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Highlights

- Neuropathic pain (NP) in SCI has both EEG predictors and early markers
- Reduced EEG reactivity to eyes opening and reduced alpha power predict NP in SCI
- EEG predictors may predict NP earlier than sensory tests

Electroencephalographic Predictors of Neuropathic Pain in Subacute Spinal Cord Injury

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Abstract

It is widely believed that cortical changes are a consequence of long standing neuropathic pain (NP). In this paper we demonstrate that NP in people with subacute spinal cord injury (SCI) has characteristic electroencephalographic (EEG) markers which precede the onset of pain. EEG was recorded in a relaxed state and during motor imagination tasks in 10 able bodied participants and 31 subacute SCI participants (11 with NP, 10 without NP and 10 who developed pain within 6 months of EEG recording). All 20 SCI participants initially without NP were tested for mechanically induced allodynia but only one person, who later developed pain, reported an unpleasant sensation. The EEG reactivity to opening eyes was reduced in the alpha band and absent in the theta and beta bands in participants who later developed pain, and it was reduced in participants who already had pain. Alpha band power was reduced at BA7 in both the relaxed state and during motor imagination in participants who either had or later developed pain compared to participants without pain. All SCI groups had reduced dominant alpha frequency and beta band power at BA7.

Electroencephalographic reactivity to eyes opening, and reduced spontaneous and induced alpha activity over the parietal cortex were predictors of future NP as well as markers of existing NP.

Clinical Trial Registration Number: NCT02178917

Perspectives: We demonstrate that brain activity in subacute SCI contains both early markers and predictors of NP, which may manifest before sensory discomfort. These markers and predictors may complement known sensory phenotypes of NP. They may exist in other patient groups suffering from NP of central origin.

Keywords: Spinal Cord Injury, NP, motor cortex, spinothalamic tract

1. Introduction

Spinal cord injury (SCI) results in multiple secondary consequences that may appear within weeks post injury though some might take years to develop.[14, 38, 39] Neuropathic pain (NP) of central origin is one of the most debilitating secondary consequences of SCI. The prevalence of NP in SCI is around 50% [38, 39] and most patients develop this type of pain within the first year of SCI.

At a supraspinal level, NP of central origin causes both structural and biochemical changes.[16, 37] An important consequence influencing oscillatory brain activity is thalamo-cortical dysrhythmia.[37] This phenomenon is caused by the hyperpolarisation of thalamic neurons and low threshold calcium spike firing. This exerts a rhythmic influence on thalamo-cortical modules in the theta frequency band, keeping these structures in the state of reduced activity. In SCI patients with below level NP, increased theta band power is considered the main EEG signature of pain.[8, 22, 26] Previous EEG studies of central NP in SCI also reported reduced alpha band EEG power and a shift of the dominant alpha frequency towards lower frequencies.[8, 18 ,22, 26] Recently Camfferman *et al.*[9] suggested that reduced alpha band power might be an indicator of chronic pain in general.

Another EEG maker of NP in SCI is reduced reactivity of the alpha rhythm to eyes opening.[8, 46] This has been attributed to altered inputs from the thalamus.[8]

NP also affects induced EEG activity. Our group [46] showed that Event-Related Desynchronsation (ERD) [35] during motor imagination is affected by central NP in SCI, confirming results of fMRI studies [16] which showed increased activity of the primary motor cortex due to central NP. We further showed that excessive ERD over the sensory-motor cortex diminishes, concomitant with a reduction in pain following several months of neurofeedback therapy.[17]

It is believed that NP in most cases of SCI arises gradually, due to increased excitability of the nervous system.[11, 13] Unpleasant sensory hyper-excitability to mechanical, thermal and nociceptive stimuli may develop even before the first pain symptoms.[15, 48]

While altered sensations to thermal and mechanical stimuli are important predictors of future NP post SCI, these sensations are also considered diagnostic signs of NP. The open question is therefore whether brain oscillatory activity can serve as a neurological measure of

more subtle changes within the central nervous system. A recent study on rodents confirmed that increased theta band power, similar to that observed in humans, accompanies the onset of pain [24] and that it can be reduced within days or weeks by taking pregabalin, a medication often used in SCI patents to treat NP. There are however no studies looking at predictors of pain at the cortical level in humans.

In this study we investigated the relationship between the onset of pain and changes in the resting state and induced EEG activity in patients with SCI. We hypothesised that EEG may reveal 'predictive' markers of pain, and that these markers further evolve after a person starts feeling pain. We also hypothesised that EEG predictors of pain could be detected even before the onset of sensory symptoms such as allodynia and hyperalgesia.

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 were age between 18 and 75, participants capable of understanding the task and having no known other major neurological disorder or injury (i.e. stroke, brain injury, epilepsy, multiple sclerosis, cerebral palsy). Exclusion criteria for patients with diagnosed NP were the presence of acute pain or peripheral neuropathy below the level of injury or the presence of any pain above the level of injury. The distinction between acute and chronic pain is sometimes determined by an arbitrary interval of time since onset; the two most commonly used markers being 3 months and 6 months since onset.[38] NP can also be studied in an early stage, due to its characteristic location, sensory descriptors and responsiveness to a certain group of antidepressants and anticonvulsants.[27] All patients were within months of SCI, still hospitalised and undergoing inpatient primary rehabilitation.

There has been no confirmed relationship between the incidence of NP and sex, age, level or completeness of injury. Therefore, patients of both sexes, paraplegic and tetraplegic, complete or incomplete were included in the study, similar to the recruitment criteria applied in a study of sensory predictors of pain.[15] There were two groups of patients: ten patients who already had below level NP diagnosed at the time of the experiment (pain level ≥ 4 on the Visual Numerical Scale (VNS), where zero means no pain and ten means 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 NP used descriptors typical of below injury level

NP such as constant burning or stinging and intermittent shooting. Some patients also described NP at injury level typically as 'a tight rope' squeezing pain. The number of patients allocated to the without pain group was based on the published literature showing that nearly half of patients with SCI eventually develop pain within the first year of SCI.[15, 39] Patients who did not have pain at the time of the experiment were followed up for six months. After that period they were further divided into groups that had not developed chronic pain and that did eventually develop NP. For EEG analysis participants were therefore divided into four groups:

1. Ten able bodied (AB) participants (three female, seven male, age 35±7)
2. Eleven patients with NP (PWP) at the time of EEG recording (four female, seven male, age 45±17)
3. Ten patients who eventually developed NP (PDP) after EEG recording (one female, nine male, age 47±16).
4. Ten patients who did not develop NP (PNP) pain within six months of EEG recording (one female, nine male, age 42±13)

Information about the patient groups is provided in Table 1.

Approximately ten participants per group were chosen based on the results of our previous study with spinal cord injured patients with chronic NP [46] and on other published literature that included EEG analysis during motor imagination.[28, 35]

All participants signed an informed consent. The study was performed in accordance with the Declaration of Helsinki. For patient participants, ethical approval was provided by the West of Scotland Research Ethics Committee while for able-bodied participants it was provided by the University Ethics Committee.

Patents in PWP group were taking the following medications: pregabalin (patients 1,5,9), tramadol (patients 3,4) and gabapentin (patients 2,10 and 11). Patients in other groups did not take any medications for the treatment of chronic pain and did not report any chronic pain.

Table 1 about here

2.1.1. Analysis of Variance

We compared descriptive (pain) and demographic factors (age, level of injury and time after injury) between groups using ANOVA, and compared the completeness of injury using a non-parametric Kruskal-Wallis test. The level of injury was assigned a number from 1 to 21, corresponding to the injury levels C1 to L2. The completeness of injury was determined using the four ASIA (American Spinal Injury Association) scoring levels, A to D numbered from 1 to 4. Although it is sometimes believed that there is no relation between the level or completeness of injury and pain,[38] tetraplegic patients have been reported to be more likely to develop below level pain than paraplegic patients.[25, 38] A recent study by Mahning *et al*.[25] also indicates that patients with complete injury (ASIA A) have the most severe pain.

Medication was not included as a factor, as only 8 out of the 11 PWP were taking any and these included analgesics and anticonvulsants. These medications might reduce the dominant alpha frequency and increase the theta and delta band power.[3] Response to mechanical stimuli was also not included as a factor as it was tested in PDP group only with 1 out of 10 participants reporting a response. In addition almost half SCI patients had complete injury (ASIA A) and did not respond to the sensory test. Differences due to sex were not investigated since two of the groups had only one female patient. All model residuals were tested for normality of distribution using an Anderson Darling test ($p > 0.05$) and found to be normal.

Quantitative EEG data was grouped according to the spatial location (lobes) and frequency bands: theta (4-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz) and the following spatial locations were selected: frontal; F1, F2,F3,F4 and F4, occipital; O1,O2,Oz, POz,PO3 and PO4 and parietalP1,P2 and Pz covering Brodmann's Area (BA) 7. The first two regions were selected based on the largest expected eyes closed/eyes opened (EC/EO) reactivity .[2] Parietal locations were selected based on post-hoc source analysis using sLORETA (covering BA 7). Spearman's Rho correlations between EC/EO power ratio values and demographic and descriptive factors were examined in theta, alpha and beta bands separately over the frontal, occipital and parietal locations. Where correlations were significant, general linear model ANOVAs were performed and the models adjusted to give the greatest adjusted R^2 values.

Similar analyses were not performed with sLORETA results because of the difficulty in separating results of individual participants and of selecting relevant voxels for the analysis. Regions of interest included up to 39 voxels, the activity of which was correlated due to

spatial proximity. sLORETA analyses were performed separately for upper and lower extremity motor imagery, depending on the level of injury.

2.2 Experimental Procedures

2.2.1 Questionnaires

All patients were asked to fill out "the Brief Pain Inventory" [10] and patients with pain have marked the painful areas of the body on a body chart. Patients in PWP group were also asked to fill out the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire (LANSS).[6] Patients in the PWP group with complete injuries (ASIA A) had no response to mechanical stimuli, thus allodynia and hyperalgesia could not be tested. There were 5 out of 11 PWP patients with complete injuries and for that reason results of the LANSS test were excluded from the analysis.

2.2.2. Sensory Tests

The level of injury (sensory and motor) was assessed using the International Standards for Neurological Classification of Spinal Cord Injury produced by the American Spinal Injury Association. The sensory assessment included a determination of light touch and pinprick for all dermatomes on both sides on the body, which are also indicative of allodynia and hyperalgesia. The sensory profiles of patients with no pain at the time of EEG recording (PNP and PDP) were evaluated by testing the perceptual threshold using monofilaments. A perceptual threshold was defined as the lowest stimulus intensity at which SCI patients reported sensation. They were examined for mechanical wind-up by using monofilament no. 6.65, which provides the most sensitive mechanical test for the prediction of pain in SCI patients.[48] Mechanical wind-up is a repeatable mechanical stimulus of identical intensity, which causes gradually increasing pain. Stimuli were applied four consecutive times on patients' feet and shanks, every 3s [48] 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.

Somatosensory SCI phenotypes can be classified into 7 groups including those with thermal/mechanical sensory loss, and groups with dominantly thermal or mechanical allodynia or hyperalgesia.[47] ASIA A patients in this study had no sensation to mechanical stimuli thus the mechanical test had no predictive value for them. Therefore the predictive

value of sensory tests was applied to ASIA B-D patients in PDP (4 out of 10) and PNP (4 out of 10) groups.

2.2.3. EEG Recording

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

Previous studies showed that markers of long standing NP are present in both spontaneous and induced states, such as during motor imagination.[8, 22, 46] For this reason EEG activity was recorded first in a relaxed state with eyes opened and eyes closed (spontaneous EEG), followed by EEG recording during cue based motor imagination.

Spontaneous EEG activity was recorded in both relaxed states for 2 min each and repeated twice, alternating between the states, in order to leave at least 3min of EEG recording after noise removal. 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 eye movement, while during the eyes closed relaxed state, they were asked to relax.

Motor imagination in chronic paraplegic patients with NP produced a distinctive pain related dynamic response, even in the absence of nociceptive stimuli.[16, 46] These responses may be affected by NP through two mechanisms: the over-activation of the motor cortex during imagined movement and changes in the baseline, i.e. spontaneous EEG.[17]

Induced EEG activity was recorded during cue based motor imagination. The task paradigm was implemented using rtsBCI software (Guger technology, Austria). This is an experimental paradigm widely used in motor imagery-based brain computer interface studies.[28] Participants sit at a desk in the front of a computer screen at a distance of about 1.5m. At the beginning of each trial, a warning cue (a cross +) appears in the middle of the screen, followed one second later by an initiation cue. The initiation cue is an arrow pointing

either to the right, to the left or down. Participants are instructed to imagine waving with their right hand (symbol →), left hand (symbol ←) or to imagine tapping with both feet (symbol ↓) with a frequency of approximately 1 Hz, while the cue stays on a screen for 3s. Both feet were included in the tapping task because it is hard to distinguish between the cortical activities of each separate foot due to the anatomical location of the motor cortex of feet. The order of cueing was random and there was a resting period of between 3 and 5s between trials. Participants performed 180 trials (60 of each type) in 6 experimental sub sessions within the same experimental session. Each sub-session included 30 trials and lasted about 5min.

2.3 Data analysis

2.3.1. EEG Pre processing

Both spontaneous and induced EEG were exported to the EEGlab toolbox in Matlab.[12] EEG signals were then visually inspected and signals with artefact which had an amplitude ≥ 100 μV or were present across all electrodes were manually removed. On average, no more than 3 out of 60 trials were 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[4] 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.

2.3.2. EEG in a Relaxed Eyes Opened and Eyes Closed State

Analysis of EEG in a relaxed state was performed to test for the following markers of long standing NP: EEG power in the theta, alpha and beta range, dominant alpha frequency and reactivity to eyes opening in the theta, alpha and beta range. All three measures are known markers of NP in chronic SCI and are related to deafferentation of the excitatory inputs to the thalamus. Increased theta and beta band power arise as a result of hyperpolarisation of thalamic neurons, leading to a low-threshold calcium spike burst, producing a wide spread slow wave (theta) activity which can be recorded by EEG. Through a mechanism called "edge effect" cortical activity is facilitated in the beta/gamma range, a mechanism that has

been associated with pain.[37] Reduction in alpha power is believed to be a general marker of chronic pain.[9]

A shift of the dominant alpha frequency has been found in several neurological disorders[30] and is explained by thalamo-cortical dysrhythmia.[19] This involves high frequency bursts mediated by metabotropic glutamate receptors (mGluR1a), which are believed to play a role in NP.[31] The high frequency bursts occur in a continuum of frequency ranges (from 2 to 13 Hz) thus covering both the theta and alpha range. A membrane that is depolarised to a lesser extent is related to the lower frequency.[19]

The reduced reactivity to opening eyes (suppression of EEG power) is related to the inability of the thalamo-cortical mechanism to adjust to the sensory input.[8] In able-bodied individuals, EEG power in the delta, theta, alpha and beta bands is higher in the eyes closed than in the eyes opened state.[2] It is believed that a wide spread cortical increase of alpha band power when closing the eyes reflects changes in the arousal level while more focal changes in power in the other frequency bands reflect cortical processing of visual input rather than just changes in the arousal level.[2]

EEG group analyses were performed in EEGLab over the 4 groups (AB, PWP, PDP and PNP) and two conditions (eyes opened and eyes closed). To calculate the power spectrum density a Welsh periodogram method was used and implemented in EEGLab. The difference in power between groups in a chosen frequency band was calculated based on a bootstrapping method with a significance level of $p \leq 0.05$. The location of a dominant peak was determined as the maximum in a power spectrum over 8 to 13 Hz for each participant, and each electrode location and averaged values were obtained by averaging across electrodes and participants within the same group. The power of the dominant peak was calculated in a frequency band + 2Hz and -2Hz around a dominant peak. Reactivity between EO and EC state for a selected frequency band was presented as an EC/EO ratio of power based on the selected frequency band. A comparison of the power and frequency of the dominant peak between and within groups, during EO and EC relaxed state was performed using nonparametric Wilcoxon rank-sum test. A correction for multiple comparisons was performed using the false discovery rate.[5] Although this method is widely used in EEG analysis, it assumes that measurements are independent, which is not in general the case of multi electrode EEG measurement, where neighboring electrodes are likely to record activity

from a common source. Therefore correction for multiple comparisons methods are known to prevent false positive at the cost of allowing false negative error. For this reason we show both results before and after correction for multiple comparisons.

2.3.3. Event Related Synchronisation/Desynchronization During Motor Imagination

Group analyses were performed in EEGLab over the 4 groups (AB, PWP, PDP and PNP) and three conditions (imagined movements of the right hand, left hand and of both feet). The Event Related Synchronisation /Desynhronisation (ERS/ERD) was computed using EEGlab. ERD/ERS analysis was performed on the EEG data within a frequency range 3 to 45Hz using Morlet Wavelets.[26] The Hanning-tapered window was applied and the number of cycles of the wavelet was set to 3, with a minimum of 3 wavelet cycles per window at the lowest frequency. The baseline period used for ERS/ERD analysis was from 1.9 to 1.1s before the warning cue for each trial. The ERS/ERD was averaged over trails and participants within the same group, separated according to the imagination condition. A scalp map based on averaged ERS/ERD over a specific time window and over a specific frequency band was also used for group analyses. A non-parametric two way ANOVA with a significance level of $p \leq 0.05$ was used in order to assess the differences between the groups and conditions. A correction for multiple comparisons was performed using the false discovery rate method.

2.3.4. sLORETA Analysis

EEG recording has a very good time resolution but compared to MRI it lacks good spatial resolution. In order to improve the spatial resolution of recorded brain activity, and to estimate the activity of sources in deeper cortical structures, standardised Low Resolution Electromagnetic Tomography sLORETA analyses were performed.[34] sLORETA was used to estimate the cortical three dimensional distribution of the EEG sources current density. This method is a linear minimum norm inverse solution to an EEG 3D localisation inverse problem. This model has been extensively validated and was found to have no localisation bias.[34, 40] The sLORETA cortical map is computed for 6239 voxel partitions of intracerebral volume at 5 mm spatial resolution. Brodmann's areas are reported using the Montreal Neurological Institute (MNI) space with correction to the Talairach space. [43]

sLORETA analysis was performed on spontaneous EEG data and on EEG data during imagined movements for all 4 groups. For spontaneous EEG, data for each subject was split

into 4s long time windows. The current source density was computed in sLORETA for each time window in three frequency bands including theta 4-7Hz, alpha 8-12Hz and beta 13-30Hz. Theta band was reduced to 7 Hz rather than to 8 Hz to avoid the overlap with the dominant alpha peak which in patients was shifted towards the lower frequencies. The frequency dependent changes in cortical structures were compared between the groups during the eyes opened and the eyes closed states. Significance was set at $p \leq 0.05$. A non-parametric permutation test [29] with 5000 randomisations implemented in the sLORETA package was used to compute corrected *p* values.

For induced EEG, trials were split into 1s long time windows and exported to sLORETA. The current source density was computed in sLORETA for each time window in theta 4-8Hz, alpha 8-12Hz and beta 20-30Hz frequency bands. Selection of frequency bands was based on observation of ERD maps, selecting frequency bands with the strongest ERD. A 1s long baseline was taken from 2s to 1s before the warning cue for each movement imagination trial. The frequency dependent changes in brain activation were compared between the groups for all three movement imagination conditions. The same statistical method as described above was used to compute corrected *p* values.

Although sLORETA can be used with 32 EEG channels only, the larger number of electrodes increases the precision of spatial localisation.[41] Based on Song *et al*. results we assume that the localisation imprecision should be within one sLORETA voxel (5mm). From that reason, any BA containing 1-2 voxels located on a border with another BA with a larger number of voxels was excluded from the analysis.

3. Results

3.1. The Analysis of Variance

The average age was 47±16 years for PDP, 45±17 years for PWP, 42±13 years for PNP and 35±7 years for AB. For patient groups, the time post injury was 9±6 weeks for PDP, 16±8 weeks for PWP and 10±5 weeks for PNP. There were no significant differences in age ($F(2, 28) = 0.24$, $p = 0.787$), time post injury ($F(2, 28) = 3.17$, $p = 0.057$) or ASIA impairment scale ($F(2, 28) = 0.20$, $p = 0.820$) between groups.

The average pain score for PDP was 4.3±2.2 VNS and 6.5±1.3 VNS for PWP. The average injury level for PWP was 10.32±6.26 points, 8.5±6.6 points for PDP and 16.05±3.73

points for PNP. The pain scores ($F(1, 19) = 8.53$, P = 0.009) and injury levels ($F(2, 28) = 4.79$, P = 0.016) differed between groups. Bonferroni post hoc analysis revealed that the PWP group scored 2.2 VNS points higher than the PDP group (0.8, 3.8) 95% confidence interval (CI), $t(19) = 2.92$, $p = 0.005$. Patients with no pain (PNP) had injury levels that were 8 levels (1, 14) 95% CI lower than the PDP group ($t(18) = 2.96$, p = 0.019).

3.2. Spontaneous EEG Activity

3.2.1. EEG Reactivity and Dominant Frequency

Group AB had the largest reactivity of all groups in all three frequency bands, present on most electrodes covering the whole cortex (Fig 1). Both PWP and PDP groups had a reduced reactivity to opening eyes in all three frequency bands. Group PNP had less reactivity than AB on central electrodes only, in alpha and beta bands. The largest differences between PNP and PDP were found for reactivity in theta and beta bands where PDP did not show a significant reactivity at any electrode. PWP demonstrated theta reactivity on a number of electrodes over the whole cortex. In the alpha band both PDP and PWP groups had the largest reactivity in the frontal and the parieto-occipital areas. In the beta band, PWP had a significant reactivity at electrode P6 only, PNP showed reactivity at the occipital electrodes while AB had a wide spread reactivity.

A significant correlation was found between injury level and beta band EC/EO power ratio in the frontal areas, and between the pain score and the theta band EC/EO power ratio in the occipital area. No correlations were found between the injury level or pain score and EC/EO ratio in the parietal area in any frequency band.

There were significant correlations between injury level and beta band EC/EO power ratio at electrode locations F1 ($rs = 0.451$, $p = 0.014$), F2 ($rs = 0.397$, $p = 0.033$) and F4 ($rs = 0.534$, $p = 0.003$) across all SCI participants, with higher injury levels corresponding to higher values. For the electrode with the strongest correlation, F4, injury level was able to explain 20% of the variance in beta EC/EO power values ($F(1, 27) = 7.79$, $p = 0.010$) with no more variance explained when controlling for pain groupings (R^2 adjusted 19%, $F(2, 25) = 0.30$, $p = 0.741$). The PNP group had significantly lower injury levels than the PDP and the PWP groups, and this was the only patient group with significant differences between EC and EO

beta power at F4. This results might therefore reflect lower injury level rather than the absence of pain in the PNP group.

Figure 1 about here

There were significant negative correlations between pain scores and the theta band EC/EO ratio at electrode locations PO3 (*rs* -0.473, $p = 0.035$), O1 (*rs* -0.501, $p = 0.024$) and O2 (*rs* -0.467, $p = 0.038$) over all SCI participants. Higher pain scores were associated with smaller theta EC/EO ratio values in these areas. The relationship accounted for 26% of the variance in theta band EC/EO ratio at electrode location O1 ($F(1, 18) = 6.66$, $p = 0.019$) with no more variance explained in the model when controlling for pain groupings (R^2 adjusted 22%, $F(1, 17) = 0.22$, $p = 0.643$).

Although the PWP group had significantly higher pain scores than the PDP group, they had a larger numbers of electrodes with significant differences in the alpha EC/EO power ratio than the PDP group.

All three patient groups had a reduced dominant alpha frequency compared to the able-bodied. Dominant frequencies in the eyes open and eyes closed state respectively were 10.4±1.0 Hz and 10.0±0.6 for AB, 9.6±1.1 Hz and 9.2±1.0 Hz for PNP, 9.3±1.4Hz and 8.6±1.0 Hz for PDP and 9.5±1.5 Hz and 9.0±1.4 Hz for PWP. Figure 2 shows electrode locations with significant differences in the dominant frequency in the eyes opened and eyes closed state between different groups, the grey colour indicates significant electrodes before a correction for multiple comparisons and the black colour after correction for multiple comparisons. The difference was larger for the eyes closed state and existed almost exclusively between AB and patients.

Figure 2 shows individual power spectrum density for each participant in each group in the eyes open and eyes closed state over a representative electrode POz to demonstrate that results are representative of the whole group rather than caused by outliers.

Figure 2 about here

Significant differences in the dominant frequency were found between AB and all patient groups. However, these differences were present on the largest number of electrodes when comparing between AB and PDP and smallest between AB and PNP (Fig. 3). The effect of

the injury level and the level of pain on the dominant frequency was not examined because of the absence of any significant difference between patient groups.

Figure 3 about here

3.1.2. sLORETA analysis of spontaneous EEG activity

In all cases, areas of significant difference were found in the parietal cortex (BA7) (Table 2, sLORETA images Fig. 4). There was no difference between PDP and PWP groups. Groups differed in the alpha band for the eyes closed state only, whereas differences in the beta band, were found in the eyes opened state only. There were no differences between groups in the theta band.

The PNP group had a significantly higher alpha band power than both PDP and PWP, over the left hemisphere, indicating that alpha power was reduced before the onset of pain and stayed reduced when pain developed. In addition, PDP had a lower bilateral alpha power than the AB group. There were no significant differences between AB and PNP.

In the beta band (13-30 Hz), differences were found between AB and all three patient groups parietally at BA7 on the right hemisphere for PNP and PDP, and bilaterally for PWP (Table 2). Thus reduced beta band power seems to be a dominant indicator of sub-acute spinal cord injury rather than of pain.

Table 2 about here

Figure 4 about here

3.2. Induced EEG Activity During Motor Imagination

3.2.1. Analysis of Event Related Synchronisation and Desynchronisation.

Figure 5 shows ERS/ERD for all four groups, for imagined movement of the upper and lower limbs at electrodes located over the motor cortex of the left arm (C4), legs (Cz) and the right arm (C3). In AB group two distinctive ERD frequency bands, in the alpha and beta range can be noticed. For the PNP group, alpha desynchronisation was dominant, while for the PDP

group alpha and beta bands together form one large desynchronisation band. In the PWP group, desynchronisation spreads from the theta to the beta band.

Figure 5 about here

Figure 6 about here

Figure 6 shows scalp maps for ERS/ERD for feet (Fig 6A), left hand (Fig 6B) and right hand (Fig. 6C). Event related desynchronsation is dominant in all subfigures. Columns in each subfigure represent frequency bands: theta, alpha and higher beta (20-30 Hz). Higher beta was chosen as a sub-band of the beta band where larger differences among groups were noticed during analysis of ERS/ERD over individual electrodes. The four rows correspond to the four different groups of participants.

In the alpha band, contralateral ERD during imagination of left and right hand movement is visible for the AB group while all patient groups have a widespread, non-lateralised ERD. In the theta band, ERD is not visible in the AB group but can be noticed in all three groups of patients. The PDP group had ERD lateralised to the left cortex, irrespective of movement. Scalp maps in the PWP group also have visible theta ERD but with no clearly defined spatial distribution. Groups PNP had less visible ERD, mostly in the parieto-occipital region.

In the beta band, scalp maps of the AB group show contralateral ERD for imagined movements of both hands. Groups PDP and PWP had centrally localised ERD, irrespective of the limb while the PNP group had no visible ERD.

After a correction for multiple comparisons of scalp maps with more than one significant electrode location, there was no significant difference between groups. However electrode locations showing differences were clustered, therefore it is possible that correction induced false negative errors.

3.2.2. sLORETA Analysis of Induced Cortical Activity

Significant differences were found in the alpha band only (Table 3). Both AB and PNP groups showed significantly stronger desynchronsation than the PDP and PWP groups. The area of largest difference was located in the right hemisphere BA7, independent of the limb. PNP had stronger activity than PDP in the right parietal cortex (BA 7), for motor imagination of all three limbs and stronger activity than the PWP in the left parietal cortex, for motor imagination of all three limbs (BA7). No significant differences were found between groups in the theta and beta bands.

Table 3 about here

In the PNP group all participants were paraplegic, i.e. could move their hands, while groups PDP and PWP were a mixture of paraplegics and tetraplegics. This might influence the results of upper limb motor imagination. However PNP also had significantly higher activity than PDP and PWP during lower limbs motor imagination. In addition, there was no significant difference between AB and the PNP group although the PNP had paralysed lower limbs. This indicates that paralysis had little effect on these results. Furthermore, there was no significant difference between groups in the activation of the premotor and motor cortex (BA6 and BA4), which are the areas of strongest activity during imagined and real movement

In this study the largest differences among groups were found in both spontaneous and induced tasks in BA7. Thus it is most likely that results during imagined movement reflect differences between groups in spontaneous EEG activity.

4 Discussion

This study demonstrates that cortical changes due to spinal cord injury that lead to the development of central NP occur early post injury.

We have demonstrated that some EEG features of long standing NP are also present in sub-acute injury. These features were found in the PDP group, irrespective of the presence of pain at the time of recording. The most prominent features characterising "future" pain was a reduced reactivity between EO and EC. Both pain related groups, PDP and PWP, had reduced reactivity in the alpha and beta bands as compared to pain free groups. Theta band reactivity was reduced in PWP group and completely absent in the PDP group: this indicates that theta band reactivity to eyes opening might be a feature that evolves through the process of developing pain. Reduced reactivity was also reported in patients with chronic NP [8, 46] and was attributed to dysfunction of the thalamo-cortical mechanism that fails to adjust to changes in sensory input.

In this study we found a shift towards a lower dominant frequency in all three patient groups as compared to able bodied with no significant difference between the three groups of patients. Thus for subacute spinal cord injury a reduced frequency in the dominant alpha peak is mainly the marker of pain rather than injury though it might be additionally influenced by the injury. This "slowing down" is considered one of the main markers of NP [8, 22, 46] though

it has been reported that chronic SCI without pain produces a similar effect.[45] It is a novel result that this phenomena occurs early, within months post injury.

Another feature which characterised "future" pain was lower alpha activity in the parietal cortex (BA7). Several studies on chronic patients found no effect of pain on the alpha activity [8, 46] though Jensen *et al*.[22] found increased alpha activity in the frontal region in SCI patients with NP. On the other hand Camfferman et al.[9] recently suggested that reduced alpha activity is a signature of a chronic pain in general.

Interestingly, sLORETA analysis found no strong evidence of increased theta and beta band power in either PDP or PWP although they are considered standard markers of chronic central NP.[8, 22, 36, 42, 46] Increased theta and related beta band power is believed to be closely related to thalamo-cortical dysrhythmia [37] caused by hyperpolarisation of thalamic neurons. The thalamo-cortical network has a tendency to maintain a given functional modality, i.e. to reinforce the hyperpolarised state over time. Thus the level of theta and beta activity might increase over time and might not be measurable on the cortical level early after injury. A lack of EEG reactivity in the theta band found in pain related groups might be the first sign of these changes.

Brain activity induced through motor imagination is affected by both chronic pain and chronic injury and these two demonstrated distinctive responses to imagined movements.[46] In this study, after correction for multiple comparison, which in general does not take into account spatial correlation, no difference was found in ERD/ERS between groups. Spatial cortical representation of ERD in alpha bands showed wide spread non-lateralised ERD in all patients groups, probably related to injury rather than pain.[32] Parietal theta band ERD was noticed in pain related groups, though its statistical significance was not confirmed.

sLORETA analysis of deeper current sources found less activity in the alpha band in pain related groups compared with pain free group over BA7. It is however likely that this reflects the reduced baseline activity in the PDP and PWP as it was found at the same BA, and it does not demonstrate any difference between groups in the premotor or primary motor areas (BA4, BA6). Thus it seems that the over-activity of the motor cortex due to NP is a gradual process that cannot be seen early after injury even in patients who already have developed NP.

The parietal location of the largest difference between groups and the absence of significant difference in the affective or cognitive pain related areas [20] indicates that changes in cortical activity due to NP emerge first in the sensory cortex. This supports the hypothesis

that changes in the sensory cortex are one of the main causes of chronic pain in general, rather than an epiphenomena following nerve injury.[23]

Contrary to Zeilig *et al.* [48] we found that only one patient responded to mechanical stimulus, although both studies included patients with similar times post-injury. One possible explanation is that while we only performed the wind-up test, Zeilig's study included a battery of tests which might have resulted in increased sensitisation. The other difference was that in the current study more than half the patients had a complete injury, while in Zeilig *et al.* all patients were sensory incomplete. The wind up test was hard to perform in about 60% of patients in PNP and PDP groups because they had a complete injury and did not have any sensation under the level of the injury. Sensory tests in the transition zone, which would possibly provide additional information were not performed in this study.

There are several limitation of this study. The first one is that we did not record EEG in patients once they had developed pain so we had different participants in a group that eventually developed pain and in a group with pain. We also did not follow up patients for longer than 6 months, so it is possible that some patients in the PNP group later developed pain. While age and completeness of injury were matched between groups, level of injury was not matched between the PNP and pain related groups PDP and PWP. Unfortunately it was not possible to extract sLORETA features to measure the influence of the level of injury but movement imagination of the upper and lower limbs was tested separately. The effect of injury and of medications could not be separated in the PWP group because the majority of patients were prescribed anticonvulsant medications.

With respect to EEG recording, the main limitation was that the number of EEG electrodes in this study was relatively low (48 electrodes): according to the literature [41] this could increase the imprecision up to the size of one 5mm voxel.

The number of participants per group was relatively small but it was comparable with the number of patients in other EEG studies of NP.[8, 22, 46] Experimental procedures for testing motor imagination were adopted from brain computer interface studies that typically have about ten participants per group.[28] It should be noted that because every single participants had 60 repetition of each experimental condition, it was adequate to apply bootstrapping statistical procedures for assessing statistical significance. Larger numbers of participants might improve sensitivity and reveal more features which characterise the onset of NP.

This study gives important evidence of early predictors of future, and markers of recently developed NP. In the future, a machine learning algorithm might be developed to predict the risk of each individual patient developing NP, based on their EEG. This might lead to characterisation of EEG NP phenotypes and targeted treatments. The results indicate that EEG based predictors of pain might have wider application than sensory testing because EEG tests could be applied to people with complete loss of mechanical and thermal sensation. Longitudinal studies should be performed to understand progression of EEG markers of NP during progression from a subacute to chronic SCI.

5. References

1. American Clinical Neurophysiology Society Guideline 5: Guidelines for standard electrode position nomenclature. J Clin Neurophysiol 23:107–110, 2006
2. Barry RJ, Clarke AR, Johnstone SJ, Magee CA, Rushby JA: EEG differences between eyes-closed and eyes-open resting conditions. Clin Neurophysiol 118:2765-73, 2007
3. Bauer G, Bauer R: EEG, drug effects and central neural system poisoning: In Niedermeyer E, da Silva L (eds): Electroencephalography, Basic Principle, Clinical Applications and Related Fields. Philadelphia, Lippincott Williams & Wilkins, 2005, pp 701-723
4. Bell AJ, Sejnowski TJ: An information-maximization approach to blind separation and blind deconvolution. Neural Comput 7:1129–1159,1995
5. Benjamini Y, Yekutieli D: The control of the false discovery rate in multiple testing under dependency. Ann Statist 29:1165–1188,2001
6. Bennett M: The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs.. Pain 92:147-57,2001
7. Blair R, Karniski W: An alternative method for significance testing of waveform difference potentials. Psychophysiology 1993;30:518–524.
8. Boord P, Siddall PJ, Tran Y, Herbert D, Middleton J, Craig A: Electroencephalographic slowing and reduced reactivity in NP following spinal cord injury. Spinal Cord 46:118–123,2008

9. Camfferman D, Moseley GL, Gertz K, Pettet MW, Jensen MP: Waking EEG Cortical Markers of Chronic Pain and Sleepiness. Pain Med 18:1921-1931,2017

10. 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

11. Defrin R, Ohry A, Blumen N Urca G: Characterisation of chronic pain and somatosensory function in spinal cord injury subjects. Pain 89:253-263,2001

12. 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

13. Finnerup, NB & Jensen, TS: Spinal cord injury pain-mechanisms and treatment Eur J Neurol 11:73-82,2004

14. Finnerup NB: Pain in patients with spinal cord injury, Pain. 154:S71-S76,2013

15. Finnerup NB, Norrbrink C, Trok K, Piehl F, Johannesen IL, Sørensen JC, Jensen TS, Werhagen L: Phenotypes and predictors of pain following traumatic spinal cord injury: a prospective study.J Pain 15:40-8,2014

16. Gustin SM, Wrigley PJ, Siddall P., Henderson L.A: Brain anatomy changes associated with persistent NP following spinal cord injury. Cereb Cortex 20:1409–1419,2010

17. Hasan MA, Fraser M, Conway BA, Allan DB, Vučković A: Reversed cortical over-activity during movement imagination following neurofeedback treatment for central NP. Clin Neurophysiol 127:3118-27,2016

18. Herbert D, Tran Y, Craig A, Boord P, Middleton J, Siddall P: Altered brain wave activity in persons with chronic spinal cord injury. Int J Neurosci 117:1731-4,2007

19. Hughes SW, Crunelli V: Thalamic mechanisms of EEG alpha rhythms and their pathological implications. Neuroscientist 11:357-72,2005

20. Jensen MP: A neuropsychological model of pain: research and clinical implications. J Pain 11:2-12.2010

21. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, Treede RD: A new definition of NP. Pain 52, 2204–2205,2011

22. Jensen MP, Sherlin LH, Gertz KJ, Braden AL, Kupper AE, Gianas A, Howe JD, Hakimian S: Brain EEG activity correlates of chronic pain in persons with spinal cord injury: Clinical implications. Spinal Cord 51:55–58,2013

23. Kim W, Kim SK, Nabekura J: Functional and structural plasticity in the primary somatosensory cortex associated with chronic pain. J Neurochem 141:499-506,2017

24. LeBlanc BW, Bowary PM, Chao YC, Lii TR, Saab CY: Electroencephalographic signatures of pain and analgesia in rats. Pain 157:2330-40,2016

25. Mahnig S, Landmann G, Stockinger L, Opsommer E: Pain assessment according to the International Spinal Cord Injury Pain classification in patients with spinal cord injury referred to a multidisciplinary pain center. Spinal Cord 54(10):809-815,2016

26. Makeig S: Auditory event-related dynamics of the EEG spectrum and effects of exposure to tones. Electroencephalogr Clin Neurophysiol. 86:283–293,1993

27. Mehta S, Guy SD, Bryce TN, Craven BC, N B Finnerup NB, Hitzig SL, Orenczuk S, Siddall PJ, Widerström-Noga E, Casalino A, Côté I, Harvery D, Kras-Dupuis A, Lau B, Middleton JW, Moulin DE, Connell CO, Parrent AG, Potter P, Short C, Teasell R, Townson A, Truchon C, Wolfe D, Bradbury CL, Loh E: CanPain SCI Clinical Practice Guidelines for Rehabilitation Management of NP after Spinal Cord: screening and diagnosis recommendations. Spinal Cord 54, S7–13,2016

28. Neuper C, Wörtz M, Pfurtscheller G: ERS/ERD patterns reflecting sensorimotor activation and deactivation: In Neuper C, Klimesh W (eds): Prog Brain Res. Amsterdam, Elsevier; 2006, pp 211-222

29. Nichols TE , Holmes AP: Nonparametric Permutation Tests for Functional Neuroimaging: a primer with examples. Human Brain Mapping 15:1-25,2001

30. Niedermeyer E: Alpha rhythms as physiological and abnormal phenomena. Int J Psychophysiol 26:31-49,1997

31. Osikowicz M, Mika J, Przewlocka B: The glutamatergic system as a target for NP relief. Exp Physiol 98:372-84, 2013

32. Osuagwu BC, Wallace L, Fraser M, Vuckovic A: Rehabilitation of hand in subacute tetraplegic patients based on brain computer interface and functional electrical stimulation: a randomised pilot study. J Neural Eng 13:065002,2016

33. Pacual-Marqui RD: Standardized low resolution brain electromagnetic tomography (SLORETA): Technical details. Methods Find Exp Clin Pharmacol 24:5-12,2002

34. Pascual-Marqui RD: Discrete, 3D distributed, linear imaging methods of electric neuronal activity. part 1: Exact, zero error localization arXiv: 0710.3341,2007

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

36. 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

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

38. 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 103:249–257,2003

39. Siddall PJ, Middleton JW: Spinal cord injury-induced pain: mechanisms and treatments. Pain Manag 5:493-507:2015

40. Sekihara K, Sahani M, Nagarajan SS: Localization bias and spatial resolution of adaptive and non-adaptive spatial filters for MEG source reconstruction. Neuroimage 25:1056–1067,2005

41. Song J, Davey C, Poulsen C, Luu P, Turovets S, Anderson E, Li K, Tucker D: EEG source localization: Sensor density and head surface coverage. J Neurosci Methods 256:9-21,2015

42. Stern J, Jeanmonod D, Sarnthein J: Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. Neuroimage 31:721–731,2006

43. Talairach J, Tournoux P: Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: An approach to cerebral imaging. Thieme, 1988.

44. Tan G, Jensen MP, Thornby JI, Shanti BF: Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 5:133-7,2004

45. Tran Y, Boord P, Middleton J, Craig A: Levels of brain wave activity (8-13 Hz) in persons with spinal cord injury. Spinal Cord 42:73–79,2004

46. 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 15:645-55,2014

47. Widerström-Noga E: Neuropathic Pain and Spinal Cord Injury: Phenotypes and Pharmacological Management. Drugs 77:967-984,2017

48. Zeilig G, Enosh S, Rubin-Asher D, Lehr B, Defrin R:The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. Brain 135:418-430,2012

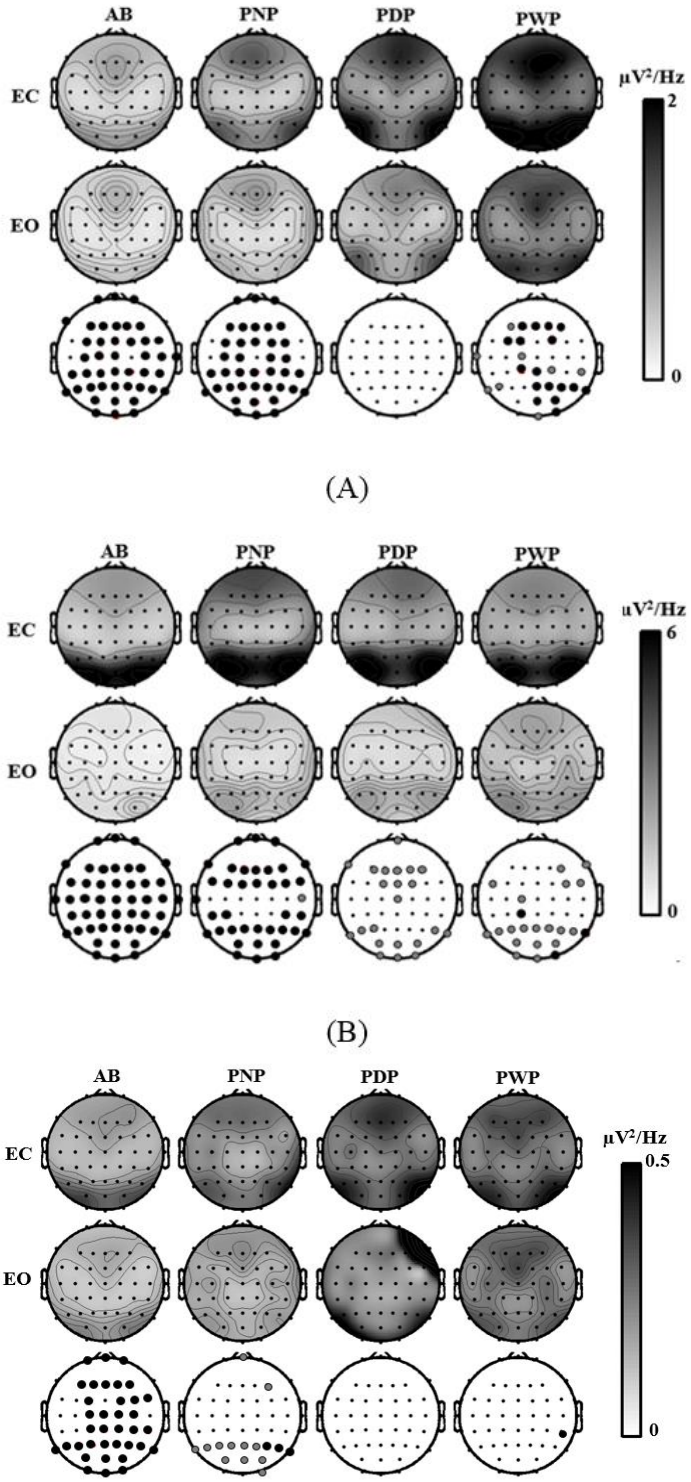
Table Legends

Table 1. Demographic information **of** study participants . ASIA A: complete sensory and motor function loss; B incomplete sensory, complete motor function loss; C and D incomplete sensory and motor loss. Level of injury: C cervical, T thoracic, L lumbar. PDP; participants who developed pain, PWP; participants with pain, PNP; participants with no pain, AB; able bodied participants.

Table 2 sLORETA localisation**.** Areas with significant differences of cortical activity in alpha (8-12Hz) EEG frequency band during eyes closed (EC) relaxed state and in beta (13-30Hz) EEG frequency band during eyes opened (EO) relaxed state. MNI: The Montreal Neurological Institute and Hospital (MNI) coordinate system. R, Right; L, Left

Table 3. sLORETA localisation. Areas of statistically significant differences of cortical activity between groups during motor imagination. MI: Motor imagination. F: feet; RH: right hand; LH: left hand.

Figure 1. Scalp maps showing power in the theta (A), alpha (B) and beta (C) frequency band. Upper row EC: eyes closed, middle row EO: eyes opened; bottom row: statistically significant differences. Each dot presents the location of an EEG electrode. Black dots: with correction for multiple comparison. Grey dots: without correction for multiple comparison. PDP: patient group that later developed pain, PNP: patient group without pain; PWP: patient group with pain, AB: able bodied group.



(C)

Figure 2. Power spectrum density for each individual participant (blue lines) and average power spectrum density per group (thick black line) for the eyes open (EO) and the eyes closed (EC) state at electrode location POz. PDP: patient group that later developed pain, PNP: patient group without pain; PWP: patient group with pain, AB: able bodied group

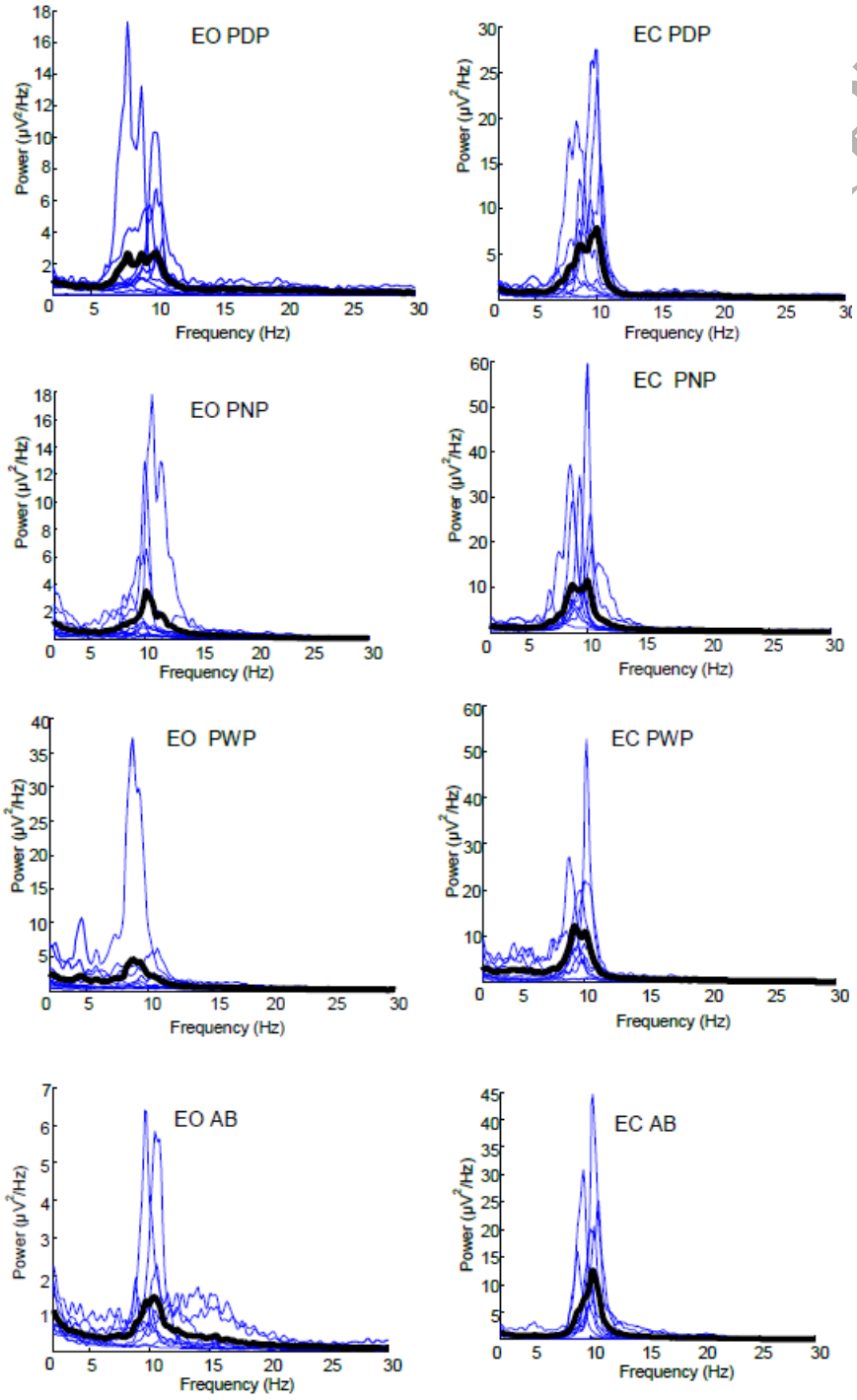


Figure 3 The comparison of the dominant peak frequency between pairs of groups during the eyes open (A) and the eyes closed (B) relaxed states. A top view of a head, with circles representing electrode locations. Small triangles repesent the nose. Electrodes with statistically significant differences and correction for multiple comparisons are presented by black dots while grey dots mark electrodes with statistically significant differences (p=0.05) without correction for multiple comparison. PDP: patient group who later developed pain, PNP: patient group without pain; PWP: patient group with pain, AB: able bodied group.

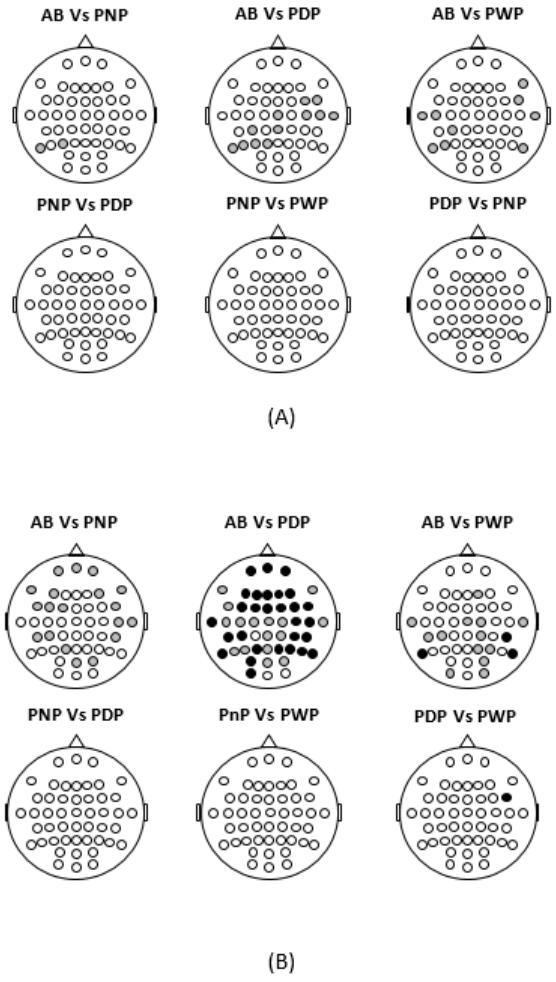


Figure 4. sLORETA localisation of statistically significant differences in resting state EEG activity between groups. A-C alpha band, eyes opened, D-F beta band, eyes closed (Results shown in Table 2 in the main text). The surface cortical presentations show all differences between pairs of groups. Cross sectional figures show areas which corresponds to significant voxels from Table 2. PDP: patient group who later developed pain, PNP: patient group without pain; PWP: patient group with pain, AB: able bodied group

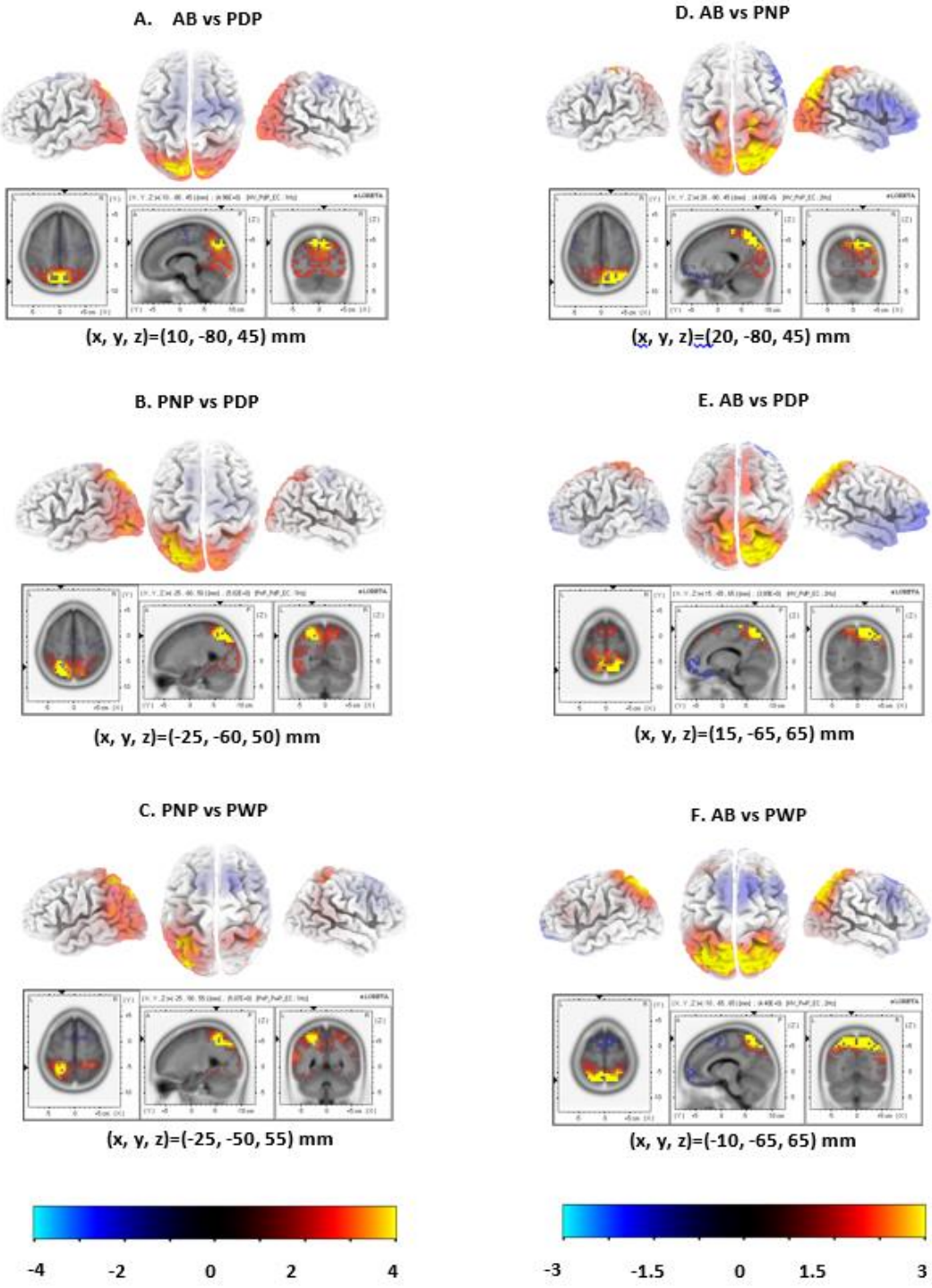


Figure 5. Group ERD/ERS maps of cue-based motor imagination. Electrode locations Cz for feet, C4 for the left hand and C3 for the right hand. A dashed vertical line at t=0 represents the moment when an initiation cue appears on the screen. Positive values (red) stand for ERDS and negative values (blue) for ERD. PDP: patient group who later developed pain, PNP: patient group without pain; PWP: patient group with pain, AB: able bodied group.

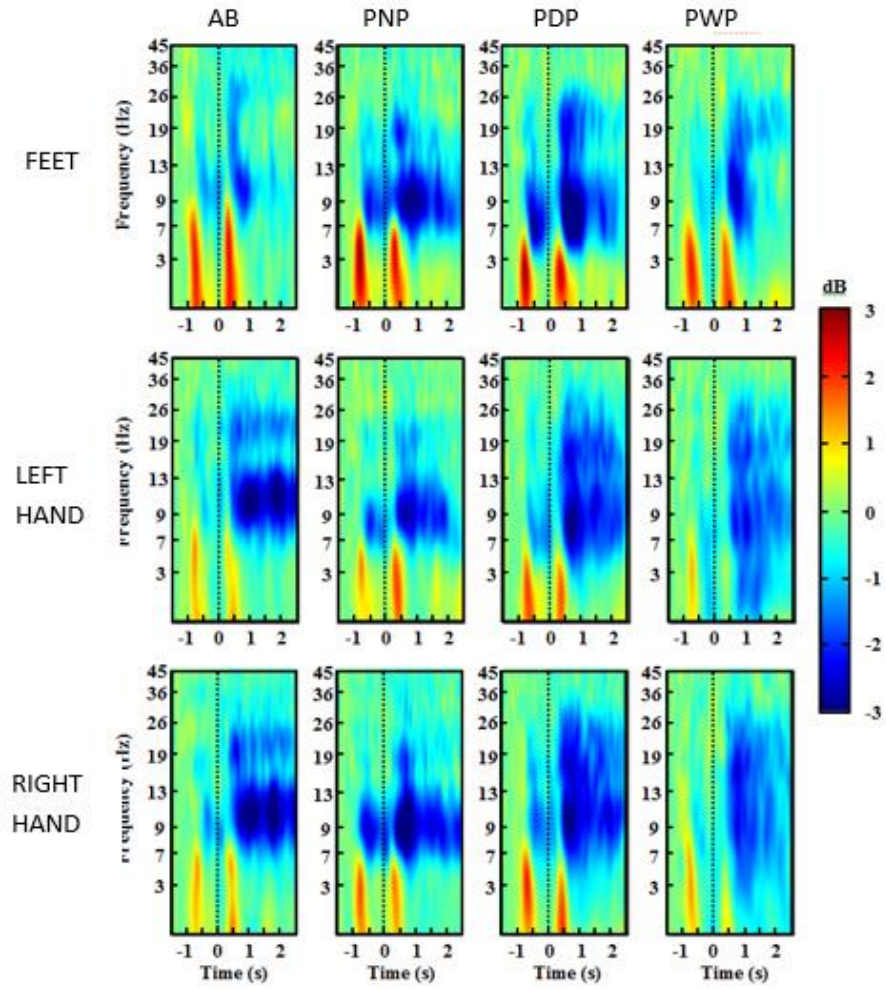


Figure 6. Scalp maps based on ERD/ERS for all four groups (facing the top of the page). The cortical activity averaged in theta (4-8Hz), alpha (8-12Hz), and beta (20-30Hz) frequency bands and over 0.5 to 1.5s during imagined movement of the feet, left hand and right hand. Positive values (red) stand for ERS and negative values (blue) for ERD. Each dot presents one electrode. PDP: patient group who later developed pain, PNP: patient group without pain; PWP: patient group with pain, AB: able bodied group

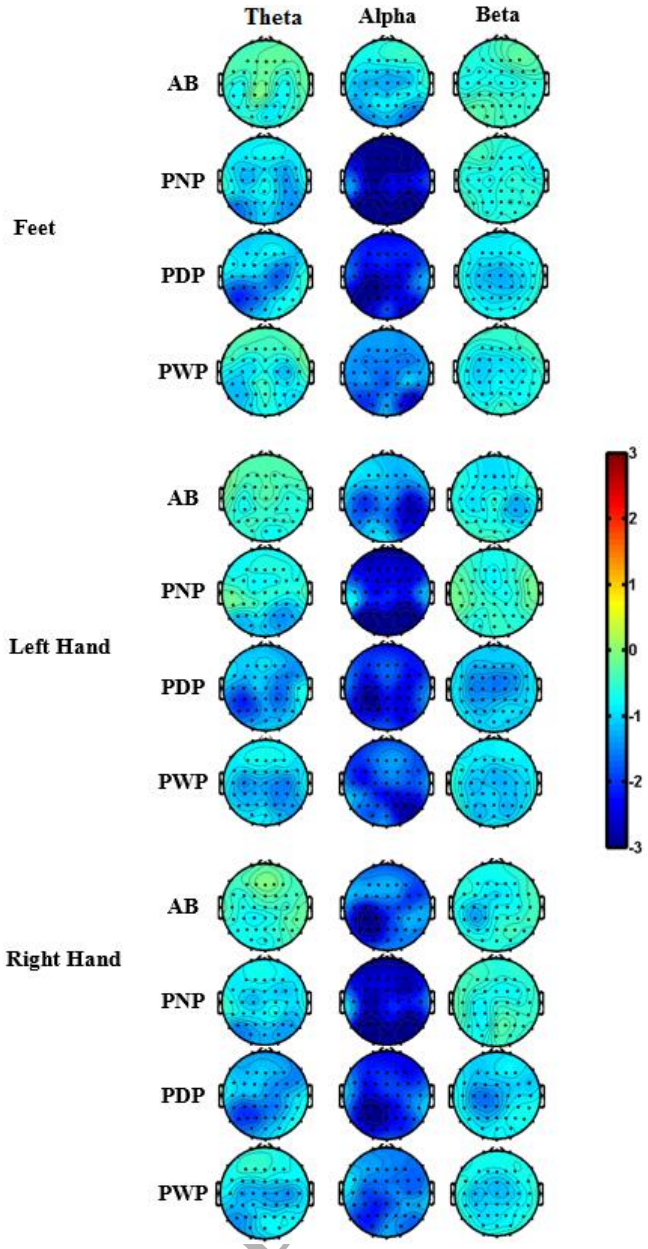


Table 1. Demographic information of study participants.

No.	Age	Pain VNS	Level of injury	ASIA	Weeks after SCI	Weeks Pain	Location of pain
					PDP	Weeks before pain	
1	52	7	C3/C4	D	12	8	Hands and upper back
2	51	7	C3/C4	B	8	12	At and below level
3	70	4	T7/T8	D	9	6	Feet
4	49	2	T12	A	6	10	At and below level
5	19	6	C5/C6	A	12	4	Hands
6	69	1	L2	B	6	4	Left leg
7	32	4	T3	A	24	8	At and below level
8	46	4	T5	A	6	7	At and below level
9	49	6	T6	A	4	2	At and below level
10	32	2	C3	A	6	4	Hands
Aver	47±16	4.3±2.2			9±6	6±3	
					PWP	Weeks with pain	
1	33	9	T12	B	20	20	At and below level
2	59	6	T7/T8	A	12	12	At and below level
3	64	7	C3/C4	D	16	16	Shoulders
4	27	5	C5/C6	A	17	15	Hands and buttock
5	32	5	T3	A	24	6	At and below level
6	30	7	T10	A	12	12	Legs and feet
7	59	5	T8	C	26	26	At level and feet
8	29	6	C3	D	6	6	Right hand
9	37	8	T6	B	28	28	Right leg
10	49	7	C4	A	6	6	Hands
11	75	7	T6	C	6	6	At and below level
Aver	45±17	6.5±1.3			16±8	14±8	

				PNP
1	51	T7,T10	D	12
2	22	L1	B	12
3	47	T11	D	7
4	41	T12	A	4
5	59	T6	A	12
6	43	T6/T7	B	21
7	24	L1	A	7
8	38	L1	A	4
9	62	T3,T5	A	10
10	34	T6	A	10
Aver	42± 13			10±5
				AB
1	37			
2	32			
3	36			
4	34			
5	32			
6	27			
7	45			
8	34			
9	49			
10	27			
Aver	35±7			

ASIA A: complete sensory and motor function loss; B incomplete sensory, complete motor function loss; C and D incomplete sensory and motor loss. Level of injury: C cervical, T thoracic, L lumbar. PDP; participants who developed pain, PWP; participants with pain, PNP; participants with no pain, AB; able bodied participants.

Table 2. sLORETA localisation.Areas with significant differences of cortical activity in alpha (8-12Hz) EEG frequency band during eyes closed (EC) relaxed state and in beta (13-30Hz) EEG frequency band during eyes opened (EO) relaxed state.

					Voxel with maximum t value			
Groups	**Brain Lobe**	**Brodmann area**	**Brain Hemisphere**	**Number of Voxel**	**Statistics t-values**	**MNI Coordinate**		
						x	**y**	**z**
			Alpha Band					
AB vs PDP	Parietal	7	L and R	39	4.96	10	-80	45
PNP vs PDP	Parietal	7	L	28	5.02	-25	-60	50
PNP vs PDP	Parietal	7	L	8	5.07	-25	-50	55
AB vs PNP	Parietal	7	R	5	4.65	20	-80	
AB vs PDP	Parietal	7	R	5	3.90	15	-65	
AB vs PWP	Parietal	7	L and R	11	4.40	-10	-65	

MNI: The Montreal Neurological Institute and Hospital (MNI) coordinate system. R, Right; L, Left.

Table 3. sLORETA localisation. Areas of statistical significant difference of cortical activity between groups during imagination of movement.

						Voxel with maximum t value			
Groups	**MI**	**Brain Lobe**	**Brodmann area**	**Brain Hemisphere**	**Nr of Voxel**	**Statistics t-values**	**MNI Coordinate**		
							x	**y**	**z**
AB vs PDP	LH	Parietal	7	R	32	-4.76	15	-80	45
AB vs PDP	RH	Parietal	7	R	18	-4.58	20	-75	55
AB vs PWP	RH	Parietal	7	R	1	-4.06	30	-70	55
PNP vs PDP	F	Parietal	7	R	6	-4.37	20	-75	55
PNP vs PDP	LH	Parietal	7	R	11	-4.12	10	-65	40
PNP vs PDP	RH	Parietal	7	R	6	-4.46	15	-75	55
PNP vs PWP	F	Parietal	7	L	5	-3.91	-35	-60	50
PNP vs PWP	LH	Parietal	7	L	15	-4.54	-30	-70	50
PNP vs PWP	RH	Parietal	7	L	27	-4.73	-30	-65	50

MI: Motor imagination. F: feet; RH: right hand; LH: left hand.