

Median Frequency Revisited

An Approach to Improve a Classic Spectral Electroencephalographic Parameter for the Separation of Consciousness from Unconsciousness

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Background: In the past, several electroencephalographic parameters have been presented and discussed with regard to their reliability in discerning consciousness from unconsciousness. Some of them, such as the median frequency and spectral edge frequency, are based on classic spectral analysis, and it has been demonstrated that they are of limited capacity in differing consciousness and unconsciousness.

Methods: A generalized approach based on the Fourier transform is presented to improve the performance of electroencephalographic parameters with respect to the separation of consciousness from unconsciousness. Electroencephalographic data from two similar clinical studies (for parameter development and evaluation) in adult patients undergoing general anesthesia with sevoflurane or propofol are used. The study period was from induction of anesthesia until patients followed command after surgery and includes a reduction of the hypnotic agent after tracheal intubation until patients followed command. Prediction probability was calculated to assess the ability of the parameters to separate consciousness from unconsciousness.

Results: On the basis of the training set of 40 patients, a new spectral parameter called *weighted spectral median frequency* was designed, achieving a prediction probability of 0.82 on the basis of the "classic" electroencephalographic frequency range up to 30 Hz. Next, in the evaluation data set, the prediction probability was 0.79, which is higher than the prediction probability of median frequency (0.58) or spectral edge frequency (0.59) and the Bispectral Index (0.68) as calculated from the same data set.

Conclusions: A more general approach of the design of spectral parameters leads to a new electroencephalographic spectral parameter that separates consciousness from unconsciousness significantly better than the Bispectral Index.

ELECTROENCEPHALOGRAPHY-based monitoring of the hypnotic component of anesthesia has gained popularity because it may help to complete the information given by vital signs during surgery. "Depth-of-anesthesia" monitors use algorithms to compute suitable values from the

electroencephalographic signal (called *parameters*). The parameters are combined to calculate an index, which represents the hypnotic component of anesthesia. Currently, these monitors are of limited value in discerning consciousness from unconsciousness,¹ and the question of whether the used algorithms can be improved should be considered. In the current investigation, signal analysis methods based on the spectrum of the electroencephalogram are used, and a generalization of the classic electroencephalographic parameters median frequency (MF)² and spectral edge frequency (SEF95)^{3,4} is introduced. This new definition is adapted to the special characteristics of electroencephalographic signals, and the resulting parameters are tested for their ability to discern consciousness from unconsciousness, reflected by the ability to follow command. The parameters are assessed using data at the transition from consciousness to unconsciousness (or *vice versa*). Electroencephalographic data were from two different patient studies, one for parameter development, the other for parameter evaluation.

Materials and Methods

Protocol Design and Data Collection

The current analysis is based on data from two clinical studies, denoted as study A and study B, with similar study design approved by the ethics committee of the Technische Universität München, Faculty of Medicine, Munich, Germany. In each of the studies, 40 consenting adult patients undergoing general anesthesia were enrolled.^{1,5} In both studies, the study period was from induction of anesthesia until patients followed command after surgery and included a reduction of the hypnotic agent after tracheal intubation until patients followed command. Patients with contraindications to the study drugs, a history of psychiatric or neurologic disease, drug abuse or medication known to affect the central nervous system, pregnancy, or indication for rapid-sequence induction were excluded from the study. In study A, patients were randomly assigned to an anesthetic regimen with remifentanyl (minimum infusion rate $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and sevoflurane ($n = 20$) or remifentanyl and propofol ($n = 20$). In study B, the sevoflurane and propofol groups were divided into two subgroups with either "low infusion rate" of remifentanyl ($0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or "high infusion rate" ($0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Without premedication, remifentanyl in-

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fusion was started *via* a cannula in the cubital vein. In 30-s intervals, patients were asked to squeeze the investigator's hand. A response was verified by an immediate repetition of the command that also required a response. This prevents a misinterpretation of involuntary movement as a response. Anesthesia was slowly induced with sevoflurane inhalation or propofol injection (0.7 mg/kg, followed by 20 mg every 30 s). The first time when the patient did not squeeze the investigator's hand to command was labeled as loss of consciousness (LOC1). Additional propofol or sevoflurane was given to increase depth of anesthesia, and a tourniquet was used to occlude the circulation of the right forearm for 5 min to retain the ability to move the hand to command, before succinylcholine (1.0 mg/kg) was given (isolated forearm technique of Tunstall).⁶ After intubation, sevoflurane or propofol was stopped until patients followed command (return of consciousness [ROC1]). Thereafter, sevoflurane (5 vol%) or propofol (20-mg boluses) was readministered to induce anesthesia again slowly. The time when patients stopped responding to command again was defined as loss of consciousness 2 (LOC2), and requests to squeeze the hand were stopped. Anesthetic drugs were administered according to clinical practice, and surgery was performed. At the end of surgery, requests to squeeze the hand were recommenced, and sevoflurane, propofol, and remifentanyl were discontinued. Return of consciousness 2 (ROC2) was observed at the first verified response to command. Recovered from anesthesia, patients were asked for signs of recall in the recovery room. This interview⁷ was repeated within 48 h in the ward. Standard monitoring parameters were measured with a Datex AS/3 (Datex-Ohmeda Division Instrumentation Corp., Helsinki, Finland) compact anesthesia monitor. For data transfer and storage, a personal computer with NeuMonD (Department of Anesthesiology, Klinikum rechts der Isar, Technische Universität München) was used. NeuMonD is a software program developed by members of the research group allowing the recording of monitoring data and the electronic storage of events and comments during the study.⁸ In addition to standard monitoring, electroencephalogram and auditory evoked potentials were measured (study A). Two channel electroencephalographic signals at electrode positions AT1, M2, Fpz (reference), and F7 (ground) were recorded on a second personal computer with synchronized system time. This auditory evoked potential/electroencephalographic device has been designed specifically for intraoperative use as described previously.⁹ Electroencephalogram and concomitant trigger information of auditory evoked potentials were stored with a sampling rate of $f_s = 1,000$ Hz and 12-bit amplitude resolution. In study B, electroencephalogram was recorded using the Aspect A-1000 electroencephalographic monitor (BIS[®] version 3.3; Aspect Medical Systems Inc., Newton, MA). A two-channel referential electroencephalogram was obtained

with ZipPrep Ag/AgCl electrodes in positions AT1, AT2, Fz (reference), and Fp1 (ground, electrode positions according to the international 10–20 system). The high pass was set at 0.25 Hz, no low pass was used, and the notch filter (50 Hz) was enabled. Electroencephalogram was continuously digitized at 256 Hz per channel and simultaneously recorded with standard monitoring parameters. For data analysis in both studies, a time window duration $T = 8$ s was used.

Signal processing and statistical analysis were performed using LabVIEW 6.0 (National Instruments, Austin, TX; 2000), MATLAB 6.0 Release 12 (The MathWorks, Inc., Natick, MA; 2000), Microsoft Access 2002 (Microsoft Corporation, Redmond, WA), and R 2.4.0 (R Foundation for Statistical Computing, Vienna, Austria; 2006) on personal computers with Windows NT/XP (Microsoft Corporation; 2002).

Median Frequency and Spectral Edge Frequency

The electroencephalogram is obtained by recording the electrical activity of the brain. Scalp electrodes are used to detect electrical activity on the surface of the head. This reflects the activity of action potentials of cortical neurons, in particular superposition of postsynaptic potentials mainly generated in layer V of the cerebral cortex.¹⁰ Different rhythms are observed, and in the past, the following frequency bands related to brain activity were introduced for classification: the δ band, including a frequency range up to 4 Hz; the θ band [4 Hz, 8 Hz], the α band [8 Hz, 12 Hz], and the β band [12 Hz, 30 Hz]. Spectral analysis—as calculated by (discrete) Fourier transform—seems to be an appropriate method to analyze electroencephalographic time series, because it follows this approach of signal analysis. Although the spectrum including amplitude and phase contains not more information as the time series, some signal characteristics are more evident by observing the spectrum of the signal. To reduce dimension of the spectrum, suitable parameters can be extracted and assessed, such that they correspond to the observed patient states.

Parameters derived from the electroencephalographic power spectrum have been shown to indicate—at least to some extent—anesthetic effects. Two of those parameters are the median frequency (MF or SEF50)² and spectral edge frequency (SEF95)^{3,4} between low and high cutoff frequency f_{low} and f_{high} . MF provides an overall average frequency and roughly decreases with increasing “depth of anesthesia.” This is consistent with the expectation that in “deeper” anesthesia, high-frequency components of the superficial neuronal areas are replaced by low-frequency components.¹⁰ Unfortunately, some effects limit the usefulness of this general observation. These may in part be related to the presence of muscle activity, *i.e.*, electromyogram superposed to the electroencephalo-

graphic signal. Electromyogram may change mainly the spectrum of the electroencephalographic time signal such that most of the electroencephalographic parameters are influenced by the presence of eye blinks and electromyogram-related high-frequency components. Changes of the electroencephalographic time signal may not primarily reflect the level of general anesthesia, but a specific drug effect (which subsequently influences the level of anesthesia). As an example, this occurs on the lower end of the frequency spectrum, where opioids induce increasing amplitudes of the electroencephalographic δ band (without primarily effecting the level of hypnosis). On the other hand, relatively deep propofol anesthesia is also reflected by increasing δ activity, but this time the level of hypnosis is increased. As this example illustrates, changes of an electroencephalographic parameter may be drug specific and can not be used equally for all types of general anesthesia. On the higher end of the frequency spectrum, the behavior of most parameters is affected by a characteristic biphasic reaction, which occurs during induction of anesthesia. This was shown for electroencephalographic amplitude and SEF95 during the transition from consciousness to unconsciousness and is reflected by an initial increase of the effect variable followed by a decrease at higher concentrations.¹¹

WSMF, a Generalization of MF

In general, a parameter is characterized by numerous variables, e.g., its low and high cutoff frequency f_{low} and f_{high} , and each of them augments the parameter dimension by one. The setting of these variables may considerably affect the behavior of the parameter itself, e.g., its capability to distinguish consciousness from unconsciousness. Therefore, the influence of variable settings must be examined. This was mostly neglected in the past.

The parameter weighted spectral median frequency (WSMF) can be seen as a generalization of MF: Given an electroencephalographic signal s , the amplitude spectrum $A(f)$ of s is computed by a discrete Fourier transform. The amplitudes are then weighted by the p th power, where the influence of the value p is explained below. The “area” of the weighted spectrum $A^p(f)$ delimited by the frequency axis between the cutoff frequencies f_{low} and f_{high} is divided into two parts at the frequency called WSMF. The frequency WSMF is such that the complete “area” between f_{low} and f_{high} multiplied by r is equal to the “area” between f_{low} and WSMF.

A value $p = 1$ defines the computation of WSMF based on the amplitude spectrum. $p = 2$ computes WSMF using the power spectrum as for MF and SEF95. Particularly $p < 1$ allows a non linear attenuation of high amplitudes and leads to an equalization of amplitude differences. It may provide a more stable behavior of

WSMF when artifacts containing high amplitudes occur. The variable r can be denoted as splitting ratio and defines how much the spectrum up to WSMF is weighted in relation to the total spectrum between f_{low} and f_{high} . $r = 0.5$ as defined for MF provides a symmetrical weight of the spectrum below and above the frequency WSMF, where $r = 0.95$ as for SEF95 means that the spectrum above WSMF obtain a main emphasis. A mathematical description of WSMF can be found in appendix 1.

A generalization WSMF of MF with four variables f_{low} , f_{high} , p , r for parameter configuration is obtained. Their values with suitable bounds are denoted by the four-dimensional set I (see equation (4) in appendix 1 for an exact definition). Therefore, WSMF defines an own parameter for every setting f_{low} , f_{high} , p , r . To simplify notation, a particular parameter WSMF with settings f_{low} , f_{high} , p , r is denoted by $WSMF_{f_{low}-f_{high}}$, if there is no risk of confusion by different settings of p and r . For a general configuration, the notation WSMF is used without indication of its variables.

Settings of f_{low} , f_{high} , p , r for the Development of WSMF

To obtain best possible classification results for separating consciousness and unconsciousness of the parameters WSMF with settings of f_{low} , f_{high} , p , r , a discrete and finite subset of I is determined. This allows the computation of WSMF for a finite number of settings in I .

The technical equipment for data acquisition described above determines the lower bound of 0.5 Hz for f_{low} . The upper bound for f_{high} is set to approximately 50 Hz. Therefore, the signal does not exclusively reflect electroencephalogram, but may also include electromyogram in further analysis. The exponent p indicates how much WSMF is affected by high amplitudes in the spectrum A . For calculation of the classic MF, $p = 2$, i.e., the power spectrum is chosen, such that high frequencies with small amplitudes, which may be typical for consciousness, are not sufficiently weighted when electromyographic components are absent. Therefore, it seems very promising to consider also smaller values for the variable p , and its range is defined between 0.1 and 2.4. The splitting ratio r is generally defined in the open interval with $0 < r < 1$, and therefore settings between 0.05 and 0.95 are considered, such that MF and SEF95 are included in the analysis.^{3,4} It allows a crossover between MF and SEF95. The low-frequency resolution of the discrete Fourier transform and the time stability of WSMF are mainly affected by the setting of T and increase monotonically with increasing values of T . As stated above, in the current analysis, $T = 8$ s.

Summarizing, the following settings for the variables f_{low} , f_{high} , p , r are used (subset of I ; see equation (4) in appendix 1):

$$f_{\text{low}} \in \{0.50, 1, 2, \dots, 15 \text{ Hz}\} \text{ (16 settings)}$$

$$f_{\text{high}} \in \{25, 27, \dots, 53 \text{ Hz}\} \text{ (15 settings)}$$

$$p \in \{0.1, 0.2, \dots, 2.4\} \text{ (24 settings)}$$

$$r \in \{0.05, 0.10, \dots, 0.95\} \text{ (19 settings).} \quad (1)$$

The resulting configurations of WSMF are included for parameter development.

Statistical Analysis

Prediction probability (P_K) has been established in anesthesia¹² as a statistical method to assess the capability of a parameter to discern different levels of anesthesia, e.g., consciousness and unconsciousness. The aim of the P_K analysis is to quantify the association between the (clinically) observed anesthetic level and the parameter values, in this case of WSMF. A short description can be found in appendix 2.

To give an estimation of suitable configurations of WSMF, the extremes of the P_K values with respect to the settings of f_{low} , f_{high} , p , r in I are computed using study A. P_K analysis is then applied on study B to provide a further assessment of the capability of WSMF indicating the changes from consciousness to unconsciousness (or *vice versa*).

The P_K analysis used below is defined on the basis of a set of electroencephalographic signals (samples) of $T = 8$ s length directly preceding or after the transition between consciousness and unconsciousness. Study A and study B involved 40 patients each. Because two signals were analyzed at every clinical event LOC1, LOC2, ROC1, and ROC2, a maximum of 320 signals was available from study A and study B (see Protocol Design and Data Collection section). The signals are situated either completely in a phase of consciousness or in a phase of unconsciousness. For study A (development study), 306 signals (152 assigned to consciousness and 154 assigned to unconsciousness) and for study B (evaluation study), 286 signals (135 assigned to consciousness and 151 assigned to unconsciousness) were used for P_K analysis. Fourteen (study A) and 34 (study B) signals containing artifacts expressed by signals of constant amplitude (flat line) or values exceeding the measuring range of 250 μV were manually (study A) or automatically (study B) excluded from analysis.

Ninety-five percent confidence intervals based on the number of samples including Bonferroni correction were used to compare P_K values of selected parameters of study B, where P_K values are significantly different if the corresponding confidence intervals are disjoint.

Results

Particular Cases of WSMF

To provide an intuitive idea of the behavior of WSMF, both the stability of the parameter and its ability to distinguish consciousness from unconsciousness are examined using an exemplarily electroencephalographic signal of study A for some particular settings of f_{low} , f_{high} , p , r .

Figure 1 shows time series of two categories of WSMF, one computed with the full "classic" electroencephalographic frequency range from 0.5 to 30 Hz, represented by MF ($f_{\text{low}} = 0.5$ Hz, $f_{\text{high}} = 30$ Hz, $p = 2$, $r = 0.5$)² and SEF95 ($f_{\text{low}} = 0.5$ Hz, $f_{\text{high}} = 30$ Hz, $p = 2$, $r = 0.95$)^{3,4} and a second with an higher low cutoff frequency, represented by WSMF₈₋₄₉ ($f_{\text{low}} = 8$ Hz, $f_{\text{high}} = 49$ Hz, $p = 1$, $r = 0.5$) and WSMF₈₋₃₀ ($f_{\text{low}} = 8$ Hz, $f_{\text{high}} = 30$ Hz, $p = 0.4$, $r = 0.5$). WSMF₈₋₄₉ and WSMF₈₋₃₀ allow a much better appreciation of the hypnotic component of anesthesia than MF and SEF95; in particular, they are more stable and show improved monotonic behavior, *i.e.*, their values are decreasing during increasing levels of hypnosis and *vice versa*. Note that all four parameters show a certain amount of inappropriately low values during consciousness. Furthermore, all parameter time series are affected by the characteristic biphasic reaction during induction of anesthesia,¹¹ expressed by an increase of the parameter values before loss of consciousness (LOC1 and LOC2) after propofol administration.

The aim is to find a parameter WSMF with appropriate settings of f_{low} , f_{high} , p , r that reflects the hypnotic component of anesthesia, such that it is as robust as possible against electromyographic artifacts and that it operates in the "classic" electroencephalographic spectrum up to 30 Hz, because detection of consciousness should not be based on electromyographic activity.

Influence of the Exponent p and the Splitting Ratio r on WSMF

Two observations were made when WSMF was applied on development study A using the discrete settings of the variables as in equation (1).

First, $P_K \geq 0.82$ for WSMF can be achieved at every level of the splitting ratio r including frequencies up to 30 Hz only, *i.e.*, with $f_{\text{high}} \leq 30$ Hz. $P_K \geq 0.82$ is considered to be of "similar grade" as the maximal P_K value of 0.824.

Second, for each chosen frequency range from f_{low} to f_{high} , *i.e.*, $[f_{\text{low}}, f_{\text{high}}]$, it can be observed that at constant levels of P_K , the splitting ratio r decreases with decreasing exponent p , as shown in figure 2. This implies that a high value of p combined with a high value of r leads to a better P_K value than a high value of p combined with a low value of r . For example, there is $P_K = 0.73$ in case of SEF95 ($p = 2$, $r = 0.95$) and $P_K = 0.55$ in case of MF

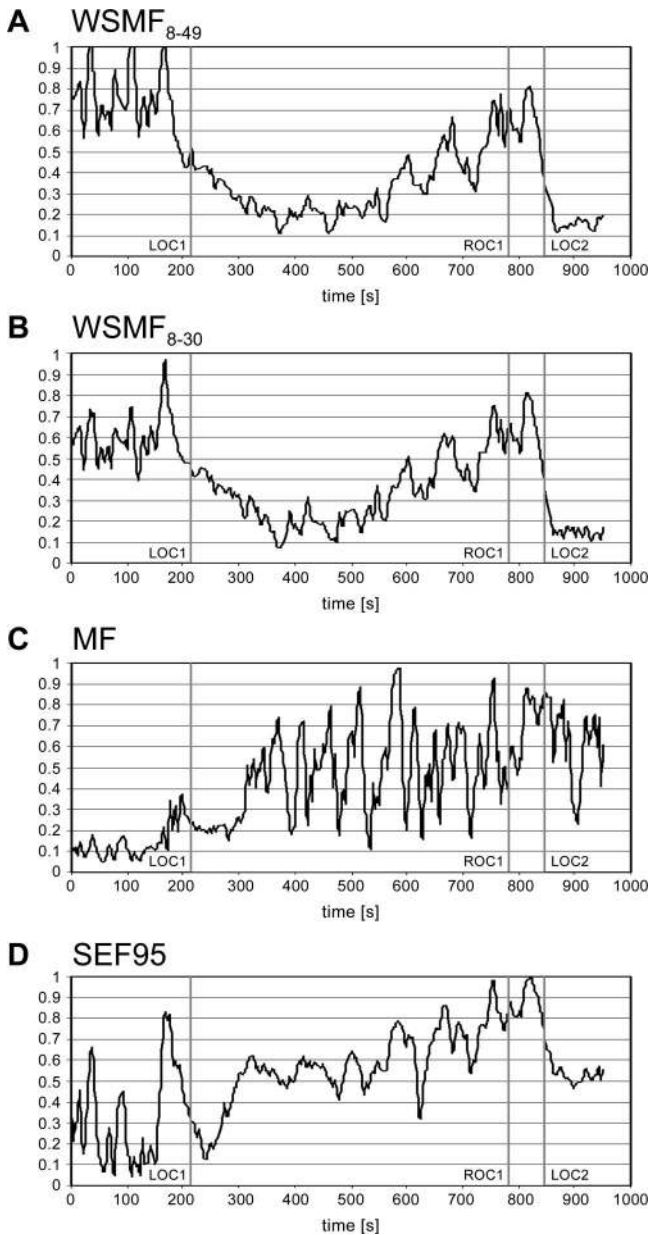


Fig. 1. Induction of anesthesia in a randomly selected patient (propofol): Parameter time series based on study A of weighted spectral median frequency (WSMF₈₋₄₉, A; WSMF₈₋₃₀, B), median frequency (MF; C), and spectral edge frequency (SEF95; D). Parameter values are normalized to the interval [0, 1]. The gray lines indicate changes of the level of consciousness: loss of consciousness at induction (LOC1: 214 s), return of consciousness after intubation (ROC1: 784 s), followed by second loss of consciousness (LOC2: 846 s). WSMF₈₋₄₉ and WSMF₈₋₃₀ indicate better the state of consciousness than MF and SEF95. Parameter calculation was performed in time steps of 4 s using a signal of 8 s length (overlapping factor 2).

($p = 2, r = 0.5$). Both observations suggest that the variables p and r are in a way related, and one of them can be chosen to some extent arbitrarily.

Further ranges [f_{low}, f_{high}] show that the splitting ratio $r < 0.6$ is favorable if $f_{high} \leq 30$ Hz is assumed. $r = 0.5$ is selected, giving a direct relation of WSMF to the classic parameter MF. This leads to a reduced number of set-

tings with

$$f_{low} \in \{0.50, 1, 2, \dots, 15 \text{ Hz}\} \text{ (16 settings)}$$

$$f_{high} \in \{25, 27, \dots, 53 \text{ Hz}\} \text{ (15 settings)}$$

$$p \in \{0.1, 0.2, \dots, 2.4\} \text{ (24 settings)}$$

$$r = 0.5 \text{ (1 setting)}$$

(2)

containing three variables f_{low}, f_{high}, p only and 5,760 configurations of WSMF. The totality of settings of the variables is denoted by $I_{discrete}$ (three-dimensional finite set).

Optimization of the Configuration of WSMF Using Study A

Based on data from development study A, figures 3A and B show the behavior of WSMF at the transition between consciousness and unconsciousness with settings of f_{low}, f_{high}, p in the three-dimensional set $I_{discrete}$ as defined in (2) and visualized in drawing a four-dimensional cube. The fourth dimension indicates the results of P_K analysis and is superposed as colors at every point of $I_{discrete}$.

Maximum P_K values are obtained for settings of f_{low}, f_{high}, p within the cube, *i.e.*, inside $I_{discrete}$, where two “clusters” can be observed (fig. 3C). The first “high-frequency cluster” provides parameters WSMF operating at frequencies with f_{high} above 40 Hz and exponents $p \in [1.0, 1.5]$. The frequency range is bounded at the lower limit around $f_{low} \cong 8$ Hz. The second “low-frequency cluster” is much more interesting, because it reflects analysis of the “classic” electroencephalographic range, *i.e.*, frequencies up to 30 Hz, whereas in high-frequency ranges, electroencephalographic activity overlaps with electromyographic activity. The frequency f_{low} remains the same as in the “high-frequency cluster,” *i.e.*, $f_{low} \cong 8$ Hz. To illustrate the behavior of WSMF, some slices through $I_{discrete}$ are selected at fixed f_{low} (fig. 4). A comparison of the three slices confirms favorable results for WSMF defining f_{low} in the range of 8 Hz. A change of f_{low} in the range between 7 and 10 Hz does not considerably change the characteristics of WSMF, and $P_K = 0.82$ while $f_{high} \leq 30$ Hz is maintained. This behavior can be explained in part by the reduced influence of opioid-induced δ -band activation and eye blinks during induction of anesthesia, which are mainly present in the lower-frequency range.

In contrast, the classic MF with a frequency range defined by $f_{low} \leq 1$ Hz provides $P_K \leq 0.60$ for any chosen frequency f_{high} and seems to be less adequate in separating consciousness from unconsciousness (fig.

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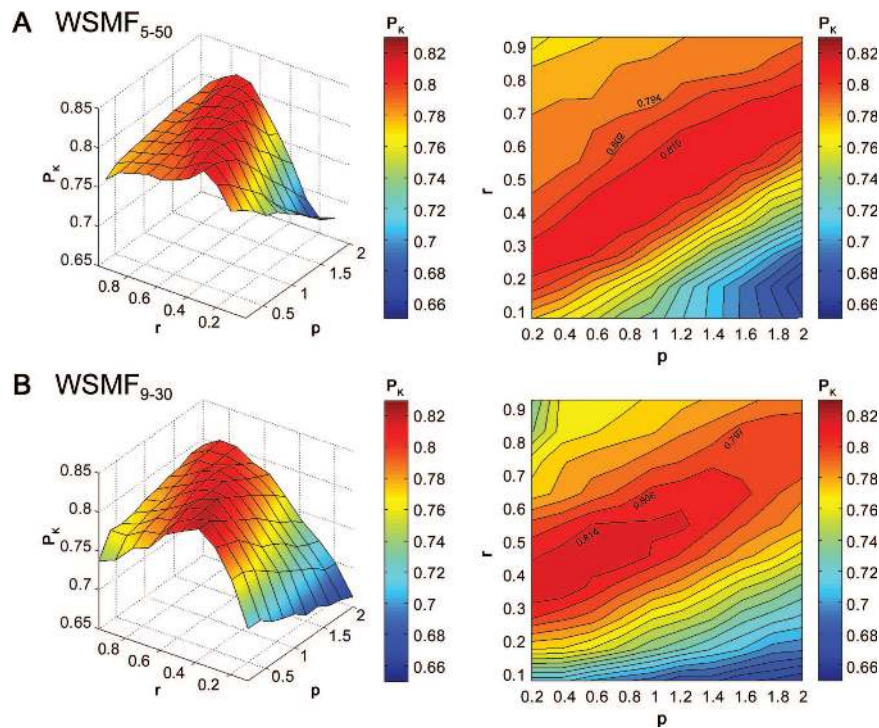


Fig. 2. Prediction probability (P_K) of weighted spectral median frequency (WSMF) based on development study A at fixed cutoff frequencies $f_{low} = 5$ Hz, $f_{high} = 50$ Hz (A) and $f_{low} = 9$ Hz, $f_{high} = 30$ Hz (B). For the exponent p (x -axis), settings between 0.2 and 2.0 are displayed; for the splitting ratio r (y -axis), settings between 0.1 and 0.95 are displayed. The resulting P_K values of WSMF with corresponding settings of p and r are plotted as third dimension (z -axis, left) and represented as superposed colors, where the scaling of the P_K values is indicated by gradient bars. A relation between p and r can be observed if values of $P_K \geq 0.80$ are assumed (red area). The P_K values are interpolated giving a continuous approximation of the discrete settings to obtain a better presentation (left and right).

4A). Finally, choosing $f_{low} > 10$ Hz, essential information in the α or even β band is ignored and the performance of WSMF decreases, as shown in figure 4C. However, this decrease is not as dramatic as with $f_{low} < 5$ Hz. P_K analysis shows that the correlation to the anesthetic state is improved when p decreases.

As a result of these observations, two configurations of

WSMF within both clusters of $I_{discrete}$ and leading to maximal P_K values are selected: WSMF₈₋₄₉ ($f_{low} = 8$ Hz, $f_{high} = 49$ Hz, $p = 1$, $r = 0.5$) and WSMF₈₋₃₀ ($f_{low} = 8$ Hz, $f_{high} = 30$ Hz, $p = 0.4$, $r = 0.5$). MF and SEF95 are outside both clusters, and their computation is based on the power spectrum ($p = 2$) using the full “classic” electroencephalographic frequency range from 0.5 to 30 Hz.

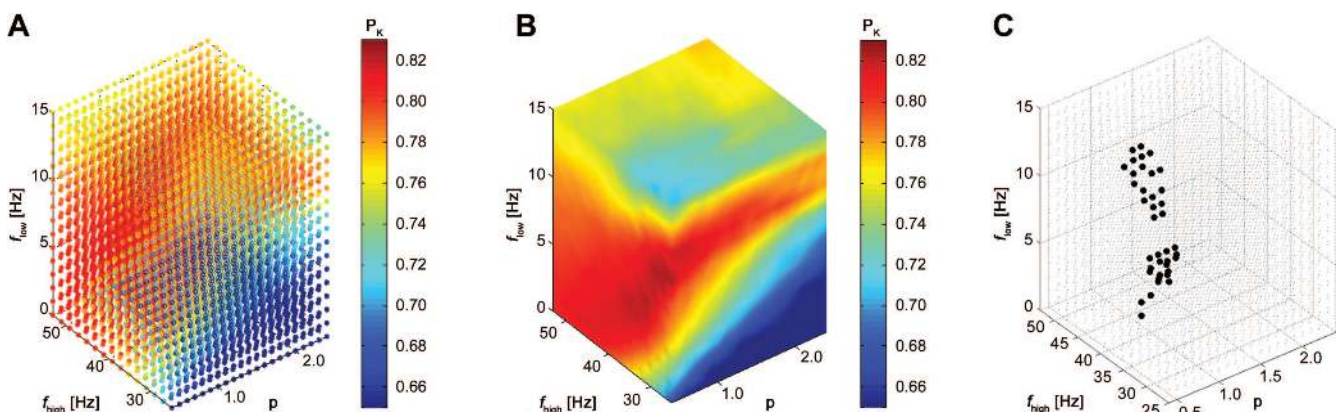


Fig. 3. Prediction probability (P_K) of weighted spectral median frequency (WSMF) based on development study A. Settings of the exponent p (x -axis) are displayed between 0.4 and 2.4; settings of the cutoff frequencies f_{high} (y -axis) and f_{low} (z -axis) are displayed between 25 Hz and 53 Hz and between 0.5 Hz and 15 Hz, respectively. In A and B, the P_K values at the corresponding setting of f_{low} , f_{high} , p are represented as superposed colors, where the scaling of the P_K values is indicated by gradient bars. A maximal P_K value of 0.824 results for WSMF with $f_{low} = 8$ Hz, $f_{high} = 30$ Hz, and $p = 0.4$ that is situated near the frontal edge of the cube (dark red area). The cube in B is interpolated, giving a continuous approximation of the discrete settings to obtain a better presentation. The cube in C shows only values of $P_K \geq 0.82$, which are represented by black dots. They occur as two “clusters,” one as “high-frequency cluster” with $f_{high} \geq 40$ Hz and one as “low-frequency cluster” with $f_{high} \leq 30$ Hz.

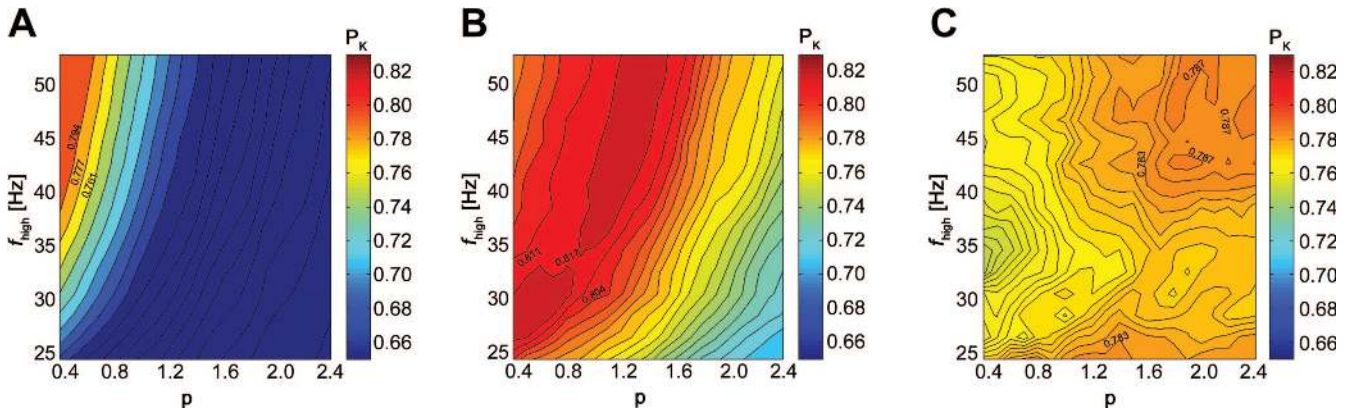


Fig. 4. Prediction probability (P_K) of weighted spectral median frequency (WSMF) based on development study A at three fixed levels of the low cutoff frequency f_{low} with variable settings of the exponent p (x -axis) between 0.4 and 2.4 and high cutoff frequency f_{high} (y -axis) between 25 Hz and 53 Hz. In A, $f_{low} = 0.5$ Hz; in B, $f_{low} = 8$ Hz; and in C, $f_{low} = 13$ Hz. The resulting P_K values of WSMF with the corresponding settings of p and f_{high} are represented as *superposed colors*, where the scaling of the P_K values is indicated by *gradient bars*. P_K values are interpolated. A contains the configuration of median frequency (MF) with $f_{low} = 0.5$ Hz, $f_{high} = 30$ Hz, $p = 2$, $r = 0.5$ leading to a P_K of 0.55 (all P_K values smaller than 0.66 are represented by *dark blue*). B contains the configurations of WSMF that provide maximal P_K values in the range of 0.82 within both “clusters” shown in figure 3C (*dark red areas*): $f_{low} = 8$ Hz, $f_{high} = 49$ Hz, $p = 1$, $r = 0.5$ (denoted by WSMF₈₋₄₉) and $f_{low} = 8$ Hz, $f_{high} = 30$ Hz, $p = 0.4$, $r = 0.5$ (denoted by WSMF₈₋₃₀).

Evaluation of the Configuration of WSMF Using Study B

Study B was used to evaluate the results obtained by study A. The main focus of this analysis was to evaluate whether the selected parameters WSMF₈₋₄₉ and WSMF₈₋₃₀ within both “clusters” in figure 3C maintain their ability to separate consciousness from unconsciousness when applied to data of study B.

Table 1 shows the P_K statistics of both studies at the transition from consciousness to unconsciousness. Although the corresponding P_K values are different for both studies, WSMF₈₋₄₉ and WSMF₈₋₃₀ obtain significantly better results ($P_K = 0.82$ and $P_K = 0.79$) in comparison with MF and SEF95 ($P_K = 0.58$ and $P_K = 0.59$), where confidence intervals considering the number of samples were performed for the involved parameters.

If frequencies higher than 30 Hz are included in the analysis, the parameter WSMF₈₋₄₉ in the “high-frequency cluster” of $I_{discrete}$ in figure 3C provide $P_K = 0.82$ using study B, which is similar to WSMF₈₋₃₀ with $P_K = 0.79$.

Table 1. Prediction Probability Values for Different Settings

Configuration of WSMF	P_K Study A	P_K Study B
WSMF ₈₋₄₉	0.82 (0.77–0.87)	0.82 (0.77–0.87)
WSMF ₈₋₃₀	0.82 (0.77–0.86)	0.79 (0.72–0.84)
MF	0.55 (0.50–0.62)	0.58 (0.53–0.66)
SEF95	0.73 (0.67–0.79)	0.59 (0.52–0.66)

The table shows prediction probability (P_K) values with 95% confidence intervals for the separation of consciousness from unconsciousness calculated from study A and study B for different settings of weighted spectral median frequency (WSMF): WSMF between cutoff frequencies 8 and 30 Hz (WSMF₈₋₃₀), WSMF between cutoff frequencies 8 and 49 Hz (WSMF₈₋₄₉), median frequency (MF), and spectral edge frequency (SEF95).

Discussion

Spectral analysis based on the linear Fourier transform is still a powerful mathematical tool, which can be used effectively to design electroencephalographic parameters indicating the hypnotic component of anesthesia. Apparently, despite nonlinear characteristics of the electroencephalogram,^{4,13-15} the signal properties described by harmonic signal decomposition allow the development of electroencephalographic parameters which produce a good resolution during the transition from consciousness to unconsciousness (or *vice versa*).

So far, different settings and their interaction have mostly been disregarded in attempts to improve the quality of such a parameter. The parameter should be adjusted carefully. For this purpose, it must be examined not only at a few discrete settings, but as far as possible with respect to a wide range of configurations.

Generalization of MF and SEF95 gives a class of new parameters denoted by WSMF. To provide appropriate configurations with respect to the requirements above, it is crucial to find suitable frequency ranges in which the parameter leads to reliable results. The choice of a low cutoff frequency $f_{low} \in [7 \text{ Hz}, 10 \text{ Hz}]$ and a high cutoff frequency $f_{high} \in [25 \text{ Hz}, 30 \text{ Hz}]$ in combination with a real-valued exponent of the amplitude $p \leq 1$ leads to improved results, in particular when compared with MF and SEF95 based on the power spectrum ($p = 2$) of the full “classic” electroencephalographic frequency range from 0.5 to 30 Hz. This can be explained by the low-frequency spectrum signals generated by muscle activity of eye blinks. MF and SEF95 are in particular affected, because a choice of $f_{low} = 0.5$ Hz may even compromise a differentiation between eye blinks and δ activity (fig. 1). With respect to separation of consciousness to uncon-

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consciousness, a classification rate of $P_K \geq 0.79$ for $W_{SMF_{8-30}}$ ($f_{low} = 8$ Hz, $f_{high} = 30$ Hz, $p = 0.4$, $r = 0.5$) is reached both in study A (development study) and in study B (evaluation study). As a consequence of the limited frequency range, the influence of electromyogram or eye blinks is avoided, and the influence of drug specific effects on the δ band is reduced. While a low cutoff frequency of around 8 Hz leads to an improved behavior of WSMF at the transition between consciousness and unconsciousness, it may also limit the capability of WSMF to indicate "deeper" anesthesia that may be characterized by δ activity. The statistical comparison of $W_{SMF_{8-30}}$ and $W_{SMF_{8-49}}$ ($f_{low} = 8$ Hz, $f_{high} = 49$ Hz, $p = 1$, $r = 0.5$) shows a significant improvement in comparison with MF and SEF95.

On the data basis of study B, $W_{SMF_{8-49}}$ provides similar $P_K = 0.82$ in comparison with $W_{SMF_{8-30}}$ ($P_K = 0.79$). In general, inclusion of high-frequency components (> 30 Hz) may be useful in the detection of awareness. But, in particular if measured on the forehead, electroencephalographic signals may overlap with electromyographic signals, *i.e.*, activity of forehead muscles, which are characterized by high frequency activity. As a consequence, increase of high-frequency activity during awareness may reflect increasing muscle activity on the patient's forehead. Therefore, inclusion of frequencies above 30 Hz bears the risk that a parameter does not primarily reflect activity of the main target organ of anesthesia, the brain, but may also rely on increasing muscle activity. Because the frequency range of electromyogram overlaps with the high-frequency electroencephalographic range, the presence of (high-frequency) electromyographic activity may lead to an overestimation of high-frequency electroencephalographic activity, and an increase of spectral energy at high frequencies, which will increase calculated parameter values. This increase, however, is based on electromyographic rather than electroencephalographic activation. Therefore, a parameter that includes high-frequency components may also be a surrogate measure (muscle activity) of the hypnotic component of anesthesia. The use of this surrogate parameter bears the risk that a patient who is fully awake but paralyzed by neuromuscular blockers may not be detected as "awake," because no electromyogram is detected.

Using recorded signals of both studies, the analysis of BIS[®], a commercially available monitor based on electroencephalogram, produces $P_K = 0.74$ (study A) and $P_K = 0.68$ (study B),^{1,5} which is significantly lower than the results of $W_{SMF_{8-30}}$ or even $W_{SMF_{8-49}}$. These results are consistent with previous studies, where BIS values show a high correlation with propofol target concentrations, whereas the discrimination between consciousness and unconsciousness is less than ideal.¹⁶

The current investigation shows that a more general

approach of a parameter is essential to understand the interaction between the configuration and the behavior of the parameter applied on electroencephalographic signals. Suitable settings lead to a significant improvement in representing the hypnotic component of anesthesia. In a further step, analysis must be performed not only for the two states consciousness and unconsciousness, but for the entire range from light sedation to general anesthesia. It should be evaluated whether the good performance of WSMF can be further improved by combining the parameter with other electroencephalographic parameters.

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Definition of WSMF

In the continuous case, *i.e.*, assuming a time-continuous electroencephalographic signal s , the complex spectrum is computed by the Fourier transform

$$c(f) = \int_{-\infty}^{\infty} s(t) \cdot e^{-i2\pi ft} dt, \quad (1)$$

and $A(f) = |c(f)|$ is the amplitude spectrum of the electroencephalographic signal s (s contains in the presented case $T \cdot f_s = 8,000$ samples, $T = 8$ s, $f_s = 1$ kHz, where $s(t) = 0$ if $t \notin [0, T]$). Then the weighted spectral median frequency (WSMF) is defined as

$$\int_{f_{low}}^{W_{SMF}} A^p(f) df = r \cdot \int_{f_{low}}^{f_{high}} A^p(f) df \quad (2)$$

with high and low cutoff frequencies f_{low} , f_{high} , and p as the exponent of the amplitude A . The variable r can be denoted as splitting ratio and defines how much the spectrum up to WSMF is weighted in relation to the total spectrum between f_{low} and f_{high} . A value $p = 1$ defines the computation of WSMF based on the amplitude spectrum, and $p = 2$ defines a computation using the power spectrum. A different notation of equation (2) is obtained if the total band is split according $[f_{low}, f_{high}] = [f_{low}, W_{SMF}] [W_{SMF}, f_{high}]$, such that

$$\int_{f_{low}}^{W_{SMF}} A^p(f) df = q \cdot \int_{W_{SMF}}^{f_{high}} A^p(f) df \quad (3)$$

with $q = r/(1 - r)$. In case of $r = 0.5$, *i.e.*, $q = 1$ as given for MF, WSMF is the frequency that splits $[f_{low}, f_{high}]$ in two sub-bands of equal weights.

WSMF is a generalization of MF using 4 variables f_{low} , f_{high} , p , r for parameter configuration. Their values are in the set denoted by

$$I = [\tilde{f}_{low}, \hat{f}_{low}] \times [\tilde{f}_{high}, \hat{f}_{high}] \times [\tilde{p}, \hat{p}] \times [\tilde{r}, \hat{r}] \quad (4)$$

for suitable bounds of I (\tilde{a} denotes the lower and \hat{a} the upper bound of a variable a).

Because of the discrete recording of electroencephalogram in the current investigation, all computations were performed using a discrete Fourier transform. To reduce the leakage effect due to the boundary of the analyzed electroencephalographic signal s , a Hamming window was used for the calculation of WSMF.

P_K Statistics

P_K statistics are closely related to the definition of Kim's $d_{y,x}^{12}$: Let $x = (x_1, x_2, \dots, x_n)$ be the vector of obtained parameter values

computed from n signal intervals s_1, \dots, s_n and $y = (y_1, y_2, \dots, y_n)$ the corresponding observed anesthetic state, in our case $y_i \in \{0$ (unconscious), 1 (conscious)}. Then d_{y^*x} differs three cases, (A) the probability p_c , that a pair (x_i, x_j) ($i, j \in \{1, \dots, n\}, i \neq j$) of arbitrary drawn parameter values is in concordance with the anesthetic level (y_i, y_j), i.e., $y_i > y_j \Rightarrow x_i > x_j$, (B) the probability p_d that it is in discordance, i.e., $y_i > y_j \Rightarrow x_i < x_j$ and (C) the probability p_t that a parameter value is assigned to more than one anesthetic level, i.e., $y_i \neq y_j \Rightarrow x_i = x_j$. The definition

$$d_{y^*x} = \frac{p_c - p_d}{p_c + p_d + p_t} \quad (1)$$

implies $d_{y^*x} \uparrow$ with $p_c \uparrow, p_d \downarrow, p_t \downarrow$, and $d_{y^*x} \in [-1, 1]$. By the affine transformation $P_K = (d_{y^*x} + 1)/2$, the index d_{y^*x} is mirrored at 0.5, such that $P_K = 1$ gives a completely concordant relation between x and y , $P_K = 0$ implies completely discordant relation, and $P_K = 0.5$ means that there is no relation between x and y .

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