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ARAŞTIRMA / RESEARCH

Cognitive flexibility among female migraine patients: case–control study

Kadın migren hastalarında bilişsel esneklik: vaka-kontrol çalışması

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Abstract

Purpose: The aim of this study was to determine if cognition is affected in female migraine sufferers by comparing cognitive domains with a healthy control group.
Materials and Methods: Fifty patients with migraine and 50 healthy controls (all female) were enrolled in this cross-sectional case–control study. The Beck Depression test, Beck Anxiety test, California Verbal Learning Test, Montreal Cognitive Assessment Scale, and Wisconsin Card Sorting Test (WCST) were performed in both groups.
Results: Using a multivariate logistic regression model of migraine, WCST non-perseverative error (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.028–2.568; $p = 0.03$), WCST percent of perseverative error (OR, 0.23; 95%CI, 0.071–0.786; $p = 0.01$), WCST perseverative response (OR, 4.55; 95%CI, 1.272–16.298; $p = 0.02$), no alcohol consumption (OR, 0.006; 95%CI, 0.000–0.943; $p = 0.04$), family history of hypertension (OR, 4.46; 95%CI, 1.114–17.915; $p = 0.03$), family history of migraine (OR, 4.028; 95%CI, 1.027–15.799; $p = 0.04$), and no family history of stroke (OR, 0.034; 95%CI, 0.003–0.448; $p = 0.01$) were significant factors
Conclusion: Among WCST scores, non-perseverative error provides insight into the patient's problem solving ability. Meanwhile, percent perseverative error and perseverative response scores provide insight into cognitive flexibility ability. Therefore, in our study group, patients with migraine show better problem solving and cognitive flexibility ability than the healthy control group.

Keywords:. Migraine, cognition, executive function, cognitive flexibility, problem solving

Öz

Amaç: Bu çalışmadaki amacımız kadın migren hastalarıyla sağlıklı kontrol grubun farklı kognitif becerilerini uygun nöropsikolojik testlerle kıyaslamak ve kadın migren hastalarında kognitif etkilenmenin eğer var ise, ne yönde olduğunu göstermektir.
Gereç ve Yöntem: Bu kesitsel vaka-kontrol çalışmasına elli kadın migren hastası ve elli sağlıklı kontrol kadın katılımcı dahil edilmiştir. Beck Depresyon testi, Beck Anksiyete testi, California Sözel Öğrenme Testi, Montreal Kognitif Değerlendirme Ölçeği ve Wisconsin Kard Eşleme Testi (WKET) her iki gruba uygulanan testlerdi.
Bulgular: WKET perseverative olmayan hata (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.028–2.568; $p = 0.03$), WKET perseveratif hata yüzdesi (OR, 0.23; 95%CI, 0.071–0.786; $p = 0.01$), WKET perseveratif tepki (OR, 4.55; 95%CI, 1.272–16.298; $p = 0.02$), alkol kullanmama (OR, 0.006; 95%CI, 0.000–0.943; $p = 0.04$), ailede hipertansiyon hikayesi (OR, 4.46; 95%CI, 1.114–17.915; $p = 0.03$), ailede migren hikayesi (OR, 4.028; 95%CI, 1.027–15.799; $p = 0.04$), and ailede inme hikayesi olmaması (OR, 0.034; 95%CI, 0.003–0.448; $p = 0.01$) migreni oluşturan multivaryat lojistik regresyon modelinde yer aldı.
Sonuç: WKET skorlarından perseveratif olmayan hata kişinin problem çözme becerisini gösterir. Perseveratif hata yüzdesi ve perseveratif tepki ise kişinin bilişsel esnekliğini yani değişken görevler karşısında devam ettirdiği beceriyi gösterir. Dolayısıyla çalışma grubumuzda kadın migren hastalarında sağlıklı kontrol gruba göre problem çözme yeteneği ve bilişsel esneklik kabiliyetinin daha üstün olduğu gösterildi.
Anahtar kelimeler: Migren, kognisyon, yürütücü işlevler, bilişsel esneklik, problem çözme

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INTRODUCTION

Migraine headache is one of the top-ten debilitating diseases worldwide, mostly affecting women[1,2]. Migraine has many known co-morbidities however, cognition in migraine is a controversial issue. Studies have shown that migraine patients show cognitive decline in subgroups of cognitive abilities. Specifically, studies have compared cognitive performance in patients with migraine and non-migraine headaches[3], migraine patients with healthy controls[4], and migraine with aura (MwA) and migraine without aura (MwoA)[5, 6]. Further, studies have been performed in a community setting[4,7], while others took place in a clinical setting[3, 8-10]. Contrarily, some studies have reported no cognitive decline in migraine patients[11-19] Among those, there were both cross-sectional[11,12,16-18] and longitudinal studies[13,15].

Interestingly, there are recent studies suggesting that migraine patients might have better cognition than the general healthy population. For example, Kalaydjian et al., [20] compared migraineurs with non-migraineurs and found that patients with MwA showed less temporal impairment on cognitive assessment when compared with non-migraineurs. Wen et al., used the Mini-Mental State Examination, 15-word learning test, letter–digit substitution test, Stroop test, verbal fluency test, and Purdue pegboard test to compare three different groups: non-migraineurs, migraineurs, or possible migraineurs. They showed better results in executive function and fine motor skills, especially in patients with MwA[21].

Baschi et al., compared visuospatial memory and learning between patients with MwoA and healthy controls. Participants with MwoA had apparent better skills in visuospatial memory and learning than healthy controls[22].

Because of these intriguing findings, we designed a study to compare interictal cognitive performance of women migraine patients with age-, sex-, and education-matched healthy volunteers. Participants with moderate or severe anxiety and depression were excluded. Then by performing various neuropsychological tests, we compared multiple aspects of executive function, namely, attention, concentration, working memory, problem solving, cognitive flexibility, verbal learning, verbal memory, short-term memory, visuospatial abilities, and language and time–place orientation in migraine patients and healthy controls.

MATERIAL AND METHODS

Subjects and study design

Fifty patients with migraine and 50 healthy controls (all female) were enrolled in this cross-sectional case–control study. The patients with migraine were examined at the Neurology outpatient service of Gebze Fatih General Hospital. Assessment of all subjects took place between December 2017 and May 2018. Healthy volunteers were age-, education-, and sex-matched, and were all staff of the same hospital.

Female participants aged 18–65 years old were included. In total, 100 patients were first recruited. Participants were screened for severe depression or severe anxiety according to Beck Depression and Beck Anxiety questionnaires, and were excluded if these diagnoses were made (n = 18).

According to ICHD-3 beta[23], patients with a headache count ≥ 15 days per month, which elaborated or was significantly aggravated during usage of painkillers for more than three months were eliminated due to the presence of probable medication overuse headache (MOH). Patients with headaches using non-steroid NSAIDs, aspirin, and acetaminophen for > 15 days per month, combination pain relievers, triptans, and opioids for > 10 days per month, or butalbital-containing compounds for more than four days per month were suspected of having MOH and were excluded. In total, 41 patients with migraine and 41 healthy subjects were included in the study group.

Informed consent was obtained from each participant included in this study. The study was performed in accordance with the Declaration of Helsinki and was validated by the Ethics Committee of Community Hospitals Association, Turkish Ministry of Health (location: Kocaeli, date: 11.02.2015, number: 2770).

Covariate assignment

A headache questionnaire was completed by all subjects. All were examined by an expert neurologist. Sociodemographic data contained information on age and education. Smoking status was categorized into three different groups: present smoker, non-smoker, and ex-smoker. Present smokers+ex-smokers and non-smokers were checked against each other.

Alcohol consumption was examined by considering drinking habits the preceding week. Patients' self-reports declared a family history of migraine and special headache features such as locus, interval, intensity, and aura. Headache intervals were recorded in years, relative mean headache prevalence per month was obtained for the last year, pain continuance was recorded in minutes, and general pain severity was recorded using a visual analog scale between 0 and 10. Accompanying symptoms such as photophobia, phonophobia, nausea, and vomiting were also recorded. Migraine diagnosis was determined according to the International Classification of Headache Disorders-3 beta (ICHD-3 beta) diagnostic criteria[23].

Family history of hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), obesity, stroke, and cardiac disease were obtained from patients' self-reports. Medication usage was recorded for treatment of migraine attacks (simple analgesics, triptans, ergot alkaloids, non-steroidal anti-inflammatory drugs [NSAIDs] [e.g., flurbiprofen, naproxen sodium, dexketoprofen trometamol], usage of anti-emetics [i.e., trimetobenzamide, metoclopramide, ondansetron], prophylactic treatments (beta-blockers, anti-depressants, calcium channel blockers, and anti-epileptics), and usage of medications for other reasons (including anti-hypertensive medication, anti-diabetic medication, and oral contraceptives). Endogenous migraine triggers were recorded including: physical exercise, mental stress, fasting < 12 hours, fasting > 12 hours, sleep deprivation, and menstruation. Similarly, exogenous migraine triggers were recorded. These included: exposure to sunlight, a noisy environment, cold exposure, hot exposure, change of weather conditions, traveling, washing of the cranial region, hair dryer exposure, smelling intense odors such as perfume, and ingestion of wine, chocolate, cheese, onions, spicy food, tea, and coffee.

Neuropsychological tests

All participants were first screened using the Beck Depression test and Beck Anxiety test, and participants who had moderate or severe depression or anxiety were excluded from the study. To assess verbal learning and memory of participants, the California Verbal Learning Test (CVLT) was performed. The Montreal Cognitive Assessment Scale (MoCA) was performed to obtain a general overview on different parameters of cognition (e.g., visual/spatial, cube copy, executive cognition, trail making test, clock draw test, naming task, immediate memory, attention, language, abstraction test, delayed recall, orientation task). The Wisconsin Card Sorting Test (WCST) was performed to examine problem solving, cognitive flexibility, and executive function. Validated Turkish versions of above mentioned neuropsychological tests were used in this study[24, 25, 26, 27, 28].

Wisconsin Card Sorting Test

The WCST is a generally used neuropsychological test that measures executive function in terms of concept design, planning and cognitive flexibility, visual spatial working memory, derivable reasoning, problem solving, and set shifting ability (either Milner or Heaton forms)[29,30,31].

In the Heaton form, the WCST comprises four key cards and 128 response cards with geometric figures that differ according to three comprehensive measures (color, form, or number). The assignment demands subjects to discover the accurate classification rule by trial and error and the examiner's guidance. Once the participant picks the correct rule, they should conserve this sorting principle across varying stimulus forms while disregarding the other (now inapplicable) stimulus dimensions. After ten consecutive accurate matches, the classification rule changes without admonitory, claiming a flexible replacement in set. The WCST is not time limited and sorting continues until all cards are sorted or a maximum of six accurate sorting bars has been achieved.

Although Heaton's correction standard attempts 16 distinct scores, our analysis was confined to variables shown in the literature to predominantly use a three-factor model of the WCST. This approach implies: percent perseverative error and perseverative response (cognitive flexibility), non-perseverative error (problem solving), and failure to maintain set (response maintenance)[32].

California Verbal Learning Test

The CVLT[33] is one of the most broadly used neuropsychological tests globally. It specially evaluates episodic verbal learning and memory[34]. The test accomplishes this by connecting memory problems with deteriorating accomplishment on specific assignments. It imposes encoding and recall and recognition during auditory–verbal presentation of a stimulus. The CVLT is a more accurate measure

of episodic memory compared with other verbal learning tests. In addition to evaluating how much a subject has learnt the verbal stimuli, it also determines which strategies are used and provides information on the types of errors. The CVLT indicates free and cued recall, serial position effects (including primacy and recency), semantic clustering, intrusions, interference, and recognition. The California Verbal Learning Test-II (CVLT-II) is an updated version of the original CVLT, which was standardized in 2000. There is also a latest version, the California Verbal Learning Test-III, which was released in 2017. Here, the original CVLT was used for our study.

Montreal Cognitive Assessment Scale

The MoCA is a broadly used screening test for diagnosing cognitive impairment[35]. It was first confirmed for evaluation of mild cognitive impairment, and has latterly been clinically adopted in many other contextures.

The MoCA test consists of one page and the total score is 30 points. It is undertaken in around 10 minutes. The MoCA assesses several cognitive domains, specifically, short-term memory recall task, visuospatial abilities, and multiple aspects of executive function, namely, attention, concentration, and working memory, language, and orientation to time and place. MoCA scores range between 0 and 30. A score of ≥ 26 is considered normal.

Statistical analysis

Qualitative variables were analyzed by Chi-square test and Fisher's exact test. Student's *t*-test for independent samples and Mann–Whitney *U* test were used to compare quantitative variables in the migraine and control groups. After descriptive analysis, variables with $P < 0.25$ were included in multivariate logistic regression analysis. The variables included in the multivariate logistic regression analysis were: WCST perseverative response, WCST categories achieved, WCST non-perseverative error, WCST % perseverative error, WCST failure to maintain set, smoking, alcohol usage, having DM, having HT, having HL, having obesity, having cardiac disease, family history of HT, family history of DM, family history of HL, family history of migraine, family history of stroke, family history of obesity, family history of cardiac disease, Beck Depression total score, Beck Anxiety total score, MoCA total score, CVLT response discrimination, CVLT tendency for response, CVLT perseveration, CVLT free recall, and CVLT cued recall.

Multivariate analysis was used to distinguish significant determinants for having migraine. Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 17.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. $p < 0.05$ was considered statistically significant.

RESULTS

Mean age and total years of education between the migraine and healthy control groups did not differ (Table 1). Chronic usage of medication ($p = 0.08$), usage of oral contraceptive ($p = 0.04$), having a diagnosis of HT ($p = 0.04$), and family history of HT ($p = 0.03$) were more common in the migraine group (Table 1). All WCST test parameters were the same between the migraine and control groups except for "complete categories" ($p = 0.006$) (Table 2). All CVLT subgroup parameters were the same between the two groups of participants (Table 2). Moreover, MoCA test total and subgroup scores were the same for the migraine and control groups. Beck Depression and Beck Anxiety scores were also the same between the migraine and control groups (Table 2).

Among migraineurs, photophobia was the most common symptom. An exogenous trigger was experienced by 92.5% of migraine patients (Table 3). Noise was the most common (64.3%) (Table 3). An endogenous trigger was noted by all patients. Menstruation was the most common trigger (92.9%), followed by mental stress (88.1%), and < 12 hours of hunger (88.1%) (Table 3).

In the multivariate logistic regression model of migraine, WCST non-perseverative error (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.028–2.568; $p = 0.03$), WCST percent of perseverative error (OR, 0.23; 95%CI, 0.071–0.786; $p = 0.01$), WCST perseverative response (OR, 4.55; 95%CI, 1.272–16.298; $p = 0.02$), no alcohol consumption (OR, 0.006; 95%CI, 0.000–0.943; $p = 0.04$), family history of HT (OR, 4.46; 95%CI, 1.114–17.915; $p = 0.03$), family history of migraine (OR, 4.028; 95%CI, 1.027–15.799; $p = 0.04$), and no family history of stroke (OR, 0.034; 95%CI, 0.003–0.448; $p = 0.01$) were significant factors (Table 4). In correlation analysis of headache characteristics and WCST scores, there was positive correlation between total years with migraine and WCST non-perseverative error (Table 5).

Table 1. Clinical characteristics of the migraine and control groups

	Migraine $n = 41$	Control $n = 41$	p value
Age, mean (SD)	36.3 (7.1)	35.4 (7.0)	0.70
Years of education, mean (SD)	13.4 (2.3)	13.7 (2.0)	0.68
Chronic usage of medication, *n* (%)	13 (31)	1 (2.4)	0.008
Usage of oral contraceptive, *n* (%)	4 (9.5)	0	0.04
Cigarette smoking, *n* (%)	14 (33.3)	12 (29.3)	0.63
Alcohol, *n* (%)	5 (11.9)	35 (85.4)	1
HT, *n* (%)	4 (9.5)	0	0.04
DM, *n* (%)	2 (4.8)	0	0.15
HL, *n* (%)	1 (2.4)	1 (2.4)	1
Obesity, *n* (%)	1 (2.4)	1 (2.4)	0.31
Hx of cardiac disease, *n* (%)	1 (2.4)	0	-
Family hx of HT, *n* (%)	31 (73.8)	18 (43.9)	0.003
Family hx of DM, *n* (%)	19 (45.2)	16 (39)	0.50
Family hx of HL, *n* (%)	19 (45.2)	14 (34.1)	0.26
Family hx of migraine, *n* (%)	21 (50)	10 (24.4)	0.12
Family hx of stroke, *n* (%)	3 (7.1)	6 (14.6)	0.28
Family hx of obesity, *n* (%)	3 (7.1)	3 (7.3)	1
Family hx of cardiac disease, *n* (%)	23 (54.8)	18 (43.9)	0.26

$p < 0.05$, level of significance. SD: standard deviation, HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, hx: history.

Table 2. Wisconsin Card Sorting Test, California Verbal Learning Test, and Montreal Cognitive Assessment Scale test scores for the migraine and control groups

	Migraine $n = 41$	Control $n = 41$	p value
Age, mean (SD)	36.3 (7.1)	35.4 (7.0)	0.70
Years of education, mean (SD)	13.4 (2.3)	13.7 (2.0)	0.68
WCST total trial, mean (SD)	76.4 (10.7)	82.7 (21.5)	0.84
WCST total errors, mean (SD)	11.1 (4.1)	17.3 (17.5)	0.43
WCST total corrects, mean (SD)	65.3 (7.4)	65.3 (8.5)	0.64
WCST categories completed, mean (SD)	6.0 (0)	5.4 (1.3)	0.006
WCST Perseverative response, mean (SD)	2.2 (3.5)	8.3 (16.9)	0.14
WCST Perseverative error, mean (SD)	2.0 (3.4)	8.9 (17.8)	0.14
WCST Non-perseverative error, mean (SD)	9.0 (1.6)	8.9 (3.8)	0.17
WCST Percent perseverative error, mean (SD)	2.3 (3.4)	7.6 (13.7)	0.14
WCST Trials to 1st category, mean (SD)	13.3 (4.8)	17.5 (15.0)	0.74
WCST Concept level response, mean (SD)	63.1 (6.1)	60.0 (12.0)	0.10
WCST % Concept level response, mean (SD)	83.1 (4.7)	75.0 (21.8)	0.53
WCST Failure-to-maintain-set, mean (SD)	0.3 (0.7)	0.3 (0.7)	0.89
WCST Learning to learn, mean (SD)	-0.2 (2.1)	0.4 (2.9)	0.38
CVLT response discrimination, mean (SD)	88.9 (5.6)	89.1 (5.9)	0.92
CVLT tendency for response, mean (SD)	-0.2 (0.4)	-0.1 (0.3)	0.52
CVLT perseveration, mean (SD)	3.8 (3.1)	4.1 (3.1)	0.58
CVLT free recall, mean (SD)	2.7 (2.7)	3.0 (3.7)	0.86
CVLT cued recall, mean (SD)	0.9 (1.1)	1.0 (1.9)	0.71
Beck depression total, mean (SD)	10.0 (7.5)	10.1 (7.6)	0.90
Beck anxiety total, mean (SD)	8.0 (6.6)	8.6 (8.6)	0.79
MoCA total score, mean (SD)	24.8 (2.6)	25.1 (2.6)	0.61
MoCA visual-spatial, mean (SD)	3.8 (0.9)	3.9 (0.8)	0.98
MoCA naming, mean (SD)	2.7 (0.5)	2.6 (0.4)	0.52
MoCA memory, mean (SD)	0.0 (0)	0.0 (0)	1.0
MoCA attention, mean (SD)	4.9 (1.3)	4.8 (1.3)	0.81

MoCA language, mean (SD)	2.6 (0.5)	2.6 (0.5)	0.81
MoCA abstract, mean (SD)	1.6 (0.4)	1.6 (0.5)	0.75
MoCA delayed recall, mean (SD)	3.1 (1.2)	3.4 (1.05)	0.16
MoCA orientation, mean (SD)	5.9 (0.1)	5.9 (0.1)	1.0

$p < 0.05$, level of significance. HT: hypertension, SD: standard deviation, WCST: Wisconsin Card Sorting Test, CVLT: California Verbal Learning Test, MoCA: Montreal Cognitive Assessment Scale.

Table 3. Migraine characteristics, triggers, and treatment features for the migraine group

Variables	**Migraine** ***n*** **= 41**
Severity of pain, mean (SD)	7.1 (1.4)
Monthly frequency of pain, mean (SD)	5.5 (4.7)
Duration of pain during attack, mean (SD)	22.2 (20.4)
Years with migraine, mean (SD)	13.1 (7.5)
Localization unilateral, *n* (%)	31 (73)
Localization bilateral, *n* (%)	10 (23.8)
Nausea, *n* (%)	33 (78.6)
Vomiting, *n* (%)	13 (31)
Photophobia, *n* (%)	40 (95.2)
Phonophobia, *n* (%)	37 (88.1)
Exogenous trigger, *n* (%)	39 (92.9)
Sun, *n* (%)	24 (57.1)
Noise, *n* (%)	27 (64.3)
Cold, *n* (%)	6 (14.3)
Hot, *n* (%)	9 (21.4)
Weather changes, *n* (%)	10 (23.8)
Travelling, *n* (%)	9 (21.4)
Head wash, *n* (%)	4 (9.5)
Blow dry, *n* (%)	2 (4.8)
Perfume, *n* (%)	14 (33.3)
Chocolate, *n* (%)	4 (9.5)
Wine, *n* (%)	2 (4.8)
Cheese, *n* (%)	4 (9.5)
Onion, *n* (%)	2 (4.8)
Spicy food, *n* (%)	1 (2.4)
Tea, *n* (%)	1 (2.4)
Coffee, *n* (%)	7 (16.7)
Endogenous triggers, *n* (%)	41 (100)
Physical stress, *n* (%)	24 (57.1)
Mental stress, *n* (%)	37 (88.1)
Hunger < 12 hours, *n* (%)	37 (88.1)
Hunger > 12 hours, *n* (%)	31 (73.8)
Deprivation of sleep, *n* (%)	29 (69)
Menstruation, *n* (%)	39 (92.9)
Allodynia, *n* (%)	22 (52.4)
Static, *n* (%)	22 (52.4)
Dynamic, *n* (%)	18 (42.9)
Increased hotness, *n* (%)	15 (35.7)
Increased coldness, *n* (%)	4 (9.5)
Cephalic, *n* (%)	22 (52.4)
Extracephalic, *n* (%)	10 (23.8)
Migraine without aura, *n* (%)	38 (95.2)
Migraine with aura, *n* (%)	3 (7.1)
Pure menstrual migraine, *n* (%)	3 (7.1)
Menstrual migraine, *n* (%)	35 (83.3)
Chronic migraine, *n* (%)	3 (7.1)

Medical treatment during attack, *n* (%)	39 (92.9)
Simple analgesic, *n* (%)	13 (31)
NSAID, *n* (%)	34 (81)
Anti-emetic, *n* (%)	13 (31)
Tryptan, *n* (%)	25 (59.5)
Effectiveness of medical treatment during attack, *n* (%)	30 (71.4)
Prophylactic treatment, *n* (%)	7 (16.7)
Beta blockers, *n* (%)	1 (2.4)
Antidepressant treatment, *n* (%)	1 (2.4)
Antiepileptic treatment, *n* (%)	3 (7.1)
Calcium channel blockers, *n* (%)	3 (7.1)

p < 0.05, level of significance. SD: standard deviation, NSAID: non-steroidal anti-inflammatory drugs.

Table 4. Results of multivariate logistic regression analysis for a model of migraine

Independent variables	Parameter estimation value	Level of significance	Exp (B)	95% Lower confidence limit	95% Upper confidence limit
Non-perseverative error	0.48	0.03	1.62	1.028	2.568
Percent perseverative error	1.44	0.01	0.23	0.071	0.786
Perseverative response	1.51	0.02	4.55	1.272	16.298
Alcohol consumption	-5.13	0.04	0.006	0.000	0.943
Family history hypertension	1.49	0.03	4.46	1.114	17.915
Family history migraine	1.39	0.04	4.028	1.027	15.799
Family history stroke	-3.39	0.01	0.034	0.003	0.448
Constant	-195.095	0.99	0.000		

$p < 0.05$, level of significance.

Table 5. Correlation analysis of Wisconsin Card Sorting Test scores and headache characteristics in the migraine group (n = 41).

	WCST Perseverative response	WCST Perseverative error	WCST Non-perseverative error	WCST Percent perseverative error
Severity of pain	0.106	0.202	0.254	0.129
Monthly frequency of pain	0.487	0.598	0.455	0.393
Duration of pain during attack	1.000	0.898	0.680	0.873
Years with migraine	0.713	0.822	0.000*	0.588

$p < 0.05$, level of significance. WCST: Wisconsin Card Sorting Test.

DISCUSSION

Our results show that women migraine patients have better WCST results, especially in non-perseverative error, percent perseverative error, and perseverative response. Among the WCST scores, non-perseverative error provides insight into problem solving ability of the patient. Percent perseverative error and perseverative response scores provide insight into cognitive flexibility ability of the patient[32]. Therefore, in our study group, between age-, sex-, and education-matched individuals, patients with migraine had better problem solving and cognitive flexibility ability than the healthy control group.

Cognitive flexibility is a concept that is an arising feature of effective executive function. It is frequently evaluated in the clinic using set task switching behavioral batteries. An assignment can be described

as a tryout with one set of directives that require accomplished consummation. In task switching, subjects must interchange between assignments with distinct directives when given an actuator[36, 37].

In continually unstable surroundings, subjects must first distinguish how the environment has been altered by steering attention to flow-through components. Then, by discovering that a former tactic is not applicable in the latest setting, subjects must restrain former reactions and reconstitute a novel tactic. Subjects pass in data and exploit it concurrently to resiliently shift reactions from one scheme to another. Cognitive flexibility is not purely an aggregate of administering diverse executive functions, but also bears shifting or reframing of one's reaction series to the new target.

Current meta-analyses of studies that concentrate on cognitive flexibility in healthy subjects have discovered a diversified mesh of frontoparietal regions involved in flexible switching, including the anterior cingulate, right anterior insula, premotor cortex, inferior and superior parietal cortices, inferior temporal cortex, occipital cortex, caudate, and thalamus[38,39]. Continual work is trying to conclude how these brain areas affect each other to create a compatible network that renders cognitive flexibility.

Like our study, other studies have found that migraine patients perform better than healthy subjects in cognition reliant on different brain areas. Wen *et al*., conducted a population-based study in 2016 that included a geriatric population[21]. They found that subjects with MwA had better general cognition compared with individuals without migraine. This difference was driven by better performance in executive function and fine motor skill domains. They used the Stroop color–word interference and verbal fluency tests, which are time-dependent tests reflecting processing speed or attention (which are both components of executive function).

Kalaydjian *et al*., conducted a longitudinal study involving 204 migraine patients and 1,244 non-migraineurs[20]. They found that patients with MwA showed less deterioration on cognitive assessments over a 12 year period compared with non-migraineurs. Our study was cross-sectional, therefore we were unable to examine temporal changes in patient performance. Also, we examined general cognition with MoCA but did not detect any differences between the migraine and healthy control groups. Additionally, mean age in our study group was younger than their sample group (mean age = 36.3 years).

Another study by Baschi *et al*., examined cognitive skills for visuospatial memory and learning between patients with MwoA (n = 21) and healthy controls (n = 21). Subjects with MwoA showed higher scores than healthy controls in tests evaluating both short- and long-term visuospatial memory[22]. The authors' suggested that occipito–parietal hyperexcitability, which is a characteristic feature of the migraine brain, might possibly explain these results. In this study, we did not perform any specially designed test to analyze visuospatial memory. However, in the visual/spatial score of the MoCA test, we did not detect any difference between the two groups of patients with migraine and healthy controls.

Despite the presence of studies showing that migraine patients show better performances on different cognitive subdomains, there are studies that demonstrate cognition is unaffected in migraine and further studies that show that cognitive abilities in migraine patients might be disrupted. These are summarized as follows.

Martins *et al*., examined interictal performance of patients with migraine and non-migraine headaches in cognitive tasks, and compared their results with healthy controls[3]. They enrolled adults aged 50 or above, who were administered a neurobehavioral battery that evaluated various executive measures. They found that cognitive decline was not specific to migraine but might be associated with headache because the presence of headaches was related to worsened performance on a few measures of executive function (specifically, sustained attention and processing speed). These results do not correlate with our results, but the age difference between our patients and their study group should be considered (mean age in our group is 36.3 years).

Furthermore, in a review by de Araujo *et al*., results of 23 studies concentrated on migraine and cognition were compared[40]. Fifteen reported cognitive decline on neuropsychological tests in migraine patients, especially tests of memory, attention, and information processing speed were abnormal. They argued that migraine comorbidities, such as depression and anxiety, may have impacted cognitive performance. Also, the usage of prophylactic drugs (such as topiramate) was suggested as a potential confounder. Because of these studies, we performed

Beck Depression and Beck Anxiety tests to screen for the presence of these disorders, and excluded individuals with moderate or severe depression or anxiety. Additionally, we recorded the usage of all prophylactic medications and observed that among our 41 migraine patients, seven were using prophylactic treatment and only three were using topiramate.

In 2015 Gil-Gouveia *et al.*, performed another systematic review on migraine and cognition[41]. This time, the reviewed studies had assessed cognition during the migraine attack, with five studies eligible. All of these studies documented a sub-domain of reversible cognitive impairment during the migraine attack. The most reported impact was on executive function, but the difference in evaluating test and small sample sizes prevented any definite conclusions. Comparatively, these study designs were completely different from our study because they involved assessment of cognition during the migraine attack.

Lo Buono *et al.*, conducted a study evaluating cognitive function and psychological symptoms in migraine patients, with and without aura[5]. They found that patients having MwoA showed decreased success in semantic verbal fluency, delayed memory, and set-shifting, while MwA showed a significant difference in delayed memory and set-shifting. They did not find any correlation between cognitive function and mood. In our study group, among 41 migraine patients there were only three patients with MwA, therefore we could not make any group comparisons.

Tunç *et al.*, examined cognitive performance of migraine patients with and without aura, and examined correlation of white matter hyperintensities and psychological symptoms with cognitive test scores[6]. They concluded that MwA may be associated with lower cognitive performance (lower scores in subscales regarding visuospatial/executive functions: naming, memory, attention, and abstraction), which correlated with depression and anxiety but not white matter hyperintensities. In our study we did not perform any brain imaging of our patients, therefore we could not compare cognitive scores with white matter hyperintensities.

Pellegrino *et al.*, determined whether migraine is associated with cognitive performance among participants of the Brazilian Longitudinal Study of Adult Health, ELSA-Brasil. They measured cognitive performance within the consortium to establish a registry for the Alzheimer's Disease word list memory test, semantic fluency test, and Trail Making Test version B. They concluded that all migraine headaches were significantly and independently associated with a poorer cognitive performance[7].

Alternatively, some studies were unable to find any cognitive changes in migraine patients. Using a population-based large sample, Gaist *et al.*, (2005) examined cognitive status of middle-aged twins with migraines and compared them with headache-free twins. Mean values in all cognitive tests were similar between the two groups. They concluded that a diagnosis of migraine was not associated with cognitive decline in middle-aged individuals[11].

Baars *et al.*, examined migraine patients and healthy controls enrolled in the Maastricht Aging Study (MAAS). They administered cognitive tests at baseline and after 6 years. They did not find any differences between the groups. Indeed, they did not find any evidence of migraines affecting cognition. Also, they did not find any negative or positive effect of migraine-related medication use on cognition. This study is especially valuable in terms of its longitudinal design[13]. Our study is cross-sectional, and assesses a relatively younger patient group.

Rist *et al.*, highlighted the importance of longitudinal studies regarding the association between cognitive decline and migraine. They particularly reviewed the results of longitudinal studies that used population-based samples. The results of the MAAS, Baltimore Epidemiologic Catchment Area Study (ECA), Epidemiology of Vascular Ageing Study (EVA), and Women's Health Study (WHS) were compared and evaluated. Results of MAAS, ECA, and EVA studies found that migraine was not associated with increased cognitive impairment over time, and might even show less decline in various particular tests[14].

Foti *et al.*, prepared a descriptive review on cognitive impairment in migraine patients[19]. Sixteen studies met the inclusion criteria. In most studies, cognitive deficits during the migraine attack were confirmed, but interictal cognitive state was uncertain. It was suggested that specific characteristics of migraine-like attack frequency should be added to the list of confounders while examining the cognitive state of migraineurs. In our study, correlation analysis between WCST score and headache characteristics (monthly frequency of pain, severity of pain, duration of pain during attack, years with migraine) was

performed. A positive correlation between years with migraine and WCST non-perseverative error was found. Therefore, it can be argued that compared with the healthy population, our sample of migraine patients have better cognitive flexibility and problem solving scores of WCST. Moreover, when migraine patients are compared between each other, the problem solving scores of patients having a longer history of migraine show a declining trend.

Finally, when it comes to the question of why migraine patients should have better cognitive flexibility and problem solving ability, this topic is up for discussion. Loehrer *et al*., compared cerebral blood flow in the interictal period between migraineurs and healthy controls, and showed that migraineurs in the attack-free period have increased total cerebral blood flow, especially basilar artery flow, compared with controls[41]. Therefore, although migraine is known to cause microvascular pathology (because of known associations with ischemic or hemorrhagic stroke), other evidence states that migraine brain might have better cerebral blood flow. This type of mechanism might increase certain subgroups of cognitive abilities in migraine patients. Further, a recent review demonstrated that migraineurs experience recurrent cognitive deterioration during the course of attacks but revert to pre-attack levels interictally[42].

In summary, compared with healthy individuals, cognitive abilities of migraine patients might be disrupted during attacks but this compromised function of brain structure might lead to compensatory neurovascular changes ensuring better cognition afterwards. Another study verifies similar results, establishing the absence of association between migraine and dementia risk[43].

Ultimately, in this relatively younger patient group of migraineurs, having this chronic and debilitating disease might encourage them to be more careful about their exogenous and endogenous triggers (such as eating habits, sleeping and exercise behavior, and medication use), which may lead them to have a "healthier" lifestyle that would support their cognitive abilities.

One limitation of our study, other than those mentioned, was the sample size of our study. Our results should be verified with a larger migraine population to compare different groups of migraine patients such as MwA and MwoA. Further, a broader neuropsychological battery involving visuospatial memory tests, and more detailed tests of attention and executive function would be recommended. The results of longitudinal studies comparing baselines and every 10 years of individuals would also provide more specific and valuable results.

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REFERENCES

1. Leonardi M, Raggi A. Burden of migraine: international perspectives. Neurol Sci. 2013;34:117–8.
2. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. Neurol Clin. 2009;27:321–34.
3. Martins IP, Gil-Gouveia R, Silva C, Maruta C, Oliveira AG. Migraine, headaches, and cognition. Headache. 2012;52:1471-82.
4. Mulder EJ, Linssen WH, Passchier J, Orlebeke JF, de Geus EJ. Interictal and postictal cognitive changes in migraine. Cephalalgia. 1999;19:557-65.
5. Lo Buono V, Bonanno L, Corallo F, Palmeri R, Allone C, Lo Presti R et al. Cognitive functions and psychological symptoms in migraine: a study on patients with and without aura. Int J Neurosci. 2019;129 :588-592.
6. Tunç A, Tekeşin AK, Güngen BD, Arda E. Cognitive performance in young and middle-aged adults with migraine: Investigating the correlation with white matter hyperintensities and psychological symptoms. Neurol Neurochir Pol. 2018;52:470-6.
7. Pellegrino BC, Goulart AC, Santos IS, Suemoto CK, Lotufo PA, Bensenor IJ. Migraine and cognitive function: Baseline findings from the Brazilian Longitudinal Study of Adult Health: ELSA-Brasil. Cephalalgia. 2018;38:1525-34.

8. D'Andrea G, Nertempi P, Milone FF, Joseph R, Cananzi AR. Personality and memory in childhood migraine. Cephalalgia. 1989;9:25–8.
9. Parisi P, Verrotti A, Paolino MC, Urbano A, Bernabucci M, Castaldo R et al. Headache and cognitive profile in children: a cross-sectional controlled study. J Headache Pain. 2010;11:45–51.
10. Moutran AR, Villa TR, Diaz LA, Noffs MH, Pinto MM, Gabbai AA, et al. Migraine and cognition in children: a controlled study. Arq Neuropsiquiatr. 2011;69:192–5.
11. Gaist D, Pedersen L, Madsen C, Tsiropoulos I, Bak S, Sindrup S, et al. Long-term effects of migraine on cognitive function: a population-based study of Danish twins. Neurology. 2005;64:600-7.
12. Pearson AJ, Chronicle EP, Maylor EA, Bruce LA. Cognitive function is not impaired in people with a long history of migraine: a blinded study. Cephalalgia. 2006;26:74–80.
13. Baars MA, van Boxtel MP, Jolles J. Migraine does not affect cognitive decline: results from the Maastricht aging study. Headache. 2010 50 176-84.
14. Rist PM, Kurth T. Migraine and cognitive decline: a topical review. Headache. 2013;53:589-98.
15. Rist PM, Dufouil C, Glymour MM, Tzourio C, Kurth T. Migraine and cognitive decline in the population-based EVA study. Cephalalgia. 2011; 31:1291–300.
16. Leijdekkers ML, Passchier J, Goudswaard P, Menges LJ, Orlebeke JF. Migraine patients cognitively impaired? Headache. 1990;30:352–8.
17. Jelicic M, van Boxtel MP, Houx PJ, Jolles J. Does migraine headache affect cognitive function in the elderly? Report from the Maastricht Aging Study (MAAS). Headache. 2000;40:715–9.
18. Palmer JE, Chronicle EP. Cognitive processing in migraine: a failure to find facilitation in patients with aura. Cephalalgia. 1998;18:125–32.
19. Foti M, Lo Buono V, Corallo F, Palmeri R, Bramanti P, Marino S. Neuropsychological assessment in migraine patients: a descriptive review on cognitive implications. Neurol Sci. 2017;38:553-62.
20. Kalaydjian A, Zandi PP, Swartz KL, Eaton WW, Lyketsos C. How migraines impact cognitive function: findings from the Baltimore ECA. Neurology. 2007;68:1417-24.
21. Wen K, Nguyen NT, Hofman A, Ikram MA, Franco OH. Migraine is associated with better cognition in the middle-aged and elderly: the Rotterdam Study. Eur J Neurol 2016;23:1510-6.
22. Baschi R, Monastero R, Cosentino G, Costa V, Giglia G, Fierro B, et al. Visuospatial learning is fostered in migraine: evidence by a neuropsychological study. Neurol Sci. 2019;40:2343-8
23. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808.
24. Ulusoy M, Sahin NH, Erkmen H. Turkish version of the beck anxiety inventory: psychometric properties. J Cogn Psychother. 1998;12:163-72.
25. Karakaş S, Eski R, Başar E. Türk Kültürü için Standardizasyonu Yapılmış Nöropsikolojik Testler Topluluğu: BİLNOT Bataryası. 32. Ulusal Nöroloji Kongresi Kitabı. Türk Nöroloji Dergisi ve Bakırköy Ruh ve Sinir Hastalıkları Hastanesi. 1996, İstanbul, Ufuk Mat.
26. Ozdilek, B. & Kenangil, G. Validation of the Turkish version of the Montreal Cognitive Assessment Scale (MoCA-TR) in patients with parkinson's disease. Clin Neuropsychol. 2014;28:333-43.
27. Karakaş S, Irak M, Kurt M, Erzengin ÖU. Wisconsin Kart Eşleme Testi ve Stroop Testi TBAG Formu: Ölçülen özellikler açısından karşılaştırmalı analiz. 3P Dergisi. 1999;7:179-92.
28. Karakaş S. Bilnot Bataryası El Kitabı: Nöropsikolojik Testler Için Araştırma Ve Geliştirme Çalışmaları. (2. baskı). Ankara, Eryılmaz Offset, 2004.
29. Milner B. Effect of different brain lesions on card sorting. Arch Neurol. 1963;9:100–10.
30. Heaton RK. Wisconsin Card Sorting Test Manual. Odessa, FL, Psychological Assessment Resources, 1981.
31. Heaton HK, Cheloune GJ, Tally JL, Kay GG, Curtiss G. Wisconsin Card Sorting Test Manual Revised and Expanded. Odessa, FL, Psychological Assessment Resources, 1993.
32. Greve KW, Stickle TR, Love JM, Bianchini KJ, Stanford MS. Latent structure of the Wisconsin Card Sorting Test: a confirmatory factor analysis. Arch Clin Neuropsychol. 2005;20:355–64.
33. Delis, DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test: Adult Version: Manual. San Antonio, Psychological Corporation, 1987.
34. Elwood, RW. The California Verbal Learning Test: psychometric characteristics and clinical application. Neuropsychol Rev. 1995;5:173–201.
35. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
36. Monsell S. Task switching. Trends Cogn Sci. 2003;7:134–40.
37. Badre D, Wagner AD. Computational and neurobiological mechanisms underlying cognitive flexibility. Proc Natl Acad Sci U S A. 2006;103:7186–91.
38. Kim C, Cilles SE, Johnson NF, Gold BT. Domain general and domain preferential brain regions associated with different types of task switching: a meta-analysis. Hum Brain Mapp. 2012;33:130–42.
39. Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving

diverse executive functions. Cogn Affect Behav Neurosci. 2012;12:241–268.
40. de Araújo CM, Barbosa IG, Lemos SMA, Domingues RB, Teixeira AL. Cognitive impairment in migraine: A systematic review. Dement Neuropsychol. 2012;6:74-9.
41. Gil-Gouveia R, Oliveira AG, Martins IP. Assessment of cognitive dysfunction during migraine attacks: a systematic review. J Neurol. 2015;262:654-65.
42. Loehrer E, Vernooij MW, van der Lugt A, Hofman A, Ikram MA. Migraine and cerebral blood flow in the general population. Cephalalgia. 2015;35:190–8.
43. Stræte Røttereng AK, Bosnes O, Stordal E, Zwart JA, Linde M, Stovner LJ, et al. Headache as a predictor for dementia: The HUNT Study. J Headache Pain. 2015;16:89.