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Response inhibition, set shifting, and complex executive function in patients with chronic lower back pain

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ABSTRACT

Objective: The aim of our study was to evaluate how response inhibition, set shifting, and complex executive function (represented by risky decision-making) are altered in chronic lower back pain patients.

Materials and methods: A total of 29 patients with chronic lower back pain (CLBP >6 months) aged 49–69 years and 30 healthy volunteers matched for age, gender, and education were enrolled in a case–control study. The study was conducted in the Departments of Neurology and Neurosurgery of Panevėžys Regional Hospital, Lithuania. Pain was evaluated by the visual analog scale, Pakula Pain Questionnaire (Lithuanian analog of McGill Pain Questionnaire), and Fibromyalgia Tender Points Examination. A battery of neuropsychological tests used included Stroop Test Victoria version, Trail Making Test parts A and B, and Game of Dice Task (GDT).

Results: CLBP patients did not score significantly worse in any examined neuropsychological tests. Response Inhibition correlated inversely with number of tender points in CLBP patients. GDT performance showed no significant difference in net score (number of safe minus risky decisions). Unexpectedly, both groups favored risky decisions.

Conclusions: We found no statistically significant difference in response inhibition, set shifting, or complex executive function between CLBP patients and healthy older adults. Moreover, a risky decision-making pattern found in the Lithuanian population may underscore the importance of cultural context when examining complex executive function. However, further studies are needed to prove this point.

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1. Introduction

The relationship between chronic pain and cognition is bidirectional: pain may alter cognitive functions [1], while cognitive processes may influence pain perception [2], and predispose pain chronicity [3]. Researchers proposed several mechanisms to explain the impact of chronic pain on cognition [4–9], although they failed to observe a common neuropsychological pattern [1].

Executive function – a subset of cognitive processes – represents a set of abilities that are crucial for guiding one's thoughts and everyday life actions. These are elusive to define [10], and difficult to measure. They include the capacity of intentional behavior, planning and decision-making, purposive action and ability to monitor, self-correct and regulate performance [11].

Chronic pain and executive function have a shared neural substrate mainly in prefrontal regions [2,12–14], however, the evidence for impairment of executive function in pain patients is inconsistent [15–17]. It is important to investigate the link between executive function and pain, because its impairment may translate to the deterioration of the aforementioned capacities in the activities of everyday life.

The unity/diversity framework classifies executive function into four cognitive components: updating, set shifting, response inhibition, and complex executive function [18,19]. A recent meta-analytical review, based on the unity/diversity framework, found a small-to-moderate impairment in executive function performance in people with chronic pain, although 25 studies included in the review had a high risk of bias [20]. Three of them specifically involved patients with chronic lower back pain (CLBP) and had conflicting conclusions: in one of them healthy controls performed significantly better in set shifting [17], another showed no difference in response inhibition [15], while in the third CLBP patients performed significantly better in response inhibition in walk, but not in sit condition [21]. This indicates that study design may play an important role in measuring executive function performance.

In addition, some previous studies found correlation between pain intensity and response inhibition (defined as executive function) [16,22], while others reported a significant association with set shifting (defined as psychomotor speed), but not with executive function [23]. There are also studies that reported a positive relation between executive function and chronic pain in a subset of older adults [24,25]; however, the evidence is scarce.

The aim of our study was to evaluate how response inhibition, set shifting, and complex executive function are altered particularly in chronic lower back pain condition. In this case–control study, we compared two homogeneous populations of CLBP patients and healthy controls by numerous pain parameters and multiple executive function tests.

2. Materials and methods

2.1. *Participants*

The study population comprised 29 patients (13 men and 16 women, aged 49–69 years), treated for constant chronic (>6 months) lower back pain of any etiology in the Departments of Neurology and Neurosurgery of Panevėžys Regional Hospital. Among them, 13 patients were aged less than 60 years, whereas 16 were aged 60 years and more. Before being examined, subjects had to indicate that they did not meet any of the exclusion criteria, which were a history of a neurological or psychiatric illness, brain injury or trauma as well as use of neuromodulating drugs, other than analgesics. Subjects had to complete a pain drawing by shading all painful areas – only those with lower back pain as their primary complaint were included in the study. Sociodemographic data are summarized in Table 1.

The control group (CG) included 30 healthy volunteers (14 men and 16 women, aged 49–74 years) without pain, mostly recruited museum and dormitory guards of nearby towns, not meeting the exclusion criteria. Thirteen subjects were under 60 years old, whereas 17 were sixty and older. The groups were matched for age, gender and education.

The Hospital Anxiety and Depression Scale (HADS) [26] was administered to account for possible differences in anxiety and depression.

Overall 83 subjects were surveyed for both groups of whom 24 were excluded after a careful revision (16 CLBP patients and 8 healthy volunteers accordingly): 5 were excluded due to age (over 75 years old), 3 did not meet our chronic pain criterion (>6 months), 10 were found to have a history of neurological or psychiatric disease, 5 had most intense pain location different than lower back, and 1 subject had 22 years of education and was excluded as an outlier not to skew the sample.

Table 1 – Sociodemographic and pain-related data.

	CLBP patients (n = 29)	CG (n = 30)	P
Gender, *n*			
Male	13	14	0.887
Female	16	16	
Age, years	59.6 (6.0)	60.7 (7.0)	0.606
Education, years	13.0 (2.9)[b]	13.7 (2.6)[c]	0.339
Subjective health state in VAS	60 (24)	33 (25)	<0.001
HADS depression score	5.4 (3.5)	3.8 (2.9)	0.086
HADS anxiety score	6.6 (3.5)	4.3 (2.9)	0.015
Pain duration, months	91 (159)[d]		
Current pain in VAS	56 (24)		
Pain last week in VAS	61 (17)		
Worst pain last week in VAS	81 (13)		
Pakula Pain Questionnaire[a]			
Affective component	28.0 (12.0)		
Sensory component	37.3 (15.3)		
Tender Points Examination tender points	6.9 (5.4)[d]		

Values are mean (standard deviation) unless otherwise stated. CLBP, chronic lower back pain; CG, control group; HADS, Hospital Anxiety and Depression Scale; VAS, visual analog scale (0–100 mm) with a higher score indicating poorer health and worse pain.

[a] Lithuanian analog to McGill Pain Questionnaire.

[b] n = 26.

[c] n = 27.

[d] n = 28.

All patients and volunteers gave written informed consent and did not receive any financial compensation. The study was conducted in accordance with the Declaration of Helsinki and an approval was granted by a local bioethics committee (BC-MF-11).

2.2. Pain assessment and neuropsychological tests

The patients and healthy controls were evaluated prospectively using a battery of neuropsychological tests. Additionally, pain questionnaires were delivered to CLBP patients. Pain parameters are summarized in Table 1.

2.2.1. Pain assessment

The participants' subjective pain sensation (pain duration, current pain, average and worst pain last week) and current health state were evaluated using the visual analog scale (VAS) [27]. Subjects had to indicate their health status from ''totally healthy'' to ''totally unhealthy'', whereas, VAS for pain ranged from ''no pain'' to ''worst possible pain.'' The Pakula Pain Questionnaire – a Lithuanian analog of the McGill Pain Questionnaire [28] – was used to determine the dominant pain component. It includes 59 words describing affective and sensory aspects of pain, semantically clustered into small groups with a coefficient assigned according to its descriptive strength. The final scores of pain's affective and sensory components were then calculated.

To measure individual pain threshold we used the Tender Points Examination (TPE) [29]: a dolorimeter was applied to 18 standard fibromyalgia tender points with a force of up to 4 kg.

2.2.2. Neuropsychological assessment

A battery of neuropsychological tests was used to evaluate subjects' response inhibition, set shifting, and complex executive function (in this study represented by risky decision-making). Updating was not part of our investigation, as the choice of neuropsychological tests employed was largely influenced by their availability in the Lithuanian language. All neuropsychological tests employed in our study have previously been linguistically adapted for use in the Lithuanian population. The personnel administering the cognitive tests was not blinded to the pain condition of the participants.

The Stroop Test Victoria version was used to assess the ease with which a person can maintain a goal in mind and suppress a habitual response in favor of a less familiar one [30]. The test consists of three parts. In the first two parts the subjects are asked to name the colors of 24 colored dots (color naming) and 24 random colored words (word naming), arranged into 4 columns. In the third part subjects have to name the colors of words, spelled in an incongruent color name (e.g., the word ''red'' is written in blue) (interference). Time for the completion of each task and color-word interference (interference minus color naming time) are measured. The Stroop Test Victoria version was chosen in particular, as it was the only Stroop Test version validated and previously used in Lithuania in a subset of adolescents with idiopathic generalized epilepsy [31].

Set shifting was measured by the Trail Making Test (TMT) [32]. TMT part A consists of connecting 25 randomly arrayed dots in numerical order, whereas TMT part B asks to connect dots alternating between numbers and letters in alphabetical order. Time needed to complete each part was evaluated. The participants were also asked to encircle the dots which is not according to standardized test instructions, and could have amounted to a longer time-to-completion [33].

A linguistically adapted Lithuanian version of Game of Dice Task (GDT) [34] – a task measuring decision-making under risk – was used in the Lithuanian population for the first time. This computerized gambling task involves guessing what number would appear in each of 18 rolls of a die. In contrast to popular gambling tasks (such as Iowa Gambling Task [35]) in which the rules for gains and losses are implicit, Game of Dice Task was developed to have explicit and stable rules. Explicit rules resemble real-life situations better, as decisions followed by reinforcement or punishment often depend on explicit probabilities, and therefore, strategic procedures and specific executive functions maintain substantial impact [34]. The participants were instructed to maximize their imaginary starting capital of 1000 Lt (Lithuanian litas) [~290 €], which is equal to the minimal monthly salary in Lithuania. Subjects were offered to choose either one or a combination of two (e.g., 1 2), three (e.g., 1 2 3), or four (e.g., 3 4 5 6) numbers. The gains and losses of each choice were associated with a probability of occurrence, amounting to 1000 Lt [~290 €], 500 Lt [~145 €], 200 Lt [~58 €], and 100 Lt [~29 €] respectively. The choices of one or two numbers (probability of winning being less than 50%) were considered as risky or disadvantageous, whereas the choices of three and four numbers (probability of winning being 50% and higher) were considered as non-risky or advantageous. Net score was calculated by subtracting the number of disadvantageous choices from the number of advantageous choices according to the equation: (number of choices of three numbers + four numbers) – (number of choices of one number + two numbers) [35]. Higher net score, therefore, signifies better performance on the task.

2.3. Statistical analysis

All analyses were performed using R version 3.1.0 (Copyright (C) 2014 The R Foundation for Statistical Computing). The chi-square test was used to determine the possible gender differences between the two groups. The Shapiro–Wilk normality test showed that values for age, education, VAS subjective pain score, HADS scores, different neuropsychological test outcomes, as well as mean frequency of each GDT alternative were distributed non-parametrically in either one of the two groups. Therefore, the Mann–Whitney–Wilcoxon test was employed to test for any between-group difference.

Stroop color-word interference represented response inhibition. Set shifting was represented by TMT part B – time taken to join numbers and letter trail in sequence. Finally, complex executive function corresponded to risky decision-making, which was assessed with the Game of Dice Task net score (safe minus risky decisions) [34]. Scores were adjusted so that higher values always represent better performance. Kendall tau rank correlations were calculated between cognitive domains and different pain parameters. Significance was set at $P < 0.05$.

3. Results

3.1. Pain parameters

The average pain duration in CLBP group was 91 months (SD, 159 months) and their reported current pain intensity on average was 56 out of 100 on VAS scale (SD, 24). The sensory pain component was more pronounced than the affective, as measured by the Lithuanian Pakula Pain Questionnaire (37.3 and 28.0, respectively). Nine subjects qualified for fibromyalgia in TPE (11 or more painful tender points) on average having 6.9 tender points (Table 1).

3.2. Educational and psychological assessment

There was no significant difference in total years of education between groups. CLBP patients had significantly higher HADS anxiety scores and evaluated their health state significantly worse comparing to CG. Three patients met depression criteria and another three qualified for anxiety (a score of 11 or more for each) according to the HADS. None of the controls scored within the clinical depression or anxiety range.

3.3. Neuropsychological tests and Game of Dice Task

3.3.1. Between-group analysis

Patients did not score significantly worse in any examined neuropsychological functions (Table 2). GDT performance showed no significant difference in net score (number of safe minus risky decisions) or mean frequencies of each alternative chosen.

The performance on Trail Making Test part A and B in the control group was lower than expected when considering the normative data. This was most likely due to participants having been asked not only to draw a line connecting the dots with numbers and letters of increasing order, but also to encircle them, amounting to a longer time-to-completion.

3.3.2. Correlations between cognitive domains and different pain parameters

Pain duration, its intensity at the moment of examination, and average as well as worst intensity in the previous week did not correlate significantly with any of the three cognitive domains (Table 3). The only significant inverse correlation was between response inhibition and number of tender points, showing that subjects with better response inhibition had fewer tender

Table 2 – Results of the neuropsychological test battery.

Test	CLBP patients	CG	P
Victoria Stroop Test, s	(n = 28)	(n = 30)	
Color naming	17.6 (5.0)	16.3 (4.5)	0.426
Word naming	21.9 (6.1)	19.4 (6.2)	0.141
Interference	37.4 (12.6)	35 (17.6)	0.161
Interference – color naming	19.8 (11.5)	18.7 (15.7)	0.216
Trail Making Test, s	n = 27	n = 28	
TMT part A	73 (44.7)	66.6 (23.3)	0.973
TMT part B	124 (52.5)	112.2 (41.0)	0.573
Game of Dice Task	n = 26	n = 27	
Net score (safe minus risky decisions)	−8.6 (10.4)	−7.5 (11.9)	0.675
	n = 17	n = 20	
Net score (safe minus risky decisions) without persevered	−3.6 (9.7)	−5.6 (11)	0.444

Values are mean (standard deviation) unless otherwise stated.
CLBP, chronic lower back pain; CG, control group.

Table 3 – Kendall tau rank correlation coefficients between cognitive domains and pain parameters in chronic lower back pain patients.

	Response inhibition	Complex executive function	Set shifting
Pain duration	0.121	0.123	−0.034
Current pain	−0.059	−0.089	−0.109
Average pain last week	−0.202	−0.281	−0.154
Worst pain last week	0.005	−0.038	−0.122
Affective component	−0.161	−0.111	−0.124
Sensory component	−0.262	−0.134	−0.043
Tender points	−0.472[†]	−0.159	−0.067
HADS anxiety score	−0.103	0.100	−0.044
HADS depression score	0.025	−0.064	0.038

Higher values represent stronger pain, higher affective and sensory score, more tender points and better performance in cognitive domains, respectively.
HADS, Hospital Anxiety and Depression Scale.
[†] $P < 0.001$.

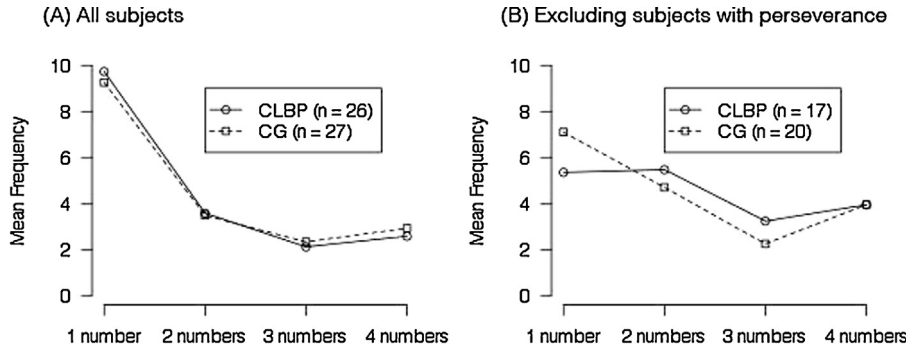

Figure – Game of Dice Task performance. Mean frequency of every alternative chosen. "1 number" and "2 numbers" refer to risky choices, whereas "3 numbers" and "4 numbers" are safe alternatives. Perseverance is defined as having chosen only one particular GDT alternative for all 18 consecutive times. CLBP, chronic lower back pain; CG, control group; GDT, game of dice task.

points. Similar results were found even if subjects meeting HADS depression and anxiety criteria were excluded.

Neither of the cognitive domains correlated with pain's affective and sensory component, and HADS depression and anxiety scores.

3.3.3. *Side findings*

Since GDT was performed in a Lithuanian population for the first time, an unexpected finding was observed in the risk-taking pattern of healthy volunteers: CG seemed to favor risky decisions (Figure A). Even though nine CLBP patients and seven healthy volunteers showed perseverance, choosing only one of the four GDT alternatives for all 18 consecutive times, a similar tendency prevailed after exclusion of these subjects from statistical analysis (Figure B).

4. Discussion

The results of our study showed that compared to control subjects, chronic lower back pain patients aged 49–69 years did not statistically significantly differ in any of the three cognitive domains – response inhibition, set shifting, and complex executive function – when matched for age, gender and education. Nevertheless, it should be noted that although statistical significance was not reached, it took longer for CLBP patients to complete all of the executive tasks. According to a recent systematic review and meta-analysis, small to moderate impairments were found in people with chronic pain, across all three cognitive domains – a result, which, however, was not obvious in discrete smaller samples [20]. This could be the case in our study as well.

Another review of clinical and preclinical research on the effect of pain on cognitive functions concluded that clinical studies provide a strong basis for the theory that cognitive functions are impaired in chronic pain patients [1]. However, there is no obvious common pattern between studies as deficits were often observed in some cognitive domains but not in others.

There are also some studies that report no association between chronic pain and impaired executive function [1] or even a positive one in a subset of older adults [24,25]. Some researchers propose that this inconsistency might be due to age having a moderating role in relationship between pain and cognition [25]. They propose two possible explanations: at an older age factors that cause natural age-related cognitive decline may interfere with a simple relationship between pain and cognition. Alternatively, this might also be due to an age-related reduced integrity of a shared neural substrate. To our knowledge, five previous studies involve patients with one standard deviation of their mean age above fifty years and produce contradictory results: two find negative [22,17], whereas the rest find no or even a positive correlation between pain intensity and TMT part B (and TMT part B ratio) score [24,25,36]. We speculate that due to the high mean age of participants in our study (59.6 ± 6.0 years), age might have had a moderating role in relationship between pain and cognition. Additional research is needed to prove this point, and we believe that more mechanisms should be taken into consideration.

The study design (i.e., groups of mixed pain conditions, different pain patterns, difference in education, big age range) may also play a major role. Different compositions of possible mechanisms include altered chemistry and receptor availability [37,38], disrupted default mode resting state [4,39], division of limited resources in discrete brain regions [6], changes in reward/aversion system [12,40–42], neurodegeneration [7,38], different pain pattern [1], psychological disturbances [9,37], co-morbidities [8,43] and effects of medication [44–47]. Not all of these mechanisms are direct and immediate. They are also difficult to measure. Nevertheless, they may account in part for the irregular pattern of cognitive function impairment.

In our study pain duration did not correlate significantly with any of the cognitive domains. It is noteworthy that pain duration was indicated by the patient, rather than acquired from medical documentation. Therefore, this measure was prone to approximation, especially in cases when pain duration amounted for multiple years. This may have prevented significant correlation. Moreover, no significant correlation was found between pain measurements and both executive and non-executive tasks (TMT part A, Stroop color naming and Stroop word naming). Nevertheless, a negative tendency was observed with almost all of the pain parameters, although the only significant inverse correlation was between

response inhibition and number of tender points. This may indicate that objective pain measurements (in this case testing with a dolorimeter) may have a greater sensitivity comparing pain perception across different subjects. However, a different study design is required to confirm this point.

In our sample complex executive function (represented by risky decision-making) correlated significantly with response inhibition, but correlation with set shifting did not reach statistical significance. It is known that augmented central processing of pain in diffuse pain conditions may be related to reduced reward/aversion signaling [48]. As we found no significant difference between the groups in measured neuropsychological functions, we hypothesize that risky decision-making might be influenced more by disordered attention modulation or other dysfunction of reward/aversion circuitry rather than be due to a primary dysfunction of prefrontal cortex. However, a different study design is needed to prove this point as well as to determine if this is the result of the current sample or more representative of the larger population.

The strengths of our study are that we investigated a homogeneous group of participants within a narrow age range (49–69 years), specific pathology (only CLBP patients) and its timeframe (>6 months of pain), having been matched for age, gender and education with healthy controls. The HADS and the Pakula Pain Questionnaire were employed to account for the influence of pain affective components on the findings. Ample quantitative as well as qualitative pain parameters were used to test for correlation and results did not change even if subjects meeting HADS depression and anxiety criteria were excluded.

Some limitations include a small sample size, because of which some of the observed trends may not have reached statistical significance. In addition to this, the control group did not complete a battery of neuropsychological tests in order to exclude mild cognitive impairment. Nor did control group complete pain questionnaires, as no reported pain was an inclusion criteria for this group. Although GDT instructions were adapted with two-directional translation and corrected for cultural differences, a very high number of participants showed perseverance (nine CLBP patients and seven healthy volunteers), choosing only one of the four alternatives for all 18 consecutive times. Since perseverance was observed in both groups, this may indicate that translational aspects could have played a role. Nevertheless, the pattern of risky decision-making remains even after exclusion of these subjects from statistical analysis. Moreover, a cultural feature of low motivation and effort to succeed is possible. Attentional aspect might have also been influenced, because the rules of computerized GDT have been read out loud and computer interaction was assisted by the investigators due to technophobia, prevalent amongst older individuals. Additionally, in the Trail Making Test, subjects were asked not only to connect the dots, but also to encircle them. This could explain a longer than expected time-to-completion [33] due to a simple mistake which was only noticed after a significant sample size had been achieved. However, the conditions were similar for all subjects and we believe that Set Shifting could still be compared between the two groups.

Future research directions include testing executive function in other pain conditions in larger homogeneous samples, as opposed to mixed pain groups. The relation between cognitive function and daily function (e.g., activities of daily living, work, and/or social independence) in this population in addition to more subjective pain measures could be investigated. Moreover, normative data for Game of Dice Task should be obtained in Lithuania to draw further conclusions about the risky decision-making pattern in Lithuania. Also, the role of emotional dysregulation and reward processing in impaired decision-making situations should be further clarified. Parameters and tests for reward/aversion circuitry should be taken into account, when testing homogeneous groups for cognitive dysfunction. Moreover, patients with depression could be included in the sample as an additional comparison group, as executive dysfunction may co-vary with depression.

5. Conclusions

We found no statistically significant difference in response inhibition, set shifting and complex executive function between chronic lower back pain patients and healthy volunteers. However, a lack of common neuropsychological pattern among studies indicates the importance of additional research in homogeneous samples of patients with uniform pain characteristics. In, addition, a risky decision-making pattern found in the Lithuanian population may underscore the importance of cultural context when examining complex executive function. Further studies are needed to prove this point.

Conflict of interest

None to declare.

Authors' contributions

D.V. and K.P. designed the study. R.M. and D.V. collected the data and wrote the paper. R.M. was responsible for carrying out the statistical analysis. E.S. analyzed and interpreted the data. All authors discussed the results and commented on the manuscript.

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