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The Relation of Pain Chronification Factors and Neurocognition in Chronical Pain Syndrome A Secondary Analysis of a Prospective Clinical Study

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Abstract

Objective: In the ICD-11, pain duration of at least three-months was maintained as main criterion for defining chronic pain. Psychosocial risk factors, commonly referred to as "yellow flags", offer insights into psychological risk factors that contribute to the process of chronification. Psychological factors that contribute to chronification are associated with neurocognitive performance. Thus, our research investigates the impact of pain duration, a key indicator of pain chronification, along with other pertinent psychological factors influencing chronicity, on neurocognitive functioning.

Methods: A cohort of 40 patients with chronic pain syndrome (CP) and 41 healthy controls (HC) with no significant between group differences in age, gender, education, or intelligence underwent thorough assessments. Assessments included comprehensive neurocognitive evaluations conducted at three time points and a standardized driving simulator task.

Results: The results of this study demonstrate that relations of pain duration on neurocognition exist, but nearly disappear when considering relevant factors contributing to chronicity. The results revealed key factors associated with chronification, referred to as "yellow flags", with predictive impacts on neurocognition.

These factors encompassed affective pain perception and pain-induced psychological helplessness, serving as indicators of pain processing.

Conclusion: The study underscores the significance of understanding factors contributing to pain chronification and their impact on cognition. Yellow flags and their impact on cognition should be given more consideration in basic science as well as in clinical and therapeutic settings.

Keywords: Chronical Pain Syndrome; Neurocognition; Pain Duration; Chronification Factors; Yellow Flags

Abbreviations

ICD: International Classification of Diseases; MWT-B: Multiple-Choice Vocabulary Test; MADRS: Montgomery-Asberg Depression Rating Scale; VTS: Vienna Test System; NRS: Numerical Rating Scale; SES: Schmerzempfindungsskala; FESV: Fragebogen zur Erfassung der Schmerzverarbeitung; ICADTS: International Council on Alcohol, Drugs, and Traffic Safety.

Introduction

The International Association for the Study of Chronic Pain (1979) defines pain as an unpleasant sensation linked to actual or potential tissue harm [1]. Chronic pain, as per the current International Classification of Diseases (ICD-11), persists for more than three months and is categorized into chronic primary and chronic secondary pain. Chronic primary pain endures for over three months, accompanied by emotional distress or significant functional impairment, unrelated to another chronic pain condition such as fibromyalgia [2]. Chronic secondary pain persists despite underlying conditions are widely known and treated, with both coded (e.g., cancer pain). Unlike acute pain, chronic pain lacks a meaningful warning function, evolving into an independent disease with social and economic burdens [1].

The process of pain chronification involves complex interactions among biological, psychological, and social factors [3]. Psychosocial risk factors, known as "yellow flags" are identified, providing insights into psychological risk factors contributing to chronification [4]. Yellow flags include depressive mood, unfavorable emotional, cognitive, and behavioral pain processing, as well as chronic stressors in personal and professional life [5]. Red flags indicate potentially hazardous courses, requiring urgent intervention, while green flags denote individual resources such as coping strategies and supportive environments counteracting chronification. Furthermore, impaired neurocognition is considered an independent factor in chronicity, too. Chronification, work ability and social relations are linked to changes in neurocognition across various psychiatric disorders e.g. Schizophrenia [6,7]. CP report subjective and objective cognitive deficits in overall performance, attention, memory, and executive functions compared to HC [8]. Pain chronicity factors are associated with neurocognition in CP. Research on pain duration's impact on neurocognition is inconclusive, with some studies suggesting negative effects and others reporting positive associations [9,10]. Chronic pain is diverse, requiring consideration of specific pain types when evaluating cognitive impairments. Studies focus on various pain types, such as fibromyalgia, chronic musculoskeletal pain, migraines, complex regional pain syndrome, cancer pain, and neuropathic pain. Generalized pain is posited to exert a more substantial impact on neurocognition compared to localized pain [11]. Higher self-reported pain intensity is associated with poorer neurocognitive assessments [12-16]. Neurocognitive constraints persist even after controlling for affective symptoms, but should not be neglected in total [11]. Pain medications can have varying effects on neurocognition no effects or even an improvement [17-19]. The duration of medication use plays a crucial role, with effects disappearing or improving with prolonged use [20,21].

The main objective of the present study was to investigate the association between pain duration and neurocognition and to disclose the influence of the above mentioned chronification factors on neurocognition in chronic pain syndrome. Therefore, we hypothesized, 1) that the duration of pain is negatively associated with performance in standardized neuropsychological test procedures and 2) that this association should persist even when potential influencing factors are controlled.

Materials and Methods

Participants

Between February 2020 and March 2022, 41 CP were recruited from the in-house Interdisciplinary Multi-modal Pain Therapy and its outpatient facilities at the SRH Clinic Karlsbad-Langensteinbach, BW, Germany.

Inclusion criteria encompassed age ≥ 18 years, legal consent, a history of chronic pain for a minimum of three months in line with ICD-10 criteria (≥ grade II as per von Korff et al., 1992), stable medication for the preceding two weeks, an IQ > 85 determined by the Multiple-Choice Vocabulary Test (MWT-B) and proficient German-language fluency [22]. Exclusion criteria involved documented or suspected neurological diseases and current/past substance abuse (illicit drugs, alcohol). Throughout the study, all participants continued to receive regular medical and psychotherapeutic treatments. One participant was excluded due to a recent diagnosis of encephalomyelitis disseminate during their hospital stay. HC, numbering, were recruited through the distribution of flyers. They also met the inclusion criteria: age ≥ 18 years, legal consent, absence of current or historical chronic pain, an IQ > 85 according to the MWT-B and sufficient German-language fluency [22]. Exclusion criteria for HC included current or historical mental disorders according to ICD-10 criteria and documented or suspected neurological diseases.

Diagnosis and inclusion criteria were verified by an experienced psychologist who conducted a medical history

assessment, utilized the Beck Depression Inventory (BDI-II), and administered the Montgomery-Asberg Depression Rating Scale (MADRS) [23,24]. HC received a compensation of 40€ for their participation. The study, with a preregistered analysis plan in the independent institutional registry (German Clinical Trials Register ID: DRKS00022033), obtained approval from the ethics committee of the medical faculty at Heidelberg University (S-120/2019). The research adhered to the World Medical Association's Declaration of Helsinki (October 2013) and Good Clinical Practice. All participants provided written informed consent.

Study Design and Procedures

Parallelization was implemented based on age, gender, and educational attainment, with participants allocated to specific groups according to the aforementioned criteria. Following the pre-baseline assessment of socio-demographic and psychopathological factors through questionnaires, all participants underwent the same sequence of tests in two sessions spanning one week. A standardized driving simulation was administered at a third time point, with each assessment lasting one hour. The correlation between cognition and driving ability, evaluated through a driving simulator, will be the subject of a separate publication and is beyond the scope of the present paper. The Vienna Test System (VTS) involves a preparatory phase before each assessment session. Throughout the study, an experienced psychologist, particularly adept in neuropsychological assessments and the VTS, was available to address any queries arising during the preparatory phase (e.g., clarifying instructions) and to assist with potential technical challenges. However, the data collection itself was conducted independently, without external support.

The present article only discusses the relationships between pain chronicity factors and neurocognitive values in CP. For the results of group comparisons regarding neurocognition, we refer to the article by Schmidt, et al. [8].

Materials

For a comprehensive list of assessment materials, please refer to Table 1. Premorbid Intelligence. To estimate premorbid intelligence, the Multiple-Choice Vocabulary Test B (MWT-B) was employed [22]. Participants with values ranging from 15 to 37 were included, indicating at least an average intelligence score.

Inventory of assessment material.

Assessment tool	Point of Time (T)	Abbreviation of the Test and author
Socio-demographics		
– Socio-demographic questionnaire	_	Self-devised
Premorbid Intelligence		
– Multiple - Choice Vocabulary Test	_	Lehrl S [22]
Clinical Chronical Pain		
– German pain questionnaire	T0 pre baseline assessment	DSF Petzke F, et al. [25]
– Numerical Rating Scale		NRS
– Pain Perception scale		SES Geissner E [26]
– Questionnaire for Assessment of Level of Coping with Pain		FESV Geissner E [27]
Depressive Symptoms		
– Beck Depression Inventory II	_	BDI-II Hautzinger M, et al. [23]
– Montgomery-Åsberg Depression Rating Scale	_	MADRS Montgomery SA, et al. [24]

Neurocognitive Assessment		
Attention		
– Processing speed: Trail Making Test-L Version A	T1	TMT-A[b]
– Divided Attention: Perception and attention functions battery		WAF-G[b]
– Reaction time: Reaction Test		RT (presented at beginning and end of T2)
– Concentration performance: Cognitrone		COG
– Obtaining and overview: Adaptive Tachistoscopic Traffic Perception Test		ATAVT
– Visual orientation performance and visual perception: Visual Pursuit Test	T2	LVT
– Reactive stress tolerance/ ability to react under complex stimulus conditions: Determination Test		DT
Memory		
– Figural short-term/ long-term memory/ Recognition: Figural Memory Test	T1	FGT[b]
Executive functioning		
– Mental flexibility: Trail Making Test- L Version B	T1	TMT-B[b]
– Response inhibition: Response Inhibition		INHIB[b]
– Working Memory: N-Back-verbal		NBV[b]
– Planning ability: Tower of London-F		Tol-F[b]
Subjective cognitive deficits		
– Mental Ability Questionnaire	T1	FLei[b]

[a]Derived from the assessment battery within the Vienna Test System [28].
[b]Derived from the Cognitive Basic Assessment battery (CogBat-S1) [29].
Table 1: Inventory of assessment material.

Depressive Symptoms

Depressive symptoms were assessed using the Beck Depression Inventory, (BDI- II), a 21-item self-report instrument evaluating the severity of depressive symptoms across cognitive, behavioral, affective, and somatic domains [23]. The Montgomery-Åsberg Depression Rating Scale (MADRS), a clinician-administered instrument, was also employed to assess depression severity, with scores categorized into mild, moderate, and severe [24].

Clinical Chronic Pain

Participants completed a questionnaire gathering the history. The questionnaire also included sections from the German Pain Questionnaire (DSF) in paper form [25]. It covered a detailed subjective description of pain (pain sketch, characteristics, localization, intensity, etc.), pain-related impairment, the illness's course detailing prior treatments, medication, surgeries, and medical/psychiatric history. For the interpretation of the pain sketch, an analysis was conducted using an evaluation developed with the assistance of an experienced neurologist and pain therapist. In this process, the areas of the head, cervical spine/arms, thoracic spine/thorax, lumbar spine/legs, and multiple pain regions in the drawing were quantified. There was a consent to use the doctor's report. It contained an assessment by the practitioner regarding yellow flags.

Clinical pain assessment utilized the Numerical Rating Scale (NRS), where participants rated present pain intensity, average and maximum pain intensity experienced in the past four weeks, and anticipated pain intensity after successful treatment on a numerical scale from 0 ("no pain") to 10 ("maximum pain possible"). The clinical pain experience of CP was further evaluated through the pain perception scale ("Schmerzempfindungsskala" - SES), consisting of 24 items rated on a four-point scale [26]. The SES allowed the assessment of two subscales in CP: "affective" and "sensory." Cognitive processing, coping with pain, and pain-related distress were measured using the questionnaire for the Assessment of Level of Coping with Pain ("Fragebogen zur Erfassung der Schmerzverarbeitung" –FESV), covering three domains: 1) pain-related distress, 2) cognitive coping

strategies, and 3) behaviorally oriented strategies [27].

Neuropsychological Assessment

The study assessed neuropsychological functions using a battery of 13 tests from the Vienna Test System [28], including eight tests from the computer-based Cognitive Basic Assessment battery (COGBAT-S1, Aschenbrenner, et al. [29]. These tests, sensitive to cognitive impairments in psychiatric patients, covered attention, memory, and executive functions. The COGBAT, integrated into the VTS NEURO framework, is designed for evaluating fundamental cognitive functions, adhering to quality criteria like objectivity, reliability, validity, efficiency, utility, and standardization. The Mental Ability Questionnaire (FLei) within COGBAT subjectively evaluated mental abilities, utilizing a self-report questionnaire with good internal consistency, and assessing perceived cognitive performance in areas such as attention, memory, and executive functions. Participants' perceptions of cognitive functions over the past six months were measured using a four-point response scale. All tests used are well-known and validated assessments, covering key areas included in standard clinical neuropsychological assessment procedures. The battery of tests covers essential areas of standard clinical neuropsychological assessment procedures: Attention: Encompassing processing speed, divided attention, reaction time, concentration performance, obtaining and overview, visual orientation performance and visual perception, reactive stress tolerance, and the ability to react under complex stimulus conditions.

Memory: Including the assessment of figural short-term and long-term memory, as well as recognition.

Executive Functioning: The assessment comprises mental flexibility, response inhibition, working memory, and planning ability.

Statistical Analysis

The sample size for mean differences between the two groups was determined using *G-Power* 3.1, considering power, significance level, and effect size (medium, d = .5) [30]. With a significance level of 5% and 80% power, the initial sample size was N = 108, accounting for a 5% dropout rate. In March 2022, reassessment using existing data led to a random sample of N = 40 ($n1$ = 20, $n2$ = 20), confirming the adequacy of the original sample size for the exploratory design. Data collection concluded ahead of schedule.

Statistical analyses were conducted using *SPSS* version 26 (Armonk, NY, USA). The significance threshold for all tests was set at $p \leq 0.05$, and values of $p \leq 0.1$ were defined as a trend toward significance. The Kolmogorov Smirnov test was applied to analyze numerical variables and determine the distribution type. Parametric tests were used for data with normal distribution, while non-parametric tests, such as the Mann-Whitney U test, were employed for non-normally distributed data. Between-group comparisons for continuous variables were conducted with independent sample t-tests or Mann-Whitney U tests. Non-continuous variables were compared using χ^2 tests, e.g., for sex distribution. Cohen's d effect size was computed using mean differences and the pooled standard deviation. Neuropsychological test procedures were conducted using raw data, covering assessments related to attention, memory, executive functions, and self-assessment of cognitive performance. Standardized z-values were computed based on the mean and standard deviation, polarized into one direction, with higher z-scores indicating better neurocognitive performance. A theory-driven aggregation of all variables within their respective dimensions was performed, resulting in an overall index value termed "overall cognition".

This comprehensive index incorporated subjective cognitive deficits, attention, memory, and executive functioning, providing a consolidated assessment of pertinent cognitive dimensions with averaged domain values.

The assumed *Pearson*- correlations between pain duration (pain duration in years) and performance in standardized neuropsychological tests was expected to persist even when controlling for additional potential influencing factors. Control was achieved through a linear regression model incorporating all predefined potential influencing factors. Predictors included the 1. type of pain (generalized pain according to pain sketch), 2. pain intensity (NRS: current pain intensity), 3. pain perception (SES: affective), pain processing (FESV: helplessness/ depression), 4. depression (BDI-II), and 5. pain medication (International Council on Alcohol, Drugs, and Traffic Safety (ICADTS): Category III).1 Criterion variables were the performances in the neuropsychological test procedures.

In considering medications for chronic pain treatment, a standardized guideline proposed by the ICADTS in 1995 was applied. This guideline utilizes blood alcohol equivalence doses to categorize psychotropic substances, categorizing Category III drugs as posing potential hazards.

Results

Socio-demography and depressive symptoms

For detailed demographic and clinical characteristics of patient and control groups, please refer to Table 2.

	CP (n = 40)		HC (n = 41)		Test statistics	
					t-/Chi^2 value	p-value
Variables						
Age (years)	M = 53.28	_	M = 46.71	_	-1.87	>.05
	SD = 13.75	_	SD = 18.35	_	_	_
	Range = 28 – 84	_	*Range* = 21 - 82	_	_	_
Sex						
Men	n = 15	37.00%	n = 15	37.00%	0.01	>.05
Women	n = 25	63.00%	n = 26	63.00%	_	_
Educational level						
General school	n = 13	32.50%	n = 8	19.60%	1.68	>.05
Secondary school	n = 16	40.00%	n = 11	26.80%	_	_
Abitur	n = 5	12.50%	n = 11	26.80%	_	_
Graduate degree	n = 6	15.00%	n = 11	26.80%	_	_
IQ (MWT-B)						
Depression	n = 12	30.00%	n = 0	0.00%	1.38	>.05
(F32.x/F33.x)	_	_	_	_	_	_
Self-Rated						
Beck Depression	M = 18.72	_	M = 4.6	_	-6.39	<.001**
Inventory (BDI-II)[c/e]	SD = 13.49	_	SD = 4.1	_	_	_
	Range = 0 - 53	_	*Range* = 0 - 13	_	_	_
Clinician-Rated						
Montgomery-Åsberg	M = 13.95	_	M = 2.2	_	-8.36	<.001**
Depression Rating Scale	SD = 8.6	_	SD = 2.6	_	_	_
(MADRS)[d]	*Range* = 0 - 32	_	*Range* = 0 - 8	_	_	_

CP = Chronic pain patients, HC = Healthy controls. M = mean, SD = standard deviation, range, number and percentage within each group.

[c]BDI-II: 14–19 mild, 20–28 moderate, > 29 severe depressive symptoms.

[d]MADRS: 12–21 mild, 21–28 moderate, > 28 severe depressive symptoms.

[e]Assumed additional potential influencing chronification factors on neurocognition (adjusted for).

Table 2: Demographic and clinical characteristics of the patient and control group.

All analyses were conducted based on data from a total of 81 participants, comprising 63% females and 37% males, with a mean age of 49.59 years (SD = 16.48) and an age range of 21 to 84 years. The study sample consisted of 40 CP and 41 HC. There were no significant differences between CP and HC groups in terms of age ($t(79) = -1.87$, $p = .07$), education ($t(79) = 1.68$, $p = .09$), IQ score ($t(77) = 1.38$, $p = .17$), and sex distribution (χ^2 (1) = 0.01, p = .93). Additionally, 86% CP received psychiatric diagnoses, with 30% having a diagnosis of an affective disorder. A significant difference between groups was observed in terms of depression severity, as measured by the BDI-II and MADRS. Patients had significantly higher BDI-II scores ($t(79) = -6.39$, $p < .001$). Chronic pain patients were rated as having mild depressive symptoms in clinician reports via MADRS ($t(79) = -8.36$, $p < .001$).

Clinical Pain

The following results pertain to the groups of CP. The mean persistence of chronic pain symptoms was 9.8 years (SD = 9.7). When classified according to the type of pain based on ICD-11, 75% were diagnosed with chronic primary pain, and 25% with chronic secondary pain. The distribution of pain in the CP cohort is as follows: 2.5% localized pain in the region head, 7.5% involve the cervical spine and arms, 12.5% the lumbar spine and legs, and 77.5% manifest as generalized pain, affecting multiple regions. The average number of yellow flags was 5 (M = 5.15, SD = 3.5). Among the

patients, 8% used opioids for pain medication, while 70% received antidepressants. For a thorough overview of the clinical features of CP, please refer to Table 3.

Variables	CP (*n* = 40)
Chronic primary pain	*n* = 30 (75%)
Chronic secondary pain	*n* = 10 (25%9
Pain duration (years)[e]	*M* = 9.8
	SD = 9.7
	Range = 1 – 38
Pain location	
Head	*n* = 1 (2.5%)
Cervical spine/ arms	*n* = 3 (7.5%)
Lumber Spine/ legs	*n* = 5 (12.5%)
Generalized e	*n* = 31 (77.5%)
Numerical Rating Scale (NRS)	
Current pain intensitye	*M* = 4.75
	SD = 2.66
	Range = 0 - 10
Pain Perception Scale (SES)	
Sensory	*M* = 24.55
	SD = 6.86
	Range = 13 - 39
Affective	*M* = 38.63
	SD = 13.15
	Range = 19 - 95
Questionnaire for Assessment of Level of Coping with Pain (FESV) Cognitive coping strategies	
Action-oriented coping	*M* = 10.95
	SD = 3.62
	Range = 3 - 18
Cognitive restructuring	*M* = 13.05
	SD = 5.2
	Range = 4 - 24
Self-efficacy	*M* = 13.87
	SD = 4.5
	Range = 3 - 18
Behaviourally oriented strategies	
Mental distraction	*M* = 8.57
	SD = 4.41
	Range = 3 - 18
Counter Activities	*M* = 10.92
	SD = 4.4
	Range = 4 - 21

Relaxation	*M* = 13.25
	SD = 5.31
	Range = 4 - 24
Pain-related distress	
Helplessness/ depression[e]	*M* = 19.38
	SD = 7.1
	Range = 5 - 30
Anxiety	*M* = 14.93
	SD = 6.25
	Range = 4 - 24
Anger	*M* = 16.95
	SD = 7.5
	Range = 6 - 30
yellow flags (doctor's report)	*M* = 5.15
	SD = 3.5
	Range = 0 - 13

CP = Chronic pain patients. *M* = mean, *SD* = standard deviation, range, range, number and percentage within each group.
[e]Assumed additional potential influencing chronification factors on neurocognition (adjusted for).
Table 3: Pain characteristics of the patient group.

Pain Duration and Neurocognition

We hypothesized that there is a negative association between the duration of pain and performance in standardized neuropsychological test procedures evaluating attention, memory, and executive functions in CP.

Attention: A significant negative moderate correlation was observed between pain duration and concentration performance (mean time rights: $r = -.33$, $p < .05$), and between pain duration and obtaining an overview (processing time, $r = -.28$, $p < .05$). Significant moderate correlations were found between pain duration and reactive stress tolerance (false reactions, $r = .28$, $p < .05$; median reaction time, $r = -.39$, $p < .05$). Memory: A moderate negative correlation was found between pain duration and immediate recall ($r = -.27$, $p = .05$). 24

Executive functions: A moderate negative correlation was observed between pain duration and the Mean reaction time of inhibition response ($r = -.27$, $p = .05$).

Index Values: No significant correlations were found between pain duration and index values of attention ($r = -.13$, $p = .22$), memory ($r = -.20$, $p = .11$), executive functions ($r = -.06$, $p = .36$), as well as the cognition index value ($r = -.17$, $p = .14$).

Pain chronification Factors and Neurocognition

The relationship between pain duration and neurocognitive performance is expected to remain significant even after adjusting for the influencing factors, including pain localization, intensity, perception/processing, depressive symptoms, and medication. Attention: Adjusted for influencing chronification factors, a regression coefficient for pain duration of *beta*= .37, $p < .05$ was obtained for reactive stress tolerance (false reactions), and a regression coefficient of *beta* = -.34, $p < .05$ for Median reaction time. Memory and Executive Functions: No significant effects of predictors on the dependent variable were found. Index Values: No significant correlations were found between pain duration and index values of attention (*beta* = -.02, $p = .89$), memory (*beta* = -.12, $p = .49$), executive functions (*beta* = -.03, $p = .89$), as well as the overall cognition index value (*beta* = -.07, $p = .65$).

Table 4 shows the correlations between pain duration and neurocognitive variables and adjusted for additional potential influencing chronification factors, Table 5 depicts the correlations between pain duration and neurocognitive index values and adjusted for chronification factors in CP.

Neurocognitive Variables	Pain duration		Pain duration adjusted	
Attention				
Processing Speed (TMT-A)	*r*	-.21	*β*	-.17
Reaction time	*p*	>.05		>.05
Divided Attention (WAF-G)	*r*	-.24	*β*	-.14
Mean reaction time	*p*	>.05		>.05
Divided Attention (WAF-G)	*r*	.08	*β*	.11
Dispersion of reaction time	*p*	>.05		>.05
Divided Attention (WAF-G)	*r*	.08	*β*	.1
Misses	*p*	>.05		>.05
Divided Attention (WAF-G)	*r*	.15	*β*	.17
False alarm	*p*	>.05		>.05
Concentration performance (COG)	*r*	-.21	*β*	-.19
Mean time correct rejection	*p*	>.05		>.05
Concentration performance (COG)	*r*	.17	*β*	.28
Sum of correct rejection	*p*	>.05		>.05
Concentration performance (COG)	*r*	.04	*β*	.23
Sum rights	*p*	>.05		>.05
Concentration performance (COG)	*r*	**-.33***	*β*	-.32
Mean time rights	*p*	**<.05**		>.05
Obtaining and overview (ATAVT)	*r*	-.14	*β*	-.05
Obtaining and overview	*p*	>.05		>.05
Obtaining and overview (ATAVT)	*r*	**-.28***	*β*	-.24
Processing time	*p*	**<.05**		>.05
Reactive stress tolerance (DT)	*r*	**.48***	*β*	-.12
Reactive stress tolerance (right reactions)	*p*	**>.05**		>.05
Reactive stress tolerance (DT)	*r*	**.28***	*β*	**.37***
False reactions	*p*	**<.05**		**>.05**
Reactive stress tolerance (DT)	*r*	.16	*β*	.24
Misses	*p*	>.05		>.05
Memory				
Reactive stress tolerance (DT)	*r*	**-.39***	*β*	**-.34***
Median reaction time	*p*	**<.05**		**<.05**
Visual orientation performance and visual perception (LVT)	*r*	.26	*β*	.24
Visual orientation performance and visual perception	*p*	>.05		<.05
Visual orientation performance and visual perception (LVT)	*r*	.15	*β*	.13
Median time right answers	*p*	>.05		>.05
Reaction time (RT1)	*r*	-.02	*β*	.00
Reaction time at the beginning	*p*	>.05		>.05
Reaction time (RT2)	*r*	-.14	*β*	-.12
Reaction time at the end	*p*	>.05		>.05
Figural memory (FGT)	*r*	-.15	*β*	-.09
Learning sum	*p*	0.18		.61

Figural memory (FGT)	*r*	**-.27***	*β*	-.15
Immediate recall	*p*	**<.05**		.37
Figural memory (FGT)	*r*	-.15	*β*	-.05
Delayed recall	*p*	.17		.77
Figural memory (FGT)	*r*	-.11	*β*	-.09
Recognition	*p*	.26		.62
Executive functioning				
Mental Flexibility (TMT-B)	*r*	-.03	*β*	.02
Reaction time	*p*	>.05		>.05
Working Memory (NBV)	*r*	.04	*β*	-.06
Working memory performance	*p*	>.05		>.05
Working Memory (NBV)	*r*	.19	*β*	.18
Misses	*p*	>.05		>.05
Working Memory (NBV)	*r*	-.11	*β*	-.04
Mean time right answers	*p*	>.05		>.05
Planning Ability (ToL-F)	*r*	-.07	*β*	-.08
Planning ability	*p*	>.05		>.05
Inhibition Response (INHIB)	*r*	.05	*β*	.10
Error of commission	*p*	>.05		>.05
Inhibition Response (INHIB)	*r*	-.09	*β*	.06
Error of omission	*p*	>.05		>.05
Inhibition Response (INHIB)	*r*	-.27*	*β*	-0.27
Mean rejection time	*p*	<.05		>.05

r = Correlation of *z*-scores according to Pearson between the respective subdomain and pain duration, *β* = Specification of the regression coefficient *beta*, *p* = the correlation is significant at the level of *p* = .05 (one-sided).

Table 4: Correlations between pain duration and neurocognitive variables and adjusted for additional potential influencing chronification factors in the patient group.

Index Values	Pain duration		Pain duration	
Attention	*r*	-0.13	*β*	-.02
	p	>.05		>.05
Memory	*r*	-0.2	*β*	-.12
	p	>.05		>.05
Executive Functioning	*r*	-.06	*β*	-.03
	p	>.05		>.05
Overall Cognition	*r*	-.17	*β*	-.7
	p	>.05		>.05

r = Correlation of *z*-scores according to Pearson between the respective index values and pain duration, *β* Specification of the regression coefficient *beta*, *p* = the correlation is significant at the level of *p* = .05 (one-sided).

Table 5: Correlations between pain duration and neurocognitive index values and adjusted for chronification factors in the patient group.

Discussion

A research gap exists in the differentiated and comprehensive study of factors influencing neurocognition in patients with pain chronification. Initially, we hypothesized a negative link between pain duration and performance in neuropsychological tests. Furthermore, we hypothesized that this association persists even after considering potential influencing chronification factors.

Pain Duration, Pain Chronification Factors and Neurocognition

In the present study, it was assumed that pain duration is negatively associated with performance in neurocognitive tests assessing neurocognition. Within attention functions, anticipated negative correlations emerged between pain duration, concentration performance, obtaining an overview, and reaction time of reactive stress tolerance. Interestingly, the number of false reactions within reactive stress tolerance decreased with pain duration. Within memory functions, pain duration was negatively associated with short- term delayed recall. Reaction time of inhibition performance correlated within executive functions with pain duration. The results suggest that there are relations between pain duration and neurocognition in CP, especially in the domain of attention.

A closer examination of the literature reveals informative predictors such as type of pain, pain intensity, pain perception, pain processing, depression and pain medication that could also be linked to neurocognitive deviations in CP. Moderate associations between pain duration and neurocognition under control persisted only for Reactive stress tolerance (Determination Test). The primary variable under examination is reactive stress tolerance, characterized as the ability to react effectively in stressful conditions. The longer the pain persists, the more reaction time increased and the number of false reactions decreases. Combining these findings, it implies that pain chronification leads to longer reaction times within reactive stress tolerance, thereby reducing the number of errors. This phenomenon is well-supported by the Speed-Accuracy Tradeoff, denoting the compensation of error rate through a slower but more accurate working style [31]. This study demonstrates that, taking into account all potential factors contributing to chronicity, there are no significant influences of pain duration on neurocognition that persist with the exception of Reactive stress tolerance.

Pain chronification: But differently?

Factors of chronification gain more importance in the concept of Multimodal Pain Therapy [4]. Instead of examining pain duration, a secondary analysis focused on analyzing the relationships between selected factors contributing to chronicity - “yellow flags”- and neurocognitive values, within CP. The analysis involved again above-mentioned adjustments for influencing factors. It was observed that particularly affective pain perception (SES) and perceived helplessness in pain processing (FESV) influence the outcome of neurocognition. Associations were in the moderate to high range (Tables 6 & 7). Significant associations were observed between affective pain perception and cognitive processing Speed (*beta* = .46, $p < .05$), divided attention (mean reaction time: *beta* = .68, $p < .01$; false Alarm: *beta* = .51, $p < .05$), concentration performance (sum of correct rejections: *beta* = -.65, $p < .05$); sum rights: *beta* = .78, $p < .01$), obtaining and overview (*beta* = .66, $p < .01$), reactive stress tolerance (*beta* = .48, $p < .05$), and the index value attention (*beta* = .78, $p < .01$). Within memory functions, affective pain perception exhibited significant associations with Immediate recall (*beta* = .51., $p < .05$), delayed recall (*beta* = .50, $p < .05$), and the index value memory (*beta* = .53, $p < .05$). In terms of executive functions, significant correlations were identified with mental flexibility (*beta* = .71, $p < .01$). The index value overall cognition displayed a notable association with affective pain perception across all dimensions (*beta* = -.7, $p < .01$).

Attention		SES Adjusted	FESV Adjusted
Processing Speed (TMT-A)	*β*	**.46***	**-0.5**
Reaction time	*p*	**<.05**	**<.05**
Divided Attention (WAF-G)	*β*	**-.68***	-.28
Mean reaction time	*p*	**<.01**	>.05
Divided Attention (WAF-G)	*β*	.04	.2
Dispersion of reaction time	*p*	>.05	>.05
Divided Attention (WAF-G)	*β*	.38	-.5
Misses	*p*	>.05	>.05
Divided Attention (WAF-G)	*β*	.51	-.16

False alarm	*p*	<.05	<.05
Concentration performance (COG)	*β*	.33	-.19
Mean time correct rejection	*p*	>.05	>.05
Concentration performance (COG)	*β*	**.65***	-.41
Sum of correct rejection	*p*	**<.05**	>.05
Concentration performance (COG)	*β*	**.78***	**-.83***
Sum rights	*p*	**<.01**	**<.01**
Concentration performance (COG)	*β*	.32	-.18
Mean time rights	*p*	>.05	>.05
Obtaining and overview (ATAVT)	*β*	**.66***	**-.74***
Obtaining and overview	*p*	**<.01**	**<.01**
Obtaining and overview (ATAVT)	*β*	.28	**-.56***
Processing time	*p*	>.05	**<.05**
Reactive stress tolerance (DT)	*β*	**.48***	**-.5***
Reactive stress tolerance (right reactions)	*p*	**<.05**	**<.05**
Reactive stress tolerance (DT)	*β*	.21	-.14
False reactions	*β*	>.05	>.05
Reactive stress tolerance (DT)	*p*	.21	.33
Misses	*β*	>.05	>.05
Reactive stress tolerance (DT)	*p*	.21	**-.34***
Median reaction time	*β*	>.05	**.04**
Visual orientation performance and visual perception (LVT)	*β*	.04	.1
Visual orientation performance and visual perception	*p*	>.05	>.05
Visual orientation performance and visual perception (LVT)	*β*	.08	.02
Median time right answers	*p*	>.05	>.05
Reaction time (RT1)	*β*	.34	-.2
Reaction time at the beginning	*p*	>.05	>.05
Reaction time (RT2)	*β*	.18	-.34
Reaction time at the end	*p*	>.05	>.05
Figural memory (FGT)	*β*	.43	-.13
Learning sum	*p*	>.05	>.05
Memory			
Figural memory (FGT)	*β*	**-.50***	-.13
Immediate recall	*p*	**<.05**	>.05
Figural memory (FGT)	*β*	**.5***	-.13
Delayed recall	*p*	**<.05**	-.2
Figural memory (FGT)	*β*	.32	-.2
Recognition	*p*	>.05	>.05
Executive Functioning			
Mental Flexibility (TMT-B)	*β*	**.71***	-.13
Reaction time	*p*	**<.01**	>.05
Working Memory (NBV)	*β*	-.12	.16

Working memory performance	*p*	>.05	<.05
Working Memory (NBV)	*β*	.1	-.4
Misses	*p*	**>.05**	**>.05**
Working Memory (NBV)	*β*	-.03	.13
Mean time right answers	*p*	>.05	>.05
Planning Ability (ToL-F)	*β*	.16	.1
Planning ability	*p*	>.05	>.05
Inhibition Response (INHIB)	*β*	.26	-.29
Error of commission	*p*	>.05	>.05
Inhibition Response (INHIB)	*β*	.31	-.47
Error of omission	*p*	>.05	>.05
Inhibition Response (INHIB)	*β*	.1	-.28
Mean rejection time	*p*	>.05	>.05

SES: affective pain perception, FESV: perceived helplessness in pain processing, *β* = Specification of the regression coefficient *beta* between the respective subdomain and SES and FESV, *p* = the correlation is significant at the level of *p* = .05 (one-sided).
Table 6: Correlations between neurocognitive variables and chronification factors in the patient group.

Index Values		SES Adjusted	FESV Adjusted
Attention	*β*	**.78***	**-.72***
	p	**<.01**	**<.01**
Memory	*β*	**.53***	-.1
	p	**<.05**	>.05
Executive Functioning	*β*	.31	-.25
	p	>.05	>.05
Overall Cognition	*β*	**.69***	-.44
	p	**<.01**	>.05

SES: affective pain perception, FESV: perceived helplessness in pain processing, *β* = Specification of the regression coefficient *beta* between the respective index values and SES and FESV, *p* = the correlation is significant at the level of *p* = .05 (one-sided).
Table 7: Correlations between neurocognitive index values chronification factors in the patient group.

Pain-related psychological impairment, considered a contributing factor to chronicity, showed correlations with cognitive processing speed (*beta* = -.5, *p* < .05), concentration performance (*beta* = -.83, *p* < .01), obtaining and overview (*beta* = -.74, *p* < .01; processing time: *beta* = -56, *p* < .05), reactive stress tolerance (*beta* = -.50, *p* < .05), and the index value attention (*beta* = -.72, *p* < .01). However, no significant correlations were observed with the memory and executive functions. A moderate correlation was identified for the index value overall cognition (*beta* = -.44, *p* = .05).

Conclusion

Implications for Treatment

Although the ICD-11 includes a revised classification of chronic pain, the time criterion was maintained. It is questionable to what extent this time criterion is still "up to date" and whether it would not be more beneficial to rely entirely on models/factors of chronification. Especially since these can be easily and economically assessed through standardized and well-established test procedures (SES, FESV). Future studies should be based on these findings. Both diagnostic and psychotherapeutic consideration (including red and green flags) in the conceptualization of Multimodal Pain Therapy appears indispensable and necessary.

Strength and Limitations

The reported secondary analysis provides indications that there are relations between the yellow flags and neurocognitive values, exceeding those observed between pain duration and neurocognition. A cause-and-effect relationship cannot be assumed based on these correlational

results. In future studies, additional factors contributing to chronicity from psychopathology (e.g., sleep disorders), social life (e.g., social withdrawal), and occupation (e.g., retention procedures, unemployment) should be considered. Furthermore, there is a significant need for additional research to delve into the relation between neurocognition in CP and its relationship with health conditions, daily functioning, and therapeutic outcomes.

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