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Single-trial Laser-evoked Potentials Feature Extraction for Prediction of Pain Perception

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Abstract— **Pain is a highly subjective experience, and the availability of an objective assessment of pain perception would be of great importance for both basic and clinical applications. The objective of the present study is to develop a novel approach to extract pain-related features from single-trial laser-evoked potentials (LEPs) for classification of pain perception. The single-trial LEP feature extraction approach combines a spatial filtering using common spatial pattern (CSP) and a multiple linear regression (MLR). The CSP method is effective in separating laser-evoked EEG response from ongoing EEG activity, while MLR is capable of automatically estimating the amplitudes and latencies of N2 and P2 from single-trial LEP waveforms. The extracted single-trial LEP features are used in a Naïve Bayes classifier to classify different levels of pain perceived by the subjects. The experimental results show that the proposed single-trial LEP feature extraction approach can effectively extract pain-related LEP features for achieving high classification accuracy.**

I. Introduction

Pain is an unpleasant multidimensional experience associated with real or potential tissue damage [1]. Therefore, pain experience does not simply reflect sensory information but can be substantially influenced by various psycho-physiological factors. Since pain is a subjective first-person experience (IASP definition), self-report (e.g., Visual Analogue Scales [VAS]) is the gold standard for the determination of the presence, absence, and intensity of pain in clinical practice [2]. While self-report of pain provides important clinical information for the adequate treatment of pain patients in most situations, it fails to be used in some vulnerable populations (e.g., patients with disorders of consciousness, including coma, vegetative state, and minimally conscious state) [3]. Lack or any inaccuracy of pain assessment can lead to inadequate or suboptimal treatment of pain in these vulnerable patients, which may lead to various additional clinical problems (e.g., psychological distress or depression, the development of chronic pain) [4,5]. Therefore, the availability of a physiology-based and quantitative assessment of pain that complements the self-report of pain would be of great importance in clinical applications.

Nowadays, electroencephalographic (EEG) responses elicited by nociceptive laser heat pulses that selectively excite nociceptive free nerve endings in the epidermis [6] are widely adopted to investigate the peripheral and central processing of nociceptive sensory input [7,8]. Such laser-evoked potentials (LEPs) are mediated by the activation of type-II Aδ mechano-heat nociceptors [9] and spinothalamic neurons in the anterolateral quadrant of the spinal cord [8] and currently represent the best available tool to assess the spinothalamic function in patients [10]. LEPs consist of several transient responses that are time locked and phase locked to the onset of laser stimuli. The largest LEP response consists in a biphasic negative-positive complex (N2 and P2 waves, peaking at approximately 200 and 350 ms when stimulating the hand dorsum), maximal at the scalp vertex [6], and largely reflecting the activity of the bilateral operculoinsular and anterior cingulate cortex [11]. The strong relationships between the N2 and P2 amplitudes in LEPs and the intensity of pain have been well characterized [12-15], which inspires us to explore the possibility of quantitative assessment of pain based on the single-trial LEP features (i.e., latencies and amplitudes of N2 and P2 waves).

The aim of the present study was to predict the intensity of pain perception from single-trial LEP features. The key issue to be addressed is how to separate pain-related LEP features from ongoing EEG signals. In this study, a new single-trial LEP feature extraction and classification approach was developed to address the key issue involved. The proposed single-trial LEP feature extraction method combines common spatial pattern (CSP), which performs a spatial filtering to enhance the LEP waveforms, and multiple linear regression (MLR), which could automatically quantify the pain-related LEP features. Further, a Naïve Bayes classifier is used in two single-trial LEP classification problems: 1) to distinguish LEP from resting EEG, and 2) to predict different levels of pain perception. The experimental results show that the proposed single-trial LEP feature extraction and classification approach can achieve very high classification accuracy.

II. Methods

A. Experiment setup

Twenty-nine healthy participants (9 females and 20 males) aged 17-25 years (mean 22.2 ± 1.9), without a history of chronic pain, participated in the study. All participants gave written informed consent, and the local ethics committee approved the experimental procedures.

Radiant-heat stimuli were generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (Electronical Engineering, Italy). Laser pulses were directed at the dorsum of left hand on a squared area (5 x 5 cm) defined prior to the beginning of the experimental session. A He-Ne laser pointed to the area to be stimulated. The pulse duration was 4 ms, and four different

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energies (E1: 2.5 J; E2: 3 J; E3: 3.5 J; E4: 4 J) of stimulation were used. After each stimulus, the laser beam target was shifted by approximately 1 cm in a random direction, to avoid nociceptor fatigue or sensitization.

Ten laser pulses at each of the four stimulus energies (E1-E4) were delivered, in random order, for a total of 40 pulses per participant. The inter-stimulus interval was ranged between 10 and 15 s. An auditory tone was delivered 3~6 s after the presentation of each laser pulse to remind the participants to rate the intensity of the painful sensation elicited by the laser stimulus, using a VAS ranging from 0 (no pain) to 10 (pain as bad as it could be).

Participants were seated in a comfortable chair in a silent, temperature-controlled room. They wore protective goggles and were asked to focus their attention on the stimuli and relax their muscles. The EEG data were recorded using a 64-channel Brain Products system (Brain Products GmbH, Munich, Germany; pass band: 0.01–100 Hz; sampling rate: 1,000 Hz) using a standard EEG cap based on the extended 10–20 system. The nose was used as the reference channel and electrooculographic signals were simultaneously recorded from eyelids and orbits.

B. Feature selection

As low-amplitude stimulus-evoked responses are embedded in a high amount of noise caused by background ongoing EEG and other non-cortical artifacts, the signal-to-noise ratio (SNR) of LEPs is very low. Across-trial averaging, which is the most widely used approach to increase the SNR of LEPs, is not suitable for the study of pain prediction because the pain intensity varies substantially from trial to trial. Here we describe a single-trial LEP detection and quantification approach to extract LEP features for pain prediction at the single-trial level. The proposed approach consists of four steps, (i) bandpass filtering (BPF), (ii) independent component analysis (ICA), (iii) common spatial pattern (CSP), and (iv) multiple linear regression (MLR). The Flowchart of this procedure is described in Fig. 1. The four EEG processing methods in the single-trial LEP detection approach will be detailed below.

1) Bandpass filtering (BPF)

Continuous EEG data were band-pass filtered between 1 and 30 Hz because the laser-evoked EEG activity is mainly observed in this frequency range [16]. EEG trials are then extracted using an analysis window of 1,000 ms (500 ms pre-stimulus and 500 ms post-stimulus) and baseline corrected using the pre-stimulus interval.

2) Independent component analysis (ICA)

Next, EEG trials contaminated by eye-blinks and movements are corrected using the ICA algorithm [17-19]. In all datasets, these independent components have a large EOG channel contribution and a frontal scalp distribution is rejected and the remaining independent components are used to reconstruct EEG trials.

3) Common spatial pattern (CSP)

Although ICA, as a popular spatial filtering method, is effective in isolating EOG and EMG artifacts, its performance in finding components related to brain activity is still not satisfactory [20]. In the study, we applied another popular spatial filtering method, CSP, for separating laser-evoked EEG activity. The idea of CSP is to find a spatial filter such that the projected signals will have maximum differences in variance between two classes. CSP has been shown to be a powerful technique in brain-computer interface research to discriminate different mental intentions [21]. If the pre-stimulus and post-stimulus EEG waveforms are regarded as two classes and fed into CSP, the components with the maximum discriminative power between pre-stimulus and post-stimulus activities can be identified from two classes. The components extracted from the post-stimulus activity can be considered as the stimulus evoked components and will be used to reconstruct the stimulus evoked EEG activity. When applying CSP in detecting single-trial LEP waveforms, the procedures and algorithms can be described as below. First, pre-stimulus and post-stimulus EEG waveforms of the same data length form two classes, and the two classes of waveforms recorded over all channels from the same trial will generate two matrices $\mathbf{X}_{\text{pre}}, \mathbf{X}_{\text{post}} \in \mathrm{P}^{N\times T}$, where N is the number of channels and T is the number of samples per channel. CSP solves the following generalized eigenvalue problem

$$\left\langle \mathbf{X}_{\text{post}} \mathbf{X}_{\text{post}}^{T} \right\rangle \mathbf{w} = \lambda \left\langle \mathbf{X}_{\text{pre}} \mathbf{X}_{\text{pre}}^{T} \right\rangle \mathbf{w} \qquad (1)$$

to find the generalized eigenvector or the projection vector $\mathbf{w}$ to simultaneously minimalize the variance of $\mathbf{X}_{\text{pre}}$ and maximize the variance of $\mathbf{X}_{\text{pre}}$, where $\langle \cdot \rangle$ is the averaging operator for trials in the same class and λ is the generalized eigenvalue. The projection $\mathbf{W} = [\mathbf{w}_1, \cdots, \mathbf{w}_N] \in \mathrm{P}^{N\times N}$, where $\mathbf{w}_1, \cdots, \mathbf{w}_N$ are the eigenvectors obtained from (1), is called as the spatial filter, $\mathbf{A} = \mathbf{W}^{-1} \in \mathrm{P}^{N\times N}$ is called as the spatial pattern. In this study, three eigenvectors corresponding to the largest eigenvalues were selected for reconstruction of the EEG waveforms of all channels.

4) Multiple linear regression (MLR)

The combination of BPF, ICA, and CSP can effectively improve the SNR of single-trial LEPs, but the measurement of LEP latency and amplitudes require manual operation and has the risk of uncertainty caused by researchers or surgeons. For a more objective measurement, we apply a multiple linear regression method [22] to automatically estimate the amplitudes and latencies of N2 and P2 from single-trial LEP waveforms from Cz channel, which shows the maximum amplitude of N2-P2 complex in the time domain. Denote $y_N(t)$ and $y_P(t)$ as the templates of N2 and P2 waves, which can generally be obtained as the averages of all trials of each participant, and $f(t)$ as the signal trial LEP waveforms that varies as a function of time t. The MLR method describes $f(t)$ as the weighted sum of the shifted versions of averages of N2 and P2 as follows

$$f(t) = a_N y_N(t + l_N) + a_P y_P(t + l_P), \qquad (2)$$

where a_N and a_P are the weights of N2 and P2 averages, and l_N and l_P are the latency shift values of the N2 and P2 templates, respectively. Since the N2 and P2 peaks of the LEPs reflect the activity of the different neural generators [11], and their amplitudes can be differentially modulated by

several experimental factors (e.g., spatial attention and probability of perception) [23,24], we model the N2 and P2 waves separately, thus avoiding the assumption that all generators contributing to the LEP responses covary linearly [22]. By using the Taylor expansion, the MLR model can be written as

$$\begin{aligned} f(t) &\approx a_N y_N(t) + l_N a_N y'_N(t) + a_P y_P(t) + l_P a_P y'_P(t) + \varepsilon \\ &= \beta_1 y_N(t) + \beta_2 y'_N(t) + \beta_3(t) y_P(t) + \beta_4 y'_P(t) + \beta_5, \end{aligned} \quad (3)$$

where $y'_N(t)$ and $y'_P(t)$ are the temporal derivatives of N2 and P2 averages, respectively, and ε is the residual term. Thus the single trial LEP waveform is approximated using the sum of the weighted averages of the N2 and P2 waves and their respective temporal derivatives. All the MLR coefficients β_1, β_2, $\cdots$, β_5 are used as the features in the following classification.

C. Pattern classification

The Naïve Bayes classifier is applied for prediction of pain perception. With the assumption of conditional independence between the features given the class, the Naïve Bayes method can classify the sample as a member of a class with giving the highest probability score evaluated by its features.

Leave one out cross validation (LOOCV) is used throughout the single-trial LEP feature extraction and classification. Suppose there are N LEP trials for one participant. The LOOCV is applied by using N-1 trials as the training set and the remaining one trial from the same participant as the test sample. This procedure will be repeated N times such that each trial for this individual has been used once as the test sample.

It should be noted that the LOOCV strategy is applied not only for selecting tuning parameters of the classifier, but also for single-trial feature extraction. In each repetition, the CSP filtering is performed on the training set and the resulting spatial filter is applied to both training and testing trials to reconstruct single-trial LEP activity. For MLR analysis, the averages of N2 and P2 waves and their temporal derivatives are calculated from the training trials and used as a basis set in the MLR for both the training and testing trials. The MLR coefficients β_1, β_2, $\cdots$, β_5 for both training and testing trials are used as the features for classification.

III. Results

A. Single-trial LEP Extraction

Figure 1 describes the whole process of single-trial LEP analysis. Four steps are included in the procedure, which are BPF and ICA, CSP and MLR. Step by step, the LEP features, which decode the information of pain intensity, would be retained and enhanced, and the unwanted noise would be removed.

To evaluate the denoising effect of each step in the proposed single trial LEP feature extraction approach, a similarity index (SMI), which is the power ratio between the "LEP-like" data in a testing trial and the residual, is defined. Let $\bar{z}$ be the average of the training trials and z_k be the kth testing trial. The SMI is calculated as

$$SMI = 10 \log_{10}\left(\frac{\sigma^2(P)}{\sigma^2(R)}\right), \quad (4)$$

where $P = \frac{\bar{z}^T z_k}{\bar{z}^T \bar{z}} \bar{z}$ is the orthogonal projection of z_k on to $\bar{z}$ and $R = z_k - P$ is the residual part. A large SMI means testing trial z_k is more similar to the average $\bar{z}$ (which assumed to be a clean LEP signal because noise is smoothed out by across-trial averaging), and vice versa. In Fig. 1, the value of SMI is gradually increased by the operation in each step. One-way ANOVA results indicate that the SMI has been significant improved by MLR ($p<0.01$).

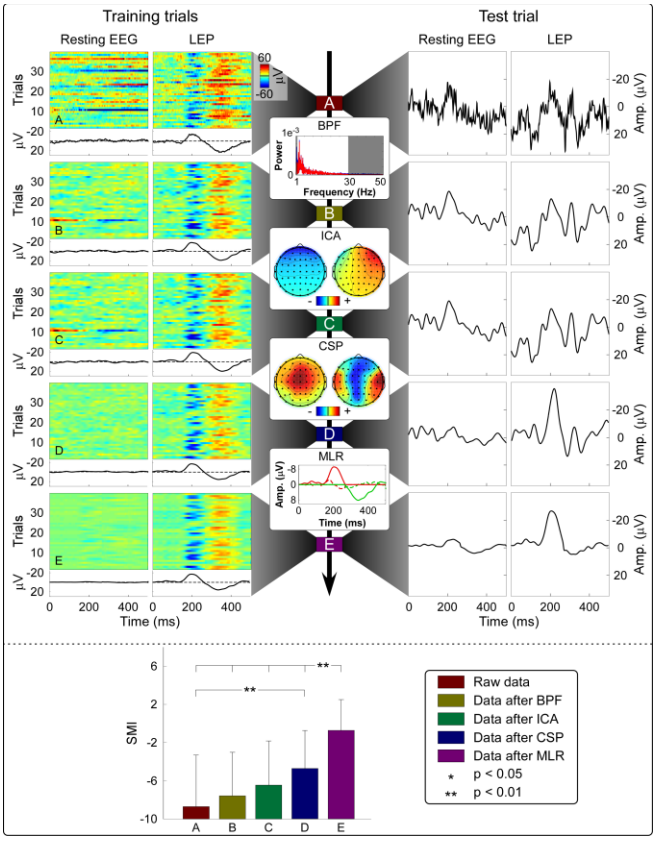

Figure 1. Flowchart describing the procedure to enhance the SNR of single-trial LEP responses.
Top panel: The EEG responses (A, both resting EEG and LEP responses, and for both training and test), measured at Cz, were band-pass filtered between 1 and 30 Hz (step 1). In the training dataset, noise trials in the filtered EEG responses (B) were corrected using ICA algorithm (step 2), and the ICA corrected EEG responses (C) were spatial filtered using CSP algorithm (step 3). The spatial filtered EEG responses (D) were further modeled using a MLR analysis (step 4). This procedure generated both single-trial EEG responses with enhanced SNR (E) and the corresponding filter models (ICA, CSP, and MLR models), which were applied on the testing data to significantly enhance the SNR of testing data (from top to bottom).
Bottom panel: The effect of each step in the described single-trial analysis procedure was tested using one-way repeated-measures ANOVA on SMI.

B. Prediction of Pain Perception

Basically, two major problems exist in the prediction of pain perception. One is to distinguish LEP from resting EEG. The other problem is to predict the intensity of pain perception from single-trial LEP. With the proposed method, the classification accuracy for LEP vs. resting EEG is 84.39±

8.11%. And the accuracy in the classification of two level pain intensity (high pain: VAS > 5; low pain: VAS ≤ 5) is 84.83 ± 7.41%. The results are quite close to each other.

Furthermore, a more complicated five-level classification problem is studied. The intensity of pain perception for each single trial LEP is divided into four levels (I1: VAS < 2.5, I2: 2.5 ≤ VAS <5, I3: 5 ≤ VAS <7.5, I4: VAS ≤ 7.5), and resting EEG is also considered as one level of no pain (I0).

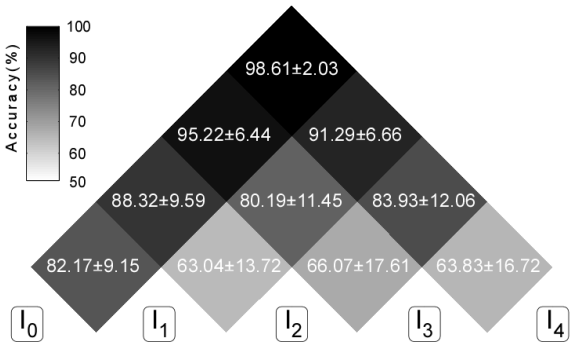

Figure 2. The pairwise classification accuracies with their standard deviation for the five classes, which are resting EEG (I0), I1, I2, I3 and I4.

Fig. 2 shows the pairwise classification results of the five-level classification. It can be seen from Fig. 2 that, if the two levels of pain perception are not adjacent, the classification results are very good (> 80%). For several pairs of comparison (I0 vs. I3; I0 vs. I4; I1 vs. I4), the classification accuracy is higher than 90%. For classification of two adjacent levels of pain intensity, the accuracy is in the range of 80~90% for I0 vs. I1, and in the range of 60%~70% for I1 vs. I2, I2 vs. I3 and I3 vs. I4. Overall, it is easy to distinguish I0 (the resting EEG) from other levels of pain elicited by laser stimulation.

IV. Conclusion

In this study, a new single-trial LEP feature extraction method, which combines CSP and MLR, is proposed for classification of pain perception. CSP could enhance the quality of LEP features through a spatial filtering, while MLR was applied to automatically estimate the amplitudes and latencies of N2 and P2 from single-trial LEP waveforms, which avoids the risk of uncertainty caused by manual operation. We found that both the classification accuracies for resting EEG vs. LEP and high pain vs. low pain are higher than 80%. Moreover, the performance of the single-trial LEP feature extraction method was tested in the classification of five levels of pain perception, and the results showed that the classification accuracy is larger than 80% in most of paired comparisons. This method is expected to provide an objective and quantitative method for the prediction of pain perception, and, further, to contribute to clinical practice.

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