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Prediction of central neuropathic pain in spinal cord injury based on EEG classifier

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HIGHLIGHTS

- It is possible to predict central neuropathic pain based on the EEG findings of individual patients.
- Simple linear classifier achieved 85% classification accuracy.
- EEG band power in the eyes open and eyes closed resting states served as classification features.

ABSTRACT

Objectives: To create a classifier based on electroencephalography (EEG) to identify spinal cord injured (SCI) participants at risk of developing central neuropathic pain (CNP) by comparing them with patients who had already developed pain and with able bodied controls.
Methods: Multichannel EEG was recorded in the relaxed eyes opened and eyes closed states in 10 able bodied participants and 31 subacute SCI participants (11 with CNP, 10 without NP and 10 who later developed pain within 6 months of the EEG recording). Up to nine EEG band power features were classified using linear and non-linear classifiers.
Results: Three classifiers (artificial neural networks ANN, support vector machine SVM and linear discriminant analysis LDA) achieved similar average performances, higher than 85% on a full set of features identifying patients at risk of developing pain and achieved comparably high performance classifying between other groups. With only 10 channels, LDA and ANN achieved 86% and 83% accuracy respectively, identifying patients at risk of developing CNP.
Conclusion: Transferable learning classifier can detect patients at risk of developing CNP. EEG markers of pain appear before its physical symptoms. Simple and complex classifiers have comparable performance.
Significance: Identify patients to receive prophylaxic treatment of CNP.

1. Introduction

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

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

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developing CNP. Although sensory tests may predict CNP, altered responses to sensory stimulus indicate that patients have already experienced some discomfort.

It is believed that at a cortical level CNP causes thalamo-cortical dysrhythmia, this is manifested as increased theta and beta band EEG power, reduced alpha band power and slowed-down dominant alpha frequency (Sarnthein et al., 2006; Stern et al., 2006; Boord et al., 2008; Jensen et al., 2013; Vuckovic et al., 2014). These EEG markers of CNP were reversible following treatments that reduced pain (Sarnthein et al., 2006; Hasan et al., 2016), indicating that changes in EEG might not only be a consequence of pain but also be related to the cause of CNP, supporting a hypothesis that long standing changes in brain activity may lead to more pain independent of its aetiology (Vartiainen et al., 2009). To test this hypothesis we performed EEG recordings in 20 patients with subacute SCI without pain and followed them up for 6 months (Jarjees, 2017).[2] We showed that a group of SCI patients who developed pain within 6 months of the EEG recording had significantly different alpha and beta band resting state EEGs in BA40 and BA7 compared to a group of SCI patients who did not develop pain over the same period (Jarjees, 2017). Similar results have been demonstrated in a study on rodents, showing that increased EEG theta band power, accompanied the onset of pain, i.e that it is not a consequence of a long-standing pain, as previously believed (LeBlanc et al., 2016).

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

2. Methods

2.1. Participants

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

Participants were divided into four groups for EEG analysis:

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

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

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

2.2. Experimental procedures

2.2.1. EEG recording

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

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

2.2.2. Sensory testing

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

2.3. Data analysis

2.3.1. Demographic analysis

We compared demographic (level of injury, time post injury and age) and descriptive factors (pain) between groups using

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