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Cognitive reserve and well-being in migraine patients: a multidimensional approach to migraine assessment in an Italian tertiary headache center

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ABSTRACT
Background: Migraine is a painful neurological condition affecting emotional, cognitive, and daily life functioning. Cognitive reserve (CR) is a protective factor against neurological damage and deterioration, but its proxies have been under-investigated in migraine. The present cross-sectional study aims to investigate the relationship between CR and several self-reported health measures in migraine; and how these health measures differ between CR grades.
Methods: Data were collected from an Italian tertiary center between 2022 and 2023. One hundred and eighty eligible outpatients aged from 18 to 75 years were administered a protocol consisting of: the Migraine Disability Assessment; Brief Pain Inventory (BPI); Numeric Rating Scale; Short Form-36; Self-Rating Anxiety Scale; Self-rating Depression Scale (SDS). In addition, years of illness, frequency and intensity of migraine attacks, and Cognitive Reserve Index as a gradable measure of CR, were also collected. Spearman correlation and ANOVAs were performed, setting p significance at <0.05.
Results: A negative correlation between perceived pain intensity, attacks, and socio-behavioral proxies of CR emerged. Higher CR was also associated with fewer headache attacks (rs=-0.176; p=0.019). Lower intensity was found to be specifically related to leisure time (rs=-0.084; p=0.049). ANOVAs highlighted differences across graded CR levels in headache-related indices, including psychological and functional status (BPI-interference: F=4.302; p=0.026; SDS: F=3.887; p=0.033; enjoyment of life: F=3.672; p=0.043), also *post-hoc* confirmed.
Conclusions: Overall, our results suggest a link between CR levels and headache-related measures, emphasizing the importance of life-long coping strategies and healthy habits to decrease pain perception. In particular, individuals with low CR reporting higher levels of pain may benefit from integrated assessment and tailored treatment options to experience. Further studies may delve into the CR threshold hypothesis in the context of headache to identify high-risk categories of patients and foster their symptom management.

Key words: migraine, cognitive reserve, pain, functional impairment, cross-sectional, correlation model.

Introduction

Migraine is the most common neurological disease and directly affects more than one billion people worldwide (1), with an higher prevalence observed in women, compared to men (2). Although patients also often mention other signs, including dizziness and hearing loss, frequent headaches, with high level of pain, are its primary symptoms (3). Among the various painful pathologies, migraine is characterized by its chronic nature, albeit with episodic acute manifestation (4,5).

A recent review defined migraine as a neuronal network disorder (6), involving dysconnectivity across subcortical and cortical brain circuits that are important in head pain, including the prefrontal cortex, the anterior cingulate cortex, the insula, the trigeminal nervous system (7-9). Pain is a subjective perceptive phenomenon involving cognitive processing rather than a purely sensory phenomenon (10). According to this evolutionary conception of pain, pain processes require the interaction of brain areas involved in somatic sensation, emotion modulation, memory and cognitive processing, vegetative control, and motor behavior (11). These processes should also include inhibitory or facilitatory mechanisms for the control of ascending pain signals.

It is widely accepted that pain is modulated by cognition (12). There is a bi-directional relationship between cognition and pain (13). Following this new paradigm, the cognitive dimension results as a vital component of the subjective perception of pain requiring cognitive-evaluation, learning, recall of past experiences, and active decision making. Most clinical studies, focused on neurological disorders such as migraine, have found an impairment of cognitive abilities (14,15). This remarks the close connection between pain and cognitive functioning (16,17).

A comprehensive model for understanding migraine pain should include not only the extensively studied risk factors and brain injuries or disruptions, but also the protective factors (18). In this perspective, Cognitive Reserve (CR) could potentially play a crucial role.

CR involves the adaptability of cognitive processes that explains differential susceptibility to brain aging, pathology, or insult (19). It is a lifelong-improving cognitive resource, that can be determined by intellectual exercise throughout life, including educational success, marital status, constructive occupation, physical activity, and also late-life social participation (20). While it is widely accepted that pain can alter brain pathways, a higher level of CR preceding pain onset may have a neuroprotective effect (21).

Moreover, studies on chronic pain syndromes have shown a negative correlation between pain perception, anxiety, and other mental factors with CR (22,23), lending further support to the literature suggesting an integrated emotional-cognitive processing. In particular, a study conducted by Delgado and colleagues found that CR played a moderating role in the relationship between pain intensity and mental health (18), suggesting that CR may be a useful tool with a great potential in advancing the assessment and treatment of chronic pain. Indeed, the efficiency of brain networks is greater in individuals with high CR, and may act as a compensatory mechanism while coping with the disease (12).

As only a scarce literature recently addressed the role of CR in specific outpatient cohorts to understand pain and target preventive intervention, the present study aims to explore whether CR may play a role in pain perception in different forms of migraine, focusing on the relationship between CR, migraine pain, and further clinical-demographic variables.

Results

Sample characteristics. A total sample of 180 patients with migraine was included in the study. Participants were mostly women (n=141), with a mean age of 44.4±12.18 years, while men (n=39) had a mean age of 41.9±14.44 years. Among all participants, the average number of years of education was 11.6±3.56 years, whereas the mean of illness years was 16±12.77 years (**Table 1**).

The majority of patients received a diagnosis of migraine without aura (n=113), while a smaller number were diagnosed with chronic migraine (n=43). A minority of patients were diagnosed with migraine with aura (n=24) (**Table 1**).

The mean and standard deviation of the variables taken into account (**Table 2**) and how the CR of the sample is distributed according to both global CR subgroups (according to the 5 CR levels) and CR Index (CRI) subscores were calculated (**Table 3**).

Correlations between cognitive reserve and clinical-psychological variables. The correlation matrix, with Spearman's coefficient, showed a statistically significant correlation between the total and work CR and the number of attacks per month (rs: -0.176; p=0.019) (**Table 4**). Patients with higher global CR index and higher work CR level incur less in migraine attacks per month. Furthermore, correlation analyses indicated a significant association between CR related to leisure time and the perceived intensity of pain (rs: -0.084; p=0.049).

Table 1. Sample characteristics.

	N (%)	Mean	Standard deviation
Age			
Female	141 (78.33)	44.4	12.18
Male	39 (21.67)	41.9	14.44
Education		11.6	3.56
Years of illness		16.1	12.77
Diagnosis			
Migraine without aura	113 (62.8)		
Chronic migraine	43 (23.9)		
Migraine with aura	24 (13.3)		

Table 2. Mean and standard deviation of the variables taken into account.

Variable	Mean	Standard deviation
Attacks/month	8.79	7.50
CRIq	93.97	11.44
SAS	38.17	10.30
SDS	37.37	10.71
SF36 physical health	36.53	10.43
SF36 mental health	43.87	11.66
MIDAS	44.74	37.54
MAF	20.12	18.65
BPI intensity	4.05	2.75
BPI interference	3.06	2.86

CRIq, Cognitive Reserve Index questionnaire; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; SF36, Short-form Health Survey-36; MIDAS, Migraine Disability Assessment; MAF, Multidimensional Assessment of Fatigue; BPI, Brief Pain Inventory.

Table 3. Cognitive Reserve Index (CRI).

	N (%)	Mean	Standard deviation
CRI Global	180 (100)	94.1	11.4
Subgroup low	0	-	-
Subgroup medium-to-low	37 (20.6)	79,08	4,34
Subgroup medium	132 (73.4)	96,56	7,47
Subgroup medium-to-high	11 (6.1)	121,12	4,48
Subgroup high	0	-	-
CRI education	180 (100)	94.3	12.9
CRI working-activity	180 (100)	93.6	10.7
CRI leisure time	180 (100)	98.3	11.9

Differences in clinical-psychological outcomes with respect to cognitive reserve levels. The ANOVA allowed for comparisons between all the CR subgroups, excluding those with no numerosity (N=0), as per **Table 3**. Therefore, ANOVA between-group analyses referred to Medium-to-Low, Medium, and Medium-to-High global CR levels. Results showed a significant relationship between the CR index and various important variables related to migraine and their psychological well-being (**Table 5**).

Specifically, a significant association was observed between the CR index and the frequency of migraine attacks per month (F=3.408, p=0.049), suggesting that individuals with higher CR tend to experience fewer migraine episodes or result able to manage them more effectively. Furthermore, the analysis uncovered a noteworthy correlation between the CR index and levels of depression (F=3.887, p=0.033), suggesting that a higher CR may be associated with lower levels of depressive symptoms. In addition, the CR index displayed significant associations with pain interference in daily activities (F=4.302, p=0.026). In particular, the results showed the activities that are most influenced by CR are mood (F=3.705, p=0.041), sleep (F=3.599, p=0.043), social relationships (F=3.847, p=0.037), and pleasure in life (F=3.672, p=0.043). This may indicate that patients with a higher level of CR may be better able to cope with the pain associated with migraine attacks, thereby reducing the impact on their daily activities. Moreover, patients with a higher CR report a more positive overall mood, more satisfying social relationships, better sleep quality and greater enjoyment of life.

By conducting Games-Howell *post-hoc* corrections, significant differences emerged for some variables of interest, such as depression, and pain interference.

The study also revealed significant correlations between levels of CR and several relevant psychological variables. The most significant differences mainly concerned individuals with medium and medium-to-low levels of CR. Migraine patients with medium CR showed a significant tendency towards lower levels of depression (**Table 6**) and an increased sense of pleasure in life compared to those with medium-to-low levels of CR (**Table 7**). Additionally, they reported experiencing less pain interference in their daily activities than their counterparts with lower CR (**Table 8**).

Discussion

The present cross-sectional study aimed at examining CR in relation to different headache-related measures in a selected sample of migraine sufferers. Participants' recruitment from a tertiary headache center and their classification based on established diagnostic criteria (24) allows the translability of our findings to migraine outpatients referred for specialized care. Correlations and univariate analyses of variance were run using several clinical data (*i.e.,* pain intensity, pain-related interference and disability, mental and physical health, sleep, mood, and fatigue) to capture multiple dimensions of migraine, including psychological status and CR consisting of different life-long proxies (25).

Table 4. Spearman coefficient.

		CRIq global	CRI education	CRI work	CRI free-time
SAS	Spearman's Rho	-0.144	-0.117	-0.056	-0.102
	df	175	175	175	175
	p-value	0.56	0.120	0.460	0.176
SDS	Spearman's Rho	-0.139	-0.139	-0.105	-0.100
	df	175	175	175	175
	p-value	0.065	0.164	0.187	0.278
Illness years	Spearman's Rho	0.152*	0.250**	-0.074	0.056
	df	165	165	165	165
	p-value	0.50	0.001	0.340	0.475
Attacks/month	Spearman's Rho	-0.176*	-0.137	-0.169*	-0.134
	df	174	174	174	174
	p-value	0.019	0.070	0.025	0.076
MIDAS	Spearman's Rho	-0.007	-0.010	-0.019	-0.016
	df	169	169	169	169
	p-value	0.930	0.897	0.803	0.839
BPI intensity	Spearman's Rho	-0.132	-0.114	-0.096	-0.084*
	df	175	175	175	175
	p-value	0.079	0.132	0.205	0.049
BPI interference	Spearman's Rho	-0.068	-0.007	-0.100	-0.084
	df	175	175	175	175
	p-value	0.370	0.924	0.183	0.268
SF36 PH	Spearman's Rho	0.049	0.058	0.083	-0.011
	df	174	174	174	174
	p-value	0.517	0.447	0.276	0.881
SF36 MH	Spearman's Rho	0.108	0.097	0.067	0.051
	df	174	174	174	174
	p-value	0.153	0.201	0.374	0.498
MAF	Spearman's Rho	-0.056	-0.056	-0.050	-0.076
	df	173	173	173	173
	p-value	0.461	0.509	0.318	0.390

CRIq, Cognitive Reserve Index questionnaire; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; MIDAS, Migraine Disability Assessment; BPI, Brief Pain Inventory; SF36, Short-form Health Survey-36; MAF, Multidimensional Assessment of Fatigue.
*p<0.05; **p<0.01.

Table 5. One-way ANOVA (Welch).

	F	dfl1	dfl2	p
Illness years	3.051	2	30.3	0.062
Attacks/month	3.408	2	25.1	0.049*
SAS	1.599	2	26.0	0.221
SDS	3.887	2	27.1	0.033*
SF36 physical health	1.575	2	26.2	0.226
SF36 mental health	0.863	2	24.2	0.434
MIDAS	0.463	2	16.6	0.637
MAF	1.178	2	24.6	0.325
BPI intensity	1.885	2	22.6	0.175
BPI interference	4.302	2	22.0	0.026*
General activity	2.120	2	21.6	0.144
Mood	3.705	2	21.8	0.041*
Walking ability	3.232	2	21.6	0.059
Work	2.266	2	21.8	0.128
Relationships with other people	3.847	2	21.8	0.037*
Sleep	3.599	2	23.5	0.043*
Enjoyment of life	3.672	2	21.5	0.043*

SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; SF36, Short-form Health Survey-36; MIDAS, Migraine Disability Assessment; MAF, Multidimensional Assessment of Fatigue; BPI, Brief Pain Inventory.
*p<0.05.

Table 6. Games-Howell *post-hoc* test (Self-rating Depression Scale).

		Medium-to low	Medium	Medium-to-high
Medium-to-low	Mean difference	-	4.80	-0.00737
	p-value	-	0.038	1.0000
Medium	Mean difference		-	-4.81077
	p-value		-	0.193
Medium-to-high	Mean difference			-
	p-value			-

Table 7. Games-Howell post-hoc test (Enjoyment of life).

		Medium-to low	Medium	Medium-to-high
Medium-to-low	Mean difference	-	1.59	0.157
	p-value	-	0.039	0.991
Medium	Mean difference		-	-1.434
	p-value		-	0.426
Medium-to-high	Mean difference			-
	p-value			-

Table 8. Games-Howell post-hoc test (Brief Pain Inventory interference).

		Medium-to low	Medium	Medium-to-high
Medium-to-low	Mean difference	-	1.41	-0.462
	p-value	-	0.042	0.909
Medium	Mean difference		-	-1.875
	p-value		-	0.198
Medium-to-high	Mean difference			-
	p-value			-

Based on Spearman correlation, an association between years of experienced illness and CR was observed. However, the frequency of migraine attacks and their intensity were negatively associated with CR, notably leisure time. This could mean that people with higher reserve report fewer painful symptoms despite recognizing migraine chronicity. Given the close link between CR and lifestyle, stimulating or distracting coping strategies may foster long-term pain management. For instance, participation in distracting recreational and work activities, information seeking, and social support are used by cancer patients aimed at disease chronicity to curb post-surgery distress (26). Education is also associated with higher biopsychosocial outcomes and better illness perception (27,28). These mechanisms have been understudied in neurological or chronic pain conditions, and while it is true that information and supports increase illness awareness, it is equally true that subjective, emotionally triggering aspects may complicate the information seeking process (29). Within the migraine context, headache education may improve relapse frequency, despite being less effective than mindfulness in decreasing disability (30). Besides medical-pharmacological options, people with migraine tend to recur to social and lifestyle choices for daily pain management (31) that represent socio-behavioral proxies of CR (19,32,33). A balance between proactive and palliative strategies may thus enhance responses to migraine (34). Moreover, the flexible use of a multidomain index of CR (encompassing, *e.g.,* work and leisure activities) provides the possibility to exercise cognitive-functional skills over the life span, unlike crystallized reserve related to early education (27). As chronic pain may lead to social cognition deficits, these aspects should be assessed and monitored over time (23). The unpredictability of migraine can also challenge intimate and social relationships (4). Indeed, not surprisingly, we found in several migraine participants the presence of anxious-depressive symptoms being inversely associated with CR level. People with greater psychological distress typically show difficulties in social, work, functional aspects, impacting migraine experience.

The ANOVA performed showed significant differences between grades of CR in terms of perceived pain and its interference on life activities. *Post-hoc* analyses contributed to the investigation of the ways patients with different levels of CR express pain, their mood status, functioning, and enjoyment of life, and overall functioning. The most evident differences emerged between medium-to-low and medium levels of CR, suggesting a potential threshold effect, where individuals with lower CR levels may be more vulnerable to the impact of migraine symptoms. Despite the lack of research about cognitive connectivity and CR in clinical cohorts, preliminary results from a study on healthy aging found that cognitive depletion becomes more pronounced as people age, but the most evident cognitive differences were found in individuals with low CR (35). These findings lend support to the hypothesis of a potential overload of compensatory mechanisms in low CR, where also brain reserve may play a role in this process (36). Migraine is a manifold neurological disorder with fluctuating plasticity and abnormal cortical response, affecting sensory processing and executive dysfunctions, which may worsen with aging (7). Current research is advancing towards the validation of biomarkers to classify chronic migraine subtypes reflecting structural and functional brain changes (37). In view of the interplay between plasticity, brain reserve, and CR (19), it becomes critical to understand how CR proxies observed in migraine are related to information processing mechanisms involved in pain.

Consistent with our correlation findings, the ANOVA performed revealed that patients with migraine with medium CR reported significantly lower levels of depression and an increased sense of pleasure in life, as well as lower pain interference, compared to those with medium-to-low CR. Hence, also these results point to the need of promoting, especially in migraine patients, problem- and support-oriented coping strategies (14,38) that could prevent cognitive, emotional, and functional impairment.

Limitations. Despite being promising, these results require cautious interpretations as the present study adopts a cross-sectional design, with retrospective data acquisition and the absence of a healthy control group. The use of self-report tools may produce different responses based on educational level and social desirability. Moreover, given a total CR index analyzed, it should be noted that patients who reported being more involved in constructive activities at work or during their spare time, could have been engaged in these tasks due to lower symptoms. These aspects should be accounted for as our analyses do not involve the adoption of causal predictive models.

However, having included indices of functional impact of migraine, such as the MIDAS and BPI, in addition to pain frequency, intensity, and duration in years, the differences and associations explored can be useful to prevent potential misinterpretations of the CR proxies collected and analyzed. Future studies may delve into the predictive and/or mediating role of CR in headache-related impairment or the inclusion of longitudinal data that may orient both clinicians and researchers on the progression of symptoms and CR levels (notably, leisure activities) within the same outpatient cohort. The use of neuroimaging techniques can also contribute to a better understanding of plasticity and compensation mechanisms in groups of migraine sufferers with different levels of CR.

Conclusions

The present cross-sectional study sheds light on the intricate relationship between cognitive reserve (CR) and migraine outcomes. The univariate analyses and correlations performed highlight a link between CR levels and headache-related measures, including pain intensity, disability, and mental health. Lifestyle factors and coping strategies, such as engaging in stimulating activities and seeking social support, may have a positive influence on CR, consequently, migraine outcomes. In turn, the protective effect of CR may mitigate chronic migraine impact and related psychological distress. The hypothesis of a potential threshold effect, indicating that individuals with lower CR levels may be more vulnerable to the impact of migraine symptoms, warrants further research in this field to tailor interventions on individuals at higher risks for lifestyle impoverishment and more frequent or intense migraine attacks. Therefore, the main clinical implications of these results concern the integration of CR assessments into routine evaluations towards the identification of at-risk individuals. Also, the promotion of tailored approaches to CR enrichment covering the lifespan may help patients improve their pain management, treatment adherence, and overall quality of life.

Materials and Methods

Study design and subject. This was an observational, cross-sectional cohort study that has been conducted using data from a tertiary headache center, *i.e.,* the Complex Unit of Neurophysiopathology of the General University Hospital Policlinico of Bari (Italy). The subjects involved were patients who came in for a neurological examination and their enrolment lasted from April 2022 to May 2023.

The study included participants who were between 18 and 75 years of age and diagnosed with migraine without aura, migraine with aura or chronic migraine. Exclusion criteria consisted of patients being younger than 18 years or older than 75 years, being diagnosed with other headaches and neurological disorders other than migraine.

Before entering the study, all participants signed written informed consent, compliant with the WMA Helsinki Declaration. The study protocol and all the procedures involved were approved by the local Ethics Committee of the General Hospital of Bari.

Data collection. During the assessment, Neurologists with clinical experience in the field of headaches, collected remote and recent medical history. They used anamnestic information, along with data on the frequency and characteristics of headaches and the neurological examination, to diagnose migraine according to the criteria of the International Headache Society (24). In addition, each patient reported clinical information on the years of illness and the number of migraine attacks per month. The complete assessment included multidimensional measures.

The Migraine Disability Assessment (MIDAS) is a questionnaire to measure the impact headaches on people with migraine over the 3 months before compilation. The MIDAS disability grade was obtained directly from the score. Within clinical settings, a score of 0 to 5 corresponds to grade I (*i.e.,* little or no disability), 6 to 10 corresponds to grade II (*i.e.,* mild/infrequent disability), 11 to 20 is grade III (*i.e*., moderate disability), and a score of 21 or greater corresponds to grade IV (*i.e*., severe disability).

The Numeric Pain Rating Scale (NRS) is an 11-point unidimensional numerical scale. It was used to assess pain experienced by patients, who were asked to rate the intensity of their pain from 0 to 10, with 0 being *no pain at all* and 10 being *the worst pain imaginable* (39).

The assessment also included the Brief Pain Inventory (BPI), an instrument that measures the level of pain experienced by the patient in the last 24 hours and how much it has affected their functioning (40). The questionnaire contains items that report on the *sensory* dimension of pain, including its intensity, and the *reactive* dimension of pain, which refers to interference with daily functions.

The study investigated CR using the Cognitive Reserve Index Questionnaire (CRIq) (25). The CR of an individual is estimated by collecting information from their entire adult life deriving four indices: an index of total CR, an index of education, an index of work and an index of leisure time.

The CRIq includes some demographic data and 20 items grouped into three sections, education, working activity, and leisure time, each of which returns a subscore.

CRI-Education refers to years of education and training; CRI-Working Activity refers to occupational status, which can be classified based on the degree of intellectual involvement and responsibility; CRI-Leisure Time refers to constructive occupations carried out during spare time.

To yield CR levels, CRIq total raw scores may be graded as follows: less than 70 indicating low CR; 70-84 indicating medium-low CR; 85-114 corresponding to medium CR; 115-130 denoting medium-high CR; >130 referring to high CR.

Short-form Health Survey (SF-36), a 36-item questionnaire was used to assess the perception of quality of life. The questionnaire produced two indices, one for Physical Health and one for Mental Health score (PH and MH, respectively) (41).

The assessment also included the administration of the Multidimensional Assessment of Fatigue (MAF) scale, a self-administered questionnaire to measure self-reported fatigue (42).

Lastly, psychological measures of anxiety-depressive symptomatology were collected using the Self-rating Anxiety Scale – SAS (43) and the Self-rating Depression Scale – SDS (44). Each scale consists of a 20-item self-report Likert scale (from 1 to 4), aimed to measure anxiety and depression levels, yielding a total raw score from 20 to 80.

Statistical analysis. Jamovi version 2.3 was used for statistical analyses. The descriptive analyses examined the distribution of demographic, social and clinical data of the participants. The normality of the sample was checked using the Shapiro-Wilk test. For the continuous variables, Spearman coefficient (S) was used as a non-parametric test to explore the correlation between the CR index and the other variables. ANOVA was performed to assess the presence of significant differences in the clinical and psychological variables in different patient groups, we used the total CR index in its different levels (*i.e*., low; low-medium; medium; medium-high; high), as suggested by Nucci (27). In addition, Games-Howell *post-hoc* tests were employed to provide specific information on which groups were significantly different from each other. This allowed for a deeper understanding of the relationships between the variables studied. The significance threshold for all analyses was set at $p<0.05$.

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