View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Ghent University Academic Bibliography

Pain Physician 2015; 18:E841-E852 • ISSN 2150-1149

Observational Study

# Associations Between Cognitive Performance and Pain in Chronic Fatigue Syndrome: Comorbidity with Fibromyalgia Does Matter

Kelly Ickmans, PT, PhD[1-3], Mira Meeus, PT, PhD[1,4,5], Margot De Kooning, MSc[1-3,6], Luc Lambrecht, MD, PhD[7], Nathalie Pattyn, MD, PhD[2,8], and Jo Nijs, PT, PhD[1-3]

From: [1]Pain in Motion Research Group (www.paininmotion.be); [2]Department of Human Physiology and Physiotherapy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium; [3]Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium; [4]Rehabilitation Sciences and Physiotherapy, Faculty of Medicine & Health Sciences, Ghent University, Ghent, Belgium; [5]Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine & Health Sciences, University of Antwerp, Antwerp, Belgium; [6]Department of Neurology, Faculty of Medicine, University of Antwerp, Antwerp, Belgium; [7]Private practice for internal medicine, Ghent, Belgium; [8]VIPER Research Unit, Royal Military Academy, Brussels, Belgium

Address Correspondence:
Kelly Ickmans, PhD
Vrije Universiteit Brussel
Faculty of Physical Education & Physiotherapy
Medical Campus Jette
Building F-Kine, Laarbeeklaan 103, BE-1090 Brussels, Belgium
E-mail: Kelly.Ickmans@vub.ac.be

Disclaimer and Conflict of interest, see PE850.

Manuscript received: 02-10-2015
Revised manuscript received: 03-31-2015
Accepted for publication: 04-27-2015

Free full manuscript: www.painphysicianjournal.com

**Background:** In addition to the frequently reported pain complaints, performance-based cognitive capabilities in patients with chronic fatigue syndrome (CFS) with and without comorbid fibromyalgia (FM) are significantly worse than those of healthy controls. In various chronic pain populations, cognitive impairments are known to be related to pain severity. However, to the best of our knowledge, the association between cognitive performance and experimental pain measurements has never been examined in CFS patients.

**Objectives:** This study aimed to examine the association between cognitive performance and self-reported as well as experimental pain measurements in CFS patients with and without FM.

**Study Design:** Observational study.

**Setting:** The present study took place at the Vrije Universiteit Brussel and the University of Antwerp.

**Methods:** Forty-eight (18 CFS-only and 30 CFS+FM) patients and 30 healthy controls were studied. Participants first completed 3 performance-based cognitive tests designed to assess selective and sustained attention, cognitive inhibition, and working memory capacity. Seven days later, experimental pain measurements (pressure pain thresholds [PPT], temporal summation [TS], and conditioned pain modulation [CPM]) took place and participants were asked to fill out 3 questionnaires to assess self-reported pain, fatigue, and depressive symptoms.

**Results:** In the CFS+FM group, the capacity of pain inhibition was significantly associated with cognitive inhibition. Self-reported pain was significantly associated with simple reaction time in CFS-only patients. The CFS+FM but not the CFS-only group showed a significantly lower PPT and enhanced TS compared with controls.

**Limitations:** The cross-sectional nature of this study does not allow for inferences of causation.

**Conclusions:** The results underline disease heterogeneity in CFS by indicating that a measure of endogenous pain inhibition might be a significant predictor of cognitive functioning in CFS patients with FM, while self-reported pain appears more appropriate to predict cognitive functioning in CFS patients without FM.

**Key words:** Chronic fatigue syndrome, cognitive function, cognitive inhibition, chronic pain, fibromyalgia, pain inhibition, pain-related cognitive impairment, working memory

**Pain Physician 2015; 18:E841-E852**

Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by profound fatigue for 6 or more consecutive months that is not improved by bed rest and that may be worsened by physical or mental activity. In the majority of CFS patients, this chronic fatigue is accompanied by widespread and persistent pain as well (1). Chronic widespread musculoskeletal pain is the hallmark symptom of fibromyalgia (FM), and furthermore it is known that patients with CFS and patients with FM share many other symptoms and clinical features such as fatigue, sleep disturbances, cognitive dysfunction, and mood disturbances (2-5). A growing body of scientific literature designates central sensitisation (CS) as a common pathophysiological mechanism in these overlapping conditions (6-9).

CS has been defined as "an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity" (10). Clinically it manifests as an increased response to various peripheral stimuli (e.g., pressure, light, sound, cold, and heat among others) inducing hyperalgesia and allodynia (8,11).

In addition to the pain, both CFS and FM patients frequently complain of decreased cognitive capabilities (12). Accordingly, we recently demonstrated that performance-based cognitive capabilities are significantly worse both in CFS patients with and without FM compared with healthy controls (13). Indeed, an overlap exists in components of the pain neuromatrix and brain regions involved in cognitive processing (e.g., anterior cingulate cortex, insular cortex, periaqueductal gray) (14). Together with the demonstrated changes in neuroplasticity [e.g., gray matter volume reduction (15-17)] and dysregultated neurochemistry [e.g., decreased levels of brain-derived neurotrophic factor (18), increased levels of gamma-aminobutric acid (19), increased levels of pro-inflammatory cytokines (20)], these pain-induced changes in resource utilization may (in part) explain (pain-related) cognitive impairment in chronic pain patients.

Some previous studies indicated that, in patients with FM, cognitive performance is inversely related to self-reported pain (21,22), while other authors demonstrated an absence of this relationship in FM patients (15,23) and in female CFS patients (24). However, to the best of our knowledge the association between cognitive performance and experimental pain measurements and established measures of CS has never been examined in CFS patients. Examing this association can give us more insight in how cognitive dysfunctions can cluster with other symptoms and pathophysiological features of the disorder. Furthermore, since we believe that disease heterogeneity and the effect of comorbidities such as FM might play a significant role, this study aimed to examine the association between cognitive performance and self-reported as well as experimental pain measurements in CFS patients with comorbid FM.

## Methods

### Study Design and Setting

This blinded case-control study took place at the Pain in Motion research labs in Antwerp and Brussels. The study was approved by the ethics committees of the University Hospital Brussels/Vrije Universiteit Brussel and the University Hospital Antwerp, and written informed consent was obtained from all participants prior to commencement of the study.

### Participants and Assessments

Patients with CFS were recruited from a private practice for internal medicine, by calls during patient information sessions, and advertisements placed in the newsletter of a local patient support group. Written confirmation of a CFS diagnosis as defined by the United States Centers for Disease Control and Prevention (CDC) 1994 criteria for CFS (1) was required from each participant's physician before study participation. After inclusion in the study, patients with CFS were split up into a group of patients with and without comorbid FM (CFS+FM and CFS, respectively). The comorbid presence of FM was identified according to the American College of Rheumatology (ACR) 2010 criteria for fibromyalgia (25). Furthermore, a third group that consisted of healthy inactive control persons was included. Healthy [pain-free and without any (chronic) disease] inactive control persons were relatives, friends, or acquaintances of researchers, students, university personnel, or patients participating in the study. "Inactive" was defined as working in an occupation that did not require moderate to intense physical labor and performing a maximum of 3 hours of moderate physical activity/week. Moderate physical activity is defined as activity demanding at least the threefold of the energy spent passively (26).

Each study participant had to be Dutch speaking and aged between 18 and 65 years. To preclude confounding factors, participants could not suffer from intellectual disabilities and women could not be pregnant or until one year postnatal. Furthermore,

all participants, if applicable, were asked to stop antidepressive, anti-epileptic, and opioid pain medication 2 weeks prior to study participation and were asked not to undertake physical exertion, and to refrain from taking analgesics and consuming caffeine, alcohol. or nicotine on the days of the assessments.

The study consisted of 2 assessment sessions separated by 7 days. All assessments were performed by the same researchers who were blinded to whether participants were patients or controls. On the first day, after signing the informed consent form, collecting personal characteristics (age, gender, height, weight, disease duration, FM criteria, and occupational status) and checking for the presence of possible confounders, all participants completed 3 performance-based cognitive tests on a computer. Seven days later, experimental pain measurements took place and participants were asked to fill out 3 questionnaires [the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), the Checklist Individual Strength (CIS), and the Beck Depression Inventory for Primary Care (BDI-PC)]. Finally, at the end of the second assessment session, the success of assessor blinding was examined by asking whether the assessor thought the participant belonged to the patient (CFS or CFS+FM) or control group.

### *Cognitive Tests*

To investigate cognitive function the Stroop task, psychomotor vigilance task (PVT), and operation span (OSPAN) task with concomitant mathematical processing were used. All 3 tests were conducted on the same computer and in the same order (1. Stroop task, 2. PVT, 3. OSPAN) by every participant. To ensure standardization of the procedure, each test began with the presentation of written instructions for that particular test. Short breaks (± 5 minutes) between each test were allowed. Completion of the entire test battery took about 50 minutes. Each of the 3 tests have been used and described in detail in 2 of our previous studies in female CFS patients (24,27).

The *Stroop task* (28) was used to assess selective attention, cognitive inhibition, and choice reaction time (RT). In this test, different stimuli (= words or XXX) appeared in different colors (yellow, green, red, or blue) in the middle of the computer screen. The meaning of the stimulus is the task-irrelevant dimension and the color in which the stimulus is presented is the task-relevant dimension. Accordingly, participants were instructed to respond to the presented ink color in which stimuli were written, by pressing the corresponding color-key on the keyboard as quickly and as accurately as possible. The presented stimuli could be classified under 2 different conditions, namely "incongruent" (word and color are different [e.g., the word red displayed in green]) and "no word" [XXX presented in one color]). Mean response RT and accuracy were stored for each condition. In order to quantify cognitive inhibition, the RT of the no word condition was subtracted from the RT of the incongruent condition. Thus, an interference score (Stroop INT) is provided which can be seen as an indicator of the inhibition subcomponent of executive functioning. Deficits in cognitive inhibition should result in an increased Stroop INT.

The *PVT* (29) was used to assess sustained attention (or vigilance) and simple RT. Participants were instructed to respond to a visual stimulus (red spot on black background) that appeared in the middle of the screen at random inter-stimulus intervals (2 – 10 s). They were required to press the mouse button as quickly as possible whenever they perceived the appearance of the stimulus on the screen. If the participant did not respond within 500 ms, the trial was stored as a lapse. The PVT ran for a total time of 10 minutes. The mean RT of correct responses (< 500 ms) and the number of lapses were stored.

Working memory capacity was assessed using the *OSPAN task* with concomitant mathematical processing as described by Conway and Engle (30). The task began with a practice block (divided into 3 sections). First, participants got the chance to practice the simple letter span. They saw letters appear on the screen one at a time. After having seen the whole letter span they had to recall these letters in the same order they saw them. Next, participants practiced the mathematical portion of the OSPAN task. They first saw a mathematical operation appear on the screen (e.g., [7*3] – 3 = ?). Then, a number (e.g., 18) was presented on the screen and participants were instructed to indicate whether the number was the correct solution or not by clicking on "True" or "False." The final practice session consisted of performing both the letter recall and the mathematical operations together. Participants first had to solve the mathematical operation and only then saw the letter to be recalled. The dual-task design with the mathematical processing was used in order to keep the task-relevant information (letter span) active and accessible in memory during the execution of complex cognitive tasks (mathematical operations). After the completion of the 3 practice sessions, the program automatically proceeded to the experimental block which was the

same as the final practice session (mathematical operations + letter recall). The experimental block consisted of 3 sets of each set size (ranging from 3 – 7). Thus, a total of 75 letters and 75 mathematical problems were presented. At the end of the experiment, the "OSPAN total score" was registered and used for further data analyses. This score indicates the number of letters recalled in the correct position (regardless of whether the whole letter set was correct) and is a measure of working memory capacity.

## Experimental Pain Measurements

### *Pressure Pain Thresholds*

Pressure pain thresholds (PPTs) were measured at the middle of the right trapezius belly (PPT shoulder) and at the dorsal surface of the right hand middle finger midway between the first and second distal joint (PPT finger) with an analogue Fisher algometer (Force Dial, Wagner Instruments, Greenwich CT, USA) (31,32). Participants' PPTs were determined by gradually increasing the pressure provided by the algometer (at a rate of 1 kg/s) until the point the sensation first became painful (participants were instructed to say "stop" at this point). This was performed 2 times (30 seconds apart) at the shoulder and at the finger in order to calculate the mean PPT for every site. Pressure algometry has been found to be efficient and reliable in the exploration of pathophysiological mechanisms involved in pain (33,34).

### *Endogenous Pain Facilitation: Temporal Summation*

Temporal summation (TS) was examined 2 minutes after the final PPT was taken at each site (finger and shoulder). Participants were given 10 pulses to the previously determined mean PPT intensity and this pressure was maintained for one second before being released. Pressure was increased at a rate of approximately 2 kg/s for each pulse and pulses were presented with an interstimulus interval of one second. After the first, fifth, and thenth pulse, the participant was asked to verbally rate his/her pain on a Visual Analogue Scale (VAS) ranging from 0 (= no pain) to 10 (= worst possible pain). The outcome measure for TS is the difference between the tenth and the first VAS score (31,32).

### *Endogenous Pain Inhibition: Conditioned Pain Modulation*

To assess conditioned pain modulation (CPM), experimental pain measures (TS) were taken while an occlusion cuff was inflated to a painful intensity and maintained at that level on the opposing (left) arm (as a heterotopic noxious conditioning stimulus). The cuff was inflated at approximately 20 mmHg/s until the point the sensation first became painful (participants were instructed to say "stop" at this point). Next, they adapted for 30 seconds to the stimulus and subsequently rated their pain on a VAS. Cuff inflation was then increased or decreased until the participant indicated the pain level was equal to 3 on 10 on the VAS. The left arm was then rested on a table and CPM was assessed by replicating the TS assessment as described above. The outcome measure for CPM is the difference between the first VAS score before cuff inflation and the first VAS score during cuff inflation (31,32).

## Self-Reported Pain

The SF-36 is a widely used generic health status survey that consists of 36 questions which all together measure 8 health concepts: (1) physical functioning, (2) role limitations because of physical health problems, (3) bodily pain, (4) general health perceptions, (5) vitality (energy/fatigue), (6) social functioning, (7) role limitations because of emotional problems, and (8) general mental health (21). For this study we were only interested in the bodily pain concept of the SF-36. Consequently, only the bodily pain score of the SF-36 was used in the analyses. The raw score was coded and transformed into a scale from 0 to 100, with a higher score representing less bodily pain (35). The SF-36 has been documented to have reliability and validity in a wide variety of patient populations (36,37). Furthermore, it appears to be one of the most frequently used patient-reported measures in the assessment of adults with CFS (38).

## Self-Reported Fatigue

The CIS (39) consists of 20 items which altogether measure 4 dimensions of fatigue, including (1) subjective fatigue severity, (2) reduced concentration, (3) reduced motivation, and (4) reduced physical activity level. Respondents have to indicate, on a 7-point Likert scale, the degree to which each item was true for them in the 2 weeks preceding the assessment. Higher scores represent a higher level of fatigue and lower levels of concentration, motivation, and physical activity. For this study only the subjective fatigue severity dimension of the CIS was used in the analyses (as a covariate in the regression analyses). The CIS has good discriminative

validity, and its 4 dimensions have excellent consistency (Cronbach's $\alpha$ varying from 0.83 to 0.92) (39,40).

### Depression

The BDI-PC (41) was used for the assessment of depressive symptoms. It is a 7-item self-report instrument. Each of these 7 items contains 4 statements and respondents are asked to indicate the statement that best suits their feelings for the past 2 weeks including today. Within each item statements are rated on a 4-point scale ranging from 0 to 3. The BDI-PC is scored by summing all of the highest ratings for each item. Hence, the maximum total score is 21. Items are symptoms of sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticalness, and suicidal thoughts or wishes. The BDI-PC has high internal-consistency (Cronbach's $\alpha$ of 0.85) (41).

### Statistical Analysis

Data analyses were performed using IBM® SPSS® Statistics 22.0 for Windows (IBM Corp., Armonk, NY, USA). Normality of the variables was tested using the Kolmogorov-Smirnov goodness of fit test and through visual inspection of the histograms and distribution graphs. Comparability of the groups was studied with a Pearson Chi-Square test for gender distribution and occupational status and with a one-way independent analysis of variance (ANOVA) for age, body mass, height, body mass index, and disease duration.

Experimental pain, self-reported pain, fatigue, and depression measurements were compared among the groups with a one-way independent ANOVA for variables that were normally distributed. When a significant main effect was found, Bonferroni post hoc comparisons were performed to identify the significant differences among the 3 groups. Variables lacking normal distribution were compared with a non-parametric independent-samples Kruskal-Wallis test. Post hoc paired comparisons were performed when a main effect was found.

To determine the association between pain measurements and cognitive performance, correlation analyses (Pearson's and Spearman's) were performed. Because of the exploratory nature of this study and to minimize the risk of type II errors, no correction for multiple comparisons was done when calculating the statistical significance of the correlations. For all correlation analyses, only the pain outcomes that revealed the strongest association with performance on cognitive tests (based on *P*-values as well as on correlation coefficients) were considered for further regression analyses. Hence, the outcome of the correlation analyses was used only for identifying the appropriate variables for the regression analysis.

Simple linear regression analyses were performed to determine whether measurements of pain (experimental and self-reported) could be significant predictors of cognitive performance in patients with CFS and CFS+FM. Because age (14), fatigue severity (42), and depressive symptoms (43) may significantly influence cognitive function as well as pain measurements, the analyses were also performed with these variables separately entered as additional predictor variables (covariates).

For all comparisons (except for the correlation analyses), a 2-sided $P < 0.05$ was considered statistically significant. Data are reported as mean (SD) and median (Q1; Q3) within the text and the tables.

Power calculations were performed with the program G*Power 3.1.5 (Kiel, Germany) (44). Because in this report the same study samples (and hence the same sample sizes) were used as in our previous report on the association between upper limb muscle recovery and cognitive performance (13), no additional a priori sample size calculation was performed. Hence, in order to improve the interpretation of the results a post hoc power analysis for the linear regression analyses was performed when associations were not significant. This is discussed in the discussion section.

## Results

### Group Characteristics

Forty-eight patients with CFS were included in this study. These patients were split up into a group of 30 CFS patients with FM (CFS+FM) and a group of 18 CFS patients without FM (CFS). This implies that 62.5% of the included CFS patients also met the ACR 2010 criteria for FM. Furthermore, 30 healthy inactive controls were included. Table 1 shows the demographic data of the 3 study samples. The groups were comparable for gender distribution, age, body weight, and body mass index ($P > 0.05$), but not for body height [$F2,75 = 4.69$, $P = 0.012$] and occupational status [$\chi2(6) = 17.74$, $P = 0.007$]. Disease duration was not significantly different ($P = 1.0$) between the CFS+FM and CFS group.

### Cognitive Performance

For the results on cognitive performance, we refer the reader to our second report (13). Summarized,

Table 1. *Demographic data of the study samples.*

| | CFS (n = 18) | CFS+FM (n = 30) | CON (n = 30) |
|---|---|---|---|
| Age (years)[a] | 40.6 (12.5) | 40.2 (10.7) | 37.3 (14.5) |
| Women, n (%)[b] | 17 (94.4) | 29 (97.7) | 25 (83.3) |
| Body Mass (kg)[a] | 70.6 (15.3) | 68.4 (12.7) | 70.6 (15.7) |
| Height (cm)[a] | 167.9 (5.8) | 166.0 (5.2)[c] | 170.6 (6.5) |
| Body Mass Index[a] | 25.1 (5.3) | 24.8 (4.3) | 24.2 (4.7) |
| Disease Duration (months)[a] | 154.1 (186.5) | 135.0 (103.5) | 0.0 (± 0.0)[d] |
| Occupational status, n (%)[b] | 13 inactive (72.2)<br>2 part-time (11.1)<br>1 full-time (5.6)<br>2 students (11.1) | 18 inactive (60)<br>5 part-time (16.7)<br>3 full-time (10)<br>4 students (13.3) | 8 inactive (26.7)<br>2 part-time (6.7)<br>11 full-time (36.7)<br>9 students (30) |

Values are mean (SD) or number (%).
CFS = patients with chronic fatigue syndrome; CFS+FM = patients with chronic fatigue syndrome + fibromyalgia; CON = healthy inactive controls.
a Statistical analyses were performed using a one-way independent analysis of variance.
b Statistical analyses were performed using a Pearson's Chi-Square test.
c Significant difference between CFS+FM and CON ($P < 0.01$).
d Significant difference between both CFS+FM and CFS versus CON ($P < 0.001$).

these results showed that the CFS+FM group showed significantly decreased RTs (simple and choice), cognitive inhibition, and selective and sustained attention in comparison with the control group ($P < 0.05$). Although the CFS group also showed worse results on cognitive tests compared with the control group, these differences were only significant for simple RT ($P < 0.05$).

## Pain Measurements

Outcomes of the experimental and self-reported pain measurements are presented in Table 2. For the experimental pain measurements, the one-way independent ANOVAs indicated significant main effects for the PPTs measured at the shoulder (F2, 75 = 3.94, $P = 0.026$) and TS at the finger (F2, 75 = 4.17, $P = 0.019$). Subsequent post hoc analyses revealed a significantly lower PPT ($P = 0.036$) and enhanced TS ($P = 0.017$) in the CFS+FM group compared with the control group, while there were no significant differences between both patient groups nor between the CFS and control group ($P > 0.05$). PPTs at the finger, TS at the shoulder, and CPM (finger and shoulder) were comparable between the 3 groups ($P > 0.05$).

Self-reported pain, measured with the bodily pain concept of the SF-36, was significantly different among the 3 groups (F2, 75 = 41.97, $P < 0.001$). More specifically, both patient groups showed significantly lower scores (representing more bodily pain) compared with the controls (both $P > 0.001$). Additionally, the CFS+FM group scored significantly lower than the CFS group ($P = 0.004$).

### *Fatigue and Depression*

Both patient groups reported significantly more fatigue (CIS) relative to controls (H2 = 49.68, $P < 0.001$; post hoc paired comparisons indicated $P < 0.001$ in both patient groups vs. controls). A significant main effect was also found for the scores on the BDI-PC (H2 = 12.86, $P = 0.002$). Post hoc paired comparisons indicated a significantly higher BDI-PC score (representing more depressive symptoms) in the CFS+FM group compared with the control group ($P = 0.001$). No other significant differences were found ($P > 0.05$).

## Association between Pain Measurements and Cognitive Performance

### *Correlation analyses*

In the CFS+FM group, CPM measured at the finger was significantly related to OSPAN total score (r = 0.55, $P = 0.002$) and Stroop interference (r = -0.41, $P = 0.023$). No significant correlations were found between self-reported bodily pain and cognitive performance in this group ($P > 0.05$).

In the CFS group, the correlation analyses revealed significant negative correlations between CPM measured at the finger and OSPAN total score (r = -0.52, $P = 0.026$), and between PPT at the finger and the number of lapses on the PVT (r = -0.53, $P = 0.025$). Furthermore, significant negative associations were found between self-reported bodily pain and PVT RT (r = -0.68, $P = 0.002$), Stroop RT of the no-word condition (r = -0.48, $P = 0.043$) and Stroop interference (r = -0.59, $P = 0.01$).

Table 2. *Comparison of pain and self-reported measurements among the study samples.*

| | CFS (n = 18) | CFS+FM (n = 30) | CON (n = 30) |
|---|---|---|---|
| PPT finger (kg/cm²)[a] | 7.4 (5.7) | 5.7 (2) | 6.9 (2.3) |
| PPT shoulder (kg/cm²)[a] | 3.8 (3.2) | 2.5 (1.5)[c] | 3.9 (1.7) |
| TS finger[a] | 1.7 (1.4) | 2.5 (1.5)[c] | 1.4 (1.6) |
| TS shoulder[a] | 1.3 (1.7) | 2.2 (2.2) | 1.3 (1.4) |
| CPM finger[b] | 0.0 (-0.3; 0.3) | 0.0 (-1.0; 1.0) | 0.0 (-0.3; 0.0) |
| CPM shoulder[b] | 0.0 (-1.0; 0.3) | 0.0 (-0.1; 1.0) | 0.0 (-1.0; 1.0) |
| SF-36 Bodily pain[a] | 59.1 (24.3) [e] | 39.9 (19.6) | 85 (14.6)[d] |
| CIS Subjective fatigue[b] | 53.0 (49.0; 54.0) | 50.5 (45.8; 55.0) | 20.5 (12.8; 32.8)[d] |
| BDI-PC[b] | 2.0 (0.8; 4.0) | 3.0 (1.0; 7.0)c | 0.5 (0.0; 2.0) |

Values are mean (SD) or median (Q1; Q3).
CFS = patients with chronic fatigue syndrome; CFS+FM = patients with chronic fatigue syndrome + fibromyalgia; CON = healthy inactive controls.
a Statistical analyses were performed using a one-way independent analysis of variance.
b Statistical analyses were performed using an independent-samples Kruskal Wallis test.
c Significant difference between CFS+FM and CON ($P < 0.05$).
d Significant difference between both CFS+FM and CFS versus CON ($P < 0.001$).
e Significant difference between CFS+FM and CFS ($P < 0.005$).

No significant correlations between pain measurements (experimental and self-reported) and cognitive performance were found in the control group ($P > 0.05$).

## Regression Analyses

Based on the outcome of the correlation analyses, CPM measured at the finger and the bodily pain score of the SF-36 were considered, as experimental and self-reported pain measurement respectively, for further regression analyses. To determine whether pain-related measurements could be predictors of cognitive performance in patients with CFS and CFS with comorbid FM, simple linear regression analyses were performed with "CPM finger" (as experimental pain measurement) and "SF-36 bodily pain" (as self-reported pain measurement) entered as predictor variables. Table 3 presents the results of the regression analyses in both patient groups (CFS and CFS+FM) without covariates (age, fatigue, and depression). The analyses revealed that, in patients with CFS+FM, CPM is a significant predictor for a higher OSPAN total score (= better working memory capacity) ($P = 0.002$) and lower Stroop INT score (= better cognitive inhibition) ($P = 0.007$). These results remained significant when age ($R^2 = 0.34$, $\beta = 0.51$, $P = 0.004$ and $R^2 = 0.24$, $\beta = -0.45$, $P = 0.014$, respectively), fatigue ($R^2 = 0.31$, $\beta = 0.57$, $P = 0.002$ and R2 = 0.23, $\beta = -0.48$, $P = 0.011$, respectively), and depression ($R^2 = 0.30$, $\beta = 0.56$, $P = 0.002$ and $R^2 = 0.27$, $\beta = -0.43$, $P = 0.016$, respectively) were included as separate covariates in the analyses. Self-reported pain (SF-36 bodily pain) seemed neither a significant predictor for cognitive performance ($P > 0.05$) in patients with CFS+FM without covariates nor after controlling for age, fatigue, and depression ($P > 0.05$).

In the CFS-only group, CPM is a significant predictor for a worse OSPAN total score (= worse working memory capacity) ($P = 0.026$). When age was entered as a covariate, the significant negative association between CPM and OSPAN total score remained ($R^2 = 0.32$, $\beta = -0.51$, $P = 0.03$). However, including fatigue as a covariate resulted in CPM no longer being a significant predictor for OSPAN total score (R2 = 0.44, $\beta = -0.40$, $P = 0.69$) and, in contrast, becoming a significant predictor for a higher Stroop INT score (= worse cognitive inhibition) ($R^2 = 0.28$, $\beta = 0.54$, $P = 0.032$). Entering depression as a covariate resulted in a significant association between both CPM and OSPAN total score ($R^2 = 0.29$, $\beta = -0.52$, $P = 0.03$) and CPM and Stroop INT score ($R^2 = 0.33$, $\beta = 0.46$, $P = 0.047$). Self-reported pain (SF-36 bodily pain) seemed to be a significant predictor for PVT RT ($P = 0.002$) in the CFS-only group. This result remained significant when age ($R^2 = 0.50$, $\beta = -0.72$, $P = 0.001$), fatigue ($R^2 = 0.47$, $\beta = -0.68$, $P = 0.003$), and depression ($R^2 = 0.54$, $\beta = -0.80$, $P = 0.001$) were included as separate covariates.

## Success of Assessor Blinding

With regard to the CFS patients (CFS+FM and CFS-only), in 62.5% of the cases (30 out of 48) the assessor's guess about disease status was correct. In the control

*Table 3. Results of simple linear regression analyses predicting cognitive performance on experimental and self-reported pain measures in patients with CFS+FM and patients with CFS.*

| Dependent variable | Predictor variable | B | SE (B) | β | *P* - value | t | $R^2$ | B | SE (B) | β | *P* - value | t | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CFS+FM (n = 30) | | | | | | CFS (n = 18) | | | | | |
| **Predicting cognitive performance on an experimental pain measurement (CPM)** | | | | | | | | | | | | | |
| Stroop RT IC | Constant | 1208.88 | 112.4 | | | | | 1398.76 | 190.37 | | | | |
| | CPM finger | -42.69 | 77.72 | -0.10 | 0.671 | -0.43 | 0.01 | -0.75 | 180.6 | -0.00 | 0.989 | -0.14 | 0.00 |
| Stroop RT NWC | Constant | 1103.67 | 72.28 | | | | | 994.87 | 60.51 | | | | |
| | CPM finger | -116.28 | 49.97 | -0.40 | 0.929 | -0.09 | 0.00 | 109.81 | 57.41 | 0.43 | 0.799 | -0.26 | 0.00 |
| Stroop INT | Constant | 211.49 | 63.36 | | | | | 150.77 | 62.09 | | | | |
| | CPM finger | -126.73 | 43.81 | -0.48 | 0.007 | -2.89 | 0.23 | 122.50 | 58.90 | 0.46 | 0.054 | 2.08 | 0.21 |
| PVT RT | Constant | 343.41 | 8.83 | | | | | 320.97 | 8.63 | | | | |
| | CPM finger | -8.96 | 6.11 | -0.27 | 0.154 | -1.47 | 0.07 | -1.10 | 8.19 | 0.03 | 0.899 | 0.13 | 0.00 |
| PVT Lapses | Constant | 16.50 | 3.41 | | | | | 9.41 | 2.86 | | | | |
| | CPM finger | -3.56 | 2.35 | -0.28 | 0.693 | -0.40 | 0.01 | 3.31 | 2.72 | 0.29 | 0.777 | -0.29 | 0.01 |
| OSPAN | Constant | 50.43 | 2.49 | | | | | 54.52 | 2.22 | | | | |
| Total Score | CPM finger | 5.98 | 1.72 | 0.55 | **0.002** | 3.48 | 0.30 | -5.15 | 2.11 | -0.52 | **0.026** | -2.44 | 0.27 |
| **Predicting cognitive performance on self-reported pain (SF-36 bodily pain)** | | | | | | | | | | | | | |
| Stroop RT IC | Constant | 972.60 | 253.76 | | | | | 1847.24 | 496.29 | | | | |
| | SF-36 BP | 6.08 | 5.72 | 0.20 | 0.226 | 1.24 | 0.05 | -7.60 | 7.81 | -0.24 | 0.251 | -1.19 | 0.08 |
| Stroop RT NWC | Constant | 1180.39 | 180.41 | | | | | 1250.63 | 167.59 | | | | |
| | SF-36 BP | -1.48 | 4.07 | -0.07 | 0.266 | 1.14 | 0.04 | -4.12 | 2.64 | -0.36 | 0.232 | -1.24 | 0.09 |
| Stroop INT | Constant | 386.92 | 162.09 | | | | | 396.10 | 177.10 | | | | |
| | SF-36 BP | -3.92 | 3.66 | -0.20 | 0.293 | -1.07 | 0.04 | -3.92 | 2.79 | -0.33 | 0.178 | -1.41 | 0.11 |
| PVT RT | Constant | 345.51 | 21.00 | | | | | 379.70 | 16.96 | | | | |
| | SF-36 BP | -0.02 | 0.47 | -0.01 | 0.968 | -0.04 | 0.00 | -0.99 | 0.27 | -0.68 | **0.002** | -3.72 | 0.46 |
| PVT Lapses | Constant | 20.49 | 8.08 | | | | | 26.03 | 6.73 | | | | |
| | SF-36 BP | -0.09 | 0.18 | -0.09 | 0.528 | 0.62 | 0.01 | -0.28 | 0.11 | -0.55 | 0.434 | -0.80 | 0.04 |
| OSPAN | Constant | 50.74 | 6.81 | | | | | 54.98 | 6.98 | | | | |
| Total Score | SF-36 BP | -0.03 | 0.15 | -0.04 | 0.846 | -0.20 | 0.00 | -0.02 | 0.11 | -0.04 | 0.875 | -0.16 | 0.00 |

CFS = patients with chronic fatigue syndrome; CFS+FM = patients with chronic fatigue syndrome + fibromyalgia; CPM finger = conditioned pain modulation measured at the finger; SF-36 BP = bodily pain concept of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36); RT IC = reaction time incongruent condition; RT NWC = reaction time no word condition; PVT = psychomotor vigilance task; OSPAN = operation span.
Significant *P*-values are printed in bold.

group the assessor assumed correctly in 90% of the cases (27 out of 30).

## Discussion

This study was the first to investigate the association between cognitive performance and experimental pain measurements and measures of CS in patients with CFS. In addition, to extend previous investigations, CFS patients were subgrouped into CFS-only and CFS+FM patients to determine the influence of comorbid FM on CFS patients' self-reported and experimental pain outcomes and their associations with cognitive performance.

The results of this study demonstrate that the presence of comorbid FM certainly has an impact on outcomes when studying patients with CFS. More specifically, we found CFS+FM patients being more severely affected, by demonstrating hyperalgesia, enhanced

endogenous pain facilitation, and significantly more depressive symptoms compared with healthy controls, while this was not the case in the CFS-only group. Furthermore, the results indicate that a measure of endogenous pain inhibition might be a significant predictor of cognitive performance in CFS patients with comorbid FM, while a self-reported pain measure appears more appropriate to predict cognitive performance in CFS patients without FM.

Patients with CFS and comorbid FM were more disabled than CFS patients without FM, as evidenced by their lower PPTs, more enhanced TS, more self-reported pain and depressive symptoms compared to the CFS-only group. However, these differences between both patient groups only reached significance for self-reported pain. Nevertheless, the CFS+FM group showed hyperalgesia and enhanced pain facilitation. This was evidenced by a significantly lower PPT at the shoulder and enhanced TS at the finger compared with healthy controls, while CFS-only patients on the other hand showed no hyperalgesia and exhibited normal endogenous pain modulation (both pain facilitation and inhibition). These findings support our earlier suggestion (13), namely, that reducing the heterogeneity of the disorder in future research could be important to better understand and uncover mechanisms regarding the nature of divers impairments in patients with CFS.

Our results furthermore showed that CPM measured at the finger is able to predict working memory capacity and cognitive inhibition in CFS patients with FM. Associations with other cognitive variables were not significant. Nevertheless, the post hoc power analyses revealed only moderate power (≤ 71%) for detecting associations between CPM and measures of selective attention and simple RT. This means that a false negative result, probably as a result of the small sample size, cannot be excluded in these cases. Conversely, the power was sufficiently high (≥ 91%) to detect associations between CPM and measures of choice RT and sustained attention, meaning that these results were true negative. A low power (≤ 58%) was also found in 4 out of 6 regression analyses of self-reported pain and cognitive performance. This possibly explains the absence of significant associations between cognitive performance and self-reported pain in this group.

In CFS-only patients, despite the sufficiently high power and apart from one significant negative association with working memory capacity, we did not find significant associations between CPM and cognitive performance. A significant association was found between self-reported pain and simple RT, while the post hoc power analyses revealed low power (≤ 66%) for detecting significant associations between self-reported pain and measures of selective attention, choice RT and cognitive inhibition. Thus, here as well false negative results, probably because of the small sample size, cannot be excluded.

In summary, regarding the associations between cognitive performance and pain measurements, this study revealed that CPM might be a significant predictor of cognitive performance in CFS patients with comorbid FM, while self-reported pain might be a predictor of cognitive performance in CFS patients without FM. CPM efficiency represents an important brain-orchestrated inhibitory mechanism of pain processing (45). A higher CPM value reflects a more efficient pain inhibitory response. Subsequently, in the CFS+FM group, significant associations with CPM were found with cognitive tasks demanding high levels of inhibitory control (i.e., working memory and cognitive inhibition). These findings show that in CFS+FM patients inhibition of environmental and internal distractions and the capacity of pain inhibition go hand in hand. We therefore hypothesize that malfunctioning of descending inhibitory pathways (e.g., serotonergic and noradrenergic descending pathways) precludes optimal cognitive function in these patients. On the other hand, the activation of overlapping brain regions leading to competition between pain and cognition for processing resources in the brain, may explain worse inhibition of environmental and internal distractions in the presence of better pain inhibitory capacity and vice versa in CFS-only patients. These findings, together with the more pronounced cognitive problems in CFS+FM patients compared to those without FM, suggest a different – however, not necessarily mutually exclusive – neurobiological basis of pain-related cognitive impairment in both groups (13). To better understand the mechanisms underlying these cognitive dysfunctions, further research with direct monitoring of brain activity (e.g., using functional magnetic resonance imaging) is warranted.

This study suggests that endogenous pain inhibition and self-reported pain are clinically important measures in CFS patients with and without comorbid FM, respectively. Indeed, these measures are not only important tools for the evaluation of CS in these patients, but reduced values could also be an indication to clinicians to monitor their patients' cognitive function. Hence, therapy should not merely target the patients' return to physical but also to cognitive tasks.

In addition, it would be most valuable for future research to examine these associations in other chronic pain conditions, particularly in highly heterogeneous patient groups such as complex regional pain syndrome among others.

The findings of this study should be interpreted minding its methodological strengths and weaknesses. First, it should be mentioned that the groups were rather small for the regression analyses. Since the power of the non-significant associations was oftentimes rather low, this could possibly explain the absence of significance in some of these associations (i.e., possible type II errors in the associations between CPM and measures of selective attention and simple RT in the CFS+FM group and between self-reported pain and cognitive performance in both groups). Second, the cross-sectional nature of this study does not allow for inferences of causation. Additionally, given the absence of previous data regarding the association between cognitive performance and pain measurements in these subgroups, an exploratory approach was used to test several hypotheses. Although we accounted adequately for possible type I errors in the statistical analyses, the latter entails that findings must be considered cautiously. Future studies should try to account for the aforementioned limitations by increasing their sample sizes. Furthermore, the findings of this study yet again confirm the prevalent heterogeneity within people suffering from CFS and consequently, the importance of taking this into account in future research. Lastly, the generalizability of our results might be reduced because only Belgian people were studied here. Therefore, care should be taken when applying the results to foreign patient populations such the US population, among others.

The most important strength of this study is that our control group was matched to both patient groups for age, gender, and body mass index. Furthermore, both CFS groups were matched for disease duration as well. Additionally, healthy controls had to be inactive because it is known that CFS patients, in general, have a more sedentary lifestyle (46). This way, observed differences could not be due to a higher activity level of the control group. Another important strength of this study is that we anticipated sources of bias like pregnancy; use of medication, caffeine, alcohol, and nicotine; and execution of physical exertion on the days of the assessments. Moreover, we accounted statistically for age, fatigue severity, and depressive symptoms and we reduced the heterogeneity of the disease as well by including CFS patients according to the same strict diagnostic criteria and in addition dividing this group based on FM comorbidity. A final study strength worth mentioning is that we attempted to blind the assessor regarding participants' disease status. However, this was only successful in 37.5% of the patients and in 10% of the controls.

## Conclusion

In conclusion, this study shows that associations between cognitive performance and pain measurements are different in CFS patients with and without FM. Although larger confirmatory studies are needed, these study findings suggest that better endogenous pain inhibition could predict better mental health in patients with CFS and comorbid FM, while less self-reported pain could predict better mental health in CFS patients without FM. Reducing the heterogeneity of CFS in future research is important to better understand and uncover the underlying mechanisms of divers impairments, including cognitive impairments, in these patients. This will ultimately lead to improvements of guided therapy.

### Acknowledgments

The authors would like to thank Tinne Boey and Laura van Weijnen for their aid in the data input.

### Funding

The study was funded by ME Research UK, a national charity funding biomedical research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Mira Meeus is awardee of the 2012 early research career grant of the International Association for the Study of Pain (IASP), funded by the ScanDesign Foundation by INGER & JENS BRUUN. Jo Nijs is holder of the Chair "Exercise immunology and chronic fatigue in health and disease" funded by the European College for Decongestive Lymphatic Therapy, The Netherlands. Kelly Ickmans is a research fellow of ME Research UK.

### Author Contributions

J.N. and M.M. provided the concept, idea, and grant. K.I., M.D.K., and L.L. conducted the study. K.I., J.N., M.D.K., L.L., and M.M. managed the study. K.I., J.N., and N.P. analyzed and interpreted the data. All authors discussed the results, participated in writing the manuscript, and approved the final version.

## References


1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: A comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; 121:953-959.
2. Fitzcharles MA, Ste-Marie PA, Pereira JX. Fibromyalgia: Evolving concepts over the past 2 decades. *CMAJ* 2013; 185:645-651.
3. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, Martin SA, Morea J, Simon L, Strand CV, Williams DA. Fibromyalgia syndrome module at OMERACT 9: domain construct. *J Rheumatol* 2009; 36:2318-2329.
4. Bradley LA, McKendree-Smith NL, Alarcon GS. Pain complaints in patients with fibromyalgia versus chronic fatigue syndrome. *Curr Rev Pain* 2000; 4:148-157.
5. Ciccone DS, Natelson BH. Comorbid illness in women with chronic fatigue syndrome: A test of the single syndrome hypothesis. *Psychosom Med* 2003; 65:268-275.
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 fibromyalgia. *Pain* 2004; 107:7-15.
7. Meeus M, Nijs J. Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clin Rheumatol* 2007; 26:465-473.
8. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Man Ther* 2010; 15:135-141.
9. Yunus MB. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum* 2007; 36:339-356.
10. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain* 2011; 152:S2-S15.
11. Meyer RA, Campbell IT, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R (eds). *Textbook of Pain*. 3rd ed. Churchill Livingstone, Edinburgh, 1995, pp 13-44.
12. Glass JM. Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: New trends and future directions. *Curr Rheumatol Rep* 2006; 8:425-429.
13. Ickmans K, Meeus M, De Kooning M, Lambrecht L, Pattyn N, Nijs J. Can recovery of peripheral muscle function predict cognitive task performance in chronic fatigue syndrome with and without fibromyalgia? *Phys Ther* 2014; 94:511-522.
14. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: A review of clinical and preclinical research. *Prog Neurobiol* 2011; 93:385-404.
15. Luerding R, Weigand T, Bogdahn U, Schmidt-Wilcke T. Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: Structural correlates of pain-cognition interaction. *Brain* 2008; 131:3222-3231.
16. de Lange FP, Koers A, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain* 2008; 131:2172-2180.
17. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005; 26:777-781.
18. Duric V, McCarson KE. Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression. *J Pain* 2006; 7:544-555.
19. Ji G, Sun H, Fu Y, Li Z, Pais-Vieira M, Galhardo V, Neugebauer V. Cognitive impairment in pain through amygdala-driven prefrontal cortical deactivation. *J Neurosci* 2010; 30:5451-5464.
20. Alexander GM, van Rijn MA, van Hilten JJ, Perreault MJ, Schwartzman RJ. Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain* 2005; 116:213-219.
21. Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis Rheum* 2001; 44:2125-2133.
22. Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *J Clin Exp Neuropsychol* 1999; 21:477-487.
23. Alanoglu E, Ulas UH, Ozdag F, Odabasi Z, Cakci A, Vural O. Auditory event-related brain potentials in fibromyalgia syndrome. *Rheumatol Int* 2005; 25:345-349.
24. Ickmans K, Meeus M, Kos D, Clarys P, Meersdom G, Lambrecht L, Pattyn N, Nijs J. Cognitive performance is of clinical performance, but is unrelated to pain severity in women with chronic fatigue syndrome. *Clinical Rheumatology* 2013; 32:1475-1485.
25. 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 Res (Hoboken)* 2010; 62:600-610.
26. Bernstein MS, Morabia A, Sloutskis D. Definition and prevalence of sedentarism in an urban population. *Am J Public Health* 1999; 89:862-867.
27. 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.
28. Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 1935; 28:643-662.
29. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual Rt task during sustained operations. *Behavior Research Methods Instruments & Computers* 1985; 17:652-655.
30. Conway AR, Engle RW. Individual differences in working memory capacity: More evidence for a general capacity theory. *Memory* 1996; 4:577-590.
31. Cathcart S, Winefield AH, Rolan P, Lushington K. Reliability of temporal summation and diffuse noxious inhibitory control. *Pain Res Manag* 2009; 14:433-438.
32. Meeus M, Ickmans K, De Clerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Serotonergic descending inhibition in chronic pain: Design, preliminary results and early cessation of a randomized controlled trial. *In Vivo* 2011; 25:1019-1025.
33. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W. Pressure algometry in manual therapy. *Man Ther* 1996; 1:258-265.
34. Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region. The influence of skin sensitivity in pressure algometry. *Scand J Rehabil Med* 1999; 31:89-93.
35. Ware JE, Jr., Snow KK, Kosinki M, Gan-

dek B. *SF-36 Health Survey Manual and Interpretation Guide*. The Health Institute, Boston, 1993.

36. Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S, Greenfield S, Ware J. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *JAMA* 1989; 262:914-919.
37. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31:247-263.
38. Haywood KL, Staniszewska S, Chapman S. Quality and acceptability of patient-reported outcome measures used in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): A systematic review. *Qual Life Res* 2012; 21:35-52.
39. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994; 38:383-392.
40. Vercoulen JH, Alberts M, Bleijenberg G. The Checklist Individual Strength (CIS). *Gedragstherapie* 1999; 32:131-136.
41. Steer RA, Cavalieri TA, Leonard DM, Beck AT. Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. *Gen Hosp Psychiatry* 1999; 21:106-111.
42. Oncu J, Basoglu F, Kuran B. A comparison of impact of fatigue on cognitive, physical, and psychosocial status in patients with fibromyalgia and rheumatoid arthritis. *Rheumatol Int* 2013; 33:3031-3037.
43. Geisser ME, Roth RS, Robinson ME. Assessing depression among persons with chronic pain using the Center for Epidemiological Studies-Depression Scale and the Beck Depression Inventory: A comparative analysis. *Clin J Pain* 1997; 13:163-170.
44. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007; 39:175-191.
45. Le Bars D, Villanueva L. Electrophysiological evidence for the activation of descending inhibitory controls by nociceptive afferent pathways. *Prog Brain Res* 1988; 77:275-299.
46. Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, Nijs J. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: A case-control study. *Arch Phys Med Rehabil* 2011; 92:1820-1826.