·论著·

Sliding-window technique for the analysis of cerebral evoked potentials

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KEY WORDS Sliding-window Technique; Evoked potentials; Individual test threshold

SUMMARY **Objective:** To evaluate the efficiency of sliding-window technique in extracting and analyzing somatosensory evoked potentials (SEP) from multichannel electroencephalogram (EEG) data. **Methods:** A time window of certain window size was moved along the time dimension of data sets. Values within the window were averaged for each trial, and then compared with a preset control window. The probability of randomly appeared significance resulting from repeated statistical comparison was calculated utilizing simulated EEG data sets. Cluster size (number of successive significant data points with given individual significance threshold) was determined to keep the general alpha value under 0.05. To test this procedure, multichannel EEG signals were recorded and analyzed from fourteen healthy right-handed volunteers, with painful and non-painful electrical stimuli delivered to the right middle fingers. **Results:** Cluster size increased in parallel with window size and individual statistical threshold. The major SEP components of real EEG data, as well as the difference between pain and non-pain SEPs, were demonstrated to be significant with the sliding-window method. **Conclusion:** Sliding-window method is an effective tool for the analysis of SEP data.

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滑行窗口技术在痛觉脑诱发电位分析中的应用

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[关键词] 滑行窗口技术; 诱发电位; 单次检验阈值

[摘 要] 目的: 评价滑行窗口技术分析脑电诱发电位的能力。方法: 将具有一定宽度的时间窗口延时间轴滑行, 计算该窗口内的脑电电位平均值, 再与对照窗口进行统计比较, 以检验诱发电位是否具有统计显著性。利用该方法分析随机产生的模拟数据, 计算在指定单次检验阈值下, 多次统计比较导致显著性差异点连续出现的几率, 以确定可使整体α值小于0.05的cluster大小。为检验该方法的有效性, 在14名健康右利手志愿者右手中指给予痛或非痛电刺激, 记录EEG信号并采用上述技术加以分析。结果: 在整体α值确定的前提下, 作为显著性判据的cluster大小随单次检验阈值与窗宽的增加而增大。依据上述方法分析真实EEG数据, 确定了体感与痛觉诱发电位波形中具有统计学意义的成分, 以及两种波形之间的显著性差异。结论: 滑行窗口技术可有效地用于分析脑电诱发电位。

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Cerebral evoked potentials (EPs) are essential in the diagnosis of various neurological diseases. However, direct measurement of EPs are difficult because they are embedded in a background of spontaneous electroencephalographic activity (recorded as electroencephalogram, EEG), which is 10 times larger in amplitude. The conventional way to extract EP is to average data from n trials of stimulation. This will increase the signal-noise ratio (SNR) by times, because $\sqrt{n}$ EPs are time-locked with stimulation but noises are not. However, the latency variability (i.e., jitter) of the signal leads to a decrement in

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this maximal potential enhancement[1]. Also it is impossible to identify whether the observed change of average potential is due to variations across most of the trials, or merely some extraordinary changes in a few trials, i.e., it provides no information about the statistical significance. Certain approaches have been adapted to deal with the lack of time-locking for desired signals, such as weighted averaging[2], adaptive filter method[1], and single-trial extract process analysis[3], which are of special interest in recent methodological investigations. However, up to now no effort has been made to evaluate the statistical significance of an extracted EP.

In the current paper, we evaluated a sliding-window method in the analysis of EPs, which has been previously used in the study of neuronal activities[4]. Our aim is to provide the information of statistical significance, along with getting the averaged EPs from the EEG recording data.

1 Materials and Methods

1.1 Sliding windows technique

1.1.1 General procedure EEG signals were recorded as continuous data series with certain time resolution. A time window with certain window size was slid across the time dimension of EEG data sets with certain step size. Voltage values within the window were averaged for each trial of stimulation. This will be the first step to reduce random noise while keeping single-trial information intact. It could also compensate for the decrement of SNR due to the inconsistency of latencies. These mean values will then be statistically compared with the corresponding single-trial mean values of a preset control window (usually a period before stimulation) with paired *t*-test. By moving of the window, the cross-trial mean values within each window as well as the statistical significance of these mean values were extracted.

Window size is a very important factor that could influence the validity of the results in sliding-window analysis. A larger window will usually generate smoother result. However, it will also decrease the time resolution and blur away some details of the evoked potentials. Thus, it should be selected according to the nature of the interested potentials.

1.1.2 Significance threshold for repeated statistical test By definition, statistics is the calculation of probabilities. Thus, repeated statistical comparisons will raise the chance of random significance. In order to achieve a satisfying overall alpha value, the individual test threshold has to be modified. Ward[5] used a combination of minimum cluster size threshold for successive significant points and maximum individual test threshold to keep the overall statistical level below 0.05 for fMRI data analysis, which we adapted in our calculation. The underlying assumption is that true signals of significance should occur over continuous data points, whereas noise has much less of a tendency to form clusters of significant data points. Thus, simulated random signals with the same length and number of channels as the true EEG data sets were generated to perform the sliding window analysis for 1 000 times. With a given threshold for individual test, number of clusters of successive significant points with different cluster size in each of the 1 000 iterations was counted. Then the number of iterations out of the 1 000 iteration that had a given maximum cluster size was counted. This will be the estimation for the probability of a false detection occurring in the entire data set. In this way the overall alpha value with specific window size, individual test threshold, and cluster size was calculated. A significant cluster size threshold could then be nominated under these given parameters.

1.2 Subjects

Fourteen right-handed male young adults (19 - 26 years old) were recruited as paid volunteers. They were all in good health, without neurological problems, and free of medication that might affect their alertness. None of the subjects had ever taken part in a similar laboratory experiment. Informed consent was obtained from all participants prior to the study.

1.3 Stimuli and apparatus

The electrical stimulus was a constant current square-wave pulse generated from a DS7A digital stimulator (Digitimer, Ltd, England), delivered directly to the right index finger via a pair of skin electrodes (1 cm in diameter). Two different levels of amplitude were adopted, i.e., intense sensation without pain and moderate strong pain. The amplitude was usually 2 - 4 mA for the former and 5 - 10 mA for the latter, depending on the subjective feeling of each subject. The inter-stimulus interval was randomly distributed around 5 s [(5 ±1) s], and the duration of each stimulus was one millisecond.

1.4 Recording

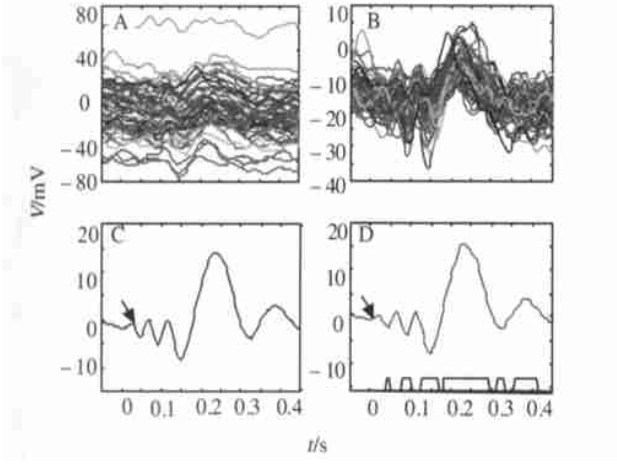
The recordings of EEG were carried out under uniform conditions (minimum noise environment, temperature 22 - 24 ℃, comfortably sat and relaxed, with eyes open) with an ANT EEG/ERP system (ANT, Inc., the Netherlands) via a 64-channel cap including 4 EOG channels (Electro-Cap International, Inc., Dayton, OH, USA). EEG data was sampled at 256 Hz together with the parameters of stimulation and event markers, with 50 trials of stimuli in a session for each amplitude, order counter-balanced. Subjects were instructed further to carefully rate the perceived painful or painless sensation 3 - 4 s after each stimulus following a continuous 0 - 10 visual rating scale (VRS). The VRS was marked with ten steps: no sensation (0), weak sensation (1), intense sensation (2), pain threshold (3), slight pain (4), mild pain (5), moderate pain (6), moderate strong pain (7), strong pain (8), very strong pain (9), and unbearable pain (10). There was a 5-minute break after the first session.

1.5 Data analysis

1.5.1 Procedures to withdraw SEP Raw data were preprocessed (visual artifact control, rereferenc-

ing to the average of all the channels, filtering with a band pass of 0 - 30 Hz, and detrending), resampled every 1/256 second around the event of interest (- 50 - 450 ms), with the eye-movement contaminated portion removed, and then exported as a matrix to MatLab (The MathWorks, Inc.). It was then subjected to the sliding-window technique with 1-point moving step. The 50-ms period immediately before stimulation was set as the control window.

1.5.2 Procedures to compare SEPs from different stimuli To compare SEPs evoked by pain and non-pain electrical stimuli, resampled EEG data were processed with a similar sliding-window technique. Within the moving window, the mean values of trials from one data set were compared with those from the other data set falling in the same window with a grouped *t*-test. Raw EEG data often drifted dramatically across trials. Thus, potential levels from different trials are highly fluctuated (Fig. 1A). This impaired the power of grouped *t*-test to pick up difference between two SEPs. We made a D-tour around this problem by calculating the difference between the mean values of each trial and the average level of the whole data set, and subtracted it from the data set. Thus, all values from different trials were detrended in a large scale and pulled to approximately the same level (Fig. 1B).



A, original single-trial data, the average levels of potential values from different trials vary a great deal and the event-related changes are hard to see; B, after detrending, the spontaneous shifting of data were eliminated and event-related changes become clear; C, SEP generated by conventional averaging method, the small peak is usually considered a component; D, result of sliding-window method. Note that the arrow-indicated small peak is actually not significant.

Figure 1 Advantages of sliding-window method

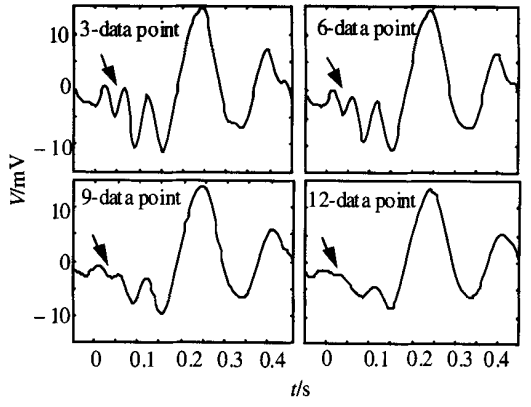
2 Results

2.1 Influence of window size on SEP calculation

Four window widths (3, 6, 9, and 12 points) were applied to generate SEP from the same data set. As shown in Fig. 2, increment of the window size lowered the temporal resolution of the population signal, yet kept the main peaks and troughs. The amplitude of the sharp peak indicated by a small arrow decreased gradually with the increment of window size, till nearly disappeared at last. Since a too-small window size will impact the noise-reducing function of the scan process, a proper window width needs to be selected according to the nature of the evoked potential under investigation. A 3-point window was selected for our real data analysis as will be shown later.

2.2 Determination of parameters

The simulated data were subjected to the sliding windows procedure for 1 000 iterations with each window size and individual test threshold. As an example, the result with one set of parameters (window width 3 and test threshold 0.005) was summarized in table 1.



The narrow peak indicated by the arrow wave decreased gradually as the window size increased from 3 to 12 data points.

Figure 2 Infuence of window size on the SEP extracted with the sliding window

Table 1 Summary of 1 000 iterations through the sliding-windows procedure with simulated data

Cluster size	Frequency	Maximal frequency	Overall alpha
1	22 858	4	1
2	5 015	329	0.996
3	1 059	504	0.667
4	153	119	0.163
5	35	33	0.044
6	6	6	0.011
7	4	4	0.005
8	1	1	0.001

Window size was set to 3 points, and individual threshold for paired *t*-test was set to 0.005.

The second column in table 1 lists the observed number of a cluster with given size. For example, within the 1 000 iterations under given condition, clusters of exactly five successive significant data points occurred 35 times. The third column shows the number of iterations in which a given cluster size turned out to be the maximal one observed. For example, in 33 of the 1 000 scanning, the largest significant cluster contained exactly 5 data points. The last column lists the overall alpha level, i.e., it estimates the probability to make a false detection from the entire data set if a given cluster size is used as the threshold. Thus, table 1 leads to the conclusion that if window size was set to 3 data points, individual test threshold to 0.005, and cluster size to 5, the

overall alpha value would be 0.044. In other words, the probability of a false detection herein was 0.044.

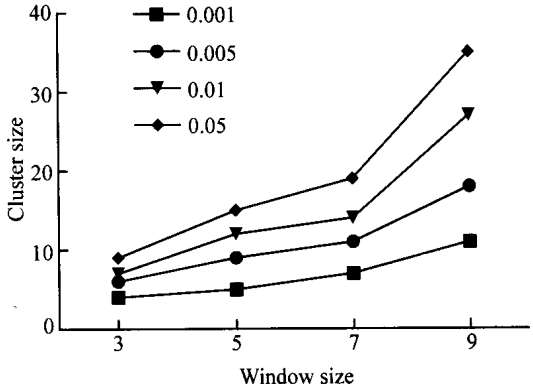
This evaluation was repeated with window widths of 3, 7, 9, and 11 points, and individual test threshold of 0.001, 0.005, 0.01, and 0.05 (Fig. 3). Larger window and looser individual test threshold leads to larger significant cluster size to keep the overall significance level satisfying. According to these results, a window size of 3 points, an individual test threshold of 0.005, and a cluster size of 5 were finally chosen as the parameters for processing real EEG data.

2.3 Components of SEP

The waveforms of SEP following non-painful and painful electrical stimuli were similar. The waveforms of pain SEP were shown in Fig. 4. Pain SEP displayed a N150 and a P250 component, maximized at Cz.

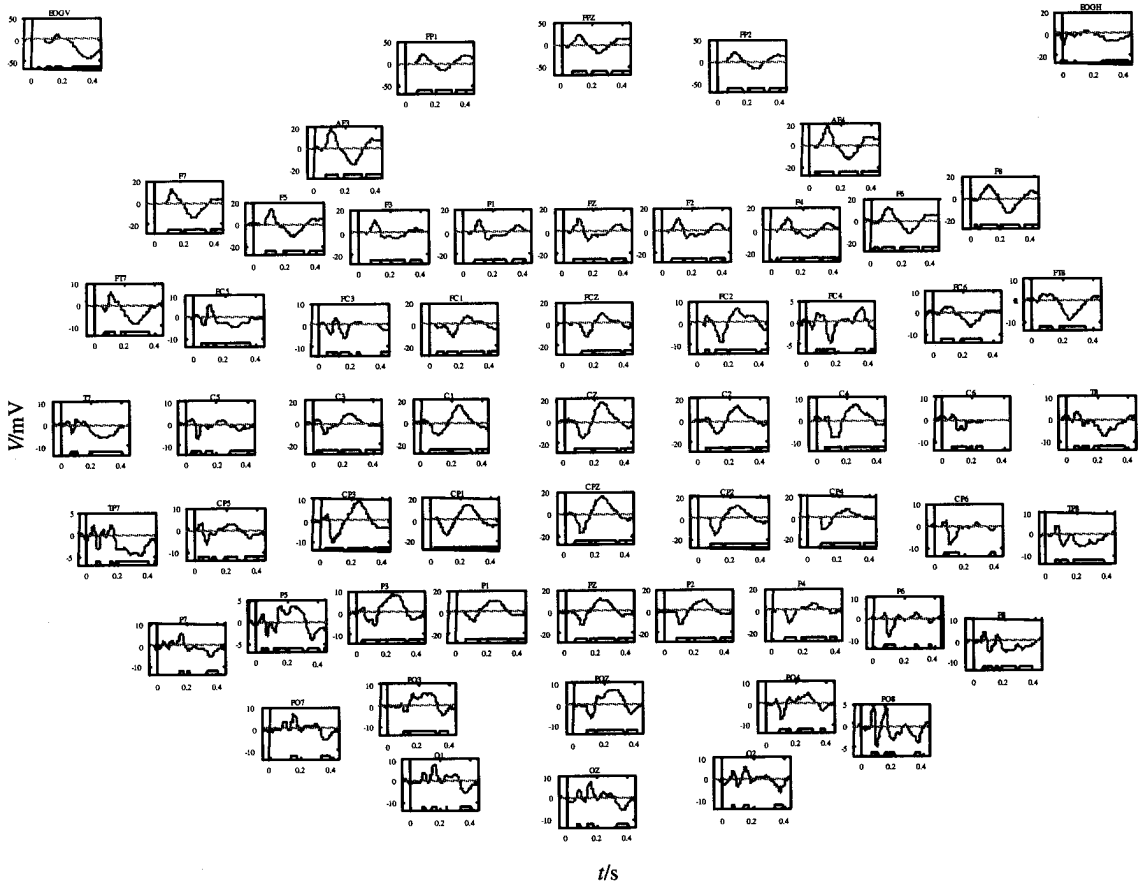
2.4 Difference between painful and painless SEPs

The subjective sensation rating for painful stimulation was 5.43 ± 0.65 ($\bar{x} \pm s$, $n = 14$), for painless stimulation 1.73 ± 0.50 ($\bar{x} \pm s$, $n = 14$). Painful or painless stimulation generated SEPs are similar in components and distribution with our experimental setup. Thus, further statistical comparison between these SEPs is necessary to reveal pain specific changes. The grouped *t*-test-based sliding windows comparison was applied for this purpose. As shown in Fig. 5, significant difference could be observed. They are mainly distributed at Fz, Cz, CPz, and Pz. The maximum difference was also located at Cz.



The cluster size increases in parallel with window size and individual test threshold.

Figure 3 Relationship between cluster size, window size, and individual test threshold



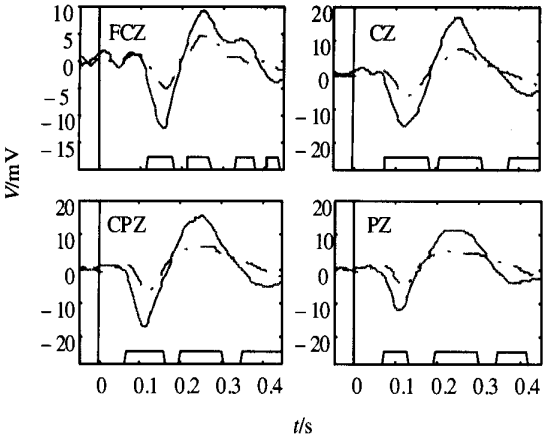
The trapezoid markers at the bottom of each subplot indicate the periods where statistically significant potential changes occur. Two components, N150 and P250, can be discriminated, especially in the channels near CZ.

Figure 4 The extracted pain SEP waveforms from one subject

3 Discussion

SEP or event-related potentials (ERP) are essential for the observation of central functional activities with very high time-resolution. However, the con-

ventional averaging method could not give any information about the statistical significance of various SEP or ERP components. Besides, it also requires a relatively large amount of trials to get a stable component from a noisy background of spontaneous EEG activity. The current study took the first step to solve these problems. As shown in Fig. 1C and 1D, some small peaks that would usually be considered a SEP component turned out to be statistically insignificant when calculated with our sliding-window method.



Pain and non-pain SEP have similar waveform and main components. The amplitudes of the former (solidline) are significantly higher than those of the latter (dash line), especially in FCZ, CZ, CPZ, and PZ channel.

Figure 5 Difference between pain and non-pain SEP of one subject in four channels

With the iteration of simulated data, we resolved the standard to judge whether a component of SEP or ERP is statistically significant by setting the threshold cluster size with a given window size and individual testing threshold. Thus, one may vary the window size according to the nature of the interested EP component and the amount of background activities or noise included in the data set. A wider window will usually remove more high-frequency changes like background noise, but it will also eliminate narrow peaks in EP waveform. On the other hand, narrower window will keep these high-frequency components of EP together with some background noise if the trial numbers are limited. Individual test threshold should also be modified according to the features of the data set. For a data with more possibility to generate significant changes, this threshold should be set more strictly, hence to raise the temporal resolution of the statistical result.

Repeated statistical comparison and repeated usage of data often make it difficult to decide theoretically how to set the significant threshold. In the method we proposed, we made a D-tour around this problem by performing the iteration with simulated data and set the threshold according to the result of simulation. This is a general methodological maneuver with large amount of data, as applied in fMRI data analysis[5].

The SEP components we detected with the sliding-window method (Fig. 4) are identical with the results from conventional averaging method, with a N150 followed by a P250 component for both non-pain SEP and pain SEP, as reported by Naka *et al*[6]. However, taking the advantage of this method, we could also describe the difference between non-pain and pain SEP. As shown in Fig. 5, the main significant difference appeared with the latency of 150 and 250 ms, where the amplitude of pain component is significantly greater than non-pain components. This is consistent with previous reports that in the case of electrical stimulation, all major components of the pain SEP are also present in non-pain SEP but with lower amplitude[7-9].

In conclusion, we report in this paper a sliding-window method for the analysis of cerebral evoked potentials. It is capable of revealing the statistical significance of SEP components, as well as comparing SEPs induced by different kinds of stimuli. We suggest that these methods should be employed in further SEP studies.

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