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Combined Multivariate Matching Pursuit and Support Vector Machine: A Way Forward to Classify Single-Sweep Evoked Potentials?

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Abstract—**Evoked brain potentials averaged over multiple sweeps provide a valuable objective measure of abnormal pain processing due to sensitization of the central nervous system. However, the average procedure cancel out important information regarding phase resetting and non-phase locked oscillations. Hence, assessment of the pain processing could be optimized by analyzing single-sweeps. To develop improved methods to assess single-sweeps, we applied a new approach in one healthy volunteer participating in a placebo controlled study of widespread hyperalgesia induced by perfusion of acid and capsaicin in the esophagus. The evoked potentials were recorded during electrical stimulations in the rectosigmoid colon. Features from the single-sweeps were extracted by a multivariate matching pursuit algorithm with Gabor atoms, and features were discriminated by a support vector machine with a linear kernel. The classification performance for the optimal number of atoms was 95% when discriminating the sensitization response from the placebo response, which was above change level compared to the performance when discriminating the two baseline responses ($P < 0.001$). The discriminative capacity was increased power in the delta, theta, and alpha frequency bands. This result corresponds to previous characteristics seen in chronic pain patients who exhibit central sensitization. The new approach to classify single-sweeps on a single subject basis might in the future prove to be a useful tool in assessing mechanisms in central sensitization, and could be applied to improve enriched enrollment of study subjects in clinical trial units.**

I. INTRODUCTION

Electroencephalography (EEG) recorded as evoked brain potentials (EPs) plays a key role in many pain studies. These studies often investigate how the central nervous system (CNS) is altered in pain patients or in healthy volunteers before and after modulation of the pain system [1;2]. The EPs are traditionally averaged over multiple sweeps [1;2]. However, although the average procedure has the advantage to improve the signal-to-noise level of the EPs and hereby enables analysis of less prominent peaks, the method also has several limitations. One important limitation is that some brain oscillations are time-locked but not phase-locked to the stimuli, and hence cancel out during the average procedure [3;4]. These oscillations are subject to increased interest in pain research, since they might play an important role in the subjective pain perception [5]. Furthermore, recent research has shown that pain components mediated by C-fibers are masked in the averages due to dominant Adelta-fiber activity [3].

Consequently, new methods to assess single-sweep pain processing are warranted. Several methods to extract features have been suggested ranging from multi-taper Fourier transform, wavelet analysis, independent component analysis, Kalman recursive filtering, coherence and various statistical approaches [3;4;6]. However, these methods lack in optimized feature extraction where only characteristics that mimic pain processing are extracted. This could be accomplished by applying a multivariate matching pursuit (MMP) algorithm to extract the common waveforms in all sweeps [6]. For each atom, this procedure would give an estimate of the amplitude for each sweep, which could then be classified by a support vector machine (SVM) to identify the discriminative capacity between EPs before and after sensitization of the CNS.

To validate if feature extraction by MMP followed by SVM classification could identify alterations in pain processing before and after sensitization of the CNS, the aims of the study were: 1) To perform single-sweep classification combining MMP and SVM; and 2) To identify mechanisms in abnormal pain processing after sensitization of the CNS.

II. METHODS

A. Study subjects

One healthy volunteer was included in this pilot study to investigate in which way chemical-induced hyperalgesia in the esophagus provokes widespread visceral hypersensitivity. The subject did not have any known gastrointestinal diseases, pain-related symptoms, or daily

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medical consumption. The local Ethical Committee (VN 2003/120mch) approved the study, which was conducted according to the Declaration of Helsinki.

B. Experimental protocol

The investigation was a randomized double-blind two-way cross-over study utilizing a heterotopic noxious conditioning stimulation (HNCS) setup [7]. The conditioning stimulus was 180ml 0.1 M HCl plus 2 mg capsaicin perfused in the esophagus on one day and saline (placebo) on the other day, while the test stimuli were performed as electrical stimulations in the rectosigmoid colon.

The study consisted of EEG recordings during electrical stimulations at baseline and ninety minutes after perfusion. Each recording consisted of thirty identical stimuli performed twice to assess reproducibility. Stimuli were applied every five seconds by a constant current stimulator (IES 230, JNI Biomedical Aps, Klarup, Denmark). To verify a subjective measure of hyperalgesia, pain perception was assessed on a visual analog scale at baseline and ninety minutes after perfusion to determine the change in current leading to moderate pain. Stimulation intensity during recordings was the current leading to pain detection threshold.

Brain activity was recorded as evoked potentials (EPs) from the vertex electrode and referenced to the left earlobe. EEG signals were sampled at 1000Hz and online notch and band-pass filtered with cut-off frequencies 0.5Hz and 300Hz (NuAmp, Neuroscan, El Paso, TX, USA).

Electrical stimulations were inflicted in the rectosigmoid colon by a 40cm long custom-designed probe. The probe had two stainless steel electrodes with an inter-electrode distance of 2mm. The electrodes were placed 19cm from the anal verge, and impedance adjusted to below 3 kOhm.

C. Data processing

The EEG data were offline filtered by a 12^{th} order zero-phase shift bandpass filter with cut-off frequencies 1 and 70 Hz. Data were then segmented into epochs from 50 ms pre- to 500 ms post stimulus, baseline corrected, and linear detrended. Recordings were cleaned by manual inspection to keep the 20 best sweeps based on the visibility of the N1-P1 complex as illustrated in Fig. 1. The 20 sweeps for each reproducibility recording were appended to obtain 40 sweeps per condition, and the time interval in the epochs was adjusted to 25 ms to 500 ms post stimulus to eliminate stimuli artifacts to be included in the analysis (Neuroscan 4.3.1, Neuroscan, El Paso, TX, USA).

Data were scaled to adjust for differences in signal level between days. The scaling was performed by calculating a factor for each of the baseline recordings that would reduce the mean peak-to-peak amplitude to 1 uV if multiplied to all sweeps. The factor for the sensitization day was multiplied to all sweeps for baseline and after treatment that day, and likewise for the placebo day. By this procedure, the mean amplitude of the baseline recordings was adjusted to be equal without altering the morphology of the sweeps. Furthermore, the ratio between the baseline recording and the recording after sensitization or placebo was preserved.

The 160 scaled sweeps were used simultaneously as input to the MMP algorithm implemented with a Gabor dictionary. MMP is an iterative algorithm, which searches a big and redundant dictionary for the components (termed atoms) which has the highest simultaneously similarities to all the sweeps. For this study, MMP was implemented with constant phase and atoms selected based on the highest value of the sum of squared correlation coefficients with all input sweeps. The algorithm was stopped after 10 iterations.

The SVM was implemented with a linear kernel with parameters optimized by 3-fold cross-validation to minimize the probability of error estimated from the training set. The system performance was evaluated by a leave-one-out strategy.

The SVM was applied to the following two-class classifications: 1) Baseline versus ninety minutes after sensitization (only sweeps from the same day were compared); 2) Baseline versus ninety minutes after placebo (only sweeps from the same day were compared); 3) Baseline from the sensitization day versus baseline from the placebo day; and 4) Ninety minutes after sensitization versus ninety minutes after placebo. All four classifications were tested for all number of atoms by first including the features from the first atom, followed by the first two atoms and continued until all number of atoms had been tested.

The performances for all four classifications were plotted as a function of number of atoms to determine the optimal number of atoms. For this number, the underlying neuronal mechanisms were assessed in terms of differences in amplitude and frequency distribution between conditions.

III. RESULTS

EEG data were recorded, and the sweeps were decomposed into atoms. The first sweep for each condition is presented in Fig. 1, where also the approximations by the 10 atoms are shown. The subjective pain scores revealed that after sensitization, the subject only tolerated 64.3% of the initial current to feel moderate pain, and hence hyperalgesia was induced.

The single-sweeps were classified for the four classification scenarios, and the performances as a function of number of atoms are presented in Fig. 2.

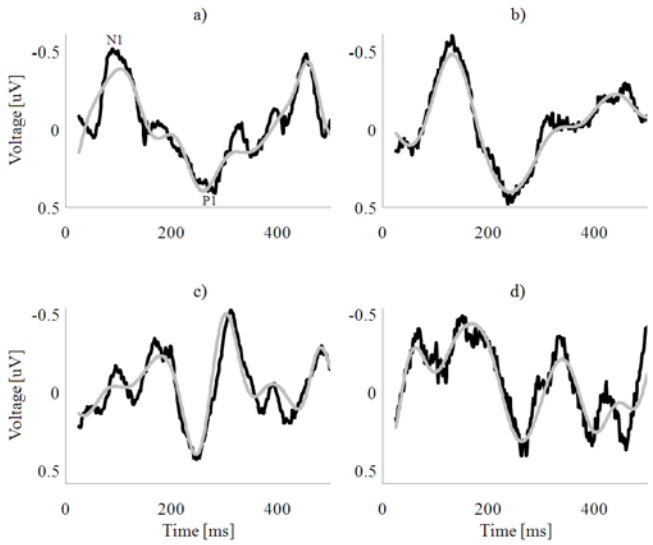

Fig. 1. Single-sweep evoked brain potentials (black) for the four conditions: a) Baseline for the sensitization day; b) Ninety minutes after sensitization; c) Baseline for the placebo day; and d) Ninety minutes after placebo. The grey curves present the approximation of the single-sweep when including all 10 atoms.

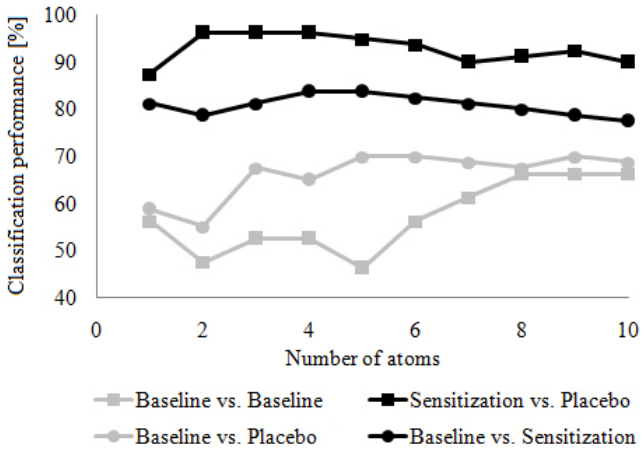

Fig. 2. Classification performance as a function of number of atoms included in the analysis.

Based on the results shown in Fig. 2, the optimal number of atoms was determined to be 5, since this value gave the highest difference between the classification of the baselines and the classification of the EPs after treatment. When including 5 atoms in the analysis, the classification between baseline and sensitization was 83.75%, baseline and placebo was 70%, the two baselines was 46.25%, and the sensitization versus placebo was 95%. When comparing the two latter performances, the performance after treatment was significantly higher than the performance when discriminating the two baselines (P<0.001, Fishers exact test). No statistical significance was evident between the performance for baseline versus sensitization and baseline versus placebo (P = 0.06, Fishers exact test).

The 5 atoms were distributed with 1 atom in the delta band (0.5 – 4 Hz), 3 atoms in the theta band (4 – 8 Hz), and 1 atom in the alpha band (8 – 12 Hz), while no atoms were present in the beta and gamma bands. All estimated single-sweep amplitudes were squared to obtain the power coefficients, and values in the same frequency band were summarized. The relative mean alteration compared to baseline was calculated for both sensitization and placebo treatment as shown in Fig. 3.

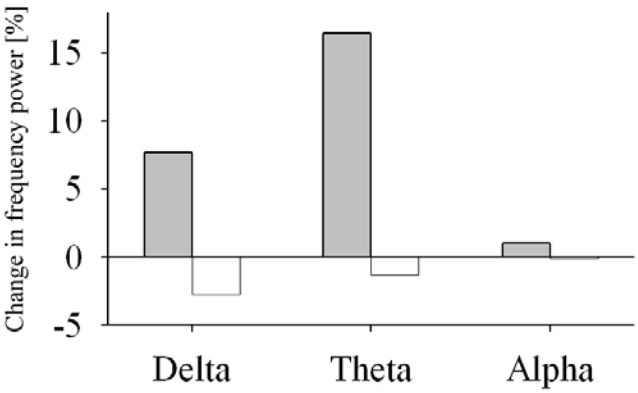

Fig. 3. Power shifts for the frequency bands represented within the first 5 atoms for sensitization (grey) and placebo (white). A positive change in frequency power indicates that more power was observed after treatment than before.

IV. DISCUSSION

This pilot study showed that combining multivariate matching pursuit and support vector machine can be used to classify single-sweep evoked brain potentials and identify mechanisms underlying sensitization of the central nervous system in healthy volunteers. A classification performance of 95% was obtained when discriminating the sensitization response from the placebo response, which was above change level compared to discrimination of the two baselines. Furthermore, it was demonstrated that the classification performance when discriminating baseline from after sensitization was higher than discriminating the baseline from after placebo. However, the difference in performance was not above change level for these two latter condition, and it should be noted that in pain research this is not a requirement, since a placebo response is expected [8].

A. Methodological considerations

The combination of MMP and SVM is a novel way of classifying single-sweeps, which we believe is a way forward in some applications. The methodology has the advantage that it does not require any a priori assumptions such as selection of a mother wavelet function, and likewise the SVM calculates the decision rule based on statistical learning, and hence finds the discriminative capacity in an objective way. Additionally, the method has the advantage that only features common in several sweeps are extracted,

which provides a more robust estimate of the signal content in noisy epochs.

Feature extraction by MMP also bridges the gap between feature extraction based on marginals, which does not take the latencies into consideration at all, and classification of time-frequency coefficients, which might be too detailed for pain research due to variations in the peak latencies in the single-sweeps. MMP decomposes the EEG traces into atoms described by both frequency and time instance, and hence the morphology of the EPs is taken into account when matches are calculated, although minor variations in latencies are ignored.

In contradiction, one could argue that by this approach the non-phase-locked information is discarded, which is partly correct. However, we chose this design to make the system more robust to noise, but other applications could be developed utilizing a MMP algorithm with variable phase.

The SVM was implemented with a linear kernel, which was sufficient to give satisfactory results.

B. Interpretation of identified mechanisms

We found increased intensity in the three low frequency bands: delta, theta, and alpha after sensitization, while power in all three bands was reduced after placebo. This is a very interesting result, since recently we published a paper in a patient population diagnosed with chronic pancreatitis, which showed the same alterations in the spontaneous EEG [9]. As chronic pancreatitis is a disease widely characterized by central sensitization, this indicates that these frequency bands reflect sensitization of the CNS.

C. Perspectives for the methodology

This pilot study demonstrated interesting perspectives for future pain studies. As we were able to identify the same mechanisms as in chronic pain patients, the method might be used for pharmacological studies investigating the underlying mechanisms of drugs affecting the CNS.

These studies are often performed in healthy volunteers, where sensitization is inflicted and confirmed only by changes in subjective pain scores. Validation of sensitization by classification of EEG responses would provide a much more objective and sensitive estimate of the modulation of the CNS, and hence only subjects displaying satisfactory results could be included in the clinical trials. This would be a major step towards enriched enrollment of study subjects to get a more precise estimate of the underlying mechanisms of the pharmacological intervention, and might in the future be a step towards mechanism-based personalized pain treatment.

D. Conclusions

This study showed that combining MMP and SVM is a new interesting approach in classifying single-sweep EEG traces, which could bring new insight into pain and pharmacology studies, but also many other applications based on classification of single-sweeps.

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