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# Neurofeedback Intervention in Fibromyalgia Syndrome; a Randomized, Controlled, Rater Blind Clinical Trial

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**Abstract** We designed a randomized, rater blind study to assess the efficacy of EEG Biofeedback (Neurofeedback-NFB) in patients with fibromyalgia syndrome (FMS). Eighteen patients received twenty sessions of NFB-sensory motor rhythm (SMR) treatment (NFB group) during 4 weeks, and eighteen patients were given 10 mg per day escitalopram treatment (control group) for 8 weeks. Visual Analog Scales for pain and fatigue, Hamilton and Beck Depression and Anxiety Inventory Scales, Fibromyalgia Impact Questionnaire and Short Form 36 were used as outcome measures which were applied at baseline and 2nd, 4th, 8th, 16th, 24th weeks. Mean amplitudes of EEG rhythms (delta, theta, alpha, SMR, beta1 and beta2) and theta/SMR ratio were also measured in NFB group. All post-treatment measurements showed significant improvements in both of the groups (for all parameters $p < 0.05$). NFB group displayed greater benefits than controls (for all parameters $p < 0.05$). Therapeutic efficacy of NFB was found to begin at 2nd week and reached to a maximum effect at 4th week. On the other hand, the improvements in SSRI treatment were also detected to begin at 2nd week but reached to a maximum effect at 8th week. No statistically significant changes were noted regarding mean amplitudes of EEG rhythms ($p > 0.05$ for all). However, theta/SMR ratio showed a significant decrease at 4th week compared to baseline in the NFB group ($p < 0.05$). These data support the efficacy of NFB as a treatment for pain, psychological symptoms and impaired quality of life associated with fibromyalgia.

**Keywords** Fibromyalgia syndrome · Neurofeedback · Escitalopram

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## Introduction

Fibromyalgia syndrome (FMS) is an acquired systemic disorder of uncertain etiology characterized by widespread musculoskeletal pain. Besides widespread pain, patients with FMS have many other symptoms like fatigue, sleep difficulties, a swollen feeling in tissues, paresthesia, cognitive dysfunction, dizziness, increased tenderness in multiple points, morning stiffness, psychological disorders, abdominal pain, dysmenorrhoea, irritable bowel syndrome, headaches and restless legs syndrome.

There is evidence for central sensitization in these conditions, but further studies are needed (Yunus 2007). A number of pathophysiological processes are explained for diffuse pain of FMS including central pain processing systems, hypothalamic pituitary adrenal axes, and the autonomic nervous system in which central pain condition is the most productive area of research. Studies with functional imaging modalities suggest that patients with FMS have a narrow range of tolerance for pain and have been interpreted as evidence for enhanced sensory processing (Mountz et al. 1995; Gracely et al. 2002; Guedj et al. 2007). The review of Williams and Clauw focuses on their current understanding of FMS as a prototypical

central pain syndrome (Williams and Clauw 2009). They make clear that the terms central augmentation or central pain threshold are different than the term central sensitization and as the tenderness or hyperalgesia occurs far away from the area of pain, central augmentation or central pain are likely to be more suitable terms for what is seen in FMS.

Various treatment strategies such as patients' education, cognitive behavioral therapy, psychotherapy, hydrotherapy, pharmacological agents like analgesics, myorelaxants, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are used in the management of FMS.

Serum tryptophan which is the precursor molecule in the synthesis of serotonin is shown to have lower levels in FMS patients (Russell et al. 1989; Moldofsky and Warsh 1978; Yunus et al. 1992). Reduced serotonin levels are associated with somatic complaints, depression, decreased non-REM (restorative) sleep and increased pain perception (Yunus et al.1992). 5-Hydroxytryptophan is the intermediate metabolite of the essential amino acid L-tryptophan in the biosynthesis of serotonin. Therapeutic administration of 5-Hydroxytryptophan has been shown to be effective in treating a wide variety of conditions, including fibromyalgia (Sarzi Puttini and Caruso 1992; Caruso et al. 1990).

TCAs are the main drugs proven to alleviate the symptoms associated with FMS. However, the usage of these drugs is restricted because of their side effects. SSRI treatment is being more widely used because of their favorable side effect profile and better patients' compliance. Citalopram is one of the well-known SSRI, also shown to be effective on main FMS symptoms (Anderberg et al. 2000). Escitalopram, the S-enantiomer of citalopram, is another SSRI has similar clinical efficacy to citalopram with fewer side effects.

Biofeedback (BF) is a group of therapeutic procedures that uses electronic or electromechanical instruments to properly measure, process and feedback to patients in the form of auditory and/or visual feedback signals by using information about their normal and/or abnormal neuromuscular and autonomic activity (Dursun 2009). BF is used to help patients develop greater awareness of and an increase in voluntary control over their physiological processes that are otherwise involuntary and unfelt events. In physiatry BF has been used in a wide range of clinical conditions such as motor weakness (Wissel et al.1989; Intiso et al. 1994), balance and gait disturbances (Dursun et al. 2004; Petrofsky 2001), spasticity (Nash et al. 1989), neurogenic bladder (Middaugh et al. 1989) and bowel dysfunctions (Chiarioni et al. 2005; Ho and Tan 1997), speech (Gentil et al. 1994; Draizar 1984) and swallowing problems (Reddy et al. 2000; Denk and Kaider 1997). It has also been used in the management of various painful conditions such as temporomandibular joint dysfunctions (Crider et al. 2005) and patellofemoral pain syndrome (Dursun et al. 2001, Yip and Ng 2006). In addition BF treatment is also suggested to be helpful for the management of FMS (Mur et al. 1999).

The exact mechanism of the BF treatment is not clear. Basmajian (1982) determined the development of new pathways or recruitment of existing cerebral pathways. Wolf (1983) suggested that feedback signals activate unused or underused synapses in executing motor commands. Although no data exist, the repetitive and concentrated practice performed in BF might be playing a role in brain plasticity (Dursun et al. 2004). However in a recently published study, there is evidence that electroencephalographic (EEG) biofeedback causes neuroplastic changes (Ros et al. 2010).

EEG biofeedback is a kind of BF modality that records EEG waves. It is an operant conditioning procedure that supports the individual's ability to modify the amplitude, frequency or coherence of the neurophysiologic dynamics of the brain (Egner and Gruzelier 2004). Therapeutic application of EEG biofeedback is often referred to as "Neurofeedback (NFB)" (Lubar 1997; Vernon et al. 2003). NFB has various clinical applications such as migraine, epilepsy, attention deficit hyperactivity disorder, alcohol abuse and post traumatic stress disorder. Sensorimotor rhythm (SMR) training is a commonly applied NFB protocol (Egner et al. 2004). SMR is normally associated with a quiet body and active mind and is thought to be generated through thalamocortical interactions during burst firing activity in ventrobasal thalamic relay nuclei associated with the suppression of somatosensory afferent gating (Howe and Sterman 1972). SMR training appears to facilitate thalamic inhibitory mechanisms. On the other hand, enhancement of SMR activity has cognitive implications such as reducing impulsiveness/hyperactivity, enhancing attention processing and semantic memory performance (Sterman 1996).

FMS patients frequently complain of deficits in memory and attention. Neuropsychological tests have revealed poor working memory and long term memory, vocabulary deficits and lower information processing speed (Grace et al. 1999; Park et al. 2001). In FMS perceptual amplification of pain, and neurosensitization are observed, both of which might be related to disinhibitory mechanisms (Howe and Sterman 1972). Ozgocmen et al. (2002, 2003), and Alanoglu et al. (2005) demonstrated reduced P300 amplitudes in patients with FMS. As P300 has been proposed to reflect the activation of inhibitory processes, these findings are important. The amplitude of P300 reflects central nervous system (CNS) inhibition; the larger the amplitude, the more the inhibition (Tomberg and Desmedt 1998). SMR training increases P300 amplitudes which support the observation

that SMR training facilitates thalamocortical inhibitory mechanisms (Egner and Gruzelier 2001). In a previous preliminary report, we revealed that SMR training alleviated the clinical symptoms of three patients with FMS (Kayıran et al. 2007).

When taking into consideration this background knowledge, we can assume that NFB treatment may play an inhibitory role on CNS, and this inhibition may alter central augmentation in FMS. In this way, we can hypothesize that NFB treatment will be effective in alleviating the symptoms and signs of FMS. In order to display this, we designed a prospective and controlled clinical study.

## Materials and Methods

The study was conducted in the outpatient clinic of Kocaeli University Physical Medicine and Rehabilitation Department between 12/15/2005 and 12/15/2007. The research protocol was approved by the Institutional Ethical Board on Human Researches (169/15). Before study procedures were initiated, a written informed consent was obtained from all patients after the study was explained and their questions were answered. Consecutive female patients who admitted to our outpatient clinic were examined for inclusion. The inclusion criteria were: (1) patients to be 16–49 years of age, (2) who meet the ACR criteria for FMS, (3) who do not receiving any medication or other treatments for FMS or any other diseases. The exclusion criteria were composed of having another major health problem (stroke, diabetes mellitus, coronary heart disease etc.), alcohol abuse, psychoactive drug treatment and any abnormality in routine laboratory tests (CBC, serum biochemistry, sedimentation and CRP levels).

This study has a rater blind randomized controlled design. Forty FMS patients were involved in this study and randomized into either NFB or control (escitalopram) group. SMR training was performed by Alien Technik 3/32 setup and BrainFeedback-3 EEG biofeedback software. EEG was recorded from C4 (according to standard 10–20 system) with 46 Hz band width and the reference electrode placed on left, and the ground electrode on the right earlobe. Signal was acquired at 256 Hz, A/D converted and band-filtered to extract delta (1–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), SMR (12–15 Hz), the beta1 (15–20 Hz), and "high beta" (22–30 Hz) components. Band amplitude values were transformed into visual feedback representations. Patients were seated on a comfortable armchair in front of a computer screen where they can involve in the selected computer game during treatment sessions. The patients were informed about the feedback system and instructed to follow the continuous feedback process and try to maximize their scores. No obvious instructions were given to the patients on how to achieve control over their EEG, but they were explained to be relaxed and concentrated on the computer game and try to widen the river which is seen on the monitor as a game. Whenever the patients could be successful on widening the river then they enhanced SMR activity and decreased theta activity relative to pre-feedback baseline measures. By this way rewards (points and auditory beeps) were gained and so their scores were increased. A treatment session was composed of ten SMR training periods where each period continued for 3 min. Therefore, each treatment session was 30 min-long and the patients were trained 5 sessions per week. Each patient was trained at the same time-period of the day during 4 weeks. Patients in the control group received Escitalopram (10 mg/day) for 8 weeks.

The symptoms concerning FMS and the clinical grading scales including Turkish versions were noted at baseline, 2nd, 4th, 8th, 16th and 24th weeks for both of the groups (Çorapçıoğlu et al. 1999; Akdemir et al. 2001; Hisli 1989; Yazıcı et al. 1998; Ulusoy et al. 1998; Koçyiğit et al. 1999; Sarmer et al. 2000). Visual Analogue Scale (VAS) for pain, VAS for fatigue, Fibromyalgia Impact Questionnaire (FIQ) and Short Form 36 (SF-36) were applied in outpatient clinic of our Physical Medicine and Rehabilitation Department. The FIQ is composed of 20 items questioning physical functioning, number of days they felt well and number of days they were unable to work because of FMS symptoms, visual analog scales marked in 1 cm increments on which the patient rates work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. SF-36 was composed of eight subscales questioning physical and mental components of health: Subscale 1 = Physical functioning, Subscale 2 = Physical role functioning, Subscale 3 = Bodily pain, Subscale 4 = Social functioning, Subscale 5 = General mental health, Subscale 6 = Emotional role functioning, Subscale 7 = Vitality, Subscale 8 = General health. Hamilton Depression Scale (HDS), Beck Depression Scale (BDS), Hamilton Anxiety Scale (HAS) and Beck Anxiety Scale (BAS) were applied in the Department of Psychiatry. The Structured Clinical Interview for DSM-III-R Personality Disorder (SCID-I) was also applied in the Psychiatry Department at baseline. The mean amplitudes of alpha, beta1, beta 2, theta, delta, SMR, and theta/SMR ratios were recorded at baseline, 2nd, 4th, 8th, 16th and 24th weeks in the NFB group. Ten consecutive feedback-free resting EEG samples, each with 1 min duration, were recorded in every evaluation in the eyes open condition to determine the mean amplitudes.

Statistical Analyses were done by using Statistical Package for Social Sciences (SPSS) 13.0 for Windows. Demographic results were descriptive and expressed as mean ± standard error. We compared the baseline

characteristics of each group using chi-square test for categorical variables, and the two-sample *t* test for continuous variables. Mann–Whitney U Test was used in between groups' analyses and Wilcoxon Signed Ranks Test and Friedman Test were used in within groups' analyses. Treatment effects were tested at a two-sided significance level of 0.05.

## Results

Forty FMS patients were involved and randomized into either NFB or control (escitalopram) group. Two patients in the NFB group and 2 patients in the control group were lost to follow up. The mean ages of the patients were similar in the NFB and control groups (31.78 ± 6.17 and 32.39 ± 6.72, respectively; $p = 0.778$). There was no statistically significant difference between the NFB and control groups regarding disease age (4.61 ± 2.52 and 4.94 ± 2.36, respectively; $p = 0.688$). The results of SCID-I revealed that nine patients in the NFB group and 10 patients in the control group had major depressive disorder ($p = 0.738$).

At the baseline, there were no statistically significant differences in scores of assessment scales except for HAS, HDS, BAS and subscale 4 of SF-36 ($p > 0.05$ for all; Tables 1, 2, and 3). In both of the groups, VAS-pain and VAS-fatigue scores decreased significantly (Friedman test; $p < 0.001$ and $p < 0.001$, respectively) (Table 1) and the values continued to be significantly lower comparing to baseline in every visit during follow up (baseline-24th week: $p < 0.001$ for both). In the NFB group, the decreases in VAS-pain and VAS-fatigue levels reached maximum at 4th week (baseline-4th week: $p < 0.001$ for both). For the control group maximum reductions were noted at 8th week (baseline-8$^{th}$ week: $p < 0.001$ for both). Mean VAS-pain and VAS-fatigue scores of the NFB group were found to be significantly lower than those of the control group in every visit during follow up (Mann–Whitney U test; $p < 0.05$ for all) (Table 1).

In both of the groups, HDS and BDS scores decreased significantly (Friedman test; $p < 0.001$ and $p < 0.001$, respectively) (Table 2) and the values continued to be significantly lower comparing to baseline in every visit during follow up (baseline-24th week: $p < 0.001$ for both). In the NFB group, the decreases in HDS and BDS levels reached maximum at 4th week (baseline-4$^{th}$ week: $p < 0.001$ for both). For the control group maximum reductions were observed at 8th week (baseline-8$^{th}$ week: $p < 0.001$ for both). Mean HDS and BDS scores of the NFB group were found to be significantly lower than those of the control group in every visit during follow up (Mann–Whitney U test; $p < 0.05$ for all) (Table 2).

In both of the groups, HAS and BAS scores decreased significantly (Friedman test; $p < 0.001$ and $p < 0.001$, respectively) (Table 3) and the values were significantly lower comparing to baseline in every visit during follow up (baseline-24th week: $p < 0.001$ for both). In the NFB group, the decreases in HAS and BAS levels reached maximum at 4th week (baseline-4th week: $p < 0.001$ for both). For the control group maximum reductions were noted at 8th week (baseline-8th week: $p < 0.001$ for both). Mean HAS and BAS scores of the NFB group were found to be significantly lower than those of the control group in every visit during follow up (Mann–Whitney U test; $p < 0.05$ for all) (Table 3).

In both of the groups, FIQ and subscales of SF-36 scores showed significant improvements (Friedman test; $p < 0.05$ and $p < 0.001$, respectively) (Figs. 1 and 2). The values of FIQ were significantly lower whereas the values of SF-36 were significantly higher comparing to baseline in every visit during follow up (baseline-24th week: $p < 0.001$ for both). In the NFB group, the decreases in FIQ levels reached maximum at 4th week (baseline-4th week: $p < 0.001$). For the control group maximum reduction were found at 8th week (baseline-8th week: $p < 0.001$).

**Table 1** VAS-pain and VAS-fatigue scores in the NFB and control groups

| VAS | Pain | | | | | Fatigue | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NFB | | Control | | Mann–Whitney U | NFB | | Control | | Mann–Whitney U |
| | Mean | SE | Mean | SE | p | Mean | SE | Mean | SE | p |
| Baseline | 8.94 | 0.189 | 9.11 | 0.231 | 0.462 | 9.00 | 0.232 | 9.19 | 0.207 | 0.521 |
| 2nd week | 4.06 | 0.317 | 6.28 | 0.428 | ***0.000*** | 4.50 | 0.439 | 6.17 | 0.375 | ***0.006*** |
| 4th week | 1.64 | 0.213 | 4.69 | 0.482 | ***0.000*** | 1.78 | 0.240 | 4.39 | 0.431 | ***0.000*** |
| 8th week | 1.92 | 0.269 | 3.25 | 0.269 | ***0.002*** | 1.86 | 0.242 | 3.36 | 0.274 | ***0.001*** |
| 16th week | 2.42 | 0.341 | 4.47 | 0.339 | ***0.000*** | 2.47 | 0.431 | 4.78 | 0.275 | ***0.000*** |
| 24th week | 2.56 | 0.357 | 5.33 | 0.302 | ***0.000*** | 2.47 | 0.353 | 5.61 | 0.335 | ***0.000*** |
| Friedman | $p < 0.001$ | | $p < 0.001$ | | | $p < 0.001$ | | $p < 0.001$ | | |

**Table 2** HDS and BDS scores in the NFB and control groups

| Depression | HDS | | | | | BDS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NFB | | Control | | Mann–Whitney U | NFB | | Control | | Mann–Whitney U |
| | Mean | SE | Mean | SE | p | Mean | SE | Mean | SE | p |
| Baseline | 16.94 | 1.349 | 20.83 | 0.733 | 0.003 | 21.50 | 2.639 | 26.00 | 2.154 | 0.152 |
| 2nd week | 9.89 | 1.022 | 15.89 | 0.953 | ***0.000*** | 7.11 | 1.143 | 17.50 | 2.150 | ***0.000*** |
| 4th week | 4.78 | 0.827 | 11.94 | 0.923 | ***0.000*** | 3.22 | 0.698 | 9.78 | 0.899 | ***0.000*** |
| 8th week | 4.83 | 0.628 | 8.22 | 0.765 | ***0.004*** | 3.28 | 0.565 | 6.33 | 0.464 | ***0.000*** |
| 16th week | 5.39 | 0.578 | 11.78 | 0.835 | ***0.000*** | 4.17 | 0.781 | 10.56 | 0.584 | ***0.000*** |
| 24th week | 6.33 | 0.583 | 13.39 | 0.776 | ***0.000*** | 4.72 | 0.881 | 12.33 | 0.498 | ***0.000*** |
| Friedman | $p < 0.001$ | | $p < 0.001$ | | | $p < 0.001$ | | $p < 0.001$ | | |

**Table 3** HAS and BAS scores in the NFB and control groups

| Anxiety | HAS | | | | | BAS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NFB | | Control | | Mann–Whitney U | NFB | | Control | | Mann–Whitney U |
| | Mean | SE | Mean | SE | p | Mean | SE | Mean | SE | p |
| Baseline | 19.72 | 1.374 | 25.06 | 1.256 | ***0.006*** | 26.17 | 2.431 | 35.56 | 2.415 | ***0.016*** |
| 2nd week | 10.89 | 1.140 | 20.11 | 1.223 | ***0.000*** | 10.00 | 1.528 | 24.72 | 2.398 | ***0.000*** |
| 4th week | 5.44 | 0.738 | 14.11 | 1.140 | ***0.000*** | 5.00 | 0.840 | 16.67 | 1.915 | ***0.000*** |
| 8th week | 5.00 | 0.709 | 8.94 | 1.027 | ***0.006*** | 5.50 | 0.926 | 10.28 | 1.323 | ***0.004*** |
| 16th week | 6.06 | 0.826 | 12.61 | 1.109 | ***0.000*** | 6.00 | 0.918 | 15.06 | 1.837 | ***0.000*** |
| 24th week | 7.11 | 0.792 | 15.22 | 1.173 | ***0.000*** | 7.17 | 1.211 | 16.67 | 1.771 | ***0.000*** |
| Friedman | $p < 0.001$ | | $p < 0.001$ | | | $p < 0.001$ | | $p < 0.001$ | | |

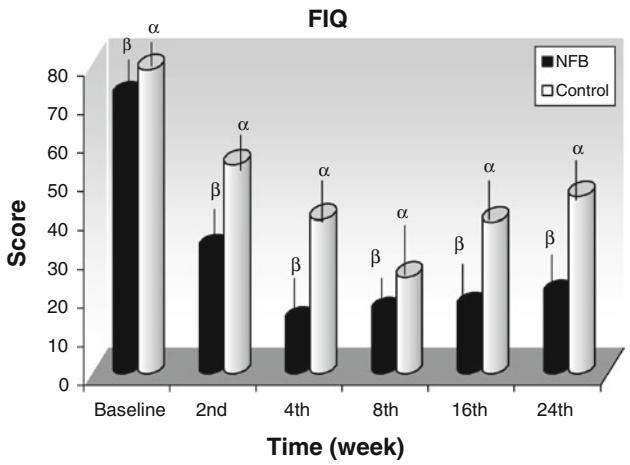


**Fig. 1** FIQ scores in the NFB and control groups ($\beta$, $\alpha$ Friedman: $p < 0.001$)

For SF-36 values, the NFB group showed maximum enhancements at 4th week (Wilcoxon test; $p < 0.01$ for all) whereas the control group at 8th week (Wilcoxon test; $p < 0.01$ for all) Regarding subscales of SF-36, the NFB group were better than those of the control group in all assessments (Mann–Whitney U test; $p < 0.05$ for all) except at 8th week evaluations where no significant differences were found between the two groups (Mann–Whitney U test; $p > 0.05$ for all).

No statistically significant changes were noted regarding mean amplitudes of EEG rhythms (Friedman test; $p > 0.05$ for all) (Table 4) However, theta/SMR ratio showed a significant decrease at 4th week compared to baseline in the NFB group (Wilcoxon test, $p < 0.05$) (Fig. 3).

## Discussion

Fibromyalgia syndrome (FMS) is a painful disorder that impairs quality of life in affected individuals. Although the exact mechanisms underlying this syndrome have not been understood yet, deactivation of inhibitory processes in CNS is postulated as a major pathology (Howe and Sterman 1972; Pillemer et al. 1997; Lautenbacher and Rollman 1997; Bennett 1999; Staud et al. 2001). On the other hand, important central nervous system mechanisms relevant for FMS pain include temporal summation of pain and central sensitization. Interventions that re-program or interrupt central sensitization could also provide significant relief for some individuals with chronic pain and the understanding that pain experience is modulated

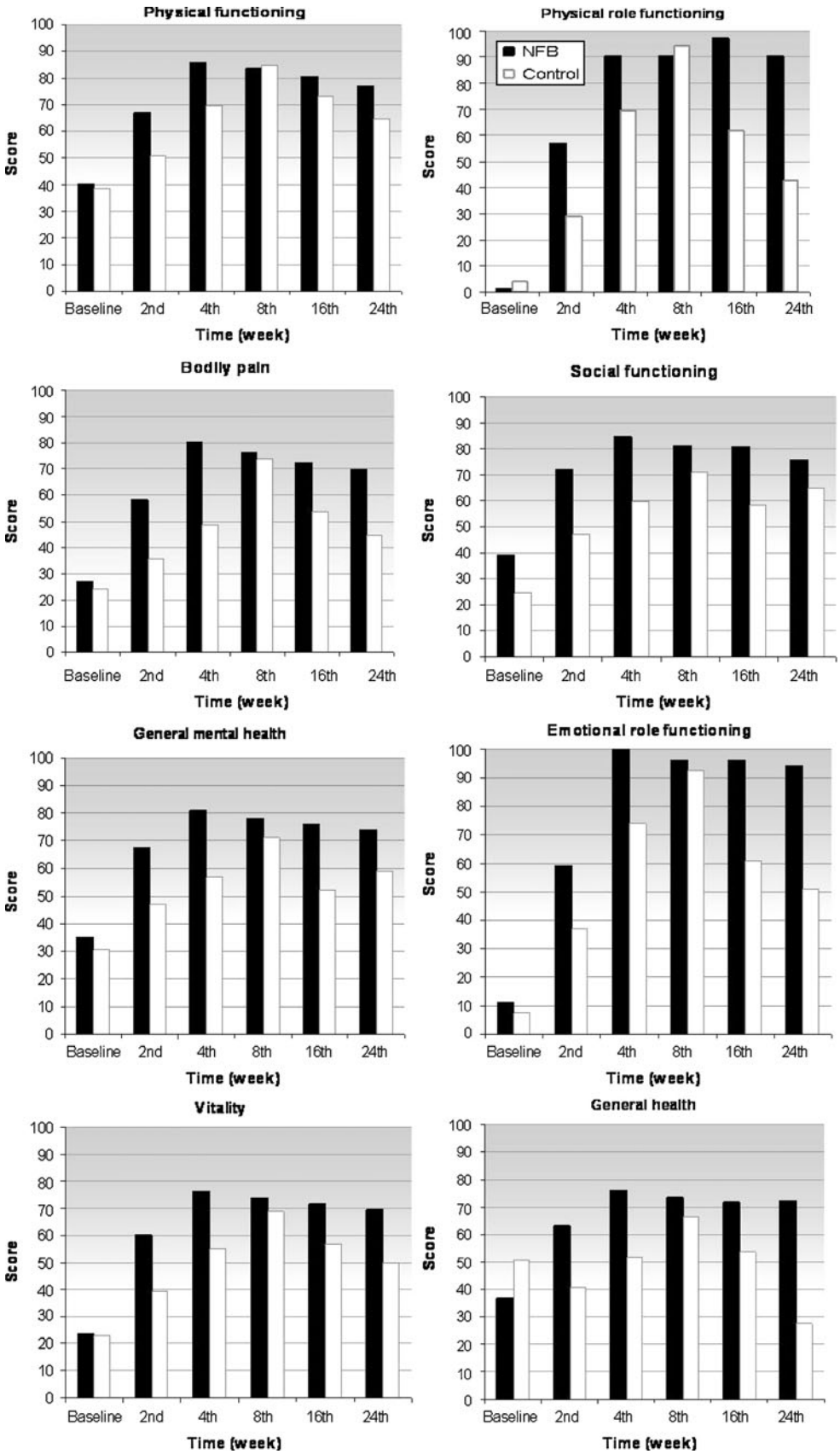


**Fig. 2** SF-36 subscale scores in the NFB and control groups

**Table 4** Mean amplitudes of rhythms in the NFB group

| Delta (μV) | Mean | SE | p* | SMR (μV) | Mean | SE | p* |
|---|---|---|---|---|---|---|---|
| Baseline | 22.37 | 2.575 | 0.133 | Baseline | 6.18 | 0.460 | 0.186 |
| 2nd week | 28.26 | 3.471 | | 2nd week | 6.96 | 0.511 | |
| 4th week | 22.82 | 1.390 | | 4th week | 6.43 | 0.376 | |
| 8th week | 25.87 | 2.362 | | 8th week | 6.52 | 0.436 | |
| 16th week | 29.67 | 3.616 | | 16th week | 6.79 | 0.462 | |
| 24th week | 23.47 | 2.574 | | 24th week | 6.53 | 0.412 | |
| Theta (μV) | Mean | SE | p* | Beta (μV) | Mean | SE | p* |
| Baseline | 14.25 | 0.878 | 0.114 | Baseline | 7.11 | 0.360 | 0.186 |
| 2nd week | 14.92 | 1.007 | | 2nd week | 7.93 | 0.563 | |
| 4th week | 12.89 | 0.598 | | 4th week | 7.80 | 0.516 | |
| 8th week | 14.15 | 0.880 | | 8th week | 7.84 | 0.555 | |
| 16th week | 15.50 | 1.089 | | 16th week | 8.54 | 0.597 | |
| 24th week | 14.60 | 0.979 | | 24th week | 7.58 | 0.575 | |
| Alpha (μV) | Mean | SE | p* | Beta2 (μV) | Mean | SE | p* |
| Baseline | 12.65 | 1.444 | 0.304 | Baseline | 9.03 | 0.562 | 0.354 |
| 2nd week | 12.59 | 1.729 | | 2nd week | 9.53 | 0.567 | |
| 4th week | 12.00 | 1.425 | | 4th week | 8.96 | 0.627 | |
| 8th week | 11.81 | 1.214 | | 8th week | 9.08 | 0.597 | |
| 16th week | 12.31 | 1.447 | | 16th week | 9.97 | 0.754 | |
| 24th week | 11.37 | 1.277 | | 24th week | 8.74 | 0.535 | |

* Friedman

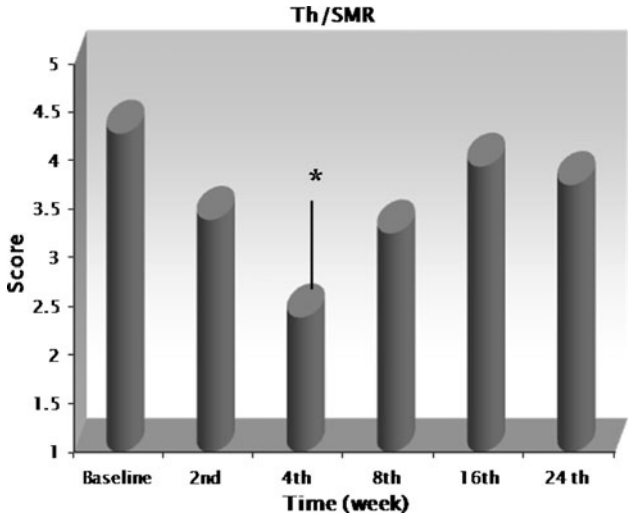


**Fig. 3** Theta/SMR ratios in the NFB group (* Wilcoxon sign test: baseline-4th week: $p < 0.05$)

at many levels of the central nervous system opens the door to interventions that might affect pain at the cortical level, including treatments such as NFB (Jensen et al. 2008). In the literature, there are very limited studies regarding treatment of chronic pain with NFB. Early clinical data suggest that some NF training protocols lead to reductions in chronic pain (Jensen et al. 2007; Othmer and Othmer 2006).

NFB-SMR training appears to facilitate thalamic inhibitory mechanisms (Sterman 2000). It could re-organize the intrinsic pathways that are involved in amplified perception of pain in FMS patients. ERP studies also supported this hypothesis by revealing that SMR training increases the amplitude and elongates the latency of P300 and therefore facilitates thalamocortical inhibitory mechanisms (Egner and Gruzelier 2001). Facilitation of the inhibitory mechanisms may be playing a positive role on central regulation of pain and alter central augmentation. This was the theoretical basis for using SMR training as a new therapeutic approach in the treatment of patients with FMS in our study.

We used VAS- pain and VAS- fatigue scores to follow up the pain and fatigue levels of the patients. Both scores were decreased significantly at the end of the study period in the NFB and control groups. However, the values of the NFB group comparing to control group were significantly lower in all post-treatment assessments, even at the end of 24th week. We postulated that the efficient and long lasting reduction in pain and fatigue in the patients with FMS might be related to the positive effects of NFB training in the facilitation of thalamocortical inhibitory mechanisms (Sterman 2000).

In previous studies, nearly half of the FMS patients were shown to have an associated psychiatric illness, mostly depression and anxiety (Uveges et al. 1990; Suhr 1999; Ahles et al. 1991; Yunus et al. 1991). Our patients were also evaluated in our psychiatry department with SCID-I for possible associated depression. In accordance with previous reported rates, approximately half of our patients were detected to have depressive symptoms. Previous clinical trials have already showed the therapeutic efficacy of NFB in a wide range of psychiatric disorders including depression and anxiety (Reiner 2008; Monastra et al. 2002; Wenck et al. 1996; Rice et al. 1993; Kop et al. 2005). The data derived from our post-treatment assessments also revealed that NFB and SSRI treatments resulted in significant improvements in depressive symptoms and anxiety. As in VAS- pain and VAS- fatigue scores, the values were significantly lower in the NFB group in all post-treatment measures. These findings underline the positive effects of the NFB treatment on psychological aspects, in addition to other symptomatology of FMS. But as the control group has significantly higher scores on depression and anxiety at baseline compared to NFB group, this can be regarded as a limitation of the relevant results.

SF-36 is a widely used scale to determine the impacts of several rheumatologic diseases, including FMS, on patients' social and physical health (Da Costa et al. 2000; Strombeck et al. 2000). Besides, EULAR study group offered the usage of FIQ in detecting the effects of FMS on

quality of life (Carville et al. 2008; Hidalgo et al. 2007; Matsutani et al. 2007; Babu et al. 2007). In a previous uncontrolled clinical trial, Mueller et al. reported that EEG-driven NFB therapy caused significant improvements in FIQ scores of FMS patients (Mueller et al. 2001). We applied FIQ and SF-36 to the patients in every assessment. Similar to all other scales, FIQ and SF-36 revealed significant improvements in both of the groups. Regarding these assessments, the values of the NFB group were significantly better than that of the control group during the study.

A significant decrease in theta/SMR ratio was observed at the end of the treatment compared to the baseline. SMR normally associates a quiet body and active mind. It is often depressed in anxiety, panic, chronic pain, migraine, attention deficit disorders, mood disorders, and other stress related disorders (Egner et al. 2004; Reiner 2008; Monastra et al. 2002; Wenck et al. 1996; Rice et al. 1993; Siniatchkin et al. 2000). Therefore, the detected decrease in theta/SMR ratio in our study is important and may show a concrete finding concerning the NFB treatment.

The therapeutic efficacy of NFB treatment was found to begin at 2nd week and reached to a maximum effect at 4th week. On the other hand, the improvements in SSRI treatment were also detected to begin at 2nd week but reached to a maximum effect at 8th week. This early effect of the NFB application may be related to a faster brain plasticity process and certainly can be considered as one of the advantages of this treatment.

The major limitation of this study is the small number of patients included which can interfere with the results of the statistical analysis. Considering the multiple measurements with a number of subscales over multiple periods in this present study, similar investigations with larger patient population are needed to clarify this limitation. Another missing point of this study is lack of any process which can lead to explain the mechanism of NFB intervention for FMS. We can only expect that SMR training ameliorates CNS dysinhibition when considering the studies showing patients with FMS have reduced P300 amplitudes, and SMR training increases the amplitudes of P300. Nevertheless, this study reveals that NFB application might be beneficial in pain, fatigue, depression, anxiety and impaired quality of life in patients with FMS. Our data suggest that the NFB application might be a novel therapeutic modality in FMS. Further studies are needed with quantitative EEG, ERP, or functional MRI to further investigate the effects of NFB on brain plasticity and determine the exact mechanisms.

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