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Time-frequency Analysis of Somatosensory Evoked Potentials for Intra-operative Spinal Cord Monitoring

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Abstract

Objective: To evaluate the potential use of time-frequency analysis and it reliability in intra-operative somatosensory evoked potential (SEP) monitoring.

Methods: One hundred and ninety one patients undergoing thoracic and/or lumbar spinal surgery were studied retrospectively. SEP signals were recorded during different stages of surgery. Averaged SEP was analyzed by short time Fourier transform (STFT). The main peak in the time-frequency interpretation of SEP was measured in peak power, peak time and peak frequency. The variability of these parameters was compared with that of amplitude and latency during different stages of surgery. The reliability of these parameters was also compared on true positive and false positive cases.

Results: During different surgical stages for the posterior tibial nerve SEP, the intra-subject variability of peak power was found to be more stable than that of amplitude, while the intra-subject variability of peak time did not show any difference with that of latency. The peak frequency presented stable during surgery. Moreover, the true positive SEP case showed that peak power may detect the potential injury earlier than amplitude does. The false positive outcomes could be reduced by the proposed method.

Conclusions: The SEP peak component was found stable and reliable during the different stages of surgery. For clinical application purpose, time-frequency analysis was suggested to be an additional monitoring method besides the conventional amplitude/latency measurement, since it provided a more reproducible and prompt response to the potential injury in intra-operative SEP monitoring.

Key words: somatosensory evoked potential (SEP), time-frequency analysis (TFA), amplitude, latency, intra-operative monitoring (IOM)

Introduction

Intrao-perative spinal cord monitoring assesses the functional integrity on the spinal cord for early detection of potential injury, allowing immediate surgical maneuvers before injury becomes irreversible (Hongxuan, et al., 2006, Nash, et al., 1974, Nuwer, 1999). Multi-modality monitoring, the widely used technique in clinical practice, has been considered as a reliable intra-operative spinal cord monitoring technique (DiCindio, et al., 2003, Eggspuehler, et al., 2007, Quraishi, et al., 2009). In multi-modality monitoring, somatosensory evoked potential (SEP) and motor evoked potential (MEP) are applied to look at sensory pathways and motor pathways, respectively. Although MEP correlates better with motor function (Sloan, et al., 2008), SEP is irreplaceable in the monitoring (DiCindio, et al., 2003, Eggspuehler, et al., 2007, Quraishi, et al., 2009). It not only assesses spinal cord sensory tracts directly but indirectly provides information about motor tracts (Deletis and Sala, 2008, Devlin and Schwartz, 2007).

In comparison with high signal-to-noise ratio (SNR) and rapid response of MEP signals, SEP, however, requires usually multiple stimulations and signal averaging due to its lower SNR (Sloan, et al., 2008). Despite of improvement of SNR by averaging, SEP peaks which directly reflect the potential injury may not be easily identified in a strong noise background. The current method of identification of SEP peaks which is based on latency and amplitude measurement seems not to meet the requirement of reliable monitoring, since the signal variability caused by noises would depress monitoring reliability (Braun, et al., 1996, Hu, et al., 2003).

To increase the reliability of monitoring, frequency analysis was proposed as a good indicator of spinal cord injury (Braun, et al., 1996, Hu, et al., 2003, Thakor, et al., 1993). Rossini et al (1981) reported that the peaks in EP waveform were stable with frequency analysis and concluded that they might be clinically useful (Noss, et al., 1996). But frequency analysis may not provide the temporal information on SEP peaks as latency and amplitude offer. Therefore, parameters based on both time and frequency domain might imply more SEP information which is associated with the functional status of the spinal cord and could further increase the reliability of intra-operative monitoring.

Time-frequency analysis (TFA) allows the study of SEP signals in the combination of time and frequency domain, which can provide both temporal and spectral information. Although it has been proposed for SEP monitoring (Braun, et al., 1996, Hu, et al., 2003), the parameters comparison between time domain and time-frequency domain are only based on a few subjects. For the clinical application of TFA in monitoring, parameters performance in the case of injury is much concerned. An accurate and prompt response to the injury of parameters is crucial for minimizing the iatrogenic risks during surgery. Moreover, a larger scale clinical data may be required for validating this technique in clinic.

This retrospective study, therefore, evaluated the potential use of TFA in monitoring, aiming to improve the reliability of spinal cord monitoring. Parameters were retrospectively compared for intra-operative spinal cord monitoring in the time-frequency domain with those in the time domain on 191 patients underwent spinal surgery, including 2 true positive cases and 6 false positive cases. This knowledge would be also helpful to understand the nature of SEP signals in time-frequency domain and evaluate the potential use of TFA to intra-operative SEP monitoring.

Methods

One hundred and ninety one patients undergoing thoracic and/or lumbar spinal surgery (149 female and 42 male) were included in this study. None of the patients had any neurological deficit before the surgery. Their ages ranged from 7 to 79 years (mean 17.4 years). Among these patients, two patients presented true positive SEP warnings and 6 presented false positive SEP warnings during surgery.

All patients received general anesthesia, induced by thiopentone (thiopental) (0.4 mg/kg) or fentanyl (1-2 μg/kg). Isoflurane (0.5 -0.8%) and nitrous oxide/oxygen (typically 60:40%) were used to maintain the anesthesia, and the concentration of the anesthetics is adjustable subject to the signal quality of SEP. This anesthesia protocol was performed in our centre for over 10 years with good successful for SEP monitoring.

To elicit SEP, a pair of stimulating electrodes was applied over both sides of posterior tibial nerve at ankle. Electrical pulse stimulation was adopted with a constant current, which is adequate to produce a consistent but adequate muscle twitch, in the range from 10-30 mA, a frequency between 5.1-5.7 Hz and a duration of 0.3 ms. The stimulation intensity was gradually increased until the largest response was recorded from scalp. Needle electrodes were used for data collection. SEP signals were recorded over Cz' (2cm posterior to Cz of 10-20 system) and Cv (on the cervical spine over the C2 process) versus Fz (Nuwer, 1999). In the case of a relatively low amplitude when recording cortical SEP, the recording site was selected the optimal one from three cortical channels near Cz' in order to get a robust peak.

All signals were recorded with a sampling rate of 5 kHz for each recording channel by an intra-operative spinal cord monitoring system (Nicolet Viking IV, Nicolet Biomedical, Madison, Wisconsin, USA), with noise reduction achieved using 20-2000 Hz bandpass filter and automatic artifact rejection. The sweeping time of SEP recording was 100 ms. Consecutive averaging was employed, with 100 times averaging. The SEP signals processed following the above-mentioned procedures were then analyzed retrospectively using Matlab (Version 7.4, MathWorks, Natick,

Massachusetts, USA).

To minimize the interference of surgical maneuvers to the intra-subject variability, the surgery was divided into five stages (Luk, et al., 1999). Stage 1: the period of the patient had been anaesthetized and positioned on the operation table before surgery; stage 2: exposure of spine; stage 3: instrumentation such as hooks, wires or screws was loaded; stage 4: deformity was corrected by rod rotation, compression, distraction, or tightening of sublaminar wires; stage 5: wound close.

A previous study(Hu, et al., 2003) by comparison of TFA methods recommend that short time Fourier transform (STFT) is the optimal TFA algorithm for SEP signals. And this method has been well established by our team (Hu, et al., 2003, Hu, et al., 2001). The STFT spectrogram for an SEP signal s(t) is defined by the following equation:

$$\mathrm{STFT}(t,\omega)\big|_{t=n\Delta t,\omega=2k\pi/N\Delta t} = \mathrm{STFT}(n,k) = \sum_{i=0}^{N-1} \mathrm{s}(i)\mathrm{w}(i-1)e^{-j2ki\pi/N}$$

where **w***(n)* is the window function, Δ*t* denotes the time sampling interval, and *N* is the block length of the window function. In this study, a 20 milliseconds Hanning window was employed according to previous study (Hu, et al., 2003, Hu, et al., 2001).

For each averaged SEP signal, the amplitude and latency were measured in the time domain and parameters in time-frequency domain, peak time, peak frequency and peak power of the energy peak in the time-frequency distribution were also computed. To compare the variability of these parameters, coefficient of variation (CV) which defined as the ratio in percentage of deviation to the mean value was calculated.

The current warning criteria for abnormal SEP is 10% prolongation of latency or/and 50% decrease of amplitude (Grundy, 1982). Although TFA was used in intra-operative SEP monitoring, no golden standard criteria have been established. In a previous study (Hu, et al., 2003), it was recommend that a 50% decrease in peak power, or a 10% increase in peak time could be considered as the criterion for intra-operative SEP monitoring. Besides, the statistical range of

peak frequency was calculated from the normal SEP data. The results presented that the range of 37-79Hz for cortical SEP and 67-111Hz for sub-cortical SEP would be a criterion of peak frequency. In this study, we used 50% decrease in peak power, or a 10% increase in peak time as criteria for abnormal SEP. The percentage change was calculated from peak power/ peak time measures with respect to the individual baseline SEP which was recorded after surgical incision but before any spine invasion.

Results

Figure 1 shows an example of TFA of SEP. In the figure, the parameters both in the time domain (amplitude and latency) and in the time-frequency domain (peak time, peak power and peak frequency) are calculated automatically after manually selecting the waveform peak and valley. The time-frequency distribution of SEP is presented as a two dimensional plot, and the intensity of the time-frequency relation is relative color. Beneath time-frequency plot, the time domain waveform of the SEP is shown.

Both cortical SEP (Cz'-Fz) and subcortical SEP (Cv-Fz) were recorded for all subjects. All the 191 patients, sub-cortical SEP is interpretable, however 176 out of 191 patients can record cortical SEP only (SEP waveform cannot be identified by the neurophysiologist). By the amplitude and latency measurement criteria, 2 true positive cases and 6 false positive cases were presented out of 191 cases. Table 1 compares the mean values of intra-subject coefficient of variation (CV) of the five parameters for SEP monitoring. The intra-subject variability of amplitude is significantly larger than that of peak power (p<0.01 by t test). Between latency intra-subject variability and those of peak time, however, it is not found significant difference (p>0.05 by t test). This means peak power is less variable within subject than amplitude, and peak time and latency presents equivalent intra-subject variability for intra-operative monitoring.

Table 2 compares the inter-subject variability of SEP parameters in different surgical stages for monitoring. The inter-subject variability of latency, peak time and peak frequency does not present any significant differences (p>0.05 by ANOVA), whereas those of SEP amplitudes and peak power do (p<0.01 by ANOVA). Both peak power and amplitude show big inter-subject variability whereas those of the other parameters are relative small. This implies that the normal statistical ranges of latency, peak time and peak frequency are more useful than those of amplitude and peak power. Therefore, in Table 3, the central values and 3σ ranges of peak time and peak frequency of normal SEP signals are presented as well in this study.

There were two patients with true positive outcomes during surgery. Patient 1 (79-year-old

female) was diagnosed as osteoporotic fracture of T12 and L4-5 bilateral recess stenosis. The operation was planned to offer the patient reduction osteotomy for the fracture T12 and then posterior decompression for the L4-5 stenosis. During surgery, SEP was monitored by conventional amplitude/latency measurement. SEP signals showed normal before ostectomy. During ostectomy, SEP was found to drop up to 60%, and disappear in bilateral recordings afterward. Subsequent wake up test was carried out and the patient was unable to move her lower limbs. Post-operation MRI showed an edema of the cord at T12. She had received 6-month physiotherapy after surgery and got gradually recovery afterward. At 6 month follow up after surgery, she was moveable and only got numbness over both feet which was residual since the surgery. This situation kept plateau after 6 months follow-up. During retrospective study, TFA was performed on the whole series of SEP signals retrospectively. Figure 2 shows the TFA diagrams of cortical SEP before and after the abnormal warning. During the whole surgery, the amplitude/peak power changes in percentage were presented in Figure 3 (a), while Figure 3 (b) showed the qualitative monitoring indication during the surgery. During the surgery, abnormal amplitude presented at 174 minutes after incision (open red arrow). Based on our practical protocol, continue SEP monitoring was performed to confirm the abnormality to avoid false positive warning was performed as soon as the abnormal SEP measured. However, SEP signals were very variable afterward so that the abnormality in amplitude was finally verified at 232 minutes (solid red arrow in Figure 3b). The retrospective TFA was applied to this series of SEP signals. Abnormality of TFA was found at 149 minutes (solid black arrow in Figure 3b) and verified at 174 minutes (open red arrow in Figure 3b). This indicates that TFA of SEP is more sensitive to injury of spinal cord for intra-operative monitoring than amplitude/latency analysis. The first abnormal TFA was found at 149 minutes, which was only one monitoring point earlier than the show point of abnormal amplitude. Reviewing the period between 149 to 174 minutes, SEP monitoring was not consecutive because of MEP detection in this interval, while MEP remained normal. For this case, multi-modality monitoring (SEP+MEP) was performed. If the abnormal TFA were found in 174 minutes (the same point as abnormal amplitude), it should have been verified in the sequent test immediately, which much earlier than the verification point of abnormal amplitude (232 minutes). It suggests the use of TFA provide a more consistent monitoring outcome than latency/amplitude measurement.

Patient 2 (59-year-old female) had thoracic spinal cord compression. The operation was spinal cord decompression from T1 to T4. During decompression, SEP was found to drop and gradually disappeared. Retrospective TFA of SEP showed abnormal as the same finding in time domain measurement. Immediately after surgery, she was complete paraplegia of both legs. Fortunately, the motor function of this lady got improvement after 12 weeks post-operative physiotherapy, and presented further recovery 3 months later. The muscle power returned to 3+ on left leg and 3 on the right leg, in comparing with 5 scores before surgery.

For these two cases, Table 4 shows a comparison of parameters both in time and time-frequency domain before and after the abnormal warnings, and the difference was also presented in this table. Although the conventional amplitude/latency measurement could detect the SEP abnormality during both the surgeries, TFA seems more sensitive, since the peak power decrease and peak time prolongation are earlier detected and higher than those of amplitude and latency.

With respect to the 6 cases with false positive outcomes by amplitude/latency measurement, Table 5 gives a comparison of parameters between time and time-frequency domain before and after the abnormal warnings. Comparing with conventional amplitude/latency measurement, the use of TFA based monitoring could exclude 2 false positive cases.

By comparing the proposed TFA technique with conventional amplitude/latency measurement, the sensitivity by TFA is 100% versus 100% that by amplitude/latency measurement, whereas the specificity by TFA is 97.9% versus 96.8% that by amplitude and latency measure.

Discussion

In clinical practice, intra-operative SEP monitoring measures the parameters in time domain only, amplitude and latency in the initial response peak (Hu, et al., 2003, Hu, et al., 2001). SEP waveforms however are usually polyphasic because of different activation and conduction velocities of the spinal cord (el-Negamy and Sedgwick, 1978). Some low frequency noises may result in apparent reduction or increase in amplitude. In addition, the noises from a variety of sources make it not easy to identify SEP peaks even with averaging signal enhancement (Noss, et al., 1996), although this may be partly overcome by the techniques, such as averaging an adequate number of trials, having several scalp recording channels available, varying the filters and stimulation rate, in order to increase the signal quality. Therefore, false outcomes would be probably caused when only temporal parameters employed.

TFA enables both temporal and spectral characteristics of SEP signals. Thus, the clinical evaluation of TFA in intra-operative monitoring was investigated to improve the reliability of spinal cord monitoring in this study. Parameters were retrospectively compared for intra-operative spinal cord monitoring in the time-frequency domain with those in the time domain on patients underwent spinal surgery. By TFA, the SEP peak component was found more sensitive to injury compared with conventional amplitude-latency measurement and stable during the different stages of surgery. For clinical application purpose, TFA was suggested to be an additional monitoring method besides the traditional one in SEP monitoring.

Stability Evaluation of TFA

TFA which offers both temporal and spectral parameters is recommended in this study for intra-operative SEP monitoring. To compare with amplitude, peak power shows a significant intra-subject stability for the both patient groups. This is consistent with our previous study (Hu, et al., 2003) in which only 34 scoliosis patients was included. For clinical application of TFA in this study, it was found that peak power presented less intra-subject variability than amplitude. This indicates that peak power may be a better parameter for SEP monitoring than amplitude. In addition, the results show that SEP time-frequency component is stable. The ranges of peak time

and peak frequency are 29-55ms and 37-79Hz for cortical SEP, and 21-39ms and 67-111Hz for subcortical SEP.

Although the inter-subject variability tends to be less concerned in monitoring than intra-subject variability (Lubicky, et al., 1989), it merits attention in the comparison study, comparing the parameter performances between the time domain and the time-frequency domain. Regarding the inter-subject variability, it was reported to be 12.9% for latency and 87% for amplitude (Lubicky, et al., 1989). This is consistent with our findings. These values tended to be high because of the wide range of patients included with regard to age, stature, and condition. About intra- subject variability, Kalkman et al. found the amplitude variability is about 25%, while in our study, it is about 20%. The main reason caused this difference is that we used needle electrodes for recording while Kalkman used surface electrodes which may cause a higher variation. Other factors may also cause this kind of variation. The intra-subject variability was reported to be a function of preoperative diagnosis, neuromuscular status, age, and procedural factors (Kalkman, et al., 1991). Besides, anesthesia and technical parameters such as digital filtering, electrode placement and stimulus rates can affect the intra-subject variability (Chen, et al., 2004, Kalkman, et al., 1991, Lubicky, et al., 1989).

Reliability Evaluation of TFA

When a parameter is used for intra-operative SEP monitoring, it should be not only stable during surgery, but also sensitive in the case of injury. The study which compared TFA with time domain measurement on SEP was conducted by Hu et al. (2001). Twenty rats were inserted screws to the thoracic spine, simulating the spinal cord compression. It was reported that, with 30% spinal cord compression, TFA monitoring represented a sensitivity of 100%, while that by time domain measurement was 85%. When spinal cord injury occurs, it is suggested that TFA provided an earlier and more sensitive indication of injury than time domain monitoring. These results are consistent with our finding on human beings. In our study, there were two true positive abnormal SEP warning cases. By comparing the temporal and time-frequency parameters as Table 4 shows, time-frequency parameters are more sensitive to the potential risk than those in time domain. Particularly for the case 1, peak power indicated the injury earlier than amplitude. This means

some corresponding surgical maneuvers could be performed earlier before injury becomes irreversible. Moreover, the cases with false positive warnings which result in surgical interruption and uncertainties were compared between the TFA and the conventional amplitude/latency measurement. It was found that TFA could reduce the false positive warnings in intra-operative SEP monitoring. In this study, TFA therefore presented to be superior to amplitude and latency measurement in improving the reliability of SE monitoring.

TFA Parameters in SEP monitoring

Using TFA, there are three parameters, peak power, peak time and peak frequency. By identifying the SEP peak in time-frequency domain, they could be calculated automatically. Peak power is the energy of SEP waveforms and in theory it is corresponding to the time domain parameter of amplitude, but more stable and sensitive than amplitude. Similarly, peak time is corresponding to latency. In this study, peak power shows a significant stability than amplitude, whereas there is not a significant difference between peak time and latency during a surgery. This indicates time-frequency could be more useful for SEP monitoring and may perform better. Peak frequency is another parameter which reflects nervous activity generated by large populations of neurons along a certain pathways, and synchronously active within a limited time period of neurons is, therefore, corresponding to a certain frequency (Geva, et al., 1997). It was reported that SEP signals consisted of definite power spectra components which are located around a stable center frequency (Hu, et al., 2001). In this study, peak frequency was found to center at 53.6Hz for cortical SEP and 81.8Hz for subcortical SEP. This information may be helpful in understand the time-frequency property of SEP signals.

Amplitude and latency used in SEP monitoring are believed to be mainly associated with dysfunction of different parts of spinal cord. It was reported that pure grey-matter ischemia causes distortion of SEP waveform without any latency changes, whereas white-matter ischemia usually first causes a latency increase (Cruccu, et al., 2008). Therefore, peak power may be a better parameter reflecting distortion rather than amplitude, since amplitude is too sensitive to instantaneous big noises. Peak power is however not sensitive to such noises. Therefore, the false outcomes may be decreased by using peak power for monitoring spinal cord dysfunction such as grey-matter ischemia. Moreover, the SEP is polypeak sometimes, and each peak may be

associated with neural activity of the spinal cord. Amplitude measures only the main peak, while peak power measures the energy of all subpeaks in addition to the main peak. This may explain why peak power is more stable than amplitude during a surgery.

Anesthesia and Other Concerns

The anesthetic issues are not the factor of enhancing time-frequency parameters' performances in IOM. It has been reported that most anesthetics depress evoked response amplitude and increase latency (Sloan and Heyer, 2002). In this study, isoflurane (0.5-0.8%) and 60% nitrous oxide (subject to signal quality) were used for anesthesia. Although it increases the latency and decreases the amplitude of N20 of cortical SEP, this anesthetic protocol is considered suitable for SEP monitoring. Moreover, the cortical SEP showed more variable than sub-cortical SEP, because SEP responses generated in cortical structures are easily affected by anesthetic agents (Sloan and Heyer, 2002). It should be noted that time-frequency parameters of SEP are more stable not because anesthetic agents affects temporal parameters only, on the contrary, they affects the time-frequency parameters in the same way (Otto, 2008). Thus, both temporal and spectral parameters affects by the anesthetic agents.

There are 15 patients whose subcortical SEPs are not interpretable. This may be mainly caused by electromyogram (EMG) activity. It was reported that SEPs could be severely interfered in some patients because they present a shivering type of muscular activity (Perot, et al., 1983). And EMG activity could be particularly significant during light anesthesia (Liu, et al., 2005). The EMG activity, therefore, may fail the SEP more possible from cervical than that from cortical.

All SEP recordings for time frequency analysis in this study were collected according to our regular protocol. Regarding to the number of trials, we routinely used 100 trials for averaging. But it actually depended on the SNR of single trial recording. In case of poor signal quality of SEP, averaging of up to 500 sweeps may be performed till the SEP waveform to be identifiable. An expert who has worked on SEP monitoring for more than 15 years was asked to determine whether more trials were required for interpretation of monitoring. Someone may raise argument on the use of 100 trials averaging rather than 200 or 500 trials averaging. In fact, the

clinical practical protocol of SEP monitoring is to determine the averaging trial number depending on the SEP waveform measurability and reproducibility. Moreover, that the small number of averaging in our institution to produce a SEP waveform which has a similar signal quality with that using surface electrode is due to careful anaesthesia maintenance, auto-artifact rejection, and proper operation room for the monitoring. Besides, 0.3ms pulse width was used for stimulation, which differs with that used by some other institutions (they usually used 0.1-0.2ms (Chandanwale, et al., 2008)). This protocol was in use in our institution for more than 10 years, and it preformed stably.

The abnormal criteria in this study are 50% deduction in peak power, or a 10% prolongation in peak time with respect to the baseline obtained at the beginning of surgery. The setting of alarm limits of these criteria was referred to previous studies, which was proposed by an animal study and verified by a clinical study (Hu, et al., 2003, Hu, et al., 2001).

This retrospective study collected a series of cases from IOM records to perform comparative study between time frequency analysis method and conventional amplitude/latency method for IOM. In comparison with conventional amplitude/latency measurement, the new method based on TFA technique is much faster because of the easier automatical identification of TFA peaks. The exact computational time, however, depends on the performance of CPU processor. In a test on a computer with Intel Core-2 CPU 2.33GHz, each TFA based measurement of SEP signal took 15.6 milliseconds. It is possible for TFA to be performed even during two consecutive SEP tests. Thus, the calculation of TFA takes no time in comparison with manually amplitude/latency measurements of SEP recording.

Limitations

Although TFA can offer more information from time and frequency domain, it cannot provide high resolution at the same time in the both domain. However, several bilinear transforms are available to further improve time and frequency resolution (Hu, et al., 2003). Another limitation in this study is that TFA processed SEP data retrospectively due to the regulations of monitoring devices which may not allow our proposed method running on the current commercial devices.

But this technique could be incorporated into the devices in practice. Finally, the small sample size of positive cases is a limitation of this study. Therefore, a prospective study with large scale clinical trials should be conducted to further evaluate the advantages and drawbacks of the proposed TFA method.

Conclusion

For clinical application purpose, TFA was adopted in SEP monitoring and the SEP peak component was found more stable and reliable during surgery. The location of the SEP peak in time-frequency domain was easily identified and therefore to be helpful in SEP automatic detection and extraction.

TFA of SEP could provide additional information besides the amplitude/latency measurement, which may further improve the sensitivity and reliability in monitoring the spinal cord during spinal surgery.

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Figure legends

Figure 1 An example of time frequency analysis on a cortical SEP

Figure 2 (a) time frequency analysis on a cortical SEP before a true positive warning (b) time frequency analysis on a cortical SEP after a true positive warning

Figure 3 amplitude/peak power changes over time during the surgery for a true positive abnormal SEP (case 1). (a) amplitude/peak power changes in percentage over time (b) amplitude/peak power changes in categorical normal-abnormal. The solid arrow indicates the start of the abnormal warning based on peak power, and the open red arrow indicates the start of the abnormal warning based on amplitude measurement, and the solid red arrow indicates the confirmed abnormal amplitude measurement.

Fig1

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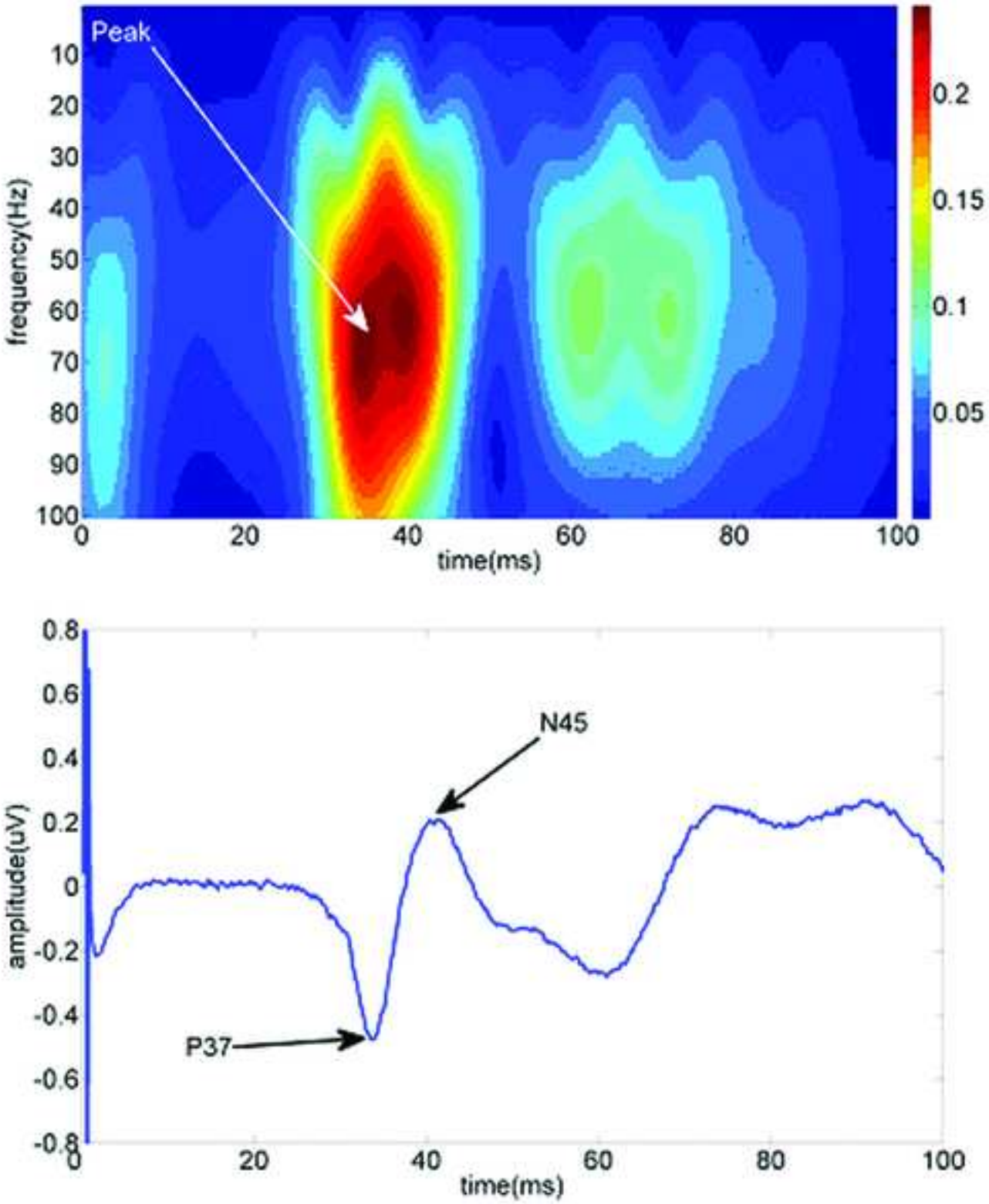

Fig2

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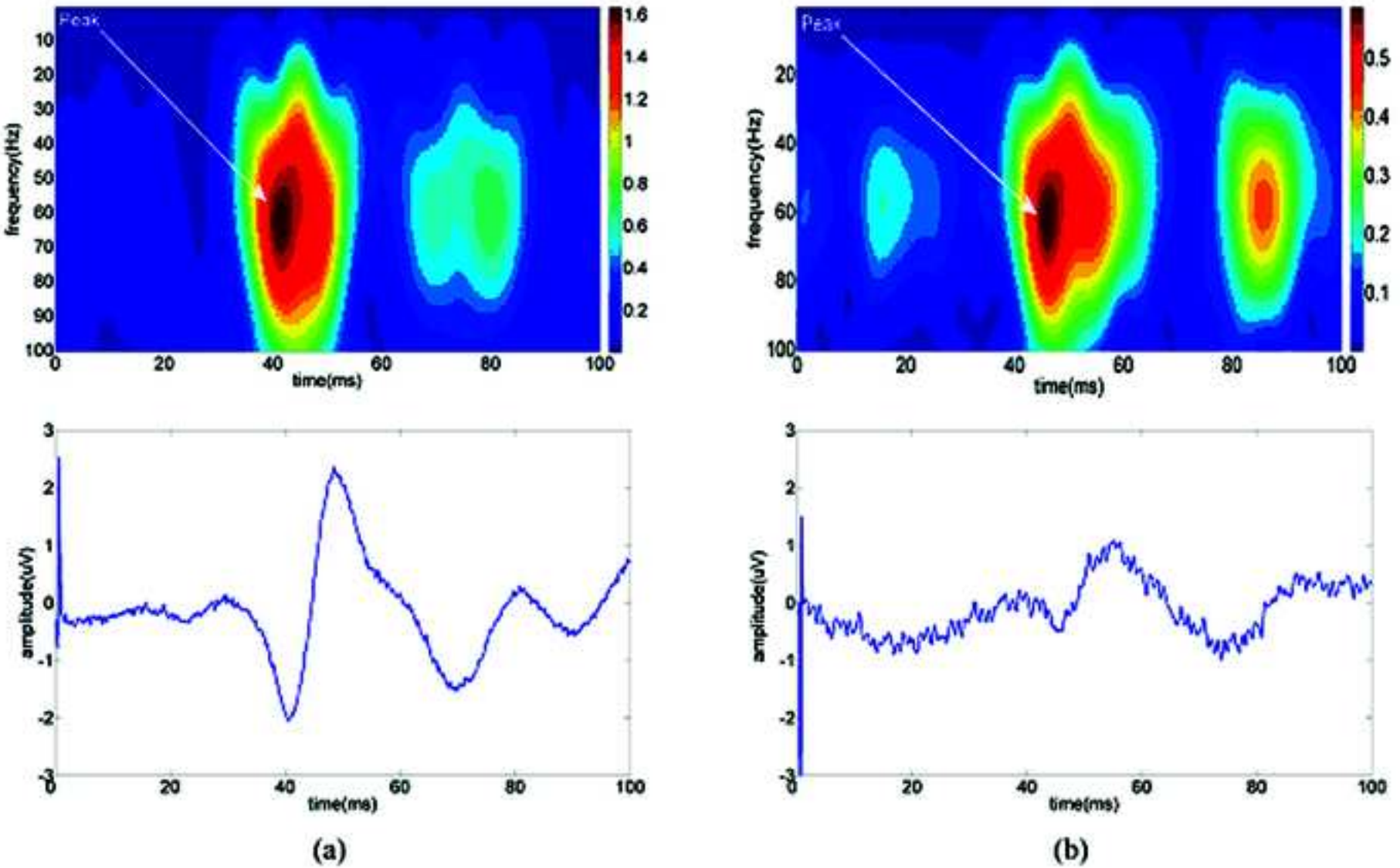

Fig3

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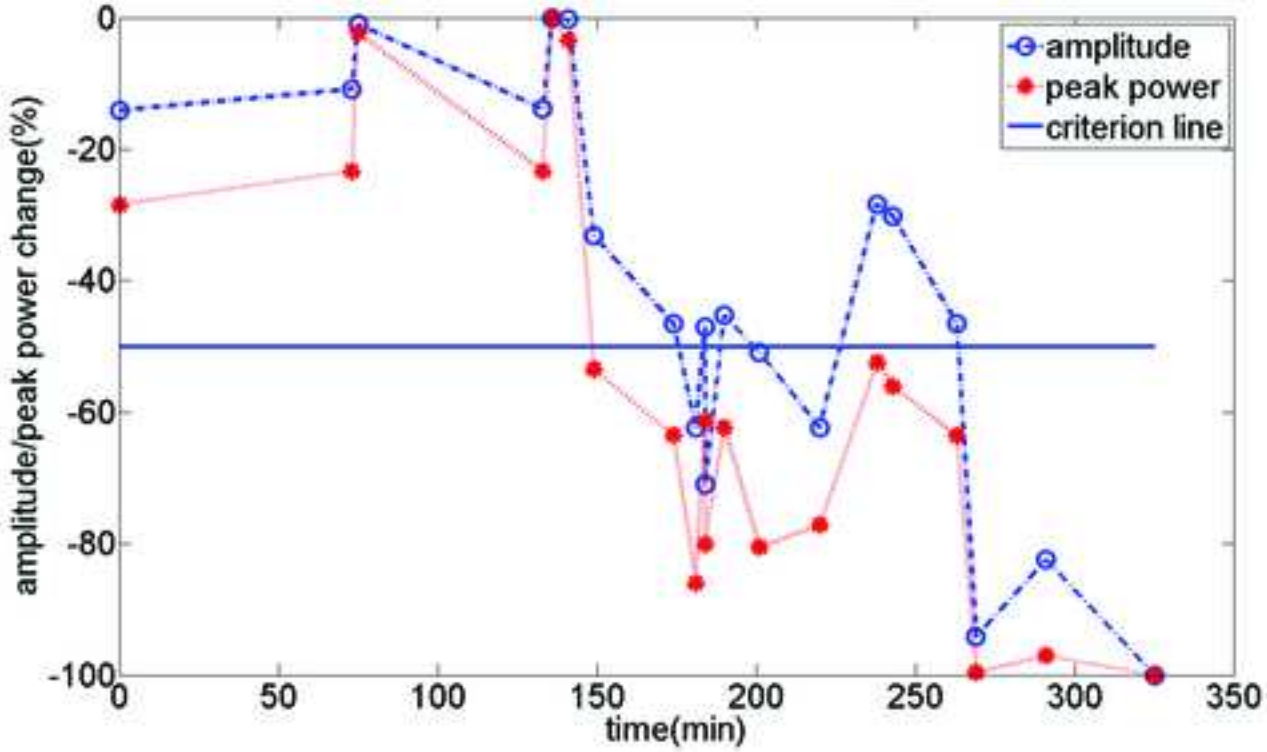
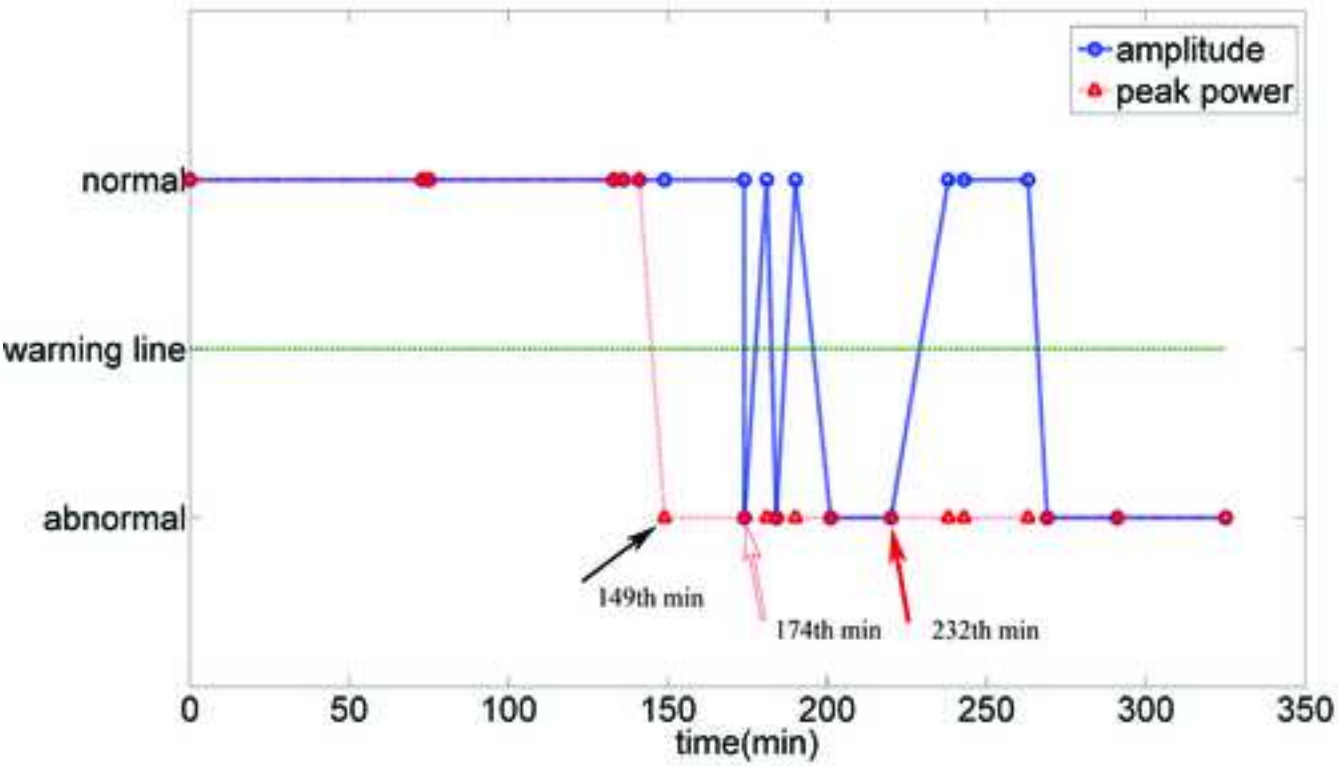


(a)



(b)

Table

Table 1 mean values of intra-subject variability of parameters for SEP monitoring

	amplitude	latency	peak power	peak time	peak frequency
Cortical SEP (Cz')	24.8%	3.7%	11.5%	6.0%	7.7%
Subcortical SEP (Cv)	19.1%	2.1%	11.2%	3.9%	3.9%

Table 2 variability of inter-subject parameters in different surgical stages for SEP monitoring

		Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
parameters in time domain						
amplitude/μV	Cz’	62%	63%	60%	57%	57%
	Cv	42%	45%	45%	44%	44%
latency/ms	Cz’	10%	10%	10%	10%	11%
	Cv	9%	9%	9%	9%	9%
parameters in time-frequency domain						
peak power	Cz’	150%	158%	159%	158%	154%
	Cv	85%	92%	90%	87%	84%
peak time/ms	Cz’	10%	10%	10%	10%	11%
	Cv	9%	9%	9%	10%	10%
peak frequency/Hz	Cz’	11%	11%	11%	12%	12%
	Cv	6%	8%	8%	8%	8%

Table 3 central values and 3σ ranges of peak time and peak frequency

	peak time /ms	peak time range /ms	peak frequency /Hz	peak frequency range /Hz
Cortical SEP (Cz')	41.2	29-55	53.6	37-79
Subcortical SEP (Cv)	30.1	21-39	81.8	67-111

Table 4 a comparison of parameters between time and time-frequency domain before and after abnormal warnings for the true positive SEP cases

		amplitude/μV	latency/ms	peak power	peak time/ms	peak frequency/Hz
Case 1	before	4.27	41	12.83	45	53
	after	1.44	46	3.57	59	14
	difference	-66%*	+12%*	-72%*	+31%*	S.
Case 2	before	1.50	42	1.59	45	41
	after	0.59	43	0.23	48	14
	difference	-61%*	+2.4%	-86%*	+6.7%	S.

*denotes significant difference according to the warning criteria, S. denotes that peak frequency changes from ‘in the normal range (37-79Hz)’ to ‘out of the normal range’ before and after abnormal warnings.

Table 5 a comparison of parameters between time and time-frequency domain before and after abnormal warnings for the false positive SEP cases

		amplitude/μV	latency/ms	peak power	peak time/ms	peak frequency/Hz
	before	2.94	34	3.27	37	57
Case 3	after	0.43	36	2.02	39	71
	difference	-85%*	+5.9%	-38%	+5.4%	N.S.
	before	3.74	36	5.53	40	42
Case 4	after	1.48	33	4.38	39	64
	difference	-60%*	-8.3%	-21%	-2.5%	N.S.
	before	3.78	36	5.69	37	54
Case 5	after	1.57	33	2.05	35	59
	difference	-58%*	-8.3%	-64%*	-5.4%	N.S.
	before	3.46	34	4.37	39	59
Case 6	after	0.77	34	1.09	37	52
	difference	-78%*	0%	-75%*	-5.1%	N.S.
	before	0.95	35	4.14	39	54
Case 7	after	0.44	36	1.84	40	42
	difference	-54%*	+2.9%	-56%*	-2.6%	N.S.
	before	2.53	41	5.92	42	48
Case 8	after	0.57	43	2.23	43	44
	difference	-77%*	+4.9%	-62%*	+2.4%	N.S.

*denotes significant difference according to the warning criteria, N.S. denotes that peak frequency is in the normal range (37-79Hz) before and after abnormal warnings.