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The cognitive impact of chronic low back pain: Positive effect of multidisciplinary pain therapy

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HIGHLIGHTS

- Chronic pain seems to impair both information processing and working memory.
- Attention and visual pattern recognition memory are not impaired in cLBP patients.
- There are interactions of cognitive function with pain, depression, anxiety, and medication.
- Multidisciplinary pain therapy may improve impaired cognitive function.

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ABSTRACT

Objectives: Little is known about the affected cognitive problems in chronic low back pain patients. For this patient cohort research mostly focused on memory of pain, rather than cognitive difficulties related to pain. Chronic pain may be associated with specific (yet undefined) cognitive deficits that affect everyday behaviour. We set out to compare the cognitive function of patients with chronic low back pain (cLBP) in the course of multidisciplinary pain treatments before and after therapy.

Methods: Thirty-three patients with cLBP and 25 healthy controls between 20 and 70 years were recruited into the study. The inclusion criteria for patients were: (1) a history of at least 12 weeks of chronic myofascial low back pain without radicular pain sensation before enrolment; (2) grade II and higher chronicity according to von Korff; (3) no opioid medication. The patients recruited had a mean pain duration of 7.13 ± 7.16 years and reported a mean pain intensity of 6.62 ± 2.04 (visual analogue score, VAS). Their mean back function according to the Funktionsfragebogen Hannover (FFbH, a questionnaire comparable with the Health Assessment Questionnaire) was $52.39 \pm 20.23\%$.

At three time points (before therapy, 3 weeks and 6 months after therapy) the study subjects were assessed prospectively with a battery of visual memory tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). These included choice reaction time (CRT), pattern recognition memory (PRM) and spatial span (SSP). In parallel, the Trail-Making Test (TMT-A, TMT-B) and the Wechsler Adult Intelligence Scale (WAIS-III) were used to evaluate intelligence and cognitive flexibility.

Results: At the beginning of MDPT (T1), it took patients with cLBP significantly longer than HC to complete TMT-A (38.29 ± 19.99 s vs 30.25 ± 14.19 s, $p = 0.047$) and TMT-B (72.10 ± 26.98 s vs 55.99 ± 22.14 s, $p = 0.034$). There were no significant differences between patients and HC in CRT, PRM and SSP. Three weeks (T2) and 6 months (T3) after MDPT, TMT-A reaction time of patients significantly improved by 6.5 s and 8.1 ms (38.3 ± 19.9 s vs 31.8 ± 12.3 s, $p = 0.02$ and 31.8 ± 12.3 s vs 30.2 ± 8.9 s, $p = 0.021$, respectively). The patients' working memory was also better 6 months after MDPT ($48.8 \pm 11.1\%$ at T1, $51.2 \pm 11.9\%$ at T2, $57.1 \pm 10.9\%$ at T3, $p = 0.008$). Significant correlations among pain, depression/anxiety, medication and neuropsychological tests were found.

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Conclusions: These findings show that patients with cLBP have slowed speeds of information processing and working memory, but no alteration in attention and recognition memory. There are clearly interactions of cognitive function with pain, depression, anxiety, and medication. MDPT may improve the impaired cognitive function of patients with cLBP.
Implication: Health professionals should contemplate the results from this study when planning therapy strategies especially when prescribing pain medications such opioids to patients with chronic low back pain.

1. Introduction

Research conducted over the past 20 years has provided evidence of cognitive deficits in people with chronic pain [1–5]. Around 45–50% of these patients report cognitive deficits such as forgetfulness (23.4%), minor accidents (23.1%), difficulty finishing tasks (20.5%), and difficulty maintaining attention (18.7%) [6,7]. However, there are many discrepancies among results from different studies. The studies performed to date have several limitations: (1) data were obtained mostly from self-report measures and questionnaires. (2) Little work has focused directly on a group of patients with homogeneous diagnoses [8,9]. Cognitive impairment varies among different pain syndromes. This explains why contradictory findings have been noted for tests of for example verbal memory, with some studies [10–12], but not all [13,14], finding that chronic pain is associated with poorer performance. Similar inconsistencies are apparent for other cognitive domains. (3) The effects of psychotropic drugs on cognitive performance are contradictory [7].

Beside, little is known about the affected cognitive domains in chronic low back pain patients. For this patient cohort research mostly focused on memory of pain, rather than cognitive difficulties related to pain [9]. Apkarian [3] proposed that chronic pain may be associated with specific (yet undefined) cognitive deficits that affect everyday's behaviour. An association between slow reaction time and chronic low back pain has been observed [e.g. 15]. A further interventional study showed that an impaired psychomotor control in patients with chronic low back pain was reversible with successful rehabilitation [16] which suggests that the slower reaction time might be a consequence of chronic low back pain.

In the current study, we set out to measure the cognitive deficits in a homogeneous group of patients whose main complaint was chronic low back pain (cLBP) and to verify the effect of a multidisciplinary treatment on cognitive impairment in cLBP. We performed a comparative and longitudinal study to test the hypothesis that information processing function and working memory are impaired in patients with cLBP but are improved by multidisciplinary pain therapy incorporating a cognitive impairment component.

2. Patients and methods

2.1. Study subjects

Study subjects were recruited from the Department of Orthopaedic Surgery. Two groups of subjects were studied: patients with chronic low back pain (group 1, $n = 33$) and healthy controls with no pain (group 2, $n = 25$). All participants gave their written, informed consent to take part in the study and for their data to be published anonymously. The study was approved by the ethics committee of the University Hospital of Heidelberg, Germany and funded by the research fund of the Department of Orthopaedic Surgery and Traumatology of the University of Heidelberg.

The inclusion criteria for patients were: (1) age between 20 and 70 years; (2) a history of at least 12 weeks of chronic myofascial low back pain without radicular pain sensation before enrolment (grade II and higher chronicity according to Von Korff (Von Korff): grade I, low disability – low intensity; grade II, low disability – high intensity; grade III, high disability – moderately limiting; grade IV, high disability – severely limiting); (3) no opioid medication (non-opioid pain medication was allowed). Healthy controls had experienced no lower back pain and taken no pain medication in the past year. The patients recruited had a mean pain duration of 7.13 ± 7.16 years and reported a mean pain intensity of 6.62 ± 2.04 (visual analogue score, VAS). Their mean back function according to the Funktionsfragebogen Hannover (FFbH, German version; a questionnaire comparable with the Health Assessment Questionnaire) was 52.39 ± 20.23%. No significant differences of age, education level between both groups were found, but statistical significant difference of sex was determined. There were more female subjects in the patient group than in the healthy group (Table 1).

The exclusion criteria for both groups were: (1) gross brain damage, learning disability; (2) major mental disorder requiring recent hospitalisation, such as schizophrenia or psychosis.

2.2. Multidisciplinary pain therapy (MDPT)

Patients with cLBP underwent inpatient multidisciplinary therapy with medical, psychological, physical and social components: This comprised 6-h sessions on 5 days each week for 3 weeks, amounting to a total of 90 h. The goal of MDPT is to restore the patients' physical and psychosocial abilities, to expand their knowledge of back protection techniques and protective behaviour, to improve positive skills for individual coping and emotional control, and to increase the patients' activity levels on return to the workplace. It integrates physical exercises, ergonomic training, psychotherapy, patient education, behaviour therapy and workplace-based interventions in individual therapy and in-group sessions.

Table 1
Characteristics of study subjects.

	Group 1 ($n = 33$) cLBP Patients	Group 2 ($n = 25$) Healthy controls	p-value
Age (year)	49.82 ± 10.23 (28–71)	45.88 ± 9.24 (35–66)	ns
Female ♀	25 (75.8%)	10 (40.0%)	$p < 0.05$
Male ♂	8 (24.2%)	15 (60.0%)	
BMI	26.4 (18.5–35.4)	27.1 (18.7–47.8)	ns
High school (%)	88.57%	66.7%	ns
Higher education level (%)	11.42%	33.3%	ns
IQ (MWT-B)	27.00 ± 4.93	28.68 ± 6.28	ns
FFbH (%)	52.39 ± 20.23	96.0 ± 10.0	$p < 0.05$
Depression (HADS) (range 0–21)	9.24 ± 4.99	4.8 ± 3.7	ns
Anxiety (HADS) (range 0–21)	10.06 ± 4.44	4.4 ± 2.9 ♂ 5.2 ± 3.4 ♀	ns
Adjuvant	NSAIDs (5%) Antidepressant(6%)	0% 0%	

After completion of this treatment programme, the patients were discharged from hospital without further interventions. They were allowed to contact the physician who had referred them for therapy, but they were advised to manage similar further pain episodes on their own without immediately contacting a physician. Further utilisation of medical services after completion of the therapy programme was not monitored.

2.3. Neuropsychological tests

Multiple choice vocabulary test (MWT-B,17): The multiple choice vocabulary test is presently available only in German (MWT = *Mehrfachwahl–Wortschatz-Test*). It can easily be administered in around 5 min. Each patient will be submitted to a total of 37 lines of five words each. Only one of these five words really exists, all others are fictitious words. Subjects are asked to identify and mark the correct words. For each correctly recognised word, the patient receives one point up to a total maximum of 37 points.

This test is supposed to be a performance measure for general intelligence, particularly for the experience-based, learning-enhanced "crystallised intelligence".

Wechsler Adult Intelligence Scale (WAIS-III): The WAIS-III (Wechsler, 1997, 18) was administered by experienced psychologist. With this test, the cognitive abilities of adults are studied. These skills are categorised into three different IQ scores: the verbal IQ, the performance IQ and total IQ.

In WAIS-III A test, the respective subjects are read, they have to play both forward and backward in the correct sequence numbers. For each correct repeated numbers, patients receive points. These point values are held in absolute terms and as percentage values.

In WAIS-III test B, patients with both numbers and letters will be presented. First, the numbers should be in ascending order given in the correct order, then the letter must also be repeated after correctly in ascending order. Again, the points and percentage values are logged.

Trail-making test (TMT): The Trail-Making Test (TMT), an easily administered measure of visual scanning ability, graphomotor speed, and mental flexibility, is widely used in neuropsychological evaluation [19]. The neurobehavioral components involved in successfully completing the separate subtests of the TMT (A and B) are difficult to distinguish, because some are shared across tasks. For example, both subtests require sufficient attention, graphomotor speed, visual scanning ability, and numeric sequencing, but TMT-B further necessitates letter sequencing, mental double tracking, and alternation (e.g., shifting between letter and number series).

2.3.1. CANTAB tests

The CANTAB is a series of computerised tests of cognition that runs on a personal computer fitted with a touch-sensitive screen (http://www.camcog.com/science/cantab-tests-all.asp). It has been standardised on many samples [20]. The CANTAB was selected for this study because of its advantages of efficiency, the achievement of highly standardised administrations, and automated response recording [21]. CANTAB subtests are also simple to administer and complete, staff training is minimal, and the tests are acceptable to severely depressed or elderly patients who lack motivation and/or find instructions hard to follow. The following three subtests were selected for the present study.

Choice reaction time (CRT): This is a two-choice reaction time test, which is useful for testing general alertness and motor speed. Stimulus and response uncertainty are introduced by having two possible stimuli and two possible responses. An arrow-shaped stimulus is displayed on either the left or the right side of the screen. The subject must press the left-hand button on the press pad if the stimulus is displayed on the left side of the screen, and the right-hand button if the stimulus is displayed on the right side of the screen. Administration time is around 7 min, depending on level of impairment. This test has 13 outcome measures, assessing correct and incorrect responses, errors of commission and omission (late and early responses), and latency (response speed).

Pattern recognition memory (PRM): This is a test of visual memory in a two-choice forced discrimination paradigm. The subject is first presented with a series of 12 visual patterns, one at a time, in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the subject is required to choose between a pattern they have already seen and a novel pattern. In this phase, the test patterns are presented in the reverse order to the original order of presentation. These two phases are then repeated, with 12 new patterns. The second recognition phase can be given either immediately or after a 20-min delay. The administration time is around 5 min, depending on level of impairment. This test has three outcome measures, including the number and percentage of correct trials and latency (speed of subject's response).

Spatial span (SSP): This test of working memory capacity assesses the ability to store information temporarily 'on-line' in order to plan further action. White squares are shown, some of which briefly change colour in a variable sequence. The subject must then touch the boxes which changed colour in the same order that they were displayed by the computer. The number of boxes increases from two at the start of the test to nine at the end, and the sequence and colour are varied through the test. The administration time is around 5 min, depending on level of impairment. This test includes outcome measures of span length (the longest sequence successfully recalled) and error measures.

2.4. Statistical analysis

The Kolmogorov–Smirnov test showed that the values of CANTAB test and the other neuropsychological tests were not normally distributed; therefore, the ANOVA test was selected for the analysis of differences between groups. The t-test was used for comparison of age, height, education level, pain intensity, and duration of pain. The chi-square test was used for testing the sex differences between groups. Spearman's rho and Pearson's correlation analyses were used to examine the relationship between cognitive functions and clinical parameters such as depression, duration of pain, and pain intensity. Multivariate tests were used for analysis of covariates. All tests were performed with PASW 18.0.1 (Predictive Analytics Software, Polar Engineering and Consulting) software for Windows. For each statistical test, the significance level was set at $p < 0.05$.

3. Results

A total of 58 subjects were recruited for the study: 33 cLBP patients (group 1) and 25 healthy controls (group 2). Table 1 shows the demographic and clinical characteristics of both groups. There were no statistically significant between-group differences in age, BMI, education, nicotine consumption, and IQ (measured by the MWT-B). The percentage of men was higher in the healthy control group (60 vs. 24%).

3.1. Cross-sectional comparison between cLBP patients and HC

Compared to healthy controls ($96.0 \pm 10.0\%$) patients ($52.39 \pm 20.23\%$) had worse back function at T1 ($p < 0.05$). Depression and anxiety scores measured by HADS were similar between groups at T1.

There was no between-group T1 difference for the intelligence measures MWT-B and WAIS-III. Furthermore, no significant

Table 2
Results of neuropsychological tests at the beginning of the MDPT.

	Group 1 ($n = 33$) cLBP patients	Group 2 ($n = 25$) Healthy controls	Mann–Whitney-test
Multiple choice vocabulary test (MWT = Mehrfachwahl–Wortschatz-test)	28.08 ± 4.87	28.68 ± 6.28	ns
Wechsler Intelligence test for adults (WAIV-III) A (percent)	48.70 ± 11.08	52.52 ± 11.82	ns
Wechsler Intelligence test for adults (WAIV-III) B (percent)	51 ± 15.57	51 ± 15.57	ns
Trial making test A (TMT-A)			
Time (s)	38.29 ± 19.99	30.25 ± 14.19	$p = 0.047$
Errors	0.06 ± 0.24	0.04 ± 0.2	ns
Trial making test B (TMT-B)			
Time (s)	72.10 ± 26.98	55.99 ± 22.14	$p = 0.034$
Errors	0.93 ± 1.58	0.00 ± 0.00	ns
Choice reaction time (CRT)			
Mean correct latency	390.16 ± 108.33	379.57 ± 92.50	ns
Maximum Correct Latency	864.55 ± 401.03	961.04 ± 699.378	ns
SD correct latency	95.94 ± 55.38	102.80 ± 83.611	ns
Percent correct trials	99.42 ± 0.936	99.72 ± 0.54	ns
Pattern recognition memory (PRM)			
Percent correct	89.78 ± 8.53	88.00 ± 11.37	ns
Spatial span (SSP)			
Span length	5.42 ± 1.03	5.84 ± 1.84	ns

differences were found between patients and healthy controls in the CRT, PRM and SSP domains of the CANTAB.

It took cLBP patients longer to complete the TMT-A ($p = 0.047$) and TMT-B ($p = 0.034$) whereas error rates in these tests were similar between groups (Table 2).

3.2. Longitudinal comparison between different time points after multidisciplinary pain therapy

Compared to T1 (baseline), patients performed 6 and 7 s faster in TMT-A at T2 (3 weeks, $p = 0.02$) and T3 (6 months, $p = 0.021$), respectively. The pattern recognition memory (PRM) was not significantly improved at T2 ($p > 0.05$) and T3 ($p > 0.05$), too. No significant difference was found between T2 and T3 ($p > 0.05$). The reaction speed of patients in repeating the vocabulary (WAIS-III) did not increased until T3 (T3 vs. T1: $p = 0.008$).

In parallel, there were significant reductions from T1 to T2 in pain intensity ($p < 0.001$), HADS depression ($p < 0.001$), anxiety scores ($p < 0.001$) and improvement of back function ($p < 0.001$) (Table 3).

3.3. Correlations between neuropsychological test results and clinical parameters

Increased pain intensity (VAS) at T1 correlated with worse PRM ($r = -0.352$, $p = 0.045$). The reduction in pain intensity correlated with TMT-B results at T2 ($r = -0.457$, $p = 0.019$).

Depression scores correlated with TMT-B errors ($r = -0.646$, $p = 0.007$) and MWT ($r = -0.356$, $p = 0.042$). The difference in depression scores between T2 and T1 correlated with TMT-A errors ($r = 0.445$, $p = 0.023$) (Fig. 1).

Anxiety scores at T1 correlated with TMT-B completion time ($r = 0.566$, $p = 0.028$) and CRT mean correct TRAILs ($r = 0.400$, $p = 0.043$).

Usage of NSAIDs and antidepressants (no opioids) correlated with CRT percentage correct TRAILs ($r = 0.381$, $p = 0.029$) and TMT-B ($r = -0.585$, $p = 0.017$) at T1; with PRM percentage correct TRAILs ($r = 0.486$, $p = 0.008$) and WAIS-III B ($r = 0.371$, $p = 0.047$) at T2; and with PRM percentage correct TRAILs ($r = 0.514$, $p = 0.017$) and TMT-A completion time ($r = -0.502$, $p = 0.020$) at T3.

No significant correlations were found between results of neuropsychological tests and either nicotine consumption or education level.

4. Discussion

In the present study we compared the cognitive performance between patients with chronic low back pain and healthy controls. Moreover, we assessed the cognitive performance longitudinally within cLBP patients directly (3 weeks) and 6 months after multimodal pain therapy using computerised tests from the CANTAB and paper-pen-based neuropsychological tests. Our findings give insight into the cognitive changes from patients with cLBP. The chronic pain seems to impair both information processing and working memory (Table 2: patient groups showed worse results in TMT-A and -B). The attention and visual pattern recognition memory of cLBP patients did not differ from those of healthy controls.

We tested the two groups for comparability and found no significant differences in age, sex, education level, intelligence level or depression/anxiety scores between the patients and the healthy controls (Table 1). Therefore, we believed that our groups fulfil the criteria for a comparative study.

The literature includes only a few investigations of the influence of low back pain on cognitive functioning. The results of these studies were inconsistent. Etherton found only slightly reduced processing speed index (PSI) of the WAIS-III in chronic pain [13]. Weiner's team found significant differences in neuropsychological testing scores between pain-free older adults (mean age 73.5 years) and those with cLBP the latter showed disturbance of immediate memory, language, delayed memory, mental flexibility and grooved pegboard test performance [14]. The third and last study compared memory dysfunction and maladaptive coping in cLBP and rheumatoid arthritis patients [22]. Both these groups of patients with chronic pain had high scores for memory complaints and low performance on memory assessment. Only the cLBP patients' measures of catastrophising and coping were significantly correlated to late memory indices.

Our findings complement the previous research and provide new insights into cognitive impairment in people with cLBP. The patients in our cLBP group presented delayed information processing speed and defective executive function before the multidisciplinary pain therapy (Table 2). They all had severe cLBP according to von Korff grading, but MRI did not detect specific pathological processes to which their pain could be attributed. They were not as old (mean age 59 years) as the patients studied by Weiner (mean 73.5 years) and had average pain duration of 7 years, average pain intensity of 6.6 (VAS) and strongly impaired back function (average 52% of normal). The average depression and anxiety scale scores tended higher than those of healthy controls but did not reach the cut-off value for a diagnosis of depression or anxiety disturbance. Therefore, the cognitive impairment of patients with cLBP might be secondarily induced by somatic damage rather than primarily induced by depression, which is highly prevalent in chronic non-cancer pain and has been shown to be associated with cognitive complaints [23].

Table 3
Results of neuropsychological tests and clinical outcomes in time course of 6 months of patients with cLBP.

	T1 (day 0)	T2 (3 weeks)	T3 (6 months)	Wilcoxon-test
TMT-A (s)	38.3 ± 19.9	31.8 ± 12.3	30.2 ± 8.9	T2/T1: $p = 0.02$ T3/T1: $p = 0.02$ T3/T2: $p > 0.05$
TMT-B (s)	74.2 ± 29.6	75.1± 35.9	77.7± 26.5	$p > 0.05$
WAIS-III (%)	48.8 ± 11.1	51.2 ±11.9	57.1 ±10.9	T3/T1: $p = 0.008$
CRT mean correct latency	390.2 ± 108.3	394.5 ± 88.5	399.4 ± 111.9	$p > 0.05$
CRT maximum correct latency	864.6 ± 401.027	1037.8 ± 432.5	1024.2 ± 567.5	$p > 0.05$
CRT SD correct latency	95.9 ± 55.4	111.3 ± 68.2	113.7 ± 72.7	$p > 0.05$
CRT percent correct trials	99.4 ± 0.9	99.55 ± 0.6	99.4 ± 1.3	$p > 0.05$
PRM percent correct	89.8 ± 8.6	91.8 ± 8.8	90.1 ± 9.4	$p > 0.05$
SSP span length	5.4 ± 1.0	5.4 ± 1.0	5.6 ± 0.8	$p > 0.05$
Pain intensity	6.62 ± 2.04	4.25 ± 1.81	ns	T2/T1: $p < 0.001$
Depression scores (HADS)	9.24 ± 4.99	3.87 ± 3.71	ns	T2/T1: $p < 0.001$
Anxiety scores (HADS)	10.06 ± 4.44	5.47 ± 3.66	ns	T2/T1: $p < 0.001$
MWT	27.00 ± 4.90	29.00 ± 4.31	30.00 ± 4.48	T2/T1: $p = 0.002$ T3/T1: $p = 0.001$ T3/T2: $p > 0.05$

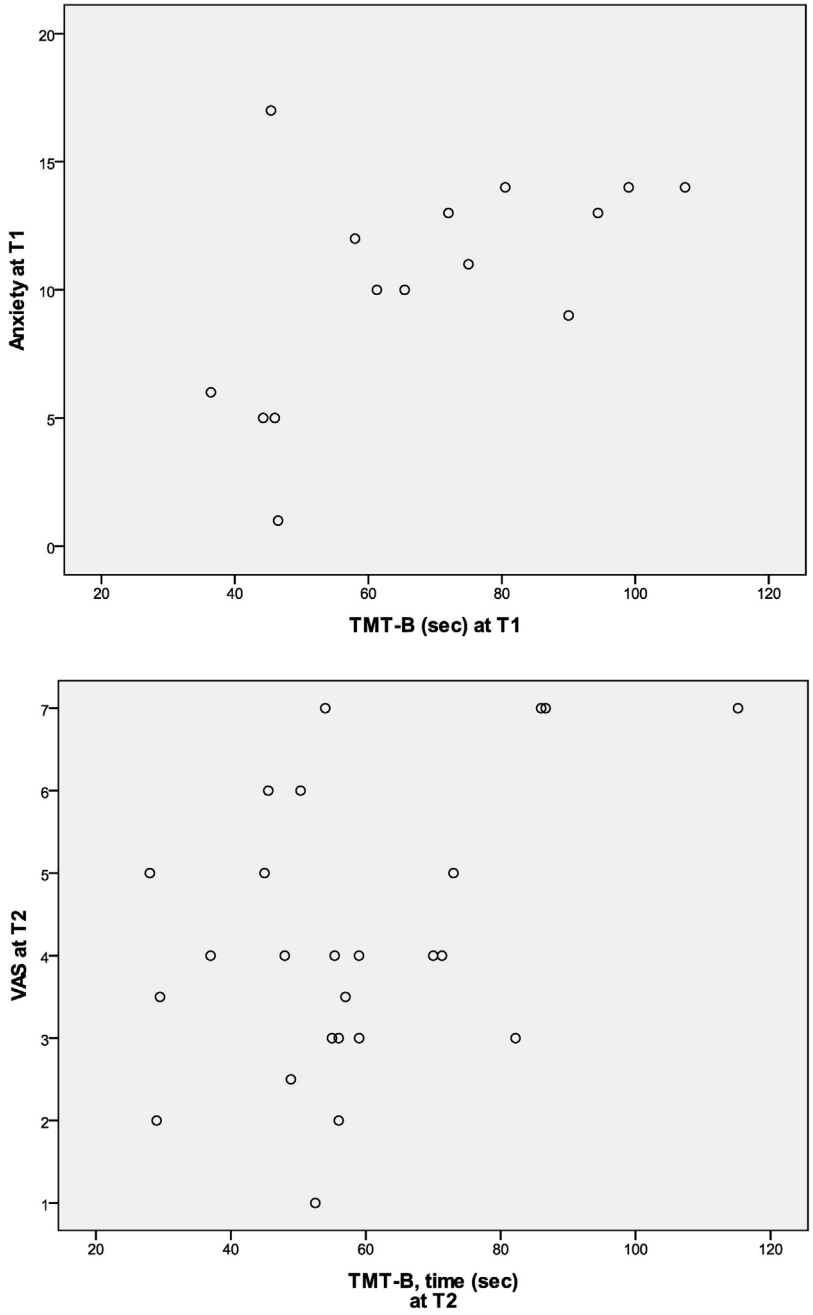

Fig. 1. Relationshipof the scores of the Trail Making Test B and Anxiety at T1 and Pain Levels at T2.

In the current study, both pain intensity (VAS) and depression/anxiety scores were found to be correlated with working memory (TMT-B) in the cLBP patients. These findings indicate interaction of pain, depression, anxiety and cognitive impairment. However, the reason for these cognitive deficits is uncertain. Low back pain may be a contributing factor, because pain itself may have an arousal effect or may act as a mental stressor. By reducing the stressor (pain), cognitive balance may be re-established [24]. Our findings indicate that the effects of pain on cognitive function may not be related in a simple fashion to its immediate sensory-discriminative features (e.g. pain intensity); concomitants of chronic pain (e.g. emotional distress, suffering and fatigue) may be important mediating variables. However, one team of researchers reported greater deficits in people with chronic fatigue syndrome without co-morbid depression [25]. A further study with a larger sample and subgroups of patients with chronic pain of different origins should be performed.

In summary, cLBP patients typically presented with maladaptive primary physical and secondary cognitive compensations for their pain disorders that become a mechanism for ongoing pain. For this group, specifically targeted physiotherapy interventions and cognitive behaviour therapy, have the potential to impact on both the physical and cognitive drives of pain, leading to resolution of the disorder. That is the rationale for our concept of multidisciplinary pain therapy (MDPT) based on a combination of physical exercise and psychological interventions.

The cognitive dysfunction of our patients had already improved only 3 weeks after MDPT. In parallel to the significant reductions in pain intensity and in depression and anxiety scores, the patients' information processing speed (TMT-A) was significantly greater than before MDPT, and this effect persisted for 6 months after the end of MDPT (Table 3). The patients' working memory was also significantly enhanced at 6 months. These results confirmed the multidimensional nature of cLBP. Although it is now widely accepted that cLBP disorders are multifactorial in nature, individual patients differ in the presence and relative influence of the various patho-anatomical, physical, neurophysiological, psychological and social factors. Our findings suggested that techniques to improve concentration and memory should be incorporated as part of a multidisciplinary pain programme for each individual patient.

Possible confounding factors such as psychiatric status, depression were considered. Patients with a psychiatric disorder, gross brain damage or learning disability were excluded from the study. Regarding depression status, our group of cLBP patients showed no difference from healthy controls. We also took medication into account, as patients with cLBP often consume NSAIDs and antidepressants. Exploring the impact of medication usage on cognitive functioning, we found significant correlations between intake of NSAIDs/antidepressants and information processing speed, working memory, and recognition memory. However, individual investigations suggest that the impact of medication may be minimal, with one study finding no difference between the performance of medicated and unmedicated persons with chronic fatigue pain and another recording significant performance decrements in unmedicated (but not medicated) chronic fatigue syndrome patients compared with controls [10].

One limitation of the current study is that the nature of the onset of the condition (sudden versus gradual) was not documented. A further study should be performed with a larger sample and subgroups of patients with chronic pain of different origins.

Ethical issues

All participants gave their written, informed consent to take part in the study and for their data to be published anonymously. The study was approved by the ethics committee of the University Hospital of Heidelberg, Germany and funded by the research fund of the Department of Orthopaedic Surgery and Traumatology of the University of Heidelberg.

Conflict of interest

None declared.

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