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DETECTION OF PAIN FROM NOCICEPTIVE LASER-EVOKED POTENTIALS USING SINGLE-TRIAL ANALYSIS AND PATTERN RECOGNITION

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ABSTRACT

Pain is an unpleasant multidimensional experience, which could be largely influenced by various peripheral and cognitive factors. Therefore, the pain experience and the related brain responses exhibit high variability from time to time and from condition to condition. The availability of an objective assessment of pain perception would be of great importance for both basic and clinical applications. In the present study, we combined single-trial analysis and pattern recognition techniques to differentiate nociceptive laser-evoked brain responses (LEPs) and resting electroencephalographical recordings (EEG). We found that quadratic classifier significantly outperformed linear classifier when separating LEP trials from resting EEG trials. Across subjects, the error rates of quadratic classifier, when it was tested on all trials (I1+I2), trials with low ratings (I1), and trials with high rating (I2), are respectively 17.5±3.5%, 20.6±4.3%, and 9.1±4.9%.

Index Terms— Pain perception, Single-trial analysis, Pattern recognition, quadratic classifier.

1. INTRODUCTION

The interpretation of the nociceptive input ensues in the conscious experience of pain. However, pain is an unpleasant multidimensional experience [1], which does not simply reflect sensory information but can be substantially influenced by various psycho-physiological factors. Because of a unique combination of peripheral (e.g. time-dependent fluctuations in baseline skin temperature, variability in the number of activated nociceptive fibres) and cognitive factors (e.g. fluctuations in vigilance, attention and task strategy) [2-4], the pain related brain responses exhibit high variability [5-6]. Thus, the diagnosis and evaluation of pain still heavily (often solely) rely on subjective, and possibly biased, verbal reports of pain in clinical applications. In addition, some patients (e.g., in minimally conscious state) are unable to communicate their pain. For these reasons, the availability of an objective assessment of pain perception that complements the subjective report would be of paramount importance in both drug discovery and clinical practice [7].

Electrophysiological brain responses elicited by nociceptive laser stimuli (laser-evoked potentials, LEPs) are considered the best tool for assessing function of nociceptive pathways in physiological and clinical studies [8-10], because laser heat pulses excite selectively $A_\delta$ and $C$ fibre free nerve endings in the superficial skin layers (i.e. without coactivating $A_\beta$ mechanoreceptors) [11-12]. LEPs have been shown to be related to the activation of slow-conducting type-II $A_\delta$ mechano-heat nociceptors [13] and spinthalamic neurons located in the anterolateral quadrant of the spinal cord [14-15]. LEPs comprise a number of waves that are time locked to the onset of the stimulus. The largest response is a negative–positive vertex potential (N2 and P2 waves, peaking at approximately 200 and 350 ms when stimulating the hand dorsum) [11].

The well-characterized relationship between the intensity of pain perception and the amplitudes of N2 and P2 of LEPs has been repeatedly confirmed by different research groups [6, 8, 16-17]. Therefore, it should be in principle be possible to predict the detection of pain from features of N2 and P2 in LEPs.

The aim of this study is to differentiate LEP trials and resting EEG trials using the combination of single-trial analysis and pattern recognition techniques. The aim was achieved through the following steps: (1) estimating single-trial features of N2 and P2 in LEPs using advance single-trial analysis technique [18]; (2) extracting important features that would be optimally used to separate LEP trials from resting EEG trials; (3) classifying the extract important features using both linear and quadratic classifiers [19]; and (4) evaluating the performance of both classifiers using both error rate and receiver operator characteristic (ROC) curve.
2. METHODS

2.1. Experimental design and EEG recording

The analyses of this study were performed on the dataset collected for a previous study [20]. Six healthy subjects (four men and two women) aged 24-42 yr (mean 29 ± 6) participated in the study. All participants gave written informed consent, and the local ethics committee approved the experimental procedures.

Noxious 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). These laser pulses activate directly and selectively nociceptive terminals located in the most superficial skin layers [21-22]. Laser pulses were directed to the dorsum of the right and left hands, in two separate sessions performed on the same day. Four different stimulus energies were used (E1: 2 J; E2: 2.5 J; E3: 3 J; E4: 3.5 J).

Stimuli were delivered in trains consisting of three consecutive stimuli (S1, S2, S3) of identical energy (E1, E2, E3 or E4), separated by a constant 1-s inter-stimulus interval. The time interval between two consecutive trains was 20 s. Three to six seconds after the end of each train, participants were asked to rate verbally the intensity of the pricking sensation elicited by each of the three laser stimuli, using a numerical rating scale ranging from 0 to 10, where 0 was defined as “no pain” and 10 was defined as “pain as bad as it can be” [23]. In each session, twenty trains at each of the four energies (E1–E4) were delivered, in random order, for a total of 80 trains per session. Note that the LEP responses elicited by S1 were used in this study.

The EEG was recorded continuously using seven Ag-AgCl electrodes placed on the scalp according to the International 10-20 system (Fz, Cz, Pz, C3, C4, T3, and T4), using the nose as a common extracephalic reference. The EEG data were preprocessed using Letswave [24], a free signal-processing toolbox developed in Delphi 7.0, and EEGLAB [25], an open source toolbox running under the MATLAB (version 7.12, Mathworks, Natick, MA, USA) environment.

Continuous EEG data were band-pass filtered from 1 to 30 Hz. EEG epochs were extracted using a window ranging from 0.5 s before to 1 s after the onset of the first stimulus (S1) and baseline corrected using the pre-stimulus time interval. Trials contaminated by eye-blinks and movements were corrected using an independent component analysis (ICA) algorithm. After artifacts rejection, EEG epochs were classified in two categories (I1–I2) according to the intensity of the painful percept elicited by the stimulus. This was achieved by rescaling the ratings of each participant between 0 and 100, defining 0 as the smallest pain rating and 100 as the largest pain rating of that participant [20].

For each participant, trials were classified in two categories (I1: ≤ 50, I2: > 50).

2.2. Single-trial feature estimation

Multiple linear regression with dispersion term (MLRd), which has been proven to provide an accurate estimation of single-trial parameters, could be able to capture the variability of the latency, amplitude, and morphology of the LEP waveform [18]. This variability can be described as follows:

\[ f(t) = k_N y_N (s_N t + a_N) + k_P y_P (s_P t + a_P) \]

where \( f(t) \) is a single-trial LEP waveform that varies as a function of time \( t \). \( f(t) \) can be modeled by the sum of the varied version of N2 wave \( (k_N y_N (s_N t + a_N)) \) and P2 wave \( (k_P y_P (s_P t + a_P)) \). \( k_N \) and \( k_P \) are the weighted constants of N2 wave and P2 wave, while \( a_N \) and \( a_P \) are the latency shift values of the N2 wave and P2 wave respectively. \( s_N \) and \( s_P \) are the time dispersion coefficients that determine the compression ratios of the width of N2 and P2 waves of single trial ERP compared to those of the average ERP, respectively.

Applying MLRd approach on both the real LEP dataset and the resting EEG dataset from the same subjects, we estimated not only the single-trial parameters of N2 and P2 peaks, but also the coefficients \( (\beta_{N1}, \beta_{N2}, \beta_{N3}, \beta_{P1}, \beta_{P2}, \beta_{P3}, \beta_C) \) that weight the fit of all regressors in MLRd to the single-trial LEP responses. Note that \( \beta_{N1}, \beta_{N2}, \beta_{N3}, \beta_{P1}, \beta_{P2}, \) and \( \beta_{P3} \) would be able to capture the variability of \( k_N, a_N, s_N, k_P, a_P, \) and \( s_P \), and \( \beta_C \) was used to capture the variability of constant vector (i.e., vector \( 1 \)) within the specified time interval.

2.3. Feature extraction

Feature extraction was used to reduce the dimension of the feature vector (all coefficients estimated from the previous step) by transforming the original feature space (\( R^N, N=14 \) in this study, 7 for N2 and 7 for P2) to a reduced feature space (\( R^D, D=2 \) in this study).

\[ z = W(\beta) \]

where \( W(.) \) is the estimated transformation, \( \beta \) is the original feature vector (\( N=14 \)), and \( z \) is the extracted feature vector (\( D=2 \)).

In this study, the feature extraction was performed based on the Bhattacharyya distance with Gaussian distributions [19], and the following feature classification was achieved based on the extracted feature vector (\( z \)) rather than the original
feature vector (β). The advantages of this feature extraction are twofold: (1) the computation complexity of the feature classification will be greatly decreased by reducing the dimension of the feature vector, and (2) the classification accuracy will be increased by preventing possible overfitting of the contaminated noise.

2.4. Pattern recognition

In the present study, both linear and quadratic pattern classifiers were used. The linear pattern classifier, also called minimum Mahalonobis distance classifier, was represented by the characteristic that the decision boundaries between compartments in the feature space were linear lines or planes. In contrast, the quadratic pattern classifier, which, in theory, was Bayes classifier with uniform cost function and with normally distributed feature vectors, was represented by the characteristic that the decision boundaries between compartments in the feature space were quadratic curves.

2.5. Evaluation

The performance of the both linear and quadratic pattern classifiers was evaluated using error rate, which was the global classification error. The global classification error involved two types of errors: type I error (false positive) and type II error (false negative). The optimal trade-off between both types of errors was assessed using a receiver operating characteristic curve (ROC curve).

3. RESULTS

3.1. Single-trail feature estimation

Figure 1 showed the N2 and P2 regressors obtained from a representative LEP waveform and the principal component analysis decomposition. For N2 and P2 respectively, three regressors (PC1, PC2 and PC3), which captured the variability of amplitude, latency, and morphology, were obtained, and were then used to fit each single-trial LEP or resting EEG waveform to obtain their respective regressor coefficients (β). In the right panel of this figure, we displayed the fitted effect of all regressors to both LEP trials and resting EEG trials.

Figure 2 showed the fitted coefficients (β) of all regressors of both LEP trials (top left part) and resting EEG trials (bottom left part) from a representative subject. After the feature extraction based on the Bhattacharyya distance with Gaussian distributions, two important features were obtained and displayed in the middle panel of this figure. Note that, in the extracted feature space, features of resting EEG trials (marked in blue cross) were distributed near zero in both axis, whereas most features of LEP trials (marked in red asterisk) were distributed far from zero (especially for feature 1). Such a feature extraction would be able to extract most important features to distinguish LEP trials from resting EEG trials, and to eliminate the contaminated noise in the original feature space.
3.3. Pattern recognition

Both Figure 2 and Table 1 provided evidence indicating that quadratic classifier significantly outperformed linear classifier in the present study. Using quadratic classifier to separate LEP trials from resting EEG trials, the error rates were 17.5±3.5%, 20.6±4.3%, and 9.1±4.9% across subjects for all trials (I1+I2), trials with low ratings (I1), and trials with high rating (I2) respectively (Table 1).

Table 1. The classification performance (error rate) on all trials (I1+I2), trials with low ratings (I1), and trials with high ratings (I2) using both linear and quadratic classifiers.

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<tr>
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<th>I1+I2</th>
<th>I1</th>
<th>I2</th>
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<tr>
<td>Linear classifier</td>
<td>19.9±4.4%</td>
<td>27.1±10.3%</td>
<td>11.6±4.9%</td>
</tr>
<tr>
<td>Quadratic classifier</td>
<td>17.5±3.5%</td>
<td>20.6±4.3%</td>
<td>9.1±4.9%</td>
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<tr>
<td>P value</td>
<td>0.016</td>
<td>0.076</td>
<td>0.006</td>
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Figure 3. Quadratic pattern classification and performance evaluation. When the quadratic classifier was tested on all trials (top panel: I1+I2), low rating trials (middle panel: I1), and high rating trials (bottom panel: I2), the error rates are 21.4%, 11.4%, and 5.4% respectively. Their relative classification performance can also be obtained from the ROC curve.
4. CONCLUSION

In the present study, we estimated single-trial LEP features using MLR technique, extracted important features using feature extraction method based on the Bhattacharyya distance with Gaussian distributions, classified these features using both linear and quadratic classifiers, and evaluated the classification performance using both error rate and the ROC curve. We found that the combination of single-trial analysis and pattern recognition techniques was able to provide a good performance to distinct LEP trials from resting EEG trials. In addition, we displayed evidence that the quadratic classifier significantly outperformed linear classifier in the present application. Across subjects, the error rates of quadratic classifier, when it was tested on all trials (I1+I2), trials with low ratings (I1), and trials with high rating (I2), were respectively 17.5±3.5%, 20.6±4.3%, and 9.1±4.9%.

5. REFERENCES


