Single-trial detection for intraoperative somatosensory evoked potentials monitoring

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Abstract Abnormalities of somatosensory evoked potentials (SEPs) provide effective evidence for impairment of the somatosensory system, so that SEPs have been widely used in both clinical diagnosis and intraoperative neurophysiological monitoring. However, due to their low signal-to-noise ratio (SNR), SEPs are generally measured using ensemble averaging across hundreds of trials, thus unavoidably producing a tardiness of SEPs to the potential damages caused by surgical maneuvers and a loss of dynamical information of cortical processing related to somatosensory inputs. Here, we aimed to enhance the SNR of single-trial SEPs using Kalman filtering and time–frequency multiple linear regression (TF-MLR) and measure their single-trial parameters, both in the time domain and in the time–frequency domain. We first showed that, Kalman filtering and TF-MLR can effectively capture the single-trial SEP responses and provide accurate estimates of single-trial SEP parameters in the time domain and time–frequency domain, respectively. Furthermore, we identified significant correlations between the stimulus intensity and a set of indicative single-trial SEP parameters, including

the correlation coefficient (between each single-trial SEPs and their average), P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase value (at the zero-crossing points between P37 and N45). Finally, based on each indicative single-trial SEP parameter, we investigated the minimum number of trials required on a single-trial basis to suggest the existence of SEP responses, thus providing important information for fast SEP extraction in intraoperative monitoring.

Keywords Somatosensory evoked potentials (SEPs) · Single-trial analysis · Kalman filtering · Time–frequency multiple linear regression (TF-MLR) · Somatosensory system · Intraoperative monitoring

Introduction

Somatosensory evoked potentials (SEPs) are cortical responses following the presentation of an electrical stimulation of large myelinated fibres (A β) (Cruccu et al. 2008) in the peripheral nerve (Devlin et al. 2006). The somatosensory system related to SEPs is the dorsal column-medial lemniscus system, which subserves mechanoreception (e.g. tactile recognition and vibration detection) (Treede 2007). Abnormalities of SEP responses provide good evidence for impairment of the somatosensory system (Cruccu et al. 2008). For this reason, SEPs have been widely used both in clinical diagnosis (Aminoff et al. 1988; Zeman and Yiannikas 1989; Yiannikas and Vucic 2008) and in intraoperative neurophysiological monitoring (Nuwer 1998; Luk et al. 2001; Deletis and Shils 2002; Minahan 2002; Hu et al. 2003; Devlin et al. 2006). The wide application of SEPs in intraoperative monitoring

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is also because of the definable latency and amplitude of short-latency SEPs for a quantitative comparison throughout a procedure (Minahan 2002). When elicited from tibial nerves, the cortical SEPs comprise a number of waves that are time locked to the onset of stimuli, and the most predominant and definite positive–negative complex is P37–N45 (peaking around 37 and 45 ms respectively) (Minahan 2002; Cruccu et al. 2008).

However, the magnitude of SEPs (about 1–2 μ V) (Nuwer et al. 1999; Cruccu et al. 2008) is several times smaller than the magnitude of the background electroencephalography (EEG) activity, thus resulting in a low signal-to-noise ratio (SNR) of SEPs in single trials (Lam et al. 2005; Hu et al. 2010b). In order to enhance the SNR and identify the SEP responses, ensemble averaging is the most widely used approach in the time domain (Dawson 1951, 1954). Nevertheless, the ensemble averaging results in two main limitations: (1) the tardiness of SEP responses to the potential damages caused by surgical maneuvers (e.g. the insufficient blood supply and the mechanical compression); (2) the loss of dynamical information, which reflects the trial-to-trial variability.

Therefore, fast SEP extraction at few-trial or even single-trial level is of special interest not only in intraoperative monitoring of spinal cord surgery, but also in study of underlying physiological nature and mechanisms of SEP generation. The availability of a fast monitoring technique (i.e. SEP detection at the single-trial level) during the intraoperative monitoring would detect the temporary malfunctioning, which is caused by the prolonged insufficient blood supply to the spinal cord or mechanical compression, at an early stage, thus preventing irreversible spinal cord damage (Wiedemayer et al. 2002; Rossi et al. 2007). In addition, the single-trial variability may reflect important factors such as changes of SEPs in different stages of surgery (e.g. scoliosis surgery) (Luk et al. 1999), and differences in stimulus parameters (duration, intensity, and rate) (Hu et al. 2001b). Hence, effective methods that can explore SEP dynamics at the level of single trial would provide a super-fast intraoperative monitoring and new insights into the functional significance of the cortical processes related to somatosensory input at different conditions (Hu et al. 2010a).

Recently, several methods have been described for enhancing the SNR of stimulus evoked brain responses, including SEPs, in single trials (Wang et al. 2010; Daly et al. 2011). An adaptive filtering method (Hu et al. 2005; Lam et al. 2005), combining adaptive noise canceller and adaptive signal enhancer, was proposed to extract SEPs fast and reliably. In addition, Nishida et al. (1993) used three kinds of band-pass filters to detect the single SEP waveform, and Rossi et al. (2007) adopted an autoregressive filter with exogenous input on single-trial SEP extraction.

Another type of fast SNR enhancement approaches is spatial filtering based on second-order blind identification (SOBI) (Tang et al. 2005), independent component analysis (ICA) (Jung et al. 2001; Pockett et al. 2007), and common spatial pattern (Huang et al. 2010, 2013; Zhao et al. 2010). These methods showed that stimulus-related brain responses can be separated from multi-channel EEG recordings, thus enhancing the SNR of cortical responses at single-trial level.

Above fast SEP extraction methods aimed to enhance the SNR in the time domain, while the identification and measurement of SEPs in the joint time–frequency domain are attracting more and more interests (Hu et al. 2001a, 2002, 2003, 2014, 2015; Zhang et al. 2009, 2010). It was found that time–frequency features of SEPs (i.e. the latency, frequency, and magnitude of the power peak in the time–frequency distribution) provided an earlier and more sensitive indication of neural injury than conventional time domain measurements (such as P37/N45). Thus, time–frequency analysis of SEPs was suggested as an effective feature extraction technique in preventing spinal cord injury during surgery (Hu et al. 2003; Zhang et al. 2009). Hence, it is expected that SEP parameters measured at the time–frequency domain can provide some novel neural information about cortical processing of somatosensory inputs.

Apart from enhancing the SNR of SEP responses, no study reported a systematical estimation of single-trial SEP parameters, both in the time domain (i.e. peak latency and amplitude) and in the time–frequency domain (i.e. peak latency, frequency, and magnitude). In addition, the relationships between these estimated single-trial SEP parameters and the stimulus parameters (e.g. the stimulus intensity) have rarely been explored. Furthermore, the minimum number of trials needed to identify and characterize single-trial SEP parameters has not been investigated in most relevant studies. To address the above issues, we firstly used a fast algorithm based on parametric modeling and Kalman filtering (von Spreckelsen and Bromm 1988), to enhance the SNR of single-trial SEPs that were recorded during intraoperative monitoring, and to estimate the single-trial latencies and amplitudes of SEP peaks (P37 and N45) in the time domain. Then, we developed a time–frequency multiple linear regression (TF-MLR) to enhance the SNR of the single-trial time–frequency distributions (TFDs) of SEPs, and to estimate the single-trial SEP parameters in the time–frequency domain (i.e. peak latency, frequency, and magnitude). In addition, we calculated the single-trial phase values (the zero-cross points between P37 and N45 and at the SEP dominant frequencies) of SEP responses. All these estimated single-trial SEP parameters, both in the time domain and in the time–frequency domain, were compared at different stimulus

intensities to assess their relationships. Finally, we investigated the minimum number of trials that can be used to identify and characterize the SEP responses when using each of the indicative single-trial SEP parameters.

Materials and methods

Subjects

SEP data were collected from six patients undergoing surgical correction for scoliosis (6 females) aged from 11 to 27 years (17 ± 5 , mean $\pm$ SD). All participants gave written informed consent, and the Institutional Review Board for Clinical Research Ethics approved the study protocol.

Experimental paradigm

Bipolar transcutaneous electrical stimuli were applied on the posterior tibial nerve (at ankle) behind the medial malleolus (Cruccu et al. 2008), with monophasic square-wave of 0.2 ms pulse duration. The stimulation rate was 5.1 Hz, and three different stimulus intensity were used (E1: 0 mA; E2: 10 mA; E3: 20 mA) to simulate the changes in SEPs. In a preliminary study we found that stimuli with E1 (0 mA) cannot produce any sensation, and stimuli with E2 (10 mA) and E3 (20 mA) produce a clear tactile sensation, related to the activation of A β skin nerve fibres. Note that the use of E1 (0 mA) was aimed to extract resting EEG trials for the following statistical comparisons (E1 trials also named resting EEG trials). During the experiment, all patients received general anaesthesia with isoflurane and 100 % Oxygen maintained below 1 MAC (between 0.6 and 1.2 %) was used throughout the surgery.

SEP recording and preprocessing

SEP data were recorded at Cz' (2 cm posterior to Cz, International 10–20 system of EEG electrode placement) and Cv (located over the 2nd cervical spinous process, C2), using Fz as reference, with subcutaneous needle electrodes. Signals were amplified 5000 times and digitized using a sampling rate of 5000 Hz (VikingSelect IOM, VIASYS Healthcare, USA). During the intraoperative spinal cord monitoring, SEP data were collected in three different blocks. In each block 40 trials for each of the three stimulus intensities (E1, E2, and E3; 120 trials in total) were recorded for off-line data analysis.

For each subject, SEP data were imported and processed using MATLAB (Mathworks Inc., Natick, USA) and EEGLAB (Delorme and Makeig 2004). Continuous SEP data were band-pass filtered between 20 and 2000 Hz (Cruccu et al. 2008; Hu et al. 2010b). SEP epochs were

then extracted using a window analysis time of 100 ms (0–100 ms post-stimulus).

Single-trial analysis

In the time domain, a fast algorithm based on parametric modeling and Kalman filtering (von Spreckelsen and Bromm 1988) for enhancing SNR of single-trial SEPs was used in this study. After Kalman filtering, single-trial SEP parameters estimated in the time domain (i.e. correlation coefficient, P37 latency and amplitude, N45 latency and amplitude, and P37–N45 peak-to-peak amplitude) were estimated and compared at different stimulus intensities.

In the time–frequency domain, the TFDs of both single-trial and average waveforms were calculated using a continuous wavelet transform (CWT) (Tognola et al. 1998; Mouraux et al. 2003; Mouraux and Iannetti 2008; Hu et al. 2010a). Then, a newly-developed TF-MLR was applied to the single-trial TFDs for estimating the single-trial latency, frequency, and magnitude of SEPs on the time–frequency plane. In addition, single-trial phase values (at the latency of zero-cross point between P37 and N45 in the average waveform extracted from the SEP dominant frequencies in the TFDs) were also calculated. Similarly, all these estimated dynamical parameters in the time–frequency domain (i.e. latency, frequency, magnitude, and phase value) were compared at different stimulus intensities.

Time domain analysis

In this study, we used the Kalman filtering to enhance SNR of single-trial SEPs, since this method has been verified to (1) accurately model both amplitude variability and latency jitter of SEP peaks and (2) greatly and rapidly enhance the SNR of single-trial brain responses (von Spreckelsen and Bromm 1988). As described in von Spreckelsen and Bromm (1988), single-trial SEP responses, recorded after an electrical stimulus, can be modeled as the sum of two different processes: spontaneous EEG activity and evoked brain potentials.

Firstly, the spontaneous EEG activity was described by an autoregressive (AR) process driven by a white noise as (Cerutti et al. 1988; Neumaier and Schneider 2001; Schneider and Neumaier 2001; Rossi et al. 2007)

$$\text{EEG}(t) = \sum_{i=1}^p a_i \text{EEG}(t-i) + w(t) \quad (1)$$

where $\text{EEG}(t)$ is the spontaneous EEG activity, a_i are the AR parameters with order p , and $w(t)$ is white noise.

In order to estimate the AR parameters a_i of the spontaneous EEG activity, the Nuttall-strand method (Marple 1987), which has been proved to provide better estimates of the AR process (Schlogl 2006), was utilized with input

noise in post-stimulus interval (10–30 ms) of each single trial. This post-stimulus interval is selected in this study, since (1) the EEG activity is considered as stationary for this interval (von Spreckelsen and Bromm 1988); (2) there is not reported time-locked response in this interval when recorded at Cz'-Fz (Minahan 2002; Cruccu et al. 2008); (3) the artifacts caused by the electrical stimuli are not presented at the selected time interval; (4) ongoing neuronal activity showed a good quality of prediction up to 50 ms and declined with a longer time delay (Arieli et al. 1996). In addition, the Schwarz's Bayesian Criterion (SBC) (Schwarz 1978) was used to estimate the model order p between 7 and 20.

Secondly, the evoked brain potentials (SEPs in this study) were modeled using an infinite impulse response (IIR) system (Cerutti et al. 1988; von Spreckelsen and Bromm 1988; Rossi et al. 2007):

$$y(t) = \sum_{i=1}^m c_i y(t-i) + \sum_{j=0}^n d_j u(t-d-j) \quad (2)$$

where $y(t)$ is the SEP signal at time t ; c_i and d_j are the output and input filter coefficients with model orders of m and n respectively; $u(t)$ is the input signal at time t , and d is the deadtime of system (the time between the electrical stimuli and the occurrence of EEG responses).

The impulse responses of the system were obtained from the averaged SEP responses with the stimulus intensity of E2 and E3 (SEP responses are considered to exist under these stimulus intensities), and both input and output coefficients were estimated by fitting the IIR system to the averaged SEP responses with the least squares approach. Here, the model orders (both m and n) were set to 10, which were reported to be appropriate (von Spreckelsen and Bromm 1988). Note that we chose 10 ms as the deadtime of the system with the aim to avoid the interference from the artifacts generated by the electrical stimuli. The same as von Spreckelsen and Bromm (1988), both the amplitude variability and latency jitter have been built into the IIR system using the time-moving covariance of the input signal.

Combining the described EEG model and EP model, a state-space model, with the SEP responses being the model state, will be set up. Then, the Kalman filtering can be used to recursively estimate the model state, i.e., to estimate the filtered single-trial SEP responses. For a detailed description of the state-space model and the Kalman filtering algorithm, please refer to von Spreckelsen and Bromm (1988).

From the Kalman filtered SEPs, we calculated the correlation coefficient (CC) between each of the single-trial SEP waveforms and their ensemble average in the post-stimulus interval (30–60 ms). The latency and amplitude of

P37 wave in each single trial were estimated by finding the most positive peak if $CC > 0$ (positive correlation) or the most negative peak if $CC < 0$ (negative correlation) within a 10-ms time window centered on the latency of the P37 response in the average waveform of each subject. The latency and amplitude of N45 response in each single trial were estimated in a similar manner. The peak-to-peak amplitude (P37-N45) was calculated by subtracting the N45 amplitude from P37 amplitude for each single trial. It should be noted that the estimated latency was biased (e.g., the mean latency across a number of resting EEG trials was significantly different from zero), since the proposed method estimated the single-trial latency within a predefined time window, which deviated from zero.

In this study, the SNR was estimated as the ratio between variance of averaged SEPs and the variance of the difference waveforms (single-trial waveform minus averaged SEP waveform) in the post-stimulus interval (10–100 ms) (Spencer 2005; Tang et al. 2005; Debener et al. 2007). SNR values before and after Kalman filtering were assessed using non-parametric Wilcoxon test, due to the non-normal distribution of the SNR values.

To assess the effect of the stimulus intensity (E1, E2, and E3), we performed a one-way analysis of variance (ANOVA) using the estimated single-trial CCs, P37 latencies and amplitudes, N45 latencies and amplitudes, and P37-N45 amplitudes. When the effect of the stimulus intensity was significant, we performed a post hoc analysis using Tukey correction.

Time-frequency domain analysis

The TFD of SEP waveforms in both single trials and averages were calculated using CWT (Stark 1992). CWT is able to construct a time-frequency representation of EEG signals that offers an optimal compromise for time and frequency resolution by adapting the window width as a function of estimated frequency (Mouraux and Iannetti 2008).

The CWT is defined as (Tognola et al. 1998):

$$F(\tau, f) = \int_t x(t) \cdot \sqrt{f/f_0} \cdot \psi^* \left(\frac{f}{f_0} \cdot (t - \tau) \right) dt \quad (3)$$

where τ and f are the time and frequency index, respectively, and $x(t)$ is the original signal in time (t) domain; $\psi(t)$ is the mother wavelet function with central frequency f_0 . The mother wavelet $\psi(t)$ used in this study is a complex Morlet wavelet. The explored frequencies were ranged from 21 to 200 Hz in steps of 1 Hz in this study. Previous studies have shown that most meaningful time-frequency features of SEPs are distributed in the specified frequency

range (Hu et al. 2001a, 2002, 2003; Zhang et al. 2009). The squared magnitude of $F(\tau, f)$ is called the scalogram.

For each evaluated frequency, the magnitude of the power spectrum was baseline-corrected by subtracting the average power of the signal enclosed in the time-interval ranging between 10 and 30 ms, which was similar with several previous studies (Pfurtscheller and Lopes da Silva 1999; Iannetti et al. 2008; Hu et al. 2010a).

After obtaining the TFDs, both for the single trials and their average, we developed and applied a TF-MLR approach to capture the SEP responses in the time–frequency domain. The multiple linear regression (MLR) approach was originally developed in the time domain by Mayhew et al. (2006) in order to estimate the latency and amplitude of event-related potentials (ERPs) in an accurate and unbiased fashion. This method has been successfully applied to the single-trial detection of the N1 wave of laser-evoked potentials (LEPs) after wavelet filtering (Hu et al. 2010a) and of auditory-evoked potentials (AEPs) collected during simultaneous EEG-fMRI recording (Mayhew et al. 2010). In this method, the template is defined using the average ERP waveform and a series of temporal derivatives in order to model independently the latency jitter of each single-trial ERP wave. This procedure is analogous to the approach commonly used to analyse functional MRI data (Friston et al. 1998), where not only the haemodynamic response function (analogous to the average ERP in this case) but also its temporal derivative is fitted to the data in a general linear model (GLM) framework.

When extending the MLR method to the time–frequency domain, we would take into account the variability not only of the latency and magnitude, but also of the frequency of SEPs. This variability can be described as follows:

$$F(t, f) = kF[(t + a), (f + b)] + \varepsilon \\ \approx kF(t, f) + ka \frac{\partial F(t, f)}{\partial t} + kb \frac{\partial F(t, f)}{\partial f} \quad (4)$$

where $F(t, f)$ is the TFD of a single-trial SEP response which represents as a joint function of time t and frequency f . This TFD $F(t, f)$ can be expressed as the sum of the single-trial SEPs: $kF[(t + \alpha), (f + b)]$ and background noise ε . k is the weighted constant; α is the latency jitter; and b is the frequency variability of SEPs respectively. Using the Taylor expansion, the single-trial TFD is approximately equal to the sum of a set of basis (average, its temporal derivative and frequency derivative) of SEPs.

In this study, the basis set was calculated from the TFD of the group average waveform measured after Kalman filtering. Firstly, in order to isolate the high amplitude signals from the background noise in the TFD, the generated TFD of the group average waveform was thresholded using a cut-off to preserve the area with amplitude larger than two standard deviations above the mean, which

follows the approach proposed by Mayhew et al. (2010). Then, the thresholded TFD was smoothed with Gaussian windows and used as the average in the basis set, whereas the temporal derivative and frequency derivative were calculated from the Gaussian smoothed TFD. Finally, the obtained basis set was regressed against each single-trial SEP TFD. All the coefficients (in Eq. 4) of each single-trial were calculated by multiple linear regression, and the corresponding fit of the SEP response was obtained by multiplying the three regressors in the basis set by their coefficients.

For the fitted single-trial TFD, we calculated the correlation coefficient (CC_{TF}) between the fitted single-trial TFD and the Gaussian smoothed TFD of the group average SEP waveform. The magnitude of the SEP in each single trial was obtained by calculating the mean of the 10 % of points displaying the highest increase if $CC_{TF} > 0$ (positive fit), or the mean of the 10 % of points displaying the highest decrease if $CC_{TF} < 0$ (negative fit) respectively. This “top 10 %” summary in each single trial would reduce the noise contribution and avoid the problem of only selecting the outlier values (Iannetti et al. 2005, 2008; Mitsis et al. 2008; Mouraux and Iannetti 2008; Mayhew et al. 2010). Finally, the corresponding single-trial latencies and frequencies were obtained by calculating the mean latencies and mean frequencies of the selected top 10 % of points.

Furthermore, for each subject, we calculated the phase values of each single trial at the time of zero-cross point between P37 and N45 on the average waveforms and at the frequency where SEP responses dominant (erpimage routine; Delorme and Makeig 2004).

To assess the effect of the stimulus intensity (E1, E2, and E3), we performed a one-way ANOVA using the single-trial parameters on the time–frequency plane (latency, frequency, and magnitude of SEPs) and the single-trial phase values. When the effect of the stimulus intensity was significant, we performed a post hoc analysis using Tukey correction.

Evaluation of the minimum number of trials

In order to assess the minimal number of trials to significantly extract SEP responses, we performed two parallel statistical analyses on the indicative single-trial parameters, which are sensitive to the stimulus intensity (i.e. CC, P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase value). On one hand, these single-trial parameters estimated from resting EEG trials (E1 trials; from the first 6 trials to the first 40 trials) were compared against zero using a one sample t test to exclude the possibility of false positive; on the other hand, these single-trial parameters estimated from SEP trials (from the first 6 trials to the first 40 trials) with the relatively stronger stimulus intensity (E3) were compared

against zero using a one sample t test, for each subject, to exclude the possibility of false negative. If (1) the single-trial parameters estimated from the resting EEG trials are not significantly different from zero ($P > 0.05$), and (2) the corresponding values estimated from the SEP trials are significantly different from zero ($P < 0.05$), we suggested that the resting EEG trials and SEP trials can be significantly distinguished using the specific parameters with the corresponding number of trials with both high sensitivity and specificity. Using this criterion, the minimal number of trials that can be used to significantly distinguish SEP trials from resting EEG trials has been assessed for each of these indicative single-trial SEP parameters.

Results

Single-trial analysis: time domain and time–frequency domain

Before estimating the single-trial parameters of P37 and N45, the SNR of single-trial SEP waveforms was

significantly enhanced by the Kalman filtering. The left panel of Fig. 1 shows the comparison of single-trial SEPs before and after Kalman filtering from a representative subject at different stimulus intensity. Among these single trials, we displayed an extreme example of single-trial raw SEP waveform, the separated ongoing EEG activity, and the filtered single-trial SEP waveform for each stimulus intensity (E1, E2, and E3) in the middle panel of Fig. 1. The Kalman filtering remarkably reduces the amount of background EEG noise, and the SEP responses are more clearly presented. Quantitatively, Kalman filtering significantly enhances the SNR of single-trial SEP responses (from 0.074 ± 0.068 to 0.115 ± 0.083 , $P = 0.028$, Wilcoxon test) (Fig. 1, right panel).

In order to obtain the TFD with the optimal time and frequency resolution (the left panel of Fig. 2), CWT was used to calculate the power spectrum of SEP responses in the time–frequency domain. In the left panel of Fig. 2 (left part), we show the CWT based TFD obtained from the group average SEP waveform. Using a two standard deviation cut-off, the thresholded TFD is characterized by a phase-locked signal increase maximal between 29 and

Fig. 1 Kalman filtering and its effect on single-trial SEP responses (an extreme case). *Left panel:* Comparison of Kalman filtering effect on single-trial SEPs elicited by different stimulus intensity. At each of the stimulus intensity (E1, E2, and E3 respectively), forty single trials from a representative subject are presented (top to bottom) in this panel. Note that, with the increase of the stimulus intensity, the SEP responses are more obviously presented. *Middle panel:* The Kalman filtering effect of a representative trial for each of the three stimulus intensity. At each of the stimulus intensity (E1, E2, and E3 respectively), one trial from the same subject are displayed from

top to bottom in this panel. The raw single-trial SEP waveform, the separated ongoing EEG activity, and the filtered single-trial SEP waveform are shown in black, blue and red lines respectively. Note how the Kalman filtering remarkably reduces the amount of background EEG noise, and the SEP responses are clearly presented with higher SNR. *Right panel:* Comparison of SNR before and after Kalman filtering for each subject. Colored lines represent single subjects. The SNR of single-trial SEP responses was significantly enhanced by Kalman filtering (from 0.074 ± 0.068 to 0.115 ± 0.083 , $P = 0.028$, Wilcoxon test). (Color figure online)

Fig. 2 Flowchart describing the procedure developed to generate the regressors for TF-MLR, and its fit examples of single-trial SEP TFDs elicited at different stimulus intensity. *Left panel:* The group averaged SEP waveform was fed to the CWT to generate the TFD of SEPs, and then baseline corrected using the time interval between 10 and 30 ms for all the estimated frequencies. x-axis: latency (s); y-axis: frequency (Hz). Following, the TFD of SEPs was thresholded using the two standard deviations cut-off. Note that the amount of background EEG noise on the time–frequency plane is remarkably reduced while the regions corresponding to SEP are clearly presented. The obtained ROI of SEPs was mainly located ranging 29–57 ms post-stimulus in latency and 30–92 Hz in frequency. The *right part* of this panel displayed three regressors, which represent the average (Gaussian smoothing), the temporal derivative and frequency derivative of SEPs on the time–frequency plane respectively (from *top to bottom*). The

temporal derivative and frequency derivative indicated that the variability of latency and frequency in single-trial TFD were modeled into the TF-MLR analysis. The TF-MLR of the three regressors against each single trial was used to model the TFD for each single-trial SEP responses. *Right panel:* TF-MLR fitted examples of single-trial TFDs of SEP responses elicited at different stimulus intensity. From *top to bottom* in this panel, TFDs from three single-trial SEPs (*left*) elicited by E1, E2, and E3 respectively were fed to TF-MLR, thus yielding the fitted results of these TFDs (*right*). Note that information which located at the SEP ROI in the time–frequency plane has been well preserved, while the information located at the SEP RONI, which reflected the background EEG noise, has been removed, thus enhancing the SNR of the SEP responses on the time–frequency plane. (Color figure online)

57 ms in time and between 30 and 92 Hz in frequency (also see the left panel of Fig. 2). In the left panel of Fig. 2 (right part), we display three regressors of SEP responses in the time–frequency plane generated from the thresholded TFD. These three regressors represent the average (Gaussian smoothing), temporal derivative and frequency derivative for SEP responses. The temporal derivative and frequency derivative indicated that the latency jitter and the variability of frequency of single-trial SEPs have been modeled into the TF-MLR analysis. In the right panel of Fig. 2, we show a single-trial fitted example using the TF-MLR approach for each of the stimulus intensity. Fitted results showed that information which located at the SEP

region-of-interest (ROI) in the time–frequency plane has been correctly preserved, while the information located at the SEP region-of-no-interest (RONI) which reflected the background EEG noise has been removed, thus enhancing the SNR of the SEP responses in the time–frequency plane.

Figure 3 shows the estimation of phase values of single-trial SEP responses from a representative subject. In the top left panel of Fig. 3, we show the average SEP waveform of this subject. The zero-cross point between P37 and N45 on the average waveform is located at 43.2 ± 1.9 ms across subjects. The bottom left panel of Fig. 3 demonstrates all the single-trial SEP waveforms across all stimulus intensity. In the top right panel, the TFD, which was obtained

Fig. 3 The estimation of phase values in single-trial SEP responses. *Top panel:* The *left part* of this panel displayed the average SEP waveform with the zero-cross point between P37 and N45 marked in the *red box*. For this subject, the latency of zero-cross point is 43 ms. The *right part* of this panel demonstrated the TFD of the group averaged SEP waveform. Note that the SEP responses in the time–frequency domain were dominant between 40 and 60 Hz in frequency, which has been marked with *black solid lines*. *Bottom*

panel: All the single-trial SEP responses across all stimulus intensity (from *bottom to top*, there are single-trial SEP waveforms elicited by E1, E2, and E3 respectively) are displayed in the *left part* of this panel. Correspondingly, the single-trial phase values at zero-cross point (43 ms) and the dominant frequencies (from 40 to 60 Hz) are shown in the *right part* of this panel. Single-trial phase values elicited by E1, E2, and E3 are showed in *blue, green, and red* respectively. (Color figure online)

from the group average waveform, displayed that the strongest SEP responses in the time–frequency domain were dominant between 40 and 60 Hz in frequency. For each subject, the single-trial phase values at zero-cross point (43.2 ± 1.9 ms) and at the dominant frequencies (from 40 to 60 Hz) were calculated, and shown in the bottom right panel of Fig. 3.

The left panel of Fig. 4 shows all the estimated single-trial parameters in the time domain and the time–frequency domain from a representative subject, and the right panel of Fig. 4 displays the relationship between the estimated single-trial parameters and the electrical stimulus intensity. The parameters CC, P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase value elicited by E1, E2, and E3 were significantly different (CC, $F = 18.04$, $P < 0.001$. P37 amplitude, $F = 21.9$, $P < 0.001$. N45 amplitude, $F = 18.961$, $P < 0.001$; P37–N45 amplitude, $F = 20.66$,

$P < 0.001$; phase value, $F = 19.034$, $P < 0.001$; see also the left panel of Fig. 4 and Table 1). Post hoc comparisons revealed that CCs elicited by E1 were significantly smaller compared with the CCs elicited by E2 ($P = 0.002$) and E3 ($P < 0.001$). The P37 amplitudes elicited by E1 were significantly smaller compared with the amplitudes elicited by E2 ($P < 0.001$) and E3 ($P < 0.001$). The N45 amplitudes elicited by E1 were significantly smaller compared with the amplitudes elicited by E2 ($P = 0.001$) and E3 ($P < 0.001$). Similarly, the P37–N45 amplitudes elicited by E1 were significantly smaller compared with the amplitudes elicited by E2 ($P < 0.001$) and E3 ($P < 0.001$). The single-trial phase values elicited by E1 were significantly smaller compared with the phase values elicited by E2 ($P = 0.004$) and E3 ($P < 0.001$). In addition, the phase values elicited by E2 were also smaller, although not significantly, compared with the phase values elicited by E3 ($P = 0.093$).

Fig. 4 Estimated single-trial parameters of SEP responses in the time domain and in the time–frequency domain. *Left panel:* single-trial parameters of SEP responses elicited at different stimulus intensity from a representative subject. CC, P37 latency, P37 amplitude, N45 latency, N45 amplitude, P37–N45 amplitude, ROI latency, ROI frequency, ROI magnitude, and phase value for single trials are displayed from *top to bottom* in this panel. The single-trial parameters elicited by E1, E2, and E3 are showed in *blue, green, and red* respectively (from *left to right* in this panel). *Right panel:* The relationship between the estimated single-trial parameters and the stimulus intensity. Single-trial parameters elicited by E1, E2, and E3 are showed in *blue, green, and red* respectively, and *vertical error bars* represent the variance across subjects (expressed as standard deviation, SD). * and ** represent $P < 0.01$ and $P < 0.001$ respectively. (Color figure online)

The P37 latencies and N45 latencies elicited by E1, E2 and E3 were not significantly different (P37 latency, $F = 0.115$, $P = 0.892$. N45 latency, $F = 0.093$, $P = 0.912$; see also the right panel of Fig. 4 and Table 1). Furthermore, the latency, frequency, and magnitude of SEP responses in the

time–frequency domain elicited by E1, E2 and E3 were not significantly different (latency, $F = 1.943$, $P = 0.178$; frequency, $F = 1.202$, $P = 0.328$; magnitude, $F = 0.308$, $P = 0.740$; see also the right panel of Fig. 4 and Table 1).

Evaluation of the minimum number of trials

In order to assess the minimum number of trials to significantly distinguish the resting EEG trials (E1 trials) and the SEP trials (E3 trials), we performed two parallel statistical analyses, and observed that (1) with the increase of the number of tested trials, the cortical activities with and without the presentation of electrical stimulus (with and without SEP responses) are easier to distinguish using all the indicative SEP parameters (CC, P37 amplitude, N45 amplitude, P37–N45 amplitude and phase value), especially when the number of tested trials is larger than 20; (2) when testing on resting EEG (E1 trials), all the estimated single-trial parameters are not significantly different from zero when using 6 and more trials ($P > 0.05$) (Fig. 5); (3) when testing on SEP trials (E3 trials), single-trial CC, P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase value are significantly different from zero at least using 10, 14, 13, 14, and 8 trials in average ($P < 0.05$) (Fig. 5).

Discussion

In this study we used the Kalman filtering and the TF-MLR approach to enhance the SNR of single-trial SEPs and to estimate a set of single-trial SEP parameters in the time domain and time–frequency domain. By assessing the effect of the stimulus intensity on each of these estimated single-trial parameters, we found that five parameters with good indicative performance and they are CC, P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase value. Importantly, when testing on SEP trials (E3 trials), CC, P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase value are significantly different from zero at least using 10, 14, 13, 14, and 8 trials in average across subjects ($P < 0.05$), while all these parameters are not significantly different from zero using 6 and more trials ($P > 0.05$) when testing on resting EEG (E1 trials).

Multiple linear regression in the time–frequency domain

Mayhew et al. (2006) showed that a MLR approach in the time domain can be used to estimate single-trial latency and amplitude of ERPs in an unbiased and accurate fashion. In this study, we expanded the basic idea of this MLR approach from the time domain to the time–frequency domain, and developed the TF-MLR approach. This

Table 1 Single-trial parameters in the time domain and the time–frequency domain at different stimulus intensity

	Stimulus intensity	
	10 mA	20 mA
Correlation coefficient	0.32 ± 0.16	0.45 ± 0.16
P37 Lat. (ms)	38.5 ± 1.96	38.7 ± 1.85
P37 amp. (μV)	1.27 ± 0.66	1.61 ± 0.40
N45 lat. (ms)	49.6 ± 3.94	49.2 ± 2.96
N45 amp. (μV)	-1.43 ± 0.74	-1.68 ± 0.51
P37–N45 amp. (μV)	2.70 ± 1.40	3.29 ± 0.90
ROI Lat. (ms)	42.2 ± 0.78	42.8 ± 0.39
ROI freq. (Hz)	49.9 ± 2.0	49.6 ± 1.7
ROI mag. (ER%)	3.40 ± 1.40	3.55 ± 0.99
Phase value (rad)	0.65 ± 0.32	0.98 ± 0.24

method was applied to fit the TFDs of each single trial and thereby was used to capture the time-locked SEP responses in the time–frequency plane from background EEG noise, thus enhancing the SNR of SEP responses. Intuitively, not

only the latency jitter, but also the variability of frequency of stimulus-related responses on the time–frequency plane, which may reflect important physiological changes, should be included in the TF-MLR analysis (left panel of Fig. 2). The use of three regressors for SEP in the TF-MLR approach is supposed to better capture the specificity of stimulus-related responses (Friman et al. 2003). While using more regressors we potentially gain in sensitivity, but may lose the specificity of the fit approach. The SEP responses are often presented with low SNR. Thus, adding more regressors into the TF-MLR analysis would also be sensitive to the background EEG noise. For these reasons, the TF-MLR approach with three regressors is able to capture the specificity of SEP responses, and provides a robust estimation of single-trial SEPs in the time–frequency plane.

In addition, the fitted single-trial TFD of SEPs only captured the information (signal) located at the SEP-specific ROI (between 29 and 57 ms in time and between 30 and 92 Hz in frequency, Fig. 2), which has been previously reported in several studies (Hu et al. 2001a, 2002, 2003), while noise in other region (RONI) in the time–

Fig. 5 The assessment of the minimum number of trials to detection SEP responses. All the indicative SEP parameters (CC, P37 amplitude, N45 amplitude, P37–N45 amplitude, and phase values), which were sensitive to the stimulus intensity, were used to assess the minimum number of trials that can significantly distinguish the resting EEG and SEP responses. Each red point represents the mean P value across subjects when comparing the single-trial parameters (using the corresponding number of trials), which were estimated

from resting EEG trials, against zero. Each green point represents the mean P value across subjects when comparing the single-trial parameters (using the corresponding number of trials), which were estimated from SEP trials, against zero. Vertical error bars represent the variance of P values across subjects (expressed as SD). In addition, the significant condition ($P = 0.05$) is marked using black solid lines. (Color figure online)

frequency plane was removed, thus providing a fitted single-trial TFD with higher SNR (right panel of Fig. 2).

Single-trial SEP estimates

We calculated the single-trial phase values at the latency of zero-cross point between P37 and N45 on the average waveform, and at the SEP dominant frequency (from 40 to 60 Hz) (Fig. 3). Importantly, we observed a significant difference of the phase values elicited by different level of stimulus intensity (E1, E2, and E3 respectively) ($F = 19.034$, $P < 0.001$, Fig. 4). The information represented as the single-trial phase values, which were rarely reported in previous studies related to SEPs, would reflect some important information, but different from the time-domain peak latencies and amplitudes, thus contributing for a comprehensive exploration of the single-trial SEP response.

When assessing the minimum number of trials using indicative parameters in single trials, we found that at least 10, 14, 13, 14, and 8 trials in average across subjects are needed to separate these parameters from zero for CC, P37 amplitude, N45 amplitude, P37-N45 amplitude, and phase value respectively ($P < 0.05$, Fig. 5). Few trials are needed when using CC and phase value compared to P37 amplitude, N45 amplitude, and P37-N45 amplitude. This may be caused by the reason that P37 amplitude, N45 amplitude, and P37-N45 amplitude are unbounded, and are sensitive to outliers when comparing with zero. In contrast, both CC and phase value are bounded (-1 to 1 , and $-\pi$ to π for CC and phase value respectively). Thus, both CC and phase values are more robust compared to the amplitudes of P37, N45, and P37-N45. In conclusion, we suggested that all these indicative parameters in single trials would be tested in intraoperative monitoring due to their different physiological meanings, and it would be better to pay more attention to both CC and phase value in single trials since they were more robust compared to the peak amplitudes or peak-to-peak amplitudes.

The indicative SEP parameters in single trials may reflect the dynamic information concerning both surgical variables (e.g. blood pressure and temperature) and experimental conditions (e.g. stimulus intensity and stimulation rate). Note that a recent report demonstrated that the application of single trial extraction on median nerve SEP recordings can provide a novel measurement to evaluate the spinal cord function, i.e., the use of single trial SEP detection could provide a very useful tool for clinical application in diagnosis and prognosis of spinal disorders (Cui et al. 2015). Specifically, the latency variability of single trial SEPs was investigated in patients with cervical spondylotic myelopathy, and it showed that patients with lower latency variability could gain a better recovery after

surgical treatment. This finding demonstrated that the dynamic analysis of SEPs could provide new information that is not available in conventional averaging method. With further development and better understanding of the relationships between indicative SEP parameters and surgical variables or experimental conditions, the dynamic features in evoked potentials would also be used for brain-computer interface and feedback neural therapy (Li et al. 2014).

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Compliance with Ethical Standards

Conflict of interest All authors have no conflict of interest.

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