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Seminowicz, David A.; de Martino, Enrico; Schabrun, Siobhan M.; Graven-Nielsen, Thomas

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Left DLPFC rTMS Reduces the Development of Long-Term Muscle Pain

David A. Seminowicz[1,2], Enrico de Martino[3], Siobhan M. Schabrun[4], Thomas Graven-Nielsen[3]

[1] Department of Neural and Pain Sciences, University of Maryland School of Dentistry, Baltimore, MD, 21201

[2] Center to Advance Chronic Pain Research, University of Maryland Baltimore, Baltimore, MD, 21201

[3] Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, The Faculty of Medicine, Aalborg University.

[4] Brain Rehabilitation and Neuroplasticity Unit (BRAiN-u), Western Sydney University, School of Science and Heath, Sydney, Australia

Please address correspondences to:
David A. Seminowicz, PhD
Department of Neural & Pain Sciences
University of Maryland School of Dentistry
650 W. Baltimore Street, 8 South
Baltimore, MD 21201
ph. 410.706.3476
dseminowicz@umaryland.edu

Abstract

The left dorsolateral prefrontal cortex (DLPFC) is involved in the experience and modulation of pain, and may be an important node linking pain and cognition. Repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC can reduce chronic and experimental pain. However, whether left DLPFC rTMS can influence the development of chronic pain is unknown. Using repeated intramuscular injection of nerve growth factor (NGF) to induce the development of sustained muscle pain (lasting weeks), thirty healthy individuals were randomized to receive 5 consecutive daily treatments of active or sham left DLPFC rTMS, starting before the first NGF injection on day 0. Muscle soreness and pain severity were collected daily for 14 days and disability on every alternate day. Before the first and one day after the last rTMS session, anxiety, depression, affect, pain catastrophizing and cognitive performance on the attention network test were assessed. Left DLPFC rTMS treatment compared to sham was associated with reduced muscle soreness, pain intensity, and painful area ($p<0.05$), and a similar trend was observed for disability. These effects were most evident during the days rTMS was applied lasting up to three days following intervention. Depression, anxiety, pain catastrophizing, and affect were unchanged. There was a trend toward improved cognitive function with rTMS compared to sham ($p=0.057$). These data indicate that repeated left DLPFC rTMS reduces the pain severity in a model of prolonged muscle pain. The findings may have implications for the development of sustained pain in clinical populations.

Keywords: pain; repetitive transcranial magnetic stimulation; nerve growth factor; brain stimulation; transition

Summary

Repetitive transcranial magnetic stimulation (rTMS) of left dorsolateral prefrontal cortex (DLPFC), compared to sham stimulation, reduces pain development in a long-lasting model of muscle pain.

Introduction

Musculoskeletal pain disorders are the largest contributors to global years lived with disability [23]. Consequently, effective and affordable strategies are urgently required to deal with this rising problem.

Our previous work has demonstrated disruption of brain cognitive networks with acute pain and with chronic pain [12;13;31;35;37;38] and we further proposed a role for cognitive network dysfunction in chronic pain disorders and possible treatments [34]. The dorsolateral prefrontal cortex (DLPFC) – particularly the left DLPFC – has been implicated in pain experience and modulation, and could be a major node mediating the interaction between pain and cognition [36]. For example, patients have shown altered abnormal cognitive-related activity in the left DLPFC when performing conflict tasks such as the attention network test [31;38]. This suggests that targeting DLPFC function could have effects on both pain and cognitive function, as well as their interaction.

Repetitive transcranial magnetic stimulation (rTMS) of the left DLPFC has been used with some success for the treatment of chronic pain conditions including migraine [11], burning mouth syndrome [47], post traumatic headache [27], post-operative pain [8;9], and fibromyalgia where analgesic effects were similar to those of FDA approved pharmaceuticals with fewer side-effects [30]. Left DLPFC rTMS has an immediate analgesic effect for prolonged capsaicin-induced pain in healthy subjects and the

mechanisms of action appear to depend on widespread cortical network effects and activation of the endogenous opioid system [45;46]. Left DLPFC rTMS also modulates dopaminergic [14] and serotonergic systems [39], which could also potentially modulate pain. Right DLPFC rTMS analgesia does not involve an endogenous opioid mechanism [17] and might be related to glutamatergic modulation [16]. Left – but not right – DLPFC rTMS reduced bilateral capsaicin pain intensity when delivered 10-20 min after capsaicin application and the analgesic effects was found after 20-30 min [10;45;46]. In line with this finding, left DLPFC rTMS increased heat pain thresholds and reduced heat hyperalgesia by capsaicin, but had no effect on cold pain thresholds [46]. Left DLPFC rTMS has also been shown to reverse motor cortex inhibition during capsaicin-induced pain in healthy participants [22]. However, the mechanisms of rTMS for pain are still the subject of considerable debate [20], in particular regarding the timing of rTMS with respect to the nociceptive event, type of pain, and duration of the analgesic effect.

Pain models have been used to study the effects of pain lasting minutes to hours (e.g. topical capsaicin) in healthy participants. However, to understand the development of sustained muscle pain, longer-lasting prolonged pain models are needed. Intramuscular injections of nerve growth factor (NGF) induces deep-tissue pain and hyperalgesia for days to weeks [1;4;44] with motor cortical adaptations [25;33].

In the present study, we randomized healthy subjects to receive left DLPFC rTMS over five days or sham rTMS to test whether rTMS could reduce pain intensity and distribution, as well as improve cognitive task performance, in a long-lasting (up to fourteen days) model of NGF-induced muscle pain. We hypothesized that left DLPFC rTMS would reduce prolonged muscle pain and improve performance on a cognitive task, relative to sham.

Materials and Methods

Participants

Thirty healthy right-handed subjects (18 female; 12 male) participated in this randomized controlled study, recruited through online advertising and flyers posted at Aalborg University. All participants were naïve to single pulse and repetitive TMS prior to enrolment, and had no history of chronic pain, neurological disorders and psychiatric disorders. Fifteen participants (9 females for each group) were randomly assigned to each of the active or sham rTMS groups. Inclusion criteria: healthy men and women aged 21-50 years; speak and understand English. Exclusion criteria: pregnancy; drug addiction defined as the use of cannabis, opioids or other drugs; previous neurologic, musculoskeletal or mental illnesses; lack of ability to cooperate; history of chronic pain or current acute pain; previous experience with rTMS; contraindications to rTMS application (history of epilepsy, metal in the head or jaw etc.); failure to pass the Transcranial Magnetic Stimulation Adult Safety Screen (TASS) (Rossi et al., 2011). Before starting experimental procedures a physical examination was performed to check the presence of full pain free range of elbow and wrist motion, and the absence of tenderness to palpation of the soft tissues in the extensor muscles of the wrist. The study was approved by the local Ethics Committee (N-20170041) and was performed in accordance with the Helsinki Declaration. Written informed consent was obtained prior to study commencement.

Study protocol

The study involved 6 sessions on 6 consecutive days (day 0 to day 5), plus online daily diaries completed up to day 14. Randomization occurred on day 0 before any assessments. Randomization was based on a predetermined, randomly generated order. Questionnaires were collected at the beginning of the

sessions on days 0 and 5. Other data collected as part of the protocol that will be reported elsewhere include motor evoked potentials, somatosensory evoked potentials, electroencephalography during cognitive task performance, quantitative sensory and motor assessment (pressure pain thresholds and wrist extensor force). On day 0 and day 2 participants received an injection of NGF into the right extensor radialis carpi brevis (ECRB) muscle in order to develop muscle pain along the radial site of the right forearm. After assessments at day 0, day 1, day 2, day 3, and day 4 participants received 20 minutes of active or sham high-frequency rTMS on the DLPFC. On day 0 and day 2 the real or sham rTMS occurred prior to the NGF injection.

Questionnaires

At day 0 and day 5, participants completed the following questionnaires: 1) State-Trait Anxiety Inventory (STAI-S, STAI-T)[41]; 2) Pain Catastrophizing Scale (PCS)[42;43]; 3) Beck Depression Inventory (BDI-II)[3]; 4) Positive and Negative Affective Schedule (PANAS)[15;48].

The area of pain was assessed using body chart drawings at days 1-5, 9, and 14 [40]. Participants drew the distribution of their NGF-induced pain on an anatomical drawing of the upper limb. The areas of the body chart drawings were calculated in arbitrary units (a.u.) using a scanning program (VistaMetrix, v.1.38.0; SkillCrest, LLC, Tucson, AZ).

Online diaries regarding muscle soreness and pain severity were completed on days 0 to 14. Muscle soreness was assessed using a modified 7-point Likert scale; 0 = 'a complete absence of soreness', 1 = 'a light soreness in the muscle felt only when touched/vague ache', 2 = 'a moderate soreness felt only when touched/a slight persistent ache', '3 = 'a light muscle soreness when lifting or carrying objects', 4 = 'a light muscle soreness, stiffness or weakness when moving the wrist without gripping an object', 5 = 'a moderate muscle soreness, stiffness or weakness when moving the wrist', 6 = 'a severe muscle soreness,

stiffness or weakness that limits the ability to move'. Pain severity was assessed on an 11-point numerical rating scale (0 = no pain, 10 = most intense pain imaginable). The Patient-rated Tennis Elbow Evaluation Questionnaire (PRTEEQ; [29], used to assess average pain and disability of the injected arm, was completed on days 0, 3, 5, 9, and 14.

Repetitive TMS procedures

Repetitive transcranial magnetic stimulation (rTMS) was delivered using a figure-of-eight shaped coil (70mm Double Air Film Coil; Magstim Super Rapid2 Plus1, Magstim Co. Ltd, Dyfed, UK). The rTMS protocol consisted of one session per day for 5 consecutive days. Each 20-minute stimulation session consisted of 80 trains of 5-second pulses with a frequency of 10 Hz and an interval of 10 seconds between each train, giving a total of 4000 pulses per day [46]. The stimulation intensity was 110% of the resting motor threshold (rMT) of the first dorsal interosseous (FDI) muscle and the coil was located according to the BeamF3 algorithm [2;32]. The BeamF3 algorithm takes as input three scalp measurements: the nasion-inion distance, the left tragus-right tragus distance through the scalp vertex, and the head circumference measured through the FPz-Oz plane in the international 10–20 EEG system. These values were entered into the freely available BeamF3 desktop application (clinicalresearcher.org/software.htm) in order to generate the coordinates to locate the rTMS coil. Sham stimulation was carried out with a sham coil of identical size, color, and shape, emitting a sound similar to that emitted by the active coil (70mm Double Air Film Sham Coil). Procedures and instructions to participants in the rTMS and sham groups were identical. Because the rTMS procedure is known to be painful, pain ratings were acquired at the end of each rTMS/sham session [7], using a 0 to 10 numerical rating scale (NRS) for pain intensity, where 0 was no pain and 10 was most intense pain imaginable.

NGF-induced muscle soreness

Muscle pain and hyperalgesia were induced by repeated injection of NGF into the ECRB muscle, which models lateral epicondylalgia [4]. Sterile solutions of recombinant human Beta-NGF were prepared by the pharmacy (Skanderborg Apotek, Denmark). NGF injections occurred on day 0 and day 2. The site of injection was cleaned with alcohol, and NGF solution (5µg/0.5 mL) was injected into the muscle belly of ECRB, guided in-plane under real-time ultrasound guidance (SonoSite M-Turbo, FUJIFILM SonoSite, Inc. - US).

Cognitive task

Participants performed the Attention Networks Test (ANT) [21] on day 0 and day 5. This task assesses cognitive function in three domains: alerting, orienting, and executive function (conflict resolution). Participants performed the task in six blocks of 5 minute according to the procedure previously reported [21]. Briefly, the task implemented in E-prime (version 3.0) involves the presentation of an arrow and the correct response is the direction of that arrow, indicated by the button on the participant's right-hand middle (right) or index (left) finger. Around the arrow, two arrows can be presented on each side, which can point in the same direction (congruent) or opposite direction (incongruent) of the center target arrow. Additional cues are given prior the target stimuli and are related to alerting in orienting. Reaction times were used as the performance measure in the task. Only the conflict (difference between congruent and incongruent reaction time) was examined, as these measures previously have been reported in the context of acute and chronic pain [31;37;38], where increased brain resources have been shown to be recruited.

Statistical analysis

All data are presented as mean and standard error of the mean (SEM). All data from all assessments were normality tested using visual inspection and the Shapiro-Wilk's test. A mixed-model analysis of variance (ANOVA) was used for all parameters to assess effects of day (days 0 to 14 for muscle soreness and pain intensity, and days 0, 5, 9, and 14 for other measures), group (rTMS, sham), and day-by-group interaction, where the factor day was repeated measures and group was between group comparisons. For procedural NRS pain scores, a one-way repeated-measure ANOVA was used with time as main factor. We further tested the association between procedural pain and muscle soreness and pain intensity the next day using Pearson correlations. Correcting against violations of sphericity, the Greenhouse-Geisser approach was used. Effect sizes (partial eta-squared ($\eta 2p$)) are reported for significant effects. Where appropriate, post-hoc analyses were performed using Bonferroni multiple comparison tests. Statistical significance was set at $P < 0.05$.

Results

Demographics

The sample sizes, sex, age, height, and weight for the sham and active groups are shown in Table 1. Groups were matched for sex (6 male, 9 females in each group). All subjects performed all sessions and no data were missing. Resting motor threshold assessed on days 0 and 5 were (mean ± S.D.) sham, day 0 42.9 ± 10.0, sham day 5 41.7 ± 8.7, active day 0 42.9 ± 11.0, active day 5 43.9 ± 9.6.

Left DLPFC rTMS reduced pain and muscle soreness

Means and standard deviations for all outcomes are reported in Supplementary Table S1 (available athttp://links.lww.com/PAIN/A636). The rTMS group had lower muscle soreness ratings (group main effect: $F_{1,28}$=8.8, p=0.006, η2p=0.24; group-by-time interaction: $F_{4.1,392}$=4.5, p=0.002, η2p=0.14, Fig 1A) and pain intensity NRS ratings (group main effect: $F_{1,28}$=6.3, p=0.018, η2p=0.19; group-by-time interaction: $F_{2.9,392}$=2.5, p=0.068, η2p=0.09, Fig 1B) than the sham group. Post-hoc tests revealed that differences in muscle soreness Likert scores were apparent at 2, 4, 5, 6, and 7 days following the first NGF injection, (p<0.05). Because these Likert score data were non-normally distributed, we also performed Kruskal-Wallis tests and found the same as the parametric tests (i.e. days 2, 4, 5, 6, and 7 were different between groups). The rTMS group also had a similar, but non-significant trend toward reduced disability as assessed by the PRTEEQ, which was apparent by day 5 (group main effect: $F_{1,28}$=2.5, p>0.1, η2p=0.08 ; group-by-time interaction: $F_{1.4,112}$=2.1, p>0.1, η2p=0.07, Fig 1C). Area of pain based on body map drawings was lower in the real rTMS compared to sham group (group main effect: $F_{1,28}$=9.6, p=0.004, η2p=0.26; group-by-time interaction: $F_{3.4,168}$=4.1, p=0.006, η2p=0.13, Fig 1D), and post-hoc tests indicated significant differences at days 3 and 5 (p<0.05).

Left DLPFC rTMS showed a trend towards improved cognitive task performance

The rTMS group had a marginally greater reduction in conflict cost (i.e., improved performance in reaction time) compared to sham at day 5 compared to baseline (group main effect: $F_{1,28}$=1.1, p>0.2, η2p=0.04; group-by-time interaction: $F_{1,28}$=3.9, p=0.057, η2p=0.12). This represented a conflict reaction time cost reduction from 96.5 ± 6.8 ms at baseline to 74.8 ± 4.2 ms at day 5 in the rTMS group, versus a reduction from 97.4 ± 4.9 ms to 89.9 ± 7.1 ms in the sham group. There were no differences between rTMS and sham groups on the alerting (41.7 ± 4.1 ms at baseline to 49.4 ± 5.3 at day 5 for rTMS group versus 34.8 ± 6.3 ms at baseline to 46.1 ± 7.1 at day 5 for sham group; group main effect: $F_{1,28}$=0.5, p>0.5; group-by-time interaction: $F_{1,28}$=0.2, p>0.5) and orienting components of the task (27.3 ± 3.7 ms at baseline to 25.6 ± 4.3 at day 5 for rTMS group versus 33.5 ± 5.8 ms at baseline to 29.2 ± 3.6 at day 5 for sham group; group main effect: $F_{1,28}$=0.9, p>0.3; group-by-time interaction: $F_{1,28}$=0.1, p>0.5).

No effects of left DLPFC rTMS on anxiety, depression, affect, or pain catastrophizing

There was no difference between groups in terms for state anxiety (group main effect: $F_{1,28}$=0.3, p>0.5; group-by-time interaction: $F_{1,28}$=0.3, p>0.5) or trait anxiety (group main effect: $F_{1,28}$=0.05, p>0.5; group-by-time interaction: $F_{1,28}$=0.4, p>0.5), depression (group main effect: $F_{1,28}$=0.4, p>0.5; group-by-time interaction: $F_{1,28}$=0.9, p>0.3), pain catastrophizing (group main effect: $F_{1,28}$=1.2, p>0.2; group-by-time interaction: $F_{1,28}$=0.6, p>0.4), or positive affect (group main effect: $F_{1,28}$=0.003, p>0.5; group-by-time interaction: $F_{1,28}$=1.2, p>0.2) or negative affect (group main effect: $F_{1,28}$=3.0, p>0.1; group-by-time interaction: $F_{1,28}$=0.1, p>0.5) on the PANAS. These characteristics are reported in Table 1.

rTMS procedural pain

The rTMS intensity used in this study was 60.1±2.5. Procedural NRS pain ratings and rTMS intensity correlated (Pearson r= 0.56, p<0.05). Procedural NRS pain ratings steadily decreased across days, from 5.6±0.8 on day 0 to 4.2±0.7, 3.8±0.6, 3.5±0.6, 2.9+0.6 for days 1 through 4, respectively ($F_{1.87,52}$=8.8, p=0.002, η2p=0.40), indicating that pain was reduced over time, consistent with previous reports. Furthermore, Pearson correlations revealed no relevant relationship between lower NGF-pain with higher procedural pain the previous day. The sham procedure was never painful. No side effects were reported and the treatment was well tolerated by all participants.

Discussion

The present results show that 5-days of treatment with left DLPFC high frequency (excitatory) rTMS can reduce the pain intensity, distribution, and muscle soreness associated with long-lasting experimental muscle pain. Moreover, no significant effect on depression, anxiety, pain catastrophizing, or affect scores was found due to rTMS, although a near-significant improvement in cognitive task performance was observed. The NGF-induced muscle pain model is thought to closely reflect the period of acute pain prior to the transition to chronic pain [4;33]. Since pain intensity is a strong predictor of the transition to chronic pain [26], interventions like left DLPFC rTMS that reduce pain during the early periods of development have the potential clinical application of preventing the persistent pain following injury or surgery.

Effects of DLPFC rTMS on pain

The mechanisms by which left DLPFC rTMS produce analgesia are yet unclear, but growing evidence points to the left DLPFC as an important region in pain experience and modulation [36]. While one study has shown that left DLPFC rTMS reduces post-operative pain, the stimulation was carried out following surgery [8]. It has yet to be tested whether rTMS prior to surgery can prevent the development of acute and chronic pain. Left DLPFC rTMS has shown promise for a number of chronic pain conditions, including migraine [11], post-traumatic headache [27], fibromyalgia [30], and burning mouth syndrome [47], although for central post-stroke pain it has been shown to be ineffective [18]. Left DLPFC rTMS could thus be an effective treatment for pain or pain prevention. In the current study, effects of rTMS were strongest on the later days of intervention and three days afterward (i.e. days 2-7), whereas minimal differences between active and sham groups were seen late (i.e. days 8-14). Further studies employing DLPFC rTMS are required to determine if a longer intervention period would have longer-lasting effects. One mechanism of left DLPFC rTMS analgesia could be activation of the descending modulatory endogenous opioidergic system [45;46], although the involvement of glutamatergic, dopaminergic, and serotonergic systems is also plausible [14;16;39].

High frequency rTMS of the left DLPFC is an effective treatment for major depressive disorder [24]. The effects on mood present another means by which left DLPFC rTMS could have analgesic effects [5;6;27;49]. We found no effect of left DLPFC rTMS on positive or negative affect, anxiety, or depression, which could have been a result of either the low scores on these questionnaires given the healthy participants involved, or the shorter period of intervention compared to typical clinical protocols for depression (weeks).

Effects of DLPFC rTMS on cognitive function

Another possibility is that the analgesic effects derived from left DLPFC rTMS occur through modulation of cognitive function [34;36]. Previous work has shown the left DLPFC stimulation can modulate cognitive function. For example, a recent study reported that transcranial direct current stimulation (tDCS) over the left DLPFC improved performance on a working memory task, which was also associated with a reduction in simultaneous pain evoked with an electrical stimulus [19]. Improved performance on a Stroop task was also reported following 7 days of high frequency left DLPFC rTMS [28]. We therefore assessed cognitive function on a similar cognitive task involving cognitive conflict and found that left DLPFC rTMS was associated with an improvement in cognitive task performance compared to sham, although this effect failed to reach statistical significance, possibly because the stimulation was not repeated for enough days or the sample size was too small. Previous work has shown that in chronic pain conditions, cognitive-related activation of the left DLPFC is increased relative to healthy controls [31;38] and following treatment, activation and connectivity of the left DLPFC normalizes [13;38]. While the relationship between left DLPFC function and pain is unclear, more extensive follow-up studies on the interaction between DLPFC stimulation, cognitive function, and pain are warranted.

Limitations

There were some notable limitations to the study. First, while our sample size was greater than in previous studies on left DLPFC for acute [46] or chronic [47] pain, it was fairly small. While the main outcomes of the study were significant, others, such as the disability and cognitive function, showed a non-significant trend. These effects are likely to reach significance with a slightly larger sample. Second, as has been reported previously, DLPFC rTMS is painful and decreases over sessions [7]. We observed

similar procedural pain intensity and decrease in procedural pain over time as previously reported [7;47]. This reduction over time has been interpreted as an analgesic effect of the rTMS, rather than habituation to the stimulation over time because the sham procedural pain evoked with electrical stimulation below the sham coil in that study did not show a change over time [7]. In addition, because our measures of pain related to the NGF were acquired a day after intervention, it seems unlikely that differences between sham and rTMS would be related to procedural pain. Another possible limitation is that the stimulation we used was at 110% of the baseline rMT, rather than re-acquiring rMT at each session. This is similar to other protocols[28]. While rMT is likely to change with the NGF model, whether this affects DLPFC response is unknown. A final limitation is that the study was single blind: while participants did not know whether they received real or sham rTMS, the experimenter involved in data collection was not blinded.

Conclusion

Five days of left DLPFC rTMS reduced the development of ongoing pain induced by an NGF-induced muscle pain model compared with the sham rTMS. These changes lasted at least three days after the intervention period and occurred in the absence of changes in mood, affect, anxiety, or pain catastrophizing. A trend of improved cognitive performance was also seen in active compared to sham rTMS. Overall this study provides early evidence for the use of left DLPFC rTMS for preventing the development of pain shortly after tissue trauma.

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Figure legend

Figure 1. Mean (± SEM, N = 15) Likert scores of muscle soreness (A), pain intensity NRS scores (B), PRTEEQ (Patient-rated Tennis Elbow Evaluation Questionnaire) scores (C), and pain area (body map) (D) following NGF injections on day-0 and day-2 in groups receiving active and sham rTMS. Note that rTMS occurred on days 0, 1, 2, 3, and 4. * Significant Bonferroni-corrected post-hoc tests for analyses with significant group-by-time interactions ($P<0.05$). Ŧ Significant main effect of group.

Table 1. Participant characteristics.

	Active rTMS group		Sham rTMS group	
Sample size	15		15	
Sex (M, F)	6, 9		6, 9	
Age (years)	26.9 ± 1.0		26 ± 1.4	
Height (cm)	170 ± 2.2		172 ± 2.9	
Weight (kg)	69 ± 3.5		75 ± 4.7	
	Day 0	Day 5	Day 0	Day 5
Depression (BDI-II)	5.7 ± 1.6	5.1 ± 1.4	7.2 ± 2.3	7.4 ± 2.6
State Anxiety (STAI-S)	42.0 ± 1.4	41.3 ± 1.6	40.5 ± 1.2	40.6 ± 1.6
Trait Anxiety (STAI-T)	47.2 ± 0.8	46.5 ± 1.1	46.5 ± 1.3	46.6 ± 1.0
Pain Catastrophizing Scale	15.8 ± 2.3	12.6 ± 2.5	11.9 ± 2.2	11.6 ± 2.3
PANAS-negative	12.7 ± 0.6	12.2 ± 0.5	11.5 ± 0.5	11.3 ± 0.5
PANAS-positive	28.1 ± 2.2	26.9 ± 2.8	26.1 ± 2.1	28.7 ± 2.5

STAI, state-trait anxiety inventory; PANAS, positive and negative affective schedule. BDI-II, Beck Depression Inventory.