to 30 Hz are mostly a sign of cortical activity. Frequencies above 30Hz can be increasingly overlapped with artefacts from the EMG[10].

Type	Frequency
Delta	0,5 – 3 Hz
Theta	4 – 7 Hz
Alpha	8 – 12 Hz
Beta	13 - 30 Hz
Gamma	30 – 100 Hz

Table 1: Classification of different EEG frequencies[14]

1.2.1 Anesthetic – induced effects on the EEG

An EEG recording from a healthy awake person shows predominantly alpha waves or beta activity. Anesthetics change EEG activity in following way:
A light sedation with anesthetics leads to an activation of alpha and beta rhythm with mostly high frequented beta waves. With increasing sedation, slow frequencies in the theta respectively delta range become prominent in the range of general anesthesia. Further augmentation of anesthetics lead to an increasing diminution of electric activity to the extent of cortical silence. So called “burst suppressions” occurs between deep anesthesia and isoelectrical EEG and is characterized by waxing and waning phases[15].

1.3 Analysis Methods

1.3.1 Concept of Entropy

Entropy is a measure of disorder, in signal theory Entropy quantifies the information content within a signal.
Shannon and Weaver first defined entropy in 1949 as complexity, irregularity and unpredictability[16]. It can also be described as chaotic pattern according to Pritchard and

Duke[17]. With entropy the complexity, respectively the information content of a signal can be determined. By definition, entropy measures variation or change in a series of events; unchanging patterns have zero entropy, or zero information[16].
A high complexity results in a high information content and hence the Entropy is also high.

1.3.2 Spectral Entropy

The concept of spectral entropy is based on a measure of information called Shannon entropy[16]. The Spectral Entropy is the Shannon entropy applied to the power spectrum of a time series, e.g. EEG[18]. First the power spectrum is calculated for the different frequency ranges and then normalized so the sum of all spectral components equals to one with

$$Q(f) = \frac{P(f)}{\sum_{f} P(f)}$$

where Q(f) is the sum of the normalized power spectral components over the considered frequency range and P(f) is the power spectrum. To obtain transformed components, the normalized power spectrum components are transformed by the Shannon functions H(f): f(x) = log (1/x):

$$H(f) = Q(f) \times \log\left(\frac{1}{Q(f)}\right)$$

The transformed components are added in the next step and the result is normalized to range between 1 (maximum irregularity) and 0 (complete regularity) by dividing the sum with the factor log (N), where N is equal to the total number of frequency components.

$$E = \frac{\sum_{f} H(f)}{\log(N)}$$

To obtain each frequency component from a time window that is ideal for that particular frequency, different sets of window duration are used within the Entropy Module optimizing between time and frequency resolution[19].

1.3.3 State Entropy

Different analytical concepts were introduced to quantify the changes of the electroencephalogram. The Datex-Ohmeda S/5 Entropy Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) was the first commercial monitor based on the entropy generating two indices, State Entropy (SE) and Response Entropy (RE)[20].

SE is computed over the frequency range from 0.8 Hz to 32 Hz and is designed to monitor the depth of hypnosis. For frequencies below 2 Hz the largest time window with 60.12 s is used. The non-dimensional value which represents the state of consciousness respectively the depth of anesthesia is very stable and ranges between 0 (no EEG activity) and 91 (awake) and can never be higher than RE[9]. Low entropy values indicate unconsciousness[21].

SE includes the EEG-dominant part of the spectrum and consequently reflects mainly the influence of anesthesia on the cortical state of the patient. It is an slowly reacting parameter with a reaction time of 15-30s[9]. During adequate anesthesia, RE and SE should have the same values due to absence of frontal EMG activity.

1.3.4 Response Entropy

RE is computed over a frequency range from 0.8 Hz to 47 Hz and includes both, the EEG-dominant and EMG-dominant areas of the spectrum. For frequencies between 32 and 47 Hz the shortest time window with 1.92 s is used. RE is a non-dimensional value between 100 (awake) and 0 (no EEG or FEMG activity). Low Entropy numbers indicate unconsciousness (Table 2)[21,22].

Muscle activity during anesthesia creates a significant EMG component which can be measured from the forehead of a patient in the form of a biopotential signal mostly at frequencies higher than 30 Hz. The lower frequencies up to 30 Hz are dominated by the EEG signal but at higher frequencies EEG power decreases exponentially[23]. A sudden appearance of EMG signal data might be created due to an external stimulus like a painful stimulus in a surgical event. Such a response may result if the level of analgesia is insufficient[23].

RE includes the EEG-dominant part of the spectrum and the frontal EMG activity. The reason for using higher frequency bandpass in RE is to allow faster response from the monitor in relation to clinical state[23]. Other EEG monitors like the BIS attempt to filter EMG signal from their data interpretation, the Entropy algorithm posits that EMG data are useful and may in some circumstances be more sensitive to light level of unconsciousness or analgesia than EEG[24].

	RE	SE
Patient fully awake and accessible	100	91
General anesthesia	60-40	60-40
Supression of cortical activity	0	0

Table 2: Values of RE and SE [9]

Due to the high frequencies of the facial muscles RE is an quick – adapted parameter with an reaction time of 2s[9] [9]. RE–SE difference may indicate nociception or inadequate anesthesia. If the difference between RE and SE averages more than 10, it is likely that the patient is going to move[9].

1.3.5 Bispectral Index

To measure the hypnotic component of anesthesia, EEG is the method of choice. As parameters like blood pressure, heart rate, secretion of tears and sweat may not suffice to detect intraoperative awareness or to quantify the central effects of anesthesia, several measures have been introduced during the last decades for this purpose[25].
The most widely adopted EEG measure of anesthetic drug effect is Bispectral Index (BIS™ monitor, Aspect Medical Systems, Newton, MA, USA). To collect the EEG, BIS uses a sensor placed in the forehead and temple of the patient[26].

To compute the BIS, several variables derived from the electroencephalographic time domain (burst-suppression analysis), frequency domain (power spectrum, bispectrum:

interfrequency phase relationships) are analysed and combined into a single index representing the actual hypnotic level. The BIS monitor provides a single dimensionless number which ranges from 0 to 100 with specific ranges (e.g., 40–60) reported to reflect a low probability of consciousness under general anesthesia[27] (Table 3).

BIS Index	Stadium
80 – 100	Awakeness, reaction to normal sound level
60 – 80	Sedation
40 – 60	General anesthesia
20 – 40	Deep anesthesia
0 – 20	"Burst suppression"
0	EEG silence; isoelectric EEG

Table 3: BIS values [28]

A BIS value of 0 equals isoelectric EEG, values close to 100 are expected in a fully awake adult, and BIS between 40 and 60 indicates general anesthesia[29].
Consequently, the BIS monitor gives the anesthesist an indication of the hypnotic level of anesthesia and it allows to adjust the amount of anesthetic agent to the need of the patient, possibly resulting in faster recovery from anesthesia. Also the BIS monitor may reduce the incidence of intraoperative awareness[30].
As with other types of EEG monitors evaluating the hypnotic component of anesthesia, the calculation algorithm and the exact weighting of all sub-parameter that lead to the BIS is not available from the proprietors. Therefore, although the principles of BIS and other monitors are known, the exact method in each case is not[31].

1.3.6 Fast Fourier Transformation

Every periodic function can be presented as an infinite sum of sine and cosine waves of different frequency[32]. The native integral - based approach to computing a Fourier transform is very complex and hence calculation times are long even if processed with a computer. Cooley and Tukey published 1965 an algorithm[33] for efficient computation of

Fourier series from digitized data. This algorithm is known as the DFT[34]. For recorded EEG, Fourier analysis is performed using the DFT. Therewith, it is possible to get information about frequencies and amplitudes in the EEG. The FFT is an efficient algorithm for computing the DFT of a sequence with second data values[35].

The results of an EEG Fourier transform are graphically displayed as a power versus frequency histogram in clinical monitoring applications. Originally the phase spectrum has been considered as uninteresting in EEG monitoring. The BIS uses information from both, the power and the phase spectra[34]. The concordance between frequency and EEG can be represented as covariance.

The frequency spectrum is relatively independent from the start point of an epoch (relative to the waveforms contained), the Fourier phase spectrum is highly dependent on the start point of sampling and thus very variable[34].

The power spectrum is the result of the FFT which makes it able to estimate the distribution of the frequencies in the observed EEG segment. Using the power spectrum, it is possible to evaluate the frequency distribution in EEG segments visually. To create the power spectrum, the EEG is divided into separate sine waves with different frequencies. The power spectrum indicates to which extent each frequency is represented[36].

1.4 Aim of the study

Several studies demonstrated a correlation between the hypnotic component of anesthesia and SE[22],[37] respectively BIS[38], [39]. As investigated in a study, a BIS below 60 may significantly reduce the risk of intraoperative awareness[40].

However, several studies exist in which intraoperative awareness appears even though the BIS is below 60. In a study of Schneider et al., 9 from 80 patients sustain intraoperative awareness with a BIS below 60 [41].

The aim of the clinical study this work is based on, is to investigate to what extent SE correlates with the hypnotic component of general anesthesia at the transition of awareness and unconsciousness as shown for the BIS[42]. For this purpose, the ability of SE to differentiate recorded EEG at the states “awake” and “unconscious” 30s before and 30s after LOC and ROC is evaluated. This involves a critical range, in fact the transition between consciousness and unconsciousness is considered and not the stable values that can be obtained during deep anesthesia or at complete awareness.

In another step, EEG recorded during surgical procedures was replayed to SE and BIS simultaneously and the resulting indices were compared. This helps to evaluate the ability of SE to indicate the state of consciousness and to prevent intraoperative awareness. Mean values, SD and PK values for BIS cited in this study were taken from the publication from Bracher[42], where the study design was equal: Replayed EEG data were used to compute the index values and all values were taken from the transition of consciousness and unconsciousness.

2 Materials and Methods

2.1 Study design

The ethics committee of the Technische Universität München, Munich, Germany approved the study in which patients gave informed written consent to the protocol.
Inclusion criteria for the participants of the study were an age over 18 years with an ASA physical status of I or II[43],[3] and undergoing elective surgery under general anesthesia with tracheal intubation.

ASA Physical Status Classification System

I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes

Patients with contraindications to the used drugs, drug abuse, medication affecting the central nervous system, pregnancy, a history of psychiatric or neurological disease or indication for rapid sequence induction were excluded from the study.

Two groups with 40 patients in total were formed using blocked randomization. One group with n= 20 patients received anesthesia with sevoflurane inhalation and remifentanil infusion (sevo group) while the other group with n= 20 patients was having total intravenous anesthesia with propofol injection and remifentanil infusion (propofol group).

2.2 Procedure

After arrival in the induction room, an intravenous line was inserted into a large forearm vein and standard monitoring including noninvasive measurements of blood pressure, oxygen saturation and ECG were applied.
Inspiratory oxygen, end-tidal carbon dioxide and sevoflurane concentration (group 2) and respiratory parameters were monitored with a Datex® AS/3 compact monitor (Datex Ohmeda, Helsinki, Finland). EEG was recorded with the biomed device[44] at 1 kHz sampling rate and a pass band of 0.5 to 400 Hz and stored on a personal computer.

Patients did not receive any premedication before surgery. A slow induction of anesthesia was performed: Oxygen was given by face mask and lactated Ringer´s solution was administered. ECG, Pulse oximeter and blood pressure cuff were applied. Remifentanil was applied via a cannula in the cubital vein starting at 0,2 µg/kg/min. During induction and recovery, the patient was asked every 30s to squeeze the investigator´s hand to assess the patients state of consciousness. In order to exclude misinterpretation of involuntary movement as response, the command was immediately repeated also requiring a response.
Depending on the group, anesthesia was started with sevoflurane mask induction (sevo group) or propofol injection with 0.7 mg kg^{1} and additional 20mg every 30s (propofol group). The first time the patient did not response to the command was defined as loss of consciousness 1 (LOC 1). Additional propofol or sevoflurane was given after LOC 1 to increase the level of anesthesia. The patients were ventilated with face mask. The right upper arm was occluded with a tourniquet over systolic blood pressure to separate circulation from the rest of the body and to maintain the ability to move the hand despite of relaxation (Tunstall´s isolated forearm technique)[45]. Then 1mg/kg succinylcholine was given.

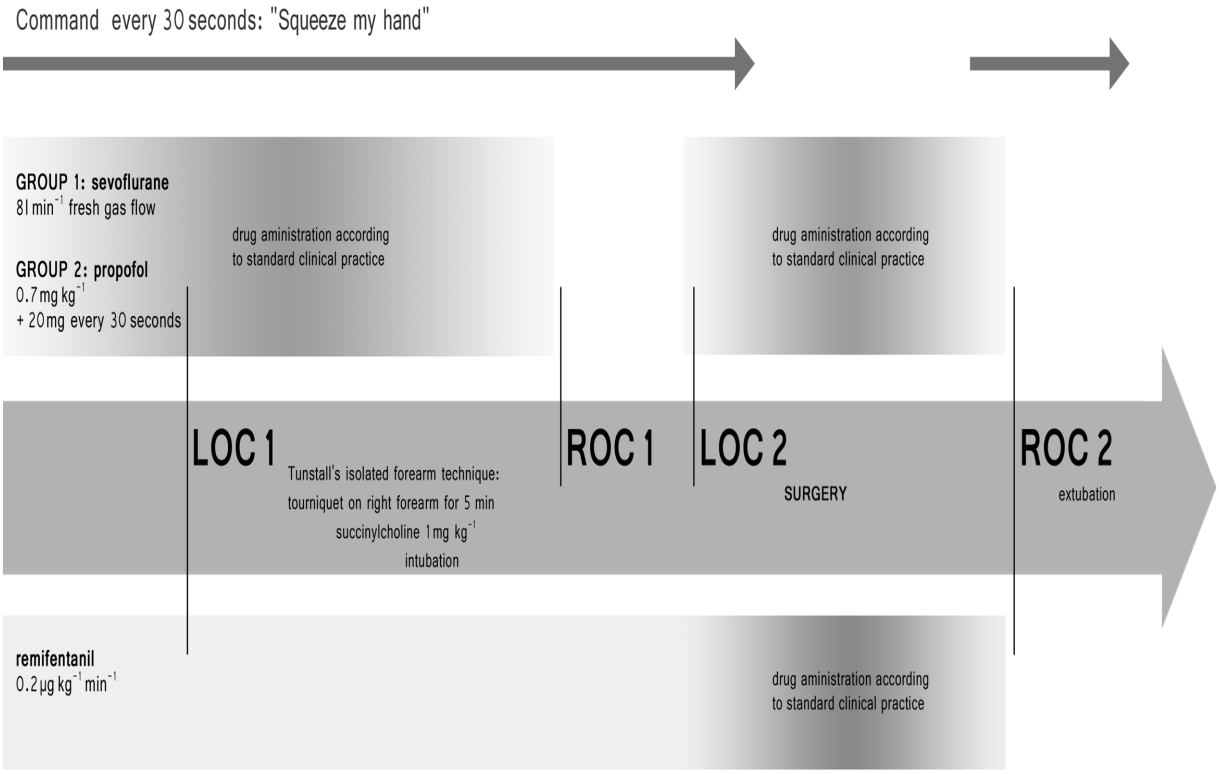

Figure 4: Study design

The trachea was intubated and the patient was ventilated. The application of remifentanil was continued while sevoflurane or propofol application was stopped so that the depth of sedation decreases until the patient followed the investigator´s command again. This was defined as return of consciousness 1 (ROC 1).

After ROC 1, sevoflurane inhalation (5 Vol%) or propofol bolus injection (20 mg every 20s until loss of consciousness) was given again until patients stopped squeezing the investigator´s hand. This was defined as loss of consciousness 2 (LOC 2) (Figure 4).

After LOC 2, the commands were discontinued, propofol, sevoflurane and remifentanil were applied according to clinical practice and surgery was performed. The emergence phase started after surgery with discontinuation of the anesthetic drugs and patients were asked to squeeze hands again. When the first verified response to a command was achieved, return of consciousness 2 (ROC 2) was defined.

Patients were continuously monitored in the recovery room. Afterwards they were tested for recall using a standardized interview[46] detecting intraoperative awareness which was repeated within 48h on the ward.

Postoperative interview questions according to Brice:

1. What is the last thing you remember before you went to sleep for your operation?
2. What is the first thing you remember after your operation?
3. Can you remember anything in between these two periods?
4. Did you dream during your operation?
5. What was the worst thing about your operation?

2.3 Recording the EEG

The first electrode (AT 1) was applied at the left temporal region between the lateral edge of the eye and the upper edge of the ear. The second electrode was placed on the right mastoid (M2). Fpz was set as reference and F7 was ground. All electrodes were positioned according to the international 10-20 system[12]. Before electrode application the skin was prepared with alcohol to obtain impedances of less than 5 kΩ.
EEG was recorded from ZipPrep electrodes (Aspect Medical Systems, Newton, MA).
Recording of a two-channel referential EEG was performed with a 1 kHz digitizing rate and an analogue band-pass from 0.5Hz (high pass) to 400Hz (low pass).

The recorded EEG was replayed[14] to the entropy module (SE and RE) at the transitions phases and in a second experiment the entire recordings were simultaneously replayed to the entropy module and BIS.
For SE, 9796 valid data pairs in the sevoflurane and 7507 valid data pairs in the propofol group, a total of 48h EEG, were used for analysis.

2.4 Statistical Analysis

To evaluate the performance of the EEG parameter objectively different statistical analysis methods can be used to clarify to which extent the received data (SE and RE indices) reflect the underlying process (state of consciousness).

The PK is a measure to differentiate between two different states and evaluates the performance of SE and BIS to distinguish between the states “awake” and “unconscious”. It is useful to depict the performance of both monitors[47].

PK ranges between 0 and 1. A value of 0.5 means that the index value cannot separate between two states. Prediction probability is 50%, i.e. like flipping a coin. A PK of 1 means correct classification for every measurement and a PK of 0 is obtained when a monitor indicates exactly the opposite of the clinical status in all cases. According to Smith and Dutton[47] PK is an appropriate measure for evaluating the performance of anesthetic depth indicators. As a measure of association, the PK shows how reliable the index differentiates between awareness and unconsciousness.

To compare SE and BIS, Pearson’s correlation coefficient (r) is calculated as a measure of the linear dependence between two variables x and y, giving a value between +1 and -1 inclusive. Is $r > 0$ a positive correlation exists, $r < 0$ means a negative correlation. A value close to 0 means that no linear correlation exists whereas values close to 1 (>0.8) mean strong correlation[48].

To depict the index values of SE and RE at the transitions boxplots are used. The box itself represents the band in which are 50% of the mean data which are the index values of SE and RE at the transition of consciousness and unconsciousness. The whiskers are the lines which enlarge the box and indicate the values outside of this 50%. The boxplot also indicates if any of the observed index values can be considered as outliers[49,50].

Bland-Altmann plot was used to analyze the agreement of the index values during simultaneous replay of the recorded EEG to SE and BIS. In its horizontal lines the average of SE and BIS index values are represented whereas the vertical line shows the difference between SE and BIS.

Consistent characteristics are demonstrated as mean values and SD. The t-test ($p<0.05$) is applied to compare the groups for unrelated samples.

3 Results

3.1 Demographic Data

In the study, a total of 40 patients undergoing surgery are analyzed. The patients are split in two groups with different drug regimen.
Both groups consist of 20 patients, 17 female, and 23 male.
The mean age, height, sex, weight and ASA physical status in the sevo and propofol group are stated as follows (Table 4).

Group	Height, Mean ± SD in cm	Weight, Mean ± SD in kg	Age, Mean ± SD, yr	Sex, F/M , n	ASA Physical Status I/ II
Sevo	172 ± 7	77 ± 14	44 ± 14	8 / 12	12 / 18
Propofol	173 ± 11	74 ± 13	42 ± 15	9 / 11	14 / 6

Table 4: Demographic data

According to the t-test there are no significant differences ($p<0.05$) between the propofol group and the sevo group regarding height, weight, age, sex, or of ASA physical status.

3.2 State Entropy values at transitions

The boxplot (Figure 5) represents the index values during transition of awareness and unconsciousness according to the time sequence of loss and return of consciousness (LOC & ROC).
Calculations are adjusted in such a way that the index values were not used directly from the transition, but 30 seconds after loss or regain of consciousness.

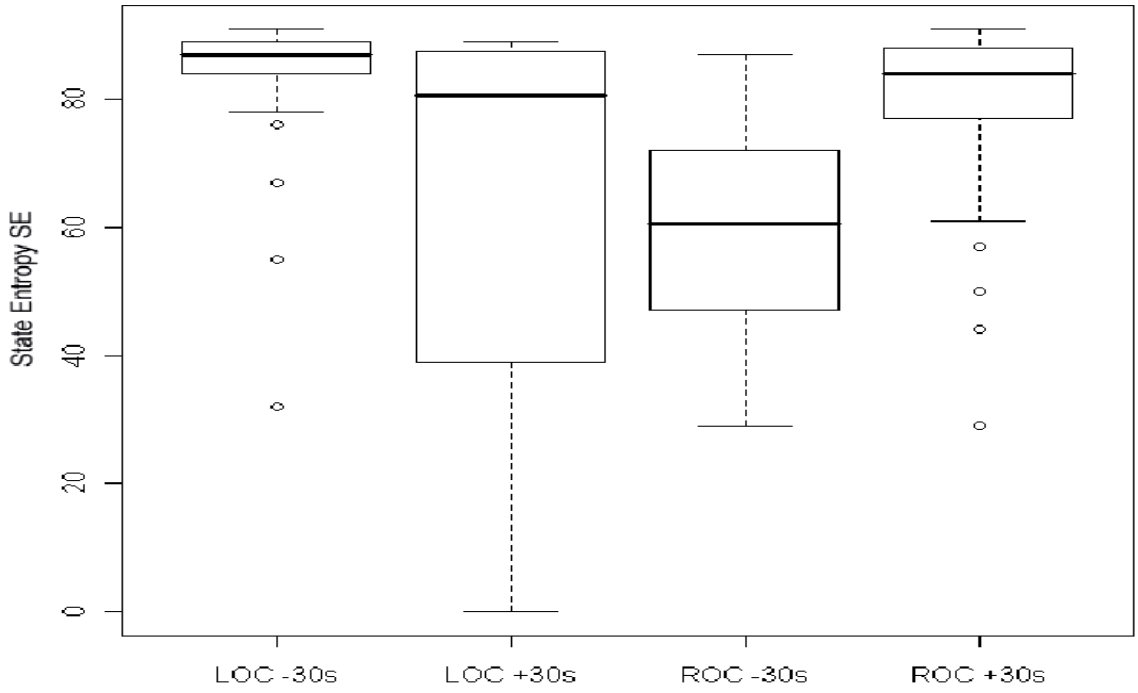

Figure 5: Performance SE in the sevo group

The boxplot for SE in the sevo group (Figure 5) displays the full range of all measured index values, from minimum to maximum. The length of the box shows the interquartile range (IQR) which varies the most at LOC +30s. At LOC -30s and at ROC +30s the IQR is very narrow which assumes a good accordance between all measured index values and the state at the transition of consciousness. The median of all index values at LOC -30s, LOC +30s , ROC -30s and ROC +30 is marked as the line in the box itself. Values outlying the 50% of data inside the box are depicted as the whiskers which highest variation range can be seen at LOC +30s. Index values outlying the whiskers are plotted as dots.

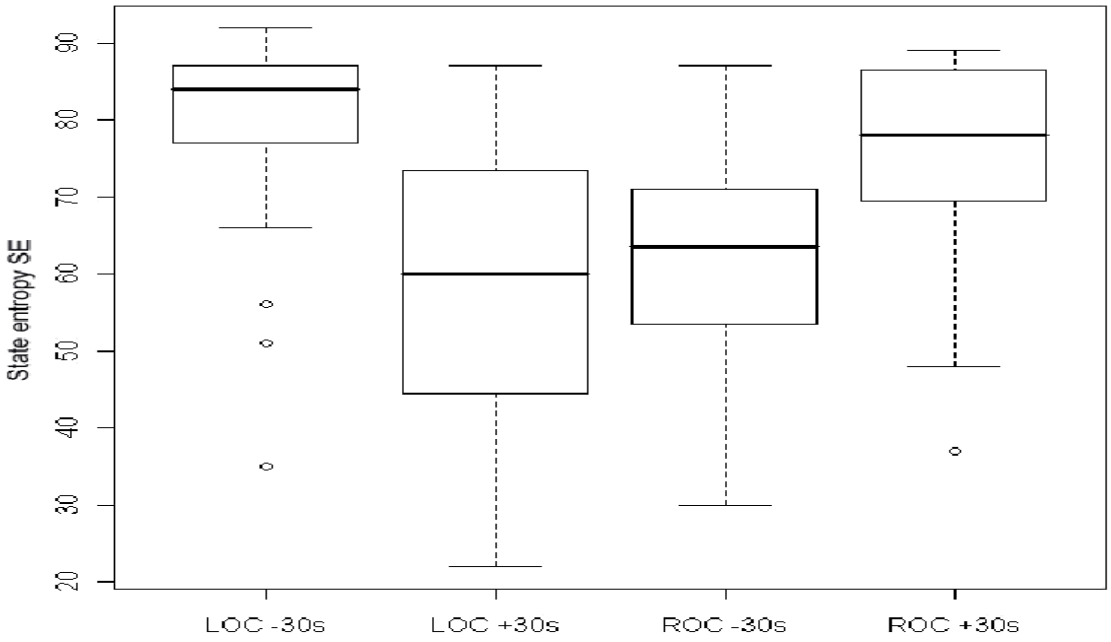

Figure 6: Performance SE in the propofol group

For the propofol (Figure 6) group the allocation of all index values at the transition between consciousness and unconsciousness is similar to the sevo group. The lowest IQR is seen at LOC -30s whereas the widest IQR can be stated at LOC +30s with 50% of all index values between 45 and 75 approximately.

The index values were measured and recorded every 10 s at SE. From all index values in the sevo and the propofol group the mean value and SD were calculated as shown below (Table 5 and Table 6):

	Mean values	SD
LOC1 -30s	84.3	8.83
LOC1 +30s	58.65	25.88
ROC1 -30s	52.6	15.84
ROC1 +30s	81.15	9.84
LOC2 -30s	83.1	12.51
LOC2 +30s	72.94	27.50
ROC2 -30s	65.58	12.70
ROC2 +30s	79.42	14.07

Table 5: Mean index and SD of SE in the sevo group

	Mean values	SD
LOC1 -30s	84.16	4.95
LOC1 +30s	54.21	22.82
ROC1 -30s	60.68	16.56
ROC1 +30s	77.05	10.34
LOC2 -30s	75.00	14.30
LOC2 +30s	63.42	14.18
ROC2 -30s	62.19	10.01
ROC2 +30s	76.81	11.24

Table 6: Mean index and SD of SE in the propofol group

3.3 Response Entropy values at transitions

This boxplot (Figure 7) depicts the index values for RE 30 seconds after loss or regaining consciousness according to the time sequence.

It shows the dispersion of all measured index values in the sevo group. The IQR at LOC -30s and ROC +30s is very low and ranges between 95 and 100 approximately. At LOC +30s the IQR varies the most which shows a weak accordance between the measured index values and the state of consciousness.

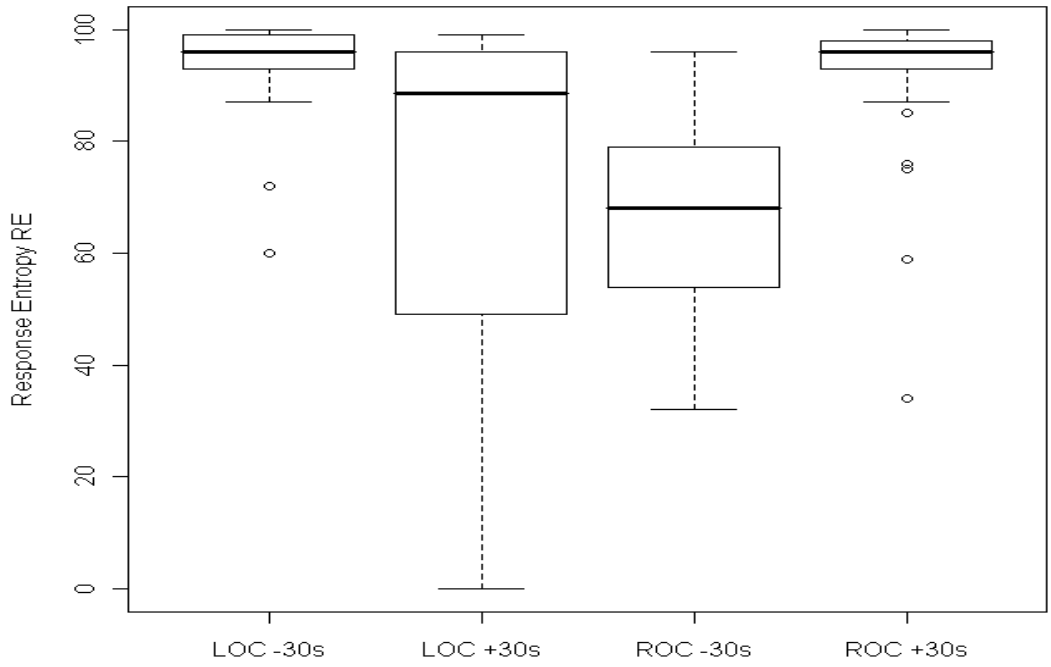

Figure 7: Performance RE in the sevo group

The boxplot below (Figure 8) shows the box plots of RE in the propofol group. At LOC -30s and at ROC +30s half of the recorded index values range between 85 and 95 whereas at LOC +30s the IQR ranges from about 50 – 75. Outliers are shown at LOC -30s and at ROC +30s. (Table 8).

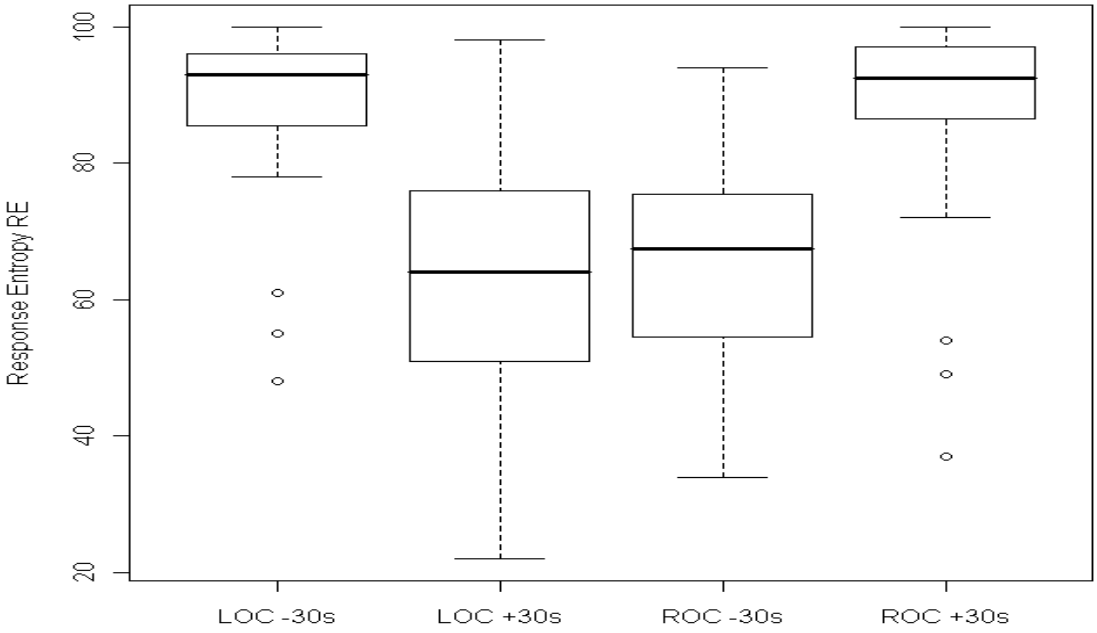

Figure 8: Performance RE in the propofol group

The index values of RE were measured and recorded every 10 s. Again the mean value and SD were calculated from the measured index values

	Mean values	SD
LOC1 -30s	94.3	8.89
LOC1 +30s	68.25	27.45
ROC1 -30s	60.7	17.02
ROC1 +30s	93.85	5.64
LOC2 -30s	94.36	6.13
LOC2 +30s	80.04	30.16
ROC2 -30s	73.68	12.62
ROC2 +30s	92.57	14.47

Table 7: Mean index values and SD of RE in the sevo group

	Mean values	SD
LOC1 -30s	90.84	6.91
LOC1 +30s	58.00	24.51
ROC1 -30s	65.47	17.61
ROC1 +30s	88.32	11.21
LOC2 -30s	85.79	14.85
LOC2 +30s	67.68	12.47
ROC2 -30s	66.63	13.53
ROC2 +30s	90.81	11.94

Table 8: Mean index values and SD of RE in the propofol group

3.4 PK values

To calculate the PK the index values are compared with the level of consciousness of the patients. Index values 30 seconds before and 30 seconds after loss of consciousness are analyzed.

	PK (SE) ± SD
Sevo group (LOC & ROC)	0.78 ± 0.04
Propofol group (LOC & ROC)	0.83 ± 0.03
Total (sevo + propofol)	0.80 ± 0.03

Table 9: PK values and SD of SE

In the current study, PK for SE at the sevo group for LOC is 0.71 ± 0.06 and for the propofol group it is 0.84 ± 0.04.
For ROC it is 0.87 ± 0.04 in the sevo group and 0.81 ± 0.05 for the propofol group.
For the sevo group the PK of LOC and ROC is 0.78 ± 0.04 and for the propofol group the PK of LOC and ROC is 0.83 ± 0.03. In total the PK for LOC and ROC in both groups is 0.80 ± 0.03

	PK (RE) ± SD
sevo group (LOC & ROC)	0.84 ± 0.03
Propofol group (LOC & ROC)	0.88 ± 0.03
Total (sevo + propofol)	0.85 ± 0.02

Table 10: PK values and SD of RE

For RE the PK at the sevo group for LOC is 0.76 ± 0.05 and for the propofol group it is 0.89 ± 0.04.
For ROC it is 0.93 ± 0.03 in the sevo group and 0.88 ± 0.04 for the propofol group.
For the sevo group the PK of LOC and ROC is 0.84 ± 0.03 and for the propofol group the PK of LOC and ROC is 0.88 ± 0.03. In total the PK for LOC and ROC in both groups is 0.85 ± 0.02.

3.5 Correlation between SE and BIS

3.5.1 Correlation coefficient and plot

Pearson's correlation between BIS and SE was 0.86 in the sevo group and 0.68 in the propofol group. The total correlation was 0.78.

The plot (Figure 9) shows the course of SE and BIS when identical data is replayed to the monitors. The time is stated in 10 seconds and depicts the period of all patients undergoing surgery. The black graph shows the BIS monitor values, the grey graph indicates the progress of the SE values.

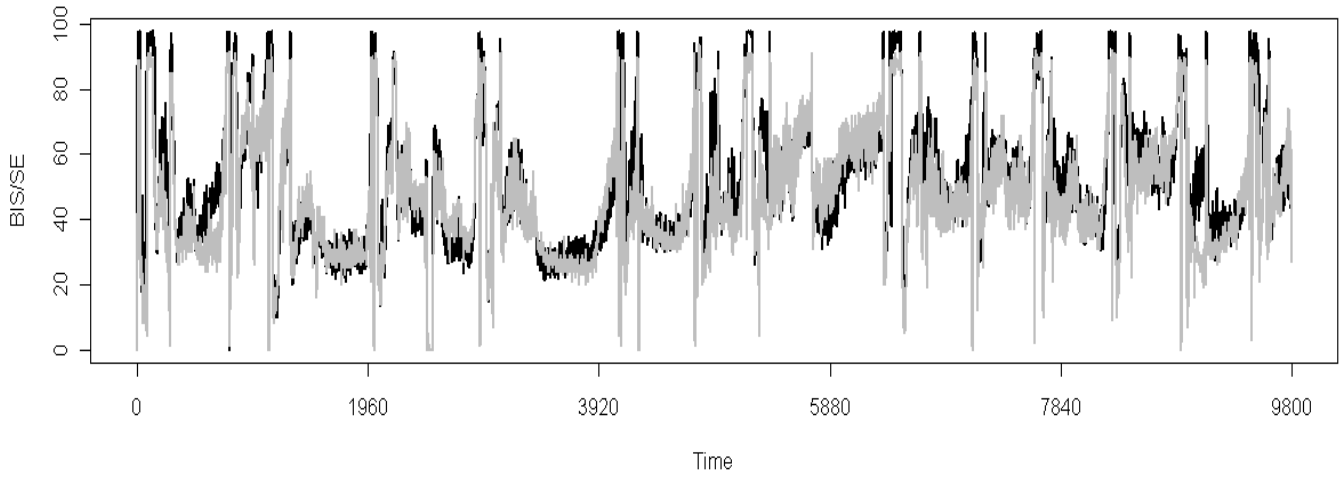

Figure 9: Correlation between BIS and SE in the sevo group

Figure 10 shows the SE and BIS values when identical EEG is played back. The black graph shows the BIS values, the grey graph the SE values.

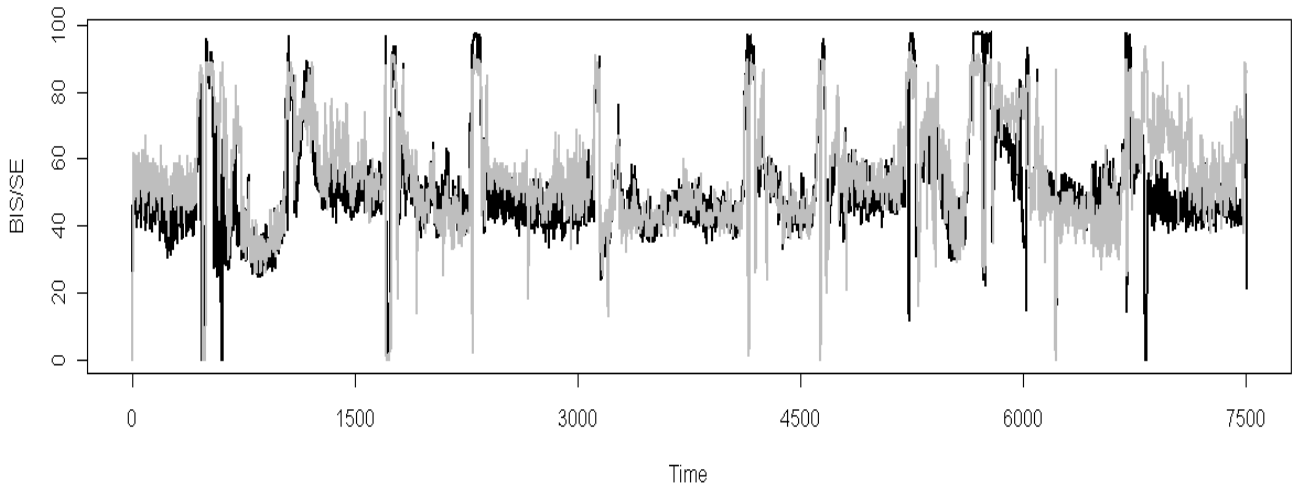

Figure 10: Correlation between BIS and SE in the propofol group

3.5.2 Concordance and invalid data

To measure the agreement of the index values in the anesthetic intervals, the concordance is defined. There are no significant differences in the sevo group compared to the propofol group. The accordance in light, general and deep anesthesia in both groups was > 70%. The concordance in both groups (sevo and propofol) for light anesthesia is 17% which means that both, SE and BIS showed at the same time the same state of light anesthesia. For general anesthesia, it is 36% and for deep anesthesia 18%.
In just 1% the BIS shows deep anesthesia whereas SE indicates light anesthesia and vice versa in 1% the BIS shows light anesthesia whereas SE indicates deep anesthesia. (Table 9)

			BIS	
		light anesthesia	general anesthesia	deep anesthesia
	light anesthesia	0.17	0.06	0.01

SE	general anesthesia	0.06	0.36	0.06
	deep anesthesia	0.01	0.09	0.18

Table 11: General concordance

At some time, the Datex monitor and the Aspect 2000 show instead of the right index values the information “invalid values”. In these cases, data pairs with invalid data are dismissed.

For BIS, 216 data points in the sevo group and 578 in the propofol group were invalid. For the SE the invalid data points were 88 in the sevo group whereas in the propofol group 30 data pairs were invalid.

In 9 cases both, BIS and SE were invalid in the sevo group and At no time BIS and SE were invalid at the same time in the propofol group.

3.5.3 Bland - Altmann-Plot

The Bland-Altman plot indicates agreement between SE and BIS. In the graph below only every 6th index pair was taken which is a time interval between recorded pairs of 60s. This reduces interdependence between recorded index values and justifies the use of the Bland – Altmann – Plot.

The solid horizontal line represents the mean difference between SE and BIS whereas the two outer horizontal lines show the 95% limits of agreement. 94.9% of all data points are between the two outer horizontal lines which shows a good overall agreement.

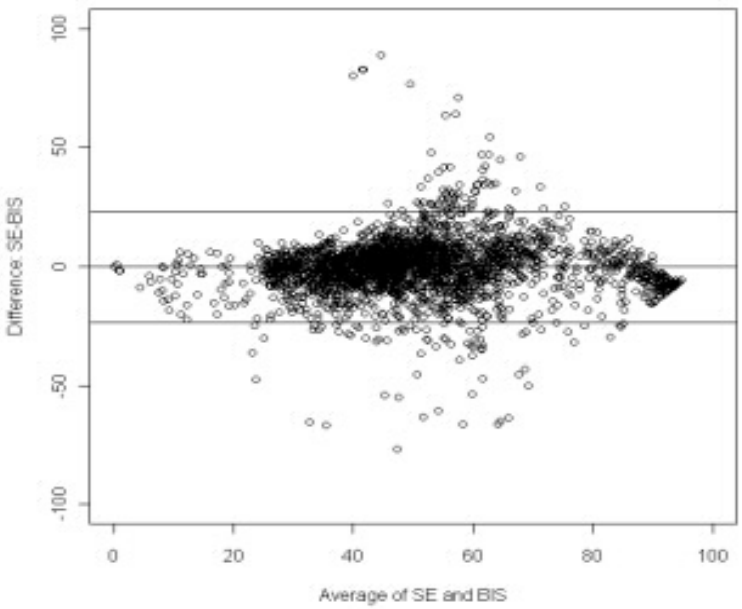

Figure 12: Bland – Altmann – Plot with every 6th value (i.e. one data pair / min)

4 Discussion

4.1 Reanalysis

The first part of this study examines to which extent the SE and RE index can correctly measure the level of consciousness at the transition between consciousness and unconsciousness. In a second step the correlation between SE and BIS based on the entire data was examined.
For this purpose, the patients were divided into two groups with different drug regimen. An EEG was recorded from the patients during anesthesia (sevo group: remifentanil and sevoflurane, propofol group: remifentanil and propofol). Consciousness was assessed by asking the patient to press the investigator´s hand. Anesthetics were applied until loss of consciousness, subsequently reduced again until the patient follows the command of the investigator again. To perform the surgical procedure, anesthetic was given again.
The recorded EEG was then played back to Aspect 2000 and the Datex-Ohmeda entropy module to analyse the received indices. Indices 30s before and after the event were used to evaluate performance of the monitors to distinguish between consciousness and unconsciousness.

The key issue of the reanalysis is the question whether the indices differentiate between consciousness and unconsciousness at the transition of the level of consciousness (respectively 30s before and after the change). In this study, the index values are measured twice at loss of consciousness (LOC 1 and LOC 2) and twice at return of consciousness (ROC 1 and ROC 2).
To evaluate the performance of the EEG monitors objectively it is necessary to clarify to which extent the received data (the SE and RE indices) reflects the underlying process (state of consciousness). For this purpose, different statistical analysis methods can be applied: For SE and RE the mean values, SD and PK values were calculated.

At the transition between awareness and unconsciousness, respectively 30 seconds before and after loss and return of consciousness the SE values are measured; after first loss of consciousness (LOC1) the mean value is 54.2 ± 22.8 and after ROC 1 it is 77.1 ± 10.3 in the propofol group. RE values in the propofol group are similar during induction

and emergence periods of our study: After the first LOC the mean RE value is 58 ± 24.5 and 88 ± 11 after ROC 1. These values show a good agreement between the state of consciousness of a patient and the calculated index.

White and colleagues[51] compared State and Response Entropy versus BIS Index values during the perioperative period and found a mean value of 88 ± 2 for SE and 96 ± 3 for RE during preinduction just as preincision values of 38 ± 12 for SE and 40 ± 13 for RE.

Ellerkmann et al.[52] compared BIS and Spectral Entropy in anesthesia with propofol by calculating the coefficient of determination in a bisigmoidal model just as the PK. In his study, the PK of SE (0.77) and of RE (0.76) are slightly lower than the PK of SE (0.80) and of RE (0.85) from the actual study.
Ellerkmann also investigated the effects of sevoflurane on the EEG[19] and calculated PK values of 0.82 for RE and 0.84 for SE which are comparable with results from the current study.

Vanluchene et al.[53] analysed Spectral Entropy as an electroencephalographic measure of anesthetic drug effect with propofol. All patients received 50 mg/min propofol until either burst suppression greater than 80% or mean arterial pressure less than 50mmHg was observed. As a result, the PK of both SE (0.86) and RE (0.89) were in particular higher than in our study where the values originate from the transition between consciousness and unconsciousness.

In a study of Takamatsu et al.[54] Entropy indices and BIS indices were analysed for anesthesia with sevoflurane. All index values were measured in stable phases of anesthesia. The median values (range) of SE and RE at LOC were 85 (25-96) and 92 (38-99). The PK values of SE and RE at LOC were 0.825 and 0.841 and therefore similar to the PK values of this study where the index values were taken from the transition between consciousness and unconsciousness.

Both, the BIS and SE monitors can quantify the EEG effects which has also similarly been published by Bruhn J et al., 2001 with propofol anesthesia. In contrast, no replayed data were used but continuously processed EEG variables[55].

According to Kreuer et al.[56] the PK for BIS is > 0.95 in differentiation between different level of anesthesia with propofol. The lower PK of 0.80 ± 0.03 for SE and 0.83 ± 0.04 for BIS in this study can be explained by differences in the time of assessment: as the study of Kreuer et al.[56] used values from deep anesthesia with only one change of consciousness up to complete awareness, a separation may be easier than analysis of values from the transition between awareness and unconsciousness - which are levels (and index values) very close to each other.
In this study, the critical range is involved by measuring the values 30 seconds before and after loss and return of consciousness.

Results from a study by Schneider et al.[57] 2005 with almost the same study structure showed similar values: The PK in differentiation between wakefulness and unconsciousness for BIS with propofol respectively sevoflurane was 0.73.
Reasons for the difference (0.83 and 0.73) may be found in the different version of the BIS. Schneider et al. 2005 used the Aspect Monitor 2000 with the 3.4 version of BIS. Further developments of the algorithm, as implemented in the 4.0 software version, may have led to better discrimination between consciousness and unconsciousness. On the other hand, in the previous study only 15 sec BIS calculation time was allowed after LOC, which may also explain better values in the present analysis with a calculation time of 30 sec.

The PK of BIS in a study of Bruhn et al.[58] with Desflurane anesthesia was measured with 0.82 which shows a good agreement to the BIS PK of this study. However, in the study design of Bruhn et al. values taken from stable phases were measured and not, as in the current study, values from the transition between clinical states.

4.2 Correlation

As the same data set is used for both monitors, a direct comparison between the BIS and SE is possible.
A few studies only have looked at the relationship between BIS and SE. A recent report has emphasized that BIS and entropy changes according to modifications of the patient anesthetic state may differ in time and amplitude[24].

White and colleagues[51] have reported a good correlation between SE and BIS during induction (r=0.77) and emergence (r=0.86) from general anesthesia with propofol and desflurane. BIS was slower than Entropy in responding to the onset of burst suppression with increasing levels of propofol-induced hypnosis. It is also shown that both monitoring systems were capable of discriminating between the awake and anesthetized states[51].
Bonhomme et al.[22] found an excellent correlation between BIS and SE (r=0.84) and an even better correlation using a sigmoid rather than a linear model (r=0.87).
Schmidt et al.[20] compared the Spectral Entropy and the BIS in anesthesia with propofol and remifentanil. The Spearman Rank Correlation (r) was also calculated between BIS, SE and RE. In this study 20 women with gynecological operation were included. Between SE and BIS high correlation resulted (r= 0.83) just as between RE and BIS (r= 0.84). BIS index values from 65 to 40 could be assigned in 84% to the SE values from 59 to 30.

Pearson's correlation between BIS and SE in this study was 0.86 in the sevo group and 0.68 in the propofol group. The total correlation was 0.78 for both groups but as stated by Bland and Altman, the correlation coefficient r measures the strength of a relationship between two variables, not the agreement between them. So a good correlation does not necessarily imply good agreement[59].
To obtain perfect correlation all points on a scale have to lie along any straight line whereas to get a good agreement all points have to lie along the line of equality. To determine the degree of agreement between two measurement techniques Bland-Altman analysis is the appropriate statistical test[59].
In this study, the Bland-Altman plot shows that 94.9% of all data points are between the two outer horizontal lines which indicates a good agreement between the BIS and SE monitors.
Reasons for low correlation can be the lack of congruence seen in the plots in figure 9 and 10. At some point in the propofol group the indices of SE are higher for a longer time than the indices of BIS. The sevo group shows a better correlation between the BIS and SE whereas in the propofol group the mutual accordance shows a lesser extent. Still, there were no significant differences in concordance between groups.
For the calculation of an index value, all available monitors require a certain period of time. The exact amount of time has not been disclosed by the manufacturers and is unknown for most monitors[60]. Differences between indices in calculation time to indicate the different states from awake to light anesthesia to deep anesthesia may be a reason for

low correlation. If one monitor already shows the transition e.g. from awake to unconsciousness before the other monitor does, the difference between SE and BIS index values is higher and consequently the correlation is lower (Table 13). This may in particular be critical for detection of awareness or at transitions from awareness to unconsciousness or vice versa[60].

A low concordance may be due to the following reasons: even if BIS and SE show corresponding index values which are close to each other, one monitor can indicate with a value e.g. of 82 the state of wakefulness whereas the other monitor with a value of 78 indicates the state of light anesthesia. Hence in this study the agreement in light, general and deep anesthesia in the sevo and the propofol group was > 70%.

Only 1% of the observations show a BIS index detecting deep anesthesia whereas SE indicates light anesthesia and vice versa.

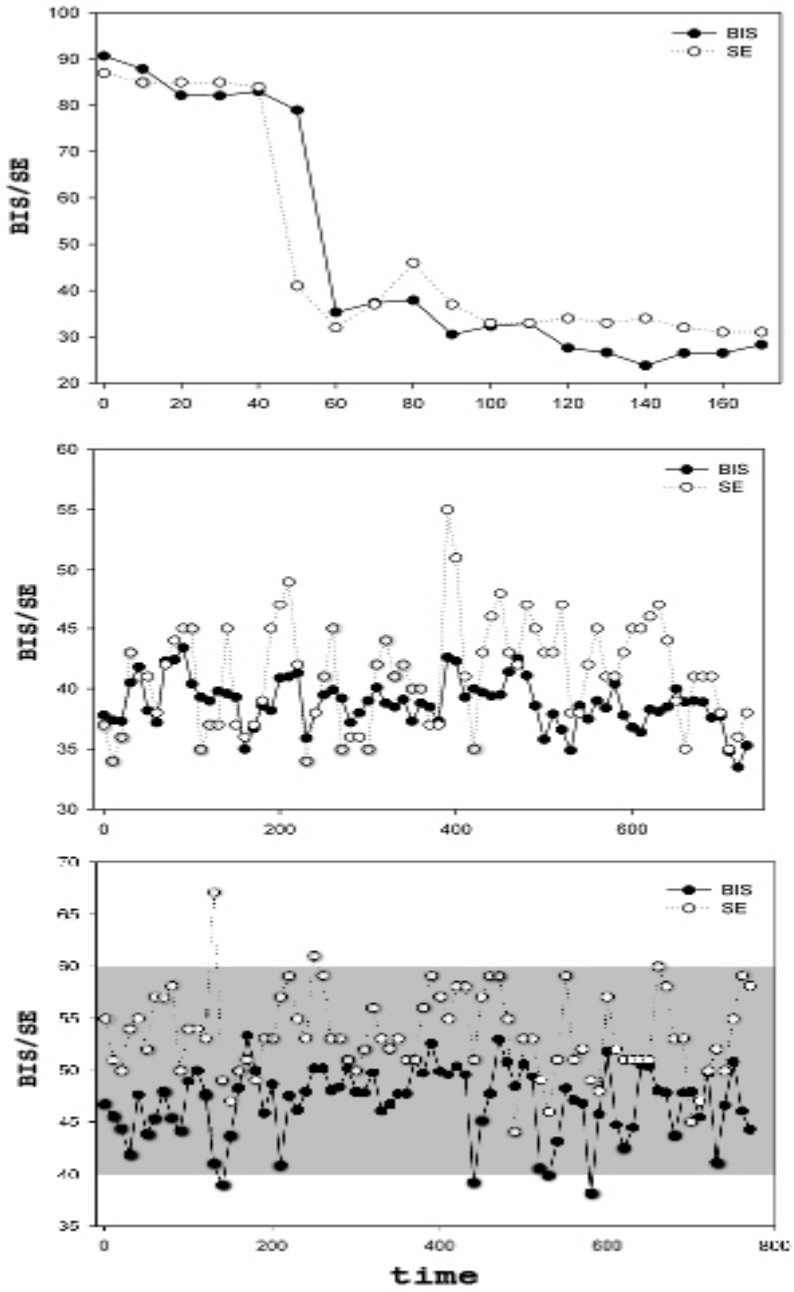

Figure 13: Reasons for low correlation:

Top: different reaction times of SE and BIS. The figure shows the transition from consciousness to general anesthesia. SE decreases faster than BIS.
Middle: BIS remains mainly constant while SE oscillates around the BIS
Bottom: BIS and SE are mostly in the interval for "general anesthsia". SE is higher than BIS.
Black dots show BIS values, white dots represent the trend of SE values

The monitors BIS and SE were manufactured to collect the data directly from the patient. In this study, an EEG player is used which is supposed to guarantee the direct

comparability of both monitors. It can be asked whether this approach leads to a marginal higher error rate even though this computer-based construction is tested to record and play back EEG data and adjudged valid[14]. In addition, processed EEG indices calculated from the identical set of EEG may not perfectly correlate to themselves. Underlying EEG-parameters (e.g. bispectrum, bicoherence) may fluctuate in the underlying EEG. With a second analysis, the time window for analysis of the underlying parameter may be slightly shifted (from milliseconds to few seconds), and this may change the value of underlying parameters (e.g. the bispectrum), resulting in different index values. This has already been shown for parallel recordings of BIS[61,62].

To avoid a low correlation the study design contains identical data which is played back on both monitors. This shows better results since 2 monitors positioned on the front can cause crosstalk and interhemispheric differences[61,63].

5 Conclusion

To minimize the risk of intraoperative awareness, shorten the duration of anesthesia and to reduce potential over- and underdosing of anesthetics, it can be recommended to introduce adequate monitor systems. They deliver fast information about the patients` state of anesthesia and hence make a contribution to further advance of monitoring anesthesia. SE is an EEG-based monitor used in anesthesia to assess the level of sedation from patients.

In this study, its validity to differentiate between consciousness and unconsciousness during transition phases is analysed. Conscious patients can follow verbal instructions whereas patients in general anesthesia are not responsive to verbal commands. All data were compared with the results of the BIS monitor respectively correlations were calculated from the entire data.

For this purpose, 30 s before and after a patient´s change of consciousness index values from both monitors are collected and compared. Collecting data at the transition of consciousness respectively 30s before and after LOC and ROC involves a critical time range because the evaluated phases “patient is awake” and “patient is in general anesthesia” are sometimes close together.

In other studies, values are taken by collecting data in continuing general anesthesia and first wake up reaction which present results from a more stable phase of anesthesia[36].

As a component of the Spectral Entropy, SE (and RE) values are derived, evaluated and compared to the BIS. 40 patients undergoing surgery are investigated and their BIS respectively SE are measured and index values are correlated.

In this study, the PK for SE is 0.80 ± 0.03 and for BIS t is 0.83 ± 0.04 for the sevo and the propofol group. This shows that SE and BIS seem to be similar in their performance to predict the state of consciousness at the transition between awareness and unconsciousness.

BIS and SE show a good overall correlation with r= 0.78. Therewith SE guided and SE guided anesthesia will probably follow the same course and both monitors allegorize being a good parameter to control the depth of anesthesia.

6 List of figures and tables

7 List of abbreviations

ASA:	American Society of Anesthesiologists
BIS:	Bispectral Index
cm:	centimeter
DFT:	discrete fourier transformation
e.g.:	example given
ECG:	electrocardiogram
EEG:	electroencephalogram
EMG:	electromyogram
FFT:	fast fourier transformation
h :	hours
Hz:	hertz
kg:	kilogram
kHz:	kilohertz
kΩ:	kilohm
log:	logarithm
mg:	milligram
min:	minute
n :	number
PK:	prediction probability
r:	correlation coefficient, spearman rank correlation
RE:	Response Entropy
s :	seconds
SD:	standard deviation
SE:	State Entropy
Vol. %:	volume percent
µg:	microgram

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