A New Approach for Single-trial Detection of Laser-evoked Potentials and its Application to Pain Prediction

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Abstract—**Single-trial detection of evoked brain potentials is essential for many research topics in neural engineering and neuroscience. In present study, a novel approach, which combines common spatial pattern (CSP) and multiple linear regression (MLR), is proposed to for single-trial detection of pain-related laser-evoked potentials (LEPs). The CSP method is effective in separating laser-evoked EEG response from ongoing EEG activity, while MLR makes an automatic and reliable estimation of the amplitudes and latencies of N2 and P2 from single-trial LEP waveforms. The MLR coefficients are further used for the prediction of pain perception, which is of great importance for both basic and clinical applications. The prediction is performed with both binary (classification of low pain and high pain) and continuous (regression on a continuous scale from 0 to 10) outcomes. The results show that the proposed methods could provide reliable performance at both with- and cross-individual levels.**

Keywords-common spatial pattern; laser-evoked potentials; multiple linear regression; pain prediction; single-trial analysis

I. INTRODUCTION

Pain is a perception signaled by the real or potential tissue damage [1]. Pain assessment allows the healthcare providers to characterize the pain, clarify its impact, and evaluate other medical and psychosocial problems, which is important for the adequate treatment of pain patients. Since pain is a subjective first-person experience, self-report is the gold standard for the determination of the presence, absence, and intensity of pain in clinical practice [2]. However, it fails in some non-communicative 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 depression, the development of chronic pain) [4, 5].

Recently, laser evoked potential (LEP) has been introduced to investigate the peripheral and central processing of nociceptive sensory input [7, 8]. 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 [9]. The strong relationships between the N2 and P2 amplitudes in LEPs and the intensity of pain have been well characterized [10-13], 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 serious noise contamination makes the pain prediction through LEP difficult. The response of the single-trial LEP is embedded in the large amplitude of the background ongoing EEG and other non-cortical artifacts. Hence, the key issue, addressed in pain prediction from single-trial LEP, is how to effectively remove the noise and extract reliable features from the single trial LEP. In this study, a new single-trial LEP feature extraction approach, which combines common spatial pattern (CSP) and multiple linear regression (MLR), was developed to address the key issue involved. 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 [15]. CSP performs a spatial filtering to simultaneously enhance the LEP waveforms and remove background ongoing EEG greatly. And MLR could automatically quantify the pain-related LEP features. After the feature extraction, both classification and regression is performed for the binary and continuous pain prediction at both with- and cross-individual level. The experimental results show that the proposed single-trial LEP feature extraction method can effectively remove the noise and achieve a reliable performance for pain prediction. The results from several classifiers and regression methods show no significant different in pain prediction.

*Research supported by HKU CRCG Seed Funding for Applied Research (201209160022) and a GRF grant from the Research Grants Council of the Hong Kong SAR (HKU785913).

978-1-4799-0434-1/13/$31.00 ©2013 IEEE ICICS 2013

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.

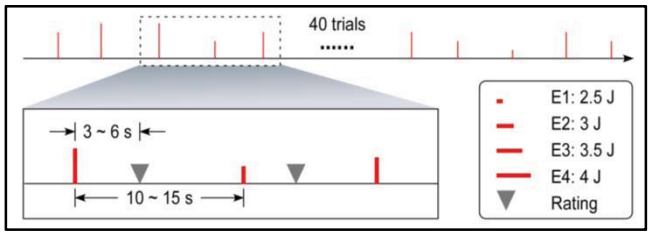

Figure 1. Experiment design and laser evoked brain potentials.

As illustrated in Fig. 1, Laser pulses (Electronical Engineering, Italy) were directed at the dorsum of left hand on a squared area (5 x 5 cm). Ten laser pulses at each of the four stimulus energies (E1: 2.5 J; E2: 3 J; E3: 3.5 J; E4: 4 J) were delivered randomly for a total of 40 pulses per participant. The pulse duration was 4 ms, and the inter-stimulus interval was ranged between 10 and 15 s. After each stimulus, the laser beam target was shifted by approximately 1 cm in a random direction, to avoid nociceptor fatigue or sensitization. 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). 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

To extract the reliable LEP features for pain prediction, common spatial pattern (CSP) and multiple linear regression (MLR) was used jointly. The whole process is as follows. First, all data was filtered by a bandpass filter (BPF) with the cut-off frequencies 1 and 30Hz. Second, EEG trials contaminated by eye-blinks and movements are corrected using Independent component analysis (ICA) algorithm. Then, CSP was adopted to further enhance the SNR of LEP responses by retrieving stimulus-evoked EEG responses from spontaneous EEG activity. Finally, MLR was used to automatically parameterize single-trial LEP responses using MLR coefficients, which captured the variability of single-trial N2 and P2 latency and amplitude. The details for CSP and MLR are as follows.

1) 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 [14]. In the study, we applied another popular spatial filtering method, CSP, for separating laser-evoked EEG activity. In the CSP algorithm, the pre-stimulus and post-stimulus EEG waveforms are regarded as two classes. Then the components with the maximum discriminative power between pre-stimulus and post-stimulus activities can be identified from two classes. The components corresponding to the maximum variance of 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 $\boldsymbol{X}_{\text{pre}}, \boldsymbol{X}_{\text{post}} \in \mathbb{R}^{N\times T}$, where N is the number of channels and T is the number of samples per channel. CSP solves the following generalized eigenvalue problem

$$\left\langle \boldsymbol{X}_{\text{post}} \boldsymbol{X}_{\text{post}}^{T} \right\rangle \boldsymbol{w} = \lambda \left\langle \boldsymbol{X}_{\text{pre}} \boldsymbol{X}_{\text{pre}}^{T} \right\rangle \boldsymbol{w} \tag{1}$$

to find the projection vector $\boldsymbol{w}$, which could simultaneously minimalizes the variance of $\boldsymbol{X}_{\text{pre}}$ and maximize the variance of $\boldsymbol{X}_{\text{pre}}$, where $\langle\cdot\rangle$ is the averaging operator for trials in the same class and λ is the generalized eigenvalue. Three eigenvectors corresponding to the largest eigenvalues were selected for reconstruction of the EEG waveforms of all channels.

2) 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 [16] to automatically estimate the amplitudes and latencies of N2 and P2 from single-trial LEP waveforms from Cz. 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, and performs the Taylor expansion as follows

$$\begin{aligned} f(t) &= a_N y_N(t+l_N) + a_P y_P(t+l_P) \\ &\approx a_N y_N(t) + l_N a_N y'_N(t) + a_P y_P(t) + l_P a_P y'_P(t) + \varepsilon \\ &= \beta_1 y_N(t) + \beta_2 y'_N(t) + \beta_3(t) y_P(t) + \beta_4 y'_P(t) + \beta_5, \end{aligned} \tag{2}$$

where a_N and a_P are the weights of N2 and P2 averages, l_N and l_P are the latency shift values of the N2 and P2

templates, $y'_N(t)$ 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.

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

$$SMI = 10\log_{10}\left(\frac{\sigma^2(P)}{\sigma^2(R)}\right), \tag{3}$$

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.

C. Pattern Recognition

In this study, the work of pain prediction includes two parts, which are classification of low pain and high pain, and regression of pain perception intensity. The MLR coefficients β_1, β_2, $\cdots$, β_5 were extracted from both training and testing trials (see Cross validation section for details), and were used as LEP features for subsequent pain prediction.

For the low pain and high pain classification, LEP trials were labeled into two categories according to the pain perception ratings for each participant (low pain: VAS < 5, and high pain: VAS ≥ 5). Three classifiers are investigated for the classification, which were Naïve Bayes, LDA and SVM. The classification accuracy is used to evaluate the results.

Similarly, three regression methods were adopted to model the relationship between single-trial LEP features and the corresponding intensity of pain perception for continuous prediction of the pain perception from the LEP features. Beside the Ordinary Least Square (OLS) linear estimator, we also tested the performance of lasso and ridge regression. Both ridge and lasso estimators imposed a constraint (ridge: L2 norm; lasso: L1 norm) on the regression coefficients to decrease the prediction variance at the expense of slightly increased bias and to address the problem of multicolinearity. The prediction performance was evaluated using the Mean Absolute Error (MAE), which can be written as follows:

$$MAE = \frac{1}{N}\sum_{n=1}^{N}\left|I_n - \hat{I}_n\right|, \tag{4}$$

where I_n and $\hat{I}_n$ are the real and predicted intensity of pain perception for trial n, and N is the number of trials of each participant for within-individual prediction, or of all participants for cross-individual prediction.

Leave-one-out cross validation (LOOCV) was used in two stages of data analysis: (1) single-trial LEP feature extraction (CSP and MLR) and (2) prediction of pain perception (classification and regression). For example, when we perform CSP analysis, the spatial filter was obtained from all training trials, and applied to both training and test trials to enhance their SNRs. It should be noted that different LOOCV strategies were adopted to predict pain perception at both the within- and cross-individual levels. In the present study, there were 29 participants with 40 LEP trials each. At the within-individual level, LOOCV was achieved by dividing 40 LEP trials into 39 training trials and 1 test trial, and the same procedure was repeatedly performed 40 times to make sure that each LEP trial was used as the test trial for once. At the cross-individual level, LOOCV was achieved by dividing 29 subjects into 28 training subjects and 1 test subject, and similarly, the same procedure was repeatedly performed 29 times to make sure that each subject was used as the test subject once (all LEP trials from this subject were used as test trials). Considering the substantial inter-individual variability of both LEP features and pain perception (e.g., one participant has high LEP responses and low pain perception, while another participant may have low LEP responses and high pain perception), both single-trial LEP features and single-trial ratings of pain perception intensity were normalized for each participant at the cross-individual level.

III. Results

A. Feature extraction

Figure 2 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. As shown in the bottom panel of Fig. 2, 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 ($p < 0.01$).

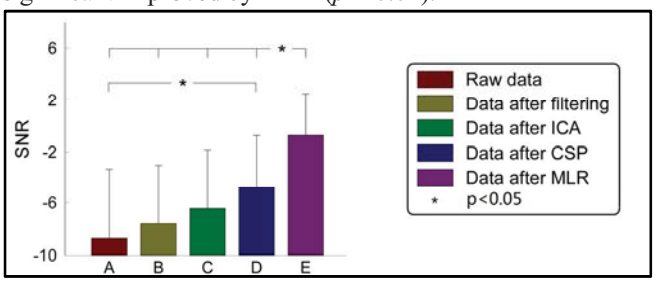

Figure 2. The SMI of four steps (BPF, ICA, CSP and MLR) in the single-trial analysis procedure One-way repeated-measures ANOVA was performed.

B. Classification of low pain and high pain

Table I summarized the classification accuracy for classification of low pain and high pain using MLR coefficients. Naïve Bayes and SVM achieved the highest prediction accuracy (86.29 ± 8.36 and 80.86 ± 8.16) at within- and cross-individual levels respectively. As revealed by one-way repeated-measures ANOVA, no significant difference of prediction accuracy among different classifiers at both within- and cross-individual levels (within-individual classification, $F = 0.14$, $p = 0.87$; cross-individual classification, $F < 10^{-6}$, $p = 1.00$).

TABLE I. PERFORMANCE OF DIFFERENT CLASSIFIERS (NAÏVE BAYES, LDA, AND SVM; ASSESSED USING PREDICTION ACCURACY) TO PREDICT THE INTENSITY OF PAIN PERCEPTION (THE BEST PERFORMANCE FOR WITHIN- AND CROSS-INDIVIDUAL LEVELS WAS RESPECTIVELY MARKED IN BOLD). GAUSSIAN RADIAL BASIS FUNCTION WAS USED AS THE KERNEL IN SVM.

	Within-individual	Cross-individual
Naïve Bayes	**86.29±8.36**	80.26±8.22
LDA	81.98±10.88	80.69±8.34
SVM	84.66±9.65	**80.86±8.16**

C. Regression of pain perception intensity

The performance of different estimators (OLS, ridge, and lasso) to estimate the regression model was summarized in Table II. At within-individual level, both ridge and lasso estimators outperformed OLS estimator slightly, while their performance was almost identical at cross-individual level. As revealed by one-way repeated-measures ANOVA, there was no significant difference of prediction performance (assessed using MAE) among different regression estimators at within- and cross-individual levels (within-individual regression, $F = 1.25$, $p = 0.29$; cross-individual regression, $F = 0.16$, $p = 0.86$). It should be noted that the performance of ridge or lasso is highly dependent on the hyper-parameters used, which are normally selected using the cross-validation that is very time-consuming.

TABLE II. PERFORMANCE OF DIFFERENT CLASSIFIERS (NAÏVE BAYES, LDA, AND SVM; ASSESSED USING PREDICTION ACCURACY) TO PREDICT THE INTENSITY OF PAIN PERCEPTION (THE BEST PERFORMANCE FOR WITHIN- AND CROSS-INDIVIDUAL LEVELS WAS RESPECTIVELY MARKED IN BOLD). GAUSSIAN RADIAL BASIS FUNCTION WAS USED AS THE KERNEL IN SVM.

	Within-individual	Cross-individual
OLS	1.031±0.1	1.821±0.2
Ridge	1.014±0.1	1.821±0.2
Lasso	**1.013±0.1**	**1.821±0.2**

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. Our results showed that the proposed approach provided an accuracy of 86.3 ± 8.4% (within-individual) and 80.3 ± 8.5% (cross-individual) for classification of low pain and high pain using Naïve Bayes classifier, and an MAE of 1.031 ± 0.136 (within-individual) and 1.821 ± 0.202 (cross-individual) for regression on a continuous scale from 0 to 10 using OLS. The results from other classifiers and regression methods show no significant difference. The proposed approach may help establish a fast and reliable tool for automated prediction of pain, which could be potentially adopted in various basic and clinical applications.

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