Study of a Neurofeedback methodology for treatment of chronic pain in clinical context

Joana Correia Vaz Sousa
joana.v.sousa@tecnico.ulisboa.pt

Instituto Superior Técnico, Lisboa, Portugal

June 2019

Abstract

Chronic pain is a worldwide health problem characterized by physical debilitation and often accompanied by anxiety, depression, and cognitive impairment. Previous research suggests that Neurofeedback (NF), a type of biofeedback in which individuals are trained to self-regulate their brain activity, has demonstrated its potential as a therapeutic complementary/alternative approach to help chronic pain patients. In this thesis, an EEG-NF training protocol was designed and implemented in 7 patients with chronic back pain, aiming to decrease their pain level and discomfort. The training comprised 16 sessions, in which an alpha/theta protocol was applied at Cz to enhance alpha activity and simultaneously inhibit theta. Since only 4 out of 7 participants have already completed the treatment, the analysis was performed from the first to the seventh session. Considering all participants, a significant raise of the alpha/theta ratio was observed within session, as well as a significant decrease of the theta relative amplitude. Across sessions, only a significant increase was observed for the alpha band. No significant changes were obtained regarding psychological and cognitive improvements, neither a significant decrease in pain was observed after 7 training sessions. Although improvements were seen in patients' training performance over the first half of the procedure, it is important to further evaluate the outcomes for the whole treatment. By increasing sample size and adding a control group it is expected that stronger conclusions can be drawn. Nonetheless, these findings provide preliminary support for the NF potential efficacy in the treatment of chronic back pain, suggesting further investigation is needed for a deeper understanding.
Keywords: Chronic Pain, Neurofeedback, Electroencephalography, Alpha/theta ratio

1. Introduction

Pain is considered chronic when it persists beyond the estimated period of recovery from an injury, which could last for several weeks or longer. Besides the discomfort and unpleasantness, chronic pain (CP) is associated with fear, anxiety, depression, sleep deprivation, and cognitive impairment [1]. Unlike acute pain, CP does not promote any beneficial function and it significantly compromises individuals' quality of life [2]. Indeed, it is a global health care problem that produces a serious impact on economics and society. This condition is predominant in North America, Europe, and Australia, affecting 10.1-55.2% of the adult population [3]. In Portugal, CP prevalence is estimated in 36.7%, and it is expected to rise as the lifespan of population increases [4]. Currently, the administration of medication, such as analgesics, opioids or muscle relaxants, is the approach most commonly used to treat CP. However, pharmacotherapy alone may be inefficient, cause side effects and, in a long-term, can cause addiction [5]. Therefore, innovative methods are required to complement the ordinary ones in order to promote a greater pain management.

Through medical imaging techniques, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), evidence demonstrates that individuals with CP usually manifest abnormal oscillatory activity in specific brain areas [6]. Studies concerning spontaneous brain activity assessment have identified specific frequencies of neural oscillations' activity that might be associated with pain and its perception [7]. Jensen et al. (2009) affirm that both the experience of pain in healthy subjects and individuals suffering from chronic pain are associated with a lower alpha activity [8]. Moreover, lower amplitudes of alpha are suggested to be related with increased pain perception, since its decreased activity facilitates information transfer through thalamocortical and corticocortical pathways [9, 10]. Furthermore, studies comparing the power spectra in chronic pain patients and healthy controls reported the presence of overactivations within the theta and beta frequency ranges

[6, 8, 11]. The peak frequency has been another EEG parameter used to assess differences between chronic patients and controls. In chronic subjects, experiments have found a shifting of the dominant peak towards lower frequencies, which was correlated with an "increase in psychopathology or a reduction in life satisfaction" [7, 12].

Neurofeedback (NF) is a type of biofeedback in which individuals are trained to self-regulate their brain activity. This can be achieved, for instance, by rewarding the increase or inhibition of the magnitude of oscillations in specific bandwidths [9, 13]. During this procedure, the information of the EEG that is being recorded is extracted and given to the subject by a real-time feedback loop in a visual and/or audio format. It is through these feedbacks that the subject becomes aware of the variations that occur during the training, giving him/her the ability to analyze and voluntarily modulate their progress in order to improve their performance [14]. NF is a non-invasive approach of brain activity regulation that does not imply the administration of pharmacological compounds into the brain, or the introduction of magnetic or electrical activity, avoiding brain dependency on external factors for better functioning [15]. NF has been diversely applied in both medical context, encompassing the treatment of attention deficit/hyperactivity disorder [16, 17], epilepsy [18, 19], schizophrenia [20, 21], depression [22, 23] and pain, and in non-clinical areas including, for instance, the improvement of cognitive, memory, artistic and sporting performances in healthy subjects.

Regarding the effects of NF in individuals suffering from CP, several investigations have been performed throughout the years having a common main goal: to decrease the intensity and the severity of pain. Although no large-scale clinical trial has been completed to date, a number of case series and preliminary studies have been published, providing a better insight of the NF potential benefits [5]. These include experiments in patients suffering from migraines [24, 25], fibromyalgia [26–28], complex regional pain syndrome [29], spinal cord injury [30], and chemotherapy-induced peripheral neuropathy [31]. The benefits reported by these investigations appear to be "moderate at best", and some of them lack of deeper understanding of NF long-term effects. However, there is evidence that NF can actually alter brain activity and might thus be used as a complementary approach to treat CP and other conditions [5].

Due to the fact that no investigation has been carried out to date regarding NF in chronic back pain (CBP), a preliminary research aiming to investigate the existence of NF potential benefits in patients suffering from this condition would be a valuable contribution to the field. With this project, treatment parameters, including sessions' duration, reinforced/inhibited bandwidths, training electrode(s), among others, can be assessed regarding their efficacy and be further refined, in order to design a protocol that could be applied in a clinical context.

Therefore, this work aimed to investigate the potential benefits of applying a NF training protocol, specifically the enhancement of the Individual Alpha Band/Individual Theta Band ratio (IAB/ITB) relative amplitude, in patients suffering from CBP. The specific objectives of this project were the: (i) development and implementation of an EEG-NF protocol targeting IAB/ITB ratio for attenuating the experience of pain; (ii) assessment of possible alterations of the EEG signal throughout the treatment; (iii) evaluation of NF efficacy and applicability in patients with chronic back pain by assessing their well-being and pain level in a pre- and post-treatment state; and (iv) analysis of the NF training's impact on patients cognitive performance.

2. Methods

2.1. Participants

Eleven subjects with CBP were recruited from the Unidade Multidisciplinar da Dor (UMD), at Centro Hospitalar Lisboa Norte (CHLN), for a period of 3 months. Three of them quit after the pre-treatment evaluation due to personal issues, and one subject dropped out after 3 sessions of training. From the remaining seven patients (6 females and 1 male), four participants completed all 16 training sessions, one performed 9 sessions, and two subjects reached to the 7th session. The ages of the group were ranged between 26 and 62 (mean=45.57±13.09).

This project was revised and approved by the Ethics Committee of the Centro Académico de Medicina de Lisboa and CHLN. An informed consent comprising the description of the protocol, possible side effects and exclusion criteria was provided to all participants. Before signing it, patients were informed that the collected data could be published keeping the anonymity. Participants were all volunteers, and no monetary award was given for their cooperation in this study.

2.2. Acquisition Equipment

Acquisitions were carried out in a room provided by the UMD at CHLN, or in a room of the Evolutionary Systems and Biomedical Engineering Lab (LaSEEB), a research lab of Institute for Systems and Robotics (ISR), at Instituto Superior Técnico (IST) facilities. For signals' acquisition, an EEG cap with 20 electrodes (including the ground electrode) was placed on subjects head according to the International 10-20 System, using the left and right mastoids as references for common mode rejection. The signal was recorded by *Somnium* software platform, with a sampling frequency of 250 Hz, from the following electrodes: Fp1, F7, F3, T3, C3, T5, P3, O1, Fz, Cz, Pz, Fp2, F8, F4, T4, C4, T6, P4 and O2. For signal amplification, EEG amplifier Vertex 723 Q was used (produced by Meditron Electromedicina Ltda, São Paulo, Brazil), with an analog band-pass filter between 0.1 and 70 Hz, directly connected to the cap. An impedance below 10 kΩ was maintained for all electrodes.

2.3. Design

Patients were provided with 1-2 sessions per week, completing a total of 16 sessions. Each session had a duration of approximately 1h30, except the 1st, 7th and last session, which lasted around 2h30, and in which cognitive tests were conducted. On recruitment day, all subjects performed a set of six psychological tests before starting the NF treatment. This set was again applied after the 7th session and at the end of the treatment. Regarding NF sessions workflow, the participants answered to a Pain Rating Scale, in the beginning of the session and right after the NF training. Resting baselines were preceded by a 2-minute relaxed state and assessed for both Eyes Open (EO) and Eyes Closed (EC), recorded twice, alternately, for 1 minute each, at the beginning and at the end of each session. The active baseline (AB) was also measured after each resting baseline. Cognitive tests were performed before the NF training in the 1st session, and after the second active baseline in the 7th and last session. The NF training consisted of 5 blocks, and each one was composed by 10 trials of 30 seconds, with a 5-seconds interval between them. Total NF time in each session was around 30 minutes. To conclude the session, participants answered the Mental State Questionnaire. A transfer training was performed from session 12 to 16, during which no feedback was provided. For that purpose, a 1-min block composed of 2 transfer trials of 30 seconds each was added after the 5 training blocks.

2.4. Protocol

Based on the review of previous studies regarding chronic pain and NF, the training protocol aims to enhance IAB and, simultaneously, decrease ITB band at Cz. Although other electrode training sites have been used in NF to treat chronic pain, it is possible to obtain global effects on brain activity and avoid abnormal imbalances in left/right hemispheres by using a central site [5]. Regarding the training frequency ranges applied in this protocol, the goal was (1) to increase activity hypothesized to be correlated with reduced pain information processing, and (2) to decrease brain activity thought to be associated with the processing of nociceptive information [5, 6, 9]. Therefore, since lower alpha activity has been associated with increased pain perception, and patients with chronic pain exhibit overactivations within theta frequency range, the training consisted of increasing the IAB/ITB ratio.

2.4.1 Individual Alpha Band and Individual Theta Band

The first resting baseline was measured to define the IAB of each subject. For that purpose, the signal was recorded for EO and EC and properly labeled after artifact removal. The crossing of both spectra provide the IAB boundaries, i.e. the Lower Transition Frequency (LTF) and Higher Transition Frequency (HTF), as well as the Individual Alpha Frequency (IAF). Although theses values are automatically generated by the software, the researcher was allowed to adjust them manually. Therefore, a specific metric was created to obtain an IAB as accurate as possible, taking into account subjects' individual characteristics. Based on the approach of *Individual Bands and Fixed Widths* (see [32]), the metric developed on the present investigation relies on using IAF as an anchor point, and fixing alpha bandwidth (4 Hz), in order to calculate IAB boundaries. If $IAF \leq 10\ Hz$, one has

$$LTF = IAF - 2\Big[1 - \frac{|IAF - 10|}{10}\Big] \tag{1}$$

and $HTF = LTF + 4\ Hz$.
Otherwise,

$$HTF = IAF + 2\Big[1 - \frac{|IAF - 10|}{10}\Big] \tag{2}$$

and $LTF = HTF - 4\ Hz$.

To define ITB, the subject's LTF was used as the upper value of the theta band, with the lower limit being $LTF - 4\ Hz$. However, if $LTF - 4\ Hz < 4\ Hz$, the lower limit of ITB was maintained at 4 Hz, since signal acquisition becomes more sensitive to eye blinking artifacts at lower frequencies.

2.5. Neurofeedback training

The EEG training platform integrated in the *Somnium* software was used for the NF training.

2.5.1 Feedback parameters and display

Based on [33], the feedback parameter is given by the alpha/theta ratio ($IAB\ RelativeAmplitude/ITB\ RelativeAmplitude$), being the IAB and ITB computed by the following equations:

$$IAB\ RelativeAmplitude = \frac{\frac{\sum_{k=LTF/\Delta f}^{HTF/\Delta f} X(k)}{HTF - LTF}}{\frac{\sum_{k=3.9}^{30} X(k)}{30 - 3.9}} \tag{3}$$

$$ITB\ RelativeAmplitude = \frac{\frac{\sum_{k=4/\Delta f}^{LTF/\Delta f} X(k)}{LTF-4}}{\frac{\sum_{k=3.9/\Delta f}^{30/\Delta f} X(k)}{30-3.9}}, \quad (4)$$

in which $X(k)$ is the frequency spectrum amplitude calculated by fast Fourier transformation (FFT), with a sliding window of 2 seconds that shifted every 0.125 seconds, Δf is the frequency resolution of the FFT, and k is the spectrum index [34].

Regarding the NF display, two 3D objects (a sphere and a cube in a gray background) were used to reflect the feedback parameters in real time according to the protocol settings previously established. The feedback received by the participant depends on the achievement of two goals. Goal 1 relies on the relation between the EEG signal that is being measured and a threshold value previously defined. In this case, Goal 1 is achieved when alpha/theta ratio value is above the threshold. Goal 1 is reflected when the sphere increases its size and goes from white to purple. Goal 2 is accomplished when Goal 1 is continuously achieved for more than 2 seconds, and the cube rises. The threshold was set to 1 in the 1st session, and it could be adjusted according to the percentage of time that the alpha/theta ratio was above the threshold in each session. If the percentage of time was higher than 60% or lower than 20%, threshold was increased or decreased by 0.1, respectively, in order to hinder or facilitate the NF training level.

2.5.2 Training

Before starting the training, it was explained to the participants that they should first concentrate on turning the sphere purple and increase its size as much as possible. For that purpose, subjects were encouraged to use several mental strategies during the training and were advised to use a single one per block to see which ones produced better results for repeating them afterwards. Transfer training was performed to assess the participants' ability to control cortical activity without visual feedback. During the *transfer* trials, participants faced a static screen, focusing on a certain point to avoid muscle artifacts during EEG signal acquisition.

2.5.3 Active baseline

Based on the works of [35] and [36], an assessment of 1-min recording in an open-eyes active state was performed succeeding each resting baseline. The active task was created based on the NF training display to assure comparability regarding the degree of visual stimulation. It consisted of a slideshow with purple and white circles that appeared randomly, in which the subject was asked to count the number of white circles. In each session, all the patients performed the same set of two distinct active tasks (pre- and post-NF), and this set was different throughout sessions.

2.6. Measures

2.6.1 Psychological tests

A set of six psychological tests (applied in Portuguese and validated for the Portuguese population) was filled out by the patients for a pre-treatment, intermedium, and post-treatment evaluation of their well-being, health state and pain condition. The tests were performed by the patients in the following order: West Haven-Yale Multidimensional Pain Inventory (WHY-MPI) [37], Pain Catastrophizing Scale (PCS) [38], 36-Item Short Form Survey (SF-36) [39], Symptom Checklist 90 (SCL-90) [40], State-Trait Anxiety Inventory (STAI), and Beck Depression Inventory (BDI) [41].

2.6.2 Cognitive tests

In order to evaluate the effects of the NF training in participants memory, attention and mental rotation skill, five cognitive tests were carried out in the first, seventh, and last sessions: Digit Span (Forward and Backwards), N-Back, OddBall, and Rotation test. The Digit Span consisted of 10 trials showing random digits, where the person is asked to repeat them in the same (*Forward*) or reverse (*Backwards*) order. The first sequence was composed by 3 digits, and its length increased in each trial, being the last one composed by 13 digits. For the N-back test, it was performed a 3-Back task with random numbers, in which the participant had to decide if the current item was the same appearing three positions before. Twenty-three trials were performed, which resulted in 20 answers. In the OddBall test, a series of geometrical shapes were randomly displayed, and the participant was asked to click on the image's center only when a circle appeared. In the Rotation test, two 3D figures were displayed, side by side, and the participant had to decide if they are the same or not. Twenty trials were presented.

2.6.3 Pain rating scale and Mental State Questionnaire

The pain rating scale used in this experiment was the Wong-Baker Faces Pain Rating Scale, which is a tool used worldwide to help the patients communicate about their pain so that its management can be addressed. This scale consists of six distinct cartoon faces, being each one of them associated with a certain state of pain, and also a numeric scale rated from 0 to 10 [42]. In this study, the scale was first explained to the subjects so they could be able to choose the face that best depicted the pain that they were experiencing. The scale was presented to patients before each set of passive baselines, in order to evaluate whether the NF training had immediate effects on their pain state or not. The Mental State Questionnaire (provided by [43]) assessed patients' *concentration*, *motivation*, *sleepiness*, and *stress* during training. This questionnaire provides information regarding the influence of these four factors in subjects' training performance.

2.7. Data pre-processing and extraction

Since not all the recruited participants reached to the post-treatment evaluation, the data analysis was performed on the period between the pre-treatment ($t0$) and intermedium ($t1$) evaluation. The pre-processing and extraction of information from the raw EEG was performed using *Somnium* tools. Artifacts emerged during baselines' measurement were manually removed (with the exception of eye movements) to avoid misinterpretation. To reduce the occurrence of low frequency artifacts, the signal was normalized from 3.99 Hz to 30 Hz. The registration of the baselines was performed manually as *Eyes Open*, *Eyes Closed* and *Active Baseline* events. The events corresponding to the NF training were automatically registered. Individual reports were generated and copied from *Somnium* to Excel files and extracted with *MATLAB* for further analysis. The following frequency bands were chosen for data assessment: Alpha/Theta ratio (IAB/ITB), Individual Theta Band (from 4 Hz to LTF), Individual Alpha Band (from LTF to HTF), Individual Lower Alpha Band 1 (from LTF to LTF+(IAF-LTF/2)), Individual Lower Alpha Band 2 (from LTF+(IAF-LTF/2) to IAF), Individual Upper Alpha Band (from IAF to HTF), SMR (from 12 to 15 Hz), Beta Band 1 (from 16 to 20 Hz), and Beta Band 2 (from 20 to 28 Hz).

2.8. Data treatment

Data treatment was conducted using the *MATLAB* software (version R2016b). The visualization of plots and the statistical analyses were performed using both *MATLAB* and *R Studio* software.

2.8.1 Training performance evaluation

Based on methods previously employed in studies concerning learning [33, 43, 44], a set of learning measures was defined to evaluate training performance regarding the variation of alpha/theta ratio, within and across sessions.

- **Within sessions**

  W1: it computes, for each session (i), the difference between the last and first blocks, relative to the first block, and then averaged across all training sessions:

$$W1 = \frac{\sum_{i=1}^{\#sessions} \left(\frac{block_5 - block_1}{block_1} \right)_i}{\#sessions} \qquad (5)$$

  W2: it computes, for each session, the slope of the linear regression (m_i) that fits the evolution of the relative amplitude of a certain frequency band along blocks, and then averaged across sessions:

$$W2 = \frac{\sum_{i=1}^{\#sessions} m_i}{\#sessions}, \qquad (6)$$

- **Across sessions**

  A1: it computes the difference between the mean of the last two sessions and the mean of the first two, relative to the latter:

$$A1 = \frac{Mean(S_6, S_7) - Mean(S_1, S_2)}{Mean(S_1, S_2)} \qquad (7)$$

  A2: it computes the slope (m) of the linear regression that fits the evolution of a certain frequency band along sessions: $A2 = m$.

Participants were considered as *non-learners* when at least one of their learning measures describing the progression of the IAB/ITB ratio across sessions presented a negative value (i.e. $A1 < 0$ or $A2 < 0$ for IAB/ITB), meaning that these participants were not capable of increasing IAB/ITB along time. Five out of seven participants were classified as *learners*.

2.8.2 Evaluation of psychological effects

The assessment of possible psychological effects due to the NF training was performed through scores' changes of the 6 psychological tests applied. The results obtained at the pre-treatment evaluation ($t0$) were compared to those obtained at the intermedium evaluation ($t1$).

2.8.3 Evaluation of cognitive effects

For the Digit Span test evaluation (for both *Forward* and *Reverse*), two indicators were chosen: "Span", the maximum number of digits in a sequence that the participant recalled in the correct order; and "Score", which is calculated according to the digit span and to the ratio between the number of digits remembered in the correct order and the total digits showed. For the N-Back, OddBall and Rotation tests, the "% of Sucesses" (number of correct answers/total number of trials) was the indicator used to evaluate participants' performance. The results obtained in the 1st session ($t0$) were compared to those obtained in the 7th session ($t1$). The response time was not taken into account on any of the tests.

2.8.4 Pain rating scale and mental state evaluation

The pain ratings of each patient obtained before the training ($preNF$) were compared to those obtained after the training ($postNF$), for each session. The averaged pain score change ($\overline{\Delta\ pain}$) was computed for each patient to assess the correlation between the decrease in pain and the training performance within sessions, by using the W1 and W2 learning measures. Regarding the Mental State questionnaire, the averaged scores of the four factors, of each subject, were compared with the learning measures A1 and A2.

2.9. Statistical analysis

From Shapiro-Wilk test computation, the *normality* premise can not be assumed in this experiment since $N = 7$. Therefore, non-parametric tests and medians (instead of means) were applied. To analyze the observations' differences between $t0$ and $t1$ or pre-NF and post-NF regarding the measures used, it was applied the Wilcoxon Signed Rank test. Right-tailed tests were employed when there was a prior hypothesis of an increase, as it was the case for IAB/ITB and IAB relative amplitudes. A left-tailed test was applied in the case of ITB, which was expected to decrease over time. To assess a possible association between variables, it was applied the Spearman's rank correlation. A statistical significance 0.5% was defined.

3. Results

3.1. Neurofeedback training

The NF training analysis was performed regarding the alterations that occurred both across and within sessions. To assess trainability, the evolution of the IAB/ITB relative amplitude was examined, whereas the variation of the other frequency bands was observed in order to study at what extent they were influenced by the training.

3.1.1 Across sessions

In Figure 1, it is possible to observe an increase of the median IAB/ITB relative amplitude from the 1st to the 4th session and again from the 6th to the 7th session. Both medians of A1 and A2 were positive for IAB/ITB ratio and IAB band, whereas for the theta band these values were negative. However, the Wilcoxon Signed Rank test revealed, for both A1 and A2, that only the median of IAB was significantly larger than zero (A1, A2: $p = 0.039$), and that LA2 band median was statistically different from zero (A1: $p = 0.031$; A2: $p = 0.047$).

When considering only *learners*, the medians of both A1 and A2 were significantly larger than zero for the IAB/ITB ratio (A1: $p = 0.031$; A2: $p = 0.031$), and significantly smaller than zero concerning the ITB only for A1 (A1: $p = 0.031$; A2: $p = 0.062$).

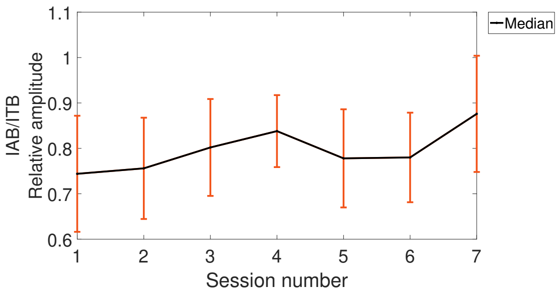

Figure 1: Evolution across sessions during NF at Cz: IAB/ITB relative amplitude; error bars show the median absolute deviation.

3.1.2 Within session

Figure 2 illustrates the behavior of IAB/ITB relative amplitude within each session (represented by the dashed curves), being the black curve a representation of the median amplitude values of all sessions. Clearly, there is an increasing trend of the IAB/ITB relative amplitude across blocks. Both W1 and W2 medians were positive for the IAB/ITB ratio, and negative for the ITB. Nonetheless, it would be expected that both learning measures' medians were positive for the IAB, which is not observed. In fact, the results from the Wilcoxon Signed Rank test reveal that the medians for both IAB/ITB and ITB were significantly larger (W1, W2: $p = 0.016$) and smaller (W1: $p = 0.039$; W2: $p = 0.016$) than zero, respectively, whereas no p-value under 0.05 was obtained for IAB or any of its components. Also, the median of W1 for Beta2 was significantly different from zero ($p = 0.047$).

Considering only *learners*, the medians of both learning measures were significantly greater than zero for IAB/ITB (W1, W2: $p = 0.031$), and lower than zero for the ITB (W1, W2: $p = 0.031$). Again, no statistically significant effects were observed regarding the IAB or its components.

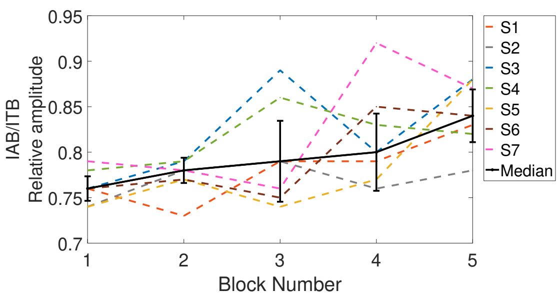

Figure 2: Evolution within session during NF at Cz: IAB/ITB relative amplitude; the dashed lines correspond to the median for all participants for a given session; error bars show the median absolute deviation.

3.2. Resting and Active Baselines

To analyze if significant differences occurred between pre- to post-NF training, the Wilcoxon Signed Rank test was performed, for EO, EC and AB, to compare IAB/ITB amplitude values of the pre-NF baseline from the 1st session with the values obtained in the post-NF baseline from the 7th session. No statistically significant changes were observed regarding the EC baseline and AB, whereas a p-value under 0.05 was obtained for the EO baseline ($p = 0.047$).

3.3. Measures' evaluation

The measures used in this experiment were analyzed in order to assess if alterations in participants' well-being, pain and cognition occurred between the first ($t0$) and seventh ($t1$) sessions.

3.3.1 Psychological tests

From the Wilcoxon Signed Rank test's results, no statistically significant differences were observed between the scores in $t0$ and $t1$ in any of the domains of all the tests performed.

3.3.2 Cognitive tests

The results obtained from the Wilcoxon Signed Rank test showed that there were significant changes from $t0$ to $t1$ in both Digit Span scores (DS Forward: $p = 0.036$; DS Reverse: $p = 0.031$), and also in the Rotation test score ($p = 0.016$). To evaluate whether the NF training performance had influenced participants' performance in cognitive tests, the Spearman's correlation was computed between the scores of each cognitive test and the learning measures across sessions (A1 and A2). It was found a significant negative correlation between the score change in Rotation test and both A1 and A2 ($r_s = -0.815, p = 0.025$).

3.3.3 Pain rating scale and Mental State Questionnaire

The results obtained from the Wilcoxon Signed Rank test revealed that there were no significant changes in pain from pre- to post-NF training in any session. The Spearman's correlation of the Δ *pain* with the IAB/ITB relative amplitude obtained in each session was computed for each patient, but no p-values under 0.05 were obtained. Also, when computing the same correlation between $\overline{\Delta\ pain}$ and W1 and W2, no significant results were observed.

Regarding the Mental State Questionnaire, subjects reported higher scores of concentration and motivation than of sleepiness and stress. However, when computing the correlation between each of the four averaged scores and each of the learning measures along sessions, i.e., A1 and A2, no significant results were obtained.

4. Discussion

4.1. Training effects

Based on the concepts of [35] work, we aimed to study *trainability*, i.e. the existence of effects resulting from the training in the target frequency, which is, in this case, the IAB/ITB ratio. Moreover, *independence* was also assessed in order to see if these potential effects had intervene or not in the other frequency bands' behavior.

4.1.1 IAB/ITB ratio, IAB and ITB

According to the results obtained for all subjects and the whole training, participants were able to learn to increase their alpha band, specifically the LA2 band. However, trainability was not verified for the IAB/ITB across sessions, presumably because participants were not able of significantly decrease their theta band throughout sessions. Within session, one may observe that the median IAB/ITB relative amplitude is gradually rising across blocks. Regarding the results from the statistical analysis, trainability was verified for the IAB/ITB ratio. Participants were able to successfully decrease their theta band, but failed on enhancing their alpha band. In Figure 2, it is possible to visualize the behavior of the alpha/theta ratio along blocks in each session. In the first two sessions, the variations of IAB/ITB relative amplitude are less pronounced than in the following sessions. This may reflect participants' ability to alter their brainwaves' activity, which becomes easier as they keep training; in other words, in a period of 5 minutes (that corresponds to one block), subjects can increase or decrease more rapidly their amplitudes as the number of sessions progresses. Nonetheless, from the 3rd session, these variations of amplitude become more pronounced from the 2nd block. Although participants already know sessions' procedure, this may happen because, in the first 5-min block, they are still trying to concentrate and disconnect from the external environment. So, the first block may be defined as an "adaptation period" within each session.

Considering only learners, participants were capable of significantly enhancing their alpha/theta ratio, not by increasing IAB, but by significantly decreasing their theta band across sessions. Statistical significance was obtained in both A1 and A2 for IAB/ITB ratio, and the median of A1 for ITB was significantly smaller than zero, but the same did not happen regarding A2. This could be explained by the fact that A1 reflects the learning progression taking into account the first and the last two training sessions, while A2, which corresponds to the slope of the linear regression along sessions, takes into consideration the seven sessions. Therefore, a slight variation of the ITB amplitude in the 3rd, 4th or 5th session may have influenced A2 computation, which in turn was reflected on the statistical analysis. Within sessions, trainability was once again verified since learners were able to significantly increase IAB/ITB and decrease ITB. Nonetheless, they were not able to considerably enhance their alpha band.

The disparity between across and within session learning (when considering all participants) has been discussed in similar studies [45, 46]. For instance, when training subjects to increase their theta/alpha ratio, Egner et al. (2002) [45] found a significant linear increase in theta/alpha ratio within session, but no significant linear or other polynomial trend across sessions was obtained. They suggested that several variables, such as the emotional state or the amount of sleep during the night before the session, may have interfered in the assessment of "between-session effects" and were hardly controllable. Moreover, authors hypothesize that a larger number of sessions (more than 5) would provide more grounded results regarding "across-session learning effects". Extrapolating to this work, since sessions' appointments were constrained by subjects' availability, the time of the day for the training was not held constant across sessions for all participants, which may have precluded the detection of significant effects along sessions.

When analyzing IAB and ITB independently, one may observe that in the circumstances where IAB/ITB ratio had significantly improved, no significant alterations were seen for the alpha band progression, but only for the theta band. According to [47], alpha and theta are related to each other but in opposite ways. Hence, it would be expected that, when enhancing IAB, ITB would decrease. However, considering all participants and the training across sessions, IAB significantly increases while ITB decreases but not substantially, which may mean that, although these bands evolve in opposite directions over time, their progression is not proportional. When separating non-learners from learners, a similar situation happened: ITB decreased significantly, and IAB was enhanced but not considerably. From this, we can speculate that non-learners learned how to increase IAB but not ITB over time. On the other hand, in the within session assessment, all patients successfully decreased ITB, but the medians of W1 and W2 were negative for IAB, meaning that trainability was not verified for the alpha band across blocks. The same happened when considering only learners. Taking this information into account, it is known that alpha and theta activities are physiologically related and diverge in opposite ways albeit not extensively along time, making it harder to obtain statistical significance when training them simultaneously. Perhaps, a protocol consisting in training both bands but in different sessions would provide a better understanding about their behavior.

4.1.2 Other frequency bands

The behavior of the relative amplitudes of other frequency bands (SMR, beta and beta2) was also assessed within and across sessions and only during the NF training, so independence could be studied. Considering all patients, trainability was verified for IAB/ITB within session, although independence was not present, since significant alterations were observed only in the beta2 band concerning W1. High-frequency neural activity has been associated to muscle activity [48], which leads us to think that this significant alteration of the beta2 band may be due to facial movements during the NF training. Across sessions, no statistically significant changes were found for the SMR, beta and beta2 bands, thus independence was verified.

4.1.3 Resting and active baselines

For the IAB/ITB ratio, no significant training effects were observed neither in the EC baseline nor in the active baseline for all subjects. However, when comparing IAB/ITB amplitude values of the pre-NF baseline measured in the 1st session with the values obtained in the post-NF baseline in the 7th session, significant changes were observed for the EO baseline. The measurement of resting baselines may be influenced by a variety of uncontrollable factors, such as subjects' intrinsic characteristics, the time of day of EEG acquisition, subjects' emotional state, among others [49]. Therefore, it is difficult to clearly know whether baseline's variations are due to NF training or external factors.

4.2. Psychological evaluation

From pre- to post-treatment evaluation, no significant differences were found in any of the domains of all the tests performed. Notwithstanding, some patients reported that they were experiencing more calmness and serenity from the moment the experiment started. As [28] referred, patients may feel better just by the simple fact of coming to the sessions.

4.3. Cognitive performance

Statistical significance was obtained for both scores of Digit Span test (Forward and Reverse), but not for the spans. Nonetheless, these results were not correlated with subjects' training performance regarding their alpha/theta ratio. Also in the Rotation test, statistical differences from $t0$ to $t1$ were obtained. However, when computing the correlation between test's scores and training performance across sessions, a negative correlation was observed (with both A1 and A2). No obvious explanation was found, possibly indicating that subjects improved their mental rotation skills due to factors that transcend NF training.

4.4. Pain and Mental State evaluation

The fact that no significant correlations were found between the four states and the training performance measures across sessions may rely on the fact that a numerical scale of five points was used for classifying each state, being participants' response based on their personal opinion and experience, and thus subjective.

From the pain rating scale results, no significant decrease in pain was observed from pre- to post-NF training in any session for all patients, nor when analyzing each subject individually. Assessing pain is usually challenging, since the scales that are frequently used lack sensitivity, and the one used in this experiment is no exception. Moreover, it is necessary to have in mind that rating pain depends on patients' pain perception, i.e. some of them may have higher tolerance comparatively to others, and thus, subjectivity may be present. On the other hand, medication is another factor to consider, since stronger analgesics can be camouflaging aggressive symptoms that patients usually feel when not taking them, which may influence their response.

5. Conclusions

The main objective of this experiment was to investigate the potential benefits of applying NF in patients suffering from chronic back pain. For this purpose, an EEG-NF protocol targeting the increase of IAB/ITB ratio, at Cz, was developed and implemented aiming to alleviate patients' pain experience.

Although some patients reported that they were experiencing tranquility as the treatment was proceeding, statistical analysis did not reveal differences in subjects' pain level. Therefore, it was considered that the protocol used may not be sufficiently specific for chronic back pain and thus further studies should be performed in order to refine it. For instance, it is believed that, due to their physical condition, subjects would benefit more from a NF training comprising less time-consuming but intensive sessions. Therefore, a rearrangement of the protocol design is suggested, including the addition of a follow-up period to assess NF long-term effects. Before starting the treatment, an EEG recording of each individual would possibly provide information regarding patients' brain activity, and, perhaps, a more personalized protocol could be designed.

Despite the improvements observed in patients' training performance over the first half of the procedure, it is important to further evaluate the outcomes for the whole treatment that was designed in first place. By increasing sample size and adding a control group, it is expected that stronger conclusions can be drawn. Nonetheless, these preliminary findings provide additional evidence for the NF potential efficacy in the treatment of chronic back pain, suggesting further investigation for a deeper understanding.

References

[1] Tim VP Bliss, Graham L Collingridge, Bong-Kiun Kaang, and Min Zhuo. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nature Reviews Neuroscience*, 17(8):485, 2016.

[2] Rohini Kuner and Herta Flor. Structural plasticity and reorganisation in chronic pain. *Nature Reviews Neuroscience*, 18(1):20, 2017.

[3] María Dueñas, Begona Ojeda, Alejandro Salazar, Juan Antonio Mico, and Inmaculada Failde. A review of chronic pain impact on patients, their social environment and the health care system. *Journal of pain research*, 9:457, 2016.

[4] Luís Filipe Azevedo, Altamiro Costa-Pereira, Liliane Mendonça, Cláudia Camila Dias, and José Manuel Castro-Lopes. Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *The journal of pain*, 13(8):773–783, 2012.

[5] Mark P Jensen, Melissa A Day, and Jordi Miró. Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nature Reviews Neurology*, 10(3):167, 2014.

[6] Herta Flor. Psychological pain interventions and neurophysiology: Implications for a mechanism-based approach. *American Psychologist*, 69(2):188, 2014.

[7] Eulalia Silva dos Santos Pinheiro, Fernanda Costa de Queiros, Pedro Montoya, Cleber Luz Santos, Marion Alves do Nascimento, Clara Hikari Ito, Manuela Silva, David Barros Nunes Santos, Silvia Benevides, José Garcia Vivas Miranda, et al. Electroencephalographic patterns in chronic pain: a systematic review of the literature. *PLoS One*, 11(2):e0149085, 2016.

[8] Mark P Jensen, Leslie H Sherlin, Shahin Hakimian, and Felipe Fregni. Neuromodulatory approaches for chronic pain management: Research findings and clinical implications. *Journal of Neurotherapy*, 13(4):196–213, 2009.

[9] Edward H Jacobs and Mark P Jensen. EEG Neurofeedback in the Treatment of Chronic Pain: A Case Series. *NeuroRegulation*, 2(2):86, 2015.

[10] Weiwei Peng, Claudio Babiloni, Yanhui Mao, and Yong Hu. Subjective pain perception mediated by alpha rhythms. *Biological psychology*, 109:141–150, 2015.

[11] Jair Stern, Daniel Jeanmonod, and Johannes Sarnthein. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *Neuroimage*, 31(2):721–731, 2006.

[12] Stefan Schmidt, José Raúl Naranjo, Christina Brenneisen, Julian Gundlach, Claudia Schultz, Holger Kaube, Thilo Hinterberger, and Daniel Jeanmonod. Pain ratings, psychological functioning and quantitative EEG in a controlled study of chronic back pain patients. *PLoS One*, 7(3):e31138, 2012.

[13] Efthymios Angelakis, Stamatina Stathopoulou, Jennifer L Frymiare, Deborah L Green, Joel F Lubar, and John Kounios. EEG neurofeedback: a brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *The clinical neuropsychologist*, 21(1):110–129, 2007.

[14] David Vernon, Ann Frick, and John Gruzelier. Neurofeedback as a treatment for ADHD: A methodological review with implications for future research. *Journal of Neurotherapy*, 8(2):53–82, 2004.

[15] Sharon Niv. Clinical efficacy and potential mechanisms of neurofeedback. *Personality and Individual Differences*, 54(6):676–686, 2013.

[16] Ulrike Leins, Gabriella Goth, Thilo Hinterberger, Christoph Klinger, Nicola Rumpf, and Ute Strehl. Neurofeedback for children with ADHD: a comparison of SCP and Theta/Beta protocols. *Applied psychophysiology and biofeedback*, 32(2):73–88, 2007.

[17] Ute Strehl, Pascal Aggensteiner, Daniel Wachtlin, Daniel Brandeis, Björn Albrecht, Maria Arana, Christiane Bach, Tobias Banaschewski, Thorsten Bogen, Andrea Flaig-Röhr, et al. Neurofeedback of slow cortical potentials in children with attention-deficit/hyperactivity disorder: a multicenter randomized trial controlling for unspecific effects. *Frontiers in human neuroscience*, 11:135, 2017.

[18] MB Sterman and L Friar. Suppression of seizures in an epileptic following sensorimotor EEG feedback training. *Electroencephalography and clinical neurophysiology*, 33(1):89–95, 1972.

[19] JL Koberda and LC Frey. Z-score LORETA neurofeedback as a potential therapy for patients with seizures and refractory epilepsy. *Neurol Neurobiol, Volume1*, 1, 2015.

[20] John Gruzelier, Elinor Hardman, Jennifer Wild, and Rashid Zaman. Learned control of slow potential interhemispheric asymmetry in schizophrenia. *International Journal of Psychophysiology*, 34(3):341–348, 1999.

[21] Wenya Nan, Feng Wan, Lanshin Chang, Sio Hang Pun, Mang I Vai, and Agostinho Rosa. An exploratory study of intensive neurofeedback training for schizophrenia. *Behavioural neurology*, 2017, 2017.

[22] San-Yu Wang, I-Mei Lin, Erik Peper, Yu-Ting Chen, Tze-Chun Tang, Yi-Chun Yeh, Yu-Che Tsai, and Che-Cheng Chu. The efficacy of neurofeedback among patients with major depressive disorder: Preliminary study. *NeuroRegulation*, 3(3):127–127, 2016.

[23] Álvaro Machado Dias and Adrian van Deusen. A new neurofeedback protocol for depression. *The Spanish journal of psychology*, 14(1):374–384, 2011.

[24] Michael Siniatchkin, Anke Hierundar, Peter Kropp, Ralf Kuhnert, Wolf-Dieter Gerber, and Ulrich Stephani. Self-regulation of slow cortical potentials in children with migraine: an exploratory study. *Applied psychophysiology and biofeedback*, 25(1):13–32, 2000.

[25] Deborah A Stokes and Martha S Lappin. Neurofeedback and biofeedback with 37 migraineurs: a clinical outcome study. *Behavioral and Brain Functions*, 6(1):9, 2010.

[26] Sadi Kayıran, Erbil Dursun, Nigar Dursun, Numan Ermutlu, and Sacit Karamürsel. Neurofeedback intervention in fibromyalgia syndrome; a randomized, controlled, rater blind clinical trial. *Applied psychophysiology and biofeedback*, 35(4):293–302, 2010.

[27] Xavier J Caro and Earl F Winter. EEG biofeedback treatment improves certain attention and somatic symptoms in fibromyalgia: a pilot study. *Applied psychophysiology and biofeedback*, 36(3):193–200, 2011.

[28] David V Nelson, Robert M Bennett, Andre Barkhuizen, Gary J Sexton, Kim D Jones, Mary Lee Esty, Len Ochs, and CC Stuart Donaldson. Neurotherapy of fibromyalgia? *Pain Medicine*, 11(6):912–919, 2010.

[29] Mark P Jensen, Caroline Grierson, Veronika Tracy-Smith, Stacy C Bacigalupi, and Siegfried Othmer. Neurofeedback treatment for pain associated with complex regional pain syndrome type I. *Journal of Neurotherapy*, 11(1):45–53, 2007.

[30] Mark P Jensen, Kevin J Gertz, Amy E Kupper, Alan L Braden, Jon D Howe, Shahin Hakimian, and Leslie H Sherlin. Steps toward developing an EEG biofeedback treatment for chronic pain. *Applied psychophysiology and biofeedback*, 38(2):101–108, 2013.

[31] Sarah Prinsloo, Diane Novy, Larry Driver, Randall Lyle, Lois Ramondetta, Cathy Eng, Jennifer McQuade, Gabriel Lopez, and Lorenzo Cohen. Randomized controlled trial of neurofeedback on chemotherapy-induced peripheral neuropathy: A pilot study. *Cancer*, 123(11):1989–1997, 2017.

[32] Michael Doppelmayr, Wolfgang Klimesch, Th Pachinger, and B Ripper. Individual differences in brain dynamics: important implications for the calculation of event-related band power. *Biological cybernetics*, 79(1):49–57, 1998.

[33] Feng Wan, Wenya Nan, Mang I Vai, and Agostinho Rosa. Resting alpha activity predicts learning ability in alpha neurofeedback. *Frontiers in human neuroscience*, 8:500, 2014.

[34] Feng Wan, Janir Nuno Da Cruz, Wenya Nan, Chi Man Wong, Mang I Vai, and Agostinho Rosa. Alpha neurofeedback training improves SSVEP-based BCI performance. *Journal of neural engineering*, 13(3):036019, 2016.

[35] Benedikt Zoefel, René J Huster, and Christoph S Herrmann. Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *Neuroimage*, 54(2):1427–1431, 2011.

[36] Carlos Escolano, Monica Aguilar, and Javier Minguez. EEG-based upper alpha neurofeedback training improves working memory performance. In *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 2327–2330. IEEE, 2011.

[37] Robert D Kerns, Dennis C Turk, and Thomas E Rudy. The west haven-yale multidimensional pain inventory (WHYMPI). *Pain*, 23(4):345–356, 1985.

[38] Michael JL Sullivan, Beverly Thorn, Jennifer A Haythornthwaite, Francis Keefe, Michelle Martin, Laurence A Bradley, and John C Lefebvre. Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical journal of pain*, 17(1):52–64, 2001.

[39] John E Ware Jr and Cathy Donald Sherbourne. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care*, pages 473–483, 1992.

[40] Mark E Maruish. *Handbook of psychological assessment in primary care settings*. Taylor & Francis, 2017.

[41] Aaron T Beck, Calvin H Ward, Mock Mendelson, Jeremiah Mock, and John Erbaugh. An inventory for measuring depression. *Archives of general psychiatry*, 4(6):561–571, 1961.

[42] Donna Lee Wong and Connie M Baker. Pain in children: comparison of assessment scales. *Pediatr Nurs*, 14(1):9–17, 1988.

[43] I. Esteves. Neurofeedback training intensity: implications on EEG-self regulation, 2017.

[44] T. Bucho. Comparison of auditory and visual modalities for EEG-neurofeedback, 2018.

[45] Tobias Egner, Emilie Strawson, and John H Gruzelier. EEG signature and phenomenology of alpha/theta neurofeedback training versus mock feedback. *Applied psychophysiology and biofeedback*, 27(4):261, 2002.

[46] Joshua Raymond, Carolyn Varney, Lesley A Parkinson, and John H Gruzelier. The effects of alpha/theta neurofeedback on personality and mood. *Cognitive brain research*, 23(2-3):287–292, 2005.

[47] Wolfgang Klimesch. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain research reviews*, 29(2-3):169–195, 1999.

[48] Suresh Muthukumaraswamy. High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations. *Frontiers in human neuroscience*, 7:138, 2013.

[49] Robert W Thatcher, Rebecca A Walker, Carl J Biver, Duane N North, and Richard Curtin. Quantitative EEG normative databases: Validation and clinical correlation. *Journal of Neurotherapy*, 7(3-4):87–121, 2003.