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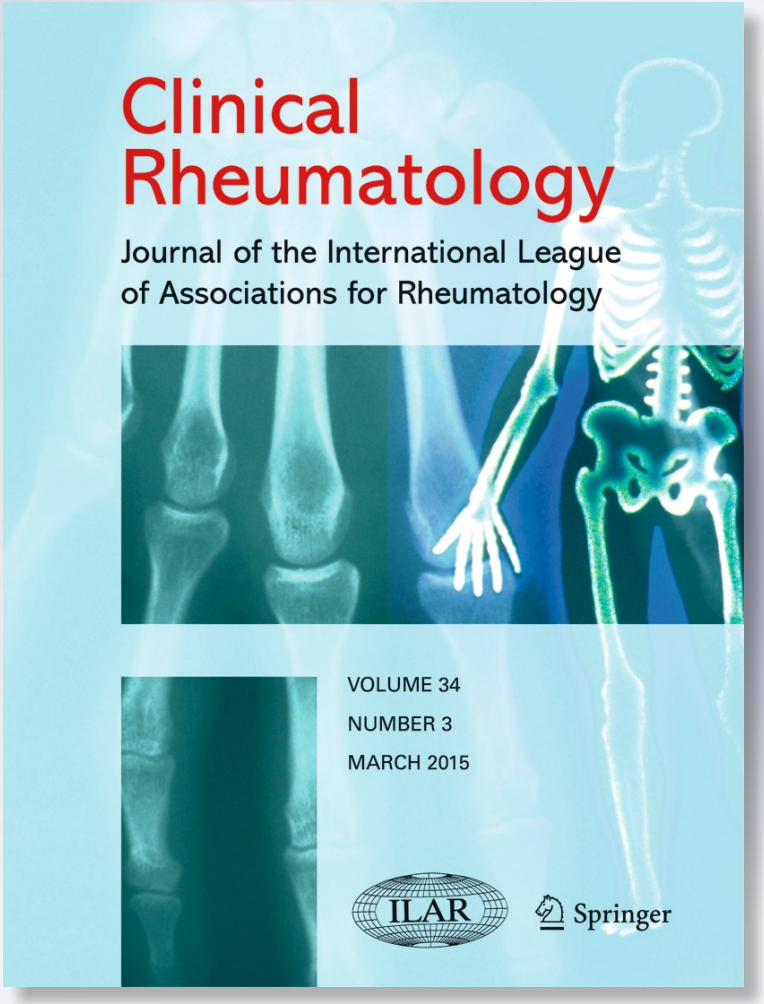

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ORIGINAL ARTICLE

Interrelationships between pain processing, cortisol and cognitive performance in chronic whiplash-associated disorders

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Abstract The present study aims at studying interactions between cognitive performance and conditioned pain modulation in patients with chronic whiplash-associated disorders (WAD) and healthy controls. In addition, the relation between cortisol concentrations and cognitive performance will be studied in patients with chronic WAD. Thirty-one subjects, 16 healthy subjects and 15 patients with chronic WAD, were enrolled and subjected to several self-report and physiological measures. Self-report measures encompassed pain rating during a procedure evaluating conditioned pain modulation. Afterward, they were subjected to physiological measures, which are cognitive tests (Stroop task, psychomotor vigilance task, and operation span task) preceded and followed by salivary cortisol concentration measurements. Chronic WAD patients performed worse in recall at the operation span task and presented longer reaction times at the psychomotor vigilance task and at the Stroop task when sleep-related words were shown ($p < .05$). Conditioned pain modulation and cortisol concentrations were not significantly different between patients and controls ($p > .05$). Only in the healthy subjects, conditioned pain modulation and baseline cortisol concentrations were correlated to cognitive performance ($p < .05$). This is the first study addressing the relation between pain inhibition and cognitive performance in chronic WAD. We did not reveal impaired pain inhibition but did reveal cognitive dysfunctions in patients with chronic WAD. In healthy subjects, pain inhibition was related to cognitive performance but not in the patient group.

Keywords Central sensitization · Chronic pain · Cognitive performance · Conditioned pain modulation · Cortisol · Diffuse noxious inhibitory controls

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Introduction

Central sensitization has been suggested in patients with chronic whiplash-associated disorders (WAD)[1, 2]. Moreover, central sensitization seems to predict the transition from acute to chronic WAD [3] and the outcome of rehabilitation for patients with chronic WAD [4].

Apart from the pain, patients with chronic WAD often complain of forgetfulness, concentration difficulties and decreased cognitive capabilities [5–7]. It seems that the mild cognitive disorders of whiplash should not be explained in terms of brain damage but are more likely a result of chronic pain and chronic fatigue itself [8]. Accordingly, decreased

cognitive performance is related to pain severity in various chronic pain populations [9, 10] and is presumed to be a feature of central sensitization [11]. It is hypothesized that malfunctioning of descending inhibitory pathways and subsequent hyperexcitability and chronic pain experience preclude optimal cognitive performance.

Long-lasting cognitive problems may be due to a distraction phenomenon secondary to long-standing cervical pain or to psychological issues [12]. On the other hand, it seems that cognitive symptoms immediately after the accident are a good predictor of sick leave 3 years later, indicating that cognitive symptoms are a clinical manifestation of mild brain trauma. Possibly, both the cognitive dysfunctions and altered central pain processing may be symptoms of mild brain trauma.

This hypothesis is supported by the findings of altered brain activity [13] and brain morphology [14] in patients with fibromyalgia and chronic WAD. Altered brain activity and morphology might influence the brain activity required to focus on cognitive tasks. Indeed, fibromyalgia patients suffer from cognitive deficits that correlate with local brain morphology in the frontal lobe and anterior cingulate gyrus [14].

Also in healthy controls, an association between cognitive performance and pain inhibition is logical. Cognitive tasks will induce sympathetic activation, which causes an increased cerebral blood flow in different (sub) cortical areas. These cortical areas have also been described to be critical for pain perception and control of pain [15]. As similar brain areas are involved, it seems rational that cognitive performance is related to endogenous pain processing.

In despite of our increased understanding of central sensitization in chronic pain patients, many issues need to be resolved. Earlier studies provided evidence for malfunctioning of conditioned pain modulation (CPM) in fibromyalgia patients [16–18]. However, CPM has not extensively been studied in WAD. To the best of our knowledge, only one study provided evidence for impaired CPM in chronic WAD [19], but the link with cognitive impairments has yet to be studied.

Besides neural mechanisms, hormonal abnormalities could also be related to cognitive performance. There is a wealth of evidence to show that changes in corticosteroid levels can have significant effects on memory performance. Whilst many studies have shown that high levels of corticosteroids can impair memory performance, others have shown that they can facilitate it [20]. Given the evidence for hypofunction of the hypothalamic-pituitary-adrenal axis in chronic WAD, the lower cortisol release in response to stressors, and the cognitive impairments in chronic WAD patients [21], studying cortisol in relation to cognitive testing in this patient population seems warranted.

Subsequently, the present investigation addressed the evaluation of cognitive performance in chronic WAD patients in relation to pain (inhibition) and cortisol concentrations.

(1) Patients with chronic WAD and healthy controls were compared regarding cognitive performance, pain thresholds and pain inhibition, and finally cortisol concentrations.
(2) The relation between cognitive performance and pain (inhibition) and cortisol concentration before and after cognitive testing was studied in patients with chronic WAD and healthy control subjects.

Methods

Study design and setting

The present case control study was approved by the ethical committee of the University Hospital of Brussels. After receiving information and filling out the informed consent and the WAD symptom list, pain thresholds and the efficacy of endogenous pain inhibition were assessed in both patients and controls. Afterwards, participants were subjected to a battery of cognitive tests on a computer. Before and after the cognitive tests, saliva samples were collected in order to assess cortisol concentrations.

Subjects

Fifteen patients with chronic WAD and 16 healthy pain-free control subjects were enrolled. Each study participant had to be Dutch speaking and aged between 18 and 65 years. Groups were comparable for age and gender.

The WAD group complied with the criteria of the Quebec Task Force (grades I to III) [7]. At the time of study participation, healthy control subjects could not suffer any pain complaints.

Participants could not be pregnant or have given birth in the preceding year and were asked to stop analgesics 48 h prior to study participation, not to undertake physical exertion, and to refrain from consuming caffeine, alcohol or nicotine on the day of the experiment.

Outcomes: cognitive function

To investigate *cognitive function*, we used the psychomotor vigilance task (PVT), the Stroop task, and the operation span task (OSPAN) with concomitant mathematical processing to assess vigilance and alertness, selective attention and concentration, and working memory, respectively. The tasks are chosen based on the outcome of a systematic literature review addressing cognitive performance of chronic patients [6].

The Stroop task was used to evaluate selective attention, focus and concentration. Our Stroop task encompassed different categories of words. The presented words/nouns could be classified under eight different conditions, namely, “category”

(animal names), "congruent" (word and ink color are the same), "incongruent" (word and ink color are different), "neutral" (neutral words), "no word" (XXX), "priming negative inverse" (e.g. the word red displayed in green immediately followed by the word green displayed in red), "priming negative simple" (e.g. the word red displayed in green immediately followed by the word blue displayed in red), and "sleep" (sleep-related words).

The emotional stimuli, being the sleep-related words, were presented embedded in a classic colour-word Stroop task. This way, attentional biases can be studied, these being expressed as longer response latencies to name the ink colour of emotional words when compared to neutral words. Furthermore, the dimensions of negative priming and inverse negative priming were also examined. Negative priming occurs if the to-be-ignored response in a first presentation becomes the subsequent relevant dimension. Inverse negative priming adds the reciprocal variation of relevant and irrelevant dimension to this. Negative priming is considered as the inhibition of one of the mechanisms of selective attention [22]. Examining this effect offers additional information on the quality of cognitive control for selecting relevant information.

Response times and accuracy were stored.

In order to assess vigilance and alertness, a simple reaction time task can be applied. The PVT [23] has been widely validated in applied research as a measure of vigilance. The task is based on a simple visual reaction time test apparatus originally developed by Wilkinson and Houghton [24]. The PVT ran for a period of 10min. The subjects were required to respond to a visual stimulus (red spot on a black screen) presented at a variable interval (2,000–10,000 ms) by pressing the right mouse button with the index of the dominant hand. If a response had not been made in 500 ms, the trial was stored as a lapse. Reaction time of correct responses (i.e. under 500 ms) and number of lapses was stored.

Working memory was tested with the OSPAN with concomitant mathematical processing (based on [25]). Subjects have to recall letters displayed at a screen, one at a time, in the correct order, after performing a simple mathematical verification (e.g. 4/2+1=3). The maximum number of letters that can be recalled is the "operation span".

Subjects are instructed to keep their math accuracy at or above 85 % at all times, and time for math tasks is controlled.

The program reports five values at the end of the experiment: OSPAN score, total number correct, and math errors (three values). The first, OSPAN score, uses our traditional "absolute OSPAN" scoring method. It is the sum of all perfectly recalled sets. Total number correct is the total number of letters recalled in the correct position. Errors are reported as total number of errors, accuracy errors where the subject solved the operation incorrectly and speed errors in which the subject ran out of time in attempting to solve a given operation.

Outcomes: pain

Pressure pain thresholds (PPTs) were measured with an analogue Fisher algometer (Wagner Instruments, Greenwich ,CT 06836) on the dorsal face of the right hand middle finger, midway between the first and the second distal joints, and at the middle of the right trapezius belly, as described in previous studies [26, 27]. The force is gradually increased at a rate of 1 kg/s until the subject indicates that the pain level has been reached. The threshold is determined as the average of two measures taken 30 s apart. Pressure algometry has been found to be efficient and reliable in the exploration of pathophysiological mechanisms involved in pain [28, 29].

The efficacy of endogenous pain inhibition was assessed by a procedure of temporal and spatial summation of noxious stimuli, as described by Cathcart et al. [26] and Meeus et al. [27, 30]. This procedure evaluates the degree of temporal summation (TS) or wind up in response to ten applications (pulses) of the Fisher algometer at PPT intensity at the dorsal surface of the right hand middle finger midway between the first and second distal joints and at the middle of the right-hand side trapezius belly of the right arm. The subjects were asked to rate the intensity and unpleasantness of the pain of the first, fifth and tenth pulse on a verbal numerical rating scale (VRNS: 0=no pain to 10=worst possible pain).

CPM was assessed by replicating the TS assessment associated with a conditioning stimulus for eliciting CPM. The conditioning stimulus was an occlusion cuff at the left arm inflated to a painful intensity and maintained at that level while TS was elicited. This procedure seemed reliable, and CPM induced by the ischaemic cuff is able to dampen TS in healthy controls [26]. The same method was able to reveal dysfunctional endogenous analgesia at rest in chronic whiplash patients [19]. Both assessing the degree of TS or CPM and assessing widespread hyperalgesia, e.g. by PPT on different/distant locations are recognized as measures/indices of central sensitization [26, 31–33].

General symptom intensity was measured with the WAD symptom list. This is a self-reported measure for assessing symptom severity in patients with WAD. The questionnaire is composed of the most reported WAD symptoms in the literature and some autonomic symptoms. Every symptom is presented by a visual analogue scale (VAS) (100 mm), widely known for its reliability and validity. Previously, our research group found a good internal consistency (Cronbach α=0.92) for the WAD symptom list (unpublished data).

Outcomes: cortisol concentrations

Saliva was collected before and after each evaluation of pain inhibition with a Salivette® (Sarstedt AG, Germany). Salivettes® containing saliva were centrifuged at 2,000 g for 10min, and the filtrates were stored frozen (−20 °C). Saliva cortisol was measured by radioimmunoassay (RIA) (Diasorin

Diagnostics, Italy), using a modification of an unextracted RIA method for serum cortisol. Briefly, 200 μL of saliva was pipetted into the coated tube and incubated with 125I cortisol for 45min at 37 °C. The measurement of steroid hormones in saliva is a widely accepted alternative to the determination in plasma or serum [34, 35]. Salivary steroids correlate very well with the non-protein-bound fraction in plasma samples [36, 37].

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences 19.0© for Windows (SPSS Inc. Headquarters, Chicago, Illinois, USA). Normality of the variables was tested, and appropriate descriptive statistics were used. Comparability of the groups was studied with a Fisher exact test for gender and with a Pearson's chi square for professional situation. For all statistics, the significance level was set a priori at $p < .05$.

Cognitive performance was compared between patients and controls with an independent t test for the PVT and OSPAN. Stroop interference, priming, and emotional effects were investigated separately using a 3×2 analysis of variance (ANOVA) with condition as a within-subject factor and group as a between-subject factor. To investigate the Stroop interference effect, the ANOVA was performed on the mean reaction times of the congruent, incongruent, and no word condition. Mean reaction times of incongruent, priming negative inverse, and priming negative simple stimuli were analyzed together in order to determine possible priming effects. The presence of emotional Stroop effects was investigated by performing an ANOVA on the mean reaction times of three conditions comprising of nouns with different levels of emotional load, namely, animal names (category), neutral words, and sleep-related words. After an arcsine transformation, Stroop accuracy data were also submitted to a 3×2 ANOVA and further analyzed in the same way as the Stroop reaction time data.

Cortisol, symptom severity, pain thresholds and CPM at baseline were compared between patients and controls with an independent t test. Repeated measure ANOVAs were used to analyze the effect of cognitive stress on cortisol concentrations (p interaction).

Finally, Pearson correlation coefficients were calculated between cognitive performance and cortisol and pain measurements. Correlation between cognitive performance and cortisol on pain measurements were studied both in patients and controls.

Results

Participants

We included 15 patients with chronic WAD and 16 healthy controls, comparable for age and gender. Demographic variables of the participants are presented in Table 1.

Table 1 Characteristics of the study samples

	WAD (n=15)	CON (n=16)	p
Age (years)	41.63±11.45	40.88±13.38	.866
Gender	3 ♂ and 12 ♀	6 ♂ and 10 ♀	.433
Disease duration (months)	60.81±69.76	00.00±00.00	.002
Professional situation	7 inactive 0 students 1 part-time 7 full-time	3 inactive 3 students 3 part-time 7 full-time	.129

(p values are the significance levels of the differences between patients with chronic whiplash-associated disorder (WAD) and healthy controls (CON). Age and disease duration were compared by independent t tests, gender with a Fisher exact test professional situation with Pearson's chi square)

Cognitive performance

Firstly, we compared healthy controls and chronic WAD patients for differences in PVT and OSPAN. As presented in Table 2, chronic WAD patients presented a significant longer reaction time on the PVT test and presented significant worse recall capacities on the OSPAN.

Although there was a significant effect for the Stroop condition for interference and priming (interference reaction time: $p < .001$ and accuracy $p = .04$ and priming reaction time: $p = .029$ and accuracy $p = .019$), no significant effects for group or interaction (condition × group) were found for Stroop interference and priming for both reaction time and accuracy ($p > .05$).

For emotional effect, there was only a significant interaction effect for reaction time ($p = .02$) but not for accuracy ($p > .05$). No significant group or condition effects could be revealed. Figure 1 depicts the significant difference in reaction times between the patients and control group for words with different levels of emotional load.

Pain thresholds and inhibition

CPM and PPTs at the finger were comparable between control subjects and WAD patients. At the shoulder, PPTs were significantly lower in het patient group compared to the healthy controls, as shown in Table 2.

Symptom severity

Patients reported significantly more pain but also more sleeping problems relative to controls, as presented in Table 2. Also, other symptoms, for example excessive sweating, concentration problems, hypersensitivity for light and neck mobility, were significantly different.

Table 2 Comparability of the study samples for cognitive performance and pain measures

	WAD ($n=15$)		CON ($n=16$)		t test or Mann–Whitney U¶
	Mean	SD	Mean	SD	p
PVT Accuracy (%)	81	17	64	47	.562¶
PVT Reaction time (ms)	356.24	38.87	295.40	26.98	**.000**
OSPAN score	23.79	18.28	37.64	18.62	.058
OSPAN Total number correct	39.00	22.87	57.43	10.57	**.013**
OSPAN Total math error	6.36	3.50	8.07	7.40	.440
OSPAN Accuracy error	5.43	3.01	5.64	4.03	.875
OSPAN Speed error	0.93	1.21	2.43	6.31	.946¶
PPT finger	7.84	2.28	8.47	3.58	.569
PPT shoulder	4.02	1.60	5.75	2.88	**.048**
CPM finger	0.77	1.89	1.59	1.67	.205
CPM shoulder	1.23	2.01	1.78	1.72	.420
VAS neck pain	54.38	23.15	6.25	8.93	**.000**
VAS headache	36.63	26.86	5.88	7.94	**.000**
VAS neck mobility	50.31	29.35	6.00	10.49	**.000**
VAS dizziness	18.13	17.88	1.31	1.89	**.002**
VAS concentration problems	38.44	27.88	5.63	11.79	**.000**
VAS problems falling asleep	22.19	33.207	3.63	6.15	**.043**
VAS problems sleeping through	36.00	28.99	14.13	19.78	**.018**
VAS hypersensitivity to light	46.56	27.86	3.75	6.88	**.000**
VAS excessive sweating	31.13	30.21	10.69	17.32	**.028**

Significant differences are presented in bold font. (*PVT* psychomotor vigilance task, *OSPAN* operation span task, *WAD* chronic whiplash-associated disorder, *CON* healthy controls, *SD* standard deviation, p significance level, *PPT* pressure pain threshold, *CPM* conditioned pain modulation, *VAS* visual analogue scale)

¶ are variables who were compared with the Mann Whitney U instead of t test

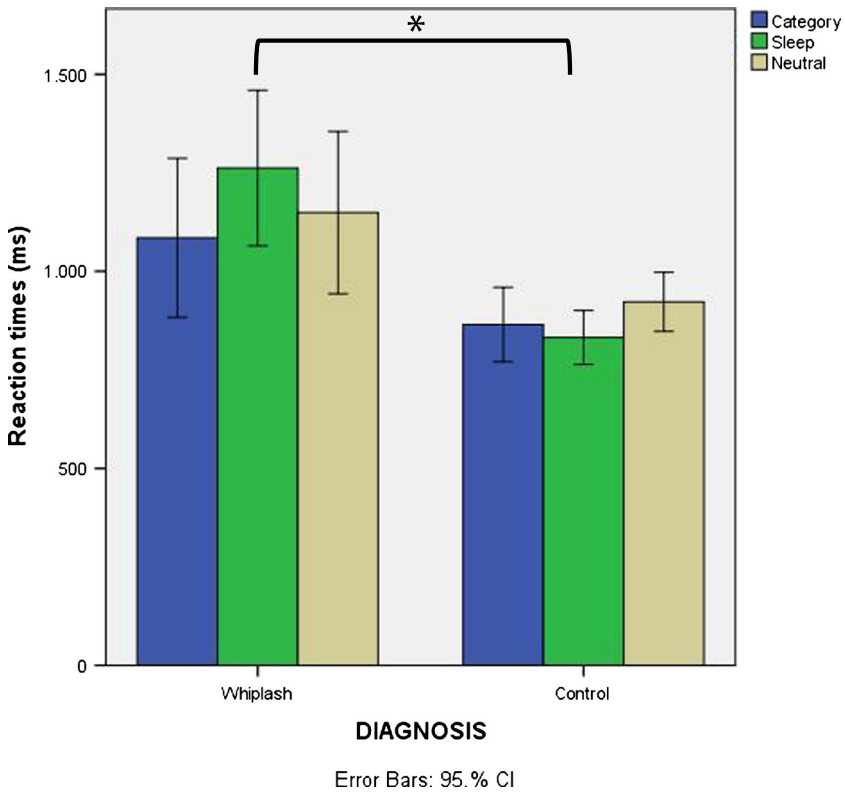

Fig. 1 Emotional Stroop effects

Cortisol

Regarding cortisol concentration in the saliva, there were no significant differences ($p > .05$) between the two groups. The mean cortisol concentration for the WAD patients was 4.19 μg/l±2.05 immediately before the cognitive tests and 3.64 μg/l±1.55 immediately after the tests. For the control subjects, concentrations were 3.94 μg/l±1.53 before and 3.78 μg/l±1.49 after the tests. In both groups, cortisol concentrations decreased after the cognitive tests, with no significant difference for the change in concentration.

Associations

In the *WAD group*, the PPT at the finger was the only variable that was significantly related to cognitive performances, as presented in Table 3. Surprisingly, positive correlations were revealed with the Stroop test reaction time and a negative correlation with the accuracy at the PVT.

Furthermore, no other significant correlations were found between pain thresholds, cortisol concentrations or cognitive performance. The pain thresholds at the shoulder were not significantly related to other variables, and cortisol was not related to pain thresholds or cognitive performance ($p > .05$).

In the *control group*, far more associations were revealed. Significant correlations were mainly observed between cortisol concentrations before the test and cognitive performance, being the higher the cortisol concentrations, the higher the reaction time on the Stroop test (Table 3). Furthermore, CPM was negatively correlated to the reaction times in the Stroop test, meaning the better endogenous pain inhibition is activated by CPM, the lower or the better the reaction times.

Discussion

This is the first study examining the relation between a measure of central sensitization and cognitive performance in patients with chronic WAD.

Cognitive performance

We found that chronic WAD patients presented significant longer reaction times on the PVT. Accuracy was not significantly different. Regarding the increased reaction time, our results are in line with the sole other study that investigated this in these patients [38]. Slower reaction times would indicate reduced vigilance. Furthermore, the PVT is commonly used in sleep deprivation studies to examine the effect of this phenomenon on attention and vigilance [39, 40]. In their

Table 3 Correlations between cognitive performance, pain measures and cortisol

		WAD						CON					
		Cort. 1	Cort. 2	PPT finger	PPT shoulder	CPM finger	CPM shoulder	Cort. 1	Cort. 2	PPT finger	PPT shoulder	CPM finger	CPM shoulder
Stroop reaction times	Category	.054	.116	.411	.310	0.377	0.046	**.675****	.281	.340	.313	**−.696****	**−.523***
	Neutral	.226	.218	**.571***	.248	0.201	0.066	**.507***	.111	.265	.318	**−.626****	**−.607***
	Non-word	.372	.335	.430	.207	0.315	−0.087	.476	.184	.345	.396	**−.547***	**−.556***
	Sleep	.275	.200	.489	.340	0.188	0.031	**.544***	.380	.395	.354	**−.560***	−0.400
	Congruent	.221	.244	**.601***	.281	0.174	0.111	**.583***	.079	.243	.280	**−.669****	**−.572***
	Incongruent	.281	.235	**.542***	.235	0.232	0.059	.491	.046	.256	.293	**−.614***	**−.596***
	Inverse negative priming	.345	.265	**.547***	.103	0.133	0.12	**.513***	.009	.188	.243	**−.530***	**−.619***
	Negative priming	.377	.271	**.516***	.064	0.133	0.121	**.564***	−.011	.188	.177	**−.644****	**−.598***
PVT	Accuracy	.176	−.157	**−.655***	−.111	0.123	−0.34	−.043	.162	.241	.185	0.409	−0.152
	Reaction time	.119	.280	.346	−.068	−0.242	0.123	.375	−.343	−.289	−.289	−0.428	−0.279
Operation Span Task	Ospan Score	−.186	−.152	−.346	−.332	−0.384	−0.197	−.045	−.005	.041	−.032	0.332	0.317
	Total number correct	−.115	−.221	−.484	−.412	−0.379	−0.22	−.106	−.044	.026	−.091	0.311	0.367
	Total math error	−.219	−.248	.078	.018	0.123	−0.135	.109	−.258	.003	.060	−0.255	−0.461
	Accuracy error	−.125	−.198	−.023	−.054	0.323	−0.092	.491	.016	.134	−.040	**−.679****	−0.289
	Speed error	−.324	−.227	.284	−186	−0.448	−0.161	−.187	−.312	−.082	.095	0.135	−0.355

Significant correlation are presented in bold font (*on .05 level; ** on .01 level). (Cort.1 or 2=Cortisol before and after cognitive tests, *PVT* psychomotor vigilance task, *WAD* chronic whiplash-associated disorder, *CON* healthy controls, *PPT* pressure pain threshold, *CPM* conditioned pain modulation)

literature review, Lim and Dinges [39] state that sleep-deprived persons show an overall slowing of responses.

Regarding the OSPAN, patients did not perform worse on the math part but performed worse in remembering the letters. So, patients presented reduced working memory, evidenced by the letter span part of the task that is the storage component.

Overall processing speed was not slower in WAD patients relative to healthy control subjects, as evidenced by the reaction times on the Stroop task. Furthermore, patients' Stroop interference effect and priming effect were not increased relative to controls. As Stroop interference reflects selective attending ability or the ability to inhibit irrelevant information, this finding demonstrates normal semantic processing in these patients. Furthermore, patients were not less accurate.

Only emotional effects of the Stroop task were significantly different between patients and controls.

Significant longer reaction times were revealed in patients when sleep-related words were shown. This means that there is no general slowing of information processing but only when there is an attentional bias (when sleep-related words are shown). To our knowledge, there is only one study that used a Stroop task in chronic WAD patients, and this study reported overall slower information processing [41], while this was only the case for the sleep-related words in our study. The fact that negative priming was not significantly different suggests that the quality of cognitive control for selecting relevant information is not lower in chronic WAD patients.

So, it seems that only emotional or threatening charged words, like sleep-related words, were able to slowdown information processing. Up to now, pain-related words were frequently used for the emotional Stroop tasks in chronic pain patients. As we tested chronic WAD patients, most of these patients also suffer other symptoms like increased fatigability. It is therefore interesting that, analogous to the previous studies that evaluated emotional bias by using pain-related words, also sleep-related words impaired information processing in the current study. Considering this finding together with the slower reaction times on the PVT test, we additionally analyzed the emotional Stroop effect with problems falling asleep and sleeping through of the WAD symptom list as covariates. In this additional analysis, the difference between patients and controls was no longer significant, suggesting that cognitive problems in chronic WAD patients might be the consequence of impaired sleeping. This highlights the need of also approaching sleeping hygiene in the treatment of chronic WAD patients.

Associations

The only variable that was related to cognitive performance in the *WAD patients* was the PPT at the finger. A positive relation was observed with the reaction times on the Stroop, and a negative relation was revealed with the accuracy on the PVT. This means that higher PPTs were related to worse performances and inversely. A possible explanation for this strange finding may be that most whiplash patients have a poor association between subjective complaints (like pain) and objective findings (like cognitive performance) [42]. Also, other factors like headaches or malingering may affect cognitive performances. The prevalence of malingering or cognitive underperformance in late post-whiplash patients is for example substantial [8]. Finally, reduced vigilance may explain worse performance in the presence of higher PPTs.

In the *control subjects*, far more correlations were significant. Cortisol concentrations before the tests were positively related to the reaction time on the Stroop, and the CPM variables, both at the finger and the shoulder, were negatively related to the reaction time on the Stroop and with the math accuracy errors on the OSPAN. A higher CPM value means a more efficient pain inhibitory response. Consequently, the better the pain inhibition, the faster participants reacted in the Stroop task and the less math errors they made.

Furthermore, cortisol concentrations before the tests were positively related to the reaction times on the Stroop task. This finding is in line with the findings that high levels of corticosteroids can impair memory performance or may indicate that those who were more stressed performed worse on the Stroop task [43].

Surprisingly, cortisol concentration after the test was not related, and cortisol concentrations decreased in both groups after the test. We expected that cognitive stress would induce increases in cortisol in control subjects, while we expected a lower cortisol release in response to a cognitive stressor in chronic WAD patients. The fact that cortisol concentration reduced in both groups may suggest that participating in an experiment or getting to the right location (in the busy traffic of a crowded city) was more stressing than performing cognitive tests for half an hour. On the other hand, it is possible that cortisol was measured too soon after the cognitive tests, since cortisol peaks would normally occur 30 min after acute stress exposure [44]. Furthermore, there are a lot of other factors that can influence cortisol levels, like smoking, physical activity, gender and genetics. But we should be aware of the fact that momentaneous salivary cortisol of different subjects on different points in time were not the focus. What mattered was the evolution in cortisol concentration before and after the test. And salivary measurements have proven to be valid to assess cortisol concentrations, also in response to various stressors [35].

So it seems that the expected associations between cognitive performance and pain inhibition and between cognitive performance and cortisol were only revealed in the healthy subjects. It could be interpreted that in those with a correct response to CPM, the central nervous system is vigilant and working efficiently, leading to better cognitive processing. Furthermore, cortisol seems to exert its normal effects because

in case of higher cortisol concentrations, memory would be impaired in healthy subjects [43].

In the WAD patients, the study hypothesis was not confirmed by the study findings. Only the PPT at the finger correlated with cognitive performance, and this correlation was the opposite of what we expected; those who were more sensitive to pain performed better at the Stroop task. Inversely, this can be interpreted as these participants being more vigilant for both pain and cognitive stimuli. But this finding is contradictory to the rationale that malfunctioning of descending inhibitory pathways and subsequent hyperexcitability precludes optimal cognitive performance. Also the absence of correlations with CPM does suggest inconsistent responses in WAD.

Limitations and suggestions for further research

First of all, the present sample sizes were small. A priori power calculations could only be based on assumptions of differences and effects, as there were no similar study results. It seems that further studies should strive for bigger samples to obtain sufficient power.

Although we standardized substance use before the test and accounted for the morning peak of cortisol (by testing in the afternoon), the fact that subjects may have been nervous before the experiment could have biased the cortisol concentrations. Furthermore, a follow-up cortisol measurement could have been performed for a more detailed image of the evolution because cortisol peaks would normally occur 30min after acute stress exposure [44].

It would be desirable to integrate malingering tests in further research, although the present results on the specific Stroop test in this study seems to suggest that patients were not malingering since they did not perform worse on the complete test.

No firm conclusions can be drawn on the causal relationships among the measurements. In healthy people, pain inhibition and cognitive performance are related, so those who present more efficient CPM performed better on cognitive tests, but we do not know if better pain inhibition leads to better concentration.

Future research could compare chronic WAD patients with other chronic pain patients, in whom sufficient evidence for impaired CPM is available, for example patients with fibromyalgia. In addition, the interaction between CPM and cognitive testing and cortisol could be compared with other non-stressing interventions, for example relaxation.

Conclusion

In conclusion, this is the first study examining the relationship between a measure of central sensitization and cognitive performance in patients with chronic WAD. The present study could not reveal differences in CPM or cortisol concentrations between chronic WAD patients and healthy controls. The patients did perform worse on working memory, simple reaction time and information processing when emotionally loaded words were shown in the Stroop task. However, this difference seems to be cofounded by sleeping problems in the WAD group.

The hypothesis concerning the relation between cognitive performance on the one hand and pain inhibition and cortisol on the other could only be confirmed in healthy subjects and not in the chronic WAD patients. Possible explanations for the absence of this relation are obscure and require further research.

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