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Comparison of patients with chronic and episodic migraine with healthy individuals by brain volume and cognitive functions

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ABSTRACT

Objectives: Migraine is a complex neurological disease. In addition to headache, individuals with migraine may develop structural changes inside the brain and cognitive impairment. There is increased evidence associated with impairments in brain volume and cognitive functions in patients with migraine. The present study aimed to investigate the impairment in memory function in individuals with migraine using brain magnetic resonance imaging, volume measurement, and neuropsychological tests.

Methods: The study included 20 patients with episodic migraine, 20 patients with chronic migraine, and 20 healthy controls. Subcortical volumes of all participants were measured by FreeSurfer, an automatic segmentation method. The Wechsler Memory Scale-Revised Form (WMS-R), Stroop test, Raven's Standard Progressive Matrices, Verbal Fluency Test, and Lines Orientation Test were applied in all the study participants.

Results: Putamen volume decreased as migraine duration increased, and subcortical gray matter, left cerebellar cortex, and bilateral thalamus volumes were lower in the chronic and episodic group compared to the control group, bilateral putamen and right cerebellar cortex volumes were lower in patients with chronic migraine compared to patients in episodic migraine and control groups. Upon neuropsychological examination, delayed memory was affected as the duration of migraine increased, and there was impairment in patients with chronic migraine upon fluency tests and mental control tests.

Conclusions: Changes in subcortical volume and cognitive effects in patients with migraine raise questions about whether migraine qualifies as a benign disease. Structural changes and cognitive impairment may contribute to migraine-associated disability, and therefore, these causalities should be investigated by future studies. Silent infarcts, white matter damage, and cortical spreading depression, which occur in migraine cases, may be associated with subcortical volume changes and thus, cognitive effects. In the context, studies with larger samples to achieve a better understanding are needed.

Keywords: Migraine, subcortical gray matter volume, Freesurfer, cognition

Migraine is a type of primary headache characterized by episodic attacks and accompanied by different levels of neurological, gastrointestinal, and autonomic symptoms. For women and men, the lifetime prevalence was reported as 18% and 6%, respectively [1]. Migraine was re-

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ported as the primary cause of disability and suffering across the world [2]. Chronic migraine is defined by occurrence of 15 or more headaches per month for a prolonged duration of more than 3 months without drug overuse. It was reported that the risk of developing chronic migraine in patients with episodic migraine is 2.5% [3, 4]. The vascular theory is considered as the earliest theory on migraine pathophysiology. It suggested that migraine aura was associated with vasoconstriction in intracranial vessels, where headache was due to vasodilation [5]. Today, neurovascular theory has adopted with regard to migraine pathophysiology. This theory suggests that vascular changes are associated with neuronal events, including cortical hyperexcitability due to abnormal neurotransmitter release, and abnormal neuronal firing [6]. Accordingly, it was suggested that abnormal neuronal excitability in the cerebral cortex, cortical spreading depression (CSD), and sensitization of the trigeminovascular system were involved in the pathophysiology of migraine. A number of previous studies reported that central and peripheral systems had effects on the trigeminal system as regard the occurrence of pain [7, 8]. With a better understanding of migraine pathophysiology, questions about whether migraine qualified as a benign disease emerged and a number of studies investigated the brain morphology of individuals with migraine to see whether it caused brain damage and whether it was associated with deterioration of cognitive functions in patients with migraine.

A range of neuroimaging methods were accommodated to elucidate the structural and functional changes in the brain regions of patients with migraine. Magnetic resonance imaging (MRI) and positron emission tomography were used to investigate the structural and functional changes, respectively [9, 10]. Cranial MRI examinations in patients with migraine typically indicated multiple, small, punctate hyperintense lesions in the deep white matter and periventricular localization on T2 and FLAIR-weighted images, where these lesions might be associated with local demyelination and gliosis [11, 12]. It was reported that the incidence of silent posterior circulation infarcts, hyperintense ischemic lesions in the cerebellum and brain stem was increased in individuals with migraine. Hyperintense white matter lesions in those individuals were attributed to oligemia, focal brain hypoperfusion, and critical hypoperfusion in small penetrating arterioles during migraine attack and aura [13]. Voxel-based morphometry (VBM) method was generally used in volume studies in patients with migraine [14]. Certain studies in the last decade used the FreeSurfer method, an automated MRI tissue segmentation method, to investigate the pathophysiology of migraine and the resultant structural changes by measuring the volume of specific brain regions in individuals with episodic and chronic migraine [15, 16].

Subjective cognitive impairment is expected in migraine cases. Individuals with migraine complain about cognitive deterioration, including impaired attention and memory. Difficulty in thinking, distraction, feeling of slowing down, and difficulty in speaking may be seen during the prodromal period, at the headache stage. Reversible cognitive disorders were reported during or after a migraine attack [17, 18]. Previous studies, which investigated the cognitive functions in patients with migraine during the non-attack period, reported inconsistent results. Certain studies found no cognitive difference between individuals with migraine and healthy individuals, where it was suggested that there was an association between migraine and dementia due to the impairment in cognitive functions during pain attack and non-attack period [19-23]. Silent infarcts and white matter lesions in individuals with migraine might be associated with stroke and cognitive disorders [13, 24].

The present study aimed to investigate impairment in memory function in patients using brain MRI volume measurements and neuropsychological tests during the non-attack period in order to demonstrate the brain damage associated with migraine.

METHODS

The study included 20 patients with episodic migraine, 20 with chronic migraine, and 20 healthy controls. They were followed up at the Headache Outpatient Clinic of Uludag University Faculty of Medicine and classified pursuant to the classification as prescribed by the Headache Classification Committee of the International Headache Society. Prior approval for the commencement of the study was obtained from the Medical Research Ethics Committee of Uludag University Faculty of Medicine upon its decision dated January 25th, 2011, No. 2011-3/21. Informed consent

forms were obtained from all patients and healthy controls. Patients aged 20-55 years, with normal results from vitamin B12 and thyroid function tests and neurological examination, with a Beck Depression Inventory score of <17, a Mini-Mental State Examination score of >24 points, without any systemic disease, and healthy controls were included in the study. The main demographic characteristics of the patients and the control group were age, sex, and educational level (patients with the same educational level were included). Disease-associated variables, including age at the onset of migraine headache, age at diagnosis, number of painful days during a month, subcortical brain volume measurement, and neuropsychological tests were evaluated. The patient group was divided into three groups: patients with <5 headache-days/month, patients with 5–15 headache-days/month, and finally patients with ≥15 headache-days/month. Accordingly, patients with ≥15 days of headache/month were included in the chronic migraine group.

Morphometric Evaluation

The brain MRIs of the patients were performed with 1.5 tesla MRI in volume sequence, and the DICOM format images were then transferred to a computer with Linux operating system. Morphometric analysis was performed by an expert neuroradiologist based on the FreeSurfer (surface-based morphometry) software (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki). Unclear images associated with patients moving during the procedure were corrected, and glare caused by variations in the B1 magnetic field was removed. The images were placed in the Talairach coordinate system and the volumes of forty-seven subcortical brain regions were measured in each patient. The measured brain regions are presented in Table 1. These values were divided by the total brain volume of the individual and head circumference sizes were excluded. The volumes of the regions were used for statistical analysis.

Neuropsychological Evaluation

All participants received neuropsychological tests as administered by the same expert psychologist and the relevant brain regions were evaluated. The neuropsychological tests in question are given in Table 2 and the evaluated brain regions are presented in Table 3.

Statistical Analysis

The Shapiro–Wilk test was used to test the normal distribution hypothesis. Accordingly, for the purposes of comparing normally distributed quantitative data between individuals in the episodic migraine, chronic migraine, and control groups, one-way analysis of variance and the least significant difference test multiple comparison tests were used for normally distributed variables, where the Kruskal Wallis test and Dunn's paired comparison test were used for variables without normal distribution. The correlation between quantitative variables was tested using the Spearman correlation coefficient. A correlation coefficient between 0.8 and 1was considered indicative of a very strong relationship, where values between 0.6 and 0.8 indicated a strong relationship, those between 0.4and 0.6 indicated a moderate relationship, and those between 0.2 and 0.4 indicated a weak relationship (reference). For the purposes of descriptive statistics, numerical variables were presented in mean ± standard deviation for normally distributed variables, where median [min-max] was used for variables without normal distribution and number and % for categorical variables. Windows version 24.0 of Statistical Package for the Social Sciences (SPSS 25.0, IBM Corporation, Armonk, New York, United States) software was used for statistical analysis and a p level of <0.05 was considered statistically significant.

RESULTS

The study included 20 (33.3%) patients with episodic and 20 (33.3%) patients with chronic migraine, and 20 (33.3%) healthy controls. Of the patients, 68.3% (n=41) were female and 31.7% (n=19) were male. The mean age of all the patients was 34.90±6.95 years (range 2253 years). The migraine duration was 6.90 ± 5.05 years and ranged 1-20 years. Of the patients with migraine, 14 had <5 days with headache, 6 had 5–15 days with headache, and 20 had ≥15 days with headache per month. There were no intergroup statistical difference by sex, age, and educational level.Demographic and clinical characteristics of the patients are presented in Table 4.

Intracranial and subcortical volume measurements based on the FreeSurfer method were compared be-

Table 1. Comparison of volume values between episodic migraine, chronic migraine and control groups

	Episodic	Chronic	Control	P value
i.volume	1459854.81±164271.42	1424297.61±103205.39	[a,b]1578758.27±141019.1	**0.002**[*]
SGM	188782 [143999-206526]	177283 [160258-205427]	[a,b]191829.5 [162598-224985]	**0.010**[+]
3.vent	980 [653-2193]	951 [600-1732]	1019.5 [629-1806]	0.966[+]
4.vent	1346 [937-2257]	1663 [1114-2592]	1608 [830-2563]	0.272[+]
Brainsystem	21305.26±2378.72	19856.86±2216.41	[b]22349.5±2742.28	**0.007**[*]
CSF	941 [724-1736]	1072 [788-1483]	1032 [760-1542]	0.497[+]
wmhipo	1182.42±402.08	1106.05±348.27	[b]1410.35±428.93	**0.045**[*]
nonwmhipo	14 [7-44]	14 [5-41]	14.5 [6-36]	0.851[+]
Optchiazma	247.58±75.66	243.38±90.21	254.95±65.71	0.892[*]
CC pos	921 [719-1214]	897 [761-1298]	983.5 [556-1165]	0.777[+]
Cc cent	502.79±136.23	437.62±73.58	510.15±97.6	0.058[*]
CC ant	871.26±114.17	857.57±116.07	917.15±154.33	0.316[*]
l.lat.vent	4561 [1721-16337]	6293 [1981-9445]	4854.5 [2370-16915]	0.115[+]
r.latvent	4366 [1538-12244]	4061 [2204-9581]	4786.5 [2602-11234]	0.329[+]
l.cerbwm	13698.11±2760.49	13778.67±1411.24	14406.55±1617.88	0.476[*]
r.cerebwm	13731.16±1667.24	13494.67±1351.87	13971.35±1304.68	0.576[*]
l.cereb ktx	50831.16±8536.96	51437.29±4005.12	[a.b]56011.05±6191.49	**0.027**[*]
r.cereb ktx	52860.74±5861.54	52222.38±4834.59	[b]56452.05±6282.37	**0.046**[*]
l.talamus	7214.16±744.83	6856.29±531.54	[a,b]7783.3±762.41	**0.001**[*]
r.talamus	7364.53±695.38	7054.95±591.16	[a,b]7906.15±906.33	**0.002**[*]
l.caudat	3664.68±413.11	3565±258.2	3725.1±476.66	0.421[*]
r.caudat	3560±376.06	3511.67±330.28	3701.25±458.29	0.284[*]
l.putamen	5422.11±680.72	5176.62±406.58	[b]5697±631.87	**0.021**[*]
r.putamen	5025.21±591.84	4811.86±446.22	[b]5279.05±580.8	**0.028**[*]
l.pallidum	1616.53±215.81	1567.33±131.78	1636.8±196.88	0.464[*]
r.pallidum	1458.58±169.04	1423.9±143.67	1509.6±186.64	0.265[*]
l.hipokamps	4235 [3517-5340]	[a]3859 [3-4272]	[b]4344.5 [2381-4916]	**<0.001**[+]
r.hipokamps	4243 [3284-5368]	[a]4032 [3405-4512]	[b]4423.5 [3868-4829]	**0.004**[+]
l.amgdala	1509 [1309-2051]	1446 [1089-1649]	1584.5 [622-1901]	0.058[+]
r.amgdala	1494 [1275-2185]	[a]1482 [1192-1679]	[b]1627.5 [1339-1929]	**0.020**[+]
l.accumbens	566.05±88.96	527.62±57.01	580.4±70.86	0.064[*]
r.accumbens	553.95±107.27	510.76±66.25	562.65±88.29	0.139[*]

Data are shown as mean±standard deviation or median [minimum-maximum]. i.volume=intracranial volume, SGM=subcortical grey matter, optchiazma=opticchiazma, 4-3 Vent=4-3. Ventricule, CSF=cerebrospinal fluid, Wmhipo=White matter hipodansite, Non WM Hipo=Non-White matter hipodansite, CC pos, cent, ant=Corpus callsoun poterior, central, anterior, lat. Vebt=latreal ventricule, cerebwm=cerebellar white matter, cereb ktx=cerebellar cortex

The values in bold face are given significance P<0.05.

[+]Kruskal Wallis test, [*]One Way ANOVA

[a]Differences with Episodic group.

[b]Differences with Chronic group.

Table 2. **Neuropsychological tets and functions it tests**

Tests	Function Tested
Verbal memory process tests	Verbal memory
Wechsler Memory Scale (WMS) VI. sub test and delayed recalling	Visual memory
WMS IV A story, B story	Verbal memory and continuing the attention (logical memory)
WMS V subtests	Attention
WMS III.	Mental control
Fluency tests	Executive functions, preservation and memory eveluation
Line Direnction Determination Test	Measurement of visual spatial perception and orientation functions
Raven Standard Progressive Matrix Test (RSPM)	Measurement of regular accurate thinking, managentment of reasoning
Stroop	Response inhibition and category change (data processing speed)

tween the groups (Table 1). Intracranial volume, subcortical gray matter, left cerebellar cortex, left thalamus, right thalamus, left cerebellar cortex, left cerebellar cortex, left thalamus, and right thalamus volumes were similar in the episodic and chronic groups, whereas the same were significantly lower in the control group (P=0.002, P=0.010, P=0.027, P=0.001 and P=0.002, respectively). While brain stem, non-white matter hypointensity, left putamen, right putamen, and right cerebellar cortex volumes were similar in the episodic migraine and control groups, these same were significantly lower in patients with chronic migraine (P=0.007, P=0.045, P=0.046, P=0.021 and P=0.028, respectively). The left hippocampus, right hippocampus and right amygdala volumes of the subjects in the episodic migraine group were significantly lower than those in the chronic migraine and control groups, whereas the same were significantly lower in the chronic group compared to the control group (P<0.001, P=0.004 and P=0.020, respectively).

The volume values of the patients were compared between the groups formed on the basis of the number of painful days per month (Table 5). There was a statistically significant intergroup difference by the right amygdala and right accumbens values (P<0.05). The right amygdala volume was lower in patients with 5-15 headache-days/month compared to patients with <5 headache-days and ≥15 days of pain per month (P=0.028). Similarly, the right accumbens volume was

Table 3. **Neuropsychological tests and related brain areas**

Test name	Releated brain area	Cognitive process measured
Digit span learning	Temporal lob, hipocampus Limbic system, frontal lob	Learning, short-term memory
Wechsler memory scale	Temporal lob, hipocampus Limbic system, frontal lob	Attention, concentration, verbal memory, visual memory, immediate memory, delayed memory
Raven	Right hemisphere, parietal lob, common brain areas	Visual spatial perception, category changeability, working memory, abstraction and scrutinizing, general ability
Stroop testi	Frontal lob	Focused attention, response inhibition, rersistance againist destroying effect, data processing

Table 4. A distribution of demographic and clinical characteristics of participants

Group n (%)	
Episodic migraine	20 (33.3)
Chronic migraine	20 (33.3)
Controls	20 (33.3)
Sex n (%)	
Female	41 (68.3)
Male	19 (31.7)
Age (mean±SD)	34.90±6.95
Migraine Duration (mean±SD)	6.90±5.05
Number of Headache-days n (%)	
<5	14 (23.31)
5–15	6 (9.99)
≥15	20 (33.3)

SS: Standard Deviation

lower in patients with 5-15 headache-days/month compared to patients with <5 headache-days and ≥15 headache-days per month (P=0.034).

The correlation between the migraine duration and volume values were analyzed (Table-6). There was a weak, statistically significant negative correlation between migraine duration and right putamen values (r=−0.328; P=0.039). In other words, the right putamen volume decreased as the migraine duration increased.

Memory test results of the study participants were compared by groups (Table 7). There was a significant intergroup difference by the total number of animals named in the Animal Fluency test and the measurement values in the mental control test of counting down from 100 by 7's. The total number of animals named in the Animal Fluency test in the chronic migraine group was 20 [10-33], which was similar to 22 [14-33] in the episodic migraine group, while the same in the control group was 25.5 [16-37], which was indicative of a statistically significant difference (p = 0.047). Similarly, the time to count backward from 100 by 7's was 79 seconds [36-236] in patients with chronic migraine and 56 seconds [13-220] in patients with episodic migraine, whereas the same was 40.5 seconds [19-120] in the control group and it was a statistically significant difference (P= 0.010).

The total number of errors in the Animal Fluency test in individuals with 5 and 15 headache-days per month was 0.5 [0-2], which was statistically significant (P= 0.027), compared to 0 [0-1] in the group with <5 headache-days and 0 [0-2] in patients with chronic migraine with ≥15 headache-days (Table 8).

The relationship between the migraine duration and memory test results was analyzed (Table 7). There was a weak negative correlation between migraine duration and delayed memory values (r=-0.341; P=0.031). Delayed memory weakened as the migraine duration increased (Table 9).

DISCUSSION

A number of previous studies reported cortical and subcortical volume changes associated with migraine attacks and the effects of migraine on cognition. The present study combined volume measurement of subcortical structures and neuropsychological evaluation.

There are various segmentation methods for brain volume assessments using manual and automated techniques. Brain parenchymal fraction, which was used bya number of previous studies in the relevant literature, is defined as the ratio of brain parenchymal volume to the total intracranial volume. Considering the volumes as total intracranial volume only without proportioning to intracranial volume may lead to inaccuracies due to differences by ex and head diameters. The volume values in the present study were proportioned to the total intracranial volume values with an aim to eliminate the inaccuracies associated with interindividual head size variables.

Increasing number of neuroimaging studies measured brain volume in patients with migraine using different methods. While most of the studies investigated the episodic migraine group with comparatively fewer number of studies focused on patients with chronic migraine [14, 16, 25]. In this study, patients with episodic and chronic migraine, along with healthy controls were included, and the results were compared between the patient groups and healthy controls based on the FreeSurfer software [26], which featured higher accuracy rate compared to the manual technique.

In the present study, the intracranial volume, subcortical gray matter, left cerebellar cortex, and left thalamus and right thalamus volumes were lower in

Table 5. The relationship between the number of painful days and volume values in the study participants

	Number of days of headache per month			
	<5	5-15	≥15	P value
i.volume	1457899.46±172294.67	1436821.36±49353.21	1425445.3±105676.06	0.778
SGM	181054.56±19115.17	179595.75±3112.13	177428±12273.86	0.780
3.vent	977.5 [600-2193]	1245 [670-1621]	945.5 [699-1732]	0.385
4.vent	1458.94±313.08	1611.5±571.58	1710.06±421.19	0.170
brainsystem	21226.22±2451.94	21427.25±601.28	19667.39±2331.45	0105
CSF	962 [724-1736]	1017 [828-1268]	933 [788-1483]	0.986
wmhipo	1142.28±395.01	1213.25±353.4	1126.61±371.18	0.919
nonwmhipo	14 [7-44]	23 [9-41]	13.5 [5-28]	0.495
Optchiazm	253.44±80.68	293.75±63.28	226.56±86.22	0.297
CC pos	922.61±163.17	943.25±111.26	928.61±128.9	0.966
Cc cent	502.72±141.15	432.25±84.41	442.5±71.19	0.216
CC ant	864.11±112.85	939.75±60.54	847.22±121.38	0.349
l.lat.vent	4683.5 [1721-16337]	6138 [2040-8484]	5864 [1981-9445]	0.349
r.latvent	4394 [1538-12244]	5621 [2906-6216]	3647 [2204-9581]	0.807
l.cerbwm	13602.39±2782.9	14967±2088.83	13605.83±1227.82	0.491
r.cerebwm	13745.72±1712.37	13361.5±1423.11	13522.83±1339.57	0.859
l.cereb ktx	50786.67±8742.87	51528.25±2154.94	51427.89±4329.17	0.952
r.cereb ktx	52839.22±5985.3	52877.25±2539.23	52133.83±5182.49	0.918
l.talamus	7201.72±772.43	6945.75±252.07	6868.72±571.57	0.314
r.talamus	7354.06±693.4	7342±445.42	7018.83±631.61	0.283
l.caudat	3647.83±424.31	3651.75±154.82	3568.11±277.34	0.767
r.caudat	3536.5±368.4	3632.75±297.03	3510.94±353.97	0.827
l.putamen	5384 [4221-7074]	5139.5 [4761-5285]	5077 [4832-6687]	0.463
r.putamen	5103.5 [4093-6408]	4738.5 [4579-4927]	4678 [4366-6289]	0.549
l.pallidum	1611.22±223.15	1523.75±107.04	1585.06±133.46	0.668
r.pallidum	1451.94±171.23	1397.25±140.68	1438.39±147.81	0.822
l.hipokamp	4252.11±507.27	3969.75±372.32	3646.06±937.65	0.057
r.hipokamp	4314.67±552.05	4107±225.87	3985.5±280.4	0.079
l.amgdala	1547.56±197.79	1415±38.65	1439.39±140.22	0.110
r.amgdala	1619.39±255.82	[a]1377±40.41	1470.11±131.24	**0.028**
l.acumbens	570.67±89.18	501.75±12.12	530.89±61.19	0.134
r.acumbens	565±95.97	[a]448±86.3	516.06±69.53	**0.034**

Data are shown as mean±standard deviation or median [minimum-maximum]. i.volume=intracranial volume, SGM=subcortical grey matter, optchiazma=opticchiazma, 4-3 Vent=4-3. Ventricule, CSF=cerebrospinal fluid, Wmhipo=White matter hipodansite, Non WM Hipo=Non-White matter hipodansite, CC pos, cent, ant=Corpus callsoun poterior, central, anterior, lat. Vebt=latreal ventricule, cerebwm=cerebellar white matter, cereb ktx=cerebellar cortex

Thevalues in bold face are given significance P<0.05.

[+]Kruskal Wallis test, [*]OneWay ANOVA

[a]Differences with <5.

[b]Differences with 5-15 group.

Table 6. The relationship between migraine duration and volume values

Migraine duration											
i.volume	r	-0.231	**optchia**	r	0.164	**l.cerb kor**	r	-0.151	**l.pallidum**	r	-0.100
	P	0.151		P	0.313		P	0.354		P	0.539
SGM	r	-0.191	**cc pos**	r	-0.008	**r.cerb kor**	r	-0.151	**r.pallidum**	r	-0.173
	P	0.238		P	0.963		P	0.353		P	0.285
P3. vent	r	-0.053	**cccent**	r	-0.110	**l.talamus**	r	-0.205	**l.hipokamps**	r	-0.116
	P	0.745		P	0.498		P	0.204		P	0.475
4. vent	r	-0.156	**cc ant**	r	-0.222	**r.talamus**	r	-0.303	**r.hipokamps**	r	-0.193
	P	0.337		P	0.168		P	0.057		P	0.232
Brain sysytem	r	0.057	**l.lat.vent**	r	0.070	**l.caudat**	r	-0.027	**l.amgdala**	r	-0.272
	P	0.726		P	0.666		P	0.871		P	0.089
CSF	r	-0.147	**r.lat.vent**	r	0.069	**r.caudat**	r	-0.128	**r.amgdala**	r	-0.088
	P	0.364		P	0.674		P	0.433		P	0.590
wmhipo	r	0.123	**l.cerbwm**	r	-0.113	**l.putamen**	r	-0.163	**Laccumbens**	r	-0.209
	P	0.450		P	0.486		P	0.315		P	0.196
nonwmhipo	r	0.057	**r.cerbwm**	r	-0.178	**r.putamen**	r	-0.328	**r.accumbens**	r	-0.279
	P	0.729		P	0.272		p	**0.039**		P	0.082

i.volume=intracranial volume, SGM=subcortical grey matter, optchiazma=opticchiazma, 4-3 Vent=4-3. Ventricule, CSF=cerebrospinal fluid, Wmhipo=White matter hipodansite, Non WM Hipo=Non-White matter hipodansite, CC pos, cent, ant=Corpus callsoun poterior, central, anterior, lat. Vebt=latreal ventricule, cerebwm=cerebellar white matter, cereb ktx=cerebellar cortex

r: Spearman correlation coefficient (n=40)

the migraine groups compared to the controls, nevertheless, there was no significant difference between the episodic and chronic migraine groups. Bashir *et al*. [14] reported low brain stem, left cerebellar cortex, and white matter volume in patients with chronic migraine. Consistent with the literature, the left cerebellar cortex volume was lower in the present study. Furthermore, brainstem and right cerebellar cortex volumes were lower in patients with chronic migraine compared to episodic migraine group and healthy controls. The brain stem is considered an important region for the pathogenesis of headache and migraine. Periaqueductal gray matter, trigeminal nerve, cuneiform nuclei, and their connections play a role in pain modulation. Balance disorder and vestibulocerebellar symptoms are frequent in patients with migraine. Previous VBM morphometric studies reported volumetric differences in the brainstem and cerebellum in patients with episodic migraine with aura, where functional MRI procedures indicated the association of periaqueductal gray matter and cuneiform nuclei with thalamus, cerebellum, insula, and cortex [27-29].

Volume loss in the brainstem and cerebellum may be associated with pain-related atrophy of pain nuclei in the brainstem, prolonged oligemia, posterior system hypoperfusion, and exposure to ischemia. As regards the pathogenesis of migraine, the thalamus is considered to transfer pain from the lower brain to the cortex via the trigemino-vascular pathway and has an important role in central sensitization, allodynia, and photophobia in migraine [30]. Shin *et al*. [15] measured the volumes of the thalamus and thalamic nuclei using the FreeSurfer method and reported the same thalamus volumes compared to healthy controls, yet found differences in volume between the thalamic nuclei. They found an increase in the volumes of medial geniculate

Table 7. A comparison of the results from memory tests between episodic migraine, chronic migraine, and control groups

	Episodic	Chronic	Control	P value
Raven reply	30.32±4.03	29.33±5.13	28.50±5.67	0.530*
Raven duration	307.16±63.23	301.52±80.75	288.85±93.36	0.766*
Stroop1	28 [22-40]	28 [21-39]	26 [19-37]	0.325+
Stroop2	39 [28-59]	39 [29-55]	38 [30-67]	0.784+
Stroop3	32 [23-50]	29 [23-71]	29 [22-39]	0.826+
Stroop4	69 [45-94]	67 [43-124]	72.5 [55-110]	0.324+
Stroop true reply	1 [0-4]	1 [0-10]	1 [0-10]	0.811+
Stroop wrong reply	0 [0-1]	0 [0-1]	0 [0-3]	0.981+
Fluency total number	22 [14-33]	20 [10-33]	[b]25.5 [16-37]	**0.047**+
Number of fluency errors	0 [0-0]	0 [0-2]	0 [0-0]	0.395+
Number of recalls per fluency repetition	0 [0-5]	0 [0-2]	0,5 [0-4]	0,532+
Error in even numbers	8.79±1.36	8.33±1.71	9.20±1.58	0.215*
fluency total number of errors	0 [0-1]	0 [0-2]	0 [0-2]	0.824+
fluency repetition	0 [0-1]	0 [0-2]	0 [0-2]	0.513+
Attention forward counting	5 [4-8]	5 [4-8]	5 [4-8]	0.073+
Attention countdown	4 [2-7]	4 [3-6]	4 [2-6]	0.430+
attention total	8 [6-15]	8 [7-14]	9 [7-12]	0.089+
MCcdd	5 [4-8]	5 [3-11]	4 [3-9]	0.671+
MCcdw	0 [0-0]	0 [0-0]	0 [0-1]	0.368+
MCcdm	13 [6-40]	13 [7-40]	14.5 [8-80]	0.265+
MCcmw	0 [0-2]	0 [0-2]	0 [0-2]	0,673+
MCcon	19 [9-70]	21 [6-56]	13,5 [6-32]	0,078+
MCcow	0 [0-4]	0 [0-5]	0 [0-2]	0.743+
MC counting by sevens	56 [13-220]	79 [36-236]	[b]40.5 [19-120]	**0.010**+
MC number of errors while counting by sevens	1 [0-6]	1 [0-9]	1 [0-7]	0.667+
MC total number	102 [59-302]	115 [65-314]	81.5 [46-172]	0.094+
MC total eror	1 [0-12]	1 [0-15]	2 [0-9]	0.957+
LMT İmmediate	14 [9-19]	15 [8-22]	16 [10-19]	0.842+
LMT delaying	14.47±3,13	13,67±3,71	14,35±3,53	0.728*
WMT instant memory	12 [6-14]	12 [5-14]	14 [5-18]	0.531+
WMPT immediate memory	6 [4-9]	6 [4-9]	7 [4-11]	0.649+
WMPT learning point	112 [90-134]	122 [80-152]	119.5 [76-141]	0.779+
WMPT reaching criteria	6 [0-9]	6 [0-10]	4.5 [0-10]	0.784+
WMPT highest learning	15 [12-15]	15 [10-15]	15 [10-15]	0.691+
WMPT learning eror point	0 [0-7]	0 [0-10]	1 [0-6]	0.228+
WMPT identifying	13 [9-15]	13 [0-15]	13 [10-15]	0.778+
WMPT total recalling	2 [0-5]	2 [0-13]	2 [0-5]	0.866+

Data are shown as mean±standard deviation or median [minimum-maximum]. MCcdd=Mental control counting down the days, MCcdw=Number of mistakes made while counting down the days, MCcdm=Duration of counting down the months, MCcon=Counting odd numbers, MCcow=Number of mistakes made when counting odd numbers, MCcmw=Number of mistakes made while counting down the days, WMT=Visual memory test, VMPT=Verbal memroy process test, LMT=Logical Memory Test

The values in bold face are given significance P<0.05.

+Kruskal Wallis test, *OneWay ANOVA

[a]Differences with Episodic group.

[b]Differences with Chronic group.

Table 8. The relationship between the number of headache-days and memory test values of the study participants

	Headache-days			
	<5	5-15	≥15	P value
Raven reply	30.22±4.12	31±1.41	29.11±5.51	0.674*
Raven duration	315.89±71.28	320.50±77.14	288.89±73.04	0.486*
Stroop1	28.5 [23-40]	26.5 [22-37]	27 [21-39]	0.797+
Stroop2	39.5 [28-59]	35.5 [31-50]	37 [29-55]	0.966+
Stroop3	32 [24-50]	31 [23-41]	28 [23-71]	0.798+
Stroop4	70 [45-94]	74 [56-92]	66.5 [43-124]	0.609+
Stroop true reply	1 [0-4]	0.5 [0-6]	1 [0-10]	0.788+
Stroop wrong reply	0 [0-1]	0 [0-0]	0 [0-1]	0.391+
Fluency total number	21.5 [14-33]	20.5 [14-33]	20.5 [10-29]	0.609+
Number of fluency errors	0 [0-0]	0 [0-0]	0 [0-2]	0.637+
Number of recalls per fluency repetition	0 [0-5]	0 [0-0]	0 [0-2]	0.147+
Error in even numbers	8 [6-12]	9.5 [8-10]	8 [5-11]	0.315+
fluency total number of errors	[a] 0 [0-1]	[b] 0.5 [0-2]	[a]0 [0-2]	**0.027**+
fluency repetition	0 [0-1]	0 [0-0]	0 [0-2]	0.637+
Attention forward counting	5 [4-8]	4 [4-5]	5 [4-8]	0.242+
Attention countdown	4 [2-7]	4 [3-4]	4 [3-6]	0.705+
attention total	8 [6-15]	8 [7-9]	8 [7-14]	0.625+
MCcdd	4.5 [4-8]	5 [4-5]	5 [3-11]	1.000+
MCcdw	0 [0-0]	0 [0-0]	0 [0-0]	1.000+
MCcdm	12.5 [6-40]	18.5 [10-23]	12.5 [7-40]	0.306+
MCcmw	0 [0-2]	0 [0-0]	0 [0-2]	0.495+
MCcon	17.5 [9-70]	24.5 [13-32]	21 [6-56]	0.442+
MCcow	0 [0-4]	0 [0-2]	0 [0-5]	0.476+
MC counting by sevens	56.5 [18-220]	76 [13-236]	76 [36-155]	0.966+
MC number of errors while counting by sevens	1 [0-6]	2.5 [0-6]	1.5 [0-9]	0.896+
MC total number	107 [59-302]	123.5 [62-314]	113.5 [65-239]	0.865+
MC total eror	1 [0-12]	3.5 [0-6]	1.5 [0-15]	0.762+
LMT İmmediate	14.5 [9-20]	12.5 [9-17]	15.5 [8-22]	0.305+
LMT delaying	26.5 [20-37]	28.5 [23-33]	30 [18-40]	0.701+
WMT instant memory	12.5 [6-14]	13 [10-14]	12 [5-14]	0.431+
WMPT immediate memory	6 [4-9]	6 [5-8]	6.5 [4-9]	0.542+
WMPT learning point	116.5 [90-134]	121.5 [111-128]	120.5 [80-152]	0.831+
WMPT reaching criteria	5.5 [0-9]	6.5 [0-8]	5.5 [0-10]	0.695+
WMPT highest learning	15 [12-15]	15 [13-15]	15 [10-15]	0.877+
WMPT learning eror point	0 [0-7]	0 [0-7]	0 [0-10]	0.804+
WMPT identifying	13 [9-15]	12.5 [12-15]	13 [0-15]	0.896+
WMPT total recalling	2 [0-5]	2.5 [0-3]	2 [0-13]	0.931+

Data are shown as mean±standard deviation or median [minimum-maximum]. MCcdd=Mental control counting down the days, MCcdw=Number of mistakes made while counting down the days, MCcdm=Duration of counting down the months, MCcon=Counting odd numbers, MCcow=Number of mistakes made when counting odd numbers, MCcmw=Number of mistakes made while counting down the days, WMT=Visual memory test, VMPT=Verbal memroy process test, LMT=Logical Memory Test

The values in bold face are given significance P<0.05.

+Kruskal Wallis test, *OneWay ANOVA

[a]Differences with<5.

Table 9. The relationship between the migraine duration and memory test values in the study participants

Raven reply	r	-0.338*	Fluency re Petition	r	0.010	MCcmw	r	-0.292	WMT instant memory	r	-0.187
	P	0.033		P	0.949		P	0.067		P	0.249
Raven duration	r	0.091	Error in even numbers	r	-0.150	MCcon	r	-0.023	WMPT 1	r	-.363*
	P	0.577		P	0.354		P	0.890		P	0.021
Stroop 1	r	0.179	Fluency total number of errors	r	-0.063	MCcow	r	-0.126	WMPT 2	r	-0.255
	P	0.269		P	0.700		P	0.437		P	0.112
Stroop 2	r	.320*	Number of recalls Per fluency repetition	r	0.110	MC counting by sevens	r	0.093	WMPT 3	r	-0.067
	P	0.044		P	0.500		P	0.568		P	0.679
Stroop 3	r	.333*	Attention forward counting	r	-0.196	MC number of errors while counting by sevens	r	0.038	WMPT 4	r	-0.058
	P	0.036		P	0.226		P	0.814		P	0.724
Stroop 4	r	0.072	Attention countdown	r	-0.018	MC total number	r	0.086	WMPT 5	r	0.082
	P	0.660		P	0.910		P	0.596		P	0.614
Stroop true rePly	r	-0.182	Attention total	r	-0.095	MC total number	r	0.001	WMPT 6	r	-0.112
	P	0.260		P	0.561		P	0.995		P	0.492
StrooP true rePly	r	-0.137	MCcdw	r	0.181	WMT instant memory	r	-0.089	WMPT 7	r	-0.341
	P	0.398		P	0.265		P	0.584		P	**0.031**
Number of fluency errors	r	-0.127	MCcdd	r	-0.039	mkags	r	-0.005	delayed memory	r	-0.086
	P	0.434		P	0.810		P	0.978		P	0.599

MCcdd=Mental control counting down the days, MCcdw=Number of mistakes made while counting down the days, MCcdm=Duration of counting down the months, MCcon=Counting odd numbers, MCcow=Number of mistakes made when counting odd numbers, MCcmw=Number of mistakes made while counting down the days, WMT=Visual memory test, VMPT=Verbal memroy process test, LMT=Logical Memory Test

r: Spearman correlation coefficient (n=40)

nuclei and right anteroventral nucleus in the migraine group and a decrease in the volume of bilateral parafasian nuclei [15]. The present study did not separately measure the volume of the thalamic nuclei, nevertheless, the left and right thalamus volumes were lower in the migraine group compared to the healthy controls. There was no difference between the migraine groups. The fact that the thalamus volumes were lower in patients with migraine was inconsistent with the result of a study of Shin *et al*. [15]. Changes in the acumbens, putamen, and hippocampus were reported in chronic pain cases [31, 32].

Subcortical gray matter volumes and morphologies in patients with migraine were also investigated by previous studies. Igor *et al*. compared subcortical gray matter volumes in patients with migraine with aura to healthy controls and found that bilateral globus pallidus and left putaminal volumes were lower in patients with migraine with aura. They found no correlation between migraine duration and frequency of attacks and subcortical gray matter structures [33]. For the purposes of the present study, the patients were not categorized as patients with or without aura, where the subcortical gray matter volume was lower in the migraine group compared to the controls, and bilateral putamen volumes were lower in the chronic migraine group. There was no difference between episodic patients with migraine and the healthy controls. Furthermore, the right putamen volume was lower in participants with longer migraine duration. The putamen is connected to the cerebral cortex, thalamus and brainstem, and it was shown that putamen volume decreased in patients with tension-type headache or lumbar disc herniation with non-migraine pain [34, 35]. The caudate and putamen form the dorsal striatum, receiving inputs from the cerebral cortex and thalamus, and the activation therein is involved in motor and cognitive functions [36].

Structural and functional changes occur in the hippocampus and amygdala, two limbic structures responsible for stress and adaptation, in cases of stress and chronic pain [37]. It was suggested that cortical spreading depression extended to the temporal neocortex to the lateral amygdala and affected CSD and amygdala activation, and that amygdala dysfunction might be associated with neuropsychological symptoms in the postdromal phase. It was suggested that amygdala was associated with pain, emotional and visual symptoms, and neuroendocrine homeostasis in migraine attacks [38].

Liu *et al*. [39] reported that bilateral amygdala and bilateral temporal gyrus functional connections increased in patients with chronic migraine compared to patients with episodic migraine. Maleki *et al*. [40] found that bilateral hippocampus volume was higher in the group with 1-2 headache-days per month compared to the group with 8-14 headache-days per month. In the present study, bilateral hippocampus volume was lower in patients with episodic migraine compared to the healthy controls. To avoid underestimation of hippocampus volumes due to depression, patients with depression were excluded in the present study based on the Beck Depression Inventory scores. Changes in hippocampus volume might be associated to the stress induced by migraine attacks. Furthermore, right amygdala volumes were lower in patients with episodic migraine compared to the control group in our study. Nuc. acumbens is a modulator of pain and has been the focus of interest in recent studies. It was suggested that this might to be related to its effect on the emotional state during migraine attack and decreased activation in the nuc. acumben during pain and decreased receptors in chronic pain occurred not only in migraine pain but also in other pain cases [32, 41]. Husoy *et al*. [34] investigated the volume and shape of the nuc. acumbens in patients with migraine and found a decrease in volume and change in shape. The present study compared the headache frequency and volumes, and accordingly, the right amygdala and right nuc. acumbens volumes of the group with 5-15 headache-days were lower compared to the groups with <5 headache-days/month and ≥15 headcahe-days/month. The fact that nuc. acumbens volume was lower in the group with 5-15 headache-days/month compared to the group with <5 headache-days/month is consistent with results reported in the relevant literature. It was an interesting result that the right amygdala and right acumbens volumes were lower in the episodic migraine group compared to the chronic group and that the comparatively low number of patients might have accounted for this result. Further studies with larger samples may report different results upon analysis of those volumetric values. All these changes in subcortical structures raise the question of

whether cortical spreading depression leads to atrophy in the most vulnerable subcortical structures.

Depression, anxiety, and education level affect cognition. Therefore, in the present study, individuals with depression that might affect cognitive tests were excluded from the study and groups with the same level of education were included with an aim to rule out errors associated with education in the course of the neuropsychological evaluation.

Patients with migraine, who had volumetric changes in brain, may also have impaired cognitive functions. Previous studies reported inconsistent results in that regard. While certain studies did not report any cognitive impairment associated with migraine, some others suggested that there was a decrease in various cognitive functions, including sensorimotor function, attention, information formation, language, and memory, and other reported that scores from recent memory tests were lower, processing speed was slower, information formation was less, and verbal memory was poorer in patients with migraine. It was emphasized that general cognitive performance was not impaired in patients with migraine but verbal memory tests indicated impairment [21, 42-44]. In a study on Danish twins, there was no difference between twins with and without migraine by fluency, word recall, and number sequence learning test [21]. In the present study, there was no intergroup difference by scores from the number sequence learning test, which measured verbal memory, where the total number of animals that could be named in the Animal Fluency test, which evaluated attention and concentration, was lower in the migraine group compared to the control group. As per the mental control tests, the number of errors in the test of counting backward in 7's was higher in the migraine group. There was no difference between patients with episodic and chronic migraine vis-à-vis both tests.

A meta-analysis by Gu *et al*. [45] reported that cognitive function and language function were lower in the migraine group compared to the non-migraine group, while there was no difference by visuospatial function, attention, executive functions, and memory. In the present study, there was no intergroup difference by visual memory, attention and executive functions consistent with the results reported in the relevant literature.

Previous studies suggested that patients with migraine for prolonged periods and frequent attacks might have impaired memory and attention, and prolonged visual-motor speed [46]. In the present study, delayed memory decreased as the migraine duration increased, and the number of errors made in the Animal Fluency test was higher in the migraine group with 5-15 headache-days/month compared to the other groups. It was an interesting result that the group with ≥15 headache-days per month was more successful. This inconsistent result may also be associate with the comparatively low number of patients included in this study. The inconsistencies among studies, which did not investigate the relationship between migraine and cognition, might be due to certain factors, including age, sex, migraine duration, attack frequency, attack duration, physical performance, sleep quality, comorbid depression, and anxiety.

CONCLUSION

In conclusion, primary and secondary somatosensory cortex, prefrontal, insular, anterior cingulate and thalamus play major roles in acute pain. To a lesser extent, the basal ganglia, hippocampus, amygdala, cerebellum, temporal, and parietal cortex are involved in acute pain [28, 40, 47]. Neuroimaging results indicated anatomical and functional connections and the occurrence of a number common structures in pain and memory networks. The sensory and emotional characteristics of pain overlap with memory centers. Memory disorders may occur as a result of the processing of pain inside the brain [48, 49].

Migraine is considered a complex neurological disease involving many regions in the brain and it has been suggested that migraine may lead to permanent central nervous system dysfunction, atrophy in neocortical structures, including hippocampus and amygdala, cerebellum, subcortical gray matter, and cognitive impairment. Despite a number of studies in the relevant, the pathophysiology of migraine, changes in the brain, and possible cognitive impairments have not yet been fully understood. There is a requirement for future studies with larger samples to compare neuroimaging results and cognitive functions with clinical parameters, including attack frequency, attack severity, disability rate, medication use, and depression and anxiety in patients with migraine.

Authors' Contribution

Study Conception: DKŞ, MZ, BH, NK, NT; Study Design: DKŞ, MZ, BH, NK, NT; Supervision: MZ; Funding: DKŞ, MZ, BH, NK, NT; Materials: DKŞ, BH; Data Collection and/or Processing: DKŞ, MZ, BH, NK, NT; Statistical Analysis and/or Data Interpretation: DKŞ, MZ, BH, NK, NT; Literature Review: DKŞ, MZ, BH, NK, NT; Manuscript Preparation: DKŞ, MZ, BH, NK, NT and Critical Review: DKŞ, MZ, BH, NK, NT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Availability of data and materials

The authors agree with sharing, copying, and modifying the data used in this article, even for commercial purposes, so long as appropriate credit is given, and possible changes are indicated. Ethics approval and consent to participate The present study was approved by the Ethics Committee of Uludag University Faculty of Medicine, Bursa, Turkey

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