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Reversed cortical over-activity during movement imagination following neurofeedback treatment for central neuropathic pain

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HIGHLIGHTS

- Long-term neurofeedback treatment reduced central neuropathic pain and cortical overactivity in painful paraplegia.
- Reduction of event related desynchronization induced by movement imagery was largest in the theta band.
- This effect was strongest during imagined movements of painful and paralysed legs.

ABSTRACT

Objective: One of the brain signatures of the central neuropathic pain (CNP) is the theta band over-activity of wider cortical structures, during imagination of movement. The objective of the study was to investigate whether this over-activity is reversible following the neurofeedback treatment of CNP.
Methods: Five paraplegic patients with pain in their legs underwent from twenty to forty neurofeedback sessions that significantly reduced their pain. In order to assess their dynamic cortical activity they were asked to imagine movements of all limbs a week before the first and a week after the last neurofeedback session. Using time–frequency analysis we compared EEG activity during imagination of movement before and after the therapy and further compared it with EEG signals of ten paraplegic patients with no pain and a control group of ten able-bodied people.
Results: Neurofeedback treatment resulted in reduced CNP and a wide spread reduction of cortical activity during imagination of movement. The reduction was significant in the alpha and beta band but was largest in the theta band. As a result cortical activity became similar to the activity of other two groups with no pain.
Conclusions: Reduction of CNP is accompanied by reduced cortical over-activity during movement imagination.
Significance: Understanding causes and consequences mechanism through which CNP affects cortical activity.

1. Introduction

Central neuropathic pain (CNP) is a frequent secondary consequence of spinal cord injury (SCI), affecting about 40% of patients (Siddall et al., 2003). Although CNP is caused by an injury to the somatosensory system (Haanpää et al., 2011) it can show first symptoms years after SCI. Neuroimaging studies have demonstrated changes in the resting state brain activity in the presence of CNP, which is reflected in increased thalamo-cortical coherence in the theta band (Stern et al., 2006; Sarnthein and Jeanmonod, 2008), as well as increased resting state EEG power and a dominant alpha frequency shift towards lower frequencies (Stern et al., 2006; Sarnthein et al., 2006; Boord et al., 2008; Jensen et al., 2013a; Vuckovic et al., 2014).

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Both functional magnetic resonance imaging (fMRI) and electroencephalographic (EEG) studies (Gustin et al., 2010; Vuckovic et al., 2014) reviled that the increased activation and reorganisation of the sensory-motor cortex is a distinctive signature of CNP. During imagined movements of a paralysed limb (perceived as being painful) patients with SCI and CNP show the activation of brain areas related to both motor imagination and pain processing (Gustin et al., 2010). In an EEG study by our group that included SCI patients with and without CNP and healthy controls (Vuckovic et al., 2014), we demonstrated that during imagination of movement, patient with CNP had stronger event related desynchronization (ERD) (Pfurtscheller and Lopes da Silva, 1999) the healthy controls, while patients with no pain had weakest responses of all three groups.

A recent Cochrane study (Boldt et al., 2014) lists a number of non-pharmacological non-invasive treatments of CNP for SCI patients. Most of these studies comprise of up to 10 treatment sessions, which might not be long enough to induce longer lasting cortical changes; in addition, the assessment of brain activity has not been included in the outcome measures in none of the studies. Lefaucheur et al. (2006) showed that a single dose of rTMS which reduced symptoms of CNP also restores intracortical inhibition, but does not affect the excitability of the motor cortex, as measured by the amplitude of the motor evoked potential. It is however not known, what is the effect of a prolonged treatments of CNP on closely related, altered activity of the sensory-motor cortex.

Neurofeedback is a non-invasive technique which relies on measuring brain activity in real time. It has proved useful for treatments of different types of chronic pain, including CNP (Jensen et al., 2013a; Hassan et al., 2015). Neurofeedback trains a person to change his/her brain activity at will that can lead to the reduced sensation of pain. Thus it enables a direct voluntary modulation of the activity of the cortical regions that have been affected by pain. The ability to self-regulate brain activity is what makes this technique unique compared to other neuromodulation approaches such as Transcranial Magnetic Stimulation (rTMS) or transcranial Direct Current Stimulation (tDCS) (Boldt et al., 2014) in which a patient passively receives an external stimulus that modulates cortical activity.

In our recent study, 5 patients with SCI and CNP received from 20 to 40 daily neurofeedback treatments (Hassan et al., 2015). They achieved 25% and larger reduction of pain that was accompanied with changes in the resting state EEG power, in pain-related areas of the cortex. Although resting state network of sensory-motor cortex has a close relationship with the task related brain activity (Ma et al., 2011; Várkuti et al., 2013), the activity of the motor cortex, which is uniquely related to this type of chronic pain, is best assessed during a motor task (Gustin et al., 2010).

In this study we test a hypothesis that the reduction of pain intensity is accompanied with reduced activation of the sensory-motor cortex during imagined movements.

2. Methods

2.1. Participants

A total of 25 volunteers were recruited in 3 age-matched groups:

- Group1. Five paraplegic patients with diagnosed CNP below the level of injury (age 50 ± 4, 6 males, 1 females) here called PWP (patients with pain).
- Group 2. Ten paraplegic patients with no chronic pain (age 44.4 ± 8.1, 8 males, 2 females) here called PNP (patients with no pain).
- Group 3. Ten able-bodied volunteers with no chronic pain (age 39.1 ± 10.1, 7 males, females), here called AB (able bodied).

The neurological level of injury in patient groups was determined using the American Spinal Injury Association (ASIA) impairment classification (Marion et al., 2013). All patients were at least one year post-injury with a spinal lesion at or below T1. Inclusion criteria for patients with CNP were a pharmacological treatment history for at least 6 months and a reported pain level equal or larger than 5 on the Numerical Pain Rating Scale (NPRS 0 = no pain, 10 = worst pain imaginable). Patients in PWP group were asked not to change pharmacological pain treatment during the study.

A general exclusion criteria were brain injury or other neurological conditions that might affect EEG and the presence of any chronic or acute pain at the time of the experiment. Group PWP is a subgroup of patients reported in (Vuckovic et al., 2014) that underwent neurofeedback training, described in (Hassan et al., 2015). Information about PWP patients and the outcome of the treatment can be found in Table 1. Information about PNP group is shown in Table 2. Fig. 1 shows the location of perceived pain (note that in the case of neuropathic pain the source of pain is actually not in the limbs but in the brain). Pain was typically described as stabbing, burning or squeezing.

An informed consent was obtained from all participants, and ethical approval for patients was obtained from the National health service regional Ethical Committee and for able-bodied volunteers from the University Ethical Committee.

2.2. The experimental protocol

A detailed experimental protocol is provided in Vuckovic et al. (2014) and here we provide a brief description. All groups followed the same protocol and PWP group performed the same experiment twice, first time about a week before the first neurofeedback session and second time about a week after the last neurofeedback session. Other two groups performed the experiment on one occasion only as they did not take any neurofeedback training.

Standard cue-based motor imagination experimental protocol was used (Neuper et al., 2006). Precise cueing was necessary because of the lack of muscle activity while people imagined movement. The purpose of motor imagination was to induce activity of the cortico-spinal tract, thus serving a similar purpose as single pulse TMS as in (Lefaucheur et al., 2006). We were however primarily interested in modulation of the activity of the motor cortex, therefore we measured EEG responses. Participants sit approximately 1.5 m in front of a computer monitor. They were instructed to look at the center of the monitor and to respond to a sequence of visual cues. The cues included a readiness cue (presented as a cross) at $t = -1$ s and remaining on for 4 s (Fig 2). At $t = 0$ s an initiation cue (presented as an arrow), was displayed for 1.25 s, pointing to the right, to the left or down and corresponding to the imagination of the right and left hand waving, and tapping with both feet. Participants were asked to continue to perform imaginary movements for 3 s, until the cross disappeared from the screen. In total, 60 trials of each movement type were presented to subjects, 180 trials in total. Cues were presented in smaller sub-sessions, in randomized sequences comprising 10 trials of each movement with rest periods between.

2.3. EEG recoding and analysis

A 61-channel EEG was recorded (Synamp 2; NeuroScan, Charlotte, NC) with electrodes placed according to 10–10 location standard (ACNS, 2006). Electrode location AFz was used as a ground, combined with a linked ear reference. All channels were sampled