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Detection of Consciousness by Electroencephalogram and Auditory Evoked Potentials

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Background: **A set of electroencephalographic and auditory evoked potential (AEP) parameters should be identified that allows separation of consciousness from unconsciousness (reflected by responsiveness/unresponsiveness to command).**

Methods: **Forty unpremedicated patients received anesthesia with remifentanil and either sevoflurane or propofol. With remifentanil infusion (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), patients were asked every 30 s to squeeze the investigator's hand. Sevoflurane or propofol was given until loss of consciousness. After intubation, propofol or sevoflurane was stopped until patients followed the command (return of consciousness). Thereafter, propofol or sevoflurane was started again (loss of consciousness), and surgery was performed. Return of consciousness was observed after surgery. The electroencephalogram and AEP from immediately before and after the transitions were selected. Logistic regression was calculated to identify models for the separation between consciousness and unconsciousness. For the top 10 models, 1,000-fold cross-validation was performed. Backward variable selection was applied to identify a minimal model. Prediction probability was calculated. The digitized electroencephalogram was replayed, and the Bispectral Index was measured and accordingly analyzed.**

Results: **The best full model (prediction probability 0.89) contained 15 AEP and 4 electroencephalographic parameters. The best minimal model (prediction probability 0.87) contained 2 AEP and 2 electroencephalographic parameters (median frequency of the amplitude spectrum from 8–30 Hz and approximate entropy). The prediction probability of the Bispectral Index was 0.737.**

Conclusions: **A combination of electroencephalographic and AEP parameters can be used to differentiate between consciousness and unconsciousness even in a very challenging data set. The minimal model contains a combination of AEP and electroencephalographic parameters and has a higher prediction probability than Bispectral Index for the separation between consciousness and unconsciousness.**

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DURING the past years, monitoring of anesthetic effects on the main target of anesthesia, the brain, has gained increasing attention. Monitoring of the spontaneous electroencephalogram has been suggested. The electroencephalogram reflects effects of anesthetic drugs. Visual interpretation of the electroencephalogram during anesthesia is time-consuming and requires long experience. As a consequence, several processing methods have been suggested that reduce the electroencephalogram to a numerical value. An alternative approach for assessment of electric brain activity is the observation of auditory evoked potentials (AEPs). It has been suggested that AEPs may be of particular value for the separation of consciousness from unconsciousness.[1] Both the electroencephalogram and AEP signals are recorded from the scalp. The electroencephalogram reflects spontaneous cortical activity, whereas the AEP shows electrical activity not only from the cortical surface, but also from deeper regions of the brain. The AEP consists of characteristic peaks and troughs that are related to specific neuroanatomical structures of the auditory pathway.[2] The early component of the AEP represents the brainstem response, which is almost unaffected by anesthetics. In the range of 20–100 ms after the auditory stimulus, the midlatency components of the AEP follow. General anesthesia induces characteristic changes of the midlatency components: Peak latencies increase and peak amplitudes decrease. For visual analysis of AEPs, peaks must be identified for measurement of amplitudes and latencies. Similar to visual analysis of the electroencephalogram, this requires experience and may be time-consuming. Therefore, several processing methods have been suggested to reduce AEP information to a numerical value.

The use of these processed electroencephalographic and AEP variables may allow an easy quantification of electroencephalographic and AEP properties. During the past decades, several processing methods have been suggested. In the current study, a set of electroencephalographic and AEP parameters based on statistical, spectral, entropy, and chaos analysis was tested. Based on calculated electroencephalographic and AEP parameters, a set of parameters should be identified that allows separation of consciousness (reflected by responsiveness to command) from unconsciousness at the transition between these stages.

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Materials and Methods

Patient Selection and Randomization

Forty adult patients with an American Society of Anesthesiologists physical status of I or II who were scheduled to undergo elective surgery during general anesthesia were enrolled in the study. Patients gave informed written consent to the protocol, which was approved by the ethics committee of the Technische Universität München, Munich, Germany, and involved a reduction of the hypnotic agent until patients followed a command after tracheal intubation. Patients with contraindications to the study drugs, 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. Patients received either anesthesia with sevoflurane and remifentanil (group 1) or total intravenous anesthesia with propofol and remifentanil (group 2). In both groups, the minimum remifentanil infusion rate was 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Blocked randomization was performed to enroll 20 patients in each group.

Monitoring

Noninvasive measurements of blood pressure; heart rate; oxygen saturation; inspiratory oxygen, end-tidal carbon dioxide, and sevoflurane concentrations; and respiratory parameters were monitored with a Datex® AS/3 compact monitor (Datex Ohmeda, Helsinki, Finland). Data were stored on a personal computer. Synchronized to standard monitoring parameters, electroencephalograms and AEPs were recorded using a specially designed amplifier that has been described previously.[3] At electrode positions, the skin was prepared with alcohol to obtain impedances of less than 5 kΩ. ZipPrep electrodes (Aspect Medical Systems, Newton, MA) were applied at the left temporal region between the lateral edge of the eye and the upper edge of the ear (AT1), above the right mastoid (M2), Fpz (reference), and F7 (ground, electrode positions according to the international 10-20 system). A two-channel referential electroencephalogram was recorded using an analog filter of 0.5 Hz (high pass) and 400 Hz (low pass). The electroencephalogram was continuously digitized and recorded on a personal computer with a rate of 1 kHz per channel. Binaural rarefaction clicks were applied at 70 dB above hearing level using insert earphones (AW 180; Oticon, Strandvejen, Denmark). Stimulus frequency was 8.3291 Hz with a 10% variation of the interstimulus interval. AEPs were averaged from 300 sweeps and displayed together with the electroencephalogram. AEP trigger information was stored with the electroencephalogram for off-line averaging and analysis of AEPs.

Anesthetic Procedure

No premedication was given before induction. A slow induction of anesthesia was performed: Oxygen was given by mask, lactated Ringer's solution was administered, and remifentanil infusion was started at 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *via* a cannula in the cubital vein. Every 30 s, patients were asked to squeeze the investigator's hand. To differentiate a response to command from involuntary movement, the response was verified by an immediate repetition of the command that also required a response. Anesthesia was started with sevoflurane mask induction (group 1) or propofol injections (0.7 mg/kg, followed by 20 mg every 30 s; group 2). Loss of consciousness was defined as the first time when the patient did not squeeze the investigator's hand to command. After loss of consciousness 1, additional propofol or sevoflurane was given to increase depth of anesthesia. The circulation of the right forearm was occluded for 5 min to retain the ability to move the hand to command, before succinylcholine (1.0 mg/kg) was given (Tunstall isolated forearm technique).[4] The trachea was then intubated. After intubation, sevoflurane or propofol was stopped until patients followed the command again (return of consciousness). After return of consciousness 1, sevoflurane inhalation (5 vol%) or propofol bolus injection (20 mg every 20 s until loss of consciousness) followed by continuous infusion was recommenced. When patients stopped responding to command again, loss of consciousness 2 was noted, and requests to squeeze the investigator's hand were stopped. Sevoflurane, propofol, and remifentanil were administered according to clinical practice, and surgery was performed. At the end of surgery, patients were asked every 30 s to squeeze the investigator's hand. Sevoflurane, propofol, and remifentanil were discontinued. Return of consciousness 2 was defined as the first verified response to command, *i.e.*, a repeated squeeze of the hand.

Table 1. Postoperative Interview Questions

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?

After recovery from anesthesia in the recovery room, patients were tested for recall using a standardized interview (table 1).[5] This interview was repeated within 48 h in the ward.

Data Basis

Electroencephalographic Data. A digital low-pass filter of 30 Hz was used to reduce the influence of muscle activity (electromyogram) on the electroencephalogram. Electroencephalographic data were segmented into blocks of 8 s in duration. At loss of consciousness 1 and 2, the segment that preceded the last response was selected for "consciousness," and the first segment that followed the first unanswered command was selected for "unconsciousness." At return of consciousness 1 and

Table 2. Parameters of the Electroencephalogram

Basic Parameters	Statistical Parameters	Amplitude Spectrum	Power Spectrum	Nonlinear Parameters
Root mean square	Skewness	Median frequency 8–30 Hz	Absolute power 21–30 Hz	Shannon entropy
Morphology	Kurtosis		Relative power 21–30 Hz	Spectral entropy
1st Derivative: root mean square	Normed kurtosis			First time-derivative order-proxy
2nd Derivative: mean absolute amplitude				Approximate entropy
2nd Derivative: root mean square				Lempel-Ziv complexity
2nd Derivative: variance				
2nd Derivative: form factor				
2nd Derivative: crest factor				

Nineteen parameters from the electroencephalogram were used for calculation of the logistic regression.

2, the segment that preceded the last unanswered command was selected for "unconsciousness," and the segment after the first response was selected for "consciousness." Electroencephalographic segments were reviewed, and signal quality was rated. Segments with very low quality were excluded from the analysis. Based on basic, statistical, spectral, complexity, and entropy analysis, 19 parameters were calculated from the electroencephalogram (table 2). In addition to the well-described parameters, signal morphology[6] was calculated:

$$\mathrm{Morph_i} = \sum_{t=0}^{n-2} (|s_i(t+1) - s_i(t)|)^{1/2},$$

where s_i is the ith 1-s signal vector of a digitized electroencephalogram signal containing n = 1,000 signal samples, and $t = 0, 1, \ldots, (n-1)$ is the time index of the samples within s_i. The median frequency of the amplitude spectrum was calculated from 8 to 30 Hz. Higher frequencies were excluded, because they may overlap with muscle activity (electromyogram). The high-pass filter of 8 Hz excludes the δ band of the electroencephalogram from analysis. This reduces the influence of opioid-induced activation of the δ band, which may not be related to the state of consciousness. In addition, it reduces the influence of eye-blink artifacts, which are in the same frequency range.

AEP Data. Before averaging of electroencephalographic sweeps, a digital 25-Hz high-pass filter was applied, and for each data section of 2 s, the DC component (mean value) was removed. AEPs were averaged from 300 sweeps. AEPs were selected following the same principle as described for electroencephalographic data, *i.e.*, at loss of consciousness the last signal before the last response to command and the first signal after loss of response to command were selected, and *vice versa* at return of consciousness. Based on basic, advanced, and complexity analysis, nine parameters calculated from the AEP were chosen (table 3). Wavelet transform was performed as described in a previous article.[7] The selected Daubechies 3 mother wavelet allows a good approximation of the AEP signal characteristics.

Table 3. Parameters of the Auditory Evoked Potential

AEP (0–120 ms)	MLAEP (24–120 ms)	Wavelet Transform (Daubechies 3 Wavelet)
Morphology	Signal energy	Detail level 2, coefficient 11
Mean absolute amplitude	Morphology	Detail level 2, coefficient 13
1st Derivative: mean absolute amplitude	Mean absolute amplitude	Detail level 2, coefficient 23
2nd Derivative: mean absolute amplitude	1st Derivative: mean absolute amplitude	Detail level 2, coefficient 24
	2nd Derivative: absolute maximum amplitude	Detail level 2, coefficient 25
		Detail level 2, coefficient 26
		Detail level 2, coefficient 27
		Detail level 3, coefficient 4
		Detail level 3, coefficient 11
		Detail level 3, coefficient 18
		Detail level 4, coefficient 3
		Detail level 4, coefficient 4
		Detail level 4, coefficient 5
		Detail level 4, coefficient 6

Twenty-three parameters from the auditory evoked potential (AEP) were used for calculation of the logistic regression. Parameters were calculated from the auditory evoked potential up to 120 ms (AEP 0–120 ms, left and right columns) or the midlatency range of the auditory evoked potential (MLAEP 24–120 ms, middle column).

Table 4. Demographic Data

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

There were no significant differences between the propofol group and the sevoflurane group in height, weight, age, sex, or American Society of Anesthesiologists (ASA) physical status.

Discrete wavelet decomposition (Matlab version 6.5.0.180913a (R13), wavelet toolbox version 2.2; Mathworks, Natick, MA) was performed up to level 6. The results of this wavelet transform are 146 wavelet coefficients that represent different signal components and describe time–frequency characteristics (waveform, structural details) of the AEP. To reduce redundancy of information and avoid multicolinearity, the number of wavelet coefficients was reduced by visual inspection of single coefficient values and correlation analysis. This eliminated highly correlated coefficients (absolute value of correlation coefficients > 0.9), leaving a parameter set of 96 wavelet coefficients. Based on experience from previous studies, additional selection procedures based on fuzzy decision trees[8] and an automatic training procedure for classificators were applied to identify a set of relevant coefficients. The fuzzy decision trees and the specific classificators (Kohonen maps and support vector machines[9]) were established by separately using data from a database that contains hemodynamic, respiratory, electroencephalographic, and AEP data from different patient and volunteer studies.[10] A comparison based on the frequency of occurrence in the particular sets of relevant coefficients results in a final set of 14 wavelet coefficients (table 3).

Statistical Analysis

Demographic data of groups 1 and 2 were calculated. Values are mean ± SD, unless stated otherwise.

Bivariate correlation matrices were calculated for all 42 parameters, and 19 sets of noncorrelated parameters were built. The probability of being awake (P) is modeled in terms of log odds by a linear function of the independent explanatory variables x (multivariate logistic regression):

$$\log(P/(1 - P)) = \alpha + \mathrm{x}'\beta,$$

where α is called the intercept, x is the matrix of explanatory variables, and β is the vector of regression coefficients. In the full model, 19 influence variables, one of each set, are considered. The number of parameters was reduced to the most relevant ones using backward selection with significance level to stay of 0.05 (minimal model).

Classification tables were obtained by classifying patients as conscious if the estimated probability of consciousness:

$$P = \exp(\alpha + \mathrm{x}'\beta)/(1 + \exp(\alpha + \mathrm{x}'\beta)) > 0.5.$$

On the basis of classification, sensitivity, and specificity, odds ratios including 95% confidence intervals and goodness-of-fit criteria (Akaike Information Criterion, Bayesian Information Criterion, adjusted goodness of fit (R^2)) were calculated for each of the 270 regression models. Receiver operating characteristics (ROC) were applied to analyze different classification cut points, and prediction probability (P_K) values were calculated. The regression models were ranked by sensitivity and specificity, and for the top 10 models, 1,000-fold cross-validation was performed with the Monte-Carlo technique[11] using 50% of the data set for training and the remaining patients as the test data set. Separation between test and training data set bases on random numbers. For each validation step, a logistic model is estimated on the training data set, and for each observation of the test data set, the probability of consciousness conditionally on influence variables is calculated. Observations with $P > 0.5$ are classified as conscious, otherwise as unconscious by the model. Accuracy of classification (relative frequency of correctly classified observations) is calculated for each validation step. The mean and SE of accuracy are given over all 1,000 validation steps.

To test whether the observed effects are drug specific, sensitivity, specificity, classification rates, and the area under the ROC curve of the best minimal model were calculated separately for each group. The best minimal model had been developed only from data immediately before and after loss and return of consciousness. To evaluate its performance as a potential monitor of awareness, it was tested with additional data. Therefore, the output value was calculated every 30 s from the start of the study to 10 min after loss of consciousness 2, and from 10 min before return of consciousness 2 to the end of the study. The 30-s interval was chosen because it corresponds with the clinical assessment of consciousness, *i.e.*, the command "squeeze my hand." Lowess interpolation with a smoothness factor of 0.15 was applied for visualizing the classification through observation time.

In addition, digitized data from the electroencephalographic channel (AT1–Fpz) were replayed on a specially designed digital/analog signal converter. This converter allows replay of recorded electroencephalographic data as analog signal, *i.e.*, electric activity at the electrode recording sites. The Bispectral Index (BIS) was calculated from the recorded electroencephalographic data

Table 5. Results of Electroencephalographic Parameters

Parameter	Consciousness, Mean ± SD	Unconsciousness, Mean ± SD
Median frequency 8–30 Hz	17.44 ± 2.55	14.95 ± 1.86
Absolute power 21–30 Hz	59.87 ± 111.79	16.43 ± 26.62
2nd Derivative: variance	$3.86 \times 10^{10} \pm 6.98 \times 10^{10}$	$1.31 \times 10^{10} \pm 1.82 \times 10^{10}$
2nd Derivative: mean absolute amplitude	$1.28 \times 10^{5} \pm 8.68 \times 10^{4}$	$7.90 \times 10^{4} \pm 4.41 \times 10^{4}$
2nd Derivative: root mean square	$1.60 \times 10^{5} \pm 1.07 \times 10^{5}$	$9.94 \times 10^{4} \pm 5.46 \times 10^{4}$
2nd Derivative: crest factor	3.26 ± 0.40	3.65 ± 0.61
Relative power 21–30 Hz	9.92 ± 12.36	3.90 ± 5.62
1st Derivative: root mean square	$1.22 \times 10^{3} \pm 685.78$	915.21 ± 424.67
First time-derivative order-proxy	6.97 ± 0.48	6.70 ± 0.46
Morphology	877.06 ± 226.27	766.61 ± 181.13
Approximate entropy	0.25 ± 0.12	0.20 ± 0.09
2nd Derivative: form factor	1.25 ± 0.02	1.26 ± 0.03
Lempel-Ziv complexity	0.14 ± 0.05	0.12 ± 0.04
Kurtosis	$-3.90 \times 10^{5} \pm 2.44 \times 10^{6}$	$-3.91 \times 10^{5} \pm 1.68 \times 10^{6}$
Normed kurtosis	0.03 ± 0.40	−0.03 ± 0.42
Root mean square	22.16 ± 12.66	21.13 ± 13.07
Spectral entropy	2.37 ± 0.65	2.31 ± 0.57
Skewness	$-496.32 \pm 9.01 \times 10^{3}$	$206.22 \pm 7.23 \times 10^{3}$

using an Aspect A-2000 monitor (software revision 3.4; Aspect Medical Systems). Prediction probability (P_K) was calculated from the last BIS values before loss or return of consciousness and the values 15 s after loss or return of consciousness. As for the electroencephalographic/AEP parameters, the 30-s interval was chosen because it reflects the time interval of the clinical assessment of consciousness. After a change of the state of consciousness, a 15-s interval was added to allow calculation of the according BIS value.

Results

Demographic Data

Table 4 shows demographic data of the patients. There were no significant differences between groups 1 and 2. In the postoperative interviews, no patient recalled the period of consciousness.

Electrophysiologic Data

The data set consisted of 150 electroencephalogram/AEP pairs from unconsciousness and 126 electroencephalogram/AEP pairs from consciousness.

Electroencephalographic Data

The best monoparameters calculated from the electroencephalogram were the median frequency of the range from 8 to 30 Hz with an area of 0.78 under the ROC curve, and the absolute power from the frequency band from 21 to 30 Hz with an area of 0.77 under the ROC curve. Detailed results for monoparameters calculated from the electroencephalogram are shown in table 5.

AEP Data

With the exception of wavelet parameters, all monoparameters calculated from the AEP had an area between 0.78 and 0.80 under the ROC curve. Table 6 shows detailed results of the analysis of AEPs.

Combined Data Set

The best full model had a sensitivity of 72.2% and a specificity of 85.3%. It contained 15 parameters that were calculated from the AEP: 14 wavelet coefficients (coefficients 11, 13, and 23–27 from detail level 2: *db3_d2_11*, *db3_d2_13*, *db3_d2_23*–*db3_d2_27*; coefficients 4, 11, and 18 from detail level 3: *db3_d3_4*, *db3_d3_11*, *db3_d3_18*; and coefficients 3–6 from detail level 4: *db3_d4_3*–*db3_d4_6*) and the mean absolute amplitude of the first derivate of the midlatency range of the AEP (24–120 ms). In addition, it contained 4 parameters that were calculated from the electroencephalogram: approximate entropy, kurtosis, skewness, and the median frequency of the frequency range 8–30 Hz.

The best minimal multivariate logistic regression model results in the following equation:

$$\log(P/(1 - P)) = a + x1'b1 + x2'b2 + x3'b3 + x4'b4,$$

with intercept a, regression coefficients bi, i = 1, . . . , 4 and x1: wavelet analysis of the AEP: detail level 3, coefficient 11, x2: wavelet analysis of the AEP: detail level 4, coefficient 5, x3: approximate entropy of the electroencephalogram, x4: median frequency of the electroencephalogram from 8 to 30 Hz. The best minimal model had a sensitivity of 75.4% and a specificity of 84.0%. It contained two AEP parameters (wavelet coefficient 11 from detail level 3: *db3_d3_11* and coefficient 5 from detail level 4: *db3_d4_5*) and two electroencephalographic parameters (median frequency of the amplitude spectrum from 8 to 30 Hz and approximate entropy). The odds ratio and result of logistic regression for this minimal subset are presented in table 7. Detailed results

Table 5. Continued

Sensitivity	Specificity	PPV	NPV	ROC Area	Threshold	$P_K \pm SE$
0.70	0.73	0.69	0.74	0.78	15.94	0.78 ± 0.03
0.66	0.77	0.71	0.73	0.77	15.97	0.77 ± 0.03
0.63	0.72	0.66	0.70	0.73	1.31×10^9	0.73 ± 0.03
0.62	0.74	0.67	0.70	0.72	9.35×10^4	0.72 ± 0.03
0.63	0.73	0.66	0.70	0.72	1.15×10^5	0.72 ± 0.03
0.76	0.61	0.62	0.75	0.71	3.42	0.29 ± 0.03
0.66	0.71	0.66	0.71	0.71	3.46	0.71 ± 0.03
0.60	0.63	0.58	0.66	0.65	926.25	0.65 ± 0.03
0.60	0.63	0.58	0.66	0.65	6.82	0.65 ± 0.03
0.59	0.66	0.59	0.66	0.64	815.49	0.64 ± 0.03
0.54	0.69	0.59	0.64	0.64	0.23	0.64 ± 0.03
0.70	0.53	0.55	0.68	0.62	1.26	0.38 ± 0.03
0.42	0.83	0.68	0.63	0.62	0.15	0.62 ± 0.03
0.30	0.90	0.72	0.61	0.58	2.02×10^4	0.58 ± 0.03
0.69	0.47	0.52	0.64	0.57	−0.11	0.57 ± 0.03
0.68	0.51	0.54	0.66	0.56	2.67	0.56 ± 0.03
0.69	0.49	0.53	0.65	0.55	15.72	0.55 ± 0.03
0.42	0.75	0.59	0.61	0.54	2.74	0.54 ± 0.04
0.58	0.53	0.51	0.60	0.54	−20.10	0.46 ± 0.03

Parameter values during consciousness and unconsciousness (mean ± SD). For each parameter, sensitivity, specificity, positive predictive value (PPV, the percentage of cases with consciousness out of all cases that were indicated as being conscious), and negative predictive value (NPV, the percentage of unconscious cases out of all cases that were indicated as unconscious) for detection of consciousness are given. Furthermore, the area under the receiver operating characteristic curve (ROC area) and the prediction probability (P_K) are given.

for the best models are available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.#

Drug-specific analysis of the performance of the best minimal model showed a classification rate of 81.8% in the sevoflurane group and 81.3% in the propofol group. Sensitivity was 82.0% and specificity was 81.6% in the sevoflurane group; sensitivity was 75.4% and specificity was 86.5% in the propofol group. The area under the ROC curve was 0.917 in the sevoflurane group and 0.900 in the propofol group. Detailed results of the best minimal model are shown in figure 1. ROC curves of the best full and minimal model are shown in figure 2. Cross-validation showed a mean classification rate of 75.68% (SE 0.10%) for the best full model and 79.61% (SE 0.08%) for the best minimal model. The area under the ROC curve was 0.89 for the best full model and 0.87 for the best minimal model. Analysis of BIS values calculated from the replayed electroencephalogram showed a prediction probability of 0.737 (0.028).

Figure 3 shows results of the best minimal model over time.

Discussion

These results show that a combination of electroencephalographic and AEP parameters can be used to differentiate between consciousness and unconsciousness in surgical patients. For the current study, consciousness was defined as a response to the command "squeeze my hand." This response requires intact working of short-term memory, a memory function of limited capacity that spans several seconds. This must not be confused with (explicit) long-term memory, which is usually thought of when the term *memory* is used. The difference between explicit long-term and short-term memory explains why none of our patients recalled the period of consciousness. To avoid an influence of amnesic drugs, no benzodiazepine premedication had been given. Therefore, the absence of recall reflects the hypnotic state of our study patients during the period of consciousness with intact short-term and disrupted explicit long-term memory. The relation between responsiveness and memory is not entirely clear. As previously shown, subanesthetic concentrations of anesthetic drugs may already have an amnesic effect.[12,13] Consequently, the absence of recall does not guarantee unconsciousness during anesthesia. Absence of recall may not be sufficient for surgical anesthesia, because implicit (unconscious) memory may be present, and harmful consequences[14,15] may be associated with implicit memory.[16] As a consequence, we used responsiveness to command as a conservative measure of consciousness. This identifies those patients who may soon become capable of formulating recall.[1]

The combination of slow induction of anesthesia, the use of two different drug regimens, and the use of a response to command as a classifying criterion produces a very challenging data set. Periods that are used for the analysis are very close to each other both in time and in patient status (immediately before and after the transition between consciousness and unconsciousness). As our results show, even in this challenging data set, dif-

In the Web Enhancement, detailed results of logistic regression are shown. A table shows misclassifications, sensitivity, specificity, and results of the cross-validation for the best 12 full models and the results of the variable selection (including the best reduced model).

Table 6. Results of Auditory Evoked Potential Parameters

Parameter Name	Consciousness, Mean ± SD	Unconsciousness, Mean ± SD	Sensitivity	Specificity	PPV	NPV	ROC Area	Threshold	P_K ± SE
MLAEP (24–120ms)									
1st Derivative: mean absolute amplitude	336.99 ± 190.64	161.84 ± 149.04	0.83	0.68	0.69	0.83	0.80	163.00	0.80 ± 0.03
2nd Derivative: absolute maximum amplitude	$9.04 \times 10^5 \pm 5.36 \times 10^5$	$4.10 \times 10^5 \pm 4.08 \times 10^5$	0.86	0.67	0.68	0.85	0.80	3.79×10^5	0.80 ± 0.03
Morphology	55.88 ± 16.42	36.63 ± 16.80	0.84	0.66	0.68	0.83	0.80	39.65	0.80 ± 0.03
Signal energy	7.36 ± 4.01	4.00 ± 2.84	0.69	0.80	0.74	0.75	0.79	5.37	0.79 ± 0.03
Mean absolute amplitude	0.60 ± 0.33	0.33 ± 0.23	0.73	0.76	0.72	0.77	0.79	0.40	0.79 ± 0.03
AEP (0–120 ms)									
1st Derivative: mean absolute amplitude	367.85 ± 221.01	178.17 ± 160.40	0.84	0.65	0.67	0.83	0.79	163.68	0.79 ± 0.03
Morphology	71.05 ± 21.23	47.18 ± 20.79	0.79	0.71	0.70	0.80	0.79	55.52	0.79 ± 0.03
2nd Derivative: mean absolute amplitude	$2.86 \times 10^5 \pm 1.75 \times 10^5$	$1.34 \times 10^5 \pm 1.27 \times 10^5$	0.82	0.67	0.67	0.81	0.79	1.35×10^5	0.79 ± 0.03
Mean absolute amplitude	0.66 ± 0.37	0.36 ± 0.26	0.75	0.73	0.70	0.77	0.78	0.41	0.78 ± 0.03
Wavelet transform (Daubechies 3 wavelet)									
Detail level 3, coefficient 4	−0.85 ± 2.58	−0.04 ± 0.93	0.49	0.85	0.73	0.66	0.63	−0.45	0.37 ± 0.04
Detail level 4, coefficient 4	0.72 ± 2.02	0.15 ± 1.37	0.60	0.71	0.64	0.68	0.62	0.63	0.62 ± 0.04
Detail level 4, coefficient 5	−0.83 ± 1.66	−0.27 ± 0.85	0.47	0.78	0.64	0.64	0.60	−0.76	0.40 ± 0.04
Detail level 3, coefficient 11	0.16 ± 1.13	−0.04 ± 0.68	0.47	0.83	0.70	0.65	0.58	0.27	0.58 ± 0.04
Detail level 4, coefficient 6	−0.15 ± 1.60	0.14 ± 0.94	0.40	0.84	0.68	0.63	0.57	−0.42	0.43 ± 0.04
Detail level 3, coefficient 18	0.00 ± 0.14	−0.02 ± 0.12	0.40	0.87	0.72	0.63	0.56	0.05	0.56 ± 0.04
Detail level 2, coefficient 11	−0.15 ± 0.92	0.02 ± 0.49	0.48	0.77	0.64	0.64	0.56	−0.12	0.44 ± 0.04
Detail level 4, coefficient 3	1.96 ± 4.29	0.90 ± 2.29	0.38	0.81	0.62	0.61	0.56	1.37	0.56 ± 0.04
Detail level 2, coefficient 25	0.08 ± 0.67	0.08 ± 0.46	0.48	0.76	0.63	0.63	0.55	0.15	0.55 ± 0.04
Detail level 2, coefficient 23	0.03 ± 0.83	−0.01 ± 0.40	0.44	0.83	0.68	0.64	0.54	0.18	0.54 ± 0.04
Detail level 2, coefficient 24	−0.08 ± 0.86	0.02 ± 0.40	0.40	0.85	0.70	0.63	0.54	−0.21	0.46 ± 0.04
Detail level 2, coefficient 26	0.05 ± 0.66	0.01 ± 0.45	0.30	0.89	0.69	0.60	0.51	0.33	0.51 ± 0.04
Detail level 2, coefficient 27	−0.05 ± 0.75	0.01 ± 0.48	0.38	0.82	0.64	0.61	0.51	0.17	0.51 ± 0.04
Detail level 2, coefficient 13	−0.09 ± 0.78	−0.07 ± 0.44	0.27	0.92	0.74	0.60	0.50	0.36	0.50 ± 0.04

Parameter values during consciousness and unconsciousness (mean ± SD). Parameters were analyzed from the midlatency range of auditory evoked potentials (MLAEP, 24–120 ms) or from the auditory evoked potential up to 120 ms (AEP). For each parameter, sensitivity, specificity, positive predictive value (PPV, the percentage of cases with consciousness out of all cases that were indicated as being conscious), and negative predictive value (NPV, the percentage of unconscious cases out of all cases that were indicated as unconscious) for detection of consciousness are given. Furthermore, the area under the receiver operating characteristic curve (ROC area) and the prediction probability (P_K) are given.

Table 7. Minimal Model

Effect	*P* Value	Odds Ratio	95% Wald Confidence Limits	
AEP: db 3, detail level 3, coefficient 11	0.0097	1.654	1.130	2.420
AEP: db 3, detail level 4, coefficient 5	0.0009	0.618	0.465	0.820
EEG: median frequency 8–30 Hz	0.0030	1.285	1.089	1.517
EEG: approximate entropy	< 0.0001	16.062	6.584	39.183

The best minimal model for detection of consciousness contains two auditory evoked potential (AEP) parameters of wavelet transform with Daubechies 3 wavelet (db3), and two electroencephalographic (EEG) parameters. The table shows *P* values, odds ratios, and 95% confidence intervals from logistic regression.

ferentiation between consciousness and unconsciousness can be reached by a combination of electroencephalographic and AEP parameters. The best minimal model has a higher sensitivity (75.4% *vs.* 72.2%) but a lower specificity (84.0% *vs.* 85.3%) than the best full model. For the minimal model, two electroencephalographic and two AEP parameters were selected. This supports the view that both the electroencephalogram and AEP contain important information about the effect of anesthetics on the state of consciousness and should be used in parallel rather than in competition with each other.[17] Because the current study is focused on simultaneous analysis of the AEP and electroencephalogram, electroencephalographic parameters may in part be influenced by the ongoing auditory stimuli.

One of the parameters is the median frequency of the electroencephalographic amplitude spectrum from 8 to 30 Hz. Spectral analysis of the electroencephalogram has been used for decades. So far, mainly the power spectrum has been used. In contrast to spectral edge frequency and median frequency, which are calculated from the electroencephalographic power spectrum, the suggested parameter is calculated from the amplitude spectrum, *i.e.*, the electroencephalographic amplitude is used rather than the electroencephalographic power (amplitude^2). This reduces at least in part the influence of frequencies with high amplitude. The use of a high-pass filter of 8 Hz means that both the θ and the δ band of the electroencephalogram were omitted from analysis. The low-pass filter of 30 Hz excludes the γ band from analysis. On one hand, this may exclude important information, because higher frequencies may be of particular value for separation between consciousness and unconsciousness.[18] On the other hand, frequencies higher than 30 Hz are prone to muscle artifacts, especially with electrode positions at the forehead. The omission of this frequency range reduces influence of muscle activity (electromyogram) and shifts the focus of analysis to electroencephalographic signals. These reflect reactions of the main target of general anesthesia, the brain. Despite of their usefulness, high-frequency components may mainly derive from frontal electromyographic activ-

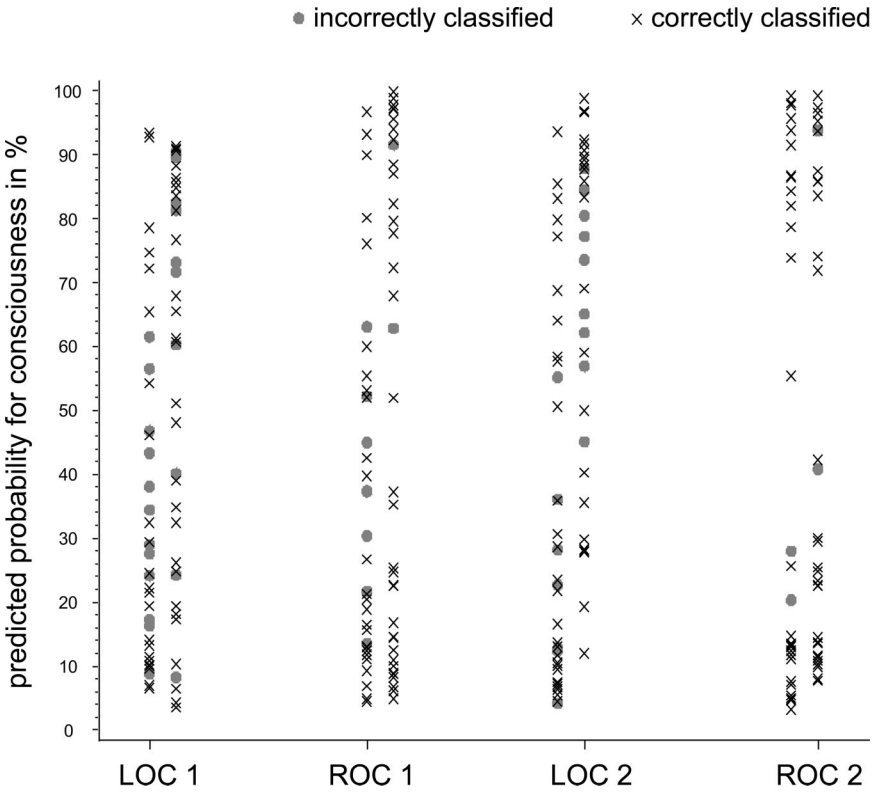

Fig. 1. The graph shows classification results of the best minimal model at loss of consciousness 1 (LOC 1), while patients followed command after tracheal intubation (return of consciousness 1 [ROC 1]), loss of consciousness after the period of responsiveness (LOC 2), and return of consciousness after surgery (ROC 2). The data 30 s before the LOC or ROC and the first data after LOC or ROC were analyzed, *i.e.*, at each transition between consciousness and unconsciousness one data pair (conscious/unconscious) is analyzed. The separation line between consciousness and unconsciousness is at a value of 50%. The graph shows correct (x) and incorrect (●) classifications in the remifentanil–sevoflurane (*left column*) and remifentanil–propofol group (*right column*).

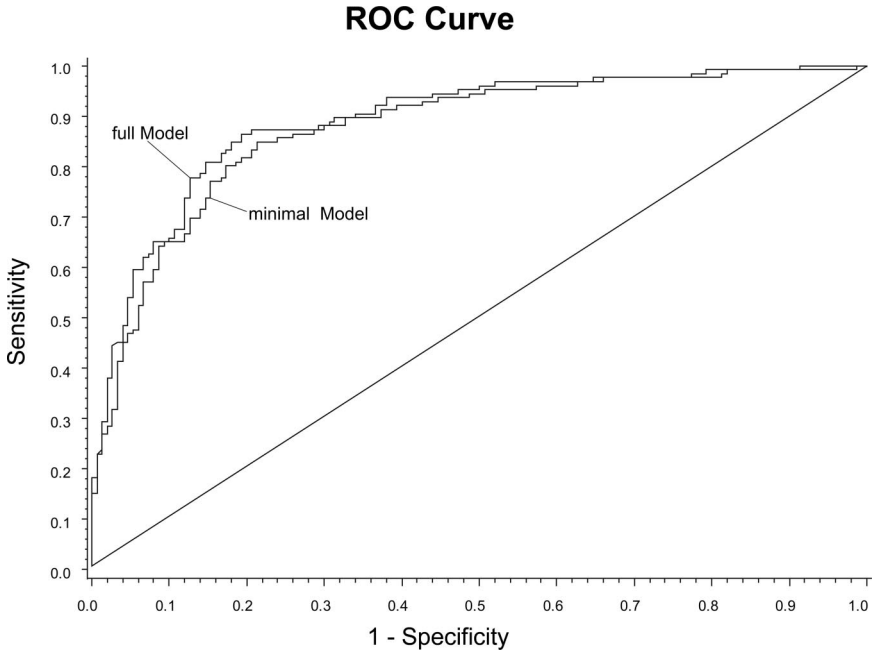

Fig. 2. Receiver operating characteristic (ROC) curve for the best full and the best minimal model.

ity, thus still be a surrogate parameter of anesthetic depth, and be influenced by the use of muscle relaxants. As the results of the current analysis indicate, the suggested spectral parameter of the electroencephalogram bears information that is important for separation of consciousness from unconsciousness, even if it is limited to the α and β bands of the electroencephalogram.

The second parameter is approximate entropy of the electroencephalogram. For the calculation of approximate entropy, also a 30-Hz low-pass filter was used to reduce the influence of the electromyogram. Measures of complexity and entropy have already been suggested as a monitor of anesthetic effects.[19,20] As the current study shows, these measures may be of particular value for the differentiation between consciousness and unconsciousness.

In addition to the two electroencephalographic parameters, the minimal model contains two parameters derived from the AEP. Both AEP parameters are the result of wavelet transform. Wavelet transform is in principle similar to Fourier transform, but instead of sine waves, variations of a mother wavelet, *i.e.*, a signal of finite length, are applied for the signal transform. Wavelet analysis characterizes a signal in a time–frequency domain: The mother wavelet is dilated and contracted along the time axis to extract frequency information. In

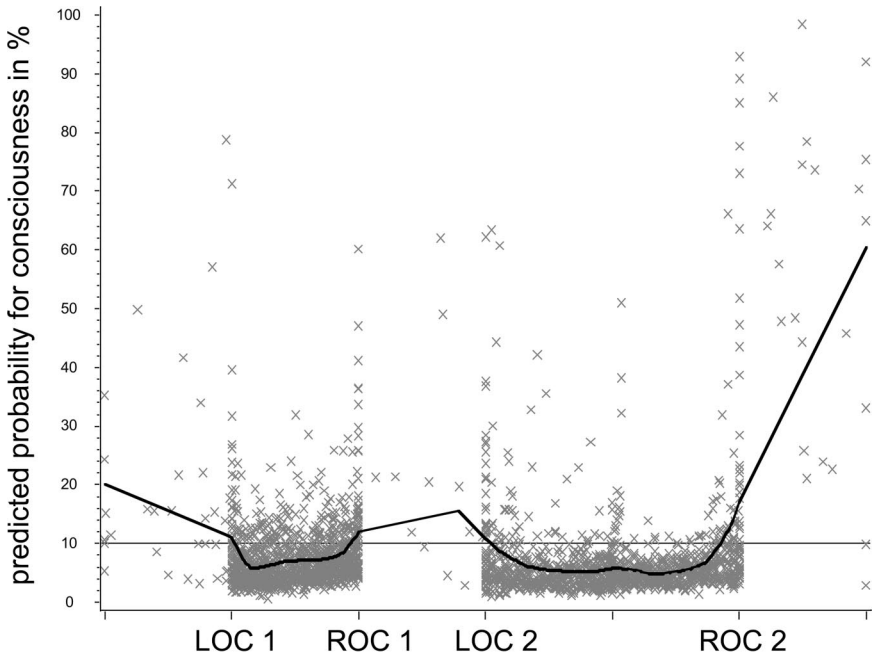

Fig. 3. Results of the best minimal model over time. The output value was calculated every 30 s from the start of the study until 10 min after loss of consciousness 2 (LOC 2) after the period of responsiveness, which includes loss of consciousness 1 at induction of anesthesia (LOC 1), and return of consciousness 1 after intubation (ROC 1). Additional data were from 10 min before return of consciousness 2 (ROC 2) until the end of the study. The 30-s interval was chosen because it corresponds with the clinical assessment of hypnosis, *i.e.*, the command "squeeze my hand." Lowess interpolation with smoothness factor 0.15 was applied for visualizing the classification through observation time. The best classification is reached with a cutoff value of 10% (*horizontal line*).

addition, it is shifted along the time axis to extract time information about changes in frequencies and amplitudes. Consistent with previous results,[7] the Daubechies 3 mother wavelet was chosen because it allows a good approximation of AEP signal characteristics (*i.e.*, time–frequency components). As our results indicate, this approach extracts information from the AEP that contributes to the differentiation between consciousness and unconsciousness even in this very challenging data set. The selected coefficients represent two subsequent waveforms that are located in the midlatency range of the AEP. The coefficient *db3_d4_5* was also selected in a previous study as part of an index that discriminates between consciousness and unresponsiveness during propofol sedation and anesthesia[7] and represents an earlier component with a lower frequency.

As the comparable classification results and areas under the ROC curves indicate, results of the best minimal model are equally valid for either remifentanil with sevoflurane or propofol. Before this model is used for other drug combinations, it must specifically be tested to validate its performance.

In the current study, the area under the ROC curve was used as a measure of the performance of the best models. For a comparison of two levels (*i.e.*, consciousness and unconsciousness in the current study), the area under the ROC curve is comparable to prediction probability (P_K).[21] The area under the ROC curve is a value between 0.5 and 1, whereas P_K is a value in the range between 0 and 1. A value of 0.5 means that the parameter indicates the anesthetic state as good as a random process, *e.g.*, flipping a coin. A P_K (or ROC area) of 1 means a correct classification in 100%, and a P_K value of 0 means a false identification in 100%. Using a very similar study design, a previous study showed that BIS® (Aspect Medical Systems) and Patient State Index (Physiometrix, North Billerica, MA), two commercially available monitors based on the electroencephalogram, only have a prediction probability (P_K) of less than 0.7.[22] These values are confirmed by results of the analysis of BIS values from recorded electroencephalogram in the current study, showing a P_K value of 0.737. These results are consistent with a previous study, where BIS values showed a high correlation with propofol target concentrations, whereas the discrimination between "awake" and "unconscious" was less than ideal.[23] Interestingly, BetaRatio, one of the subcomponents of the BIS,[24] was also calculated from the challenging data set of the study mentioned above[22] and had a P_K of 0.825.[25] In the current study, the area under the ROC curve was 0.89 for the best full model and 0.87 for the best minimal model. These values are better than results of BIS (P_K 0.737) measured from the identical data set and indicate that separation between consciousness and unconsciousness can be improved if a combination of calculated electroencephalographic and AEP parameters is used. Interestingly, the minimal model consists of both AEP and electroencephalographic parameters, which supports the role of both monitoring methods in the differentiation between consciousness and unconsciousness.

These parameters have not been tested for their ability to monitor the complete range of anesthesia. As the performance of the best minimal model over time (as shown in fig. 3) indicates, they can be used as indicators of consciousness over a wider range of hypnotic depth.

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