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# Reduced Activation at the Cortical Level Following Neurofeedback Treatment is Associated with Reduction in Central Neuropathic Pain Intensity

Muhammad Abul Hasan[1,2], Aleksandra Vuckovic[1], Matthew Fraser[3], Bernard Conway[4], Bahman Nasseroleslami[4,5], David B Allan[3]
[1] University of Glasgow, Glasgow, UK. [2] NED University Karachi, Pakistan. [3] Sothern General Hospital, UK. [4] University of Strathclyde, Glasgow, UK. [5] Northeastern University, Boston, USA.
m.hasan.1@research.gla.ac.uk, Aleksandra.Vuckovic@glasgow.ac.uk

**Abstract**

The aim of the study was to investigate the effect of neurofeedback (NF) training on Central neuropathic pain in patients with chronic paraplegia. Training consisted of 20-40 NF sessions in which patients were asked to voluntarily reduce the theta (4-8 Hz) and beta (20-30 Hz) band power and to increase the alpha band (9-12 Hz) power over the sensory-motor cortex. A whole head EEG was recorded before the first and after the last training day to assess long-term effect of NF. Four out of five patients reported clinically significant (>30%) reduction in pain. Multichannel LORETA analysis indicated that reduced pain intensity might be associated with reduced cortical and sub-cortical activity in the areas known to be involved in processing of chronic pain.

## 1 Introduction

Central Neuropathic Pain (CNP) is caused by a lesion or disease to the somatsosensory system having a prevalence of 40 % in spinal cord injured (SCI) population (Werhagen et al. 2004). CNP is perceived as coming from the body, while it is actually generated in the brain and is mainly associated with the overactivation of the cortex (Samthein et al. 2006). Noninvasive interventions such as repetitive Transcranial Magentic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) reduce cortical and/or sub-cortical activity thus reducing pain (Moseley and Flor 2012).

Similar to rTMS and tDCS, neurofeedback (NF) is also a neuromodulation technique which is based on voluntary modulation of brain activity. Although NF has been successfully used for different types of chronic pain such as fibromyalgia and migraine (Kayiran et al. 2010), its efficiency on CNP has not been confirmed. In a recent study we showed that paraplegic patients with CNP have increased power in theta band, lower frequency of dominant alpha peak and increased Event Related Desynchronisation (ERD) in the theta, alpha and beta band (Vuckovic et al. 2014). Based on that study, we created a NF protocol for treatment of CNP, presented in this paper.

# 2 Methods

## 2.1 Patients

Seven paraplegic patients with CNP larger than 5 (Visual Analogue Scale, range 0 to 10) participated in the study. All patients had pain in their limbs. Ethical permission was obtained from the NHS Ethical Committee for the Greater Glasgow and Clyde. Experiments were performed at Queen Elizabeth National Spinal Injuries Unit, Glasgow, UK.

## 2.2 Experimental Procedures

The experiment consisted of an initial assessment, NF training, and final assessment. On the initial and final assessment, patients' EEG was recorded (Synamp$^2$, Neuroscan, USA) with 61 channels in a relaxed state and during motor imagery of the upper and the lower limbs. In a cue-based experimental paradigm patients were asked to imagine moving their right hand, left hand and feet in a semi-random order. There were 60 repetition of each type of imagined movements (MI). The electrodes were placed according to the standard 10-10 locations using an ear-linked reference and AFz as ground. Sampling frequency was 250 Hz and impedance was kept below 5kΩ. For MI data, noise was removed using Independent Component Analysis (ICA). ERD and Event-related synchronization (ERS) was calculated based on wavelets (Makeig 1993). For spontaneous EEG recording, after manually removing sections with extensive noise (>100 μV), at least 3 min of recording was left for the analysis. The sLORETA (Pascual-Marqui 2002) computed cortical map/image (estimated current density) for 6239 voxels at 5 mm spatial resolution.

For NF training custom made software was designed in Simulink/Matlab and Graphical User Interface was developed in LabView. EEG was recorded using usbamp (Guger technologies, Austria). Prior to each training session patients' EEG (256 sample/sec) was recorded in relaxed, eyes opened state, from C3, C4, P4 and Cz to determine the baseline for training for that day, though a single site was used for training at a time. The relative power, with respect to power in 2-30Hz band was calculated for the 'inhibit' theta (4-8 Hz), 'reward' alpha (9-12Hz) and 'inhibit' beta (20-30Hz) bands, being determined based on (Vuckovic et al. 2014). Patients were trained to reduce a relative power in the inhibit bands and to increase it in the reward band. Alpha ≥9Hz was selected in order to shift the dominant frequency towards higher frequencies (Vuckovic et al. 2014). The threshold was set 10% above the reward and 10% below the inhibit bands. The power of both inhibits and a reward band was shown on a computer screen in the form of vertical bars that changed a size and color from red to green. Power was calculated in real time using moving average filter of 5$^{th}$ order. Training was based on the operant conditioning and patients were instructed to 'do whatever necessary' to keep the bars green.

For statistical analysis over a full spectrum, the EEG was divided into 4s epochs and power was calculated for each epoch. Following this, a parametric unpaired ttest was applied over epochs to compare power between each two conditions (Pre NF versus during NF, and Pre NF versus Post NF).

# 3 Results

Five out of seven patients completed the study. Two patients dropped out after 3 NF sessions due to family and transport problems. From the remaining five patients, four patients received 40 sessions and the fifth patient received 20 sessions. Patients received therapy 1-3 sessions per week.

## 3.1 Effect of NF Training on Pain Intensity and Power

All five patients achieved a statistically significant ($p \leq 0.05$) reduction of pain (Table 1) and in four patients this reduction was clinically significant (>30%). Patients reported immediate reduction of pain during NF; reduction of pain gradually increased over training sessions and lasted for several weeks after terminating the therapy. Initially we tested several locations over the primary motor cortex which included C3, Cz and C4. In patients with incomplete paraplegia (preserved sensation) we occasionally observed the uncontrolled movements of legs (spasm) which was higher when practicing from C3 than from C4, so we chose C4 as a preferred training site to reduce discomfort. Interestingly, NF training from Cz, located over the motor cortex corresponding to 'painful' paralyzed legs resulted in smallest reduction of pain. Patients received 30 min training in total per session.

Figure 1 shows power in one patient before, during and after NF for a single training day. The patient increases the alpha and theta power, and decreases the beta power (black thick line on x-axis: Pre NF versus NF). This effect can also be noticed several minutes after NF training (grey thick line on x-axis: Post NF versus NF). We present PSD of an individual patient rather than the average value across the whole group because the exact frequency bands in which EEG was modulated varied among patients.

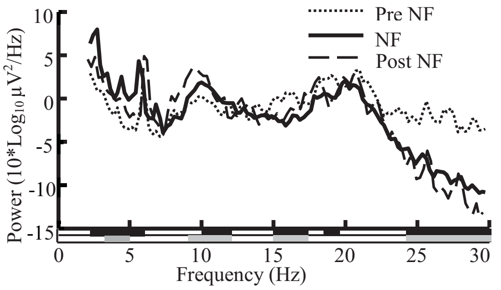


Figure 1: Power of fifth patient before NF training session (dotted line), during NF (solid line) and after NF training session (dashed line).

| No | Injury level | Pain (before/after) | |
|---|---|---|---|
| 1 | T5 complete | 6/5, | p=0.05 |
| 2 | T6 complete | 7/5, | p=0.0004 |
| 3 | T6 incomplete | 6/2, | p=0.0001 |
| 4 | T6 incomplete | 9/5, | p=0.0002 |
| 5 | T6 incomplete | 9/5, | p=0.006 |

Table 1: Patients characteristics and change in pain intensity following long-term NF training. Wilcoxon paired test was applied to find statistically significant change in pain intensity over all training days (Pre NF versus NF).

## 3.2 Long-Term Effect of NF

The reduction of brain activity was noticed in the theta, alpha and beta bands in cortical areas including sensory-motor and limbic cortices. Figure 2 shows the difference in sLORETA estimate of current density in relaxed EO state before and after NF therapy averaged over all 5 patients. A wide-spread reduction of the activity could be noticed at the Anterior Cingulate Cortex, (BA 24) in the beta band (12-15 Hz). Figure 3 shows ERS/ ERD at Cz site during MI of legs. Reduced activity after NF can be noticed mainly in the theta band and in beta band.

# 4 Conclusion and Discussion

The paper presents the effect of NF training on reduction on CNP and on related neurological measures. Although patients learned to modulate brain activity and reported reduction in pain that lasted for several weeks, a regular NF therapy on large number of patients would be needed to further confirm the effect of NF therapy. The reduced cortical activity in all frequency bands mainly in the theta and beta bands shows that reduction in pain is associated with reduced power in relaxed state and reduced ERD. These results are in accordance to previous studies on EEG signatures of CNP (Sarnthein et al. 2006; Vuckovic et al. 2014).

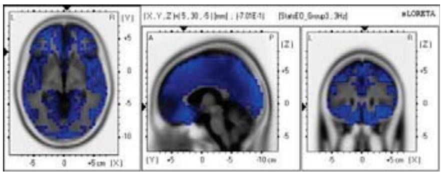

Figure 2: LORETA images showing reduction of activity (after-before NF) in 12-15 Hz band averaged over 5 patients, in ACC (BA 24).

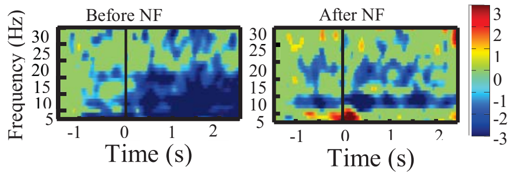


Figure 3: Patient 1, ERS/ERD at Cz before (left) and after treatment (right). Significance level set p=0.05 with false discovery rate.

# 5 Acknowledgements

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