

Randomized Trial

Effects of Stress and Relaxation on Central Pain Modulation in Chronic Whiplash and Fibromyalgia Patients Compared to Healthy Controls

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Background: Compelling evidence has demonstrated that impaired central pain modulation contributes to persistent pain in patients with chronic whiplash associated disorders (WAD) and fibromyalgia (FM). However, there is limited research concerning the influence of stress and relaxation on central pain modulation in patients with chronic WAD and FM.

Objectives: The present study aims to investigate the effects of acute cognitive stress and relaxation on central pain modulation in chronic WAD and FM patients compared to healthy individuals.

Study Design: A randomized crossover design was employed.

Setting: The present study took place at the University of Brussels, the University Hospital Brussels, and the University of Antwerp.

Methods: Fifty-nine participants (16 chronic WAD patients, 21 FM, 22 pain-free controls) were enrolled and subjected to various pain measurements. Temporal summation (TS) of pain and conditioned pain modulation (CPM) were evaluated. Subsequently, participants were randomly allocated to either a group that received progressive relaxation therapy or a group that performed a battery of cognitive tests (= cognitive stressor). Afterwards, all pain measurements were repeated. One week later participant groups were switched.

Results: A significant difference was found between the groups in the change in TS in response to relaxation ($P = 0.008$) and cognitive stress ($P = 0.003$). TS decreased in response to relaxation and cognitive stress in chronic WAD patients and controls. In contrast, TS increased after both interventions in FM patients. CPM efficacy decreased in all 3 groups in response to relaxation ($P = 0.002$) and cognitive stress ($P = 0.001$).

Limitations: The obtained results only apply for a single session of muscle relaxation therapy and cognitive stress, whereby no conclusions can be made for effects on pain perception and modulation of chronic cognitive stress and long-term relaxation therapies.

Conclusions: A single relaxation session as well as cognitive stress may have negative acute effects on pain modulation in patients with FM, while cognitive stress and relaxation did not worsen bottom-up sensitization in chronic WAD patients and healthy persons. However, endogenous pain inhibition, assessed using a CPM paradigm, worsened in chronic WAD and FM patients, as well as in healthy people following both interventions.

Key words: Chronic pain, central sensitization, endogenous pain inhibition, temporal summation of pain, cognitive stressor, relaxation, fibromyalgia, whiplash-associated disorders

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Nowadays, there is compelling evidence for impaired central pain modulation or central sensitization (CS) as the common underlying pathophysiological mechanism of chronic pain in conditions such as chronic whiplash associated disorders (WAD) and fibromyalgia (FM) (1-3). CS is defined as an exaggerated responsiveness of the central nervous system to nociceptive and non-nociceptive stimuli, like pressure, electrical stimuli, temperature, light, and medication (4-8).

Enhanced bottom-up sensitization, being an exaggerated efficient nociceptive transmission, is a possible feature in CS (9,10). To assess the efficacy of this bottom-up sensitization, evaluation of temporal summation (TS), characterized by the increase in pain ratings after repetitive noxious stimulation at a constant intensity, has frequently been performed (11,12). In addition, it has been shown that malfunctioning of descending pain-inhibitory pathways is involved in the CS process (13). This can lead to increased nociceptive transmission to the brain because of the lack of dampening or filtering of the incoming information. The conditioned pain modulation (CPM) paradigm is often used to evaluate the efficacy of endogenous pain inhibition, and relies on the "pain-inhibits-pain" mechanism (12). Enhanced TS of pain (14,15), impaired endogenous pain inhibition (16-19), and inefficient CPM (20,21) have been demonstrated in patients with chronic WAD and FM.

Furthermore, a growing body of research shows abnormalities in stress-regulating systems in chronic pain patients, including WAD and FM (22-24). It has been demonstrated that stress can have a major impact on pain perception (25,26) by either suppressing pain (stress-induced analgesia) or exacerbating it (stress-induced hyperalgesia) (25,27-29). Stress-induced analgesia during exercise is presumed to result from the release of endogenous opioids and growth factors (30,31) and activation of nociceptive inhibitory mechanisms orchestrated by the brain (32,33). Previous research has demonstrated dysfunctional exercise-induced analgesia in chronic WAD and FM patients (17-19).

The exact mechanisms involved in stress-induced hyperalgesia have to be further unravelled (34). To date, it is suggested that neurotransmitters and neuroendocrine alterations play a role in this phenomenon. In addition, alterations in brain pathways mediating excitatory and inhibitory systems likely give rise to stress-induced hyperalgesia (34).

Apart from persistent pain, chronic WAD and FM patients frequently complain of cognitive disturbances,

including concentration and memory problems (35-40). Decreased cognitive function seems to be related to pain severity in patients with chronic WAD and FM (40-42), and is presumed to be a feature of CS (3,5).

Interestingly, an overlap exists in brain regions involved in cognitive function and areas of the pain matrix (e.g., periaqueductal gray, anterior cingulate cortex) (40). However, the influence of cognitive stress on central pain modulation has not yet been clearly described in patients with CS pain.

Inversely, there is conflicting evidence regarding the effects of relaxation therapy on pain ratings (43). There is a lack of research concerning the effects of relaxation on central pain modulation in chronic pain patients. Further it is unclear whether stress and relaxation have similar or different effects on pain modulation in these patients. An example for a non-stressful intervention is the progressive muscle relaxation therapy (PRT) (44).

Possibly, performing cognitive challenging tasks may serve as a stressor for patients already suffering concentration and memory problems, which may further burden the central nervous system leading to enhanced disinhibition and more pain. On the contrary, it is hypothesized that cognitive stress, caused by cognitive tasks, can diminish pain ratings as a result of the so-called "distraction effect," described by Eccleston and Crombez (45).

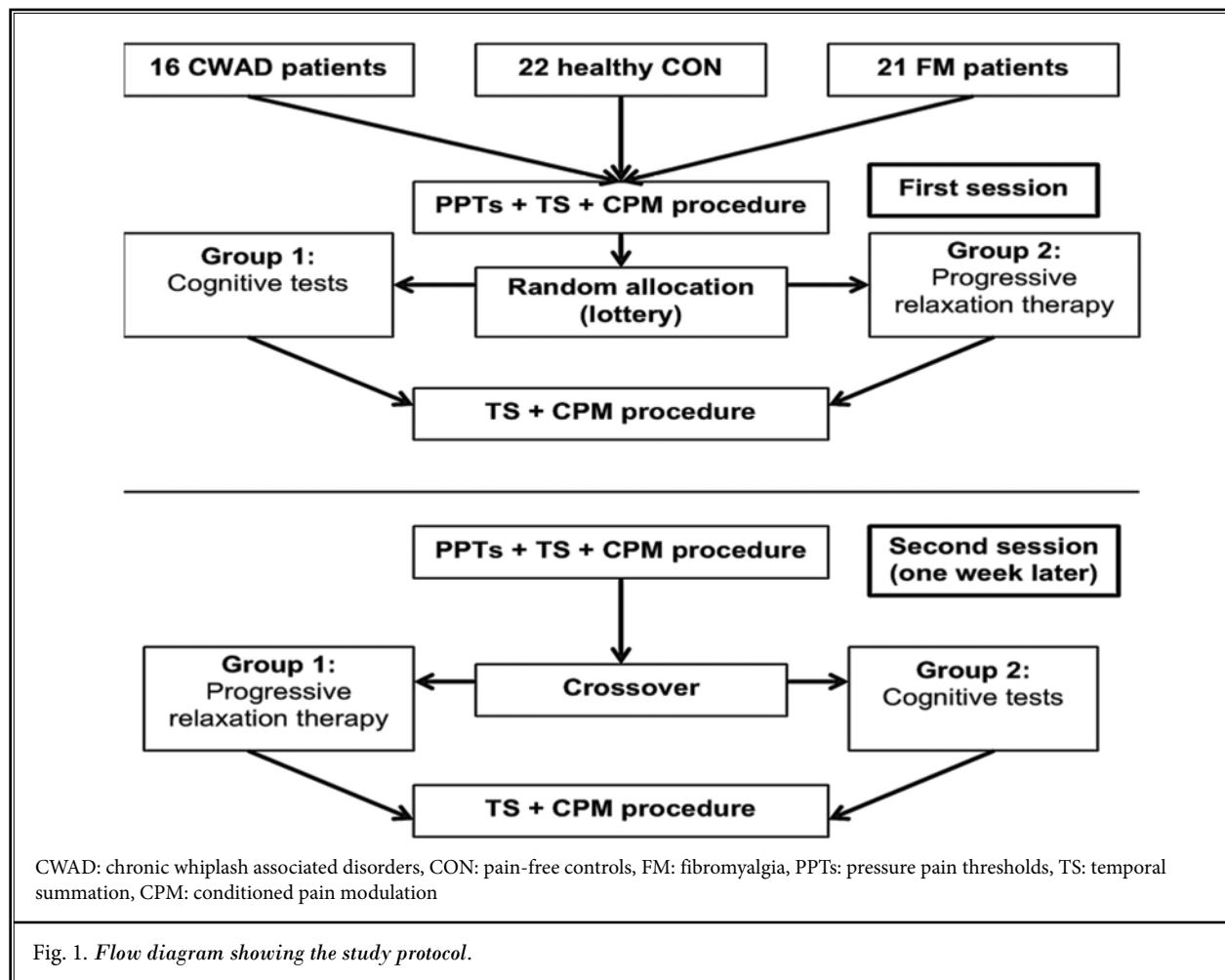
Further, it is hypothesized that muscles are more relaxed after the PRT, leading to temporary pain relief (46). On the contrary, another hypothesis is that the PRT leads to more body awareness, leading to more pain.

The present study aimed at investigating the effects of cognitive tasks (to induce cognitive stress) and a single relaxation session on central pain modulation in patients with chronic WAD and FM compared to healthy pain-free individuals.

METHODS

Study Design and Setting

A randomized crossover design was employed as illustrated in Fig. 1. The present experimental study took place from July 2010 until December 2013 at the University of Antwerp, the University of Brussels, and the University Hospital Brussels. Participants received detailed study information and gave written informed consent prior to study enrollment. This research was approved by the Ethics Committee of the University Hospital Brussels. The current study is registered with the ClinicalTrials.gov Identifier number NCT01172795.



Participants

Sixteen patients with chronic WAD, 21 patients with FM, and 22 healthy pain-free controls were included. Chronic WAD and FM patients were recruited in cooperation with rheumatologists and physical medicine and rehabilitation physicians. Healthy controls were recruited through acquaintances of patients, students, researchers, and university staff. Each study participant had to be Dutch speaking and aged between 18 and 65 years.

The chronic WAD group fulfilled the criteria of the Quebec Task Force (grade II to III) (35). Chronic neck pain due to a whiplash event was defined as pain lasting longer than 3 months. The FM group complied with the diagnostic criteria for FM as defined by the 1990 American College of Rheumatology (ACR) (36,47). Chronic WAD patients fulfilling the diagnostic criteria for FM and FM patients reporting a history of a whiplash trauma were

not eligible for study participation. Healthy individuals were pain-free at the time of study participation. In addition, participants suffering metabolic, cardiovascular, or inflammatory disorders were excluded.

In order to preclude confounding factors, pregnant women and women less than one year postnatal were excluded. Furthermore, all participants were asked to stop analgesics 48 hours prior to study participation, not to undertake physical exertion, and to refrain from consuming caffeine, alcohol, and nicotine on the day of the experiments.

Based on an a priori power calculation, we aimed at recruiting a total sample size of at least 45 participants (G*Power 3.1.2). This a priori power analysis was performed for the within-between interaction in repeated measures ANOVA with 3 groups, 3 measurements (baseline mean pain measures, pain measures

after relaxation, pain measures after cognitive tests), an effect size of 0.25, a significance level of 0.05, and a minimum power of 0.90.

Research Procedure

First, participants were subjected to various pain measurements. Pressure pain thresholds (PPTs), TS, and CPM were evaluated. Subsequently, participants were randomly allocated (by lottery) to either a group that performed a battery of cognitive tests or a group that received PRT. To randomize, each participant chose a folded ticket, which indicated the order of the intervention, on the first test day. Afterwards, all pain measurements were repeated. One week later participant groups were switched.

Experimental Pain Measures

To investigate the presence of CS, 3 critical aspects of the central pain system were assessed (48-51). First, PPTs were measured with a digital algometer (Wagner Instruments, Greenwich). Secondly, TS of pain was examined. Finally, a CPM paradigm was conducted to assess the efficacy of endogenous pain inhibition. All pain measurements were performed by a researcher blinded to the group allocation.

Pressure Pain Thresholds and Temporal Summation of Pressure Pain

The PPT was measured at the middle of the right trapezius belly, midway between the processus spinosus of the seventh cervical vertebra and the lateral edge of the acromion using a digital algometer (Wagner Instruments, Greenwich). The pressure was increased at a rate of approximately 1 kg/s until participants said "stop" at the moment the sensation became uncomfortable. Consequently, the pressure was immediately released. The pressure established on that moment was determined as the PPT, measured in kg/cm². Two PPT measurements (interval 30 seconds) were performed, from which a mean PPT value was calculated. The use of pressure algometry has been found to be an efficient and reliable technique in the determination of PPTs and subsequently the examination of hyperalgesia (52-54).

TS of pressure pain was elicited at the trapezius by administering 10 consecutive pressure pulses using the algometer. For each pulse of the TS procedure, the pressure was increased at a rate of approximately 2 kg/s until the previously determined PPT was reached and maintained for one second (48). Pressure pulses were presented with an inter-stimulus interval of one second.

Participants were instructed to rate their perceived pain intensity during the first, fifth, and tenth pressure pulse using a verbal numeric rating scale (VNRS). The TS pain score was obtained by subtracting the first VNRS score from the last VNRS. The higher the TS score, the more extensive/efficacious the nociceptive transmission to the brain. This TS procedure has been found to be reliable and valid (48).

Conditioned Pain Modulation

CPM was induced by inflating an occlusion cuff (conditioning stimulus) placed around the left arm, opposite of the test stimulus, to a painful intensity. The test stimulus was applied at the contralateral body side and consisted of the TS procedure, which was repeated during cuff inflation. Therefore the cuff was inflated at a constant rate (20 mmHg/s) until the participant reported pain. Participants then adapted to the stimulus for 30 seconds and rated the pain on the VNRS. Subsequently, the cuff inflation was adjusted until participants indicated a pain intensity of 3 out of 10 on the VNRS. The CPM procedure started as soon as the cuff inflation was adjusted. During the CPM procedure the left arm rested on a table and the TS assessment was repeated at the right trapezius as described above (48). Efficacy of CPM was examined by subtracting the VNRS from the first pressure pulse prior to and during cuff inflation. This CPM procedure has been found reliable, and CPM induced by ischemic cuff inflation is able to reduce TS in healthy controls (48) and has been previously used to examine CPM efficacy in CWAD (55,56) and FM (57).

Interventions

Progressive Muscle Relaxation Therapy

The relaxation intervention consisted of PRT. The participant was positioned in a comfortable supine position on a treatment table. A Dutch audio fragment was played and the participant listened to the instructions that were given. The participants were instructed to alternately contract and relax different skeletal muscle groups in order to create awareness of muscle tension and relaxation. The participant was guided to progressively proceed through all major muscle groups, relaxing them one at a time, and eventually leading to total muscle relaxation (44,58). The relaxation session had a duration of 30 minutes.

Cognitive Stress

The cognitive stress intervention encompassed

the performance of 3 cognitive tests, the Stroop task, Psychomotor vigilance task (PVT), and Operation span (OSPAN) task. In order to standardize the procedure, all tests were conducted on the same computer and in a fixed order (Stroop, PVT, OSPAN). The cognitive tests were quite challenging and had a total duration of approximately 30 to 45 minutes. Each of the 3 tests has been used and described in detail in 3 of our previous studies in patients with chronic CS pain (59-61).

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences 22.0 (SPSS Inc. Headquarters, Chicago, Illinois, USA). Statistical significance was set a priori at $\alpha = 0.05$.

Comparability of groups for age, gender distribution, disease duration, and medication use was examined with the one-way ANOVA or Chi-square test. First, a paired-samples t-test was performed to ensure there were no significant differences between the baseline pain measurements at the day of the relaxation and cognitive intervention. Then, the mean of the 2 baseline measures (before relaxation and before cognitive intervention) of each pain measurement was calculated and used for further data analyses.

Repeated measures ANOVA were performed using 3 levels. The first level was the mean baseline pain measure, calculated as described above. The second level was the pain measure after relaxation. The third level was the same pain measure, however acquired after the cognitive tests.

First, possible interaction effects between each pain measure and "study group" were explored. If there was no significant interaction effect, the main within and between subject effects were inspected. To see the nature of the effects, a simple contrast was examined and the first level was set as the reference category. Group differences were further explored with a one-way ANOVA test. Bonferroni correction was used as post-hoc test.

RESULTS

Baseline Characteristics

Demographic characteristics, medication use, and baseline pain measures of the participants are presented in Table 1. Fifty-nine participants (16 chronic WAD patients, 21 FM patients, and 22 pain-free controls), comparable for age and gender distribution, were included for the baseline measures on the first session

day and were randomly assigned. Fifty-seven participants (15 chronic WAD patients, 20 FM patients, and 22 controls) were included on the second session day and were subjected to the pain measures and intervention. Two patients (1 chronic WAD, 1 FM) were lost to follow-up because they did not show up at the second intervention day. Consequently, there are 2 missing values for the TS and CPM measurements.

The paired-samples t-test in each study group displayed no significant differences between the baseline pain measurements at the experimental day of the relaxation and cognitive intervention ($P > 0.05$) (Table 1).

Effects of Relaxation and Cognitive Stress on Central Pain Modulation

Temporal Summation of Pressure Pain

A significant interaction effect was found for the change in TS between study groups (Table 2) after relaxation ($P = 0.008$) and after the cognitive tests ($P = 0.003$) (Table 3 and Fig. 2).

TS, measured at the trapezius muscle, decreased significantly in response to the relaxation and cognitive stress intervention in healthy persons ($P < 0.01$). Additionally, chronic WAD patients displayed a trend for reduced TS scores after both interventions. In contrast, TS showed a trend to increase in response to the relaxation and cognitive stress intervention in the FM group.

Conditioned Pain Modulation

A significant main within-subjects time effect was found for CPM in every study group (Table 2), being a decreased CPM efficacy after relaxation ($P = 0.002$) and after the cognitive tests ($P = 0.001$) (Table 3 and Fig. 3).

CPM efficacy diminished significantly after both interventions in healthy persons ($P < 0.05$). Furthermore, chronic WAD patients demonstrated significantly decreased CPM efficacy after the PRT ($P < 0.05$).

DISCUSSION

The present study is the first to examine the effects of a single relaxation session and a cognitive stressor on central pain modulation in chronic WAD and FM patients compared to healthy individuals. The study results indicate that both types of interventions enhance TS of pain in FM, indicating an increased nociceptive transmission to the brain in these patients (bottom-up sensitization). In contrast, chronic WAD patients and healthy controls experienced acute positive effects on bottom-up sensitization, as both relaxation and cogni-

Table 1. Baseline characteristics of the patients (CWAD and FM) and healthy controls^a.

Characteristics ^a	CWAD (n=16)	FM (n=21)	CON (n=22)	P value ANOVA	P value Post-hoc Bonferroni		
					CWAD -FM	CON -CWAD	CON -FM
Age (y) ^b	41.62 (11.45)	44.52 (9.47)	38.00 (13.90)	0.202			
Gender (male; female) ^c	3 ; 13	5 ; 16	8 ; 14	0.442			
Disease duration (m) ^b	60.80 (69.70)	96.30 (73.10)	0 (0)	<0.001	0.219	0.004d	<0.001e
Pain medication use (yes, no) ^c	0 ; 16	4 ; 17	1 ; 21	0.084			
Antidepressiva use (yes, no) ^c	4 ; 12	7 ; 14	1 ; 21	<0.001	0.583	0.066	0.015e
Benzodiazepines & muscle relaxants (yes, no) ^c	1 ; 15	1 ; 20	1 ; 21				
Baseline pain measure^f							
PPT trapezius (kg/cm ²)	relaxation						
	4.12 (1.65)	2.90 (2.49)	5.32 (3.28)				
	cognition						
4.02 (1,53)	2.47 (2,97)	4.96 (3.33)					
Paired samples t-tests	0.741	0.264	0.384				
TS (VNRS)	relaxation						
	3.37 (1.94)	4.21 (2.07)	2.20 (1.86)				
	cognition						
3.23 (1.68)	3.42 (1.80)	1.77 (1.80)					
Paired samples t-test	0.823	0.203	0.168				
CPM (VNRS)	relaxation						
	0.69 (1.31)	0.52 (1.50)	0.59 (1.50)				
	cognition						
0.93 (0.88)	0.35 (1.98)	0.91 (0.97)					
Paired samples t-test	0.578	0.739	0.390				

a = Values are presented as means and SD for continuous data and as absolute frequencies for categorical data. b= Statistical analyses were performed using a one-way ANOVA. c= Statistical analyses were performed using a Pearson Chi-square test. d = Significant differences between CWAD patients and controls ($P < 0.017$). e= Significant differences between FM patients and controls ($P < 0.017$). f= Values are presented as mean value and SD. Significant differences are presented in bold font. y: years, m: months, PPT: Pressure pain threshold, VNRS: Verbal numeric rating scale, TS: Temporal summation, CPM: Conditioned pain modulation, ns= not significant, CWAD: chronic whiplash-associated disorders, FM: fibromyalgia, CON: healthy controls

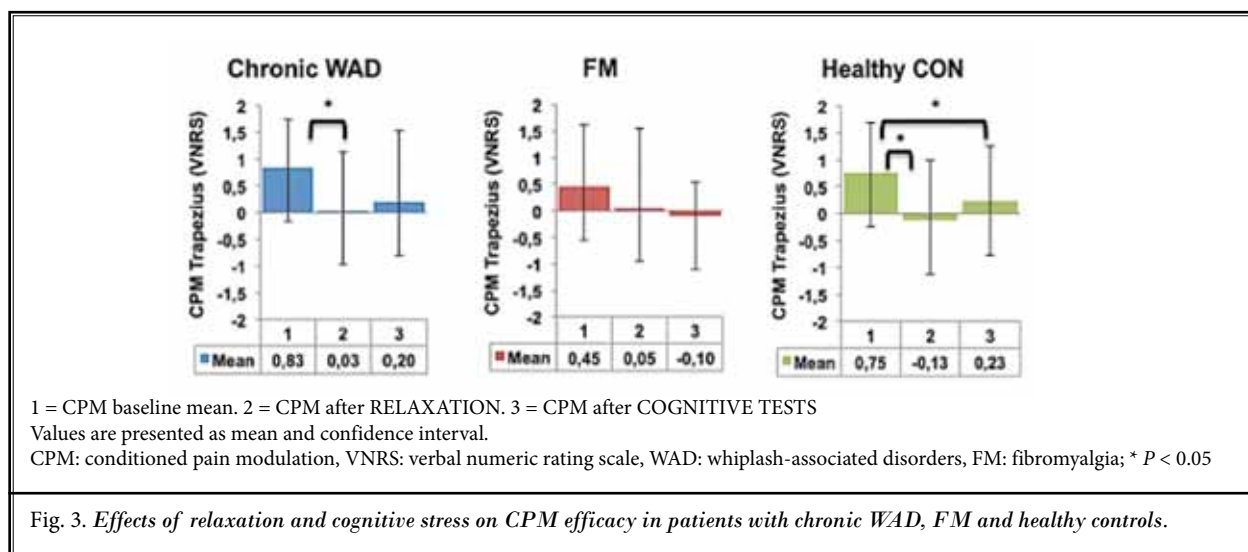
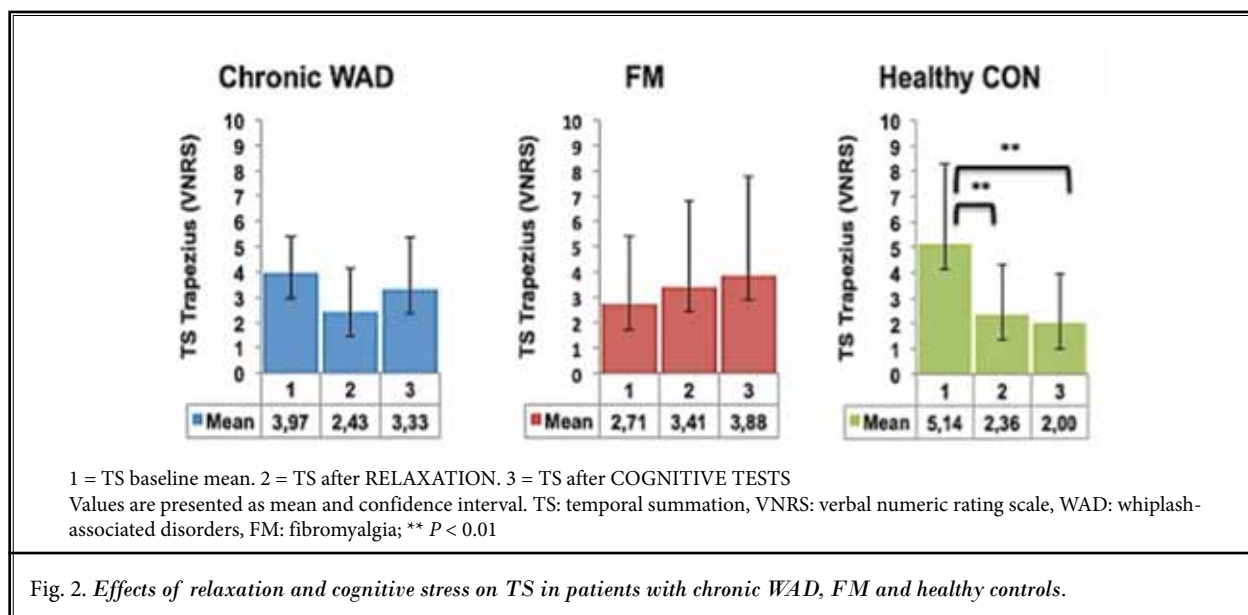
Table 2. Main effects: Repeated measures analysis of variance (3 study groups).

Outcome measure	Interaction effect (outcome time&group)	Within-subjects: time effect	Between-subjects: group effect
TS trapezius	$P = 0.003$	$P = NA$	$P = NA$
CPM trapezius	$P = 0.755$	$P = 0.002$	$P = 0.639$

TS: temporal summation, CPM: conditioned pain modulation, NA: not applicable

Table 3. Contrasts: Repeated measures analysis of variance (3 study groups).

Within-subjects contrasts (simple first)	After relaxation vs. baseline mean	After cognition vs. baseline mean
TS trapezius*group	$P = 0.008$	$P = 0.003$
CPM trapezius	$P = 0.002$	$P = 0.001$



tive stress reduced TS of pain. However, both interventions resulted in decreased CPM efficacy in healthy people as well as in those suffering from chronic pain (chronic WAD and FM), indicating that they have a detrimental effect on endogenous pain inhibition.

Possibly, performing the cognitive tasks served as a high cognitive stressor for FM patients, already suffering attention and memory problems (62,63), which further burdened the central nervous system leading to further disinhibition and more pain (self-reported hyperalgesia). In line with these results, Crettaz and

colleagues (28) reported enhanced pain sensitivity to pressure stimuli in FM patients, but not in healthy participants following psychological stress, induced using the Trier Social stress test. Stress-induced hyperalgesia has been demonstrated in FM in other studies as well (64,65). However, these studies have not investigated the effect of stress on TS and CPM.

In contrast, unpublished study results show that chronic WAD patients encounter less attention and memory problems than FM patients (66). Therefore, it can be hypothesized that chronic WAD patients and

healthy individuals may have experienced the cognitive tests as less challenging and less stressful. Accordingly, this could have led to decreased nociceptive ascending transmission, so diminished TS. Indeed, previous researchers have reported that the perceived severity of the stressor can influence pain modulation (26).

Secondly, it is possible that the cognitive tasks diminished pain sensitivity as a result of the previously mentioned "distraction effect" (45). This may be the explanation in the chronic WAD and control group, since TS of pain was reduced after the cognitive stressor.

Regarding the PRT, the format of the relaxation may have served as a physical stressor in the FM group, but to a lesser extent or not in the chronic WAD and control groups. This relaxation technique requires alternate tightening and relaxing of different muscle groups aimed at decreasing overall muscle tension (67). In chronic WAD and FM, PRT has the advantage of emphasizing the difference between muscles that are relaxed and those that are tensed, since a subgroup of patients continuously tense their muscles which can contribute to persistent pain (68). However, it may be that some FM patients tensed their (already painful) muscles too tightly and focused their attention even more on the pain during the relaxation session, which could have resulted in exacerbating pain and enhanced TS. There is one controlled trial in which the effects of biofeedback PRT using surface EMG were compared with the effects of a fitness program or a usual-care treatment (6 months) (69). PRT was indeed not effective in reducing pain perception or psychological distress, including stress and anxiety levels (69). Recently, a systematic review regarding the effects of relaxation therapy on pain also showed limited evidence supporting the use of muscle relaxation as a sole treatment for reducing pain in FM patients (43). The authors suggested that PRT was not effective as a standalone treatment strategy but that it could possibly improve pain relief when used in combination with other strategies, such as exercise and guided imagery.

In line with our results of diminished TS after the PRT in healthy individuals, Emery et al (70) found an increased nociceptive flexion reflex threshold, which is an objective indication for reduced central hyperexcitability, after a single progressive relaxation session in healthy pain-free adults.

Interesting, this study found decreased CPM efficacy following PRT and a cognitive stressor in patients with chronic WAD and FM as well as in healthy persons. Previous work has shown that CPM responses depend

on the interplay between physical and psychological mechanisms (71), influenced by cognitive factors, including attention, distraction, and expectations. It is possible that adequate CPM activation after the interventions was affected by these factors. Additionally, it could be that before a second CPM activation, a recovery period is needed after a previous CPM activation. Previous studies have also demonstrated worsened CPM responses following a second CPM measurement (72,73). Therefore, it may be that each successive conditioned noxious stimulus decreases CPM efficacy.

Kristian et al (73) investigated the effect of a simple mental stressor (mathematical calculations) and a non-stressful intervention (passive listening to a tale for children) on CPM of heat pain in healthy participants. They found a reduced CPM effect following the stressful as well as the non-stressful intervention, which is in line with our observations.

Limitations, Strengths, and Suggestions for Further Research

The present crossover study has a few study limitations that have to be taken into consideration. First, the obtained results only apply for a single session of muscle relaxation therapy and cognitive stress, whereby no conclusions can be made for effects on pain perception and modulation of chronic cognitive stress and long-term relaxation therapies. Second, the number of study participants ($n = 59$) was rather small, whereby bigger samples in each group could have provided more generalizable results. Thirdly, the use of antidepressiva was significantly different between FM patients and healthy persons. Fourthly, the results of the CPM measures are characterized by wide confidence intervals. However, the variance for CPM of the 3 study groups was not significantly different ($P > 0.05$). At last, autonomic variables, anxiety, and individuals' perception of stress were not measured in this study. Therefore, future protocols could adjust for these variables and include the assessment of the individual's perceived level of mental stress during the stressful and non-stressful task. Measurement of cortisol and catecholamine levels could give valuable information on the perceived level of stress.

Despite these limitations, the current study also has important strengths. First, the used randomized longitudinal crossover design, in which all participants are exposed to both tasks and serve as their own controls, minimizes bias and variability. Second, sources of bias like medication use were anticipated and well defined

diagnostic criteria were utilized for chronic WAD and FM. Finally, this paper adds relevant knowledge to the current literature regarding stress-pain and relaxation-pain interactions in patients with chronic WAD and FM.

Future studies are warranted to help further elucidate the complex relation between stress, relaxation, and pain, and the involved underlying mechanisms. It could be interesting to examine the effects of other relaxation techniques like mindfulness, yoga, mind-body exercises, or visualization on pain modulation in patients with CS pain.

Further, inclusion of EMG biofeedback would provide a more accurate assessment of actual muscle relaxation.

The current study obtained new insight in the effect of acute stress and relaxation on central pain modulation in the investigated population. The unravelling of influencing factors on central pain modulation is in our opinion an important first step in order to adapt future interventions for chronic pain patients adequately.

It remains an important challenge for researchers and therapists to develop effective therapy strategies for chronic pain patients characterized by CS.

Clinical Implications

Based on the present results, it can be summarized that acute experimental psychophysical stress due to the aforementioned interventions can lead to decreased efficacy of pain modulation, especially in patients with FM. Noteworthy is that cognitive stress exerted a similar influence on pain modulation as a PRT session.

Therapists should be aware of the possible negative and/or positive influences of cognitive demanding

tasks and relaxation techniques which depend on body and or muscle movements on pain modulation, depending on the patient's individual ability to cope with stress. By assessing and questioning patients, the nature of the effect can become clear and the program can be adapted when needed. Measuring pain sensitivity and the perceived level of stress following a stressor is valuable for identifying patients that have problems with their stress-response system.

Taken together, we suggest a multicomponent assessment and rehabilitation in which the underlying pathophysiological mechanisms should be taken into account.

CONCLUSION

In FM, one session of PRT and cognitive stress exaggerated TS, hence increased nociceptive transmission to the brain. Therefore, it can be assumed that a single relaxation session as well as cognitive stress may have negative acute effects on pain modulation in patients with FM, while cognitive stress and relaxation reduced TS in both chronic WAD patients and healthy controls. Lower TS values point towards reduced bottom-up sensitization, possibly due to a change in brain focus as a result of distraction.

Endogenous pain inhibition, measured with the CPM paradigm, worsened in response to both relaxation and cognitive stress in healthy people, chronic WAD patients, and FM patients.

These results should be taken into consideration when developing therapy strategies for patients with chronic WAD and FM.

REFERENCES

1. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: A systematic literature review. *European Journal of Pain (London, England)* 2013; 17:299-312.
2. Meeus M, Nijs J. Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clinical Rheumatology* 2007; 26: 465-473.
3. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Best Practice & Research Clinical Rheumatology* 2007; 21:481-497.
4. Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: Pathogenetic role. *Current Pain and Headache Reports* 2002; 6:259-266.
5. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual Therapy* 2010; 15:135-141.
6. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, Curatolo M. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyal-

- gia. *Pain* 2004; 107:7-15.
7. Meeus M, Nijs J, Van de Wauwer N, Toebak L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study. *Pain* 2008; 139:439-448.
 8. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis and Rheumatism* 2003; 48:1420-1429.
 9. Neziri AY, Haesler S, Petersen-Felix S, Muller M, Arendt-Nielsen L, Manresa JB, Andersen OK, Curatolo M. Generalized expansion of nociceptive reflex receptive fields in chronic pain patients. *Pain* 2010; 151:798-805.
 10. Kaya S, Hermans L, Willems T, Rousset N, Meeus M. Central sensitization in urogynecological chronic pelvic pain: A systematic literature review. *Pain Physician* 2013; 16:291-308.
 11. Bouhassira D, Gall O, Chitour D, Le Bars D. Dorsal horn convergent neurones: Negative feedback triggered by spatial summation of nociceptive afferents. *Pain* 1995; 62:195-200.
 12. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. *European Journal of Pain (London, England)* 2010; 14:339.
 13. Zusman M. Forebrain-mediated sensitization of central pain pathways: 'Non-specific' pain and a new image for MT. *Manual Therapy* 2002; 7:80-88.
 14. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain* 2002; 99:49-59.
 15. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Giani C, Zbinden AM, Radanov BP. Central hypersensitivity in chronic pain after whiplash injury. *The Clinical Journal of Pain* 2001; 17:306-315.
 16. Lemming D, Sorensen J, Graven-Nielsen T, Arendt-Nielsen L, Gerdle B. The responses to pharmacological challenges and experimental pain in patients with chronic whiplash-associated pain. *The Clinical Journal of Pain* 2005; 21:412-421.
 17. Vierck CJ, Jr., Staud R, Price DD, Cannon RL, Mauderli AP, Martin AD. The effect of maximal exercise on temporal summation of second pain (windup) in patients with fibromyalgia syndrome. *The Journal of Pain* 2001; 2:334-344.
 18. Van Oosterwijck J, Nijs J, Meeus M, Van Loo M, Paul L. Lack of endogenous pain inhibition during exercise in people with chronic whiplash associated disorders: An experimental study. *The Journal of Pain* 2012; 13:242-254.
 19. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain* 2010; 151:77-86.
 20. Kasch H, Qerama E, Bach FW, Jensen TS. Reduced cold pressor pain tolerance in non-recovered whiplash patients: A 1-year prospective study. *European Journal of Pain (London, England)* 2005; 9:561-569.
 21. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain* 2005; 114:295-302.
 22. Crofford LJ. The hypothalamic-pituitary-adrenal stress axis in fibromyalgia and chronic fatigue syndrome. *Zeitschrift fur Rheumatologie* 1998; 57 Suppl 2:67-71.
 23. Gaab J, Baumann S, Budnoik A, Gmunder H, Hottinger N, Ehler U. Reduced reactivity and enhanced negative feedback sensitivity of the hypothalamus-pituitary-adrenal axis in chronic whiplash-associated disorder. *Pain* 2005; 119:219-224.
 24. Kuehl LK, Michaux GP, Richter S, Schachinger H, Anton F. Increased basal mechanical pain sensitivity but decreased perceptual wind-up in a human model of relative hypocortisolism. *Pain* 2010; 149:539-546.
 25. Butler RK, Finn DP. Stress-induced analgesia. *Progress in Neurobiology* 2009; 88:184-202.
 26. Olango WM, Finn DP. Neurobiology of stress-induced hyperalgesia. *Current Topics in Behavioral Neurosciences* 2014; 20:251-280.
 27. Cathcart S, Petkov J, Pritchard D. Effects of induced stress on experimental pain sensitivity in chronic tension-type headache sufferers. *European Journal of Neurology* 2008; 15:552-558.
 28. Crettaz B, Marziniak M, Willeke P, Young P, Hellhammer D, Stumpf A, Burgmer M. Stress-induced allodynia -- evidence of increased pain sensitivity in healthy humans and patients with chronic pain after experimentally induced psychosocial stress. *PLoS One* 2013; 8:e69460.
 29. Martenson ME, Cetas JS, Heinricher MM. A possible neural basis for stress-induced hyperalgesia. *Pain* 2009; 142:236-244.
 30. Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. *British Journal of Sports Medicine* 1998; 32:20-24.
 31. Koltyn KF. Analgesia following exercise: A review. *Sports Medicine (Auckland, NZ)* 2000; 29:85-98.
 32. Millan MJ. Descending control of pain. *Progress in Neurobiology* 2002; 66:355-474.
 33. Ray CA, Carter JR. Central modulation of exercise-induced muscle pain in humans. *The Journal of Physiology* 2007; 585:287-294.
 34. Jennings EM, Okine BN, Roche M, Finn DP. Stress-induced hyperalgesia. *Progress in Neurobiology* 2014; 121:1-18.
 35. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, Zeiss E. Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders: Redefining "whiplash" and its management. *Spine* 1995; 20:15-735.
 36. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam, Farber, Fiechtner, Franklin, Gatter, Hamaty, Lessard, Lichtbroun, Masi, Mccain, Reynolds, Romano, Russel, Sheon The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism* 1990; 33:160-172.
 37. Seo J, Kim SH, Kim YT, Song HJ, Lee JJ, Kim SH, Han SW, Nam EJ, Kim SK, Lee HJ, Lee SJ, Chang Y. Working memory impairment in fibromyalgia patients associated with altered frontoparietal memory network. *PLoS One* 2012; 7:e37808.
 38. Nederhof E, Lemmink KA, Visscher C, Meeusen R, Mulder T. Psychomotor speed: Possibly a new marker for overtraining syndrome. *Sports Medicine (Auckland, NZ)* 2006; 36:817-828.
 39. Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology* 1999; 21:477-487.
 40. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology* 2011; 93:385-404.
 41. Antepohl W, Kiviloog L, Andersson J,

- Gerdle B. Cognitive impairment in patients with chronic whiplash-associated disorder--a matched control study. *NeuroRehabilitation* 2003; 18:307-315.
42. Weiner DK, Rudy TE, Morrow L, Slaboda J, Lieber S. The relationship between pain, neuropsychological performance, and physical function in community-dwelling older adults with chronic low back pain. *Pain Medicine (Malden, Mass)* 2006; 7:60-70.
 43. Meeus M, Nijs J, Vanderheiden T, Baert I, Descheemaeker F, Struyf F. The effect of relaxation therapy on autonomic functioning, symptoms and daily functioning, in patients with chronic fatigue syndrome or fibromyalgia: A systematic review. *Clinical Rehabilitation* 2015; 29:221-233
 44. E J. Electrical measurements concerning muscular contraction (tonus) and the cultivation of relaxation in man: Relaxation times of individuals. *American Journal of Physiology* 1934a; 108:573-580.
 45. Eccleston C, Crombez G. Pain demands attention: A cognitive-affective model of the interruptive function of pain. *Psychological Bulletin* 1999; 125:356-366.
 46. McGuigan FJ, Lehrer PM. *Progressive Relaxation: Origins, Principles, and Clinical Applications. Principles and Practice of Stress Management.* edition. 2nd Guilford Press, New York, 1993.
 47. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research* 2010; 62:600-610.
 48. Cathcart S, Winefield AH, Rolan P, Lushington K. Reliability of temporal summation and diffuse noxious inhibitory control. *Pain Research & Management* 2009; 14:433-438.
 49. Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *The Journal of Pain* 2007; 8:893-901.
 50. Meeus M, Nijs J, Huybrechts S, Truijens S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: A case control study. *Clinical Rheumatology* 2010; 29:393-398.
 51. Fernandez-Carnero J, Fernandez-de-Las-Penas C, de la Llave-Rincon AI, Ge HY, Arendt-Nielsen L. Widespread mechanical pain hypersensitivity as sign of central sensitization in unilateral epicondylalgia: A blinded, controlled study. *The Clinical Journal of Pain* 2009; 25:555-561.
 52. Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region. The influence of skin sensitivity in pressure algometry. *Scandinavian Journal of Rehabilitation Medicine* 1999; 31: 89-93.
 53. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W. Pressure algometry in manual therapy. *Manual Therapy* 1996; 1:258-265.
 54. Antonaci F, Sand T, Lucas GA. Pressure algometry in healthy subjects: Inter-examiner variability. *Scandinavian Journal of Rehabilitation Medicine* 1998; 30:3-8.
 55. Daenen L, Nijs J, Roussel N, Wouters K, Van Loo M, Cras P. Dysfunctional pain inhibition in patients with chronic whiplash-associated disorders: An experimental study. *Clinical Rheumatology* 2013; 32:23-31.
 56. De Kooning M, Daenen L, Cras P, Gidron Y, Roussel N, Nijs J. Autonomic response to pain in patients with chronic whiplash associated disorders. *Pain Physician* 2013; 16: E277-E285.
 57. Meeus M, Ickmans K, Struyf F, Hermans L, Van Noesel K, Oderkerk J, Declerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Does acetaminophen activate endogenous pain inhibition in chronic fatigue syndrome/fibromyalgia and rheumatoid arthritis? A double-blind randomized controlled cross-over trial. *Pain Physician* 2013; 16:E61-E70.
 58. Jacobson E. Electrical measurements concerning muscular contraction (tonus) and the cultivation of relaxation in man: Studies on arm flexors. *American Journal of Physiology* 1934; 107:230-248.
 59. Ickmans K, Clarys P, Nijs J, Meeus M, Aerenhouts D, Zinzen E, Aelbrecht S, Meersdom G, Lambrecht L, Pattyn N. Association between cognitive performance, physical fitness, and physical activity level in women with chronic fatigue syndrome. *Journal of Rehabilitation Research and Development* 2013; 50:795-810.
 60. Ickmans K, Meeus M, Kos D, Clarys P, Meersdom G, Lambrecht L, Pattyn N, Nijs J. Cognitive performance is of clinical importance, but is unrelated to pain severity in women with chronic fatigue syndrome. *Clinical Rheumatology* 2013; 32:1475-1485.
 61. Meeus M, Van Oosterwijk J, Ickmans K, Baert I, Coppieters I, Roussel N, Struyf F, Pattyn N, Nijs J. Interrelationships between pain processing, cortisol and cognitive performance in chronic whiplash-associated disorders. *Clinical Rheumatology* 2015; 34:545-553.
 62. Tesio V, Torta DM, Colonna F, Leombruni P, Ghiggia A, Fusaro E, Geminiani GC, Torta R, Castelli L. Are fibromyalgia patients cognitively impaired? Objective and subjective neuropsychological evidence. *Arthritis Care & Research* 2015; 67:143-150.
 63. Suhr JA. Neuropsychological impairment in fibromyalgia: Relation to depression, fatigue, and pain. *Journal of psychosomatic research* 2003; 55:321-329.
 64. Van Houdenhove B, Luyten P. Stress, depression and fibromyalgia. *Acta Neurologica Belgica* 2006; 106:149-156.
 65. Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White LR, Bang Leistad R, Helde G, Ro M. Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. *European Journal of Pain (London, England)* 2007; 11:743-755.
 66. Coppieters I, Ickmans K, Cagnie B, Nijs J, De Pauw R, Noten S, Meeus M. Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia. *Pain Physician* 2015; 18:389-401.
 67. Jacobson E. *Progressive Relaxation.* University of Chicago Press, Chicago, 1938.
 68. Elert J, Kendall SA, Larsson B, Mansson B, Gerdle B. Chronic pain and difficulty in relaxing postural muscles in patients with fibromyalgia and chronic whiplash associated disorders. *The Journal of Rheumatology* 2001; 28:1361-1368.
 69. van Santen M, Bolwijn P, Verstappen F, Bakker C, Hidding A, Houben H, van der Heijde D, Landewe R, van der Linden S. A randomized clinical trial comparing fitness and biofeedback training versus basic treatment in patients with fibromyalgia. *The Journal of Rheumatology* 2002; 29:575-581.
 70. Emery CF, France CR, Harris J, Norman G, Vanarsdalen C. Effects of progressive muscle relaxation training on nociceptive flexion reflex threshold in healthy young adults: A randomized trial. *Pain* 2008; 138:375-379.
 71. Nir RR, Yarnitsky D, Honigman L, Granot M. Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. *Pain* 2012; 153:170-176.

72. Meeus M, Hermans L, Ickmans K, Struyf F, Van Cauwenbergh D, Bronckaerts L, De Clerck LS, Moorken G, Hans G, Grosemans S, Nijs J. Endogenous pain modulation in response to exercise in patients with rheumatoid arthritis, patients with chronic fatigue syndrome and comorbid fibromyalgia, and healthy controls: A double-blind randomized controlled trial. *Pain Practice* 2015; 15:98-106..
73. Kristian B. Nilsen SEC, Line B. Holmen, Trond Sand. The effect of a mental stressor on conditioned pain modulation in healthy subjects. *Scandinavian Journal of Pain* 2012; 3:142-148.