

High-frequency Components of Auditory Evoked Potentials Are Detected in Responsive but Not in Unconscious Patients

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Background: The dose-dependent suppression of midlatency auditory evoked potentials by general anesthetics has been proposed to measure depth of anesthesia. In this study, perioperatively recorded midlatency auditory evoked potentials were analyzed in a time-frequency space to identify significant changes induced by general anesthesia.

Methods: Perioperatively recorded auditory evoked potentials of 19 patients, recorded at varying levels of anesthesia, were submitted to a multiscale analysis using the wavelet analysis. Energy contents of the signal were calculated in frequency bands 0–57.1 Hz, 57.1–114.3 Hz, 114.3–228.6 Hz, and 228.6–457.1 Hz. A Friedman test and a Dunn multiple comparisons test were performed to identify significant differences.

Results: Statistical evaluation showed a highly significant decrease of the wavelet energies for the frequency bands 57.1–114.3 Hz ($P < 0.0001$), 114.3–228.6 Hz ($P < 0.0001$), and 228.6–457.1 Hz ($P < 0.0001$) for the measuring points representing deep general anesthesia. This decrease is accompanied by a decrease in the wavelet energy of the frequency band 0–57.1 Hz of no statistical significance ($P = 0.021$) (level of significance set to $P = 0.01$). The changes are most prominent in the poststimulus interval between 10 and 30 ms.

Conclusions: This study describes the presence of high-frequency components of the auditory evoked potential. The amount of these components is higher during responsiveness when compared to unconsciousness. Temporal localization of the high-frequency components within the auditory evoked potential shows that they represent a response to the auditory stimulus. Further studies are required to identify the source of these high-frequency components.

FOR more than two decades, auditory evoked potential (AEP) monitoring has been proposed as an indica-

tor of anesthetic depth. AEPs may be of particular value for the separation of consciousness from unconsciousness.¹ Components of the AEP that reflect the level of consciousness have been identified (Nb latency and 40 Hz components). Increasing depth of anesthesia is reflected by increased latencies and decreased amplitudes of the midlatency peaks of the AEP and changes in the 40-Hz component of the midlatency auditory evoked potential.^{1–6}

Despite this recommendation, AEPs have mainly been used as a research tool rather than a standard anesthesia monitor. For research purposes, AEP analysis is mostly performed after anesthesia, *i.e.*, off-line, whereas clinical monitoring of anesthesia requires results that are available during anesthesia, *i.e.*, on-line. Recently, the AAI monitor (Danmeter, A/S, Odense, Denmark) was introduced into clinical anesthesia.⁷ It is the first commercially available monitor of the hypnotic component of anesthesia that uses both components of the electroencephalogram and AEPs. When the use of the midlatency AEP alone is planned, peaks and troughs must be identified visually. This may be difficult and prone to substantial observer bias, in particular for AEPs that were recorded during anesthesia.⁸ Automated on-line analysis of the AEP reduces observer bias and may turn AEP analysis into a useful anesthesia monitoring tool. The current study was designed to find components of the AEP that can be used to develop an on-line system that differentiates between “awake” and “unconscious.” For this purpose, different frequency bands of the AEP were analyzed by wavelet transform, and potentially useful AEP components were identified.

Materials and Methods

Twenty-one patients (14 men and 7 women) undergoing general anesthesia for hand or ear-nose-throat surgery with a mean age of 34 yr (range, 19–58 yr) participated in this study. The patients had no history of neurologic or psychiatric disorders, loss of hearing, or drug abuse. Informed written consent was obtained from all patients before the study, which was approved by the local ethics committee (Munich, Germany). Patients were premedicated with 7.5 mg midazolam per os 30 min before surgery. After arrival of the patients in the operating theater, standard perioperative monitoring (blood pressure monitoring, pulse oximetry, electrocardiography) of vital signs was started. An intravenous line

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was placed at the hand of the patient. The electroencephalographic electrodes were placed after the preoperative procedure was completed. Patients were instructed how to avoid eye movement and muscle artifacts. Neuroelectrical activity was recorded with a compact electrodiagnostic monitoring system (Neuroscreen; Jaeger & Toennies, Wuerzburg, Germany) using a bipolar montage with gold cup electrodes at Fp1/2 (frontotemporal, positive pole), A1/2 (mastoid, negative pole), and Fpz (ground, electrode positions according to the international 10-20 system). The interelectrode impedances remained below 5 k Ω throughout each recording. The electroencephalogram was amplified with a sensitivity of 100 μ V (full scale), and the amplifier band-pass was 10–1,000 Hz. Sweeps with a length of 100 ms synchronized to the auditory stimulus were digitized at 5,120 Hz with a depth of 18 bits. Sweeps with artifacts exceeding 96 μ V lasting longer than 10 ms were automatically rejected. AEPs were averaged from 1,000 completed sweeps. Auditory stimuli were applied *via* headphones (binaural rarefaction clicks, 70 dB above normal hearing level, stimulus rate of 9.3 Hz). General anesthesia was induced with remifentanyl (1 μ g/kg over 1 min) and a propofol bolus (2 mg/kg). After mask ventilation, muscle relaxation was achieved by intravenous application of atracurium (0.5 mg/kg). The airway was secured *via* tracheal intubation, and patients were ventilated to maintain oxygen saturation and carbon dioxide concentration within physiologic limits. General anesthesia was maintained by continuous intravenous application of propofol (6 mg \cdot kg $^{-1}$ \cdot h $^{-1}$) and remifentanyl (0.25 μ g \cdot kg $^{-1}$ \cdot min $^{-1}$). AEP recordings were maintained throughout general anesthesia. During general anesthesia, measurements of the AEPs were initiated every 3 min. The last recording was performed after the patient was awake and the trachea was extubated. Data of the following measuring points (MP) representing different levels of anesthesia were extracted and used for calculation:

1. awake
2. after administration of the opioid (1 μ g/kg remifentanyl over 1 min)
3. after administration of the hypnotic agent (2 mg/kg propofol), before administration of muscle relaxant
4. after tracheal intubation
5. at skin incision
6. during general anesthesia, 3 min before the administration of the anesthetic agents was stopped

7. stop of the infusion of the opioid and the hypnotic drug
8. 9 min before extubation (defined *post hoc*), after surgery
9. 6 min before extubation (defined *post hoc*)
10. 3 min before extubation (defined *post hoc*)
11. after extubation

Data analysis was conducted off-line on a personal computer after selection of the AEPs at the measuring points. A software routine programmed by the authors in the Matlab[®] (The MathWorks, Inc., Natick, MA) programming environment performed the discrete wavelet transform (Wavelet Toolbox; The MathWorks, Inc.) of the AEPs and the calculation of the wavelet energies. The Friedman test with Dunn *post hoc* test for multiple comparison was performed using GraphPad Prism evaluation version 4.00 for Windows (GraphPad Software, San Diego, CA). We used the Daubechies 4 wavelet as the mother wavelet for the multiresolution analysis. Additional information regarding the wavelet transform is available on the ANESTHESIOLOGY Web site at <http://www.anesthesiology.org>.# With the center frequency of this wavelet being around 0.7145 (normalized), the signal was projected in a full five-scale deconvolution onto frequency bands of 0–57.1 Hz (V_5), 57.1–114.3 Hz (W_5), 114.3–228.6 Hz (W_4), 228.6–457.1 Hz (W_3), 457.1–914.3 Hz (W_2), and 914.3–1828.6 Hz (W_1). With the resulting coefficients ($c_{i,j}$)², we calculated the wavelet energy E_j on the scale j to

$$E_j = \sum_i E_{i,j} = \sum_i c_{i,j}^2.$$

The total energy of the signal is

$$E_{\text{total}} = \sum_{i,j} E_{i,j} = \sum_{i,j} c_{i,j}^2.$$

Figure 1 shows an original signal, the wavelet coefficients, and the reconstructed signals for each scale. The wavelet coefficients of the frequency bands 0–57.1 Hz (V_5), 57.1–114.3 Hz (W_5), 114.3–228.6 Hz (W_4), and 228.6–457.1 Hz (W_3) were used for the calculation of the wavelet energies; the reconstructed signals show the contribution of the according frequency bands to the signal. The wavelet coefficients of the frequency bands 457.1–914.3 Hz (W_2) and 914.3–1828.6 Hz (W_1) were not further investigated because of the applied low-pass filter of 1,000 Hz (Amplifier, Neuroscreen; Jaeger/Toennies, Höchberg, Germany). We also calculated the absolute wavelet energies for blocks of approximately 10 ms in duration within the defined frequency bands at each measuring point. Because the resulting numbers of wavelet coefficients differ in the scales, the absolute energy

Principles of the continuous and discrete wavelet transform: the technical aspects of the discrete wavelet transform as a multi resolution analysis and the results of digital filtering with the Daubechies 4 wavelet are shown.

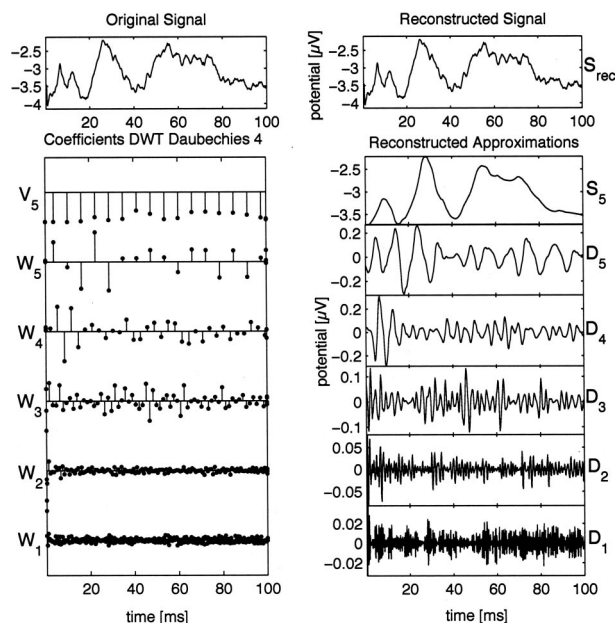


Fig. 1. Original auditory evoked potential of an awake patient, five-level digital wavelet transform (DWT) with the Daubechies 4 wavelet, resulting in the coefficients per scale (left) and the reconstructed signals according to the frequency bands (right).

density was calculated for two different grids. The grid size was determined by

$$a_j = \frac{\text{number of wavelet coefficients on scale } j}{10} \text{ and } a_j \in \mathbb{N}$$

for each frequency band. Our calculation resulted in a 9.1-ms grid for the scales V_5 and W_5 and a 10-ms grid for the scales W_4 and W_3 .

Statistical Analysis

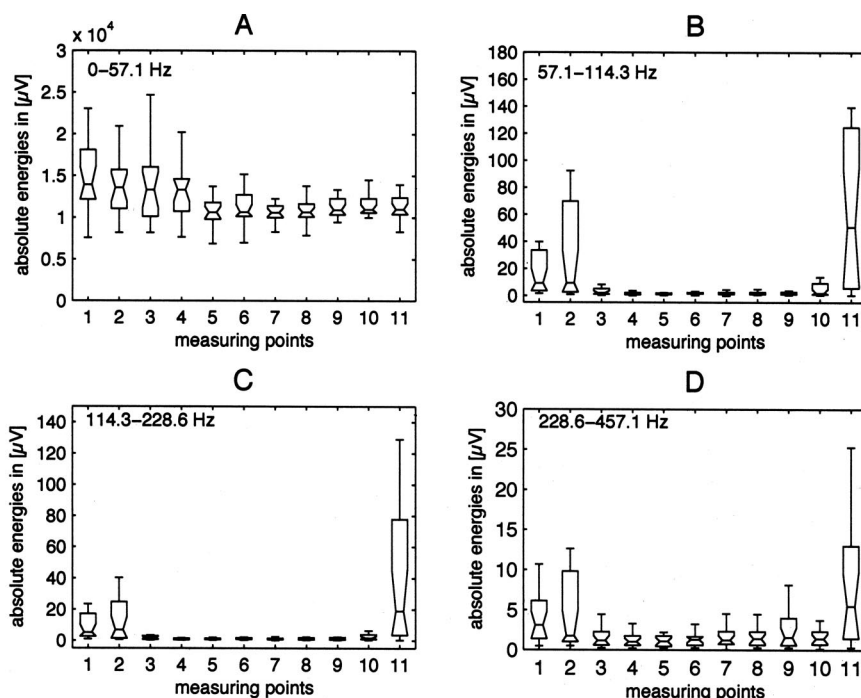
The scale-based wavelet energies of the signal were subjected to the Friedman test, returning a P value for the null hypothesis that all the scale-based wavelet energies at the different measuring points within one frequency band were drawn from the same population. We plotted the median and the lower and upper quartiles of the wavelet energies as box plots, with the lines from each end of the box indicating the extent of the rest of the data. To determine which of the measuring points show significant differences to any of the other measuring points, we performed the Dunn multiple comparison test based on the absolute wavelet energies at each measuring point. The level of significance was set at $P = 0.01$ for the Friedman test, because the same data were used to test four independent null hypotheses, one for each frequency band. For the Dunn multiple comparison test, the significance level was kept at $P < 0.05$.

Results

Data of two patients had to be excluded from the study because of technical problems during the recording. Analysis of the remaining patients showed that high-frequency oscillations (HFOs) are present in AEPs. The current study shows significant depression of these HFOs of the auditory evoked response by propofol–remifentanyl anesthesia. On the basis of the current results, it can only be speculated whether this depression of HFOs is a specific effect of the drug combination or a general phenomenon of (anesthesia-induced) unconsciousness. If very different means of obtaining loss of consciousness all produce the same response in the HFOs, this may measure brain state independent of the drug used to obtain that state.

Absolute wavelet energies for the four frequency bands were calculated for the 11 measuring points (fig. 2). The box in the box plots has lines at the lower quartile, median, and upper quartile values; the lines extending from each end of the box show the extent of the rest of the data. The comparison of energy units throughout the subplots reveal that by far the highest contribution to the total signal wavelet energy resulted from the frequencies below 57.1 Hz. Within this frequency band (fig. 2A), there is a decrease for the mean of the absolute wavelet energies throughout the course of anesthesia with a tendency to recover toward the end of anesthesia. The energy contents of the frequency bands 57.1–114.3 Hz (fig. 2B) and 114.3–228.6 Hz (fig. 2C) markedly decreased with the administration of hypnotics (measuring point 3) and after intubation (measuring point 4) by more than a factor of 10. This decrease was also prominent, although less impressive, in the frequency band 228.6–457.1 Hz (fig. 2D). The wavelet energy contents remained fairly stable until the end of the administration of the hypnotic agent (measuring point 7). With a decrease of the anesthetic effect, the wavelet energies recovered to approximately the same level at measuring point 11 (extubation/awake) as before anesthesia (measuring point 1, awake). Mean ranks of the absolute wavelet energies of the frequencies below 57.1 Hz did not show significant differences throughout the course of anesthesia, whereas the frequency bands 57.1–114.3 Hz and 114.3–228.6 Hz both showed a very similar pattern with a significant decrease ($P < 0.001$) in their contributing wavelet energy when the administration of hypnotic drugs was started. The exact results of the statistical analysis are presented in table 1. After the infusion of hypnotics had been stopped, the activity in these frequency bands remained lower than at complete wakefulness at the end of general anesthesia. The first point at which no statistical difference compared with the state awake was present was MP 8 (*i.e.*, 9 min before extubation) for the frequency band 57.1–114.3 Hz and MP 7 (after stop of

Fig. 2. Mean total wavelet energies of the scales V_5 , W_5 , W_4 , and W_3 ($n = 19$, median, lower and upper quartile range) (A–D). Measurements were taken at the clinically defined measuring points awake (1); administration of opioid (2); administration of hypnotic agent (3); after intubation (4); during surgery (5); end of infusion of hypnotics (6) and opioid (7); 9 min (8), 6 min (9), and 3 min (10) before extubation; and after extubation (11).



opioid and hypnotic drug infusion) for the frequency band 114.3–228.6 Hz. For the frequency band 228.6–457.1 Hz, measuring points 3, 4, 5, and 6 differed significantly ($P = 0.0006$) from the state when patients were extubated.

Finally, to investigate the timing information, the wavelet components that reflect the appropriate frequency bands were retransformed. The absolute wavelet energies for the frequency band 0–57.1 Hz remained fairly stable for all MP except MPs 9, 10, and 11, where an increase in the time range of 27–36 ms was prominent. The energy throughout the signal at MP 5, the state of deep general anesthesia, was lower than in all the other MPs (fig. 3A).

The retransform showed that the HFO components occur between 18 and 27 ms after stimulus in the frequency band 57.1–114.3 Hz and between 10 and 20 ms after stimulus in the frequency band 114.3–228.6 Hz (figs. 3B and C). A peak of high energy was present 10–20 ms after auditory stimulation in the frequency band 228.6–457.1 Hz and higher levels of energies throughout the signal for MP 11 (fig. 3D).

Figure 4 shows D-Flandrin time-frequency distributions for one patient at four measuring points, namely at the time points awake, after induction with remifentanyl

(fig. 4A), deep anesthesia, after tracheal intubation (fig. 4B), 9 min before extubation (fig. 4C), and 6 min before extubation (fig. 4D). With the Fourier-based D-Flandrin time-frequency distribution, we see as well a drug-induced effect between roughly 50 and 300 Hz in a time range of 15–35 ms after stimulus. At this point, we emphasize that the differences seen between figures 3 and 4 are based on the differences of the analysis technique, wavelet transform being based on wavelets (Daubechies 4 in this investigation) and D-Flandrin time-frequency analysis being based on sinusoids. Furthermore, the time-frequency analysis as shown in figure 4 is a redundant technique, comparable rather to the continuous wavelet transform.

Discussion

In the current study, we found that high-frequency components of the AEP may contribute to the differentiation between awareness and unconsciousness. The current study shows the significant depression of HFOs of the auditory evoked response by general anesthesia. For the auditory evoked response, HFOs of neuronal origin have not yet been shown. However, reports of HFOs in somatosensory and visual evoked responses show their presence in a frequency range between 80 and 800 Hz within 18–25 ms after the natural stimulus. Furthermore, several investigations have studied the changes of early somatosensory evoked potentials in awake and sleeping states. For the somatosensory evoked potential, two major frequency bands with dissociative behavior were described. The low N20 activity

Table 1. Results of the Friedman Test for the Four Frequency Bands at the Measuring Points within the Frequency Bands

	Frequency, Hz			
	0–57.1	57.1–114.3	114.3–228.6	228.6–457.1
P value	0.021	< 0.0001	< 0.0001	< 0.0001

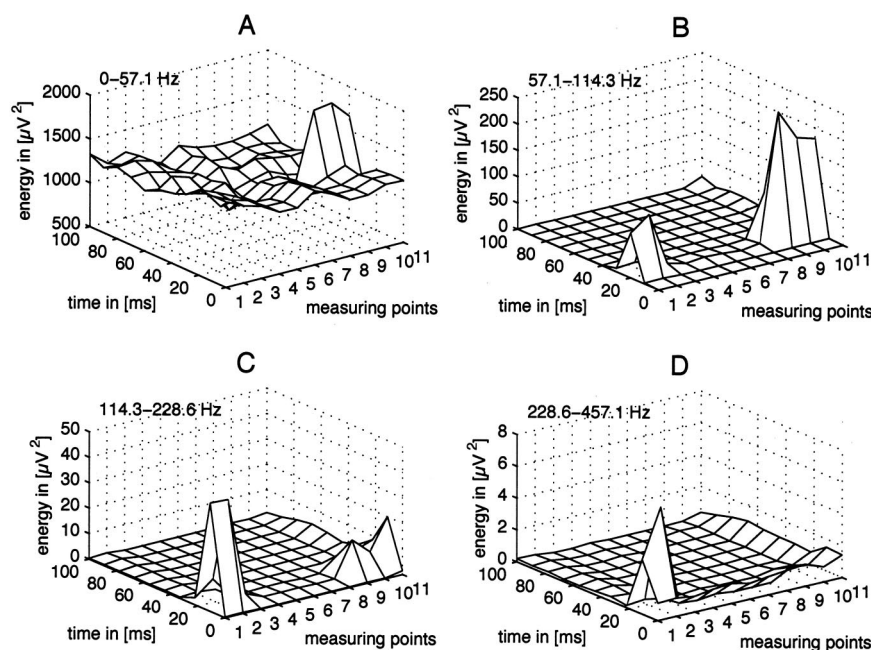


Fig. 3. Mean absolute wavelet energies for the different frequency bands on a grid based on the signal length and measuring points 1–11 ($n = 19$). The grid size was 9.1 ms for A and B and 10 ms for C and D. Prominent is the depression of high-frequency oscillations within 18–27 ms in B and within 10–20 ms in C. Note that in D, the mean wavelet energy is increased throughout the complete signal at measuring point 11. This may be interpreted as a contamination of the signal, e.g., by muscle activity.

was prolonged in latency,^{9,10} whereas high-frequency parts of the signal (above 400 Hz) diminished during sleep.^{11–13} Halboni *et al.*¹⁴ described a gradual decrease in amplitude of high-frequency (450- to 750-Hz) somatosensory evoked potentials from awake to sleep stages II and IV, whereas in rapid eye movement sleep, these signals remain almost unchanged. In addition to similar findings by Emerson *et al.*¹¹ and Yamada *et al.*,¹² source modeling demonstrated that these changes happen first on the thalamic level and second on both cortical sources.

However, the origin of HFO in the AEPs as found in the current study is not entirely clear. The timely localization of the changing high-frequency components within the AEP suggests that the origin may be a muscle response described previously.¹⁵ Therefore, caution is advised in interpreting monitoring systems based on single-dimensional values describing broad band changes in midlatency auditory evoked potentials. As time-frequency analysis of the AEP indicates, the relevant peak of the high-frequency component occurs 10–30 ms after the auditory stimulus. This may represent not only a response of the auditory pathway but a muscle response (posterior auricular muscular response). O'Beirne and Patuzzi^{15–17} published a thorough investigation about the postauricular muscular response and reported that the postauricular muscular response covers a frequency range from 10 to 200 Hz, visible within 15–25 ms after auditory stimulation. AEP analysis as performed in this study might therefore reflect not only the reaction of the main target organ of anesthesia, the brain, but a surrogate parameter, muscle response to an auditory stimulus. The monitoring of muscle activity instead of brain activity may be seen as a limitation of monitors of hypnosis based on the electroencephalogram. Calculation of the

Bispectral Index includes the γ range of the electroencephalogram, which is prone to muscle artifacts, especially when the electroencephalogram is measured on the forehead. This may explain why the administration of succinylcholine results in a decrease of the Bispectral Index in awake volunteers¹⁸ and why the administration of vecuronium in steady state anesthesia produces a decrease of the Bispectral Index in patients.¹⁹ The Datex electroencephalographic entropy module (S/5 TM Entropy Module; Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) displays state entropy and response entropy, which analyzes high-frequency (electromyographic) components of the signal.^{19–21} A recent study indicated that the AEP-based ARX index (AAI; Danmeter, A/S) also decreases after administration vecuronium.²² This may indicate that not only the analysis of the electroencephalogram but also the analysis of AEPs includes muscle activity. In our current analysis, wavelet transform was used to detect high-frequency components of the AEP. Wavelet transform is one possible method to analyze evoked potentials. Recently, it has gained interest in the analysis of these signals. Based on wavelet analysis of the midlatency component of AEP, Kochs *et al.*²³ calculated an index that detects awareness during propofol administration. The wavelet transform inherits a major advantage compared with other common techniques, e.g., Fourier transform. The Fourier transform uses sinusoids of infinite length to evaluate the spectrum of a signal. With the simple spectrum, the information about the time is lost. Several techniques can be applied to compensate for this disadvantage of Fourier transformation: With the Short-term Fourier Transformation, the signal is broken into small pieces, and the Windowed Fourier Transformation uses a windowing function (e.g., a Hamming window) to limit the

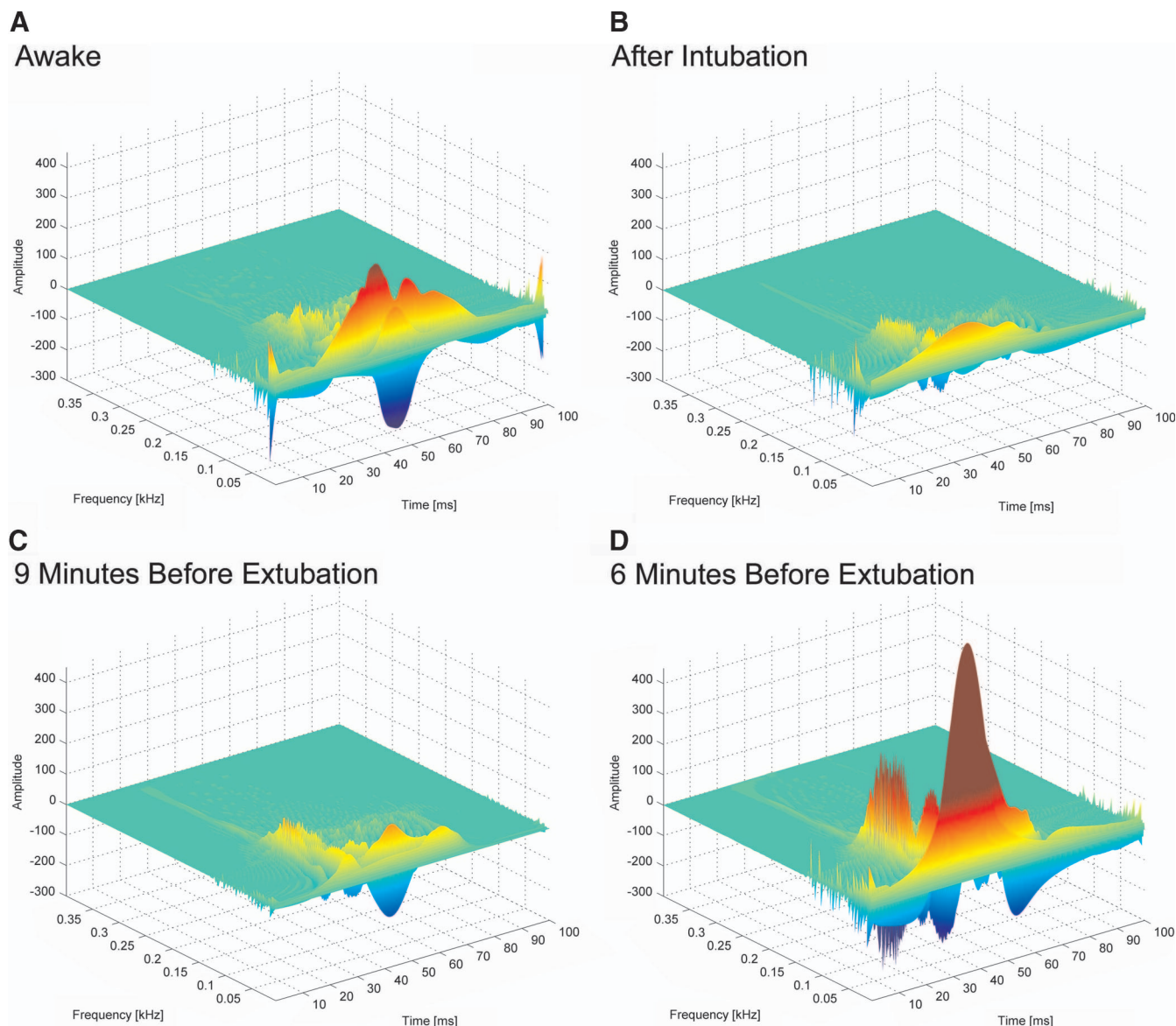


Fig. 4. D-Flandrin time-frequency distributions for one representative patient at four different measuring points: after opioid infusion (A), after intubation (B), 9 min before extubation (C), and 6 min before extubation (D). Stimulus-locked high-frequency oscillations in the time range of 15–35 ms of auditory evoked potentials are decreased during different levels of anesthesia.

length of the sinusoidal wave. With these modifications of Fourier analysis, time-frequency resolution is possible to a certain degree but is restricted to the frequency of the sinusoidal wave compared with the length of the analysis window. The wavelet transform results in a time-frequency representation that is basically achieved by filtering the signal with the digital representation of a so-called mother wavelet and its stretched versions. In contrast to Fourier analysis, the waveform of the wavelet is of finite length and compact support and, simply spoken, is normalized to size. Wavelet filtering is therefore more efficient in detecting short (in time) and unperiodic signals. In the current analysis, the maintained time resolution indicates that high-frequency components occurred in a stimulus-locked manner. This pro-

vides evidence that these components are a reaction to the auditory stimulus rather than background noise.

The exact localization of the high-frequency component, however, does not allow the identification of the underlying mechanism. It may be of neuronal or myogenic origin. Further studies are required to identify the source of the high-frequency component of the AEP and to differentiate between a neuronal and a myogenic component.

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