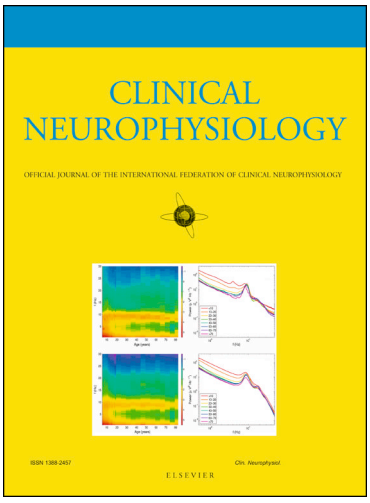

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Prediction of Central Neuropathic Pain in Spinal Cord Injury Based on EEG Classifier

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Keywords: Spinal Cord Injury, Central Neuropathic Pain, EEG, Linear Discriminant Analysis, Artificial Neural Network, Transferable Learning.

Abstract

Objectives. T**o** create a classifier based on electroencephalography (EEG) to identify spinal cord injured (SCI) participants at risk of developing central neuropathic pain (CNP) by comparing them with patients who had already developed pain and with able bodied controls.

Methods. Multichannel EEG was recorded in the relaxed eyes opened and eyes closed states in 10 able bodied participants and 31 subacute SCI participants (11 with CNP, 10 without NP and 10 who later developed pain within 6 months of the EEG recording). Up to nine EEG band power features were classified using linear and non-linear classifiers.

Results. Three classifiers (artificial neural networks ANN, support vector machine SVM and linear discriminant analysis LDA) achieved similar average performances, higher than 85% on a full set of features identifying patients at risk of developing pain and achieved comparably high performance classifying between other groups. With only 10 channels, LDA and ANN achieved 86% and 83% accuracy respectively, identifying patients at risk of developing CNP.

Conclusion. Transferable learning classifier can detect patients at risk of developing CNP. EEG markers of pain appear before its physical symptoms. Simple and complex classifiers have comparable performance.

Significance. Identify patients to receive prophylaxic treatment of CNP.

Highlights

It is possible to predict central neuropathic pain based on the EEG findings of individual patients.

Simple linear classifier achieved 85% classification accuracy.

EEG band power in the eyes open and eyes closed resting states served as classification features.

1. Introduction

Neuropathic pain affects 40-50% of Spinal Cord Injured (SCI) patients (Siddall 2003, Finnerup 2013), and is of central origin. Central neuropathic pain (CNP) is a chronic condition caused by an injury to the somatosensory system (Jensen et al. 2011)[1]. CNP is a secondary consequence of SCI, most often developing in a sub-acute phase, within a year of injury (Siddall 2003, Finnerup 2013). This type of pain has no clear correlation with gender, age, level or completeness of injury and it is often refractory to pharmacological treatments. Most importantly, to date there is no cure for CNP, once it develops it continues for life, persistently interfering with activities of daily living (Mann et al. 2013), affecting patients' sleep and often leading to depression. It is believed that CNP in SCI is the consequence of a gradual build-up of hyperexcitability, eventually resulting in pain (Zeilig et al. 2012, Finnerup et al. 2014). Preventing CNP is a hard task but there is evidence that the response to mechanical (Zeilig et al. 2012) and thermal stimuli (Finnerup et al. 2014) below the level of injury is altered in patients who are at risk of developing CNP. Although sensory tests may predict CNP, altered responses to sensory stimulus indicate that patients have already experienced some discomfort.

It is believed that at a cortical level CNP causes thalamo-cortical dysrhythmia, this is manifested as increased theta and beta band EEG power, reduced alpha band power and slowed-down dominant alpha frequency (Sarnthein et al. 2006, Stern et al. 2006, Boord et al. 2008, Jensen et al. 2013, Vuckovic et al. 2014). These EEG markers of CNP were reversible following treatments that reduced pain (Sarnthein et al. 2006, Hassan et al. 2015), indicating that changes in EEG might not only be a consequence of pain but also be related to the cause of CNP, supporting a hypothesis that long standing changes in brain activity may lead to more pain independent of its aetiology (Vartiainen et al. 2009). To test this hypothesis we performed EEG recordings in 20 patients with subacute SCI without pain and followed them up for 6 months (Jarjees 2017)[2]. We showed that a group of SCI patients who developed pain within 6 months of the EEG recording had significantly different alpha and beta band resting state EEGs in BA40 and BA7 compared to a group of SCI patients who did not develop pain

[1] SCI Spinal Cord Injury; CNP Central neuropathic Pain; PDP Patients who Develop Pain; PNP Patients who did not Develop Pain; PWP Patients With Pain; AB Able Bodied; EO Eyes Opened; EC Eyes Closed; ANN Artificial Neural Network; LDA Linear Discriminant Analysis; NB Naïve Bayesian; SVM Support Vector Machine; ASIA American Spinal Injury Association.

[2] This study is a part of a registered clinical trial NCT021789917.

over the same period (Jarjees 2017). Similar results have been demonstrated in a study on rodents, showing that increased EEG theta band power, accompanied the onset of pain, i.e that it is not a consequence of a long-standing pain, as previously believed (LeBlanc et al. 2016).

Results of these studies indicate that it might be possible to create an EEG test to predict CNP, in a similar way to sensory tests (Finnerup et al. 2014, Zeilig et al. 2012). The potential advantage of an EEG test is that it should not be affected by the completeness of injury, i.e. can be applied to people with complete sensory loss. In the current study we demonstrated a transferable classifier of EEG signals trained on one group of patients and tested on patients outside the training set. The classifier was used to identify EEG markers of existing and predictors of future CNP.

2. Methods

2.1. Participants

Thirty one patients with spinal cord injury and ten able-bodied participants with no acute or chronic pain took part in the study. General inclusion criteria for all participants were age between 18 and 75 years old, no known major neurological disorder or injury apart from the SCI and the ability to understand the task. For the CNP group, patients with peripheral neuropathy or any pain above the level of injury were excluded. Although in general, criteria for the diagnosis of chronic pain is its presence for at least 6 months, CNP can also be studied in an early stage, due to its characteristic sensory descriptors, location, and responsiveness to a certain group of anticonvulsants and antidepressants (Mehta et al. 2016). All patients in this study were within months of injury still hospitalised and receiving primary rehabilitation following spinal cord injury. Because there is no confirmed relation between the incidence of NP and gender, age, level or completeness of injury, patients of both sex, paraplegic and tetraplegic, complete or incomplete (Marion et al. 2003) were included in the study, similar to the recruitment criteria in a study of sensory predictors of pain (Finnerup et al. 2014). There were two groups of patients, ten patients who already had below level neuropathic pain at the time of the experiment (pain level ≥ 4 on the Visual Numerical Scale, were zero is no pain and ten corresponds to the worst pain imaginable) and twenty one patients who did not have neuropathic or any other chronic pain at the time of the experiment. Patients with pain described it with standard descriptors such as burning and pins and needles sensations. Patients with pain and complete loss of sensory and motor function belonged to a phenotype without response to allodynia and hyperalgesia (Widerström-Noga 2017) which thus could

not be taken as a reliable indicator of CNP. Patients who did not have pain at the time of the experiment, have been followed up for six months. After this period they were further divided into a group who eventually developed neuropathic pain and a group who did not develop pain.

Participants were divided into four groups for EEG analysis:

1. Ten able bodied (AB) participants (3F, 7M, age 35.2±7.2)
2. Eleven patients with neuropathic pain (PWP) at the time of EEG recording (4F, 7M, age 44.9±16.9)
3. Ten patients who eventually developed pain (PDP) within six months of EEG recording (1F, 9M, age 46.9±15.9).
4. Ten patients who didn't developed pain (PNP) within six months of EEG recording (1F, 9M, age 42.1±13.3)

Table 1 shows information about PDP and PWP (pain related groups) while Table 2 shows information about groups without pain, PNP and AB.

The study was performed in accordance with the Declaration of Helsinki. All participants gave informed consent. Ethical approval was obtained from the Regional National Healthcare Research Ethics Committee. For able-bodied participants ethical approval was granted by the University Ethical Committee.

Table 1 about here

Table 2 about here

2.2. Experimental Procedures

2.2.1. EEG Recording

EEG was recorded from 48 locations, over the whole scalp according to 10-10 system (American Clinical Neurophysiology Society 2006) using a modular universal amplifier usbamp (Guger technologies, Austria). A linked-ear reference was used and ground was placed at the AFz electrode location. The EEG sampling frequency was 256 Hz and it was band-pass filtered during recording between 0.5 and 60 Hz and notch filtered at 50 Hz, using 5^{th} order IIR digital Butterworth filters within the g.USBamp device. The electrode impedance was kept under 5 kΩ.

Spontaneous EEG activity was recorded in both the eyes opened (EO) and eyes closed (EC) relaxed states for 2 mins each and repeated twice, alternating between the states. During the eyes opened relaxed state, participants were instructed to stay still and to focus on a small cross, presented in the middle of a computer screen to avoid eyes movement. During the eyes closed relaxed state, they were only asked to relax.

2.2.2. Sensory testing

PDP and PNP patients were examined for mechanical wind-up, the most sensitive mechanical test for the prediction of pain post SCI (Zeilig et al. 2012). Mechanical wind-up is a repeatable mechanical stimulus using a monofilament no. 6.65, causing a gradually increasing pain. The microfilament size was chosen to match the size used in a study by Zeilig et al. The stimulus was applied four consecutive times on the patients' feet and shins, with about 3s in between stimuli (Zeilig et al. 2012) producing a stronger stimulus than a standard pinprick test. Patients were asked to rate the intensity of pain after the first and fourth stimulus on a visual numerical scale. The test was performed at the time of EEG recording, i.e. when none of the patients actually had pain symptoms. Only patient 7 who later developed pain (PDP) reported discomfort.

2.3. Data Analysis

2.3.1. Demographic Analysis

We compared demographic (level of injury, time post injury and age) and descriptive factors (pain) between groups using ANOVA, and compared the completeness of injury using a non-parametric Kruskal-Wallis test. The completeness of injury was determined using the ASIA impairment scale, A to D numbered 1 to 4. The level of injury was assigned a number from 1 to 21, corresponding to the injury levels C1 to L2. For patients with different levels of injury on the right and on the left side, the higher level of injury was recorded. Tetraplegic patients are more likely to develop below level pain than paraplegic patients (Siddall et al. 2003, Mahnig et al. 2016). A recent study (Mahnig et al. 2016) also indicates that patients with complete injury (ASIA A) have most severe pain. However, it is believed that in general, there is no relation between the level or completeness of injury and pain (Siddall et al. 2003, Finnerup 2013).

Anticonvulsant drugs used by half of the PWP group might reduce the dominant alpha frequency and increase the theta and delta band power (Bauer et al. 2005). However medications were not included in the analysis as only PWP took analgesics, and 6 out of 11

of these patients took anticonvulsants. Tramadol, taken by 2 patients, does not affect EEG if taken in 150mg doses (Friedel 1978), though overdoes may cause seizures (Ryan and Isbister 2015). Response to mechanical stimuli was also not included in analysis as it was tested in the PDP group with 1 participant only reporting a response. In addition almost half SCI patients had a complete injury (ASIA A) and did not respond to this sensory test. Since two of the groups had only one female patient, differences due to sex were not investigated. All model residuals were tested for normality of distribution using an Anderson Darling test ($p > 0.05$) and found to be normal.

2.3.2. EEG Pre processing

EEG recordings were exported to the EEGlab toolbox in Matlab (Delorme and Makeig 2004). The EEG signals were then visually inspected and signals with artefact of an amplitude ≥ 100 μV across all electrodes were manually removed. The remaining EEG signal was then re-referenced to an average reference and decomposed into 48 independent temporal components using Infomax independent component analysis algorithm (Bell and Sejnowski 1995). This was implemented in EEGlab for further noise removal. The non-EEG components were identified and removed by considering their characteristic morphology, spatial distribution and frequency content. On average 3-4 components were removed, typically containing eye movement artifacts. Following removal of noisy components, inverse transformation was performed to return to the EEG domain. Noise removal was performed for each participant following EEG recording. Patients with and without pain were recruited at the same time. The experimenter performing noise removal was not blinded with respect to the presence of pain at the time of recording. However during noise removal it was not known whether patients belonged to PWP or PNP group, this was determined 6 months later. The AB group was recorded first followed by patient groups. EEG pre-processing was performed prior to this study as a part of sLORETA analysis (Jarjees 2017). The experimenter preforming classification was not involved in EEG pre-processing.

2.3.3. Feature Extraction

An EEG sequence of 1 min 40 seconds was extracted from EO and from EC of each participant, based on the shortest available EEG in patients after noise removal. Two participants in the PDP group had less than 60 seconds of EEG recording available after manual removal of noise, and therefore they were excluded from further analysis leaving 8 participants in this group.

EEG data was divided into 10 equal sequences, 10s long (10s x10=1 min 40 s), and features were extracted from each sequence independently. In this way for N participants in a group, 10*N training sets were provided for the EC and for the EO states.

All features were based on the power of the EEG signal in selected frequency bands. Power spectrum density was calculated based on Welsh periodogram, with 50% overlap. The power of a chosen frequency band was calculated by integrating the power spectrum density over a chosen range. EEG power in the EC and in the EO states were calculated in theta (4-8 Hz), alpha (8-12 Hz), beta (13-30 Hz) (Niedermeyer 2005) and wide band (2-30 Hz) ranges. For normalisation purposes, relative power was calculated by dividing the power in the theta, alpha or beta bands by the wide band power. Additional features were calculated as a ratio between the relative powers EO/EC for each frequency band. In this way, 9 features were extracted for each channel: relative theta band power in EC and in EO, relative alpha band power in EC and in EO, relative beta band power in EC and EO, EO/EC ratio of theta band power, EO/EC ratio of alpha band power and EO/EC ratio of beta band power. All calculations were implemented in Matlab.

2.3.4. Feature Classification

Four linear and non-linear classifiers of different complexity were chosen: Linear Discriminant Analysis (LDA), Support Vector Machine (SVM), Naïve Bayesian (NB) and Artificial Neuronal Network (ANN) (Duda et al. 2000). The reason was to test which classifier had the best generalising properties of transfer learning on a relatively small number of training sets.

Linear Discriminant Analysis (Fisher 1936, Duda et al. 2000) is the method that was used to find a linear combination of features that characterise two classes. It projects measurements into another axis in which measurement of different classes are linearly separable.

$$h(t) = A^t \cdot f \tag{1}$$

Where *f* is the original set of features, *A* is transformation and *h(t)* is a linear discriminant function.

To achieve this, LDA optimises between class variance and within class variance.

$$\alpha = \frac{between\_class\_\mathrm{var}iance}{within\_class\_\mathrm{var}iance} \tag{2}$$

For the best separation of classes, α should be maximised by increasing between class variance with respect to within class variance.

LDA was implemented in Matlab, setting prior probabilities to "empirical" which means that the prior probability of class *k* is the number of training samples of class *k* divided by the total number of training samples, as classes (participants' groups) have different numbers of training data. LDA assumes that different classes have the same covariance matrix.

Naïve Bayesian classifier is based on Bayesian theory that describes the probability of an event occurring based on conditions that could be related to this event.

$$P(A \mid B) = P(A) * \frac{P(B \mid A)}{P(B)} \tag{3}$$

Where *P(A)* and *P(B)* are prior probabilities of *A* and *B* independently of the other event and *P(A|B)* is the probability of *A* when *B* is true and *P(B|A)* is the probability of *B* when *A* is true.

NB adopts "naïve" assumption that events are independent, i.e. that the presence of a particular feature in a class is unrelated to the presence of any other feature (Manning et al. 2008).

Support Vector Machine is a supervised learning method that calculates a hyperplane spatially separating training data of different classes (Cortes and Vapnik 1995). It aims to maximise margins, i.e. maximum distances between input data points belonging to different classes, which are closest to the hyperplane and which are called support vectors. The goal of SVM is to minimise the classification error while maximising hyperplane margins. It may create non-linear barriers and is therefore more suitable for complex datasets which may not be linearly separable. The separation hyperplane is in the middle of two classes and is defined as

$$w^T X + b = 0 \tag{4}$$

Where w^T is a transposition of the weights matrix, *b* is a constant (bias) and *X* are input measurements.

To determine the class of the measurement, the classifier output is assumed to be y=1 for class 1 and y= -1 for class 2. The decision rules of the classifier are given by

$$\begin{aligned} w^T X_i + b \geq 1 \quad if \quad y = +1 \\ w^T X_i + b \leq 1 \quad if \quad y = -1 \end{aligned} \tag{5}$$

where i=1…m, and m is the number of inputs.

In SVM the optimal hyperplane and the support vectors can be estimated from a small quantity of data such that SVM can have optimal generalisation of classification.

Artificial Neural Networks were inspired by the human neural system, thus they have a "neuron" as a basic unit (Principe 2000). Neurons are connected through "synapses", and neuronal weights are iteratively adapted during a training process. A feed forward ANN consists of an input layer, one or more hidden layers and one output layer. The number of neurons in the input layer corresponds to the number of training features while the number of neurons in the output layer corresponds to the number of classes. ANN used in this project was a feedforward perceptron network with one or two hidden layers with up to 10 hidden layer neurons.

The perceptron z is mathematically modelled as

$$z = \sum_{i=1}^{N} x_i w_i + b \quad \text{and} \quad y = f(z) \qquad (6)$$

-

Where x_i are inputs, N is the number of inputs, y is the output, w_i is the weight of input i, b is a bias and z is perceptron, modelled as a sigmoidal function. The back propagation algorithm passes the error signals backwards through the network during training to update the weights. We used iterative method based on Levenberg-Marquadrat algorithm (Hagan and Menhaj 1999) that in each step updates weights w_i aiming to achieve the maximum error decrease.

For each classifier, classification accuracy, sensitivity and specificity were calculated.

$$\text{Accuracy} = (TP+TN)/(TP+TN+FP+FN) \qquad (7)$$

$$\text{Specificity} = TN/(TN+FP) \qquad (8)$$

$$\text{Sensitivity} = TP/(TP+FN) \qquad (9)$$

Where TP is true positive, TN is true negative, FP is false positive and FN is false negative.

2.3.5. Statistical Analysis

A Mann-Whitney U test was used to calculate a z score for each feature F and for each channel C. This resulted in a matrix of dimensions N_C x N_F, i.e. 48x9 containing z values of the corresponding tests. Because each EEG recording was divided into 10 samples, for each channel there were 10 values of each feature f_i (i=1… N_C x N_F). For N_A participants in group

A there were $10xN_A$ values of feature f_i and for N_B participants in group B, there were N_Bx10 values of the corresponding feature f_i.

A Mann-Whitney U test was performed between these two sets each time leaving out one participant from either group A or B and repeating this N_A+N_B times. Because of a relatively large number of samples for a nonparametric test, z statistic was implemented (Gibbons and Chakraborti 2011). The final *z* value for feature $f_{i,}$ as presented in the Result section, was obtained by averaging over N_A+N_B values for each single feature. This resulted in N_C x N_F values of *z*. Finally, to rank channels from 1 to N_C, the z values for one channel over all N_F features ($N_{F=}9$) were summed up, giving 48 values, one for each channel. Summing up across all 9 features rather than choosing the best individual feature was done to avoid overfitting which might happen if the best feature for each channel was selected. When ranking channels, larger sum of *z* values corresponded to channels with higher separability between classes. Note that here a Mann-Whitney U test was not used to test equality of medians between two groups but only to rank features. All procedures were implemented in Matlab.

We compared classification results of 4 different classifiers for different numbers of EEG channels using ANOVA. Based on results of demographic analysis we performed Spearman's Rho correlations between classifier performances demographic factors and between classifier performance and the level of pain.. A 95% confidence interval was calculated for all classification results presented in figures and tables.

2.3.6. Flow Diagram

A flow diagram representing feature extraction and classification process is shown in Fig 1. There were three classification stages in total. Classification 1 (see Fig. 1) was first performed including all features N_F=9 and varying the number of channels from N_C=1 to 18. This number is close to the number of channels in the10-20 EEG system, typically available in clinical settings (though the channel locations corresponded to 10-10 rather than to 10-20 but depended on the *z* values). An "optimum" smaller subset of channels N_{CO} was defined based on a classification error and on a requirement to minimise the number of channels to create classifiers applicable for a variety of EEG devices including those with smaller numbers of electrodes.

Classification 2 was performed for each of the 9 features separately, to measure the contribution of each feature to the classification accuracy. Based on these results and on previous knowledge of EEG signatures of CNP (Vuckovic et al. 2014), features were finally

grouped to create several sets of features, each containing N_{FO} features, $N_{FO}<N_F$. We defined 5 feature subsets: 1. EO theta and EC theta (2 features per channel), 2. EO alpha and EC alpha, 3. EO beta and EC beta, 4. EO theta, EO alpha and EO beta (3 features per channel), 5. EC theta, EC alpha and EC beta. This classifier (Classifier 3) had a higher ratio between the number of training samples and features, important for classification with a relatively small number of training samples (Jayaram et al. 2016). It should be noted that although 3 classification stages were used, the first classifier only can be used when large numbers of channels is available. The purpose of classifiers 2 and 3 were to (i) reduce the number of channels and features and (ii) understand the nature of features which contribute the most to classification.

Each classifier test set was created by the leave-one-out method, repeating this as many times as the number of participants in each groups, and presenting averaged results.

Figure 1 about here

3. Results

3.1. Analysis of Demographic Factors

No differences were found in age ($F = 0.24$, $p = 0.787$), time post injury ($F = 3.17$, $p = 0.057$) or completeness of injury ($F = 0.53$, $p = 0.767$) between groups. However, pain score ($F = 8.53$, $p = 0.009$) and injury levels ($F = 4.79$, $p = 0.016$) differed between groups. The PWP group scored 2.3 points higher than the PDP group (0.8, 3.8), 95% confidence interval (CI), $p = 0.005$. Patients with no pain (PNP) had injury levels that were 8 levels (1, 14) 95% CI lower than the PDP group ($t2 = 2.96$, $p = 0.019$).

3.2. Power spectrum density in different groups

In Jarjees (2017) sLORETA group analysis of EEG, large differences were found between groups in the parietal area and the absence of statistically significant differences between the EO and EC state in theta and beta range in PDP and PWP groups. Figure 2 shows PSD in the EO and EC states for all 4 groups at a representative electrode location P2. The shaded areas represent 95% confidence intervals. All patient groups had larger maximum alpha power than the AB group, in both the EC and EO state. Whilst the ratio between average peaks in EO and EC in AB and PNP groups was roughly 1:4 and 1:5 in both PDP and PWP it was 1:2 or less. This explains why for classification between groups, in particular between AB and

patient groups one could choose either EO and EC in one band or the whole power spectrum in EC.

Figure 2 about here

The main aim of the study was to create a classifier that could correctly classify participants to PNP or PDP groups. Detailed analysis of the results was presented for this case, followed by classification results for the other five pairs of groups (PDP vs PWP, PDP vs AB, PNP vs PWP, PNP vs AB, PWP vs AB).

3.3. Classification Results

Figure 3 shows accuracy, sensitivity and specificity when all 9 features were used for classification and when the number of channels varied from 1 to 18. The average classification accuracy for LDA was 77 ± 5%, for NB 65 ±4%, for SVM 76 ±9% and for ANN 79±7.

Figure 3 about here

3.3.1. Analysis of Variance

Anderson-Darling test compared the normal distribution of classification results. Two factor ANOVA analysis (factor one classifiers and factor two the number of channels) showed that there was a statistically significant difference in classification accuracy between different classifiers ($F=40.52$, $p=0.0000$) and between different numbers of channels included in classifiers ($F=19.24$, $p=0.0000$) and that there was a statistically significant interaction between two factors ($F=1.92$, $p=0.0449$). The NB classifier has significantly lower classification accuracy than the other three classifiers, and SVM had significantly lower classification accuracy than ANN (NB vs LDA $p=1.4764e-10$, NB vs SVM $p=1.8884e-06$, NB vs ANN $p=4.2641e-10$, LDA vs SVM $p=0.6628$, SVM vs ANN $p=0.0359$, LDA vs ANN $p=0.1287$).

It can also be noticed that with regards to the LDA classifier, the accuracy and sensitivity dropped for larger numbers of channels while for ANN and SVM it reached a plateau. Drop in classification accuracy for LDA suggest that additional features decreased separability between classes. Channels were ranked based on Mann Whitney U test z score, so channel one had most discriminable feature, followed by channel 2 etc. Thus each additional channel contained less discriminable features which could potentially be redundant leading to lower classification accuracy. ANN and SVM were insensitive to adding redundant features, and

their classification accuracy remained unchanged after reaching a plateau. For this reason, the 10 best channels were selected to create a classifier based on one feature only.

3.3.2. Correlation Analysis

Correlation was analysed between LDA and ANN classification accuracy and demographic and descriptive factors. Analysis of variance of demographic factors found a significant difference in the level of injury between PDP and PNP and between PDP and PWP, as well as a significant difference in the level of pain between PDP and PWP. We performed this analysis for three representative number of channels 3, 10 and 18.

Comparing PDP and PNP groups, there was no significant ($p<0.05$) correlation between the level of injury and classification accuracy for none of 4 classifiers (including 3, 10 or 18 channels). Likewise there was no significant correlation between the level of injury and classification accuracy between PWP and PNP. There was also no significant correlation between the intensity of pain and classification accuracy between PDP and PWP. Values of R^2 and p parameters are provided in the supplementary Appendix (Table A1).

3.3.3. Feature Analysis

Figure 4 shows accuracy, sensitivity and specificity for each feature and each classifier separately. EO alpha and EO beta individual features achieved the highest accuracy, using LDA and ANN classifiers respectively. Features based on beta ratio and EO theta achieved the overall worst accuracy with all 4 classifiers and their sensitivity was also low.

For the final classifier the following sets of features were created a) EO theta and EC theta, b) EO alpha and EC alpha, c) EO beta and EC beta, d) EO theta, EO alpha and EO beta, e) EC theta, EC alpha and EC beta.

Figure 5 shows accuracy, sensitivity and specificity for feature sets a-c based on a single frequency band in the EO and EC states, which should utilise a difference in reactivity between EO and EC, in PDP and PNP. The LDA classifier based on alpha band parameters and ANN based on beta band parameters, received the highest classification accuracy (over 80%) having also comparably high sensitivity and specificity.

Figure 6 shows accuracy, sensitivity and specificity for classifiers based on the sets of features d and e which utilised the information about the overall power over the bands in both

the EO or EC states. The LDA classifier performed the best for both EO and EC and it had a good balance between accuracy, sensitivity and specificity.

For all other five pairs of groups, classification was performed following the same procedure.

Figure 5 about here

Figure 6 about here

Table 3 shows the best classification accuracy for all 6 pairs when all 9 features were included in the training/testing sets and when the number of channels varied between 1 and 18. In five out of six cases, the ANN classifier performed the best and in one case the LDA classifier showed the best performance. For ANN classifiers, structures with 1 and 2 hidden layers with up to 10 neurons per layer were tested. Judging by the number of required channels, classifications PWP vs PDP and PWP vs PNP were the most complex tasks. The best classification accuracy between PDP and PNP was 89%, with also comparably high sensitivity and specificity. Classification accuracy between all 6 pairs of groups was high, between 87% and 90%.

Table 3 about here

Tables 4 and 5 show classification results based on 10 channels only, with the optimal subset of features, considering ANN and LDA classifiers for PNP vs PDP, AB vs PDP, AB vs PNP, AB vs PWP, PNP vs PWP and PDP and PWP. Both ANN and LDA classifiers achieved comparably high classification accuracies over 80% with the exception of LDA for PDP vs PWP. Importantly, these results show that the chosen EEG features are linearly separable. This is relevant because it is much easier to set LDA than ANN parameters. ANN structures with larger numbers of neurons were used to improve classification accuracy. The most difficult task was to classify between PDP and PWP, requiring the largest number of neurons for ANN and achieving the lowest classification accuracy for LDA. This is not surprising, because both groups' EEGs contained some signatures of CNP. The best classification results were achieved between AB and PNP for both ANN and LDA classifiers.

Classifiers of six different pairs had different "optimal" features, i.e. features used to achieve the highest classification accuracy. Alpha band features were optimal only for PDP vs PNP. For AB vs PDP and AB vs PNP optimal features comprised of power of all three

bands in EC. For classification between PWP and any other group, optimal features were in the beta band.

Figure 7 shows the location of the best 10 channels (used for classification presented in Tables 2 and 3) for six different pairs. Some electrode clustering could be noticed in the left centro-parietal area for classification between PDP and both groups without pain, AB and PNP as well as for classification between PNP and PWP. For classification between AB and PWP two clusters of electrodes in the occipital and frontal region can be noticed and for classification between AB and PNP clustering can be observed towards the parietal and occipital areas. Electrodes with the largest separability between PDP and PWP were located towards the temporal areas on both sides of the cortex. Note that due to the nature of EEG recording, clusters of neighboring electrodes most likely recorded cortical activity from the same source.

Table 4 about here

Table 5 about here

Figure 7 about here

4. Discussion

This study showed that it was possible to identify, at the individual participant level, the presence of CNP markers, based only on spontaneous EEG. Classification accuracies between 87% and 90% were achieved. From the published literature, it is known that in the chronic stage post injury, both SCI and CNP patients have identifiable EEG markers (Sarnthein et al. 2006, Stern et al. 2006, Boord et al. 2008, Jensen et al. 2013, Vuckovic et al. 2014). This was however evident only when average EEG activity of a representative group, rather than individual EEG was analysed. Furthermore, patients in these studies had chronic pain, persisting over several years. Central neuropathic pain develops in most of SCI patients within the first 6 months of injury (Siddall et al. 2003, Finnerup et al. 2013). Therefore identifying EEG predictors of pain is most relevant in patients with subacute SCI. There are two novel aspects to this study: (i) classification/prediction at the individual participant level at different stages of developing CNP (ii) identifying these differences within a few months of injury.

This study provides evidence that although neural plasticity following SCI leading to CNP is a cumulative process, it does not take years but rather months. Also of interest is that only

one participant in the PDP group responded to sensory testing, indicating that the risk of developing pain could be detected before the participant develops sensory discomfort, providing a greater time window to apply preventive treatments.

In an animal study (LeBanc et al. 2016) it was shown that increased theta power, a marker of early onset CNP could be reversed by taking pregabalin. Similar preventive treatment might also work in humans. Interestingly, although increased theta band power is considered one the of main signatures of long standing CNP (Sarnthein et al. 2006, Stern et al. 2006, Boord et al. 2008, Vuckovic et al. 2014), none of the "optimal" 10 channel classifiers were based on theta band features. These results suggest that changes in the theta band might occur more gradually, and are therefore not evident in "early" CNP.

Although classifiers based on the entire set of features achieved the best classification accuracy, classifiers based on a subset of features provided information about the frequency band that provided the largest separability between classes. Alpha band features in both the EO and the EC states were most relevant for classification between PNP and PDP indicating possibly large differences in alpha reactivity (changes in EEG power upon opening eyes) between these two groups. Group sLORETA analysis of this data (Jarjees et al. 2017) also found significant differences between PNP and PDP in the alpha band in the parietal area (BA7). Previous studies that analyzed EEG power in patients with chronic CNP (Boord et al. 2008, Vuckovic et al. 2014) reported reduced reactivity (ration of EO and EC power), attributed to thalamo-cortical dysrhythmia (Boord et al. 2008). That can explain why combining alpha power in both EO and EC provided good classification accuracy.

On the other hand, beta band features in EO and EC provided the best separability between PWP and all other groups, indicating that EEG markers of pain evolve during the transition from PNP to PDP and then from PDP to PWP.

We did not follow up patients for longer than 6 months after the initial EEG recording, thus some patients in the PNP group might later have developed pain. EEG responses could also change over time as a consequence of chronic paralysis even without pain (Tran et al. 2004). Central neuropathic pain typically develops in six months post injury (Siddall et al. 2003) therefore in this study we focused on the subacute SCI phase to identify patients who had not yet developed pain.

Electrodes with larger separability between PDP and groups without pain (PNP and AB) were found in the left parietal cortex, corresponding to the secondary somato-sensory cortex.

Other areas known to be involved in processing of long standing chronic pain such as the anterior cingulate cortex, insular cortex and ventrolateral orbitofrontal cortex (Jensen 2010) could not be easily assessed by surface EEG, but our sLORETA analysis (Jarjees 2017) found no significant differences in these areas.

We used four different classifiers of different complexity in order to find a compromise between achieving good classification accuracy and overfitting. Transferable learning classifiers based on LDA and SVM, used here, have been previously used to separate EEG data in Brain Computer Interface studies (Pan and Jang 2010, Krauledat et al. 2008, Fazli et al. 2009, Vinay Jayaram 2015). We also included NB classifiers because of their relatively simple structure and the ANN classifier due to its ability to classify non-linear problems and greater possibility to adapt its structure (the number of neurons and hidden layers) for a given problem. ANN, LDA and SVM achieved comparable classification accuracy but ANN and LDA had higher sensitivity and specificity than SVM. The only disadvantage of LDA, unlike ANN and SVM, was that increasing the number of features leaded to redundancy and a decrease in performance. SVM had comparable classification results to ANN and LDA and although it would require slightly more parameter setting than LDA, it would also be a good classifier candidate. NB performed significantly worse than other classifiers, probably because of its assumption of independence of classified features. None of the classifiers were sensitive to the level of injury or pain, three out of four classifiers was mainly due to high separability of selected features, based on published literature (Sarnthein et al. 2006, Stern et al. 2006, Boord et al. 2008, Jensen et al. 2013, Vuckovic et al. 2014,) and a group sLORETA analysis of these datasets (Jarjees 2017).

The fact that in most cases LDA performed as well as ANN is very encouraging because of LDA's simple structure. Classification accuracy of 85.6% was achieved by LDA based on alpha band and 10 channels, close to best classification accuracy of 89% achieved by ANN and 12 EEG channels. Importantly, specificity and selectivity were comparably high, indicating that classifiers were not biased towards false positives or false negatives. NB performed significantly worse than the other three classifiers.

Finally, although the maximum classification accuracy of 89% between PDP and PNP was relatively high, for clinical applications, accuracies should be closer to 100%. In order to achieve this, larger datasets would be required. For practical purposes, to predict the chance of developing pain (e.g. to classify between patients that would belong to PNP or PDP) one

could either use multichannel recording and all features or if less electrodes are available, record EEG from the parietal area and use EEG power in the EO and EC state in theta, alpha and beta range as classification features.

Conclusions

Early EEG signatures of CNP in SCI patients appear within months of injury, before signs of sensory discomfort, i.e. allodynia. This study demonstrates a classifier that could identify with almost 90% accuracy SCI patients at risk of developing CNP. Using transferable classifiers it was also possible to differentiate between different stages of CNP and to discriminate between AB and SCI patients with and without pain. Complex nonlinear classifiers based on ANN and simple LDA and SVM classifiers had comparable performances. For a simple classifier with a reduced number of electrodes and smaller number of features, EEG should be recorded from the parietal area and features should be based on the power in the alpha and beta bands in the EO and EC states.

Acknowledgements

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Conflict of interest

None.

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TABLES

Table 1. Demographic information of SCI patients who later developed pain (PDP) and who already had pain (PWP). ASIA A: complete sensory and motor loss; B incomplete sensory, complete motor loss; C and D incomplete sensory and motor loss. Level of injury: C cervical, T thoracic, L lumbar.

No.	Age	Pain VNS	Level of injury	Completes of injury	Weeks after injury	Weeks Pain	Medications
				PDP		Weeks before pain	
1	70	4	T7/T8	D	9	6	/
2	49	2	T12	A	6	10	/
3	19	6	C5/C6	A	12	4	/
4	69	1	L2	B	6	4	/
5	32	4	T3	A	24	8	/
6	46	4	T5	A	6	7	/
7	49	6	T6	A	4	2	/
8	32	2	C3	A	6	4	/
				PWP		Weeks with pain	
1	33	9	T12	B	20	20	pregabalin
2	59	6	T7/T8	A	12	12	gabapentin
3	64	7	C3/C4	D	16	16	tramadol
4	27	5	C5/C6	A	17	15	tramadol
5	32	5	T3	A	24	6	pregabalin
6	30	7	T10	A	12	12	/

7	59	5	T8	C	26	26	/
8	29	6	C3	D	6	6	/
9	37	8	T6	B	28	28	pregabalin
10	49	7	C4	A	6	6	gabapentin
11	75	7	T6	C	6	6	gabapentin

Table 2. Demographic information of SCI patients without pain (PNP) and able-bodied (AB) participants. ASIA A: complete sensory and motor loss; B incomplete sensory, complete motor loss; C and D incomplete sensory and motor loss. Level of injury: C cervical, T thoracic, L lumbar.

PNP					AB
No	Age	Level of Injury	Completeness of Injury	Weeks after injury	Age
1	51	T7,T10	D	12	37
2	22	L1	B	12	32
3	47	T11	D	7	36
4	41	T12	A	4	34
5	59	T6	A	12	32
6	43	T6/T7	B	21	27
7	24	L1	A	7	45
8	38	L1	A	4	34
9	62	T3,T5	A	10	49
10	34	T6	A	10	27

Table 3. Best classification results (main criteria: accuracy) for classification between different groups. Nr Channels: Number of EEG channels. ANN: Artificial Neural Networks, LDA: Linear Discriminant Analysis. All nine features per channel were used for classification. For ANN there were 2 hidden layers with 10 and 5 neurons respectively. Results presented as mean±std, numbers in square brackets represents 95% lower and upper confidence intervals.

Groups	Classifier	Nr Channels	Accuracy	Sensitivity	Specificity
PNPvsPDP	ANN	12	89±11 [88, 91]	89±13 [87, 91]	90±10 [89, 91]
ABvsPDP	ANN	17	91±10 [89, 92]	84±11 [82, 85]	96±5 [95, 98]
ABvsPNP	ANN	9	89±11 [87, 91]	88±14 [86, 90]	90±8 [89, 91]
ABvsPWP	LDA	9	88±10 [86, 89]	89±7 [88, 90]	86±12 [84, 88]
PNPvsPWP	ANN	18	87±9 [86, 89]	85±10 [84, 87]	90±8 [79, 100]
PDPvsPWP	ANN	18	87±12 [86, 89]	85±10 [84, 87]	90±7 [89, 91]

Table 4. Classification accuracy of LDA classifier for features shown in column 'Features' for the 10 best EEG channels. LDA: Linear Discriminant Analysis. Results presented as mean±std, numbers in square brackets represents 95% lower and upper confidence intervals.

LDA				
Groups	Features	Accuracy	Sensitivity	Specificity
PNP vs PDP	EO,EC alpha	86±10.1 [84, 87]	84±9 [82, 87]	87±11 [85, 89]
AB vs PDP	EC theta, alpha beta	81±9 [80, 82]	77±8 [76, 78]	84±9 [83, 85]
ABvsPNP	EC theta, alpha beta	89±10 [88, 90]	95±8 [94, 96]	83±8 [82, 84]
ABvsPWP	EO,EC beta	82±13 [80, 84]	77 ±11 [76, 79]	87±13 [85, 89]
PNPvsPWP	EO,EC beta	84±12 [82, 85]	90±6 [89, 91]	77±13 [75, 79]
PDPvsPWP	EO,EC beta	76±15 [74, 78]	86±12 [84, 87]	64±10 [62,65]

Table 5. Classification accuracy of ANN classifier for features shown in column 'Features' for the 10 best EEG channels. ANN: Artificial Neural Networks, NrL: number of hidden layers; NrN: number of neurons per layer. Results presented as mean±std, numbers in square brackets represents 95% lower and upper confidence intervals.

ANN					
Groups	Features	Accuracy	Sensitivity	Specificity	NrL/NrN
PNPvsPDP	EO, EC alpha	83±13 [81,85]	83±16 [89,85]	84±11 [82,86]	1/5
ABvsPDP	EC theta, alpha beta	83±13 [81,86]	82±13 [81,84]	83±12 [81,85]	1/6
ABvsPNP	EC theta, alpha beta	88±11 [86,90]	89±12 [87,91]	87±9 [86,88]	2/1&1
ABvsPWP	EO, EC beta	82±14 [80,84]	83±10 [81,84]	81±18 [79,84]	1/3
PNPvsPWP	EO, EC beta	86±8 [85,87]	85±9 [84,87]	86±7 [85,87]	2/4&4
PDPvsPWP	EO, EC beta	84±11 [82,85]	87±9 [86,89]	79±12 [77,81]	2/6&6

FIGURE LEGENDS

Figure 1. Flow diagram of the study. Note that although it represents three stages of classification, the first stage can be used alone with a multichannel EEG. The first classifier uses all features. The second classifier uses only one feature while the third classifier uses a sub-set of features.

Figure 2. Average power spectrum density for eyes opened (EO) and eyes closed (EC) states for each group for electrode locations P2. Shaded areas represent 95% confidence intervals. AB: able bodied, PNP: Patients with no pain, PDP: patients who eventually developed pain, PWP: patients with pain.

Figure 3. Classification accuracy (a) sensitivity (b) specificity (c) as a function of the number of EEG channels, for four different classifiers used to classify between patients who developed pain (PDP) and patients who did not develop pain (PNP) groups using all 9 features. Shaded areas correspond to 95% confidence intervals. LDA: Linear discriminant analysis, SVM: Support vector machine, ANN Artificial neural network, NB: Naïve Bayesian.

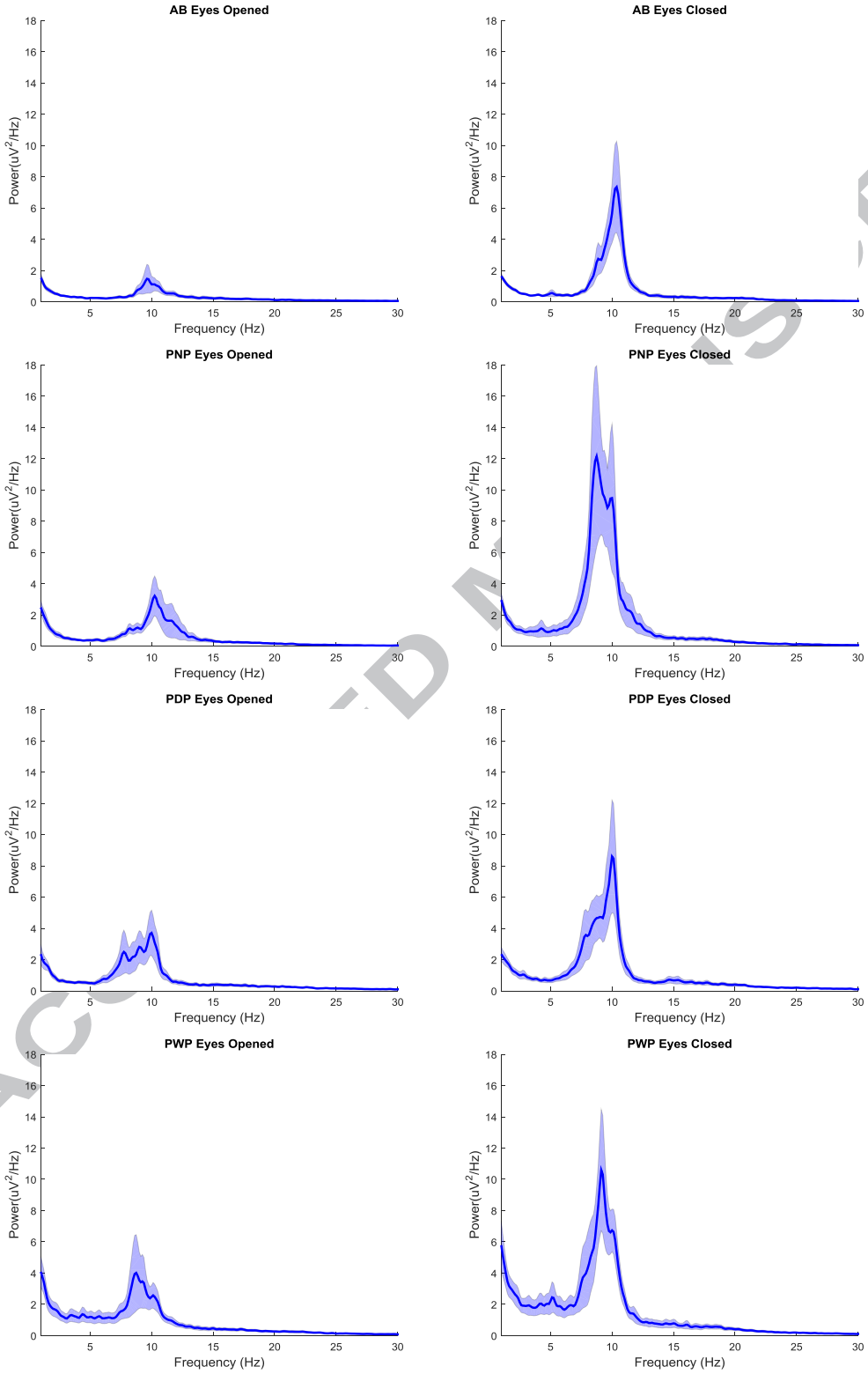
Figure 4. Classification between patients who developed pain (PDP) and patients who did not develop pain (PNP). Accuracy (a), sensitivity (b) specificity (c) of 4 different classifiers trained on a single feature on the selected 10 channels. Bars represented 95% upper and lower confidence interval. *x* axis labels: 1 EO/EC Theta, 2 EO/EC Alpha, 3 EO/EC Beta, 4. EO Theta, 5. EO Alpha, 6. EO Beta, 7. EC Theta, 8. EC Alpha, 9. EC Beta. LDA: Linear discriminant analysis, SVM: Support vector machine, ANN Artificial neural network, NB: Naïve Bayesian.

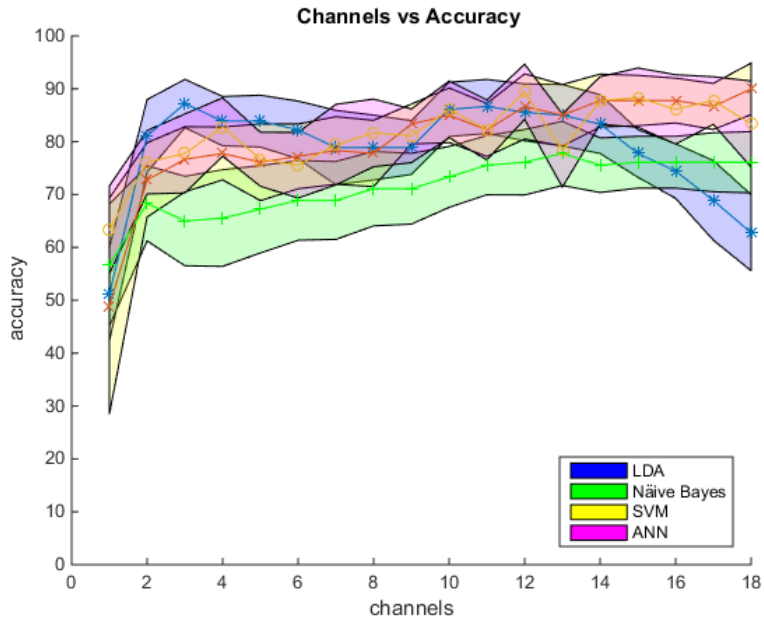
Figure 5. Classification between patients who developed pain (PDP) and patients who did not develop pain (PNP) using 4 different classifier (mean ±standard error): a) accuracy, b) selectivity, c) specificity. Selected features were EO and EC power for different frequency bands, over the 10 best EEG channels. The coloured areas represent confidence intervals while the grey shaded areas represent standard deviation. LDA: Linear discriminant analysis, SVM: Support vector machine, ANN Artificial neural network, NB: Naïve Bayesian.

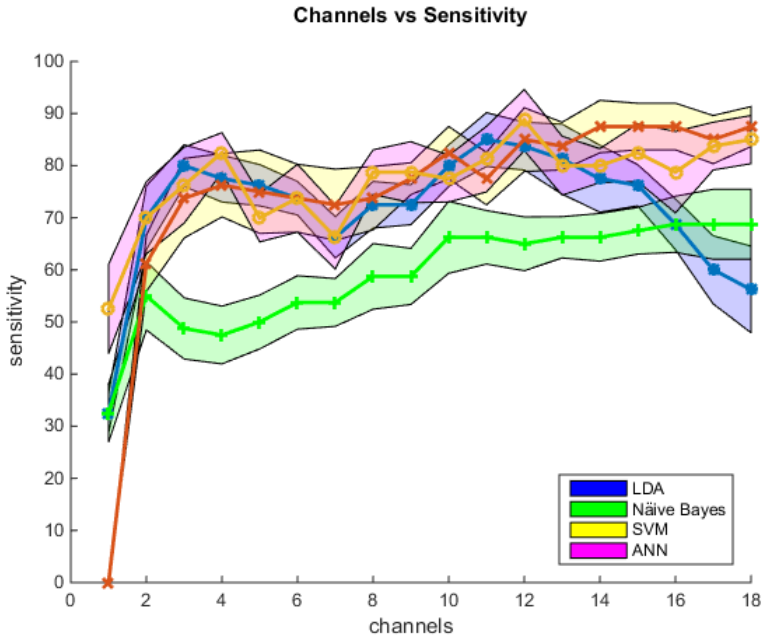
Figure 6. Classification between patients who developed pain (PDP) and patients who did not develop pain (PNP) using 4 different classifiers (mean ±standard error): a) accuracy, b) selectivity, c) specificity. Selected features were EO or EC power for all three frequency

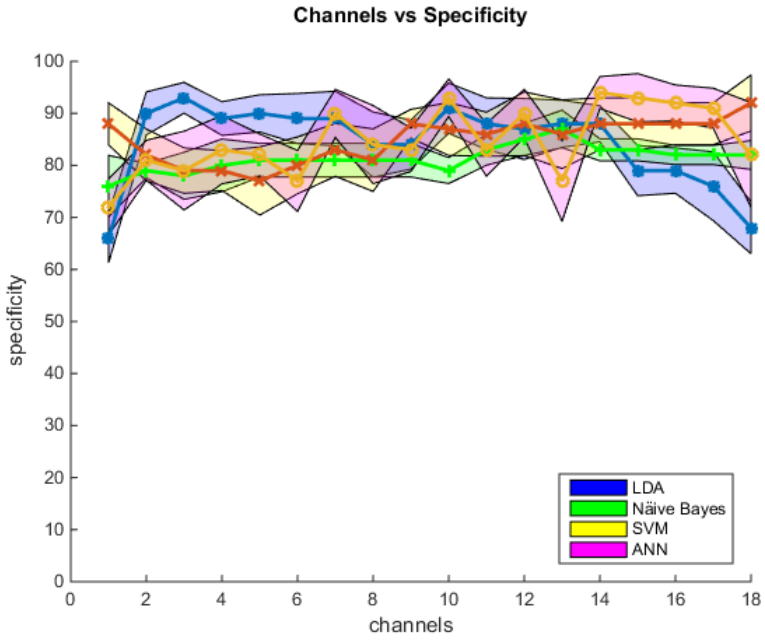
bands (theta, alpha and beta), over the 10 best EEG channels. The coloured areas represent confidence intervals while the grey shaded areas represent standard deviation LDA: Linear discriminant analysis, SVM: Support vector machine, ANN Artificial neural network, NB: Naïve Bayesian.

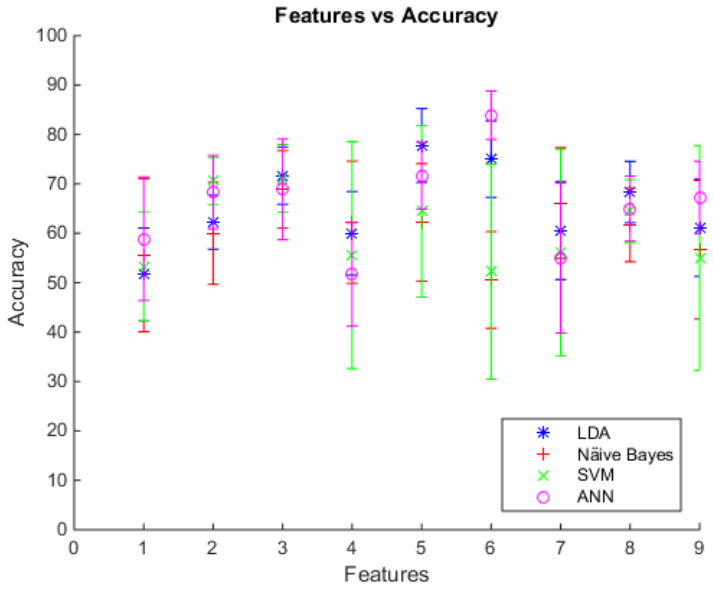
Figure 7. Location of the 10 best channels for classification between different groups. Dots represent the locations of all 48 channels; the large dots show the10 selected channels. On the scalp maps, the nose is oriented towards the top of the page. AB: able bodied, PNP: Patients with no pain, PDP: patients who eventually developed pain, PWP: patients with pain.



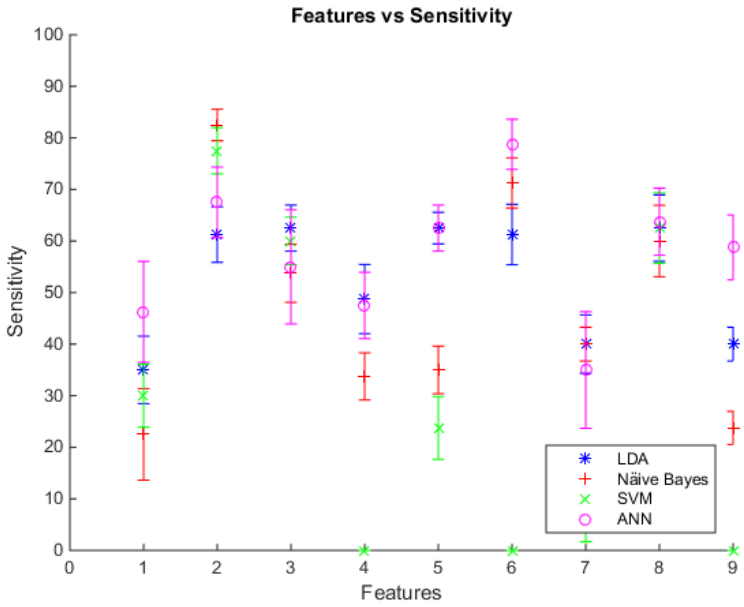




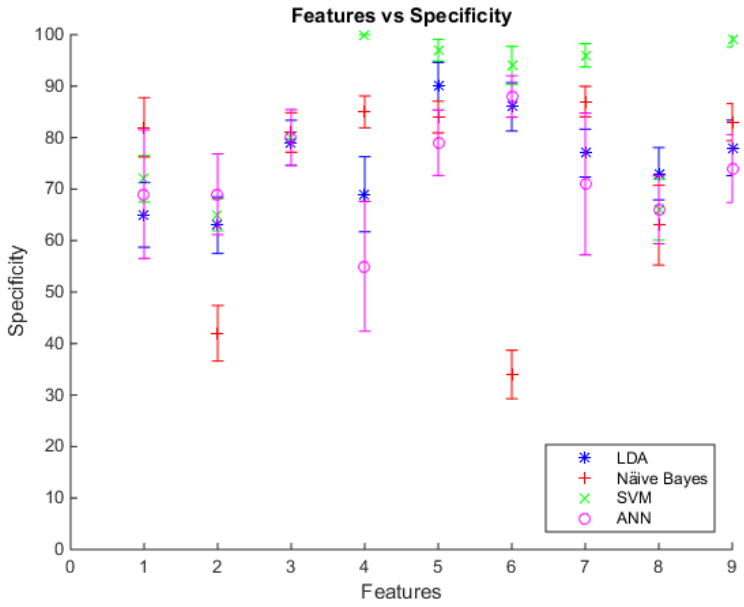



Features vs Accuracy
Accuracy
Features
LDA
Näive Bayes
SVM
ANN

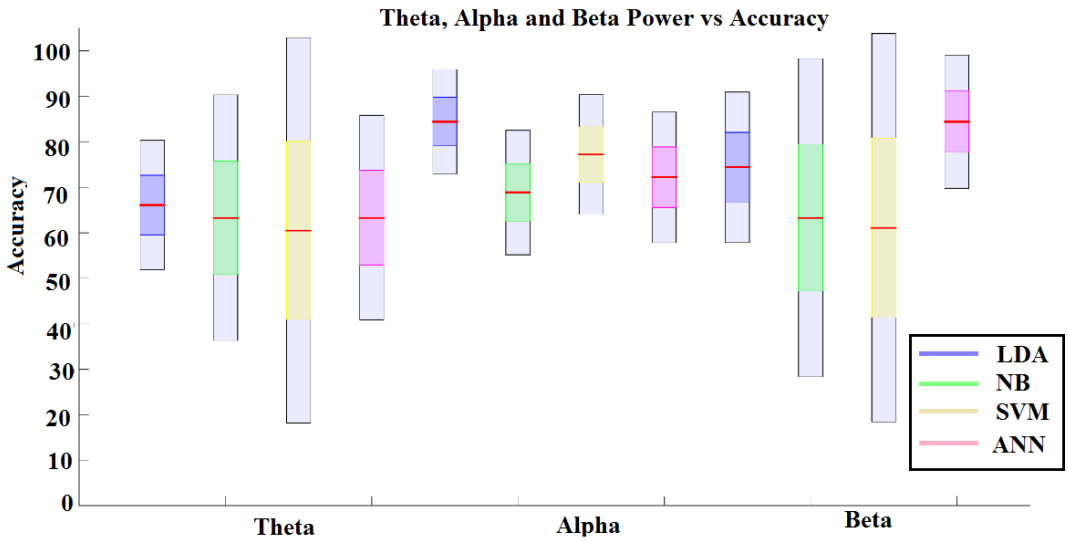
(a)


Features vs Sensitivity
Sensitivity
Features
LDA
Näive Bayes
SVM
ANN

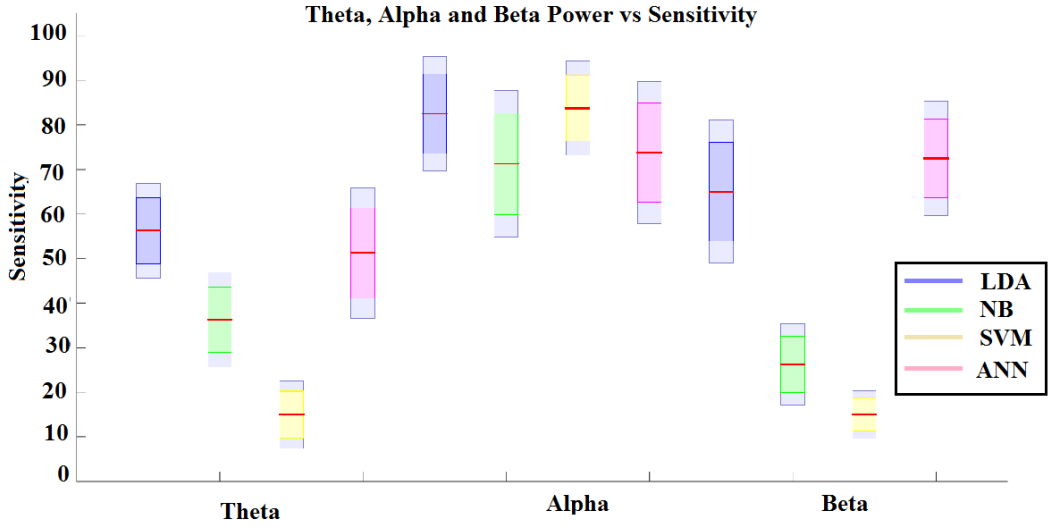
(b)


Features vs Specificity
Specificity
Features
LDA
Näive Bayes
SVM
ANN

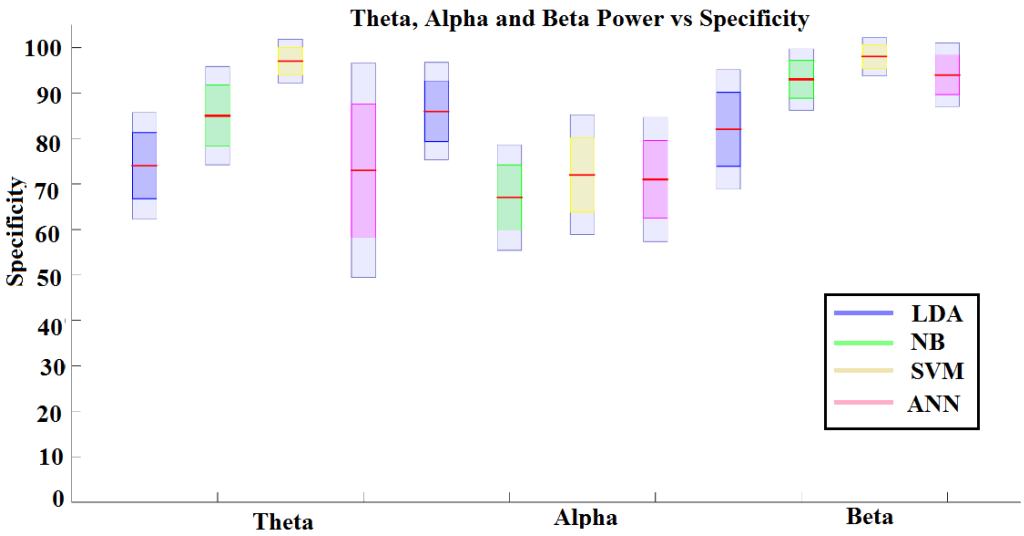
(c)



(a)

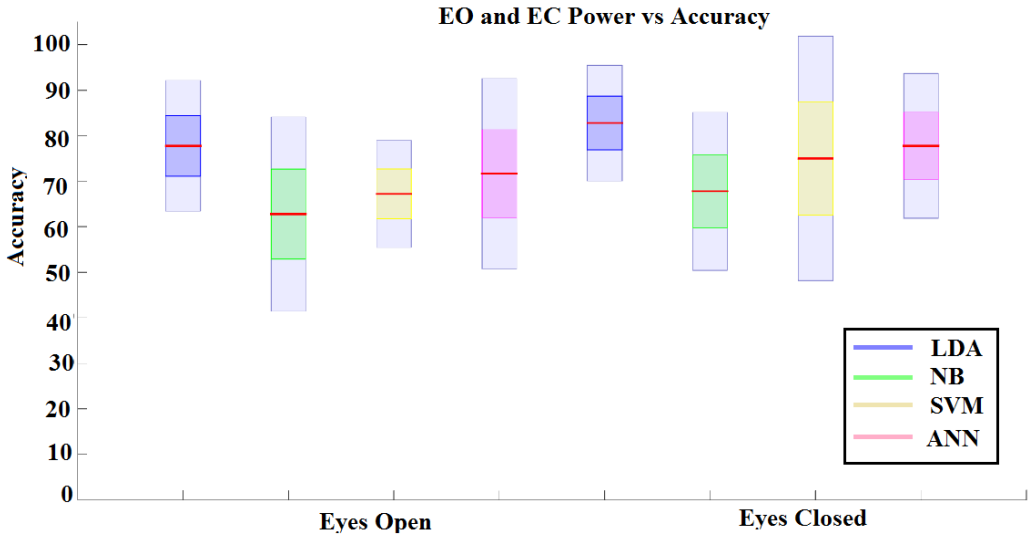


(b)

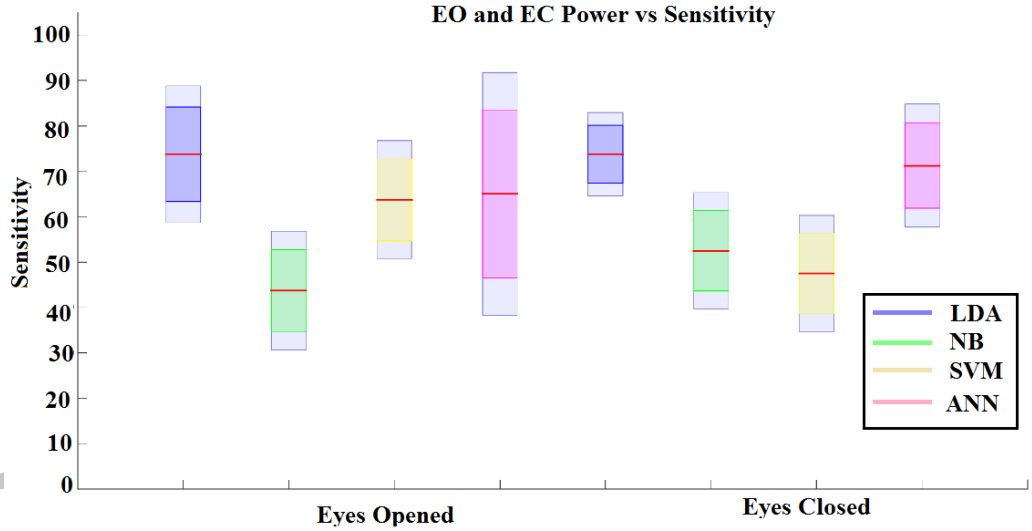


(c)

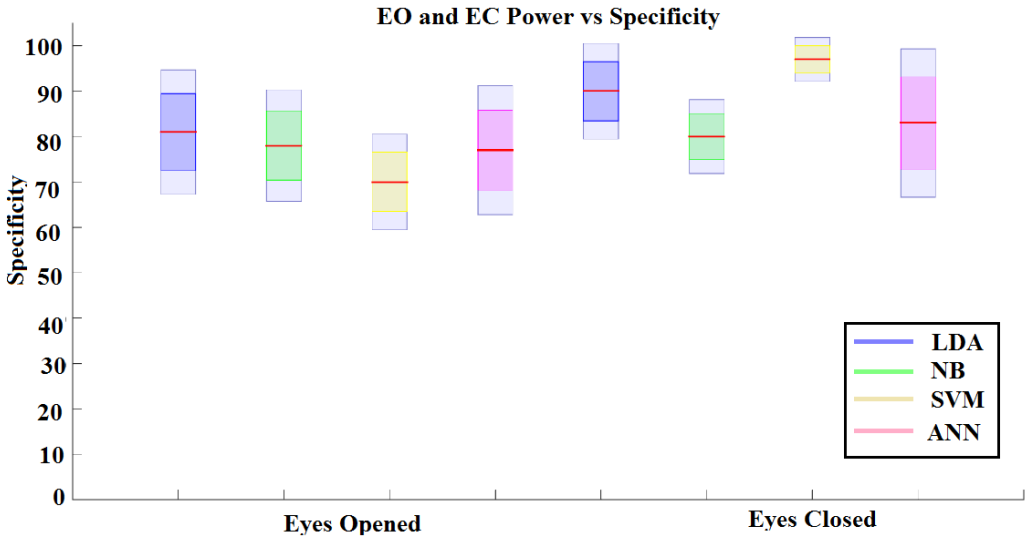
Figure 5



(a)



(b)



(c)

Figure 6