

Case-Control Study

Cognitive Performance Is Related to Central Sensitization and Health-related Quality of Life in Patients with Chronic Whiplash-Associated Disorders and Fibromyalgia

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Background: A growing body of research has demonstrated that impaired central pain modulation or central sensitization (CS) is a crucial mechanism for the development of persistent pain in chronic whiplash-associated disorders (WAD) and fibromyalgia (FM) patients. Furthermore, there is increasing evidence for cognitive dysfunctions among these patients. In addition, chronic WAD and FM patients often report problems with health-related quality of life (QoL). Yet, there is limited research concerning the interrelations between cognitive performance, indices of CS, and health-related QoL in these patients.

Objectives: (1) Examining the presence of cognitive impairment, CS, and limitations on health-related QoL in patients with chronic WAD and FM compared to healthy controls. (2) Examining interrelations between performance-based cognitive functioning, CS, and self-reported health-related QoL in these 3 study groups.

Study Design: A case-control study was conducted.

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

Methods: Fifty-nine patients (16 chronic WAD patients, 21 FM patients, and 22 pain-free volunteers) filled out the Short Form 36 item Health Survey (SF-36), a self-reported psychosocial questionnaire, to assess health-related QoL. Next, they were subjected to various pain measurements (pressure hyperalgesia, deep-tissue hyperalgesia, temporal summation [TS], and conditioned pain modulation [CPM]). Finally, participants completed a battery of performance-based cognitive tests (Stroop task, psychomotor vigilance task [PVT], and operation span task [OSPAN]).

Results: Significant cognitive impairment, bottom-up sensitization, and decreased health-related QoL were demonstrated in patients with chronic WAD and FM compared to healthy controls ($P < 0.017$). CPM was comparable between the 3 groups. Cognitive performance was significantly related to central pain modulation (deep-tissue hyperalgesia, TS, CPM) as well as to self-reported health-related QoL ($P < 0.05$). Decreased cognitive performance was related to deficient central pain modulation in healthy controls. Further, significant correlations between decreased cognitive performance and reduced health-related QoL were revealed among all study groups. Additionally, FM patients showed correlations between cognitive impairment and increased health-related QoL. Remarkably, impaired selective attention and working memory were related to less TS, whereas impaired sustained attention was correlated with dysfunctional CPM in FM patients.

Limitations: Based on the current cross-sectional study no firm conclusions can be drawn on the causality of the relations.

Conclusion: In conclusion, this paper has demonstrated significant cognitive deficits, signs of CS, and reduced health-related QoL in chronic WAD and FM patients compared to healthy individuals. Significant relations between cognitive performance and CS as well as health-related QoL were demonstrated. These results provide preliminary evidence for the clinical importance of objectively measured cognitive deficits in patients with chronic WAD and FM.

Key words: Chronic pain, fibromyalgia, whiplash, central sensitization, conditioned pain modulation, temporal summation, cognition, quality of life

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1. INTRODUCTION

A whiplash injury is caused by a sudden acceleration-deceleration of the head, mostly due to motor vehicle collisions (1,2). Up to 50% of whiplash patients develop chronic neck pain and disability (3,4). The term chronic whiplash-associated disorders (WAD) is used to describe the various symptoms that are experienced by whiplash patients beyond 3 months after the accident (1). These symptoms include persistent neck pain, referred pain, headache, dizziness, emotional and cognitive disturbance, and physical dysfunctions (5-7). Fibromyalgia (FM) is another condition characterized by various persistent symptoms (8).

The diagnosis of FM is based upon the 1990 or 2010 American College of Rheumatology (ACR) criteria (9). According to these criteria, FM patients are characterized by chronic widespread musculoskeletal pain. Additionally, FM patients experience a variety of symptoms, including sleep disturbances, fatigue, cognitive dysfunctions, and limitations in activities of daily living (8,10). Chronic pain is a predominant and common debilitating symptom in both patients with WAD and FM (11-13).

Nowadays, there is compelling evidence for impaired central pain modulation or central sensitization (CS) in both patients with chronic WAD and FM as the underlying mechanism of their pain complaints (11,13-17). CS is defined as an exaggerated responsiveness of the central nervous system to a variety of stimuli, like pressure, temperature, light, and medication among others (18,19). The CS mechanism causes hyperalgesia, allodynia, temporal summation (TS), and referred pain across multiple spinal segments, leading to chronic widespread pain (11). The augmented excitability results in a largely decreased load tolerance of the neuromusculoskeletal system. Contiguously, it has been shown that alterations in descending pain pathways are involved in the CS process (20). Malfunctioning of descending neuronal pathways can lead to more facilitation and less inhibition of the transmitted nociceptive signals to the brain.

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 (21). Earlier studies provided evidence for inefficient CPM activation in patients with chronic WAD and FM (13,22-24). In addition, TS, defined as the increase in pain ratings after repetitive stimulation at a constant intensity, is widely used in pain research to assess hyperexcitability of the central nervous system

(21,25). Interestingly, it seems that activation of CPM is able to reduce TS among healthy pain-free individuals (26). By measuring both CPM, combined with the evaluation of enhanced TS, important information regarding central nervous systems' pain modulation can be obtained.

Apart from persistent pain, chronic WAD and FM patients often experience cognitive deficits, including concentration difficulties and working memory deficits (1,9,10,27). More specifically, the cognitive deficits encompass longer reaction times, short-term memory deficits, and attention problems (28-30). Decreased cognitive function seems to be related to pain severity in various chronic pain populations (29,31), and is presumed to be a feature of CS (19). Accordingly, it is hypothesized that malfunctioning of endogenous pain inhibition and subsequent chronic pain precludes optimal cognitive performance. This hypothesis is supported by the findings of altered brain morphology (32,33) and brain activity (34,35) in patients with chronic WAD and FM.

Besides the growing evidence for the above mentioned dysfunctions, studies examining the relation between objectively measured cognitive performance, CS, and health-related quality of life (QoL) in patients with chronic WAD and FM are limited (28). Accordingly, it is necessary to further investigate the possible relations between cognitive performance, CS, and health-related QoL in patients with chronic CS pain, like those with chronic WAD or FM. It is hypothesized that cognitive impairment is related to CS and increased limitations on health-related QoL.

Therefore, the aims of the current study are: 1) to compare these aspects between 2 patients groups characterized by CS, chronic WAD and FM, and healthy controls; and 2) to investigate the interrelations between cognitive performance, CS, and self-reported health-related QoL in patients with chronic WAD and FM, and healthy pain-free controls.

2. METHODS

2.1. Study Design and Setting

The present case-control study took place at the University Hospital Brussels, the University of Brussels, and the University of Antwerp. Participants received detailed study information and gave written informed consent prior to study enrollment. All patients and healthy control subjects were unpaid volunteers. This research was approved by the Ethics committee of the University Hospital Brussels.

2.2. Participants and Assessments

The present study took place from July 2010 until December 2013. 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 physicians. Eligible patients, men and women, were contacted by phone and/or email. In addition, patients were contacted using social network and Internet sites of chronic WAD and FM associations. Healthy controls were recruited through friends, relatives, or acquaintances of students, researchers, patients, 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) (1). 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 ACR (9). FM patients reporting a history of a whiplash trauma and chronic WAD patients fulfilling the diagnostic criteria for FM were excluded from the study. At the time of study participation, healthy individuals were not allowed to suffer from any pain complaints or any (chronic) disease.

General exclusion criteria were neurologic, metabolic, cardiovascular, or inflammatory disorders. In order to preclude confounding factors, pregnant women and women 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 alcohol, caffeine, and nicotine on the day of the experiments.

2.3. Central Sensitization

To investigate central pain modulation and the presence of CS, 4 critical aspects of the central pain system were assessed (36-39). First, in order to evaluate local and widespread hyperalgesia, pressure pain thresholds (PPTs) were measured with a digital algometer (Wagner Instruments, Greenwich, CT, USA) at symptomatic and remote areas. Secondly, deep-tissue hyperalgesia was evaluated. Thirdly, TS of pressure pain was examined. Finally, a CPM paradigm was conducted to assess the efficacy of endogenous pain inhibition.

2.3.1. Pressure Hyperalgesia

The PPT was measured at 2 different sites: the dorsal side of the intermediate phalanx of the right middle finger and the middle of the right trapezius belly, midway between the processus spinosus of the seventh cervical

vertebra and the lateral edge of the acromion (40,41). On each site, 2 PPT measurements (interval 30 seconds) were performed, generating a mean PPT value per site. To determine the PPT, pressure was increased at a rate of approximately 1 kg/s and participants were asked to say "stop" at the moment the sensation became painful. Consequently, the pressure was immediately released. The pressure established on that moment was determined as the PPT, measured in kg/cm². 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 (22,42,43).

2.3.2. Deep-tissue Hyperalgesia

Deep-tissue hyperalgesia was investigated by inflating an occlusion cuff placed around the left arm. The cuff served also as the conditioned stimulus in the CPM paradigm (see further). Cuff inflation rate was constant (20 mmHg/s) and manually increased until the participant reported pain. The pressure at this moment was registered (cuff pressure) and used for further data analyses. Participants then adapted to the stimulus for 30 seconds and rated the pain on the verbal numeric rating scale (VNRS). Cuff inflation was then adjusted until participants indicated pain at a level 3 of 10 on the VNRS. Subsequent, this pressure (cuff pressure VNRS3) was stored and used for further data analyses.

2.3.3. Temporal Summation

TS was induced by means of a digital algometer (Wagner Instruments, Greenwich, CT, USA). TS was elicited by 10 consecutive pressure pulses at PPT intensity on the same places. For each pulse of the TS procedure, the pressure was increased at a rate of 2 kg/s until the previously determined PPT, where it was maintained for one second before being released. Pressure pulses were presented with an inter-stimulus interval of one second. Participants were instructed to rate the pain intensity of the first, fifth, and tenth pressure pulse according to the VNRS. TS score was obtained by subtracting the first VNRS score from the last VNRS. The higher the TS score, the more efficient the nociceptive signaling to the brain. The TS procedure is found to be reliable and valid, and is supported to use in chronic pain patients (36).

2.3.4. Conditioned Pain Modulation

CPM was induced by inflating an occlusion cuff (conditioning stimulus) on the left arm, opposite of the test stimulus, to a painful intensity (see 2.3.2), being the TS procedure repeated while wearing the cuff.

The CPM procedure started when cuff inflation was adjusted equal to a level 3 of 10 on the VNRS. The left arm was then rested on a table while TS assessment was repeated at the right side as described above (36).

Efficacy of CPM is examined by subtracting the VNRS at the first pressure pulse prior to and during cuff inflation (CPM). The efficacy of CPM on TS was assessed by subtracting TS of pressure pain (VNRS tenth pressure pulse) prior to and during cuff inflation (CPM on TS) (28). This CPM procedure is found to be reliable, and CPM induced by ischemic cuff inflation is able to reduce TS in healthy controls (36).

2.4. Cognitive Performance

Cognitive performance was assessed using a battery of 3 consecutive computer tests: the Stroop task, the psychomotor vigilance task (PVT), and the operation span task (OSPAN). In order to standardize the procedure, each test began with the presentation of written instructions for that particular test. All study participants performed the cognitive tasks on the same computer and in a fixed order (i.e., Stroop task, PVT, and OSPAN). Each of the 3 tests has been used and described in detail in 3 of our previous studies in patients with chronic CS pain (28,44,45).

2.4.1 The Stroop Task

The Stroop Task was used to evaluate selective attention, cognitive inhibition, and choice reaction time (46). Three different conditions were used, namely, "incongruent" (word and ink color are different), "non word" (XXX in a specific color), and "negative priming" (e.g., the word green displayed in red immediately followed by the word blue displayed in green).

Stroop reaction times for correct responses were taken into account for further analyses. Stroop interference effect was calculated by subtracting Stroop reaction time non-word from Stroop reaction time incongruent. Stroop interference seems to reflect one's ability to inhibit irrelevant information, and is therefore a measure of cognitive inhibitory capacity.

Negative priming is defined as the condition where the to-be-ignored response in the first presentation becomes the subsequent relevant dimension. Furthermore, negative priming is believed to rely on one of the mechanisms of selective attention (47). Hence, negative priming can provide more information about the quality of cognitive control to select relevant information.

2.4.2. The Psychomotor Vigilance Task

The PVT has been validated as a measure of sustained attention, alertness, and simple reaction time (48). Participants were instructed to respond as quickly as possible to a visual stimulus (red spot on a black screen) presented at a variable time-interval (2,000 – 10,000 ms). The trial was stored as a lapse, if a response had not been made within 500 ms. The PVT reaction time of correct responses and number of lapses were registered and used for statistical analyses. The PVT has good test-retest reliability for median response times (ICC = 0.89, $P < 0.0001$) and number of PVT lapses (ICC = 0.83, $P < 0.0001$) (49).

2.4.3. The Operation Span Task

The OSPAN task was used to assess working memory capacity (50). The OSPAN task consisted of exercises on letter recall and math operation. The "Operation span" is the maximum number of letters that can be recalled. When the test was terminated, the "OSPAN total score" was retrieved and used for further statistical analyses. The "OSPAN total score" is the sum of all perfectly recalled exercise sets. This score measures working memory capacity as it indicates the number of letters recalled in the correct position.

2.5. Self-reported Health-related QoL

The Short Form 36-item Health Survey (SF-36) was used to assess physical function, mental health, and health-related QoL (51). This self-reported questionnaire examines 2 main domains of health, namely the physical and mental component. Higher scores represent better health for that particular subitem.

The SF-36 has been demonstrated to have good reliability and validity in chronic pain patients (51).

2.6. Data Analysis

All statistical analyses were performed using IBM® SPSS® Statistics 22.0. Normality of variables was tested with the Shapiro-Wilk test and by visual evaluation of the histograms and QQ-plots. In addition, the Levene's test examined equality of variance. The assumption of data normality and equality of variance was not fulfilled. Accordingly, non-parametric tests were used for further data analyses. Comparability of groups for age, gender distribution, and disease duration was examined with the one-way ANOVA test and Chi-square test.

First, the median values of the SF-36 questionnaire, pain measurements, and performance-based cognitive

tests were compared between the 3 study groups using the Kruskal-Wallis test. When a significance level of $P < 0.05$ was found, the Mann-Whitney U test was performed for post-hoc comparisons. A significance level of $P < 0.017$ ($\alpha < 0.05/3$) was used (Bonferroni correction was applied to compensate for the multiple testing problem) and to maintain the initial significance level of $\alpha < 0.05$.

To determine the relationship between cognitive performance, CS, and health-related QoL, Spearman correlation coefficients were calculated between the results of the cognitive tests and central pain measures and SF-36 scores, respectively.

3. RESULTS

3.1. Group Characteristics

The demographic characteristics of the 3 study groups are presented in Table 1. All study groups were comparable for age and sex distribution. Further, disease duration was not significantly different between the 2 patient groups.

3.2 Comparison between Patients with Chronic WAD, FM, and Healthy Controls

3.2.1 Central Sensitization

Pressure hyperalgesia and deep-tissue hyperalgesia

Results of pressure and deep-tissue hyperalgesia are displayed in Table 2. PPTs at the shoulder and finger were significantly lower in FM patients compared to chronic WAD patients and controls. In addition, cuff pressures at the arm were significantly lower in the FM group compared to healthy participants.

Temporal summation and conditioned pain modulation

Results of TS prior to cuff inflation are shown in Table 2. No significant differences in TS were observed between chronic WAD and FM. In contrast, TS was significantly higher in both patient groups in comparison with healthy controls. The 3 study groups displayed no significant differences for the efficacy of endogenous pain inhibition (CPM).

3.2.2 Cognitive Performance

Table 3 presents the median and interquartile ranges (IQR) of the 3 performance-based cognitive tests and their subscales for the patients and controls. FM

Table 1. Demographic characteristics of the patients (cWAD and FM) and healthy controls.

Characteristics	cWAD (n = 16)	FM (n = 21)	CON (n = 22)	P value ANOVA	P value Post-hoc Bonferroni		
					cWAD vs FM	CON vs cWAD	CON vs FM
Age (y) ^b	41.62 (11.45)	44.52 (9.47)	38.00 (13.90)	0.202	1	1	0.227
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
Occupational situation ^c	7 unemployed	16 unemployed	4 unemployed				
	1 part-time	2 part-time	4 part-time				
	8 full-time	3 full-time	9 full-time				
	0 student	0 student	5 student				
Pain medication use (yes, no) ^c	0; 16	4; 17	1; 21	0.084			
Antidepressant use (yes, no) ^c	4; 12	7; 14	1; 21	< 0.001			
Other medication use (yes, no) ^c				0.448			
Benzodiazepines & muscle relaxants	1; 15	1; 20	1; 21				
Antihypertensive	0; 16	0; 21	3; 19				
Medication for hyper- or hypothyroidism	1; 15	3; 18	0; 22				
Medication for diabetes	1; 15	1; 20	0; 22				
Anti-epileptic	0; 16	0; 21	1; 21				

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 ($P < 0.017$). y: years, m: months, cWAD: chronic whiplash-associated disorders, FM: fibromyalgia, CON: healthy controls

Table 2. Comparison of pressure hyperalgesia, deep-tissue hyperalgesia, temporal summation, and conditioned pain modulation between patients (cWAD and FM) and healthy controls.

Pain Measures	cWAD (n = 16)	FM (n = 21)	CON (n = 22)	Kruskal-Wallis	Mann-Whitney U
	Median (IQR)	Median (IQR)	Median (IQR)	P value < 0.05	P value < 0.017
Pressure and deep tissue hyperalgesia					
PPT finger	7.70 (5.40 – 9.60)	3.00 (1.89 – 5.68)	6.65 (4.47 – 9.35)	0.002	FM < cWAD [°] ; FM < CON*
PPT shoulder	4.00 (2.50 – 5.20)	1.32 (1.08 – 2.60)	4.22 (2.99 – 5.80)	0.000	FM < cWAD [°] ; FM < CON*
Cuff pressure	160.00 (90.00 – 200.00)	80.00 (63.00 – 145.00)	170.00 (97.5 – 215)	0.018	FM < CON*
Cuff pressure (VNRS3)	110.00 (60.00 – 200.00)	63.00 (42 – 90)	100.00 (80 – 172)	0.020	FM < CON*
Temporal summation					
TS finger	3.50 (2.00 – 5.00)	2.00 (1.00 – 3.00)	2.00 (1.00 – 3.00)	0.025	cWAD > CON**
TS shoulder	3.00 (2.00 – 4.00)	3.00 (2.00 – 5.00)	1.00 (0.00 – 3.00)	0.009	FM > CON*; cWAD > CON**
Conditioned pain modulation					
CPM finger (VNRS1)	0.00 (0.00 – 2.00)	0.00 (0.00 – 1.00)	0.00 (0.00 – 1.00)	0.620	ns
CPM shoulder (VNRS1)	1.00 (0.00 – 2.00)	0.00 (- 0.75 – 1.00)	1.00 (0.00 – 2.00)	0.080	ns
CPM on TS finger (VNRS10)	1.00 (0.00 – 3.00)	0.00 (-0.37 – 1.00)	2.00 (0.00 – 2.00)	0.070	ns
CPM on TS shoulder (VNRS10)	1.00 (0.00 – 2.50)	1.00 (0.00 – 1.75)	1.00 (0.00 – 2.00)	0.600	ns

Values are presented as median value and interquartile range (IQR). Significant differences are presented in bold font. PPT: Pressure pain threshold, VNRS: Verbal numeric rating scale, TS: Temporal summation, CPM: Conditioned pain modulation, ns: not significant, cWAD: chronic whip-lash-associated disorders, FM: fibromyalgia, CON: healthy controls. Significant differences ($P < 0.017$) between cWAD and FM are presented as ([°]) between CON and FM are presented as (*) between CON and cWAD are presented as (**).

patients presented impaired cognitive performance on all cognitive tests compared to healthy individuals. Chronic WAD patients only demonstrated impaired performance on the PVT test (significant longer PVT reaction times and more PVT lapses) compared to healthy pain-free controls.

3.2.3 Self-reported Health-related QoL

Median values and interquartile ranges (IQR) of the SF-36 total score, mental and physical health summary score are presented in Table 4.

FM patients demonstrated higher limitations on all the SF-36 physical health domains compared to chronic WAD patients. In addition, both patient groups reported significantly more problems on physical and mental health compared to healthy participants.

3.3 Relations between Cognitive Performance, CS, and Health-related QoL

3.3.1. Cognitive Performance and Central Sensitization

In the chronic WAD group, deep-tissue hyperalgesia was the only variable that significantly correlated ($r = 0.517$, $P < 0.05$) with cognitive performance, i.e. Stroop interference (data not shown).

FM patients showed significant relations between cognitive performance and 4 measures of CS, as presented in Table 5. Longer Stroop reaction times and decreased recall capacities on the OSPAN were significantly correlated with lower TS scores. Further, an increased number of PVT lapses was significantly correlated with lower tolerable cuff pressure (VNRS3) and less efficient endogenous pain inhibition (CPM).

In the healthy control group, longer Stroop and PVT reaction times were significantly related with respectively, less CPM efficiency and lower cuff pressure (VNRS3) as demonstrated in Table 5.

Cognitive Performance Related to Central Sensitization and Quality of Life

Table 3. Comparison of cognitive performance (Stroop Task, PVT, OSPAN) between patients (cWAD and FM) and healthy controls.

COGNITIVE TESTS	cWAD (n = 16)	FM (n = 21)	CON (n = 22)	Kruskal-Wallis	Mann-Whitney U
	Median (IQR)	Median (IQR)	Median (IQR)	P value < 0.05	P value < 0.017
Stroop reaction times (ms)					
Incongruent	1082.63 (977.52 – 1326.83)	1329.17 (1134.53 – 1605.71)	998.53 (886.49 – 1157.48)	0.006	FM > CON*
Non-word	1014.61 (859.03 – 1134.20)	1226.52 (1017.99 – 1384.80)	903.39 (852.98 – 1095.35)	0.016	FM > CON*
Stroop Interference	127.79 (29.20 – 223.60)	143.53 (65.14 – 194.91)	39.17 (6.05 – 114.59)	0.025	FM > CON*
Priming negative	1063.11 (954.06 – 1572.11)	1333.89 (1168.65 – 1735.66)	983.55 (884.11 – 1203.07)	0.018	FM > CON*
Psychomotor Vigilance Task					
Reaction time (ms)	342.92 (319.50 – 382.43)	328.20 (315.34 – 362.98)	298.05 (281.96 – 315.88)	0.000	FM > CON; cWAD > CON
Lapses	12.50 (3.50 – 25.75)	10.50 (6.00 – 15.00)	3.00 (1.50 – 4.50)	0.001	FM > CON; cWAD > CON
Operation Span Task					
OSPAN Total score	46.50 (15.50 – 55.50)	41.00 (28.50 – 55.00)	55.00 (49.00 – 64.00)	0.011	FM < CON*

Values are presented as median values and interquartile range (IQR). Significant differences are presented in bold font. cWAD: chronic whiplash-associated disorders, FM: fibromyalgia, CON: healthy controls

Significant differences ($P < 0.017$) between cWAD and FM are presented as (*) between CON and FM are presented as (*) between CON and cWAD are presented as (**).

Table 4. Comparison of self-reported health-related QoL (SF-36) between patients (cWAD and FM) and healthy controls.

SF-36 QUESTIONNAIRE	cWAD (n = 16)	FM (n = 21)	CON (n = 22)	Kruskal-Wallis	Mann-Whitney U
	Median (IQR)	Median (IQR)	Median (IQR)	P value < 0.05	P value < 0.017
Quality of life					
Physical Health Total	167.50 (134.25 – 249.50)	116.00 (76.00 – 152.50)	371.00 (336.00 – 387.75)	0.000	FM < cWAD*; FM < CON*; cWAD < CON**
Mental Health Total	242.25 (150.96 – 291.50)	220.50 (159.83 – 264.00)	354.50 (337.87 – 373.54)	0.000	FM < CON*; cWAD < CON**
SF-36 Total Score	414.25 (274.25 – 546.25)	338.00 (271.83 – 382.25)	728.00 (662.25 – 748.25)	0.000	FM < CON*; cWAD < CON**

Values are presented as median values and interquartile range (IQR). Significant differences are presented in bold.

SF-36: 36-Item Short-Form Health Survey, cWAD: chronic whiplash-associated disorders, FM: fibromyalgia, CON: healthy controls

Significant differences ($P < 0.017$) between cWAD and FM are presented as (*); between CON and FM are presented as (*); between CON and cWAD are presented as (**).

No significant relations were detected between cognitive performance and PPTs in the 3 study groups (data not shown).

3.3.2. Cognitive Performance and Health-related QoL

The correlations between cognitive performance and SF-36 scores are presented in Table 6. In the chronic

WAD group decreased cognitive performance was significantly related with reduced health-related QoL (SF-36).

In the FM group a different pattern of correlations was seen. Stroop reaction times and interference were positively correlated with reduced QoL, whereas negative correlations were found between reduced QoL and PVT reaction times.

Table 5. Spearman correlations between cognitive performance and pain measures in FM patients (n = 21) and healthy controls (n = 22).

	StroopRT incongruent	StroopRT non-word	Stroop interference	StroopRT priming neg.	PVT RT	PVT LAPSES	OSPAN Total score
FM (n = 21)							
TS finger	-.341	-.402	-.303	-.155	.213	.054	.430
TS shoulder	-.505*	-.529*	-.165	-.502*	.197	-.034	.531*
Cuff pressure	-.006	-.009	.082	-.006	-.152	-.501	.189
Cuff pressure (VNRS3)	-.094	-.141	-.050	.201	-.371	-.625*	-.089
CPM finger (VNRS1)	-.053	-.100	.172	.142	-.214	-.648**	-.065
CPM shoulder (VNRS1)	-.463	-.467	-.334	-.089	.150	.099	-.187
CPM on TS fing	.129	.092	.148	.393	-.240	-.427	.055
CPM on TS sh	-.298	-.307	.064	-.089	-.194	-.530*	.075
CON (n = 22)							
TS finger	-.253	-.234	-.328	-.275	-.112	-.232	.089
TS shoulder	.045	.115	-.076	.020	.280	-.029	-.162
Cuff pressure	-.189	-.279	.007	-.260	-.047	.208	.314
Cuff pressure (VNRS3)	-.292	-.323	-.136	-.379	-.472*	-.196	.368
CPM finger (VNRS1)	-.304	-.321	-.298	-.379	-.307	.068	.292
CPM shoulder (VNRS1)	-.579**	-.539**	-.448*	-.622**	-.387	-.375	.184
CPM on TS fing	-.483*	-.452*	-.495*	-.580**	-.411	-.156	.261
CPM on TS sh	-.214	-.132	-.227	-.146	-.217	-.370	.051

Significant correlations are presented in bold. * Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed). VNRS: Verbal numeric rating scale,

CPM: Conditioned pain modulation, TS: Temporal summation, RT: Reaction time, PVT: Psychomotor vigilance task, OSPAN: Operation Span Task, neg: negative, sh: shoulder, fing: finger

Table 6. Spearman correlations between cognitive performance and health-related QoL in cWAD patients (n = 15), FM patients (n = 17), and healthy controls (n = 22).

	StroopRT incongruent	StroopRT non-word	Stroop interference	StroopRT priming neg.	PVT RT	PVT LAPSES	OSPAN Total score
cWAD							
Physical health total	-.321	-.225	-.154	-.300	-.171	.084	-.301
Mental health total	-.543*	-.500	-.304	-.518*	-.461	-.291	-.138
SF-36 Total score	-.529*	-.479	-.318	-.493	-.389	-.280	-.152
FM							
Physic health total	.535*	.466	.595*	.463	-.585*	-.352	.038
Mental health total	.147	.059	.277	.179	-.068	-.230	-.026
SF-36 Total score	.355	.240	.505*	.363	-.338	-.302	-.077
CON							
Physical health total	-.576**	-.496*	-.403	-.513*	-.194	-.195	.172
Mental health total	-.425*	-.403	-.357	-.357	-.165	-.359	.076
SF-36 Total score		-.468*	-.472*	-.489*	-.159	-.176	.206

Significant correlations are presented in bold. * Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

In the healthy control group decreased performance on the Stroop was correlated with increased limitations on health-related QoL (SF-36).

4. Discussion

The current study examined the presence of cognitive impairment, signs of CS, and health-related QoL in chronic WAD and FM patients, compared to healthy controls. Secondly, this study is the first to examine interrelations between cognitive performance, indices of CS, and self-reported health-related QoL in these 2 chronic pain populations.

Central Sensitization

Remarkably, efficacy of endogenous pain inhibition (CPM) was comparable between the 3 study groups. Yet, previous studies have revealed dysfunctional CPM in patients with chronic WAD compared to healthy controls (26). Nevertheless, significant other features of CS were demonstrated in chronic WAD and FM patients compared to controls. First, enhanced TS was shown in both patient groups. These findings of enhanced TS in chronic WAD and FM are similar to previous studies (52,53). Second, significant lower PPTs and decreased tolerable cuff pressures were revealed in FM patients compared to the other study groups, representing deep-tissue hyperalgesia at the arm in patients with FM but not in chronic WAD patients. In line with the results in the FM group, previous research has observed deep-tissue hyperalgesia among FM patients (48,54). The fact that no deep-tissue hyperalgesia was found among chronic WAD patients is in contrast with the results of Lemming et al (52), who demonstrated widespread deep-tissue hyperalgesia in patients with chronic WAD. However, the chronic WAD patients in the study of Lemming et al (52) experienced neck pain for at least 6 months and were recruited from a specific Pain and Rehabilitation Centre. Furthermore, deep-tissue hyperalgesia was measured with a computerized pneumatic cuff. Increased bottom-up sensitization, demonstrated by enhanced TS, was present in chronic WAD and FM patients compared to healthy controls. However, no significant differences were found between the 3 study groups regarding CPM; hence, the present study could not unravel impaired endogenous pain inhibition. In addition, FM patients demonstrated more pressure and deep-tissue hyperalgesia compared to chronic WAD patients.

Further, prior research has established both primary and secondary hyperalgesia, demonstrated by decreased electrical pain thresholds at the neck and lower limb in chronic WAD patients (55).

Cognitive Performance

The results of the current study showed longer choice and simple reaction times in patients with FM compared to controls, as evidenced by slower response times on the Stroop and PVT, respectively. Hence, FM patients demonstrated reduced selective and sustained attention. Furthermore, we revealed longer simple reaction times in the chronic WAD group compared to controls. In addition, both patient groups showed significantly more PVT lapses in comparison with healthy individuals. This indicates that chronic WAD and FM patients tend to make more errors of omission during the PVT cognition task. In addition, longer PVT reaction times point to the failure of sustained attention.

An increased Stroop interference effect could not be demonstrated in the chronic WAD group, but the current study did however find significant increased interference and priming effect in FM patients relative to healthy controls. These results imply that chronic WAD patients are able to inhibit irrelevant information, whereas FM patients seem to have problems with this attending ability. Increased interference effect or impaired cognitive inhibition has been demonstrated before in FM patients (56). In addition, significantly higher negative priming effects in FM patients were observed compared to controls. Therefore, this study provides preliminary evidence that FM patients experience problems with inhibiting distraction stimuli.

Furthermore, no differences were found between chronic WAD patients and controls regarding Stroop reaction times. This indicates that chronic WAD patients have normal selective attention. As reported previously, chronic WAD patients presented only delayed information processing when there was attentional bias, i.e., when sleep-related words were shown (28). On the contrary, the present study did demonstrate significantly longer Stroop reaction times in FM patients compared to healthy controls. The latter may indicate a general slowing down of information processing in patients with FM.

Regarding the OSPAN, chronic WAD patients showed normal working memory capacity. In contrast, FM patients established significant lower OSPAN scores compared to controls, illustrating reduced working memory capacity in FM patients. These findings are in line with accumulating evidence showing reduced working memory capacity in FM patients (57).

Self-reported Health-related QoL

The current study established significant limitations

on health-related QoL in patients with chronic WAD and FM compared to healthy controls. In particular, physical and mental health were impaired in these patients. Our results confirm current evidence of impaired physical and mental health in patients with chronic WAD and FM (58,59). Significantly worse scores in the FM group on domains of physical health were detected in comparison with chronic WAD patients. These results are in line with the literature, as FM patients score lower than other chronic pain conditions on health domains of bodily pain and vitality (58).

In summary, FM patients demonstrated more signs of CS, higher cognitive impairment, and more physical health problems compared with chronic WAD patients. Possible explanations for the latter findings are the fact that the included FM patients experienced on average 3 years longer disease symptoms compared to the chronic WAD patients. Additionally, it is reported that the medical diagnosis of FM most often implies the presence of CS (11,60). In contrast, chronic WAD is associated but not uniformly characterized by CS (19).

Interrelations

Table 7 depicts a clinical useful translation of the observed correlations between cognitive impairment and respectively, impaired central pain modulation and health-related QoL limitations in the 3 study groups.

Cognitive Performance and Central Sensitization

In the chronic WAD group, deep-tissue hyperalgesia was the only variable that significantly correlated to cognitive performance, i.e., cognitive inhibition. This finding suggests that deficits in cognitive inhibition are related to less deep-tissue hyperalgesia. However, malingering, headache, intelligence, and the degree of vigilance are possible factors influencing cognitive performance in chronic WAD patients, and may explain the

observed opposite relations (61). Possible explanations for the scarcely observed relations between cognitive performance and CS in chronic WAD patients are obscure and merit further detailed research.

In contrast, FM patients showed much more significant relations between cognitive performance and various indices of CS. In summary, impairment on the Stroop and OSPAN in FM patients was unexpectedly related to lower TS values, hence less bottom-up sensitization. Possibly, these results are due to an overall decreased vigilant state in FM patients for a variety of sensory input, e.g., pressure pulses. Subsequently, the sensory and nociceptive transmission to the brain during the TS experiment could be delayed. On the other hand, in accordance with our expectations, impairment on the PVT was related to deficient CPM and increased deep-tissue hyperalgesia. Previous research has reported that working memory deficits in FM patients are related to grey matter volume changes in specific brain regions, which may indicate structural correlates of pain-cognition interaction (33). In addition, it seems that chronic pain in FM patients disrupts attention and induces neuroplasticity in the central nervous system (62).

In the healthy control group, less efficient pain inhibition was related to slower reaction times on the Stroop task. Furthermore, this is the first study finding a negative relation between PVT reaction times and deep-tissue hyperalgesia.

The observations in healthy controls and part of the findings in FM patients are in line with our study hypothesis of expected correlations between decreased cognitive performance and increased indices of CS.

Cognitive Performance and Health-related QoL

In chronic WAD patients, correlations between impaired selective attention and lower health-related QoL, in particular mental health, were demonstrated.

Table 7. Direction of the correlations between cognitive impairment and respectively, impaired central pain modulation, and reduced health-related QoL.

	Impaired selective attention (Stroop)			Impaired sustained attention and reaction time (PVT)			Impaired working memory (OSPAN)		
	WAD	FM	CON	WAD	FM	CON	WAD	FM	CON
Deep-tissue hyperalgesia	1/~				~	~			
Increased TS		1/~						1/~	
Deficient CPM			~		~				
Reduced QoL (SF-36)	~	1/~	~	~	~	~			~

1/~: measurements are oppositely correlated, ~: measurements are correlated in the same direction, QoL: Quality of Life
All measurements are presented in the impaired form.

These results are in line with our hypothesis and consistent with earlier research that observed relations between psychological functioning and cognitive performance in patients with chronic WAD (63).

A different pattern of correlations was obtained in the FM group. Remarkably, impaired selective attention and deficient cognitive inhibition were correlated with higher health-related QoL, whereas impaired sustained attention was related to increased QoL limitations.

In the healthy control group, decreased selective attention and cognitive inhibition were related to lower health-related QoL.

4.1. Study Strengths, Limitations and Recommendations for Further Research

The strengths of the present study are the innovative aspect and the numerous observed significant correlations. Correlation coefficients which range from 0.36 to 0.67 are generally believed to represent moderate correlations (≤ 0.35 = weak correlation and $0.68 - 1.0$ = strong correlation) (64). In this study, all significant correlations ($P < 0.05$) were situated between the range of 0.42 and 0.82, thus moderate to strong correlations.

When interpreting the results, the following study limitations have to be taken into account. Firstly, based on the current cross-sectional study, no firm conclusions can be drawn on the causality of the relations. In the 3 study groups, longer reaction times were correlated with lower health-related QoL. However, it is uncertain if cognitive deficits lead to impaired QoL or vice versa. Moreover, malingering, concentration, education level, and IQ could have influenced the cognitive study results. Secondly, when conducting this study various confounders, including medication use were taken into account. However, it has to be noticed that antidepressiva use was significantly different between the 3 study groups. In addition, we cannot exclude possible differences in education level or other biopsychosocial characteristics between the patients and controls and that this may have created

bias in the results. Thirdly, only non-parametric statistical analyses were performed because the sample size of the current study was rather small.

Consequently, further research is warranted to investigate if CS and reduced health-related QoL lead to cognitive impairment or vice versa.

5. CONCLUSION

In conclusion, chronic WAD and FM patients encounter significant cognitive impairment, signs of CS, and decreased health-related QoL compared to healthy pain-free individuals. The current study revealed more indices of CS, higher cognitive impairment, and more limitations on health-related QoL in FM patients compared with chronic WAD patients. In particular, FM patients showed higher impairment of self-reported physical health, pressure and deep-tissue hyperalgesia, hampered selective attention, and reduced working memory capacity in comparison with chronic WAD patients.

Significant correlations between cognitive impairment and indices of CS and self-reported health-related QoL, respectively, were demonstrated among the 3 study groups. Especially in FM patients cognitive impairment appeared to be related to indices of CS. Reduced selective and sustained attention, as well as reduced working memory were correlated with less TS, so less bottom-up sensitization in FM. However, impaired sustained attention was related to increased deep-tissue hyperalgesia, deficient CPM, and reduced QoL in FM patients.

Accordingly, these results provide preliminary evidence for the clinical importance of objectively measured cognitive deficits in patients with chronic WAD and FM and the relation with CS in FM. Furthermore, in both patient groups there are distinct relations between self-reported health-related QoL and cognitive performance, albeit the specific cause-effect relationship remains unclear and requires further research.

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