

Prospective Study

Evidence of Specific Cognitive Deficits in Patients with Chronic Low Back Pain under Long-Term Substitution Treatment of Opioids

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Background: There is a growing number of patients worldwide being treated with long-term opioids for chronic non-cancer pain, although there is limited evidence for their effectiveness in improving pain and function. Opioid-use related adverse effects, especially in cognitive functioning in these patients, are rarely evaluated.

Objectives: The present study investigated the cognitive functions of patients with chronic back pain who underwent long-term opioid treatment in comparison with those patients without opioid usage and healthy controls.

Study Design: A prospective, nonrandomized, cross-sectional study.

Setting: Multidisciplinary pain management clinic, specialty referral center, University Hospital in Germany.

Methods: In a prospective cross-sectional design, 37 patients with chronic back pain who underwent long-term opioid therapy (OP) were compared with 33 patients with chronic back pain without opioid therapy (NO) and 25 healthy controls (HC). Assessment of primary outcome included cognitive function such as information processing speed, choice reaction time, pattern recognition memory, and executive function. Other data included pain, back function, depression and anxiety, use of medication, and education status. The relationship between cognitive functions and anxiety/depression was analysed.

Results: Both patient groups needed significantly longer time in information processing when compared to HC (Group 1: 41.87 ± 20.47 Group 2: 38.29 ± 19.99 Group 3: 30.25 ± 14.19). Additionally, OP patients had significantly reduced spatial memory capacity, flexibility for concept change, and impaired performance in working memory assessment compared to NO patients and HC. The impaired cognitive outcomes were significantly associated with pain intensity, depression scores, and medication use.

Limitations: Limitations include small number of patients with heterogeneous opioid therapy and the nonrandomized observational nature of the study.

Conclusions: Our findings give a differential view into the cognitive changes from chronic back pain with and without long-term opioids treatment. Chronic back pain itself impairs some distinct cognitive functions. Long-term opioid therapy adds further cognitive impairment.

Key words: Long-term opioid therapy, chronic back pain, cognitive dysfunction

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Opioid treatment for chronic non-cancer pain has been increasingly used in the last decade (1,2). Besides the concerns of addiction and dependency, tolerance, hyperalgesia, and dysfunction of the immune system (3-5), one of the major worries of maintaining opioid therapy in patients with chronic non-cancer pain in the long term is its potential for cognitive dysfunction (manifested as concentration impairment, deficits in information processing and memory, and slower psychomotor speed and reaction time).

Kendall et al (6) reviewed 30 studies which tried to answer the question "Does the long-term use of opioids interfere with the cognitive function in patients with chronic non-cancer pain?" With respect to study quality, only 13 studies fulfilled the following criteria: controlled study, patients with chronic non-cancer pain, at least one month of opioid treatment, cognitive assessment by neuropsychological tests, and written in English. In contrast to 2 randomized controlled trials (RCTs) (7,8) and 2 non-randomized comparative studies (NCSs) (9,10) which reported better information processing, attention, psychomotor speed, manual dexterity, and memory under short-term opioid treatment (< 6 months), 4 outcome research studies reported worse attention, vigilance, working memory (11-13), psychomotor speed (13,14), and sustained attention (13) compared to healthy control individuals. Hence, high quality evidence for a beneficial or detrimental effect of long-term opioid treatment on cognitive function in non-cancer pain patients is still limited (6). Furthermore, the lack of an opioid-naïve control group of patients with chronic pain was also an important limitation in several studies, as chronic pain itself may also impair cognitive function.

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 (15). Apkarian et al (16) proposed that chronic pain may be associated with specific (yet undefined) cognitive deficit that affects everyday behavior. An association between slow reaction time and chronic low back pain has been observed in 2 cross-sectional studies (1,17,18). A further interventional study showed that impaired psychomotor control in patients with chronic low back pain was reversible with successful rehabilitation (19) which suggests that the slower reaction time might be a consequence of chronic low back pain.

In the current study for the first time, we examined

the cognitive function of patients with chronic low back pain on long-term opioid therapy compared to those patients without opioid use as well as to healthy control individuals. The current study differed from the previous studies on the following points:

1. Our study focuses on a very specific group of patients;
2. Patients are homogenous (all had unspecific chronic low back pain);
3. Opioids use > 3 months and > 30mg/day;
4. Patients without opioids were also considered;
5. A new computerised neuropsychological programme (CANTAB from Cambridge) was used for the testing of cognitive function;
6. The concurrent medication which can affect cognitive function was compared between patient groups;
7. In a prospective model.

We hypothesized that patients with chronic low back pain on long-term opioid treatment would have more attention, learning, and memory deficits than patients without long-term opioid treatment.

METHODS

Patients

Patients were recruited from the Department of Orthopaedic Surgery. Three groups of subjects were studied: patients with chronic low back pain under opioid therapy for at least 3 months (group 1); patients with chronic low back pain that had not been on opioids (group 2); and healthy controls with neither pain nor opioid therapy (group 3).

The following inclusion criteria for patients were used: (1) age between 20 and 75 years, (2) patients with chronic low back pain for a minimum of 12 weeks before study enrolment (\geq grade II according to von Korff et al [20]), (3) healthy controls had no pain and no medication in the past year.

Exclusion criteria for all groups were: (1) radiculopathy, (2) gross brain damage or learning disability, (3) major psychiatric disorders requiring recent hospitalization, such as schizophrenia or psychosis.

Long-term opioid therapy was defined as intake of a daily morphine equivalent dose of at least 30 mg every day for more than 3 months (21). For a standardized data analysis, the following conversion rates between an oral dose of morphine and other opioid analgesics

were applied (one mg morphine = 0.65 mg oxycodone, 0.25 mg methadone, 5 mg tilidine, 0.01 mg fentanyl, 0.13 mg hydromorphone, 5 mg tramadol). Non-opioid pain medication in the group of opioid-naïve patients was allowed. Healthy controls had no pain and no medication in the past year.

Demographic variables such as age, gender, and years of education were obtained.

Opioid naïve patient refers to an individual who has either never had an opioid or who has not received repeated opioid dosing for a 2 to 3 week period.

Measures of anxiety and depression were drawn from the Hospital Anxiety and Depression Scale (HADS) (22), a 14-item scale that assesses affective and cognitive symptoms of anxiety (7 items) and depression (7 items).

Patients performed the tests immediately after inclusion in the study. They were seated at a desk and in front of the Cambridge Neuropsychological Test Automated Battery (CANTAB) device. The order of the neuropsychological tests was first paper-pen-based tests, then CANTAB neuropsychological tests.

Neuropsychological Tests

I. Paper-pen-based tests

1. Multiple choice vocabulary test MWT-B

For an assessment of the premorbid intelligence the multiple choice vocabulary test (MWT = Mehrfachwahl-Wortschatz-Test) which is currently only available in the German version was applied. Thirty-seven word series were listed. Each series consists of 5 words, but only one of them is meaningful. The study subject is asked to tick the meaningful word. The results correlate fairly with global IQ in healthy adults (median of $r = 0.72$ in 22 samples [23]). Moreover, test results are more insensitive to current disturbances than those of the WAIS vocabulary test (23).

2. Wechsler Adult Intelligence Scale (WAIS-III)

Based on the presenting complaint and referral question the WAIS-III (24) was administered as part of a comprehensive neuropsychological evaluation by experienced psychometrists using a flexible battery approach with a consistent core battery of tests. It provides scores for Verbal IQ, Performance IQ, and Full Scale IQ, along with 4 secondary indices (Verbal Comprehension, Working Memory, Perceptual Organization, and Processing Speed). For this study, 3 subtests of the WAIS-III were applied to all patients. (1) WAIS-III

A (short term memory): repeat of number forwards; (2) WAIS-III B (working memory): repeat of number backwards; (3) WAIS-III C (working memory): repeat of letter-number-combination.

3. Trail Making Test (TMT)

The Trail Making Test (TMT) is an easily administered measure of visual scanning, graphomotor speed, and mental flexibility, and is widely used in neuropsychological evaluations. For a detailed background and test description see (25). In the TMT-A, patients are asked to draw a line from number 1 to 25 and in TMT-B from 1 to A, then 2 to B, and at last from 12 to L.

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, information processing, 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), working memory (26), and cognitive flexibility (27). Low scores on the TMT-B could be almost entirely due to slowed motor functioning, impaired visual scanning, or inability to alternate between numbers and letters. A component analysis of TMT-B performance, then, could assist the clinician in drawing inferences regarding regional brain compromise that could aid in diagnostic clarification. The difference between the completion times of TMT-B and TMT-A (TMT B-A) reflects the executive component for visual scanning and movement time (28,29). The ratio between TMT-B / TMT-A was used as measurement of executive function (30)

II. CANTAB neuropsychological tests

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a series of computerized tests of cognition that runs on a personal computer fitted with a touch-sensitive screen. It has been standardized on many samples (31). The CANTAB was selected for this study because of its advantages of efficiency, the achievement of highly standardized administrations, and automated response recording that would be difficult to accomplish by hand. For example, response times can be recorded with millisecond precision, which can be important for scoring purposes (32). CANTAB subtests are also very simple to administer, 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. For more detailed descriptions of these tests, see the CANTAB website (www.camcog.com/science/cantab-tests-all.asp).

The following 3 subtests were selected for the present study.

1. Choice Reaction Time (CRT)

Choice Reaction Time (CRT) is a 2-choice reaction time test which is useful for testing general alertness and motor speed. In the test stimulus and response uncertainty are introduced by having 2 possible stimuli and 2 possible responses. An arrow-shaped stimulus is displayed on either the left or the right side of the screen. The patient must press the left hand button on the press pad if the stimulus is displayed on the left hand side of the screen, and the right hand button on the press pad if the stimulus is displayed on the right hand side of the screen. The time until the reaction and errors are registered. This task is a measure of alertness, simple information processing, and response organization.

2. Pattern Recognition Memory (PRM)

This is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. The patient is presented with a series of 12 visual patterns, one at a time, in the center 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. This is then repeated, with 12 new patterns. The second recognition phase can be given either immediately or after a 20 minute delay. This task measures the ability to hold information in short-term memory and rapidly retrieve it, reflecting the operation of short-term memory.

3. Spatial Span (SSP)

The test assesses working memory capacity, indexing individual ability to store information temporarily "on-line" in order to plan further action. White squares are shown, some of which briefly change color in a variable sequence. The subject must then touch the boxes which changed color in the same order that they were displayed by the computer. The number of boxes increases from 2 at the start of the test to 9 at the end, and the sequence and color are varied through the test. Spatial span assesses the working

memory capacity, and is a visuospatial analog of the digit Span test. Spatial memory is the part of memory responsible for recording information about one's environment and its spatial orientation. Spatial memory has representations within working, short-term, and long-term memory.

Statistical Analysis

Kolmogorov-Smirnov-Tests showed that the values of CANTAB-tests and the other neuropsychological tests were not normally distributed. Therefore, non-parametric hypothesis tests (Mann-Whitney-Test, Kruskal-Wallis-Test) were chosen for between group comparisons. T-test analysis was used for comparisons of age, height, BMI, pain intensity, duration of pain, and opioid usage. Chi-square tests were used for the testing of differences in categorical variables between groups. Spearman's rho and Pearson's correlation analysis were used to examine the relationship between cognitive functions and clinical parameters such as anxiety, depression, duration of pain, duration of opioid medication, dose of opioid, and subjective pain intensity. All tests were performed with SPSS v17.0 software for Windows. Data analysis was exploratory. For each statistical test, the significance level was set at $P \leq 0.05$ with no correction for multiple testing.

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

RESULTS

A total of 95 patients and healthy controls were recruited for the study: 37 subjects into group 1, 33 into group 2, and 25 into group 3. The subject characteristics are displayed in Table 1.

Table 2 shows the performed tests and their correspondent tasks.

The cognitive functions were tested in the domains of visual attention and visuomotor skills, general alertness and motor speed, short memory and working memory.

Premobid intelligence quote

Overall, there was no between group difference for the multiple choice vocabulary tests (MWT-B) (Table 3).

Chronic Opioid Therapy and Cognitive Function in Chronic Pain

Table 1. *Characteristics of study subjects.*

	Group 1 (n = 37) Opioid-positive patients	Group 2 (n = 33) Opioid-naïve patients	Group 3 (n = 25) Healthy controls	Kruskal–Wallis–Test Mann–Whitney–Test
Age (year)	53.8 ± 11.26 (36–73)	49.82 ± 10.23 (28–71)	45.88 ± 9.24 (35–66)	n.s G1 vs G2, G2 vs G3 P = 0.005 G1 vs G3,
Female	22 (59.5 %)	25 (75.8 %)	10 (40.0 %)	n.s G1 / G2, P = 0.005 G1 /G3
Male	15 (40.5 %)	8 (24.2 %)	15 (60.0 %)	n.s G1 / G3, P = 0.005 G1 / G2
BMI	28.7 (25.4–31.3)	26.4 (18.5–35.4)	27.1 (18.7–47.8)	n.s
Diagnosis	cLBP	cLBP	No pain	–
Pain history: duration of chronic pain	10.30 ± 9.95 years	7.13 years ± 7.16	0	n.s G1 vs G2
Pain intensity (VAS) Now	7.15 ± 1.84	6.62 ± 2.04	0	n.s G1 vs G2
FFbH	49.94 ± 27.24	52.39 ± 20.23	96 ± 10.00	P < 0.05 G1 vs G3, G2 vs G3
Opioid duration	19.77 ± 24.96 months	0	0	–
Morphine equivalent (mg/day)	100.23 ± 114.37	0	0	–
Depression	47.6 % 11.74 ± 4.68	44.4 % 9.24 ± 4.99	0% 4.8 ± 3.7	n.s. G1 vs G2
Anxiety	8.1% 10.39 ± 4.78	20% 10.06 ± 4.44	0% 4.4 ± 2.9 (males) 5.2 ± 3.4 (females)	n.s G1 vs G2
Medication	NSAIDs (2%) Antidepressants (1%)	NSAIDs (5%) Antidepressants (6%)	0%	n.s G1 vs G2
Education status				
High school	88.57%	66.7%	Not asked	n.s G1 vs G2
> High education level	11.42%	33.3%		
Secondary modern school	2	2		
Junior high school	24	26		
Diploma	8	3		
University degree	1	1		
No Answer	2	2		

Table 2. *Mapping of tests to the various functional areas.*

Test Name	Tested cognitive function
MWT-B	Intelligence
WAIT-III A	Short term memory
WAIT-III B/C	Working memory
TMT-A	Attention, information processing, graphomotor speed, visual scanning ability, numeric sequencing,
TMT-B	Mental double tracking and alternation, working memory and cognitive flexibility
TMT(B-A)	Executive component for visual scanning and movement time
TMT-B/TMT-A	Executive function
CRT	General alertness and motor speed (Time needed till press the botton)
PRM	Ability to hold information in short-term memory and rapidly retrieve it, reflecting the operation of short-term memory
SSP	Working memory capacity

Table 3 Mean scores on premobid intelligence quote, visuomotor skills and concentration

	Group 1 (n = 37) Opioid-positive patients	Group 2 (n = 33) Opioid-naïve patients	Group 3 (n = 25) Healthy controls	Mann-Whitney Test
Multiple choice vocabulary test				
(MWT=Mehrfachwahl-Wortschatz-Test)	28.08 ± 4.87	28.08 ± 4.87	28.68 ± 6.28	n.s
Trial making test A (TMT-A)				
Time (sec)	41.87 ± 20.47	38.29 ± 19.99	30.25 ± 14.19	<i>P</i> = 0.012 G1 vs G3 <i>P</i> = 0.047 G2 vs G3
Errors	0.08 ± 0.277	0.06 ± 0.24	0.04 ± 0.2	n.s
Trial making test B (TMT-B)				
Time (sec)	116.56 ± 71.24	72.10 ± 26.98	55.99 ± 22.14	<i>P</i> = 0.026 G1 vs G3 <i>P</i> = 0.034 G2 vs G3
Errors	2.86 ± 4.82	0.93 ± 1.58	0.00 ± 0.00	<i>P</i> = 0.005 G1 vs G3 n.s G2 vs G3 or G1
TMT-B/TMT-A	2.78 ± 3.48	1.88 ± 1.34	1.12 ± 1.55	<i>P</i> = 0.024 G1 vs G2
Choice Reaction Time (CRT)				
Mean correct latency	405.40 ± 108.920	390.16 ± 108.33	379.57 ± 92.50	n.s
Maximum Correct Latency	1031.28 ± 585.18	864.55 ± 401.03	961.04 ± 699.378	n.s
SD correct latency	113.51 ± 72.63	95.94 ± 55.38	102.80 ± 83.611	n.s
Percent correct trials	98.78 ± 3.29	99.42 ± 0.936	99.72 ± 0.54	n.s

Visual attention, visuomotor skills

The TMT-A completion time was delayed in both patient groups in comparison to healthy controls (30.25 ± 14.19 seconds) (*P* = 0.012 between group 1 and 3 (+11 seconds); *P* = 0.047 between group 2 and 3 (+8 seconds) (Fig. 1, Table 3). No between group differences were observed for the error rates. For TMT-B, group differences for both completion time and errors were observed between group 1 (116.56 ± 71.24 seconds, 2.86 ± 4.82 errors) and 3 (55.99 ± 22.14 seconds, 0.00 ± 0.00 errors), but only in completion time between group 2 (72.10 ± 26.98 seconds, 0.93 ± 1.58 errors) and 3 (55.99 ± 22.14 seconds, 0.00 ± 0.00 errors) (Fig. 1, Table 3). No differences were observed between group 1 and 2.

General alertness and motor speed

There were no between group differences of the CRT results in the mean correct latency, the maximum correct latency, SD correct latency, and percent correct trials (Table 3).

Short memory

The Pattern Recognition Memory (PRM) test revealed no between group differences in correct rates of the PRM test. Moreover, no differences were observed in repeat of number forwards (WAIS-III A) between groups (Table 4).

Executive function: working memory, concept change, rules, and interference

The ratio of TMT-B/TMT-A between patient groups (group 1 and 2) was significantly different (*P* = 0.024). The test performance of TMT-B correlated to anxiety (0.566, *P* = 0.028) and depression (0.413, *P* = 0.015) in group 2. There were no significant differences in repeat of number backwards (WAIS-IIIB) between groups, but the opioids group performed the letter-number-sequencing test (WAIS-IIIC) significantly worse than no-opioids group (*P* = 0.022) and healthy subjects (*P* = 0.037). These differences existed even after adjustment for age.

The opioids group reached the worst results of SSP test in all 3 groups. There was a significant difference in the longest sequence successfully recalled between group 1 and 3 (*P* = 0.007) and by trend significantly between group 1 and 2 (*P* = 0.052) which even existed after adjustment for age (Fig. 2). The results of group 2 did not differ from those of group 3.

Correlations between clinical parameters and neuropsychological test results

The pain intensity in group 1 but not in group 2 correlated with TMT-B error (0.468, *P* = 0.006) and time (0.490, *P* = 0.028), negatively with WAIS-III B (-0.446, *P* = 0.009), while both depression and anxiety in group 2

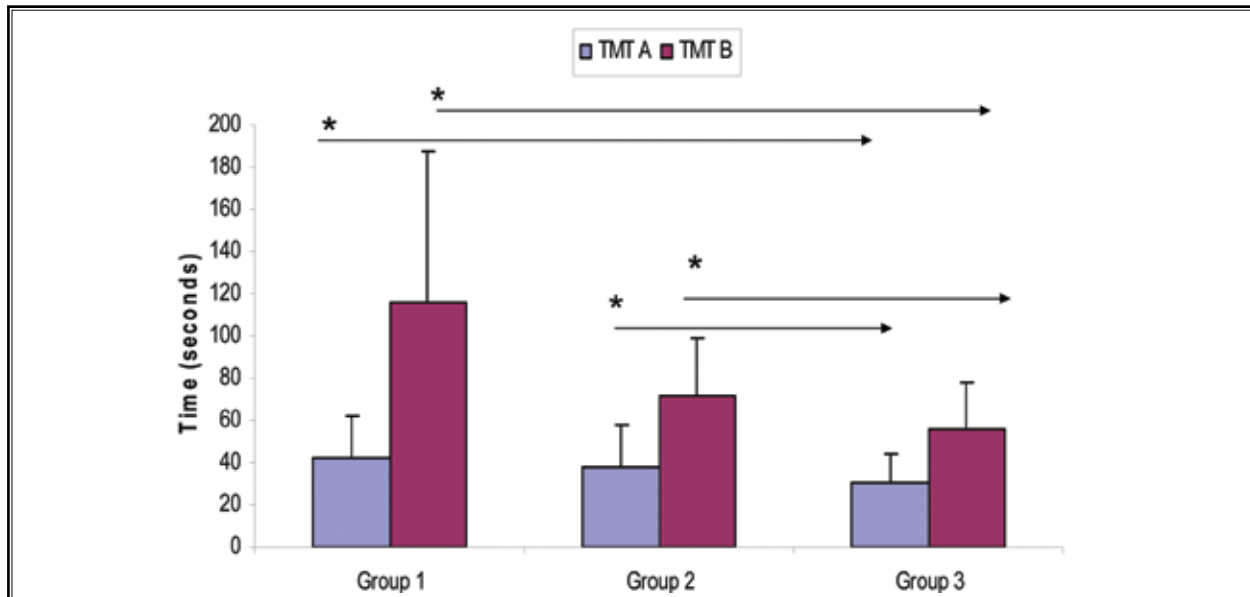


Fig. 1. To analyze the visual attention and visuomotor skills, the Trial-Making-Test-A (TMT-A, marked in blue) was performed. To analyze the mental double tracking and alternation, working memory, and cognitive flexibility, the Trial-Making-Test B (TMT-B, marked in red) was performed. The y-axis shows the time which the patients needed for revolving the task. The x-axis shows the different groups. Group 1: patients with chronic back pain and opioids treatment. Group 2: patients with chronic back pain but without opioids treatment. Group 3: healthy controls. Patients in group 1 needed 41.87 ± 20.47 seconds for completion TMT-A. Patients in group 2 needed 38.29 ± 19.99 seconds for completion TMT-A. Patients in group 3 needed 30.25 ± 14.19 seconds for completion TMT-A. The differences between group 1 and 3 (P = 0.012), between group 2 and 3 (P = 0.047) were both statistic significant. No between group differences were observed for the error rates. For TMT-B, group differences for both completion time and errors were observed between group 1 (116.56 ± 71.24 seconds, 2.86 ± 4.82 errors) and 3 (55.99 ± 22.14 seconds, 0.00 ± 0.00 errors), but only in completion time between group 2 (72.10 ± 26.98 seconds, 0.93 ± 1.58 errors) and 3 (55.99 ± 22.14 seconds, 0.00 ± 0.00 errors). No differences were observed between groups 1 and 2.

Table 4. Mean scores on short memory and executive functions.

	Group 1 (n = 37) Opioid-positive patients	Group 2 (n = 33) Opioid-naïve patients	Group 3 (n = 25) Healthy controls	Mann-Whitney Test
WAIS-III A/B (Percent) repeat number	48.89 ± 16.66	48.70 ± 11.08	52.52 ± 11.82	n.s
WAIS-III c (Percent) repeat number and letter	40.95 ± 18.52	51.00 ± 15.57	49.99 ± 14.08	P = 0.022 G1 vs G2 P = 0.037 G1 vs G3 n.s G2 vs G3
Pattern Recognition Memory (PRM) Percent correct	85.81 ± 11.00	89.78 ± 8.53	88.00 ± 11.37	n.s
Spatial span (SSP) Span Length	4.97 ± 1.19	5.42 ± 1.03	5.84 ± 1.84	P = 0.052 G1 vs G2 P = 0.007 G1 vs G3 n.s G2 vs G3

WAIS-III: Wechsler Adult Intelligence Scale(WAIS-III)

correlated with TMT-B time (-0.646, P = 0.007 and 0.400, P = 0.028, respectively). The medication of patients in group 2 correlated negatively with TMT-B errors (-0.585, P = 0.017). The test performance also correlated with depression in group 2 (-0.356, P = 0.042), although the patients in group 2 showed comparable results to healthy controls (P > 0.05).

DISCUSSION

The present study examined general cognitive functions in patients with chronic low back pain with or without long-term opioid therapy. Neuropsychological tests including visuomotor skills, short memory, and executive function were performed.

Main findings: (1) TMT-A timing was worse in

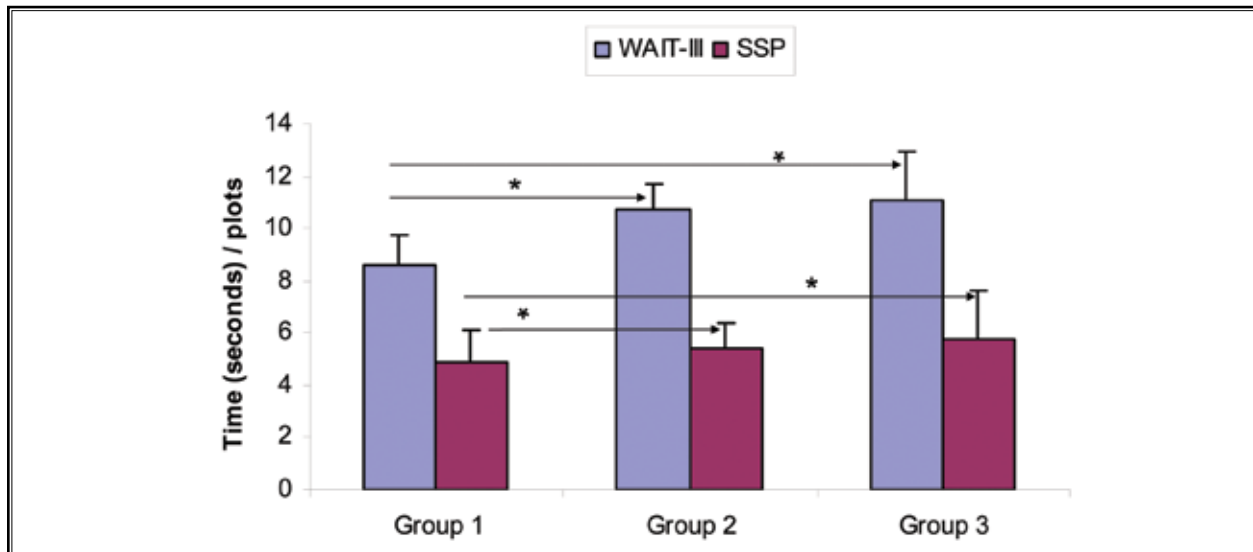


Fig. 2. To analyze executive function including the short term memory and working memory, the WAIT (marked in blue) and SSP (marked in red) were performed.

The y-axis shows the time which the patients needed for revolving the task. The x-axis shows the different groups. Group 1: patients with chronic back pain and opioids treatment. Group 2: patients with chronic back pain but without opioids treatment. Group 3: healthy controls. The patients in group 1 performed the letter-number-sequencing test (WAIS-III C) significantly worse than no-opioids group ($P = 0.022$) and healthy subjects ($P = 0.037$). And they reached the worst results of SSP test in all 3 groups. There was a significant difference in the longest sequence successfully recalled between group 1 and 3 ($P = 0.007$) and by trend significantly between group 1 and 2 ($P = 0.052$) which even existed after adjustment for age. The results of group 2 did not differ from those of group 3.

chronic low back pain patients with no additional effect of opioids. (2) TMT-B timing and errors were worse in chronic low back pain patients and even worse under opioid-treatment. (3) Repeat number letter (WAIS-III C) and SSP was worse under opioid-treatment with no additional effect of low back pain.

Most importantly, the current study found that visual attention, information processing, graphomotor speed, visual scanning ability, and numeric sequencing ability are impaired in both patient groups in comparison to healthy controls. Additionally, the executive function regarding working memory and cognitive flexibility of patients who underwent chronic opioid therapy was significantly hindered, which means that the opioids group may perform normally in simple tasks but performance could fall behind as the executive domain become more complex.

Does chronic pain cause cognitive dysfunction? Yes (TMT-A).

Does chronic opioid therapy cause cognitive dysfunction? Yes (WAIS-III C, SSP).

Does the interaction of low back pain and treatment with opioids cause cognitive dysfunction? (Yes; see TMT-B).

Or is the cognitive dysfunction in patients with chronic low back pain due to comorbidity such as depression or anxiety? Possible. But we need to analyze these theses in the further study.

Results from literature regarding the influence of different drugs on cognitive function are inconsistent. Already in 1999, Taimela and her colleagues (17) confirmed their hypothesis that chronic low back trouble (i.e., pain, psychological distress, and general disability) hampers the functioning of short-term memory, which results in decreased speed of information processing among patients with chronic low back trouble. Patients with chronic low back pain and rheumatoid arthritis had high scores of memory complaint and low performance in memory assessment when compared to normative data (33). Ling et al (34) found that patients with chronic back pain had significantly impaired short-term prospective memory in comparison to those not in pain. According to a meta-analysis, evidence of cognitive deficits in persons with chronic fatigue syndrome was found primarily in the domains of attention, memory, and reaction time (35,36).

Our findings revealed in part that patients with chronic low back pain had impaired information-

processing speed and visual scanning ability because of decreased speed of making TMT-A and B tests, and this is independent from usage of opioids. This observation may be related to the link between pain and stress and the impact of this relationship on cognitive function (37,38).

Hart et al (35) demonstrated that stress-related back pain and the resulting disability hamper short-term memory, leading to slower psychomotor speed and inadequate decision-making strategies during routine activities. Our findings regarding short-term memory are not consistent with the previous results.

The reason is not clear. It is known that painful stressor impaired short-term memory function even in healthy volunteers (39). The question is whether the pain disturbs the cognitive functioning or does the comorbidity to pain do this job?

Nikendei et al (40) compared the memory performance in somatoform pain disorder patients and found cognitive impairment in somatoform pain patients with an organic attribution of pain symptoms as compared to somatoform pain patients with a psychosocial attribution and healthy controls in both recall test and recognition test. Given our patients all had unspecific low back pain means there is no organic correlate. Therefore, the authors advised that the impairment cannot be solely traced back to the pain itself, since the 2 patient groups in their study differed neither in their current pain ratings nor in their duration of illness (40). This may be an explanation for our finding because our patients tended to have pain with a psychosocial attribution.

The cognitive functioning under opioids treatment was less investigated.

Regarding the influence of opioids on the cognitive functioning of healthy controls, a research group from United Kingdom examined the cognitive and psychomotor effects of repeated oral doses of morphine in 4 healthy subjects in a randomized double-blind 4-way crossover study (41). Their results showed that oral morphine may enhance performance in some measures of cognitive function, whereas dextropropoxyphene seems more likely to cause impairment.

Regarding the influence of opioids on the cognitive functioning of patients with chronic pain, the first study in this field focused on the Wechsler Adult Intelligence Scale (WAIS) which was administered to 2 groups of patients who were receiving low and moderate daily stabilized dosages of methadone hydrochloride (42). It was found that there were no significant differences

between subtest scores or verbal, performance, and full-scale scores of the groups measured, indicating that cognitive functioning as measured by the WAIS was not differentially affected by the low or stabilized dosages. In a similar setting, a research group from Switzerland could not find differences in attention functions and learning and memory between short-term (30 days) and long-term (6 months) of methadone maintenance treatment (43). Unfortunately, neither study measured the cognitive functioning in a control group as reference.

In the current study, we compared the cognitive functioning of patients who have used opioids for long-term with those who have not been using opioids and those who had neither pain nor opioid usage.

Except for the slower motor speed compared to patients without opioids, the opioid-positive patients made significantly more errors than healthy controls. The ratio of TMT-B/TMT-A was further significant between both patients groups. And they showed significantly worse spatial working memory (SSP) and flexibility in concept change (WAIS-III-C). These findings give reliable notice for the impaired executive function of patients who were treated by long-term opioids.

In general, the cognitive functions depend on the age, intelligence, and healthy state and drug use. Previous studies showed that trail making test (TMT) (44) and choice reaction test (CRT) (45) were increasingly impaired with increasing age, whereas the executive function was generally dependent on both age and intelligence (46). Depression and anxiety are often invoked as explanations for deficient neuropsychological test performance. The overlaps between pain, depression, and anxiety are very common in patients with medically unexplained somatic symptoms (47). Reduced memory performance in somatoform pain patients might thus also be related to comorbid anxiety or depression (48,49).

CONCLUSIONS

In the current study, the confounding factors such as age, education level, depression, and anxiety scores did not differ in both patient groups, making it unlikely that differences in these variables were contributing to the findings.

As the MWT-B results from both patient groups did not differ from each other, we assumed that patients treated with or without opioids had the same intelligence level in due consideration of age and education level.

To our knowledge this is the first time the CANTAB has been used to examine cognitive and neurological functioning of patients with chronic pain and under opioid treatment. The CANTAB has been extensively validated for assessing brain-behavior relationships in adult populations (31) and has been shown to be sensitive to detecting brain dysfunctions in the frontal, temporal, and amygdalo-hippocampal regions (50). Computer-based testing for neuropsychological variables may be an improvement on non-computerized testing in minimizing effects of additional influences that can obscure the purely cognitive component under assessment (51). The CANTAB applies computerized testing for concise, accurate measurement of a range of cognitive domains

(52). The CANTAB allows the accuracy and rigor of computerized psychological testing while also allowing for a wide range of ability, thus avoiding ceiling and floor effects.

The findings of the current study have research and clinical implications. Clinicians should warn patients that their cognitive functions may not have fully recovered and they may not be fit enough to carry out certain daily activities when they are treated by opioids for a long time. This information must be considered during the prescription of opioids and rehabilitation therapies, and suggest the addition of specific cognitive techniques to a traditional multidisciplinary program. Follow-up studies are required to delineate the time course of cognitive recovery after the withdraw of opi-

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