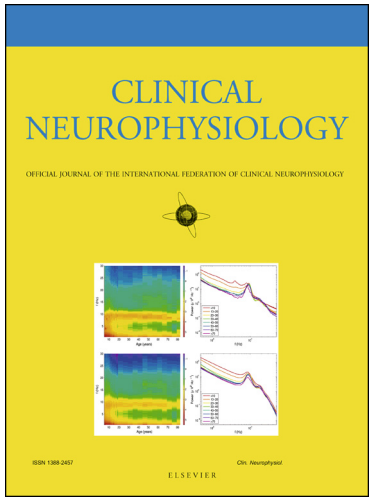

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The Influence of Central Neuropathic Pain in Paraplegic Patients on Performance of a Motor Imagery Based Brain Computer Interface[1]

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Abstract

Objective: The aim of this study was to test how the presence of Central Neuropathic Pain (CNP) influences the performance of a motor imagery based Brain Computer Interface (BCI). **Methods**: In this electroencephalography (EEG) based study, we tested BCI classification accuracy and analysed event related desynchronisation (ERD) in 3 groups of volunteers during imagined movements of their arms and legs. The groups comprised of nine able-bodied people, ten paraplegic patients with CNP (lower abdomen and legs) and nine paraplegic patients without CNP. We tested two types of classifiers: a 3 channel bipolar montage and classifiers based on Common Spatial Patterns (CSPs), with varying number of channels and CSPs. **Results**: Paraplegic patients with CNP achieved higher classification accuracy and had stronger ERD than paraplegic patients with no pain for all classifier configurations. Highest 2-class classification accuracy was achieved for CSP classifier covering wider cortical area: 82±7% for patients with CNP, 82±4% for able-bodied and 78±5% for patients with no pain. **Conclusion**: Presence of CNP improves BCI classification accuracy due to stronger and more distinct ERD. **Significance**: Results of the study show that CNP is an important confounding factor influencing the performance of motor imagery based BCI based on ERD.

Keywords: EEG, Motor imagery, BCI, paraplegia, central neuropathic pain, Event related synchronisation/desynchronisation.

Highlights

1. Motor imagery based BCI-classifier built on EEG data of paraplegic patients, gives higher classification accuracy in patients with central neuropathic pain compared to patients with no chronic pain.
2. Higher BCI classification accuracy in paraplegic patients with central neuropathic pain is accompanied with stronger event related desynchronisation during motor imagery.
3. BCI classification accuracy between feet and a hand was comparable with classification accuracy between hands, in all three groups of participants.

Introduction

Spinal cord injury may cause paralysis leaving a person highly dependent on their caregivers for most basic activities of daily living (Field Fotte 2009). Therefore various assistive devices have been used to improve patients' independence and quality of life (Poduri and Cesarz 2009). In the recent years, assistive and rehabilitation devices based on Brain Computer Interface (BCI) have been intensively explored, due to their capacity to promote combined neurological and physical recovery (Dobkin 2007, Roset et al. 2013).

Motor imagery (MI) has been a frequently used BCI strategy which can be applied for controlling assistive devices (Pfurtscheller et al. 2000, Kauhanen et al. 2006, Leeb et al. 2007) and for rehabilitation of SCI patients with incomplete injury and stroke, that have partially preserved movements (Roset et al. 2013, Pfurtscheller et al. 2009, Daly et al. 2009, Tam 2011, Onose et al. 2012). However, there are two major challenges in using MI-BCI in SCI patients: reduced brain activity and reorganisation of somatosensory-cortex (Kokotilo et al. 2009); both affecting the BCI performance. Several BCI studies (Pfurtscheller 2000, Pfurtscheller et al. 2009) showed that compared to the able-bodied, SCI patients have distinctive activation patters and reduced event related desynchronisation during MI causing poor performance of a BCI classifier. Multiple imaging studies demonstrated the reorganisation of the sensory-motor cortex, causing the posterior shift of the maximum activity and modification of the level of cortical activity during imagined or attempted movements (Green et al. 1999, Tran 2004, Kokotilo et al. 2009, Jurkiewicz et al. 2010, Vuckovic et al. 2014).

Within the BCI community it is widely accepted that the main cause of these changes is a disuse reorganisation of the cortex caused by paralysis (Kauhanen et al. 2006, Pfurtscheller et al. 2009). Although paralysis is the most obvious effect of the injury, SCI is a complex injury with multiple primary and secondary consequences (Field-Fotte 2009). It is therefore possible that some secondary consequences of SCI which contribute to the reorganisation of the cortex also affect performance of MI based BCI. One of the most frequent secondary consequences of SCI is chronic

pain. A very common subtype of the chronic pain, severely affecting around 40% of SCI population, is Central Neuropathic Pain (CNP) (Siddall 2003, Watson 2003). CNP is caused by an injury to the somato-sensory system (Haanpaa et al. 2011) but can appear months or years post-injury. An explanation for the origin of CNP is the thalamo-cortical dysrhythmia following the injury (Sarnthein and Jeanmonod 2008), suggesting that CNP is generated in the brain rather than in the body (Apkarian et al. 2009, Haanpaa et al. 2011, Henderson et al. 2013). Although the origin of CNP is within the central nervous system, it is perceived as coming from the paralysed limbs (Haanpaa et al. 2011). In SCI patients CNP is manifested as a chronic pain below the level of the injury, described as burning, tingling stabbing, shooting or aching sensation (Siddall 2003, Baastrup and Finnerup 2008). A thermosensory inhibition hypothesis (Craig 2002), explains CNP as a thermoregulatory dysfunction, that is further supported by a burning sensations, often reported by patients with CNP.

CNP equally affects patients with complete and with incomplete SCI injury (Siddall 2003). It also affects other groups of potential BCI users like stroke patients (8%) (Andersen et al. 1995) and is very frequent in amputees (80%) (Flor 2002), patients with multiple sclerosis (27%) (Osterberg et al. 2005) and Parkinson's disease (10%) (Beiske et al. 2009).

Evidence for correlation between CNP and reorganisation of the sensorimotor cortex has been shown by many studies (Flor 2002, Gustin et al. 2010a, Wrigley et al. 2009) where, due to sensory loss caused by the injury, the affected cortical somatotopy undergoes re-mapping or reorganisation, proportional to the intensity of pain. On the contrary, Makin et al. (2013) showed that in persons who suffer from CNP due to amputation, the sensory-motor cortex undergoes less reorganisation than in amputees with no pain. This result indicates that it is possible to distinguish between the effects of sensory loss and pain initiated by trauma leading to sensory loss.

While the areas of the brain involved in processing of pain normally do not involve the primary motor cortex (Apkarian et al. 2009, Jensen 2010), fMRI studies demonstrated that the presence of CNP in SCI patients causes an increased activation of the primary motor cortex during imagination

of movements (Gustin et al. 2010a, Wrigely et al. 2009). EEG studies of spontaneous brain activity also showed the increased power of the theta band and a shift of the dominant alpha peak frequency towards the theta band in paraplegic and other groups of patients suffering from CNP (Boord et al. 2008, Sarnthein et al. 2006, Stern et al. 2006, Jensen et al. 2013, Vuckovic et al. 2014). Evidence of correlation between CNP and the level of the brain activity has been shown in our previous study (Vuckovic et al.2014): we defined spontaneous and dynamic EEG signatures of CNP by comparing responses of paraplegic patients with CNP, paraplegic patients with no CNP and able-bodied people in relaxed state and during cue-based MI task. Results of that study showed that patients with CNP had strongest and spatially distinctive event related desynchronisation (ERD) during MI in the theta, alpha and beta frequency bands, with maximum activity shifted posteriorly. Theta band desynchronisation during motor imagination was a singular feature of patients with CNP. Patients with no CNP had weakest ERD, that has spatial topography comparable to those of the able-bodied group.

Given the previously mentioned evidence regarding the role of CNP, there is a possibility that performances of a MI-based BCI, which uses ERD based features, may not only vary between paralysed and able bodied people, but importantly between paralysed people with and without CNP. It should be noted that in previous reports (Gustin et al. 2008, Gustin et al. 2010b) the effect of motor imagery on CNP was not analysed for the purpose of BCI, so the effect of CNP on BCI performance is unknown. From a BCI perspective increased cortical activity during MI in patients with CNP is a desirable feature as it implies that better classification accuracy might be achieved. However, a study on SCI patients with CNP who practiced motor imagery for several weeks showed that prolonged imagination of movements of a painful part of the body worsens pain, i.e. MI is able to produce painful sensation without a peripheral input (Gustin et al. 2008, Gustin et al. 2010b). Equally important is to question whether MI as practiced for BCI has an adverse effect on CNP.

The aim of this EEG-based study was to test whether the presence of CNP in paraplegic patients influences the performance of MI based BCI. We compared performances of BCI classifiers and the accompanying ERS/ERD responses between three groups: able bodied people, paraplegic patients with no pain and paraplegic patients with CNP. These results are potentially also relevant for other patient groups suffering from CNP, e.g. stroke patients, who are typical BCI candidates.

Methods

Participants: Three groups of age-matched adults (age between 18 and 55) were recruited. The groups were:

1. Ten paraplegic patients (3F, 7M age 46.2±9.4), with diagnosed CNP below the level of injury, referred to as Patients With Pain (PWP),
2. Nine paraplegic patients with no chronic pain (2F, 7M age 43.8±9.1), referred to as Patients with No Pain (PNP),
3. Nine able bodied volunteers with no chronic pain (3F, 6M age 39.6±10.2) referred to as Able Bodied (AB).

The neurological level of SCI was determined using the American Spinal Injury Association (ASIA) Impairment Classification (Marino et al. 2003). Injury level A means the loss of motor and sensory functions while level B means the loss of motor function with some sensations preserved. All SCI patients were at least 1 year post injury and had a spinal lesion at or below T1. The inclusion criteria for patients with CNP was a positive diagnosis of CNP, reported pain level ≥ 5 on the Visual Numerical Scale (VNS ranging from 0 to 10, 0 meaning no pain and 10 meaning worst pain imaginable) and a treatment history of CNP for at least 6 months. The general exclusion criteria for all three groups were a presence of any chronic (non CNP) or acute pain at the time of the experiment; brain injury or other known neurological condition that would affect EEG interpretation or would prevent patients from understanding the experimental task. Prior to the experiment patients were asked to fill out the Brief Pain inventory (Daut et al. 1983) to assess the intensity (based on a VNS) and location of pain. Information on Patients with Pain (PWP) and

Patients with no Pain (PNP) is shown in Tables 1 and 2. The exact location of perceived pain in each patient is shown in Fig 1. All patients had pain under the level of injury, that was bilateral in 8 out of 10 patients. In some patients pain was also present over the lower abdomen and buttock. In all patients pain was present in shanks and feet.

Figure 1 about here

The ethical approval was obtained from the University of Strathclyde Ethical Committee for the able-bodied group and from National Health Service Ethical Committee for Greater Glasgow and Clyde for patients' groups. Informed consent was obtained from all participants. The same groups of patients were used in our previous study to describe dynamic signature of CNP (Vuckovic et al. 2014).

Recording Equipment: EEG was recorded from 61 channels using the Synamps^2, (Neuroscan, USA) system. Electrodes were placed according to standard 10-10 locations (ACNS 2006) using an ear-linked reference and AFz ground. Electrooculagram (EOG) was recorded from 3 channels around the right eye. All channels were sampled at 1000 Hz. Individual electrode impedances were below 5kΩ. In addition, electromyograms (EMGs) were recorded from the right and the left wrist extensor muscles and right foot dorsiflexor using the bipolar inputs to the Synamps^2 device. The purpose of EMG recording was to check for the absence of any evidence of voluntary movements when subjects attempted MI.

Experimental Procedures: An experimental protocol that instructed participants to imagine hand or lower limb movements was devised using visual cues. Participants were seated at a desk, approximately 1.5 m in front of a computer monitor. Participants were instructed to look at the centre of the monitor and were instructed to respond to a sequence of visual cues. The cues comprised at t= -1s, a readiness cue (a cross +) which remained on for 4s (Fig. 2). At t=0s an initiation cue, presented as an arrow, was displayed for 1.25s, pointing to the left ←, to the right → or down ↓ and corresponded to imagination of the left hand waving (LH), right hand waving (RH)

and tapping with both feet (F), respectively. Participants were asked to continue to perform imaginary movements until the cross disappeared from the screen (3s after the initiation cue appeared). This is a standard experimental paradigm for discrimination between imagined movements between different limbs (Pfurtscheller et al. 2006, Blankertz et al. 2007, Pfurtscheller et al. 2009). Separate imagination of the left and right feet is typically not performed, due to the anatomical location of the motor areas of left and right feet, which lie in close proximity, deeper in the central sulcus and would therefore be hard to distinguish using a classifier (Bear et al. 2007). In PNP group, RH and LH were non-paralysed parts of the body while F were paralysed. None of the limbs were painful. In PWP group, RH and LH were non-paralysed and non-painful parts of the body while F were both a paralysed and painful part of the body.

In total 60 trials of each movement type (180 trials in total) were collected from the subjects with randomised cue sequences. The whole session consisted of 6 sub-sessions with rest periods in-between. In each sub-session 10 trials of each type (30 trials in total) were presented to subjects. We collected relatively a small number of trials (60 for each limb) because of PWP group who could not successfully concentrate on a longer experiment.

Figure 2 about here

Data Pre-processing: For pre-processing of spontaneous EEG, a high-pass filter (IIR, 12db cut off frequency) was set to 1 Hz and a notch filter (IIR, 12db cut off frequency) was applied between 48-52 Hz, to remove line noise at 50 Hz. Filtering was applied forwards and then backwards to avoid phase shift. Signals were then down-sampled to 250 Hz. EEG was visually inspected and epochs containing EOG artefact and other types of noise (amplitude exceeding approximately 100 μV over all channels) were manually removed. After removing heavily contaminated epochs, signals were exported to EEGLab (Delorme and Makeig 2004). Independent Component Analysis (ICA) was performed using the Infomax algorithm (Bell and Sejnowski 1995) implemented in EEGLab for advanced noise removing purposes. ICAs representing noise was detected based on their power spectral density, time distribution, scalp maps and dipole localisation. In this way

excessive EEG removal from a limited number of trials was avoided, as no more than 2 (out of 60) trials had to be removed per dataset of a single limb. After noise removal data were converted back to EEG domain for further analysis.

Classification of Motor Imageries. We performed classification between the following two tasks: right hand vs left hand, right hand vs feet and left hand vs feet. We used bipolar montages and Common Spatial Patterns (CSP) montages. All montages were derived from the original 61 electrodes recorded with respect to the ear-linked reference. A simple bipolar montage consisted of three bipolar electrodes located over the centro-parietal cortex. Common Spatial Patterns were calculated over two different set of electrodes, namely CSP1 and CSP2. CSP1 consisted of 23 electrodes covering mainly the sensory and motor areas (Fig 3, dark circles) and CSP2 consisted of 44 electrodes (Fig 3. dark and grey circles) covering a wider cortical networks involved in pain processing. The number of CSPs in CSP1 varied from 2 to 22 to test the influence of the number of CSPs on the classification accuracy and on a difference in classification accuracies across three groups of participants. While we expected that increasing the number of electrodes used for BCI classifier will improve its classification accuracy we wanted to test whether this improvement will increase proportionally across all three groups.

Figure 3 about here

Bipolar Montage Feature Selection and Classification. Three bipolar montages were derived: C3-P3, C4-P4 and Cz-Pz. A slightly posterior location was chosen because it is known that SCI causes a posterior shift of the area of strongest activity during MI (Kokotilo et al. 2009).
Signal was filtered in 8-12Hz and 16-24 Hz bands using an IIR Butterworth filter of the 5^{th} order. Signal was then squared and smoothed/averaged over one second window. The logarithm of the resulting signal was obtained and used for classification. This provided 6 features in total used to build a BCI classifier. Each trial, from t=0s (an arrow, i.e. the initiation cue appears) till t=3s (a cross, i.e. the readiness cue dissappears) was split into smaller segments of 0.4s

Feature classification was performed using a Fisher's Linear Discriminate Analysis (LDA) (Duda et al. 2001). A leave-one-out cross validation procedure was adopted because of a relatively small number of trials. Initial classification was performed on each of the 0.4 s segment to estimate the best performing segment across the trials. LDA classifier was then computed using a training set from the chosen segment. Each trial was assigned a class by classifying each time point in the trial using the LDA classifier. A true positive rate (the ratio of correctly classified trials to the total number of trials) was adopted as a measure of the classification accuracy. Signal processing was performed using the BioSig opensource toolboxes (Vidaurre et al. 2011) in MATLAB (Mathworks Inc, USA).

Common Spatial Patterns. Before computing CSPs, the recorded signal was band-pass filtered using an IIR Butterworth filter of the 5^{th} order filter between 8 and 30 Hz. The CSP method projects multi-channel EEG data into a low-dimensional spatial sub-space in such a way that the variances of the filtered time series are optimal for discrimination (Müller-Gerking et al. 1999). After computing the spatial filters and using it to filter the signal, the variance of the resultant signal was computed for every time segment of 70 samples (approximately 30 ms) over the whole 3s trial. Classification was performed in the manner described in methods for bipolar arrangement.

Statistical Analysis of Classification Results: For each classifier, a two factor 3x3 ANOVA was used to compare classification results between three groups; this was followed by an unpaired t-test. The two factors were 'motor imagery types' RH, LH and F and 'groups' were PWP, PNP and AB. A statistical significance was set at $\alpha=0.05$.

EEG Analysis of Motor Imagery: Before performing the analysis, EEG data were re-referenced to the average reference. A 'Study' structure was designed in EEGLab to allow EEG analysis on a group level. 'Groups' were PWP, PNP and AB and 'Conditions' were motor imagery of LH, RH and F.

An extension of the ERS/ERD (Pfurtscheller and da Silva 1999), called Event Related Spectral Perturbation (ERSP), based on sinusoidal wavelets rather than on filters (Makeig 1993), was used to

allow more precise time-frequency analysis. For calculating the ERS/ERD of each single volunteer a reference period from -1.9 to -1.1s (before the cross) was adopted, time-frequency decomposition was performed in a frequency range 3-55 Hz using a sinusoidal wavelet with minimum 3 wavelet cycles per data window at lowest frequencies. Overlapping Hanning tappers windows were applied. Signal processing was implemented in EEGlab.

In order to find regions of significant ERS/ERD for each condition (on a single electrode site), a significance level was set to p=0.05 and nonparametric bootstrapping procedure (N=2000 randomisation) (Blair and Karinski 1993) was performed, comparing ERS/ERD maps between groups, applying the False Discover Rate (FDR) correction (Benjamin and Yekuteli 2001). ERS/ERD maps for a single electrode were analysed for the central areas only.

ERS/ERD scalp maps over the whole scalp (61electrodes in total) were created for three frequency bands: theta (4-8 Hz), alpha (8-12 Hz) and beta (16-24 Hz). Comparison between scalp maps of different groups or conditions was performed based on a permutation statistics (p=0.05), a Monte Carlo method. A correction for multiple comparisons was performed using the FDR. All procedures were implemented in EEGlab. Spatial analysis was limited to electrode locations defined by 10-10 system (ACNS 2006).

Results:

BCI Classification Accuracy for bipolar montage When classification was performed with 3 bipolar channels, the classification accuracies in all groups except PWP was low, just reaching the chance level of 65%. This increased chance level, higher than 50% was adopted to compensate for a small number of trials (Mueller-Putz et al. 2008).

The classification accuracy of AB group was 65±4%, of PNP group was 66±5% and of PWP group was 70±7% (Fig. 4a). The ANOVA analysis showed a statistically significant difference for a factor ‘groups’ (p=0.0188) and no statistically significant difference for a factor ‘motor imagery type’ (p=0.6302). There was no statistically significant interaction among these factors (p=0.8188). A t-test between groups showed a statistically significant difference in the classification accuracy

between PWP and PNP group (p=0.0211) and between AB and PWP group (p=0.009) but no statistically significant difference between AB and PNP group (p=0.7413).

BCI Classification Accuracy for CSP montages Classification was performed with CSPs based on two different numbers of electrodes. Classifier CSP1 was based on 23 electrodes and a variable number of CSPs. A classifier CSP2 was based on 44 electrodes and 20 CSP; the number of CSPs was chosen to maximise the overall classification accuracy.

For CSP1 a detailed analysis showing classification results between each pair of limbs for each subject was performed on two representative CSPs, CSP1A (4 CSP) and CSP1B (14 CSP). CSP1A was based on 4 CSP which is a configuration often used for BCI (Müller-Gerking et al. 1999) while CSP1B was based on 14 CSP, which is a configuration that achieved the highest overall classification accuracy. Classification results are shown in Fig 4b for CSP1A and in Fig 4c for CSP1B.

When classifier was based on a configuration with only 4 common spatial patterns (Fig 4b), the average BCI classification accuracy for PWP group was 74±9% which was comparable with the average classification accuracy for AB group of 74±7% and was higher than the classification accuracy for the PNP group of 69±8%. The ANOVA analysis showed a statistically significant difference for the factor 'groups' (p=0.433) and no statistically significant difference for a factor 'motor imagery type' (p=0.878). There was no statistically significant interaction among the two factors (p=0.682). A t-test between groups showed a statistically significant difference in the average classification accuracy between PWP and PNP group (p=0.0335) and between AB and PNP group (p=0.0343), but no statistically significant difference between AB and PWP group (p=0.808).

When the number of common spatial patterns increased to 14 (Fig. 4c), the average BCI classification accuracy for PWP group was 78±9% which was comparable with the average classification accuracy for AB group of 76±5% and was higher than the classification accuracy for the PNP group of 73±7% (Figure 4c). The ANOVA analysis showed a statistically significant difference for the factor 'groups' (p=0.02) and no statistically significant difference for a factor

'motor imagery type' (p=0.8621). There was no statistically significant interaction among the two factors (p=0.682). A t-test between groups showed a statistically significant difference in the average classification accuracy between PWP and PNP group (p=0.0018) and between AB and PNP group (p=0.0286), but no statistically significant difference between AB and PWP group (p=0.1927).

When CSPs were computed with CSP2 (44 electrodes, 20 CSP filters), including the frontal and the parietal cortex, the classification accuracy increased in all three groups but previously observed difference across groups remained. A classification accuracy of 82±7% for PWP group was very similar to the classification accuracy of 82±4% for AB group and was higher than the classification accuracy of 78±5% for PNP group (Fig. 4d).

The ANOVA analysis showed a statistically significant difference for a factor 'groups' (p=0.0118) and no statistically significant difference for a factor 'motor imagery type' (p=0. 6774). There was no statistically significant interaction among the two factors (p=0.3576). A t-test between groups showed a statistically significant difference in a classification accuracy between PWP and PNP groups (p=0.0135) and between AB and PNP groups (p=0.0030) and no statistically significant difference between AB and PWP groups (p=0.713).

Figure 4 about here

To further investigate the consistency between classification accuracies of PWP and PNP groups, a graph is produced showing classification accuracies for all three groups for CSP1 based on 23 central electrodes (Fig 5) for the variable number of common spatial patterns ranging from 2 to 22. Results show that the overall maximal classification accuracy for all three groups is achieved for 14 CSPs. Statistically significant differences between classification accuracies of PNP and PWP group was achieved for 8 out of 11 CSPs configurations while statistically significant difference between AB and PNP group was achieved for 9 out of 11 CSPs. None of the 11 classifiers showed a statistically significant difference in classification accuracy between AB and PWP groups.

To summarise, for all classifiers PNP group had significantly lower classification accuracies than the other two groups. There was no statistically significant difference in classification accuracy of MI of different limbs.

Figure 5 about here

Two patients from PWP group reported increased pain in their legs and one patient from PNP group reported an unpleasant tingling sensation (i.e. paraesthesia) in their legs. The exact pain level was however not measured, as this was an unexpected result at the time of the experiment.

Analysis of ERS/ERD Maps: Figure 6a shows ERS/ERD maps at the electrode location C3 for MI of the right hand, at Cz for MI of the feet and at C4 for MI of the left hand. These electrodes are located approximately over the primary motor cortex, as being most representative for a chosen limb, though a single EEG electrode might record the electrical activity of several sources. The column on the right shows the areas of statistically significant differences among the groups. The largest differences among 3 groups can be noticed for MI of the right hand in the alpha band, sustained over the whole periods of MI. Figure 6b shows the areas of statistically significant differences between each pair (AB vs PNP, AB vs PWP and PWP vs PNP). This widely adopted presentation method does not however show which group has stronger activity, so its interpretation requires simultaneous observation of ERS/ERD maps (Fig. 6a). Largest differences, spread over a range of frequency bands, can be noticed between PWP and PNP group across the theta, alpha and beta band for all three types of MI. These differences are caused by stronger ERD in PWP group (Fig 6a). Differences between PWP and AB group, caused by stronger ERD in PWP group, could be noticed two distinctive bands (alpha/theta and higher beta). A smaller difference, mostly in the alpha band (stronger in AB group) can be noticed between AB and PNP; being most pronounced for MI of the left hand.

Figure 6 about here

Figure 7a shows scalp maps during MI of feet in the theta, alpha and beta (16-24 Hz) band, averaged over the period of maximum ERD from t=0.4 to 0.8s post cue. Figure 7b shows the spatial

distribution of statistically significant differences between ERS/ERD of different groups during MI for maps shown in Fig 7a. Location of the dots in Fig 7b correspond to 10-10 electrode location used in the study, where only statistically significant differences between groups are shown by bold dots. PWP group had the largest and spatially distinctive ERD in all three frequency bands. They had significantly stronger ERD than PNP group in the theta and alpha band, the later being restricted to the centro-parietal region (Fig. 7b). Compared to AB group, PWP group had a statistically significant difference in ERS/ERD scalp maps in the alpha and beta band at several electrode locations at the central, frontal and parietal cortex. No surface cortical region showed statistically significant differences between AB and PNP groups in any band.

Discussion:

This study investigated the influence of central neuropathic pain on the performance of a MI based BCI classifier in patients with spinal cord injury and the relationship between BCI classifier performance and the intensity of ERD during MI. Central neuropathic pain increased event related desynchronisation during motor imagery and also improved BCI classification accuracy.

Classification results: For classifiers based on CSPs, PWP group had a comparable level of classification accuracy with AB group, independent of the number of EEG channels or the derived CSPs. For a configuration with only three bipolar channels PWP had a better classification accuracy than the other two groups. PNP group had lowest classification accuracy of all three groups for all classifiers. Of interest is a result that PWP group had a significantly higher classification accuracy than PNP even when only three centrally placed bipolar channels were used. This indicates that the area of largest differences between PWP and the other two groups is located in the centro-parietal region of the cortex as this was the only cortical area included in both CSP and in a bipolar montage. That was also confirmed by ERD analysis (Fig. 7b) which showed largest differences between PWP and PNP groups in the alpha band in the centro-parietal region.

In a detailed ERS/ERD study performed on same three groups of participants (Vuckovic et al. 2014) we showed that PWP group, that had strongest ERD, had the largest number of electrodes location with a statistically significant difference in ERD between three MI tasks. As a consequence, in this study when we applied a BCI classifier, PWP group had better classification accuracy than PNP group, in particular with CSP which can select optimal electrode location.

Increasing the number of electrodes improved classification accuracy but did not influence a difference in classification accuracy across groups. We used two sets of electrodes to cover both the sensory and motor cortex, because pain as a sensory phenomenon was expected to influence primarily the sensory area. However results showing a relation between classification accuracy among three groups are independent of the number of electrodes and of the number of CSP used for classification.

Our classification results obtained with PNP group based on CSP1A (with 4 CSP) are comparable with results of a study by Pfurtscheller et al (2009) who used CSP to classify imaginary movements in chronic paraplegic patients. In the current study, a classification accuracy increased with the increasing number of CSP only up to a certain number of common spatial patterns, after which classification accuracy decreases with increasing the number of CSP. By definition, the first few CSP are the most discriminable between groups (Mueller-Gerking et al. 1999). Too large number of CSP possibly resulted in 'over fitting' the classifier to the training set, reducing its ability to generalise classification on data from the testing set.

Of interest is the observation that there was no statistically significant difference in classification accuracy between different limbs. While all three groups had functional arms and hands, PNP group had paralysed legs and lower abdomen while PWP group had paralysis combined with pain in their legs. PWP had increased ERD response for all three types of motor imagery, not only for MI of feet, that could explain why classification between feet and one of the hands was comparable to classification between both hands. PNP had weaker ERD responses for MI of all limbs. Previous studies on spinal cord injured patients with no pain (Pfurtscheller et al 2009) and on

able-bodied people (Pfurtscheller et al. 2006) showed slightly better classification between MI of feet and a hand than between MI of two hands. They explained it by 'focal ERD/surround ERS' phenomena, often noticed during imagined movement of feet (also noticed in Vuckovic et al. 2014) that might facilitate detection of MI of feet. In addition to this, results from the literature (Tran et al. 2004, Boord et al. 2008, Jensen et al. 2013) showed that both paralysis and pain have global effect on EEG which spreads beyond the cortical presentation of the paralysed/painful limbs.

Event Related Synchronisation/Desynchronisation: The analysis of event related desynchronisation showed that PWP has stronger ERD than the other two groups over the central electrode locations for MI of both painful and non-painful limbs. Results of ERS/ERD analyses support BCI classification results showing significantly higher classification accuracy in PWP than in PNP group. In this study it was not possible to separate the effect of paralysis (including both sensory and motor impairments) and CNP, because all CNP patients were also paraplegic. However distinctive results in PNP and PWP groups suggest that brain signatures of CNP do not simply present the exaggerated brain signature of paralysis. This can appear contradictory to fMRI studies showing that in amputees and patients with spinal cord injury the extent of cortical reorganisation caused by the injury is proportional to the intensity of pain (Flor 2002, Gustin et al. 2010a, Wrigley et al. 2009). Although the number of patients in this study was relatively small, results are more in favour of a recent hypothesis (Makin et al. 2013) that sensory-motor loss and CNP caused by that loss produce distinctive brain responses. We believe that this is observation that requires attention and further investigation on the larger number of patients, ideally involving a group of patients with CNP and no sensory-motor deficit.

Interestingly, although ERD in AB group seem to be of a comparable intensity to PNP and was weaker than of PWP group, all CSP classifiers showed higher classification accuracy for AB than for PNP group. Results of bipolar classifier are in line with the analysis of ERS/ERP showing highest classification accuracy for PWP group. Classifiers in this study were limited to 8-30Hz that covers both sensory-motor rhythms in able-bodied people (8-12 Hz and 16-24 Hz, Pfurtscheller and

da Sliva 1999) and was previously used for building CSP in similar studies on paraplegic patients (Pfurtscheller et al. 2009). It is possible that more discriminative results between groups would be achieved if the theta band was also used, as both single electrode analysis and scalp maps analysis indicate significant differences between PWP and PNP group in this frequency band.

Influence of Medication for Treatment of CNP on Baseline EEG

Most of participants in PWP group used antiepileptic or antidepressant drugs as a part of their pharmacological treatment of pain. Antiepileptic drugs are known to increase resting state EEG in the theta band (Olbrich and Ams 2013) while antidepressants increase EEG amplitude in the theta and higher beta (>20 Hz) range (Bauer and Bauer 2005, Wauquier 2005). This might influence the intensity of ERD during motor imagery, but for this study, theta band was not included in analysis, thus reducing the influence of the drugs on the results of the study. Therefore, although inclusion of the theta band, believed to be a signature of CNP, would potentially improve performance of BCI classifier in PWP group, it would be hard to distinguish to which extent this is due to pain and to which extent due to medications.

It is believed that increased theta band power is related to thalamo-cortical dysrhythmia (Sarnthein and Jeanmonod 2008), and the shift of the dominant alpha frequency towards the theta band (Boord et al. 2008, Sarnthein et al. 2006, Stern et al. 2006, Jensen et al. 2013, Vuckovic et al. 2014). Patients with CNP who underwent a surgery involving a therapeutic lesion of the thalamus, reported reduction of pain that was accompanied with reduction of theta band power (Sarnthein et al. 2006).

Better classification accuracy in paraplegic patients with CNP might not directly imply that these patients are potentially better candidates for MI based BCI. In a study by Gustin et al (2008) six out of seven tested patients with SCI and CNP reported increased pain after practicing of pressing an imaginary car gas pedal for a period of a week. Incidental finding of this study also indicate that some patients may experience discomfort already during first MI sessions.

CNP is related to the lack of sensory information coming from the body (Haanpaa et al. 2011) and occurs months or years after an injury (Siddall 2003, Haanpaa et al. 2011). It is therefore likely that immediately after the injury patients would have minimal CNP symptoms. MI based BCI has been proposed as a rehabilitation therapy for SCI (Dobkin 2007, Daly et al. 2009, Tam et al. 2011, Onose et al. 2012, Roset et al. 2013). A therapy based on MI BCI would aid improvement of the sensory-motor functions thus hopefully preventing CNP. Therefore MI based BCI might be a strategy better suited for rehabilitation, especially shortly after injury, than for communication and control in long term, later after injury.

At present, due to the lack of recognition of the correlation between CNP and the activity of the motor cortex, patients are typically not assessed for pain before being recruited for a BCI study. We suggest that in future pain status pre and post motor imagination may require monitoring.

Conclusion: Central Neuropathic Pain in SCI patients affects the performance of BCI classifiers and increases the amplitude of ERD over the sensory-motor cortex during motor imagery. Higher classification accuracy in paraplegic patients with pain compared to patients with no pain was independent on the type of classifier and on the number of recording electrodes used to create a classifier. Higher classification accuracy existed independently whether the classifier was based on MI of painful or non-painful limbs, indicating globally modified cortical activity.

Conflict of Interest Statement

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

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References

American Clinical Neurophysiology Society, Guideline 5. Guidelines for standard electrode position nomenclature. J Clin Neurophysiol. 23;107–110:2006

Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS. Incidence of central post-stroke pain. Pain. 61;187-93:1995

Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 87; 81–97:2009

Baastrup C, Finnerup NB. Pharmacological management of neuropathic pain following spinal cord injury. CNS Drugs. 22;455-75:2008

Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: Prevalence and characteristics. Pain. 141;173-7:2009

Bear FB. Connors BW, Paradiso MA. Brain control of movement. In: Bear FB, Connors BW, Paradiso MA (eds). Neuroscience: Exploring the brain. Lippincott. Williams and Wilkins, 2007, pp 451-478

Bell AJ, Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. Neural Comput. **7**;1129–59:1995

Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Ann Statist. 29;1165-1188:2001

Blair R, Karniski W. An alternative method for significance testing of waveform difference potentials. Psychophysiology. 30;518-524:1993

Blankertz B, Dornhege G, Krauledat M, MuellerKR, Curio G, The non-invasive Berlin Brain-Computer Interface: fast acquisition of effective performance in untrained subjects, Neuroimage, 37;539–550:2007

Boord P, Siddall PJ, Tran Y, Herbert D, Middleton J, Craig A. Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. Spinal Cord. 46;118-23:2008

Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci. 3;655-66:2002

Daly JJ, Cheng R, Rogers J, Litinas K, Horvat K, Dohring M. Feasibility of a new application of noninvasive Brain Computer Interface (BCI): a case study of training for recovery of volitional motor control after stroke. J Neurol Phys Ther. 33;203-11:2009

Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 17;197–210:1983

Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 134;9-21:2004

Dobkin BH. Brain-computer interface technology as a tool to augment plasticity and outcomes for neurological rehabilitation. J Physiol. 579;637-42:2007

Duda RO, Hart PE, Stork DG. Pattern Classification. A Wiley-Interscience Publication. 2001, pp 215-281

Field-Fotte EC. Spinal cord injury: an overview. In: Field-Fotte EC (ed). Spinal Cord Injury Rehabilitation. CPR Press 2009, pp 3-20

Flor H. Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol. 1;182-189:2002

Green JB, Sora E, Bialy Y, Ricamato A, Thatcher RW. Cortical motor reorganization after paraplegia: an EEG study. Neurology. 53;736-43:1999

Gustin SM, Wrigley PJ, Gandevia SC, Middleton JW, Henderson LA, Siddall PJ. Movement imagery increases pain in people with neuropathic pain following complete thoracic spinal cord injury. Pain.137;237-44:2008

Gustin SM, Wrigley PJ, Siddall PJ, Henderson LA. Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. Cereb Cortex. 20;1409-19:2010a

Gustin SM, Wrigley PJ, Henderson LA, Siddall PJ. Brain circuitry underlying pain in response to imagined movement in people with spinal cord injury. Pain. 148;438-45:2010b

Haanpaa M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D et al. NeuPSIG guidelines on neuropathic pain assessment. Pain. 152;14–27:2011

Henderson LA, Peck CC, Petersen ET, Rae CD, Youssef AM, Reeves JM, Wilcox SL, Akhter R, Murray GM, Gustin SM. Chronic pain: lost inhibition? J Neurosci. 33;7574-82: 2013

Jensen MP. A neurophysiological model of pain: research and clinical implications. J Pain. 11;2-12:2010

Jensen MP, Sherlin LH, Gertz KJ, Braden AL, Kupper AE, Gianas A et al. Brain EEG activity correlates of chronic pain in persons with spinal cord injury: clinical implications. Spinal Cord. 51;55-8:2013

Jurkiewicz MT, Mikulis DJ, Fehlings MG, Verrier MC. Sensorimotor cortical activation in patients with cervical spinal cord injury with persisting paralysis. Neurorehabil Neur Rep. 24;136-40:2010

Kauhanen L, Nykopp T, Lehtonen J, Jylänki P, Heikkonen J, Rantanen P, Alaranta H, Sams M. EEG and MEG brain-computer interface for tetraplegic patients. IEEE Trans Neural Syst Rehabil Eng.14;190-3:2006

Kokotilo KJ, Eng JJ, Curt A. Reorganization and preservation of motor control of the brain in spinal cord injury: a systematic review. J Neurotrauma. 26;2113-26:2009

Leeb R, Friedman D, Müller-Putz GR, Scherer R, Slater M, Pfurtscheller G. Self-paced (asynchronous) BCI control of a wheelchair in virtual environments: a case study with a tetraplegic. Comput Intell Neurosci. 2007:79642

Makeig S. Auditory event-related dynamics of the EEG spectrum and effects of exposure to tones. Electroencephalogr Clin Neurophysiol. 86;283-93:1993

Makin TR, Scholz J, Filippini N, Henderson Slater D, Tracey I, Johansen-Berg H. Phantom pain is associated with preserved structure and function in the former hand area. Nat Commun. 4;1570:2013

Marino RJ, Barros T, Biering-Sorensen F, Burns SP, Donovan WH, Graves DE et al. International standards for neurological classification of spinal cord injury. J Spinal Cord Med. 26;50–56:2003

Müller-Gerking J, Pfurtscheller G, Flyvbjerg H. Designing optimal spatial filters for single-trial EEG classification in a movement task. Clin Neurophysiol. 110;787-98:1999

Mueller-Putz G.R, Scherer R, Brunner C, Leeb R, Pfurtscheller G. Better than random? A closer look at BCI results. Int J Electromagn. 10;52-55:2008

Onose G, Grozea C, Anghelescu A, Daia C, Sinescu CJ, Ciurea AV, Spircu T, Mirea A, Andone I, Spânu A, Popescu C, Mihăescu AS, Fazli S, Danóczy M, Popescu F. On the feasibility of

using motor imagery EEG-based brain-computer interface in chronic tetraplegics for assistive robotic arm control: a clinical test and long-term post-trial follow-up. Spinal Cord. 50;599-608:2012

Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis-prevalence and clinical characteristics. Eur J Pain. 9;531-42:2005

Pfurtscheller G, da Silva L. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol. 110;1842-1857:1999

Pfurtscheller G, Guger C, Müller G, Krausz G, Neuper C. Brain oscillations control hand orthosis in a tetraplegic. Neurosci Lett. 292;211-214:2000

Pfurtscheller G, Brunner C, Schloeg A, Lopes da Silva FH. Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks, Neuroimage 31;153–159: 2006

Pfurtscheller G, Linortner P, Winkler R, Korisek G, Müller-Putz G. Discrimination of motor imagery-induced EEG patterns in patients with complete spinal cord injury. Comput Intell Neurosci. 2009:140180

Pizzimenti A, Aragona M, Onesti E, Inghilleri M. Depression, pain and quality of life in patients with amyotrophic lateral sclerosis: a cross-sectional study. Funct Neurol. 28;115-119:2013

Poduri KR, Ceszaz T. Assistive technology. In: Field-Fotte EC (ed). Spinal cord injury rehabilitation, PR Press 2009, pp 549-650

Roset SA, Gonzalez HF, Sanchez JC. Development of an EEG based reinforcement learning Brain-Computer Interface system for rehabilitation. Conf Proc IEEE Eng Med Biol Soc. 2013, pp 1563-6

Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. Brain. 129;55-64:2006

Sarnthein J, Jeanmonod D. High thalamocortical theta coherence in patients with neurogenic pain. Neuroimage. 39;1910-7:2008.

Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain. 103;249-57:2003

Stern J, Jeanmonod D, Sarnthein J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. Neuroimage. 31;721-31:2006

Tam W, Tong K, Fei M, Gao S. A Minimal Set of Electrodes for Motor Imagery BCI to Control an Assistive Device in Chronic Stroke Subjects: A Multi-Session Study. Conf Proc IEEE Trans Neural Syst Rehabil Eng. 19;617-627:2011

Tran Y, Boord P, Middleton J, Craig A. Levels of brain wave activity (8-13 Hz) in persons with spinal cord injury. Spinal Cord. 42;73-9:2004

Vidaurre C, Sander TH, Schlög A. BioSig: The Free and Open Source Software Library for Biomedical Signal Processing. Comput Intell Neurosci. 2011:935364:2011

Vuckovic A, Hasan MA, Fraser M, Conway BA, Nasseroleslami B, Allan DB. Dynamic Oscillatory Signatures of Central Neuropathic Pain in Spinal Cord Injury. J Pain 6;645-655: 2014

Watson JC. Central neuropathic pain: syndromes, pathophysiology and treatments. In: Wilson PR, Watson PJ, Haythornthwaite JA, Jensen TS (eds). Clinical Pain Management. Chronic Pain. 2nd edition. 2003, pp 374-387

Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, et al. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain. 141;52-9:2009

Figure Legends

Figure 1. Body maps showing perceived location pain in patients in PWP group.

Figure 2. The experimental paradigm for a motor imagination task.

Figure 3. Location of a smaller set of electrodes used to build a CSP1 classifier (black dots only) and a larger set used to build a CSP2 classifier (black and grey dots). All 61 electrodes (including the ones with white circles) were included when creating ERS/ERD scalp maps.

Figure 4. Classification accuracy (mean ±STD) between two different limbs for all three groups of volunteers using bipolar montage (Fig 3a), CSP1A (Fig 3b), CSP1B (Fig. 3c) and CSP2 (Fig 3d). The numbers above bars show mean values for a single group. Abbreviations: RH: right hand; LH: left hand; F: feet; AB: able bodied; PNP patients with no pain; PWP: patients with central neuropathic pain.

Figure 5. Averaged classification accuracy for all combinations of limbs (mean±SE) for CSP1A (23 electrodes) with the variable number of CSP. Abbreviations: AB: able bodied; PNP patients with no pain; PWP: patients with central neuropathic pain.

Figure 6. ERS/ERD maps over the central cortical area during MI (a) ERS/ERD maps for motor imagery of different limbs over the electrode locations C3 for the right hand, Cz for feet and C4 for the left hand. Dashed lines at t=-1s show a moment when a readiness cue appeared at the screen while a vertical solid line at t=0s shows a moment when the initiation cue appeared on the screen.

Positive numbers are for ERS and negative for ERD. A column to the right shows areas of statistically significant differences among the groups.

(b) Ares of statistically significant differences between ERS/ERD maps between different groups, shown in Fig 5a.

Figure 7. Scalp maps of ERS/ERD during MI of feet for three groups of participants. (a) Averaged scalp maps over a period t=0.4 s to 0.8s post cue. Upper raw is for the theta band, middle raw is for the alpha band and the lower raw is for the beta band. (b) Marked electrode locations shows areas of statistically significant differences between groups for three different frequency bands.

Abbreviations: AB: able bodied; PNP patients with no pain; PWP: patients with central neuropathic pain.

Table 1. Information about patients with CNP (PWP group).

Nr	Level of injury	ASIA	Years after injury	Pain VNS	Years with pain	Medications
1	T5	A	7	7	7	Baclofen Carbamazepine Gabapentin
2	T5/6	A	11	6	11	-
3	T5	A	7	8	7	Pregabalin Gabapentin
4	L1	B	15	7	15	Gabapentin
5	T7	B	6	8	5	-
6	T6/7	B	25	10	24	Gabapentin
7	T1	A	25	5	10	Pregabalin
8	T5	A	14	5	13	Amitriptyline, Baclofen, Diazepams
9	L1	B	5	5	4	-
10	T8	B	11	1	10	Pregabalin

Table 2. Information about patients with no pain (PNP group).

Nr	Level of injury	ASIA	Years after injury
1	T7	A	7
2	T7	B	7
3	T12	A	7
4	L1	A	6
5	T2	A	2
6	T5	B	15
7	T11	A	11
8	T4	A	9
9	T7	A	15

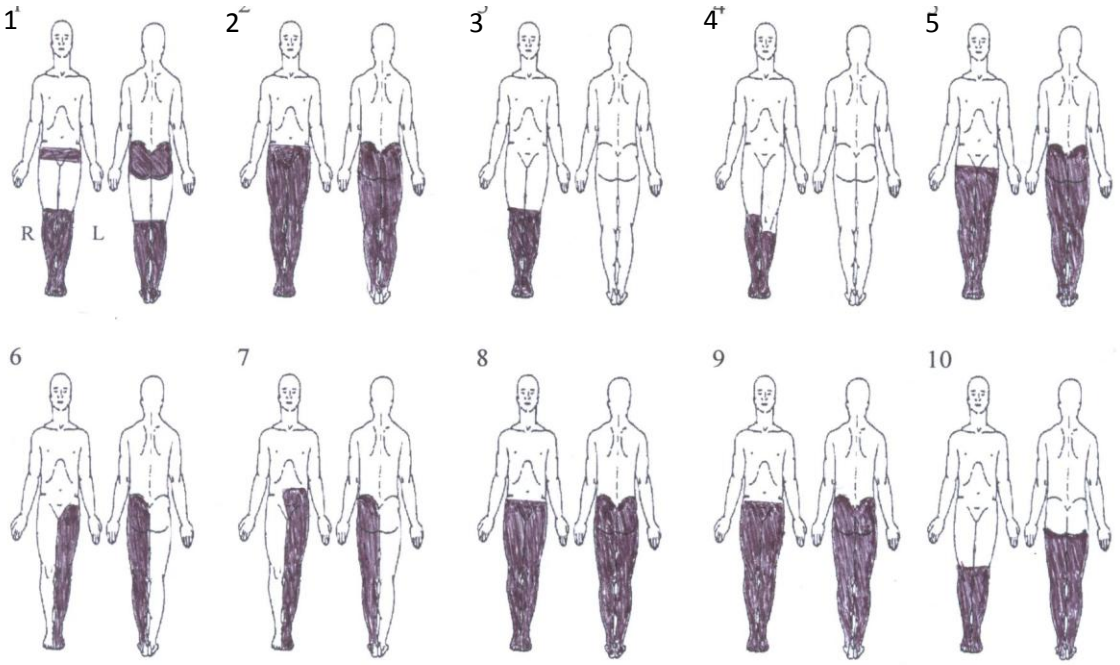


Figure 1

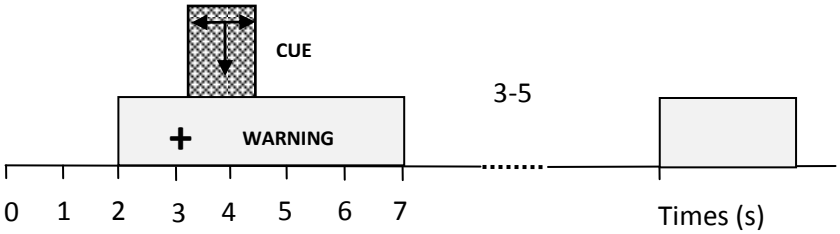


Figure 2

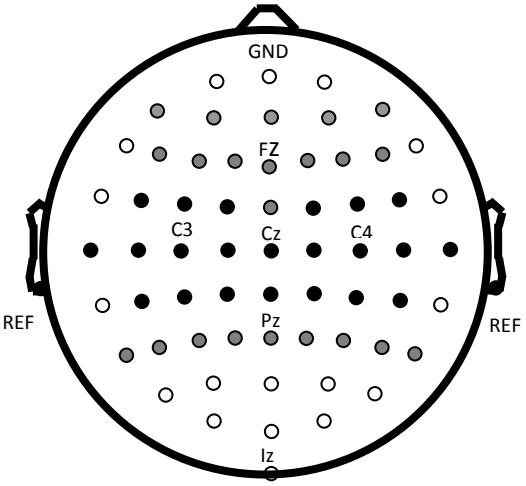


Figure 3

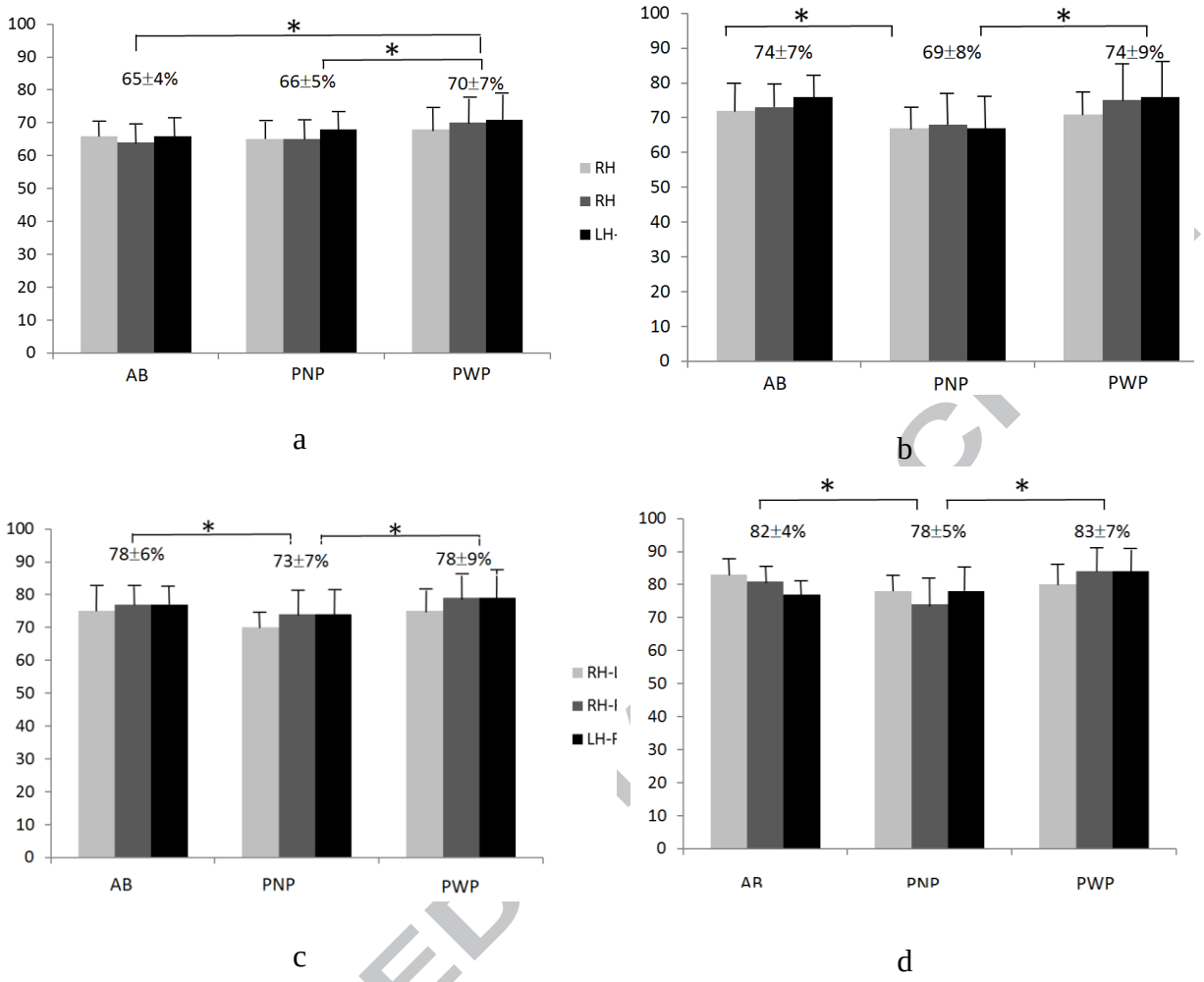


Figure 4

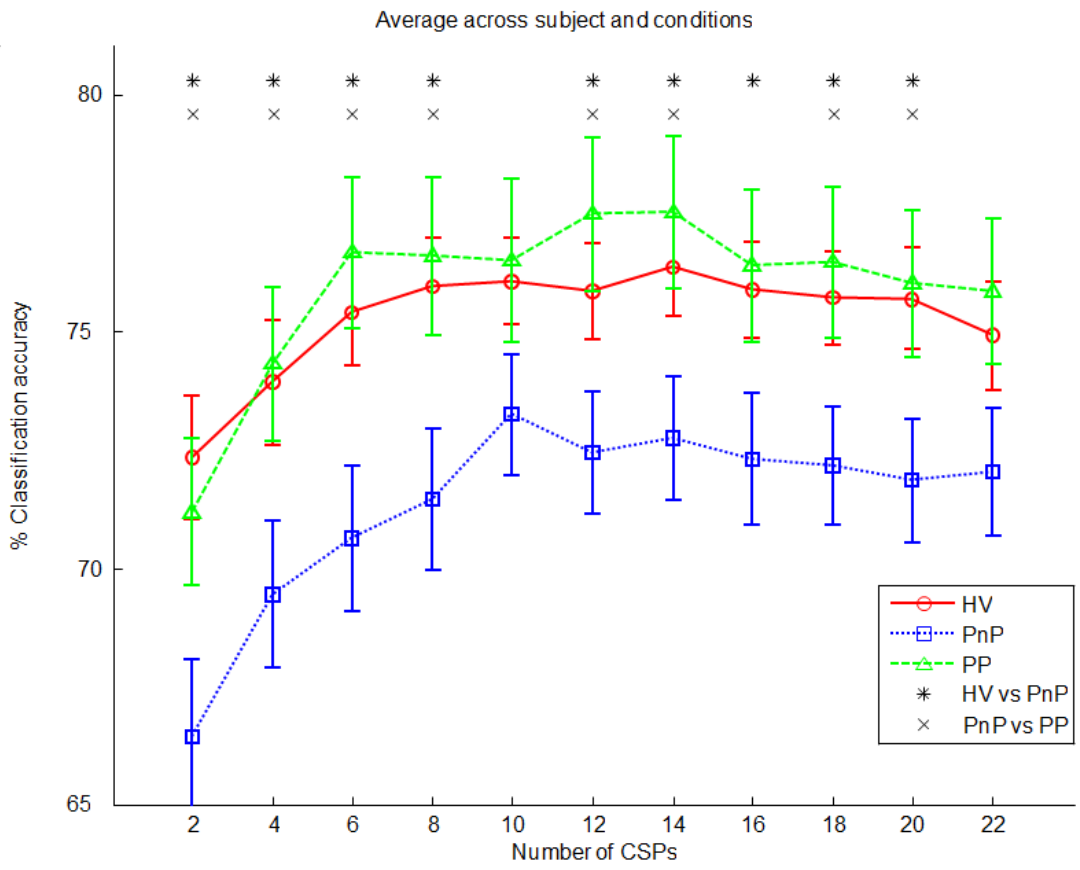


Figure 5

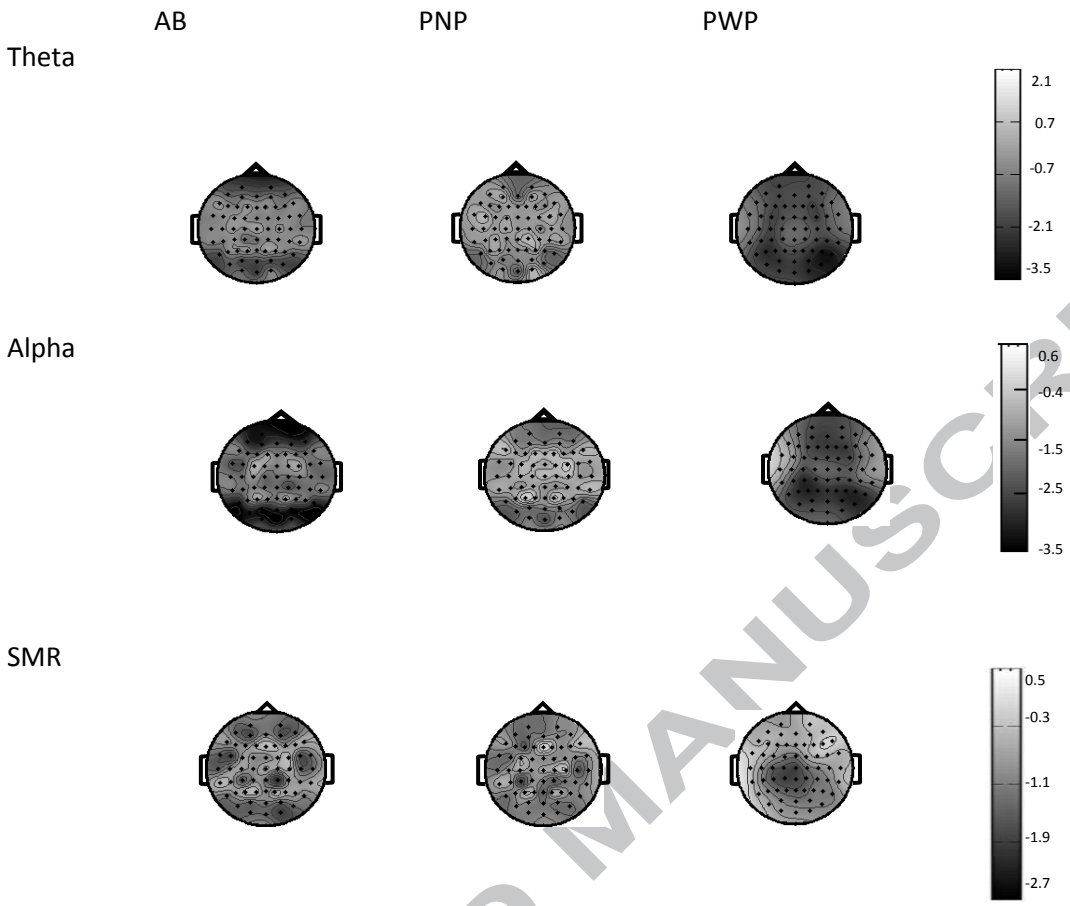


Figure 6 (a)

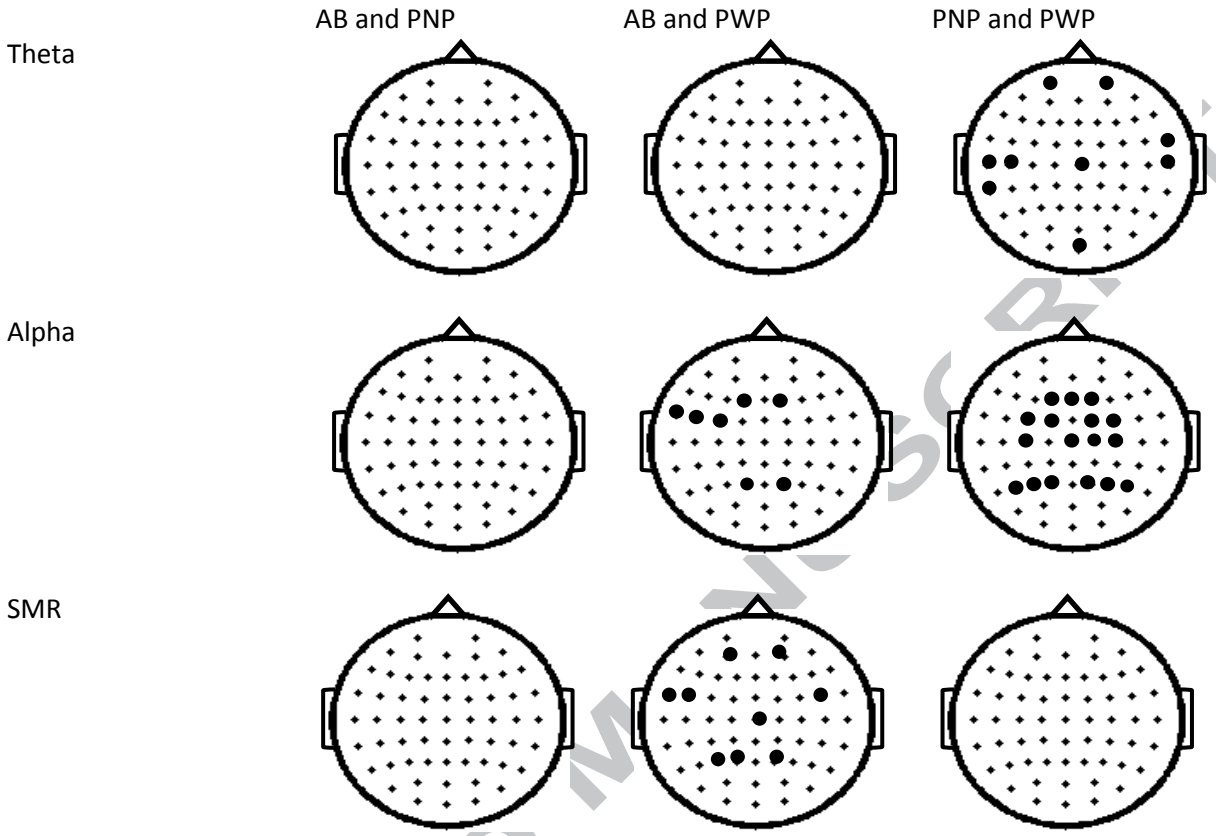
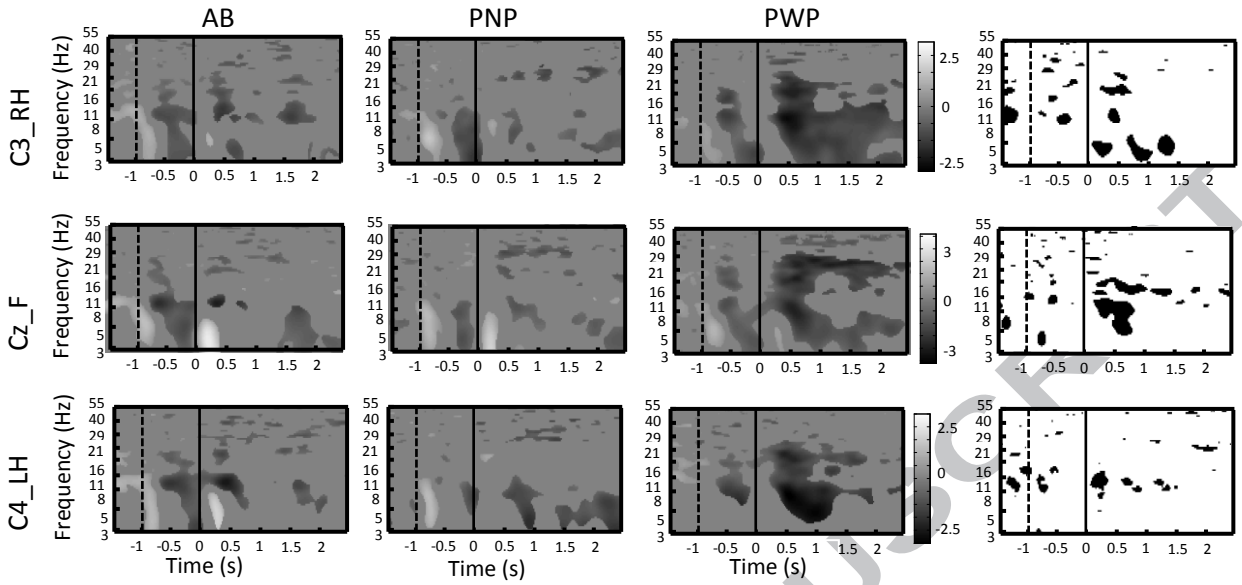
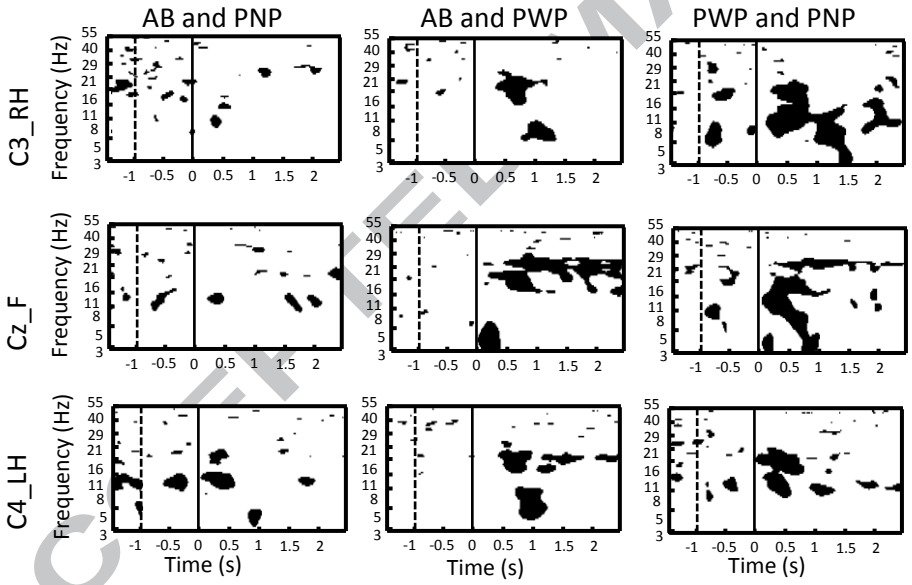


Figure 6 (b)



(a)



(b)

Figure 7