Steps Toward Developing an EEG Biofeedback Treatment for Chronic Pain

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Abstract Chronic pain, usually refractory to analgesics, is a significant problem for many individuals with spinal cord injury (SCI). Preliminary studies suggest that electroencephalography (EEG) biofeedback (also known as neurofeedback, NF) has the potential to help patients with otherwise refractory chronic pain. However, there remain many unanswered questions about the effects and mechanisms of this treatment. We studied 13 individuals with SCI and chronic pain with NF. Ten of the 13 individuals completed 4 sessions each of three different neurofeedback protocols assigned in random order for a total of 12 NF sessions. All three protocols had similar immediate effects on pain intensity. In addition, the participants reported modest pre- to post-treatment decreases in worst pain and pain unpleasantness following completion of the 12 NF sessions. These improvements were maintained at 3-month follow-up. The majority of the participants felt they benefited from and were satisfied with the treatment. No significant effects on measures of other outcome domains (sleep quality, pain interference and fatigue) were observed, although there was a non-significant trend for an increase in fatigue. Finally, pre- to post-treatment changes in EEG bandwidth activity, consistent with the training protocols, were observed in θ and α but not β frequencies. The findings provide preliminary support for the potential efficacy of NF for the treatment of SCI-related pain, and suggest that further clinical studies are warranted.

Keywords Spinal cord injury · Chronic pain · Neurofeedback

Introduction

Chronic pain is a significant problem for many individuals with spinal cord injury (SCI) (Ehde et al. 2003; Finnerup et al. 2001; Jensen et al. 2005; Turner et al. 2001). Unfortunately, treatment options for pain in persons with SCI are currently limited mostly to medication management, despite the fact that medications are often inadequate, and can have many negative side effects (Warms et al. 2002).

Neurofeedback (NF), which teaches individuals to gain control over their brain states via electroencephalography (EEG) biofeedback, has shown promise to benefit individuals with chronic pain (Gannon and Sternbach 1971; Jensen et al. 2007a; Jensen et al. 2008; Sime 2004; Stokes and Lappin 2010). For example, Kayiran and colleagues randomized 40 patients with fibromyalgia to receive either (1) twenty sessions of neurofeedback (to reinforce
12–15 Hz activity and suppress θ frequencies at C4) or (2) escitalopram (an SSRI) (Kayiran et al. 2010). They also assessed EEG activity at standard frequency bandwidths (δ, θ, α, SMR [12–15 Hz], β1 [15–20 Hz] and “high β” [22–30 Hz]) throughout treatment. Thirty-six patients completed treatment. While both treatment groups showed significant improvement, the patients who received neurofeedback training improved more on all outcome measures than those who received escitalopram. No significant changes were found in the mean amplitude of any EEG frequency bandwidth, although the investigators noted a significant decrease in the θ/SMR ratio from pre- to post-treatment in the participants who received neurofeedback.

Caro and Winter measured the response of 15 patients with fibromyalgia (FMS) who received a large number (Mean 58; Range 40–98) of NF sessions (reinforcing 12–15 Hz activity and suppressing both θ [4–7 Hz] and high β [22–30 Hz] at Cz) versus 63 patients with FMS who received standard medical care (Caro and Winter 2011). The control patients reported no improvements on any outcome measure, but the patients who received the NF training showed significant decreases in muscle tenderness ratings (by their physicians), and reported large and statistically significant decreases in self-reported pain and fatigue severity.

These findings suggest that NF may have beneficial effects on pain and other outcomes in patients with chronic pain. However, many questions remain about its use. Primary among these questions is which specific EEG bandwidths to target in treatment. We do not know if there is a single protocol that is most likely to have beneficial effects on pain, if the NF protocols should differ as a function of pain condition (e.g., migraine versus fibromyalgia), or if treatment should be tailored to the individual patient based on the results of pre-testing of baseline EEG activity (Hammond 2010). A second question concerns the overall efficacy of neurofeedback treatment. Although research indicates that at least some individuals with chronic pain report benefits from neurofeedback, we do not yet know the overall rate of treatment response. Third, other outcome domains besides pain (as suggested by the IMMPACT consensus group) such as physical functioning, psychological functioning, and sleep quality have not been assessed (Turk et al. 2003). Given that these symptoms, in addition to pain, have been reported to respond to neurofeedback (e.g., Jensen et al. 2007a; Kayiran et al. 2010), it would be useful to know which of these domains may be important to measure in NF trials.

The purpose of this study was to prospectively address these questions for NF treatment of chronic pain in persons with SCI. A group of individuals with SCI and chronic pain were given 4 sessions each of three different neurofeedback protocols assigned in random order via implementation of a Latin Square design. Pain intensity was assessed before and after each NF session, and quantitative EEG (QEEG) and multiple outcomes were assessed before treatment, after each of the 12 treatment sessions, and 3 months following the end of treatment. The study was designed to address the following questions: (1) Were there any differences between three different neurofeedback treatment protocols on their immediate effects on pain intensity?; (2) What percentage of participants demonstrated a clinically meaningful (i.e., 30 % or more reduction) in pain following (a) each session and (b) 12 sessions of neurofeedback training?; (3) What outcome domain(s) demonstrated the largest treatment effects?; (4) What were the effects of the NF treatments on EEG activity?; and (5) Did the effects of treatment on outcome or EEG activity maintain for 3 months after treatment?

Method

Participants

Thirteen participants were recruited and enrolled from a pool of 22 adults with spinal cord injury and chronic pain who had participated in a study examining baseline EEG activity in persons with SCI (Jensen et al. 2013). Ten of these completed all 12 sessions of NF training. Of the three subjects that terminated study participation, one moved out of the area because of a personal issue after completing eight NF sessions, one opted to stop participation after 11 sessions due to the overall perceived ineffectiveness, and one subject stopped participation after four sessions due to medical issues unrelated to the study. Two of the 10 subjects who completed treatment declined to complete the 3-month EEG assessments, but did provide 3-month self-report data. Thus, we have complete (self-report and EEG) pre- and post-treatment data, and self-report 3-month data for all 10 of the participants who completed treatment, and 3-month EEG data for 8 of the participants who completed treatment.

Inclusion criteria for participation in the current study were the same as those in the previous study. Our goal was to recruit participants from the pool until we had complete data for at least 10. Participants (for both studies) needed to be 18 years or older, have a diagnosis of SCI confirmed by a study physician, and be determined as otherwise healthy. Further, participants had to: (1) have incurred SCI at least 12 months prior; (2) be able to read, speak and understand English; (3) experience physical pain on a daily basis; (4) have one reported pain problem worse or more significant than other pain problems (if more than one pain problem present); (5) have onset of most significant pain problem at the time of SCI or thereafter; (6) report that the worst or most significant pain problem was related to SCI (confirmed in physical exam); (7) have had their worst or
most significant pain problem be longer than 6 months in duration; and (8) have an average intensity of worst pain in the preceding week rated as a 4 or higher on a 0–10 numerical rating scale. In the preceding study, potential participants were excluded from participating if they had a history of seizure activity or exhibited non-normative brain activity as detected following review of EEG, reported suicidal or paranoid thoughts, and/or experienced a significant non-penetrating traumatic brain injury, significant brain surgery, penetrating head trauma, and/or exhibited significant skull defects as determined during a physical exam conducted by a physician.

Measures

**Pain Intensity and Unpleasantness**

Three domains of pain intensity were measured using 0–10 numerical rating scales (NRSs; 0 = “No pain sensation”; 10 = “Most intense pain sensation imaginable”). Current pain intensity was assessed just before and just after each neurofeedback session in order to assess the immediate effects of the NF sessions on pain. To assess changes in average daily pain associated with the 12 sessions of NF treatment, participants were called on 4 days in the 7 days before and 4 days in the 7 days after treatment, as well as on 4 days at the 3-month follow-up, and were asked to report the following on each of those days: (1) average pain intensity in the past 24 h; (2) average worst pain intensity in the past 24 h (both using a 0–10 NRS of pain intensity); and (3) average pain unpleasantness in the past 24 h (using a 0–10 NRS, with 0 = “not bad at all” and 10 = “the most intense bad feeling possible for me”). The four ratings for each of these domains were then averaged into composite scores for each pain domain.

**Sleep Quality, Pain Interference, and Fatigue**

Sleep quality was assessed using the 6-item medical outcomes study sleep (MOSS) short form scale (Hays and Stewart 1992). Pain interference was measured using the 6-item Patient Reported Outcomes Measurement Information System (PROMIS) Pain Interference Short Form (PRO-PI-SF; Amtmann et al. 2010). Fatigue was assessed using the 9-item fatigue severity scale (FSS; Krupp et al. 1989). All three of these measures have support for their reliability and validity, and were administered at pre-treatment, post-treatment, and at 3-month follow-up.

**Global Treatment Satisfaction**

At post-treatment, we also asked the study participants to rate: (1) the benefits they received from neurofeedback treatment (on a 1 = “No benefit” to 5 = “Extreme benefit” scale) and comment on the specific benefits they experienced; (2) if they experienced any reduction in pain with treatment (on a 1 = “None” to 5 = “Complete relief” scale), and (3) to rate the overall satisfaction they had with treatment (on a 1 = “Very satisfied” to 7 = “Very dissatisfied” scale).

**QEEG Recording and Analysis**

Electroencephalography data were recorded from each participant at pre-treatment, post-treatment, and 3-month follow-up. In preparation for the recordings, the recording sites were prepped with Nuprep (Weaver and Company, Aurora, CO). An electrode cap with pre-measured sites based on the international 10/20 system of electrode placement system (see below for sites) was fitted to each subject. Each electrode site was filled with Electrogel (Electro-Cap International, Eaton, OH), and prepped to impedance values between each electrode and each ear reference individually, as well as between the ears, to between 3 and 5 Kohms.

The EEG was digitally recorded at 250 samples per second using the WinEEG (Mitsar, St. Petersburg, Russia) acquisition system utilizing 19 electrodes (FP1, FP2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2) referenced to A1 and A2 (linked ear montage) (Jasper 1958). The input signals were amplified (bandpass 0.3–70 Hz) and sampled at 250 Hz. EEG was recorded continuously in the awake state with eyes closed in a dimly illuminated room. During each recording, a trained researcher monitored the EEG and encouraged the subject to stay awake.

Data were then exported into the Eureka software (Sherlin and Congedo 2005), where they were plotted and carefully inspected using manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, and body movements, were removed from the stream of EEG, and the first 2 minutes of artifact free data were used for analysis. Fast-Fourier Transformation was used to compute the power spectral density for relative power bands (δ 2–3.5 Hz, θ 4–7.5 Hz, α 8–12 Hz, and β 13–21 Hz) using a 2-second (500 sample) epoch length and an overlapping window advancement factor of 32 samples.

**Neurofeedback Apparatus and Procedures**

A NeXus-4 amplifier (MindMedia, BV, The Netherlands) was used to measure and amplify the EEG signals, and BioTrace + software (MindMedia, BV, The Netherlands) was used for signal process and providing feedback to the study participants. Participants were provided with four sessions each of three different protocols, in random order.
(using a Latin square design): (1) reinforce $\alpha$ and suppress $\beta$ at T3 and T4 (protocol A); (2) reinforce 10–15 Hz and suppress $\beta$ and $\theta$ at C3–A1 and C4–A2 (protocol B); and (3) reinforce 10–15 Hz and suppress $\beta$ and $\theta$ at P3–A1 and P4–A2 (protocol C).

There is not yet strong empirical evidence for selecting one electrode site over others for NF training for pain management. T3 and T4 have been reported in some clinical case studies as useful and are near the primary sensory cortex (Jensen et al. 2007a; Sime 2004). $C_{3}$ has been used in the two published clinical trials (Caro and Winter 2011; Kayiran et al. 2010). Also, the parietal cortex, which is involved in the integration and processing of sensory stimuli, has been implicated in central sensitization to pain (Seifert et al. 2010). The primary rationale for protocol A came from the research showing associations between the experience of pain and increases in $\beta$ and decreases in $\alpha$ activity (Bromm et al. 1986a, b; Chen 1993; Huber et al. 2006; see also reviews by (Bromm and Lorenz 1998; Chen 1993, 2001), as well as from a case report indicating that training at T3 and T4 was associated with pain relief (Sime 2004). The rationales for increasing the range of bandwidth reinforcement to include SMR frequencies (12–15 Hz), comes from the clinical trials, cited above, demonstrating that patients who receive SMR training report decreases in pain. Additional support for including protocols that suppress $\beta$ (all three protocols) and $\theta$ (protocols B and C) comes from studies showing that individuals with SCI and chronic pain show more $\theta$ and $\beta$ activity than individuals with SCI and healthy controls who do not have pain (Boord et al. 2008; Llinas et al. 2005; Sarnthein et al. 2006). Therefore we selected T3 and T4, C3 and C4, and P3 and P4 as viable training sites for protocols A, B, and C, respectively.

Data Analysis

Demographic data were summarized for continuous and categorical demographic variables. To compare the three different neurofeedback treatment protocols for their immediate effects on pain intensity, we computed pre- to post-session pain intensity change scores, and averaged them across the four sessions. We then performed a one-way analysis of variance (ANOVA) to test for an overall difference in these change scores, with a plan to perform univariate t-tests between each pair of protocols in the event that the omnibus test was significant. We also computed the percentage change in pain intensity associated with each protocol and with the series of 12 sessions, in order to identify the percent of participants who reported clinically meaningful decreases (i.e., 30 % or more) in pain intensity with the neurofeedback training. To identify the outcome domains that demonstrated treatment effects, we performed a series of repeated measures analyses of variance (ANOVAs), with each outcome variable (average pain, average worst pain, pain unpleasantness, sleep quality, pain interference and fatigue) as the dependent variables, and time (pre-treatment, post-treatment, and 3-month follow-up) as the independent variable. We planned to perform univariate t-tests to examine the differences in outcome between each time point if a significant time effect emerged in these analyses. Similarly, in order to determine if there were any changes in EEG activity with NF treatment, and if these maintained for 3 months following treatment, we performed ANOVAs, with the relative activity of $\delta$, $\theta$, $\alpha$, and $\beta$ as the as the dependent variables, and time (pre-treatment, post-treatment, and 3-month follow-up) as the independent variable. As with the outcome variables, we planned to perform univariate t-tests to examine the differences in outcome between each time point if a significant time effect emerged in these analyses. Finally, we examined the responses to the post-treatment global ratings of treatment benefits, pain reduction, and satisfaction.

Results

Participant Recruitment and Flow

Of the 10 participants who received all 12 sessions of neurofeedback training, seven (70 %) were males. Eight (80 %) reported they were White, and one each self-identified as African American and Native Hawaiian or other Pacific Islander. The average age of the participants was 46.1 years (SD = 12.6 years, range = 22–66 years). They reported an average of 12.3 years (SD = 9.0 years, range = 1.6–25.2 years) since the date of their spinal cord injury. During initial medical evaluation, the primary pain problems were classified as one of six types (SCI pain, transition zone pain, radicular pain, visceral pain, mechanical spine pain, and overuse pain; Cardenas et al. 2002). The worst or most significant pain problem for eight (80 %) participants was either SCI pain or transition zone pain (i.e., neuropathic pain), whereas the worst or most significant pain problem of two (20 %) participants was mechanical spine pain (i.e., nociceptive pain).

Immediate Effects of Neurofeedback Training on Pain Intensity

The average pre- to post-session changes in pain intensity for the 10 study completers were 0.48 (SD = 0.31), 0.40 (SD = 0.66), and 0.45 (SD = 0.93) for protocols A, B, and C, respectively. Thus, the immediate impact of four sessions of the three treatment protocols on pain intensity were almost identical, with no statistically significant
differences between them ($F(2,8) = 0.05, p = .950$). The average pre- to post-session decrease was modest and less than clinically meaningful (>30% reduction) for most participants. No participant reported a clinically meaningful decrease in pain with protocol A. One reported a decrease (of 40%) with protocol B, and a different participant reported a decrease (of 43%) with protocol C.

Treatment-Related Changes in Pain Intensity and Unpleasantness

Average pre-treatment, post-treatment, and 3-month follow-up pain intensity and unpleasantness scores for the 10 study completers are presented in Table 1. As can be seen, there were pre- to post-treatment decreases in all three pain measures, although only the changes in worst pain intensity and pain unpleasantness were statistically significant. The improvements reported in worst pain intensity and pain unpleasantness maintained through the three month follow-up. However, although the majority (70%) of the participants reported some pre- to post-treatment improvements in average pain intensity, only one reported a clinically meaningful improvement (>30% decrease).

Treatment-Related Changes in Sleep Quality, Pain Interference, and Fatigue

No significant changes were noted in any of the secondary outcome measures assessing sleep quality, pain interference, or fatigue (see Table 1). There was a non-significant trend ($p = .053$) of an increase in fatigue from pre- to post-treatment that continued through the 3-month follow-up.

Treatment-Related Changes in EEG Activity

The results of the analyses examining effects of the NF treatment protocols on EEG activity showed significant effects over time for $\theta$ and $\alpha$ (see Table 2). As would be expected given the training protocols, a significant pre- to post-treatment decrease in $\theta$, and pre- to post-treatment increase in $\alpha$ activity occurred. However, activities in these bandwidths changed in the direction of baseline levels from post-treatment, and were no longer statistically significantly different from baseline levels at 3 months. Moreover, although a decrease in $\beta$ activity was targeted in all three of the NF protocols, no significant changes in $\beta$ activity from baseline were observed.

Global Ratings of Treatment Benefit and Satisfaction

Only 2 of the 10 study participants reported they experienced no treatment benefits. Three (30%) reported a little benefit, 2 (20%) some benefit, and 3 (30%) reported a lot or extreme benefit. Similarly, only 2 (20%) subjects reported they experienced no pain reduction. Three (30%) reported that they experienced “a little” pain reduction, and 5 (50%) reported that they experienced “some” (40%) or “a lot” (10%) of pain reduction. In terms of treatment satisfaction, none of the subjects reported that they were dissatisfied at any level. Three (30%) subjects reported that they were “Neither satisfied nor dissatisfied”. Two (20%) were “Slightly satisfied”, four (40%) were “Somewhat satisfied,” and one (10%) was “Very satisfied”. In addition to pain benefits, participants felt the procedures improved their relaxation skills and their concentration.

Discussion

The primary findings from this study suggest that 12 sessions of NF for SCI-related pain management focusing on decreasing $\beta$ and $\theta$ and increasing $\alpha$ activity was associated with a small (i.e., not necessarily clinically meaningful) but

### Table 1  Means and standard deviations of outcome measures assessed pre-treatment, post-treatment, and at 3-month follow-up

<table>
<thead>
<tr>
<th>Outcome domain (measure)</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>3-month follow-up</th>
<th>$F(2,8)$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pain intensity (NRS-11)</td>
<td>$5.95_{a}$ (1.70)</td>
<td>$5.36_{a}$ (1.67)</td>
<td>$5.65_{a}$ (1.90)</td>
<td>1.45</td>
<td>0.290</td>
</tr>
<tr>
<td>Worst pain intensity (NRS-11)</td>
<td>$7.54_{a}$ (1.88)</td>
<td>$6.75_b$ (1.72)</td>
<td>$6.95_b$ (2.00)</td>
<td>7.82</td>
<td>0.013</td>
</tr>
<tr>
<td>Pain unpleasantness (NRS-11)</td>
<td>$6.76_{a}$ (2.15)</td>
<td>$5.80_b$ (1.86)</td>
<td>$5.93_b$ (1.95)</td>
<td>5.98</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep problems (MOS)</td>
<td>$33.33_{a}$ (21.72)</td>
<td>$25.33_{a}$ (19.19)</td>
<td>$34.00_{a}$ (17.69)</td>
<td>2.20</td>
<td>0.174</td>
</tr>
<tr>
<td>Pain Interference (PROMIS)</td>
<td>$60.51_{a}$ (8.05)</td>
<td>$59.38_{a}$ (8.16)</td>
<td>$61.05_{a}$ (5.36)</td>
<td>0.22</td>
<td>0.802</td>
</tr>
<tr>
<td>Fatigue (FSS)</td>
<td>$3.62_{a}$ (1.61)</td>
<td>$4.11_{a}$ (1.71)</td>
<td>$4.54_{a}$ (1.04)</td>
<td>4.34</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Means with different subscripts are significantly ($p < .05$) different from one another

NRS-11 = 0–10 numerical rating scale of pain intensity, MOS medical outcomes study sleep problem index, PROMIS patient reported outcomes measurement information system pain interference scale, FSS fatigue severity scale.
Table 2 Means and standard deviations of relative bandwidth activity assessed pre-treatment, post-treatment, and at 3-month follow-up

<table>
<thead>
<tr>
<th>Bandwidth</th>
<th>Pre-treatment mean (SD)</th>
<th>Post-treatment mean (SD)</th>
<th>3-month follow-up mean (SD)</th>
<th>F (2,8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ (2–3.5 Hz)</td>
<td>3.24ₐ (1.25)</td>
<td>2.81ₐ (1.07)</td>
<td>3.18ₐ (1.08)</td>
<td>1.78</td>
<td>0.247</td>
</tr>
<tr>
<td>θ (4–7.5 Hz)</td>
<td>3.88ₐ (1.81)</td>
<td>3.27ₐ (1.73)</td>
<td>3.59ab (1.63)</td>
<td>16.30</td>
<td>0.004</td>
</tr>
<tr>
<td>α (8–12 Hz)</td>
<td>2.88ₐ (0.92)</td>
<td>3.48ₐ (1.00)</td>
<td>3.02ₐ (1.05)</td>
<td>20.53</td>
<td>0.002</td>
</tr>
<tr>
<td>β (13–21 Hz)</td>
<td>0.60ₐ (0.28)</td>
<td>0.60ₐ (0.28)</td>
<td>0.64ₐ (0.25)</td>
<td>0.46</td>
<td>0.655</td>
</tr>
</tbody>
</table>

Means with different subscripts are significantly (p < .05) different from one another

The current study has a number of important limitations that should be considered when interpreting its results. First, it was a case series and not a controlled trial. Thus, the improvements in the pain measures and the changes in EEG activity patterns observed could potentially be due to factors other than the treatment given, such as regression to the mean or random variation. A second limitation of the current study is that the 10 participants who completed the study received only 12 sessions of NF training. Some previously published NF protocols use 12 or fewer sessions (e.g., Raymond et al. 2005; Ros et al. 2009), but more than 12 sessions are more common in NF clinical studies (Bakhshayesh et al. 2011; Caro and Winter 2011; Gevensleben et al. 2009; Kayiran et al. 2010; Sime 2004). Thus, it is possible that larger effects might have been observed in the outcome measures had the participants been given more than 12 treatment sessions.

As suggested previously, it is also possible that had the subjects completed 12 sessions of a single protocol (rather than four sessions each of three different protocols), larger treatment effects would have emerged and they might have
lasted longer. The fact that treatment effects emerged at all given both (1) the relatively low dose of treatment and (2) the highly refractory nature of SCI-related pain, is promising. Research is needed to determine the number of NF treatment sessions that provide the greatest benefits for the most number of patients, as well as to determine whether the number of sessions provided has an impact on long-term maintenance of treatment gains.

Despite the limitations of the current study, the findings suggest that some individuals with refractory chronic pain associated with spinal cord injury may benefit from NF training. Although the benefits found following 12 sessions of training were small, the majority of the participants were highly satisfied with the intervention. Additional treatment development research is warranted to determine (1) if the effects found are specific (i.e., are greater than those that would be observed in patients who received control treatments); (2) if increasing the number of treatment sessions improves either or both short- and long-term outcomes; and (3) whether the type of NF protocol used [e.g., SMR training—as has been used to treat patients with fibromyalgia (Kayiran et al. 2010)—versus the protocols used in the current study] has an influence on outcome.

Acknowledgments This research was supported by a research grant from the Craig H. Neilsen foundation.

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Jensen, M. P., Hakimian, S., Sherlin, L. H., & Fregni, F. (2008). New observations on the impact of training—as has been used to treat patients with fibromyalgia (Kayiran et al. 2010)—versus the protocols used in the current study] has an influence on outcome.


