Objective identification of pain due to uterine contraction during the first stage of labour using continuous EEG signals and SVM

CHONG YEH SAI¹, NORRIMA MOKHTAR^{1,*}, HING WA YIP², LINDY LI MEI BAK³,
MOHD SHAHNAZ HASAN², HAMZAH AROF¹, PAUL CUMMING^{4,5} and
NOOR AZMI MAT ADENAN³

¹Department of Electrical Engineering, Faculty of Engineering, University of Malaya, 50603 Kuala Lumpur, Malaysia

²Department of Anaesthesiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

³Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

⁴School of Psychology and Counselling, Queensland University of Technology, Brisbane 4000, Australia

⁵QIMR Berghofer Institute, Brisbane 4006, Australia

e-mail: chongyeh.sai@siswa.um.edu.my; norrimamokhtar@um.edu.my; hwyip@ummc.edu.au;

lindy@ummc.edu.au; shahnaz@ummc.edu.au; ahamzah@um.edu.my; paul.cumming@qut.edu.au;

azmie@um.edu.my

MS received 18 June 2018; revised 27 November 2018; accepted 13 December 2018; published online 21 March 2019

Abstract. This study aimed to assess the utility of electroencephalography (EEG) as an objective marker of pain during the first stage of labour. EEG and cardiotocography (CTG) data were obtained from 10 parturient women during their first stage of labour. The study subjects reported the extent of their pain experienced due to uterine contractions, which were recorded by the CTG tracing. Simultaneous 16-channel EEG traces were obtained for spectral analysis and a subsequent machine learning classification using Support Vector Machine (SVM) aiming to predict the pain experienced in relation to uterine contractions. It was found that pain due to uterine contraction correlated positively with relative delta and beta band activities and negatively with relative theta and alpha band activities of the EEG signals. SVM using the spectral activities, statistical and non-linear features of the EEG classified the state of pain with 83% accuracy using a classification model generalizable across subjects. Furthermore, dimension reduction using Principal Component Analysis (PCA) successfully reduced the number of features used in the classification while achieving a maximum classification accuracy of 84%. Continuous EEG affords the means to assess objectively maternal pain experienced during the active contraction phase of the first stage of labour. Monitoring of the pain experience using EEG signals may complement the clinical decision-making process behind administration of epidural anaesthesia during labour. We envision future studies to investigate EEG markers of pain in other clinical states, aiming to generalize the use of EEG as an objective method of pain assessment.

Keywords. Electroencephalography (EEG); pain assessment; first stage of labour; uterine contraction; Support Vector Machine (SVM); Principal Component Analysis (PCA).

1. Introduction

Pain management is an important aspect of patient care. Physicians sometimes have difficulty in making important clinical decisions due to uncertain assessment of the extent of pain experienced by their patients. Indeed, the perception of pain is by its nature highly subjective, and there are no reliable markers of the individual's internal state. Current methods for quantifying pain intensity generally rely on the

patient's subjective rating according to a Numerical Rating Scale (NRS) or a Visual Analogue Scale (VAS) [1]. Here, patients are asked to assign a value for their experience on a scale ranging from 0 to 10, where 0 indicates no pain, and 10 represents the worst imaginable pain. However, these tests are often scored retrospectively, and are inherently subjective, being based on each individual patient's report, and the health staff interpretation of that report [2]. Obviously, such rating methods are not applicable for uncooperative or non-responsive patients, especially in cases of diminished consciousness.

*For correspondence

Various efforts have been made towards developing an objective measure quantifying pain experience, using brain imaging techniques such as functional magnetic resonance imaging (fMRI) [3], positron emission tomography (PET) and electroencephalography (EEG) [4, 5]. Given the technical difficulties and expense of fMRI and PET, EEG-based methods for pain detection would be most readily adaptable to bed-side applications. Consequently, considerable efforts have been expended in testing the potential of EEG for pain assessment in the clinic [2, 6, 7].

EEG entails the recording of brain electrical activity using an array of electrodes attached to the scalp. Conventionally, EEG signals are assigned to four frequency bands, i.e., the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (14–32 Hz) bands, each of which is attributed to different aspects of brain activity. EEG recordings are non-invasive, have excellent time resolution and are amenable for repeat testing of subjects. The EEG apparatus is portable, relatively inexpensive and suitable for close patient monitoring in a variety of circumstances, given the absence of medical contraindications or adverse effects limiting its use [8].

Measurement of event-related potentials (ERP) within the EEG recording can reveal the activation of specific brain regions following rapid phasic painful stimuli [9–11]. However, in this paradigm the brief stimuli may not faithfully simulate natural or clinical pain, even when specifically considering acute pain [6, 7, 12]. Furthermore, the recording of ERP can hardly be used as a clinical tool for monitoring of a patient's pain experience, as the short-interval ERP might bear no relation to the tonic pain experienced [13]. Therefore, continuous EEG recording is more often investigated as a tool to distinguish between different states of clinical pain conditions [14].

Frequency domain analysis has been applied to study the changes in frequency band power of EEG signals associated with the experience of pain. This can be achieved using either Fast Fourier Transform (FFT), a Regression Model (RM) or Wavelet Transform (WT) of the native EEG data [15, 16]. Changes in the relative power of individual frequency bands, in particular a decrease of alpha and increase of beta band activities, have frequently been detected upon inflicting a noxious stimulus to healthy volunteers [17–20]. Changes in the alpha band frequency and amplitude measured at bilateral temporal scalp electrodes (T7 and T8) are reported to reflect the subjective perception of tonic pain [12, 14]. However, alpha activity is not definitive of EEG responses to pain *per se*, as alpha activity is also modulated by the affective and cognitive components of pain [21]. Furthermore, suppression of alpha activity also reflects attentional demands such as alertness and expectancy [22]. Thus, changes of alpha oscillatory activities often reported in the literature seem unlikely to be pain-specific, but may in large part reflect attention modulation involved in orientation and organization of adaptive motor behaviour in response to experimentally applied painful stimuli [13, 20, 21].

Increases in beta power and in the higher frequency component of the gamma band, i.e. 30–100 Hz, have also been widely reported upon application of painful stimuli [4, 17, 19]. These changes may reflect the composite of primary responses to pain, as well as artefacts arising from increased muscle activity, as attested by electromyogram (EMG) recordings during painful stimuli administration [13, 19]. For this reason, apparent oscillation of beta and higher frequency band activities must be interpreted carefully in the context of pain perception [5]. The gamma band is particularly susceptible to high-frequency noises including the power line and EMG due to clenching of teeth or other facial muscles movement and is therefore filtered in this study. On the other hand, findings of increased delta or slow cortical activities correlating to pain experience may also be vulnerable to artefacts arising from oculomotor activities such as wincing or eye blinking that are often evoked by the experience of pain [5, 23]. In [6], the authors asserted that the relative theta activity responds dynamically to pain experience irrespective of the mode of stimulation. However, the results in the particular study were assessed from globally averaged EEG activities, and thus could not be attributed to any particular brain region by source localization.

In general, it is argued that the reported responses in EEG frequency band activities in response to painful stimuli are inconclusive, and fail to address specifically the phenomenology of pain experience [24]. As pain is multi-dimensional, with sensory, affective and cognitive modulation components in play, it is difficult to ascertain which aspects of the pain experience have actually provoked the observed EEG changes [19]. In addition, non-specific temporal changes may also mask the specifically pain-related changes in EEG signals [5].

In the present study, we have attempted to validate and resolve certain limitations of previous EEG studies of experimental pain by undertaking an investigation of unprovoked pain experienced by women due to strong uterine contractions during the active phase of the first stage of labour. This study aims to objectively determine the presence of the pain experience in an unprecedented way by measuring and analysing the EEG signals coupled with cardiotocography (CTG) assessment. Furthermore, this study is extended to search for EEG correlates by considering not just the conventional frequency bands but also the statistical and non-linear features of the EEG spectrum [25]. Finally, we used a machine learning algorithm using Support Vector Machine (SVM) to classify the presence of pain experience. The features of SVM are further optimized by dimensionality reduction using Principal Component Analysis (PCA) algorithm aiming to reduce the risk of overfitting. The classification of presence of pain experience might be used to complement a physician's decision to administer epidural anaesthesia during labour. Ultimately, we aim to develop a monitoring system to objectively classify the presence of pain, not only during labour but also generalized for a range of acute or chronic pain conditions [26].

Figure 1. (a) Recorded raw EEG signals are contaminated by high-frequency noise and electrode pop artefacts. (b) WMA is applied to remove high-frequency noise and linear trend movement at extremely low frequency. (c) Identified signal artefacts are removed by ICA.

2. Methodology

2.1 Subjects

Ten parturient women of mean age ($\pm$ SD) 29.6 (4.9) years admitted in the labour ward of the University Malaya Medical Centre (UMMC) participated in this study. The

subjects were in their active phase of first stage of labour, defined by cervical dilation of 2–10 cm. The subjects reported painful experience due to intense and frequent uterine contractions. All participating subjects were right-handed, were not receiving any medication known to affect the EEG and had no history of neurological or psychiatric disease. Informed consent was obtained from all individual

Figure 2. Pre-processing and filtering steps in the processing of the raw EEG signal.

Figure 3. An example of CTG recordings indicating cycles of uterine contraction during the first stage of labour. Simultaneously recorded EEG signals are labelled into “resting” when CTG signals are at baseline level, or “pain” states, defined by phasic uterine contraction as indicated by the CTG trace.

subjects included in the study. Each subject gave written consent to the experimental procedures, in a study conforming to the Declaration of Helsinki, and approved by the local research ethics committee (Ethical Clearance: 20156-1404).

2.2 EEG and CTG recording

An EEG acquisition equipment g.USBamp (g.tec medical engineering, Austria) was used to acquire EEG signals from the subjects. The electrodes were placed as specified by the 10–20 electrode system. Sixteen electrodes are used in the study, corresponding to channels FP1, FP2, F3, Fz, F4, T7, C3, Cz, C4, T8, P3, Pz, P4, O1, Oz and O2. The ground electrode was set at FPz [27], and the reference point was fixed on the left earlobe (A1). The recording scalp impedance was kept below 5 k Ω , with a sampling rate of 256 Hz. A notch filter of 50 Hz (Butterworth, order 4), corresponding to the local power mains, and a band pass filter of 0.5–100 Hz (Butterworth, order 8) were applied during the recordings. An example of a 5-s segment of EEG recording is shown in figure 1a. CTG was recorded

simultaneously throughout the EEG recordings, which lasted up to 30 min for each individual subject. All subjects are requested to rate their pain experience after every cycle of uterine contraction using an NRS from 0 to 10.

2.3 EEG pre-processing and filtering

Pre-processing and filtering are applied to the recorded EEG signals using the following steps (figure 2) and illustrated by the representative 5-s segment of EEG signals shown in figure 1a–c. First, Wavelet Multiresolution Analysis (WMA) is applied to decompose each channel by Discrete Wavelet Transform (DWT) to eight levels with a mother wavelet of db8 [28, 29]. Then, only the wavelet components falling within the frequency range of 0.5–32 Hz are retained, thus excluding signal noise and artefacts outside the frequency bands of interest. The resulting 5-s signal is shown in figure 1b. Later, blind source separation is applied through Independent Component Analysis (ICA) using the Matrix Pencil algorithm [30] to isolate artefactual components remaining in the frequency bands of interest, such as those due to eye blinks,

craniofacial muscle activity and electrode pop movement. ICA isolates the artefactual components into separated independent components (ICs), which are then removed [31, 32]. The residual ICs are then recombined using inverse ICA to reconstruct the original EEG signals cleared of artefacts, as shown in figure 1c. The filtering steps effectively removed minor artefactual components while imposing a minimum distortion to the cerebral activities in the frequency bands of interest [32]. Finally, the filtered EEG signals were separated into 1-s epochs and any unrecoverable noisy epochs deemed to be outliers attributable to technical difficulties were manually removed before further processing.

2.4 Labelling of EEG signals as “resting” or “pain” state according to CTG

In an effort to quantify objectively the pain experience independent of any subjective input from the subjects expressed through the NRS or VAS, we assumed that the pain experience is present during bouts of uterine contraction throughout the first stage of labour, as revealed by a surge in the CTG signal. The CTG is calibrated with resting state as the baseline level and any surge exceeding this baseline indicates the onset of cycle of uterine contraction. Each epoch of the EEG signals is labelled as either “resting” or “pain” state according to the phase of uterine contraction observed in the simultaneously recorded CTG tracing. The epochs of EEG signals outside uterine contraction episodes are labelled as “resting” state, and the epochs of recorded EEG signals with present uterine contraction are labelled as “pain” state. A representative CTG tracing corresponding to approximately 15 min of recording containing several cycles of uterine contraction defining the “resting” and “pain” states is depicted in figure 3.

2.5 Feature selection and PCA

Features of interest in both time and frequency domains were extracted from each epoch of EEG signals for use in training the machine learning algorithm and to classify the state of pain using the test data. The particular extracted features in this study included spectral activities, statistical features and non-linear features. In general, the spectral activities consist of the relative and absolute frequency band activities traditionally designated as delta, theta, alpha and beta bands. Other statistical and non-linear features also extracted for use in the classification are shown in table 1.

PCA is a multivariate method that transform multiple features to a new set of features known as the principal components [33]. The goal of PCA is to extract important information from possibly correlated features and to represent the features as orthogonal variables. Using PCA, we aim to reduce the number of features for training and

Table 1. List of extracted features from EEG epochs.

Spectral activities	Relative power of delta (%), theta (%), alpha (%) and beta (%) bands
	Absolute power of delta, theta, alpha and beta bands
Statistical features	Peak frequency and amplitude of peak frequency
	Mode, median and mean
	First quartile and third quartile values
	Variance, standard deviation, skewness, kurtosis and range
Non-linear features	Root mean square value (Vrms)
	Maximum and minimum values
	Hjorth mobility and Hjorth complexity
	Shannon’s entropy and energy entropy
	Hurst exponent
	Fractal dimension
	Number of peaks and number of valleys

testing of the machine learning algorithm for subsequent classification. This approach reduces the likelihood of overfitting when a large set of features are present in relation to the number of data points.

2.6 Classification of EEG signals with SVM

A machine learning algorithm is applied to classify the test data of filtered EEG signals to either “resting” or “pain” state. The SVM algorithm with Radial Basis Function (RBF) kernel is employed in this study. SVM is a widely used classifier in the field of supervised machine learning [34]. The goal of SVM is to construct from training data an optimal hyperplane that separates two or more datasets for classification in the test data. The optimal hyperplane is constructed in order to obtain the maximal margin from the nearest samples of different datasets, known as the support vectors. The parameters of SVM, such as gamma and soft margin constant, are optimized by iteratively conducting cross-validation within the training data. In cases where the datasets are not linearly separable in the original finite-dimensional space, the data can be re-mapped into a sufficiently higher-dimensional space using a defined kernel function, $k(x, y)$, which presumably ensures an easier separation of the datasets [35]. The hyperplane defined in the higher-dimensional space can be viewed as a non-linear separating hyperplane in the original finite-dimensional space. Therefore, this approach is also known as a non-linear SVM.

2.7 Summary of methodology

The complete procedural sequence of the study from EEG and CTG recordings to training of the SVM and obtaining a classification accuracy using test data are described in figure 4. The recorded EEG data are first filtered using the

pre-processing and filtering steps as described in section 2.3. Later, the EEG data are labelled as either “resting” or “pain” state in accordance with the CTG tracing as described in section 2.4. The EEG data are randomly assigned to training data (80%) and test data (20%). The classification model was constructed using only the training data. The model is optimized by iteratively training and testing the model with different parameters of gamma (g) and the soft margin constant (c) using five-fold cross-validation with the training data, in order to obtain the highest possible cross-validation accuracy. Once the values of the parameters g and c that yielded the highest accuracy were identified, a classification model was trained using these parameters and ran against the test data to determine the performance of the SVM.

Figure 4. The flowchart of the study beginning with EEG and CTG recordings and proceeding to classification of “resting” and “pain” state using the SVM algorithm with an RBF kernel. Five-fold cross-validation is used to identify the optimum parameters of gamma (g) and soft margin constant (c).

3. Results

The experiment protocols recorded EEG signals and CTG tracing simultaneously for 30 min for each of the 10 subjects. Thus, 18000 epochs of EEG signals in total were collected from the experiment protocols. After discarding data that had been corrupted due to technical complications such as faulty electrodes, 15030 epochs of data remained for analysis. After denoising and artefacts removal via the pre-processing and filtering steps as described in section 2.3, there then remained 9907 epochs of EEG signals, consisting of 2661 epochs corresponding to “pain” and 7246 epochs corresponding to “resting” state. The data were analysed using EEGLAB [36], and the classification of state of pain using SVM was conducted in the MATLAB environment [34].

3.1 Reported NRS due to uterine contraction

During the 30 min of EEG and CTG recording, the subjects experienced from five to eleven cycles of uterine contraction. The subjects then reported the extent of pain experienced using the NRS after each cycle of uterine contraction. Figure 5 shows the average reported NRS for each subject. It is evident that the mean intensity and relative standard deviation of pain rating caused by the uterine contractions differed between subjects. Some subjects rated a wider range of pain scores while some remained consistent throughout the whole recording session. Nonetheless, all NRS ratings of four or above given after a cycle of uterine contraction in contrast to 0 during “resting” state confirmed that the subject experienced significant pain during the cycles of uterine contraction.

3.2 Analysis of relative power of frequency bands between “resting” and “pain” states

The frequency band activities of the EEG signals recorded during the “resting” and “pain” state as defined in

Figure 5. Mean and standard deviation of NRS reported by each subject after the cycles of uterine contraction during the 30-min recording period.

Figure 6. Distribution of relative spectral activities of EEG signals corresponding to “resting” and “pain” states as defined in this study. Part (a) shows the average global distributions and (b) shows the average distributions corresponding to each channel; * and ** indicate statistical significance at $p < 0.05$ and $p < 0.01$, respectively (Bonferroni corrected for multiple comparisons).

section 2.4 are analysed and compared. Figure 6 shows the changes in relative power of frequency bands contributed by all 10 subjects, contrasting the results for “resting” and “pain” states. The differences in globally averaged EEG amplitudes are shown in figure 6a, whereas the differences observed for each separated EEG channel are depicted in figure 6b. The relative power is used in this study as it is more robust to inter-individual differences, and more reliable for detecting changes in frequency band activities than are contrasts of absolute power [6]. The magnitudes of frequency band power are normalized for each individual subject, and then averaged across the entire group, thus ensuring that each individual contributed with equal weighting to the depiction of the overall distributions [37].

Figure 7 shows the topographic representation of the frequency band power derived from that of figure 6b. In general, most of the EEG channels showed increased relative delta and beta band activities, together with decreased theta and alpha band activities in association with painful uterine contractions.

Further examination of figures 6 and 7 reveals the differences in the distribution of EEG spectral activities in relation to “resting” and “pain” states as defined in this study. Using the “resting” state as baseline and consider the transition from “resting” to “pain” state, widespread increases in relative delta and beta band activities coupled with decreased relative theta and alpha band activities are observed across the scalp. The increase in relative delta

Figure 7. Normalized topographic distribution of relative spectral activities corresponding to “resting” and “pain” states as defined in this study.

band activity was most pronounced in the frontal cortex (possibly due to residual eye blink and wincing artefacts) and the parietal brain regions. We also noticed decreased relative theta band activity in the frontal and parietal regions, possibly related to involvement of somatosensory association areas. In addition, we saw notably decreased relative alpha band activity encompassing the fronto-central and occipital regions, possibly attributable to affective and cognitive response to pain. Finally, increased relative beta band activities were observed over the entire cortical mantle, indicating hyperarousal upon transition from “resting” to “pain” state.

3.3 Ranking of features separating the “resting” and “pain” states

As a result of statistical analysis in this study, we ranked all the features in descending order of class separability criteria using independent evaluation criteria for binary classification [38]. The ranking describes the capability of a particular feature in separating the two labelled groups, namely, “resting” and “pain” states. Table 2 shows the top 30 features ranked in descending order of class separability criteria.

3.4 Classification of state of pain using SVM

As a practical application, this study aims to construct a generalized model for classification of state of pain across subjects using a supervised machine learning algorithm.

Table 2. Ranking of features in descending order of class separability criteria; * and ** indicate statistical significance at $p < 0.05$ and $p < 0.01$, respectively (Bonferroni corrected for multiple comparisons), while n.s. indicates not significant.

Ranking	Feature	Channel	Significance
1	Variance	Oz	**
2	Beta %	Pz	*
3	Theta %	P3	**
4	Standard deviation	O1	**
5	Hjorth complexity	FP2	**
6	Number of peaks	Cz	**
7	Kurtosis	Fz	*
8	Number of peaks	F3	*
9	Shannon entropy	F3	**
10	Energy entropy	F3	**
11	Peak frequency	O2	*
12	Alpha power	FP2	*
13	Theta %	FP2	*
14	Beta %	O2	n.s.
15	Range	F3	**
16	Delta power	F3	**
17	Theta power	F3	**
18	Amplitude of peak frequency	FP2	**
19	Alpha %	T8	*
20	Kurtosis	FP1	**
21	Variance	P3	*
22	Energy entropy	P4	**
23	Alpha power	Cz	n.s.
24	Beta power	Pz	*
25	Kurtosis	O2	*
26	Amplitude of peak frequency	Pz	*
27	Beta power	O1	*
28	Delta %	Cz	*
29	Vrms	F3	**
30	Alpha %	FP1	*

The classification model is constructed to predict the “resting” or “pain” internal state experienced by the subjects using the EEG signals as an objective marker. The generalized model was trained and tested using the normalized data across subjects to achieve a single composite model that is able to distinguish between “resting” and “pain” states for all subjects. The generalized model was trained and tested using SVM with an RBF kernel function.

The SVM was trained and tested using the 31 features listed in table 1 for each of the 16-channel electrodes, resulting in a total of 496 features. The model was first trained and tested using the training data within a range of parameters extending for gamma g (0.01–1 with increments of 0.01 per step) and for the soft margin constant c (1–100 with increments of 1 per step). Later, the test data were used for confirmation of the trained classification model. The results of classification are shown in the confusion matrix of table 3. The classification model achieved sensitivity of 85.4% and specificity of 80.7% with an overall accuracy of 83.0%, when the optimized parameters $g = 0.28$ and $c = 4$ are applied, as determined by five-fold

Table 3. Confusion matrix of classification result achieved by our generalized model.

	Predicted class: pain	Predicted class: resting	Classification accuracy (%)
Actual class: pain	439	75	Sensitivity: 85.4
Actual class: resting	106	444	Specificity: 80.7
Overall accuracy			Overall: 83.0

Figure 8. Classification accuracy of SVM achieved using different parameters: gamma g and soft margin constant c . The maximum classification achieved is highlighted in the figure together with the optimized parameters (X , Y , Z).

cross-validation. A three-dimensional plot to describe the variation of classification accuracy to the choice of parameters is depicted in figure 8. Results of this generalized model lend support to the development of generalizable pain assessment during labour using the EEG signals.

3.5 Dimension reduction using PCA

In this section, we attempt to reduce the number of features using PCA to reduce the risk of overfitting when high number of features are present in relation to the amount of data. After applying dimension reduction using PCA, the resulting principal components are ranked in descending order of class separability criteria based on their component variance. Figure 9 shows the classification accuracy as a function of the number of features with and without PCA under otherwise similar classification criteria. A classification accuracy above 80% can be obtained using only the top 30 features when PCA is applied. Maximum classification accuracy is achieved at 84% using 68 features in total. PCA provided features with better separability criteria compared with the set of raw features, which are less able to describe the relevant changes in the EEG characteristics in relation to the transition from “resting” to “pain” state. Table 4 and figure 10 describe the confusion matrix and the classification accuracy, which is maximal ($g = 0.4$, $c = 5$,

Figure 9. Classification accuracy against number of features ranked in descending order of class separability criteria, with and without PCA.**Table 4.** Confusion matrix of classification result achieved by the generalized model with number of features reduced to 68 using PCA.

	Predicted class: pain	Predicted class: resting	Classification accuracy (%)
Actual class: pain	448	66	Sensitivity: 87.2
Actual class: resting	104	446	Specificity: 81.1
Overall accuracy			Overall: 84.0

Figure 10. Classification accuracy of SVM achieved using different parameters: gamma g and soft margin constant c , with number of features reduced to 68 using PCA. The maximum classification achieved is highlighted in the figure together with the optimized parameters (X , Y , Z).

$\text{acc} = 84.0\%$) when using 68 features. The classification model after feature reduction is less likely to overfit as we eliminated a large number of redundant features not contributing positively to the classification model. Better classification results can also be seen on comparing figure 10 to figure 8 when different parameters are applied, indicating that the risk of overfitting is indeed reduced. The classification result supports the possibility of using EEG signals for objective identification of pain experience due to uterine contraction during the first stage of labour.

4. Discussion

This is the first research study that targets the complex problem of objective identification of pain experience during the first stage of labour using the EEG approach. We observed that the pain experience caused by uterine contraction during the first stage of labour was associated with a specific pattern of relative changes in the spectral activities of EEG signals. In general, we saw globally increased relative delta and beta activities and decreased relative theta and alpha activities. The results for natural pain are consistent with generally reported observations in experimental pain studies [4, 18, 39].

The decrease of relative alpha band activity observed in this study is unlikely to be pain-specific, contrary to speculations in some other EEG pain studies [6, 12, 13]. In general, the alpha band is primarily affected by changes in attention and alertness [21, 22], and is known to be negatively correlated with focus of attention during task performance [40]. As such, the suppression of alpha band activity commonly reported in the literature is likely to be a marker for attentional shift in response to pain, rather than pain *per se* [6, 13, 17]. We argue that the observed alpha Event-Related Desynchronization (ERD) in these earlier studies is more likely a reflection of specific attentional and memory processes that are task-related [21]. Experimental evocation of pain by application of either dermal heating or the cold pressor test arouses the subject's attention, thus inducing suppression of alpha oscillatory activity in the sensorimotor cortex, regardless of the particulars of attentional modulation applied in the particular study [13]. However, in the present study, we did not manipulate the subject's attention directly. As the pain due to uterine contraction is tonic and natural, the alpha band activities are not likely to be modulated. As a result, we hypothesize that the observed suppression of alpha oscillations over frontal cortical regions reflects the activation of anterior cingulate cortex (ACC) as a consequence of underlying attentional or affective-emotional processing due to the pain experience [21]. On the other hand, the decrease of alpha activities at the occipital region observed in this study is likely a reflection of cognitive engagement occurring when the pain experience due to uterine contraction is present.

The pain-evoked increase of delta activity observed in frontal cortical regions is likely attributable to artefacts from residual eye blinks or other ocular activities that often accompany pain experience [5]. However, we also saw increased delta activity in the parietal region of the scalp, which is not so readily attributed to blinking. In general, low-frequency activation is principally related to motivational regulation, which can be linked to negative effect and the activation of an avoidance-withdrawal system [19]. Therefore, the present finding of increased delta activity may reflect in part the functional synchronization of brain activity in the parietal lobe upon pain experience, in relation to atavistic defensive or withdrawal mechanisms [7].

On the other hand, we also saw decreased theta activity in bilateral frontal and parietal regions comprising the somatosensory cortices during uterine contractions, as also reported previously in an experimental pain study [5]. The decrease of low-frequency oscillatory activities in these regions could be related to activation of primary and secondary somatosensory cortices, in relation to the sensory modulation of painful experience. However, due to inherent limitations of the scalp EEG technique, which include low spatial resolution for cortical source mapping, we cannot unambiguously attribute the pain-related decrease in theta oscillatory activities to a particular location within the somatosensory association areas.

The observed widespread (frontal, temporal and parietal) increase in beta activity during uterine contraction is a strong indicator of hyperarousal in response to painful experience. A shift from lower-frequency to higher-frequency activity indicated the activation and synchronization between cortical areas of the well-described brain network responding to pain, comprising primary- (SI) and secondary somatosensory cortex (SII), ACC, insula, prefrontal cortex and thalamus [13, 18, 41]. SI and SII activities induced by pain have been associated with the sensory-discriminative component of pain, while ACC activation reflects the affective-emotional component due to pain [20, 21]. Our finding of broadly distributed enhancement of beta activities suggests that the pain experience modulates the cortical excitability not only of the pain and sensorimotor system but also involves a more widespread cortical system. This finding also supports the network model of pain perception, implicating involvement of multiple brain regions rather than processing within a "singular centre" [19, 24, 41]. The existence of this network is confirmed in cross-modal imaging studies using PET [42]. However, the observed widespread increase in beta activity in the present study may also be contaminated by EMG sources due to cranial muscle contraction or clenching of teeth that certainly accompany the pain of uterine contractions. Anticipating this possibility, we applied a comprehensive filtering method to isolate and remove high-frequency noise and artefactual components from the EEG signals. Therefore, we are convinced that the remaining changes in EEG signals may properly be attributed to the experience of pain evoked by uterine contractions.

Other than the conventional spectral activities, certain statistical and non-linear EEG features corresponding to pain experience that have not hitherto been studied well are also considered. Generally, our analyses showed that the EEG signals had increased amplitude and volatility during painful uterine contraction events. Thus, we saw a number of significant changes in the statistical properties related to the EEG amplitude. In particular, statistical features such as variance, range of amplitude, Vrms and non-linear features such as Hjorth activities and energy entropy all of which positively correlated with the amplitude of the EEG signals showed statistically significant changes at certain electrode

locations during the pain experience. Nonetheless, we could not identify any single statistical or non-linear feature that can be used to accurately describe the occurrence of pain experience. On the other hand, statistical features unaffected by the amplitude or volatility such as mean, median and skewness showed no such significant changes with pain.

Although no single analysed feature is sufficient to describe the overall occurrence of pain, the combined features may serve for a classification model with supervised machine learning algorithm [43]. Therefore, in addition to the analysis of changes in EEG activities, this study also attempted to classify the “resting” or “pain” state of the subjects using the SVM. The classification algorithms using SVM with an RBF kernel function achieved satisfactory results, classifying the presence of pain experience associated with uterine contraction at 83% accuracy, as benchmarked by an accuracy of 75% achieved in an earlier study with an experimental pain condition [44]. Moreover, by reducing the number of features using PCA and considering only the 68 top ranked features with highest class separability criteria, a maximum classification accuracy of 84% is achieved. Applying PCA reduced the risk of overfitting without sacrificing the overall performance of the SVM.

5. Conclusion

In conclusion, this study explored the changes in EEG activities during present pain experience associated with uterine contraction during the first stage of labour, as monitored by CTG tracing. In particular, we observed globally increased delta and beta activities together with decreased theta and alpha activities subject to the presence of pain with acute uterine contractions. However, it is generally held that changes in alpha activities may not directly reflect the pain experience, but rather the affective modulation altered by the pain. In an effort to classify the presence of pain using supervised machine learning algorithm, we achieved a classification accuracy of 83% using SVM classifier with an RBF kernel function. Furthermore, the classification model using a reduced pool of features via PCA achieved a higher accuracy of 84%, using only 68 of a total of 496 possible features. Our findings lend support to the utility of EEG signals as a clinical tool to achieve an objective method of pain assessment during the first stage of labour, which could inform a decision to administer epidural anaesthesia. This approach may prove generalizable to a number of conditions in which patients are unable to convey their internal state.

Acknowledgements

This study was supported by funding from Ministry of Higher Education, Malaysia, and University of Malaya through HIR Grant (UM.C/HIR/MOHE/ENG/16 Account

Code: D000016-16001) and PPP Grant (PG260-2015B), respectively.

Compliance with ethical standards

Conflict of interest None of the authors have potential conflicts of interest to be disclosed.

Ethical approval All procedures performed in studies involving human subjects are in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

- [1] Bijur P E, Latimer C T and Gallagher E J 2003 Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad. Emerg. Med.* 10(4): 390–392
- [2] Kumar S, Kumar A, Trikha A and Anand S 2015 Electroencephalogram based quantitative estimation of pain for balanced anaesthesia. *Measurement* 59: 296–301
- [3] Wager T D, Atlas L Y, Lindquist M A, Roy M, Woo C W and Kross E 2013 An fMRI-based neurologic signature of physical pain. *N. Engl. J. Med.* 368(15): 1388–1397
- [4] Huber M T, Bartling J, Pachur D, Woikowsky-Biedau S V and Lautenbacher S 2006 EEG responses to tonic heat pain. *Exp. Brain Res.* 173(1): 14–24
- [5] Dowman R, Rissacher D and Schuckers S 2008 EEG indices of tonic pain-related activity in the somatosensory cortices. *Clin. Neurophysiol.* 119(5): 1201–1212
- [6] Gram M, Graversen C, Olesen S S and Drewes A M 2015 Dynamic spectral indices of the electroencephalogram provide new insights into tonic pain. *Clin. Neurophysiol.* 126(4): 763–771
- [7] Hadjileontiadis L J 2015 EEG-based tonic cold pain characterization using wavelet higher order spectral features. *IEEE Trans. Biomed. Eng.* 62(8): 1981–1991
- [8] André-Obadia N, Lamblin M D and Sauleau P 2015 French recommendations on electroencephalography. *Clin. Neurophysiol.* 45(1): 1–17
- [9] Gram M, Graversen C, Nielsen A K, Arendt-Nielsen T, Mørch C D, Andresen T *et al* 2013 A novel approach to pharmaco-EEG for investigating analgesics: assessment of spectral indices in single-sweep evoked brain potentials. *Br. J. Clin. Pharmacol.* 76(6): 951–963
- [10] Le Pera D, Valeriani M, Niddam D, Chen A C and Arendt-Nielsen L 2002 Contact heat evoked potentials to painful and non-painful stimuli: effect of attention towards stimulus properties. *Brain Topogr.* 15(2): 115–123
- [11] Iannetti G D, Hughes N P, Lee M C and Mouraux A 2008 Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? *J. Neurophysiol.* 100(2): 815–828
- [12] Nir R R, Sinai A, Moont R, Harari E and Yarnitsky D 2012 Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. *Clin. Neurophysiol.* 123(3): 605–612
- [13] Peng W, Hu L, Zhang Z and Hu Y 2014 Changes of spontaneous oscillatory activity to tonic heat pain. *PLoS One* 9(3): e91052

- [14] Nir R R, Sinai A, Raz E, Sprecher E and Yarnitsky D 2010 Pain assessment by continuous EEG: association between subjective perception of tonic pain and peak frequency of alpha oscillations during stimulation and at rest. *Brain Res.* 1344: 77–86
- [15] Ocak H 2009 Automatic detection of epileptic seizures in EEG using discrete wavelet transform and approximate entropy. *Expert Syst. Appl.* 36(2): 2027–2036
- [16] Subasi A and Ercelebi E 2005 Classification of EEG signals using neural network and logistic regression. *Comput. Methods Programs Biomed.* 78(2): 87–99
- [17] Giehl J, Meyer-Brandis G, Kunz M and Lautenbacher S 2013 Responses to tonic heat pain in the ongoing EEG under conditions of controlled attention. *Somatosens. Mot. Res.* 31(1): 40–48
- [18] Shao S, Shen K, Yu K, Wilder-Smith E P V and Li X 2012 Frequency-domain EEG source analysis for acute tonic cold pain perception. *Clin. Neurophysiol.* 123(10): 2042–2049
- [19] Chang P F, Arendt-Nielsen L and Chen A C N 2002 Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. *Brain Res. Bull.* 57(5): 667–675
- [20] Bromm B and Lorenz J 1998 Neurophysiological evaluation of pain. *Electroencephalogr. Clin. Neurophysiol.* 107(4): 227–253
- [21] Peng W, Babiloni C, Mao Y and Hu Y 2015 Subjective pain perception mediated by alpha rhythms. *Biol. Psychol.* 109: 141–150
- [22] Klimesch W, Doppelmayr M, Russegger H, Pachinger T and Schwaiger J 1998 Induced alpha band power changes in the human EEG and attention. *Neurosci. Lett.* 244(2): 73–76
- [23] Hagemann D and Naumann E 2001 The effects of ocular artifacts on (lateralized) broadband power in the EEG. *Clin. Neurophysiol.* 112(2): 215–231
- [24] dos Santos Pinheiro E S, de Queiros F C, Montoya P, Santos C L, do Nascimento M A, Ito C H *et al* 2016 Electroencephalographic patterns in chronic pain: a systematic review of the literature. *PLoS One* 11(2): e0149085
- [25] Acharya U R, Sudarshan V K, Adeli H, Santhosh J, Koh J E, Puthankatti S D *et al* 2015 A novel depression diagnosis index using nonlinear features in EEG signals. *Eur. Neurol.* 74(1–2): 79–83
- [26] Davis K D, Racine E and Collett B 2012 Neuroethical issues related to the use of brain imaging: can we and should we use brain imaging as a biomarker to diagnose chronic pain? *Pain* 153(8): 1555–1559
- [27] Adam A, Ibrahim Z, Mokhtar N, Shapiai M I, Cumming P and Mubin M 2017 Improving EEG signal peak detection using feature weight learning of a neural network with random weights for eye event-related applications. *Sadhana Acad. Proc. Eng. Sci.* 42(5): 641–653
- [28] Mamun M, Al-Kadi M and Marufuzzaman M 2013 Effectiveness of wavelet denoising on electroencephalogram signals. *J. Appl. Res. Technol.* 11(1): 156–160
- [29] Sai C Y, Mokhtar N, Arof H, Cumming P and Iwahashi M 2018 Automated classification and removal of EEG artifacts with SVM and wavelet-ICA. *IEEE J. Biomed. Health Inform.* 22(3): 664–670
- [30] Chunqi C, Zhi D, Sze Fong Y and Chan F H Y 2000 A matrix-pencil approach to blind separation of colored nonstationary signals. *IEEE Trans. Signal Process.* 48(3): 900–907
- [31] Jung T P, Makeig S, Humphries C, Lee T W, McKeown M J, Iragui V *et al* 2000 Removing electroencephalographic artifacts by blind source separation. *Psychophysiology* 37(2): 163–178
- [32] Mahajan R and Morshed B I 2015 Unsupervised eye blink artifact denoising of EEG data with modified multiscale sample entropy, kurtosis, and wavelet-ICA. *IEEE J. Biomed. Health Inform.* 19(1): 158–165
- [33] Abdi H and Williams L J 2010 Principal component analysis. *WIREs Comput. Stat.* 2(4): 433–459
- [34] Chang C C and Lin C J 2011 LIBSVM: a library for support vector machines. *ACM Trans. Intell. Syst. Technol.* 2(3): 1–27
- [35] Phadke A C and Rege P P 2016 Fusion of local and global features for classification of abnormality in mammograms. *Sadhana Acad. Proc. Eng. Sci.* 41(4): 385–395
- [36] Delorme A and Makeig S 2004 EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134(1): 9–21
- [37] Kumar A and Anand S 2006 A depth of anaesthesia index from linear regression of EEG parameters. *J. Clin. Monit. Comput.* 20(2): 67–73
- [38] Dash M and Liu H 1997 Features selection for classification. *Intell. Data Anal.* 1(3): 131–156
- [39] Chang P F, Arendt-Nielsen L, Graven-Nielsen T, Svensson P and Chen A C N 2004 Comparative EEG activation to skin pain and muscle pain induced by capsaicin injection. *Int. J. Psychophysiol.* 51(2): 117–126
- [40] Ray W J and Cole H W 1985 EEG alpha activity reflects attentional demands, and beta activity reflects emotional and cognitive processes. *Science* 228(4700): 750–752
- [41] Apkarian A V, Bushnell M C, Treede R D and Zubieta J K 2005 Human brain mechanisms of pain perception and regulation in health and disease. *Eur. J. Pain* 9(4): 463–484
- [42] Kupers R, Lonsdale M N, Aasvang E and Kehlet H 2011 A positron emission tomography study of wind-up pain in chronic postherniotomy pain. *Eur. J. Pain* 15(7): 698.e1–16
- [43] Sankar A B, Selvi J A V, Kumar D and Lakshmi K S 2013 Effective enhancement of classification of respiratory states using feed forward back propagation neural networks. *Sadhana Acad. Proc. Eng. Sci.* 38(3): 377–395
- [44] Vatankhah M, Asadpour V and Fazel-Rezai R 2013 Perceptual pain classification using ANFIS adapted RBF kernel support vector machine for therapeutic usage. *Appl. Soft Comput.* 13(5): 2537–2546