USASP
US ASSOCIATION FOR THE STUDY OF PAIN

PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 22, No 8 (August), 2021: pp 905–913
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Does Cognitive Functioning Predict Chronic Pain in Older Adult? Results From the CoLaus|PsyCoLaus Longitudinal Study

Isabelle Rouch,[*,†,1] Jean-Michel Dorey,[‡,§,1] Marie-Pierre F. Strippoli,[¶] Mehdi Gholam,[¶] Pedro Marques-Vidal,[‖] Bernard Laurent,[*,††] Armin von Gunten,[§] and Martin Preisig[¶]

[*]*Memory Clinical and Research Center of Saint Etienne (CMRR) Neurology Unit, University Hospital of Saint Etienne, Saint Etienne, France,* [†]*INSERM, U1219, Bordeaux Population Health Center, University of Bordeaux, Bordeaux, France,* [‡]*Department of Aging Psychiatry, Hospital Le Vinatier, Bron, France,* [§]*Department of Psychiatry, Service of Old Age Psychiatry (SUPAA), Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland,* [¶]*Department of Psychiatry, Center for Research in Psychiatric Epidemiology and Psychopathology (CEPP), Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland,* [‖]*Department of Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland,* [††]*INSERM, U1028; CNRS, UMR5292; Neuropain team, Lyon Neuroscience Research Center, Lyon, F-69000, France*

Abstract: **Chronic pain (CP) and cognitive impairment are common in older adults. CP was found to be associated with cognitive impairment in many cross-sectional studies. However, their cross-sectional design precluded inference on temporality. Accordingly, we aimed to prospectively assess the association between cognitive functioning and the occurrence of CP in older community dwellers. Analyses were based on data of the first (FU1) and the second follow-up (FU2) of CoLaus|PsyCoLaus, a prospective cohort study conducted in the general population of Lausanne (Switzerland) including the participants aged 65 and over. Neuropsychological functioning including memory, language, attention and executive function was measured at FU1. CP was assessed at FU1 and FU2 by self-rating questionnaire. The association between cognitive scores and subsequent CP was determined using multiple logistic regressions. Among the 337 participants without CP at FU1, 107 (31.8%) developed CP at FU2. A significant association was observed between higher Stroop color-time and interference index at FU1 and a higher risk of CP at FU2 (OR = 1.02; *P* = .03 and OR = 1.49; *P* = .03, respectively). Our results suggest that patients with inhibitory deficit may be at higher risk of developing CP in the presence of painful events. A cognitive assessment could be recommended to identify frail patients in these situations.**

Perspective: ***This study suggests that presence of inhibitory deficits is associated with a higher risk of developing subsequent CP in older adults. In the presence of painful events, a cognitive assessment should be recommended to identify frail patients and to manage them carefully.***

Key Words: *Chronic pain, cognition, executive function, cohort.*

Received September 2, 2020; Revised December 8, 2020; Accepted January 13, 2021.

[1]These authors equally contributed to the manuscript as first co-authors
Conflict of interest: The authors have no conflicts of interest to declare.

Funding: The CoLaus|PsyCoLaus study was and is supported by research grants from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (grants 3200B0–105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468, 33CS30-148401 and 33CS30_177535/1).

Address reprint requests to Isabelle Rouch, Memory Clinical and Research Center of Saint Etienne (CMRR), Neurology Unit, Hospital of Saint Etienne, Avenue Albert Raimond, 42055 Saint Etienne, France. E-mail: isabelle.rouch@chu-st-etienne.fr

1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2021.01.007

Chronic pain (CP) affects more than 30% of people aged 65 and older, and its prevalence increases with increasing age.[10] Pain in older adults is often more persistent than in younger ones.[18] Regarding the cognitive domains associated with aging, the most important changes are the decrease in processing speed, working memory and executive functions.[34,27] In addition, pain-related impairments in several cognitive domains including learning and memory, attention and executive function, processing speed, and psychomotor ability have been reported in various cross-sectional

observational studies.[2,26,7,39] However, the cross-sectional design of these studies precludes inference on the direction of the relationship between CP and cognitive functioning.

Only three longitudinal community studies assessed the association between CP and cognitive decline in older adults. One of them demonstrated that CP is associated with a 10% increase in memory decline after a 10-year follow-up.[41] Similarly, a second study documented a larger decline in memory and executive functioning [38] after a 2.75 year follow-up and a third study showed a link between CP and higher decline in processing speed performance after a 15-year follow-up.[33] Conversely, there is only 1 study that assessed the prospective association between executive function and memory and the occurrence of CP.[5] This study, which included patients with breast cancer or knee arthroplasty surgery, found poorer cognitive performance in mental flexibility and visual memory to be associated with a higher risk of developing CP after a 6 to 12 months follow-up. To our knowledge, no previous study has prospectively assessed the association between cognitive functioning and the occurrence of CP in older people from the community. Hence, our goal was to determine the prospective association between cognitive functioning including memory, language, attention and executive function and the occurrence of CP after a 5-year follow-up, taking into account potential confounders including socio-demographic characteristics, lifetime major depressive disorder, psychotropic and analgesic drug intake and comorbid physical diseases.

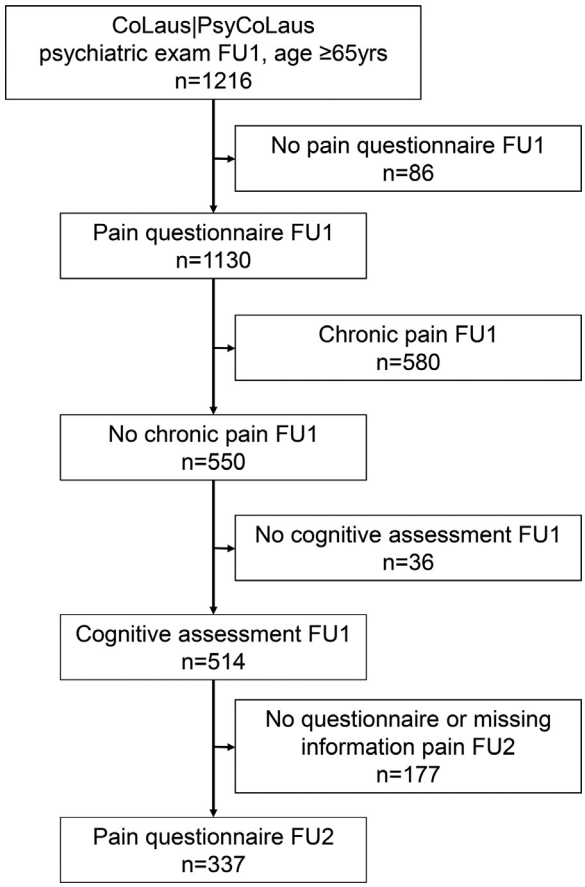

Figure 1. The selecting procedure of the study sample. Colaus PsyColaus study (N = 337).

Methods

Participants

The present data stem from CoLaus|PsyCoLaus, a population-based prospective cohort study designed to investigate cardiovascular risk factors and mental disorders in the community as well as their associations. The methodological features of this study have been previously described in detail.[20,31] CoLaus|PsyCoLaus initially included a random sample of 6,734 people (age range: 35−75 years) selected from the residents of the city of Lausanne (Switzerland) between 2003 and 2007. The distribution of age groups, sex, and geographic distributions in CoLaus|PsyCoLaus participants at baseline were similar to the source population.[20] Participants were reassessed approximately 5 (Follow-up 1, FU1) and 10 years (Follow-up 2, FU2) after the first investigation at baseline.[16,17] The present analyses are based on data from the first and second follow-ups. FU1 was carried out between 2009 and 2013, and FU2 between 2013 and 2017. The mean duration of the interval between FU1 and FU2 was 5.27 years (s.d. 0.58 years, range 2.39 −7.03). At FU1 and FU2 a neuropsychological assessment was performed in participants aged 65 and over. Among the 1216 participants of the physical exam of FU1 who were at least 65-year-old, 1130 (92.9%) also completed the pain questionnaire (Fig 1). Among them, 580 already reported CP and were excluded from the present analyses. Within the remainders (n = 550), 514 (93.4%) also accepted the cognitive assessment. Among them, 337 (61.3%) also completed the pain questionnaire at FU2 and constituted the cohort for the present analyses. Among the at least 65-year-old participants of FU1 who were exempt of CP (n = 550), those who could be included in the present analyses were younger than those who could not be included (69.4 vs 72.2 years, z = −4.44, $P < .001$), were more likely to be among the higher educational level categories ($\chi_3 = 33.0$, $P < .001$), used less frequently anxiolytics/hypnotics at FU1 (4.1% vs 11.7%; $\chi = 11.39$, $P < .001$), and scored higher on the Mini-Mental State Examination (MMSE) scale (29.42 ± 1.18 vs 28.97 ± 1.10; z = 3.13, $P = .002$).

Measurements

Pain Assessment

Information of pain was collected at FU1 and FU2 using the STOPNEP questionnaire, a detailed pain inventory designed and validated for epidemiological studies comprising 11 questions.[9,10] The first 2 questions aimed at identifying the presence of daily CP for at least 3 months. The subsequent questions only applied to participants who responded positively to these two questions. Participants were required to locate their pain from a list of body parts and, if they mentioned several locations, to report the location of the most

troublesome pain. The remaining seven questions related to the duration, intensity and characteristics of the most troublesome pain. Participants rated the duration of pain in four categories: less than 6 months, between 6 and 12 months, between 1 and 3 years, or more than 3 years. They then specified whether the pain varied in intensity during the day and reported the highest, lowest, and average intensity of pain during the past 24 hours, on three numerical rating scales (0 = no pain, 10 = worst pain imaginable) from the Brief Pain Inventory (BPI).[12] The mean BPI score corresponded to the mean of the three above scores. The BPI was validated in older adults.[21] CP was defined according to the International Association for Study of Pain (IASP),[37] as persistent or recurrent pain lasting longer than 3 month. In addition, as recommended by Bouhassira et al[9,10] we required the daily occurrence of pain during this period.

Neuropsychological Assessment

The neuropsychological assessment performed in participants aged 65 years and older at FU1 and FU2 included an overall cognitive assessment using the MMSE with a total score ranging from 0 to 30.

Verbal episodic memory was assessed using the 16-item free and cued recall test (FCSRT). The FCSRT includes a learning list of 16 written words presented with a semantic cue to control for memory encoding. Subjects were asked to retrieve the words spontaneously, then with the help of the semantic cue during three trials and, finally, free and cued delayed recall is examined after 30 minutes. The FCSRT scores included three free (FR) and total (free + cued) recalls (TR), delayed free recall (DFR), and delayed total recall (delayed free recall + delayed total recall) (DTR).[25,40]

The Letter and Category fluency test,[11] consisting of generating the highest possible number of words belonging to animal category and words beginning by P in 2 minutes, explores executive function, semantic memory and language, further assessed with an 40-item object naming test (DO 40).[15]

The Stroop Color-Word Test (Victoria version)[36] assessed executive function and selective attention. Participants were required to name colored dots (Dot test), then words printed in the same color as the dots (Word test), and finally color words printed in noncorresponding colors (Word-Color test). Each task contained 24 items and challenged participants to deal with an interference effect. The measurements used in the analyzes were: Dot test reading time ('dot time'), Word test reading time ('word time'), Word-Color test reading time ('color time') and the Stroop interference index, calculated with the following ratio: Time to name Word-Color test/time to read Dot test.

Covariates

During the physical follow-up evaluations information was collected on socio-demographic characteristics including sex, race and education as well as on medication, including analgesic, and psychotropic (antidepressants, anxiolytics/hypnotics, antiepileptics) drug use. Education was categorized into 4-levels: compulsory school, apprenticeship, high school/college and university degrees.

The body mass index (BMI) and metabolic diseases including hypertension and diabetes, which are known to be associated with both CP and cognitive impairment, were assessed using anthropomorphic and biochemical measures. Hypertension was defined by systolic blood pressure $\geq$140 and/or diastolic blood pressure $\geq$90 mm Hg and/or treatment and diabetes by fasting Glucose$\geq$7 mmol/L and/or treatment.

Diagnostic information on mental disorders including lifetime major depressive disorder (MDD) and adult anxiety disorders (panic disorder, generalized anxiety disorders, agoraphobia, social phobia) according to DSM-IV-TR[1] was elicited at each psychiatric evaluation using the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS).[30] Interviews were conducted by trained psychologists.

Statistical Analysis

Inter-group comparisons of categorical were performed using chi-square, inter-group comparisons of continuous variables were performed using, Student *t*-tests or Mann-Whitney tests.

In order to assess the associations between cognitive performance scores at FU1 and CP status at FU2, logistic regression models were applied with adjustment for age, sex, education level, hypertension, diabetes, BMI, history of lifetime MDD, psychotropic as well as analgesic drug use at FU1. These models were only applied for cognitive scores that previously revealed a significant association with CP status at FU2 in univariate analyses. Given the risk of collinearity across scores separate models for each score were applied.

The results of all the tests were considered significant at *P*value $< .05$. Statistical analyses were performed with SPSS version 21 (SPSS Software, Chicago, USA).

Informed Consent and Ethical Consideration

All participants signed a written informed consent after having received a detailed description of the goal and funding of the study. The study protocol was reviewed and approved by an ethics committee (Institutional Ethics' Committee of the University of Lausanne). All procedures are in accordance with the declaration of Helsinki.

Results

Sample Description

Among the 337 people who could be included in the present analyses, 107 participants (31.8%) developed CP between FU1 and FU2. Table 1 summarizes the locations of CP at FU2 for participants who developed CP. The

Table 1. Pain Location at 5-Year Follow-Up Among Participants With Chronic Pain at Follow-up 2.

Pain location	*N (%)*
Face	0 (0)
Neck	8 (7.25)
Shoulder	24 (22.4)
Chest	5 (4.7)
Back	**50 (46.7)**
Arms (except joints)	5 (4.7)
Elbow	4 (3.7)
Wrist or hands	**34 (31.8)**
Hip or groin	**31 (30)**
Buttock or tigh	15 (14.0)
Knee	**36 (33.6)**
Legs (except joints)	17 (15.9)
Ankle or feet	**43 (40.2)**
Other	9 (8.4)

Pain locations >25% of the participants, considered as frequent are indicated in bold.
N = 107.

most frequent localizations concerned back, hands, feet and joints including wrists, hips, ankles, groins and knees. Among participants with chronic pain at FU2, the distribution of pain duration is shown in Fig 2. The mean pain intensity score during the 24 last hours was 3.29 (SD 1.43; maximum 7.0). Divided into four categories according to pain severity, one participant of the cohort (1.1%) reported severe pain, 16 participants (18.2%) reported moderate pain, 70 participants (79.5%) reported mild pain, and one participant (1.1%) did not report any pain. A total of 19 participants had missing data for pain intensity.

The characteristics of the participants according to their CP status at FU2 are displayed in Table 2. The two groups did only differ by use of psychotropic drugs at FU1 as well as use of analgesic and psychotropic drugs at FU2.

Associations Between Cognitive Performance at FU1 and CP at FU2

Table 3 reveals the results of the cognitive tests performed at baseline according to the chronic pain status at FU2. Among all cognitive tests, only the Stroop test showed significant differences between the 2 groups. Indeed, participants who subsequently developed CP at FU2 had a weaker performance in the subtests 'color time' and 'interference index' at FU1 (Table 3).

To assess the association between the 2 Stroop test subscores and CP status at FU2 with adjustment for sociodemographic variables, education, metabolic characteristics and drug use, two separate logistic regression models were applied (Table 4). These analyses confirmed significant associations between the performance in the 2 Stroop subscores and the risk of CP at FU2. Among the potential confounders only psychotropic drug use was significantly associated with the risk of CP.

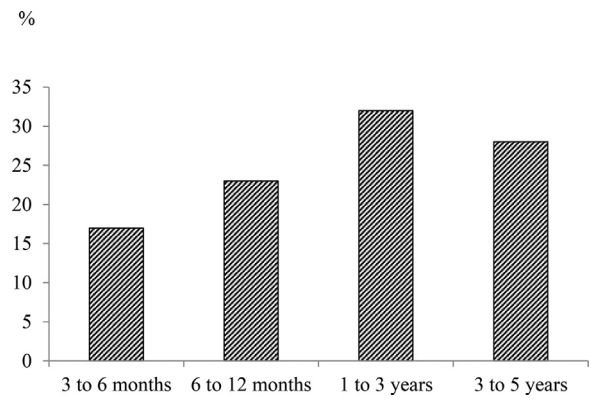

Figure 2. Distribution of pain duration at FU2 (N = 89).

Discussion

To our knowledge, our study is the first to prospectively assess the association between cognitive functioning and the risk of CP among older community dwellers. After adjustment for multiple potential confounders, we only found prospective associations between cognitive functioning and CP according to 1 cognitive test, that is, the Stroop test. Indeed, inhibitory deficits and selective attention according to 2 subscores of this test predicted an increased risk of CP after a 5-year FU in a cohort of older adults from the community who were initially free of CP. Among those who developed CP, one half presented back pain and most of them had any joints pain. These findings suggest that most CP were attributable to osteoarthritis, which is in accordance with previous reports.[22] The majority experienced pain for at least 1 year and almost 80% reported pain intensity in the mild range. As expected, pain intensity in this cohort recruited from the community was lower than in studies of treated patients. The restriction of observed prospective associations between cognition and emerging CP to cognitive inhibition, as assessed by the color time and interference index of the Stroop test, may be related to the high cognitive functioning of our cohort. Indeed, specific tests of domains of cognitive functioning including the color time and interference index of the Stroop may be more sensitive in measuring minor deficits than tests assessing overall cognitive functions such as the MMSE. Moreover, the Stroop is the only test we used that does not have a ceiling effect, which also may partly explain why we found differences only with this test.

Although the association between cognitive impairment and CP has been well established in cross-sectional research, only few prospective studies have addressed the question of the direction of this association. Among these prospective studies only one already assessed the association between cognitive performance at baseline and the subsequent development of CP.[5] However, this study used a clinical cohort of patients with breast cancer or knee arthroplasty surgery and relied on other cognitive tests (Trail Making test B to assess mental flexibility, Rey-Osterreich Complex figure

Table 2. Sample Description at FU1 According to CP Status at FU2 (N = 337).

	Chronic Pain at 5-Year Follow-up				
	All (N = 337)	Yes (N = 107)	No (N = 213)	Test Statistic	P
Sex				χ = 2.09	.15
Men, n (%)	158 (46.9)	44 (41.1)	114 (49.6)		
Women, n (%)	179 (53.1)	63 (58.9)	116 (50.4)		
Race				χ = .56	.42
Caucasian, n (%)	325 (96.4)	102 (95.3)	223 (97.0)		
Non-caucasian, n (%)	12 (3.6)		7 (3.0)		
Age at FU1, mean (s.d.)	69.14 (5.60)	70.50 (3.96)	70.51 (4.26)	t = .03*	.98
Educational level, n (%)				χ = 1.46	.69
Compulsory school, n (%)	30 (8.9)	11 (10.3)	19 (8.3)		
Apprenticeship, n (%)	147 (43.6)	50 (46.7)	97 (42.2)		
High school/college, n (%)	80 (23.7)	22 (20.6)	58 (25.2)		
University, n (%)	80 (23.7)	24 (22.4)	56 (24.3)		
Hypertension				χ = .004	.95
No, n (%)	130 (38.6)	41 (38.3)	89 (38.7)		
Yes, n (%)	207 (61.4)	66 (61.7)	141 (61.3)		
Diabetes				χ = 1.24	.26
No, n (%)	284 (84.5)	87 (81.3)	197 (86.0)		
Yes, n (%)	52 (15.5)	20 (18.7)	32 (14.0)		
Current adult anxiety disorders§ at FU1, n (%)				χ 2.73	.10
No, n (%)	326 (96.7)	101 (94.4)	225 (97.8)		
Yes, n (%)	11 (3.3)	6 (5.6)	5 (2.2)		
Lifetime major depressive disorders at FU1, n (%)				χ = .49	.78
No	220 (65.3)	67 (62.6)	153 (66.5)		
Remitted	108 (32.0)	37 (34.6)	71 (30.9)		
Current	9 (2.7)	3 (2.8)	6 (2.6)		
Analgesic drug intake at FU1				F‡ = .59	.38
No, n (%)	323 (98.8)	105 (98.1)	228 (99.1)		
Yes, n (%)	4 (1.2)	2 (1.9)	2 (0.9)		
Psychotropic drug intake at FU1				**χ = 5.81**	**.016**
No, n (%)	303 (89.9)	90 (84.1)	213 (92.6)		
Yes, n (%)	34 (10.1)	17 (15.9)	17 (7.4)		
Analgesics intake at FU2, n (%)				**χ = 12.5**	**<.001**
No, n (%)	322 (95.6)	96 (89.7)	226 (98.3)		
Yes, n (%)	15 (4.4)	11 (10.3)	4 (1.7)		
Psychotropic drug intake at FU2, n(%)				**χ = 4.45**	**.035**
No, n (%)	301 (89.3)	90 (84.1)	211 (91.7)		
Yes, n (%)	36 (10.7	17 (15.9)	19 (8.3)		
BMI, mean (s.d.)	26.11 (4.23)	26.45 (4.32)	25.95 (4.19)	Z = −.75†	.45

*Student t test.
†Mann-Whitney z.
‡Fisher test.
§Agoraphobia, panic disorder, generalize anxiety disorder, social phobia.

to assess visual cognitive performance) than ours. Moreover, in their study CP was mostly due to surgery, and the duration of follow-up between cognitive assessment and CP measurement was shorter (6−12 months). Despite these methodological differences, the 2 studies concur in demonstrating prospective links between decreased cognitive performance and the risk of CP. However, in contrast to the study on surgical patients we did not find an association between low memory scores and the development of CP. The discrepant findings could be due to a stronger association of cognitive functioning with CP that emerged within 6−12 month after surgery as compared CP occurring in the context of osteoarthritis and other chronic diseases within a 5-year period. Alternatively, this discrepancy could merely be attributable to the use of different measures for memory between the two studies. Indeed, Attal et al evaluated immediate recall of a complex figure (the Rey figure), involving visuospatial capacities and short-term visual memory, whereas in the present study, we assessed long-term verbal memory. Moreover, the FCSRT test applied in our study uses category cues to prompt recall of items not retrieved by free recall. For the recall of the Rey figure, participants had to found their own strategies for recall of the different elements of the figure. The elaboration of strategies is under the control of executive function. In addition, in our study the development of CP was unrelated to language scores on DO 40 and verbal fluency tests, which assess both language and mental flexibility. Although the observed absence of a link between language and CP in our study is in line with previous research, the prospective study

Table 3. Neuropsychological Tests Scores at FU1 According to CP Status at FU2 (N = 337).

	Chronic Pain at 5-Year Follow-up				
	All (N = 337)	Yes (N = 107)	No (N = 213)	Test Statistic	P
MMSE	29.42 (1.18)	29.49 (1.20)	29.39 (1.16)	t = −.74*	.46
DO 40	39.80 (0.59)	39.87 (0.39)	39.76 (0.66)	U = −1.31†	.19
FCSRT					
Sum of free recall	35.22 (4.86)	35.88 (4.51)	34.90 (4.99)	U = −1.85†	.07
Sum of total recall	46.51 (2.44)	46.88 (1.85)	46.33 (2.66)	U = −.81†	0.42
Delayed free recall	12.06 (2.52)	12.35 (2.41)	11.93 (2.57)	t = −1.39*	.17
Delayed total recall	15.73 (0.69)	15.75 (0.77)	15.73 (0.66)	t = −.29*	.78
Category Fluency	30.73 (8.03)	30.15 (7.35)	31.00 (8.34)	t = .89*	.37
Letter Fluency	21.57 (7.76)	21.41 (7.34)	21.64 (7.96)	t = .25*	.80
Stroop test					
Dot time	16.44 (5.38)	16.94 (6.52)	16.20 (4.74)	t = −1.16*	.25
Word time	20.27 (5.61)	20.40 (5.18)	20.21 (5.80)	t = −.27*	.78
Color time	32.39 (12.05)	34.73 (13.86)	31.30 (10.96)	t = −2.41*	**.017**
Interference index	2.05 (0.65)	2.16 (0.75)	1.98 (0.60)	t = −2.22*	**.027**

MMSE, Mini mental state examination; DO 40, Denomination of Object 40 items; FCSRT, Free and cued selective reminding test.
Significant variables are indicated in bold.
*Student t test.
†Mann-Whitney z.

Table 4. Risk of CP at FU2 by Stroop Test Performance at FU1 According to Logistic Regression (N = 337).

	OR (95% CI)	P
Model for Stroop Color time		
Stroop (Color time)	1.02 (1.00 ; 1.04)	**.03**
Age	0.99 (0.93;1.05)	.81
Sex (women)	1.40 (0.88.2.46)	.14
Educational level		
Compulsory school	-	
Apprenticeship	0.86 (0.33 ; 2.28)	.83
High school/college	1.14 (0.61 ; 2.13)	.62
University	0.68 (0.32 ; 1.44)	.31
Lifetime MDD		
No	-	
Remitted	0.91 (0.51 ; 1.62)	.71
Current	0.60 (0.12 ; 3.14)	.55
Anxiety disorder	2.81 (0.73 ; 10.72)	.13
Analgesic use	2.68 (0.33 ; 21.73)	.36
Psychotropic use	3.11 (1.34 ; 7.18)	**.008**
Intercept	0.34	.62
Model for Stroop Interference index		
Stroop (Interference index)	1.49 (1.03 ; 2.15)	**.03**
Age	1.00 (0.95 ; 1.06)	1.00
Gender (women)	1.43 (0.86 ; 2.39)	.18
Educational level		
Compulsory school	1.0 (ref)	
Apprenticeship	0.91 (0.35; 2.35)	.91
High school/college	1.17 (0.63 ; 2.18)	.56
University	0.66 (0.31 : 1.40)	.27
Lifetime MDD		
No	-	
Remitted	0.93 (0.52 ; 1.67)	.82
Current	0.51 (0.10 ; 2.69)	.43
Anxiety disorder	2.70 (0.71 ; 9.94)	.15
Analgesic use	2.75 (0.33 ; 22.63)	.35
Psychotropic use	3.40 (1.47 ; 7.83)	**.004**
Intercept	0.15	.38

Significant variables are indicated in bold.

on surgical patients as well as cross-sectional studies documented an association between reduced mental flexibility and CP. Again, these discrepant findings may be explained by the use of different measures to assess mental flexibility across studies.

Several studies have also provided evidence for an inverse prospective association between CP at baseline and subsequent cognitive decrease,[41,38] which suggests a reciprocal link between CP and cognition.

Our findings are also consistent with those of two experimental studies exploring the link between different executive domains and experimentally induced pain in healthy people. The first study including response generation (verbal fluencies), mental flexibility (TMT B), working memory (digit span backward) and inhibition (Stroop)[29] revealed that better cognitive performance according uniquely to the Stroop test was associated with lower pain sensitivity. In a second study, the neuropsychological assessment encompassed different facets of executive functions, inhibition (Stroop, Stop-signal, and Left-right), updating (Keep-track, Letter-memory, and Spatial n-back), and set-shifting (Plus-minus, Number-letter, and Local-global). This second study also showed a unique association between better Stroop performance and lower pain sensitivity.[8] Furthermore, several observational studies documented associations between Stroop test scores and CP. Coppitiers et al found lower Stroop test scores in patients with chronic whiplash associated disorder and fibromyalgia than in healthy controls.[13] Decreased Stroop performance was related to deficient central pain modulation in both fibromyalgia patients and healthy controls.[13] Similarly, Marouf et al showed that a decrease of cerebrospinal processes involved in the regulation of pain perception in a sample of healthy older people was significantly associated with a decrease in the efficacy of cognitive inhibition processes according to Stroop test. These results suggested a generalized age-related reduction in

inhibitory processes affecting both executive functions and cerebrospinal processes involved in the regulation of pain-related responses induced by competing nociceptive threats.[24]

Our results are also in line with brain imaging data, suggesting an overlap of structures involved in pain modulation and cognitive functioning. In particular, frontal brain structures play an important role in pain modulation.[3,2,6,28] Decreased prefrontal cortex cortical thickness and weaker executive performance were reported in patients with a complex regional pain syndrome compared to healthy controls.[22]

Hence, our results suggest that patients with inhibitory deficits in the context of neurocognitive disorders are at a higher risk of developing CP in the presence of painful events such as surgical interventions. A cognitive assessment could identify patients with cognitive weakness in these situations and contribute to a better management of acute pain in these populations in order to prevent the development of CP. The relationship between the integrity of cognitive functions and the ability to cope with pain was also highlighted in different studies in healthy controls and patients with chronic pain.[35,23]

The most important limitation of the present study is the relatively small number of participants who could be included in the analyses, which is a concern regarding both the generalizability of our results and potential selection bias. However, our observation of one half of participants presenting CP at baseline is in line with data of previous studies that determined age-specific CP prevalence using similar definition of CP.[10,32,42] Among participants with CP the proportion of 10% of daily users of analgesic drugs at FU2 is less than half of that of population-based studies suggesting that 25 to 30 % of older adults with CP took pain medications.[14,19] However, this low proportion of analgesic drug use is largely explained by the need of excluding approximately half of the participants, who already reported CP at FU1 and were also frequently users of analgesics. Furthermore, psychotropic drugs use was higher in participants with CP at both FU1 and FU2; in addition, anxiety disorders at FU1 were higher in the group reporting CP at FU2 (results close to significance). These results were in line with previous studies reporting that anxiety and mood disorders predicted subsequent CP.[4]

Our comparison of participants who could be included in the present analyses with those who could not revealed that included participants were younger and scored higher on the Mini-Mental State Examination (MMSE) scale. Although our analyses adjusted for these variables, selection bias cannot be precluded. Moreover, given that adjustment for analgesic and psychotropic use were based on binary (yes vs no) rather than quantitative variables, residual confounding may have persisted. Furthermore, a maximum of four participants with analgesics at FU1 and four participants with analgesics and no CP FU2 could have been erroneously classified in the "no CP" group because their pain was successfully suppressed by analgesic drugs. However, these potential misclassifications would only have very marginally affected our results.

Another limitation is the delay of approximately one year between the physical and psychiatric evaluation at FU1. Hence, it is possible that we have missed to exclude some participants from the present analyses who have developed CP in the interval between the physical and psychiatric evaluation.

Further studies with longer follow-up and repetitive cognitive evaluations are warranted to clarify the role of the evolution of cognitive functioning on the occurrence of CP and to further explore the specificity and nature of the link between the subtype of executive deficit and the type of CP. These studies should test whether the association between cognitive inhibition and CP can be replicated using neuropsychological tests other than the Stroop test and whether these association differ in function of the etiology and characteristics of CP (ie, nociceptive, neuropathic or nociplastic pain). Finally, longitudinal neuroimaging studies could try to identify areas of the frontal cortex associated with the onset of CP among those that are linked to executive functions (dlPCF) and control of pain (dlPFC and perigenual anterior cingulate cortex).

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. Washington, DC, American Psychiatric Association, 2013

2. Apkarian AV, Baliki MN, Geha PY: Towards a theory of chronic pain. Prog Neurobiol 87:81-97, 2009

3. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR: Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 24:10410-10415, 2004

4. Attal N, Masselin-Dubois A, Martinez V, Jayr C, Albi A, Fermanian J, Bouhassira D, Baudic S: Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. Brain 137:904-917, 2014

5. Attal N, Masselin-Dubois A, Martinez V, Jayr C, Albi A, Fermanian J, Bouhassira D, Baudic S: Does cognitive functioning predict chronic pain? Results from a prospective surgical cohort. Brain 137:904-917, 2014

6. Baliki MN, Schnitzer TJ, Bauer WR, Apkarian AV: Brain morphological signatures for chronic pain. PLoS ONE 6: e26010, 2011

7. Berryman C, Stanton TR, Bowering KJ, Tabor A, McFarlane A, Moseley GL: Do people with chronic pain have impaired executive function? A meta-analytical review. Clin Psychol Rev 34:563-579, 2014

8. Bjekić J, Živanović M, Purić D, Oosterman JM, Filipović SR: Pain and executive functions: A unique relationship between Stroop task and experimentally induced pain. Psychol Res 82:580-589, 2018

9. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lantéri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 114:29-36, 2005

10. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C: Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 136:380-387, 2008

11. Cardebat D, Démonet JF, Viallard G, Faure S, Puel M, Celsis P: Brain functional profiles in formal and semantic fluency tasks: A SPECT study in normals. Brain Lang 52:305-313, 1996

12. Cleeland CS, Ryan KM: Pain assessment: Global use of the brief pain inventory. Ann Acad Med Singap 23:129-138, 1994

13. Coppieters I, Ickmans K, Cagnie B, Nijs J, De Pauw R, Noten S, Meeus M: Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia. Pain Physician 18:E389-E401, 2015

14. Corsi N, Roberto A, Cortesi L, Nobili A, Mannucci PM, Corli O, Investigators REPOSI: Prevalence, characteristics and treatment of chronic pain in elderly patients hospitalized in internal medicine wards. Eur J Intern Med 55:35-39, 2018

15. Deloche G, Metz-Lutz M, Kremin H, Hannequin D, Ferrand L, Perrier D, Dordain M, Quint S, Cardebat D, Lota A, Van Der Linden M, Larroque C, Bunel G, Pichard B, Naud E: Test De Dénomination Orale De 80 Images : DO 80. Paris, ECPA, 1989

16. Dupuis M, Meier E, Rudaz D, Strippoli M-PF, Castelao E, Preisig M, Capel R, Vandeleur CL: Psychiatric symptoms and response quality to self-rated personality tests: Evidence from the PsyCoLaus study. Psychiatry Res 252:118-125, 2017

17. Dupuis M, Strippoli M-PF, Gholam-Rezaee M, Preisig M, Vandeleur CL: Mental disorders, attrition at follow-up, and questionnaire non-completion in epidemiologic research. Illustrations from the CoLaus|PsyCoLaus study. Int J Methods Psychiatr Res 28:e1805, 2019

18. Elliott A, Smith B, Hannaford P, Smith W, Bilker WB: The course of chronic pain in the community: Results of a 4-year follow-up study. *Pain* 299–307, 2002.

19. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT: Prevalence of chronic pain in the UK: A systematic review and meta-analysis of population studies. BMJ Open 6, 2016. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932255/. Accessed March 23, 2021.

20. Firmann M, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P: The CoLaus study: A population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovasc Disord 8:6, 2008

21. Kang Y, Demiris G: Self-report pain assessment tools for cognitively intact older adults: Integrative review. Int J Older People Nurs 13:e12170, 2018

22. Lee D-H, Lee K-J, Cho KIK, Noh EC, Jang JH, Kim YC, Kang D-H: Brain alterations and neurocognitive dysfunction in patients with complex regional pain syndrome. J Pain 16:580-586, 2015

23. Legrain V, Crombez G, Verhoeven K, Mouraux A: The role of working memory in the attentional control of pain. Pain 152:453-459, 2011

24. Marouf R, Caron S, Lussier M, Bherer L, Piché M, Rainville P: Reduced pain inhibition is associated with reduced cognitive inhibition in healthy aging. Pain 155:494-502, 2014

25. Matias-Guiu JA, Cabrera-Martín MN, Curiel RE, Valles-Salgado M, Rognoni T, Moreno-Ramos T, Carreras JL, Loewenstein DA, Matías-Guiu J: Comparison between FCSRT and LASSI-L to detect early stage Alzheimer's disease. J Alzheimers Dis 61:103-111, 2018

26. Moriarty O, McGuire B, Finn D: The effect of pain on cognitive function: A review of clinical and preclinical research. Prog Neurobiol 93:385-404, 2011

27. Murman DL: The impact of age on cognition. Semin Hear 36:111-121, 2015

28. Ong W-Y, Stohler CS, Herr DR: Role of the prefrontal cortex in pain processing. Mol Neurobiol 56:1137-1166, 2019

29. Oosterman JM, Dijkerman HC, Kessels RPC, Scherder EJA: A unique association between cognitive inhibition and pain sensitivity in healthy participants. Eur J Pain 14:1046-1050, 2010

30. Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F: Diagnostic interview for genetic studies (DIGS): Inter-rater and test-retest reliability of the French version. Eur Arch Psychiatry Clin Neurosci 249:174-179, 1999

31. Preisig M, Waeber G, Vollenweider P, Bovet P, Rothen S, Vandeleur C, Guex P, Middleton L, Waterworth D, Mooser V, Tozzi F, Muglia P: The PsyCoLaus study: Methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC Psychiatry 9:9, 2009

32. Rapo-Pylkkö S, Haanpää M, Liira H: Chronic pain among community-dwelling elderly: A population-based clinical study. Scand J Prim Health Care 34:159-164, 2016

33. Rouch I, Edjolo A, Laurent B, Pongan E, Dartigues J-F, Amieva H: Association between chronic pain and long-term cognitive decline in a population-based cohort of elderly participants. Pain, 2020. https://doi.org/10.1097/j.pain.0000000000002047

34. Salthouse TA: Selective review of cognitive aging. J Int Neuropsychol Soc 16:754-760, 2010

35. Sanchez CA: Working through the pain: Working memory capacity and differences in processing and storage under pain. Memory 19:226-232, 2011

36. Stroop J: Studies of interference in serial verbal reactions. J Exp Psychol 643-662, 1935

37. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen

JWS, Wang S-J: A classification of chronic pain for ICD-11. Pain 156:1003-1007, 2015

38. van der Leeuw G, Eggermont LHP, Shi L, Milberg WP, Gross AL, Hausdorff JM, Bean JF, Leveille SG: Pain and cognitive function among older adults living in the community. J Gerontol A Biol Sci Med Sci 71:398-405, 2016

39. van der Leeuw G, Leveille SG, Dong Z, Shi L, Habtemariam D, Milberg W, Hausdorff JM, Grande L, Gagnon P, McLean RR, Bean JF: Chronic pain and attention in older adults living in the community. J Am Geriatr Soc 66:1318-1324, 2018

40. Van der Linden M, Coyette F, Poitrenaud J, Kalafat M, Calicis F, Wyns C, Adam S: L'épreuve De Rappel Libre /Rappel Indicé à. Available at: http://orbi.ulg.ac.be/handle/2268/26018. Accessed March 23, 2021.

41. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK: Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. JAMA Intern Med 177:1146-1153, 2017

42. Zis P, Daskalaki A, Bountouni I, Sykioti P, Varrassi G, Paladini A: Depression and chronic pain in the elderly: Links and management challenges. Clin Interv Aging 12:709-720, 2017