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Hippocampal connectivity dynamics and volumetric alterations predict cognitive status in migraine: A resting-state fMRI study

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ABSTRACT

The etiology of cognitive decline linked to migraine remains unclear, with a growing recurrence rate and potential increased dementia risk among sufferers. Cognitive dysfunction has recently gained attention as a significant problem among migraine sufferers that can be related to alterations in hippocampal function and structure. This study explores hippocampal subfield connectivity and volume changes in migraine patients.

We recruited 90 individuals from Alanya University's Neurology Department, including 49 migraine patients and 41 controls, for functional and anatomical imaging. Using the CONN toolbox and FreeSurfer, we assessed functional connectivity and subfield volumes, respectively. Montreal Cognitive Assessment (MOCA) was used to assess cognition in the entire sample. As a result, migraine patients exhibited significantly lower MOCA scores compared to controls ($p<.001$). Also, we found significant differences in hippocampal subfields between migraine patients and control groups in terms of functional connectivity after adjusting for years of education; here we showed that the left CA3 showed higher connectivity with right MFG and right occipitolateral cortex. Furthermore, the connectivity of left fimbria with the left temporal lobe and hippocampus and the connectivity of the right hippocampal-tail with right insula, heschl's gyrus, and frontorbital cortex were lower in the migraineurs.

Additionally, volumes of specific hippocampal subfields were significantly lower in the migraineurs (whole hippocampus $p = 0.004$, whole hippocampus head $p = 0.003$, right CA1 head $p = 0.006$, and right HATA $p = 0.005$) compared to controls. In conclusion, these findings indicate that migraine-associated cognitive impairment involves significant functional and structural brain changes, particularly in the hippocampus, which may heighten dementia risk. This pioneering study unveils critical hippocampal alterations linked to cognitive function in migraine sufferers, underscoring the potential for these changes to impact dementia development.

1. Introduction

Migraine is a severe neurological disorder that remarkably impacts daily life and has been increasingly associated with cognitive dysfunction (Gil-Gouveia and Martins, 2019; Gu et al., 2022). While migraine is typically recognized for its headache episodes, recent research suggests it also affects cognitive abilities, even outside of these episodes (Cees De Groot et al., 2000; Vuralli, Ayata, and Bolay, 2018).

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Studies have shown inconsistent findings regarding cognitive impairment in migraineurs (Baars, Van Boxtel, and Jolles, 2010; Gaist et al., 2005), with some clinical studies demonstrating reduced cognitive function (Gu et al., 2022; Islamoska et al., 2020; Lee, et al., 2019; Vuralli et al., 2018). In contrast, larger population-based studies do not find significant differences compared to healthy controls (Vuralli et al., 2018).

These discrepancies may be due to the dynamic nature of cognition, which is influenced by the brain's neural networks, such as the default mode network (DMN) and hippocampal networks. Herein, the hippocampal region is known to have distinct role in memory retrieval (Stark and Squire, 2000).

On the other hand, there is mounting evidence that the hippocampus is involved in both pain processing and episodic memory, suggesting that it is essential for cognitive functions related to pain (Maleki et al., 2013).

Cognitive functions are dynamic processes strongly related to specific networks and their adaptive capacity, suggesting a significant relationship between neural connectivity and cognitive performance in different cognitive states (Z. Liu et al., 2019; Zeng et al., 2022). Herein, neural connectivity plays a crucial role in shaping cognitive dynamics, incorporating both the structural and functional characteristics of the brain's organization. For instance, studies have shown that cognitive network flexibility is strongly linked to cognitive control, supporting the crucial role of their plasticity to modify connectivity patterns for effective cognitive processes dynamically (Braun et al., 2015; Shine et al., 2016). A good example could be decreased neural flexibility in older adults, which correlates with declines in cognitive performance (Varangis, et al., 2019; Viviano et al., 2017) implicating critical alterations in the default mode network and executive control networks that interact in a dynamic-coupling manner (Beaty et al., 2015; Taya et al., 2018) during cognitive tasks. These studies together suggested that the plasticity and dynamism of these networks to adapt and reconfigure in response to cognitive demands is essential for effective and adaptive cognitive functioning, which might have critical implications for understanding the neural basis of cognitive processes in healthy and diseased states. The ability of these networks to adapt and reconfigure in response to cognitive demands is essential for effective cognitive functioning, with implications for understanding cognitive aging, recovery from brain injuries, and the neural basis of complex cognitive processes.

Resting-state functional MRI (rs-fMRI) has emerged as a critical tool for identifying these network alterations. rs-fMRI evaluates the consistency of the blood-oxygen-level-dependent (BOLD) signal, revealing changes in functional connectivity that may underlie both migraine and cognitive impairment (Behzadi et al., 2007). Notably, Xue et al. found abnormalities in several brain networks, including the DMN, which may be a marker of migraine progression (Xu et al., 2021).

The hippocampus, known for its role in memory and cognition, is altered in migraine patients. Studies indicate migraineurs may have smaller hippocampal volumes and altered connectivity between the hippocampus and other brain regions, such as the prefrontal cortex and insula (Tang et al., 2020; Zheng et al., 2018). Maleki et al. suggested an inverse correlation between hippocampal structure/function and migraine attack frequency (Maleki and Gollub, 2016). However, reduced hippocampal volumes are not consistently observed across all studies, leading to controversy over using hippocampal volume as a biomarker for cognitive impairment in migraine (Gu et al., 2022).

Interestingly, recent studies have hinted at a potential link between migraine and an increased risk of dementia, further emphasizing the need to explore hippocampal subfield integrity in migraine patients with cognitive impairment (Gu et al., 2022; Islamoska et al., 2020; Lee et al., 2019; Ren et al., 2018).

For instance, a recent meta-analysis by Jiang et al., which examined nine studies on the potential risk of dementia in migraine patients, indicated that migraine was linked to a higher risk of developing dementia (Jiang et al., 2022). Although some fMRI studies have reported modest reductions in hippocampal subfields, these findings are not universal (Maleki et al., 2013; Wei et al., 2020; Zhu et al., 2021). Therefore, evaluating hippocampal subfield volume alone may not be sufficient without considering functional connectivity (Zheng et al., 2018).

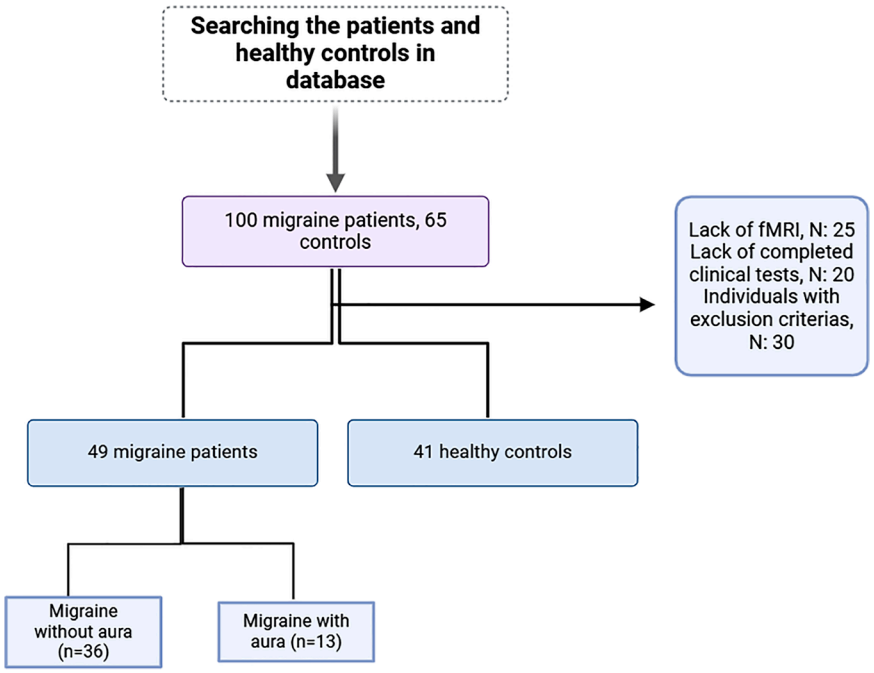
Given the unneglectable role of the hippocampus in cognition and studies that underline its role in pain processing (Whitlock et al., 2017; Zhao et al., 2023) also including migraine (Maleki et al., 2013), we were eager to evaluate its contribution to both cognitive and pain-related processes in migraine patients, which might intersect in a pathophysiological manner. In particular, current conflicting results, which were insufficient to distinguish the role of the hippocampus in cognition from a pain-related process (Preis et al., 2013; Russo et al., 2017), led us to hypothesize whether cognitive impairment and pain processing are distinct entities or intersecting processes implying that pain episodes may lead to altered brain regions associated with the presentation of painful memories at the expense of cognitive functioning.

The aim of our research is to investigate the anatomical and functional brain alterations of cognitive impairment in migraine patients. Our present study underscores the importance of investigating both the anatomical and functional integrity of hippocampal subfields in migraine patients, especially considering their increased risk of dementia. Despite the intriguing findings, further research is needed to clarify the relationship between migraine, hippocampal alterations, and cognitive impairment.

2. Methods

2.1. Participants

The process of selecting migraine patients and healthy controls began by searching a database identifying an initial sample of 100 migraine patients and 65 healthy control individuals. Some participants were excluded due to missing fMRI data (25 individuals), incomplete clinical tests (20 individuals), or other specified exclusion criteria (30 individuals). After applying these exclusions, the final sample included 49 migraine patients and 41 healthy controls. The migraine group was further divided into two subgroups: 36 patients with migraine without aura and 13 patients who had aura (Graphic 1) (Created in BioRender.com). Aura included temporary visual or sensory disturbances, nausea, and sensitivity to light and sound. Migraine patients were in the interictal phase during data collection. The diagnosis of migraine was performed by two neurologists, each with at least five years of specialized experience in headache disorders, according to International Headache Society criteria. (Society, 2013) (Headache Classification Committee of the International Headache, 2013). All evaluations of the control group



Graphic 1. Flowchart of the study design.

were performed during the study, and the national general health system was employed to verify that none of the control group members had ever been diagnosed with migraine.

The participants were recruited from the Alanya Alaaddin Keykubat University Department of Neurology, Turkey. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Montreal Cognitive

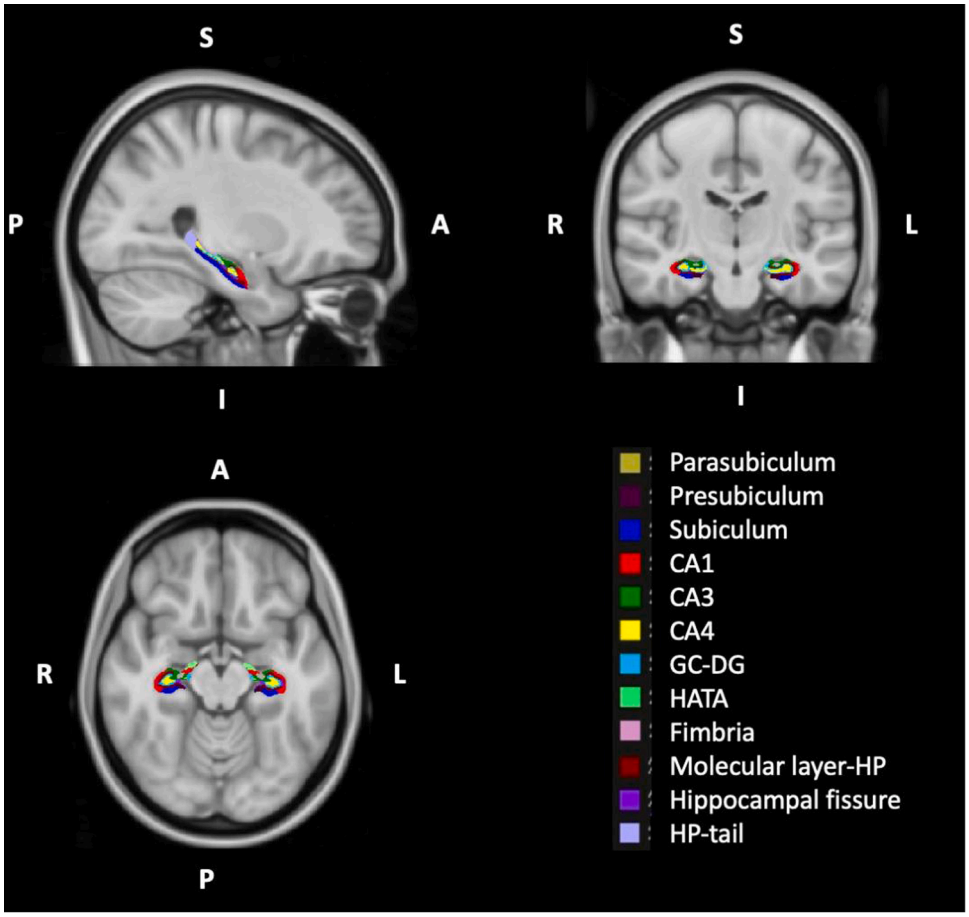


Fig. 1. Hippocampal subfields ROIs.
Coronal, axial, and sagittal sections of an MNI_152 template showing the hippocampal subfields. All subfields were generated using FreeSurfer hippocampus/amygdala segmentation tool of the MNI_152 template. MNI, Montreal Neurological Institute.

Assessment (MOCA) (Nasreddine et al., 2005) were applied to measure cognitive impairment, while the MMSE test was used to rule out dementia. The translated Turkish version of MOCA (Ozdilek and Kenangil, 2014) and MMSE (Keskinoglu et al., 2009) were used in this study.

Approval for the study was granted by the Alanya University ethical committee (Ethical report number 16,072,023/289). Approval for the study was granted by the Alanya University ethical committee (Ethical report number 16,072,023/289). G*power (ver. 3.1.6.6) software was used to determine the sample size. This showed that a sample size of 16 subjects would be required for 90 % power with a significance level of α=0.05 (Faul et al., 2009).

Participants with neurodegenerative, neuropsychiatric, chronic metabolic disease, or previous histories of trauma were excluded from the study.

Inclusion criteria for the migraine group were: 1) Between the ages of 18–70; 2) Definitive diagnosis of migraine; 3) No history of other diagnosis other than migraine; 4) Being in the interictal phase of migraine during the evaluation.

Inclusion criteria for the control group were: 1) Between the age of 18–70; 2) No history of any diseases 3) No history of drug use. Exclusion criteria were: 1) History of neurodegenerative or neuropsychological disease; 2) History of drug intake that may affect participants' cognitive status; 3) History of head trauma; 4) History of major surgery; 5) Chronic metabolic disease; 6) Abnormal levels of blood vitamin B12, vitamin D, thyroid functions, kidney or liver function levels.

2.2. MRI data acquisition

Structural and resting-state fMRI was conducted using a Signa Explorer MR device (General Electric Company, USA) with a strength of 3T at Alanya Alaaddin Keykubat University. Each T1-weighted structural scan consisted of 190 slices (TR/TE: 8.1/3.7), FOV 256 × 256 × 190 mm (FHxAPxRL), and a voxel size of 1 × 1 × 1 mm. Eyes closed resting state fMRI scan recordings were collected using an echo-planar imaging sequence (EPI). The scanning process lasted approximately 12 min, and 300 vol were recorded with the following parameters: TR 2230 ms, TE 30 ms, FOV 240 × 240 × 140 mm (RLxAPxFH), voxel size 3 × 3 × 4 mm, flip angle 77°, and slice number 35. Before ~~the~~ scanning, all participants were instructed to keep their eyes closed, relax and move as little as possible, to empty their minds, and not to fall asleep during the procedure

2.3. Extraction of hippocampal seeds

Based on our previous research, ~~the~~ bilateral hippocampal subfield seeds were extracted through Freesurfer software (version 7.1.1) (Mazaika et al., 2009; Velioglu et al., 2023).

Since there is no specific definition for hippocampal subfields in the CONN toolbox (version CONN v21a https://web.conn-toolbox.org), parcellation derived from the Harvard-Oxford Cortical and Subcortical Atlas, segmentation of the hippocampal subfields was performed in a FreeSurfer-based segmentation. This segmentation was conducted in MNI 1-mm standard space using the hippocampus/amygdala segmentation tool (segmentHA_T1.sh). The discrete hippocampal segmentation output was extracted to get bilateral hippocampal subfield ROIs in FreeSurfer's native voxel space.

These ROIs were then imported into the CONN toolbox using the Setup tab under the ROIs section, and they were labelled accordingly. Following this, the ROIs were applied to the resampled functional data in the MNI space for subsequent analyses in CONN. The hippocampal subfields of the hippocampus-amygdala-transition-area (HATA), cornu ammonis (CA)1, CA2–3, CA4, fimbria, granule cell and molecular layer of dentate gyrus (GC-ML-DG), hippocampal fissure, hippocampal tail, molecular layer, parasubiculum, presubiculum, and subiculum in each brain hemisphere were selected as seeds. The extracted seeds were transformed to the appropriate Nifti (.nii/nii.gz) format from the Freesurfer (.mgh/mgz) format (Fig. 1).

2.4. Analysis of resting-state functional connectivity (rsFC)

The participants' structural and resting-state functional images were transformed to NiFTI format from DICOM format via MRIcroGL (https://www.nitrc.org/projects/mricrogl) and imported into the Functional Connectivity Toolbox (CONN v21a https://web.conn-toolbox.org), a MATLAB (platform MAC v23a) and SPM-based software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/).

The images were preprocessed through the default functional and anatomical preprocessing pipeline, which includes realignment & unwarp, slice-timing correction, outlier detection, segmentation, normalization, and smoothing. The head movement realignment was arranged as 97th percentiles with linear motion parameters >0.9 mm and global signal $z > 3$ value thresholds. The artefact rejection tool (ART) was carried out to detect the outlier functional images (Iglesias et al., 2015). Functional data were smoothed with a six mm3 full-width Gaussian kernel at half-maximum (FWHM). The T1-weighted structural images were segmented into gray matter, white matter, and cerebrospinal fluid via tissue probability maps. In the next step, the functional data were bandpass filtered at 0.008–0.1 Hz. in order to reduce the effects of noise. The six motion parameters and first-order derivatives were then regressed, and the signals were collected from the white matter and cerebrospinal fluid as an anatomical component-based noise correction process (aCompCor) (Behzadi et al., 2007) and the confounding factors deriving from the resting condition.

The hippocampal subfields extracted through the Freesurfer were imported into the CONN toolbox for seed-to-voxel analysis. In the first-level analysis, the average BOLD time series of all ~~ROIs~~ ROI were extracted, and the correlation coefficients between the BOLD time series of each ROI and brain voxel were also computed. These correlation coefficients were then z-transformed for statistical analysis using the Fisher transformation. All ROI z-values were compared between the two groups using analysis of variance (ANOVA) at the second level, with p_{unc} <0.001 at the voxel level and family-wise error (FWE) adjusted *pFWE* <0.05 at the cluster level. The subjects' years of education were added as covariates in the second-level analysis, given the significant difference in education years between the groups.

2.5. Analysis of hippocampal subfield volumes

Volumetric analysis was performed using the "recon-all" module in Freesurfer software (v. 7.1.1 https://surfer.nmr.mgh.harvard.edu). The recon-all includes the following steps: Normalization of signal, removal of non-brain tissue, Talairach transformation, segmentation of gray and white matters, brain boundary delineation, automated topology correction, and surface deformation and reconstruction of T1 weighted structural images. Following the "recon-all," the hippocampal/amygdalar segmentation tool was performed to segment the hippocampus into its subfields. The gray matter volume of each hippocampal subfield was recorded for statistical analysis. Estimated total intracranial volume (eTIV) data were also obtained using the "recon-all" module to standardize the different brain sizes and volumes. The hippocampal/amygdala segmentation tool is based on a probabilistic atlas derived from histological specimens.

2.6. Statistical analysis

Simple descriptive statistics and cognitive scores were analyzed using the Shapiro-Wilk test to check the normality of the variables ("IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.,") with IBM SPSS Statistics for Windows, Version 25.0. Continuous variables were presented as mean (standard deviation [SD]); median (interquartile range [IQR]), and categorical variables as frequency (n) and percentage (%). An independent Samples

Table 1
The demographic features and clinical test scores of the study groups.

Variables	Group 1 (n = 36)		Group 2 (n = 13)		Group 3 (n = 41)	
	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)
Education years	12.28 (3.54)	12 (4)	12.77 (3.60)	14 (2)	15.78 (3.88)	16.00 (6)
Age	35.25 (12.16)	35.3 (24)	29.31 (12.46)	27 (7)	32.12 (10.02)	28 (9)
MOCA	24.81 (3.36)	25 (4)	24.85 (2.51)	25 (1)	27.49 (2.28)	28.00 (4)
MMSE	28.31 (1.6)	29 (2)	27.85 (1.57)	28 (3)	29.27 (1.07)	30 (2)
Gender, female (n,%)	31 (86 %)		12 (92 %)		16 (39 %)	

Group 1: Migraine patients without aura.
Group 2: Migraine patients with aura.
Group 3: Healthy controls.
Data are presented as median (interquartile range), mean (±SD) or counts (%).
MOCA: The Montreal Cognitive Assessment, ***MMSE:*** The Mini-Mental State Examination, ***n:*** number of patients, ***SD:*** Standard Deviation.

Student's *t*-test was used for normally distributed variables while for non-normally distributed variables a Mann-Whitney U test was used to analyze and compare the means of two groups. For multiple comparisons, the post hoc test was adopted for the ANOVA. A two-sided p-value ≤ 0.05 was interpreted as statistically significant. Correlations between MOCA scores and regional functional connectivity were assessed through correlation matrices, while for each variable, a Spearman's r value indicated the strength and direction of the relationship between the two variables.

Linear regression analysis with a two-step procedure was used to identify predictors of MOCA scores. All potential predictors were considered separately (univariate analysis) in the first step. Variables included in evaluating the predictive value of MOCA were age, education, and functional connectivity findings. The potential predictors were assessed in the second step using multivariable linear regression analysis (enter method) and the stepwise method. A p-value<0.05 was considered significant.

G power was used to check the effect size, with a value of 0.917 being determined (Faul et al., 2009). Analysis of co-variance (ANCOVA) was applied to investigate groupwise differences in hippocampal subfield volumes. Age and estimated eTIV were entered as covariates.

3. Results

The demographic and clinical characteristics of the study groups, consisting of migraine patients with and without aura and a healthy control group, are summarized in Table 1. A total of 100 participants consisted of 36 migraine patients withOut aura (MO), 13 migraine patients with Aura (MA), and 41 healthy objects.

The data in Table 2 revealed significant differences between migraine patients and healthy controls regarding demographic characteristics and clinical test scores. The female ratio was significantly higher (χ^2 = 23.5, $p < 0.001$) among migraine patients (87.8 %) compared to the control group (39 %). In terms of education, migraine patients had significantly lower ($p < 0.001$) education levels (12.41 ± 3.53) compared to the control group (15.78 ± 3.88). The MOCA and MMSE scores also demonstrated significant disparities. Controls had better cognitive situation than migraineurs regarding MOCA and MMSE ($p < 0.001$). No significant difference in age ($p = 0.91$) was observed

Table 3
The differences of demographic and clinical features in between the groups.

Variables	Group 1 vs Group 2 (p)	Group 1 vs Group 3 (p)	Group 2 vs Group 3 (p)	ANOVA F, p
Age	0.392	0.536	0.85	1.539, 0.22
Education years	0.966	**<0.001***	0.052	**9.313, <0.001***
MOCA	0.00	**<0.001***	**0.01***	**10.198, <0.001***
MMSE	0.76	**0.01***	**0.023***	**7.437, 0.001***
Gender	χ^2: 0.341, 0.559	**χ^2:19.3, <0.001***	**χ^2: 11.2, <0.001**	**χ^2:23.6, <0.001**

Group 1: Migraine patients without aura.
Group 2: Migraine patients with aura.
Group 3: Healthy controls.
MOCA: The Montreal Cognitive Assessment, ***MMSE:*** The Mini-Mental State Examination.
Data were analyzed with post-hoc tests in one-way ANOVA. Categorical variables were analyzed with Pearson Chi-Square test (X2). Significance level at ***p* < 0.05**.

Table 4
Right hippocampal volume analysis between the groups showing significant differences in right CA1 head, right HATA, whole hippocampal head, and whole hippocampus volumes.

	Migraine (n = 49) (mean±SD)	Control (n = 41) (mean ±SD)	F	t	p
Right CA1 head	501± 52.19	536.3 ± 70.51	3.17	2.73	**0.006***
Right HATA	54.52 ± 7.72	61.13 ± 9.70	0.35	2.89	**0.005***
Whole hippocampal head	1685.12 ± 173.39	1822.31 ± 197.34	2.47	2.81	**0.003***
Whole hippocampus	3431.47 ± 310.70	3666.79 ± 368.44	3.41	2.93	**0.004***

Data are presented as mean (SD), n: number of patients, significance level: *$p < 0.05$.
Normally distributed data were analyzed with Student's *t*-test.

Table 2
The differences between migraine patients and controls in terms of the demographic features and clinical test scores.

Variables	Migraine (n = 49)		Control (n = 41)		F	t	p
Gender (female)	43 (87.8 %)		16 (39 %)				χ^2:23.5, <0.001*
	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)			
Years of education	12.41 (3.53)	12.00 (4)	15.78 (3.88)	16.00 (6)	0.87	4.32	**< .001***
Age	33.67 (12.39)	29 (18)	32.12 (10.02)	28 (9)	4.15	-0.66	0.919
MOCA	24.82 (3.13)	25.00 (4)	27.49 (2.28)	28.00 (4)	2.003	4.54	**< .001***
MMSE	28.18 (1.59)	29 (2)	29.27 (1.07)	30 (2)	8.96	3.84	**< .001***

Data are presented as median (interquartile range), mean (±SD) or counts (%).
Normally distributed data were analyzed with Student's *t*-test; non-normally distributed data were analyzed with a Mann-Whitney *U* test and categorical variables were analyzed with Pearson Chi-Square test (X2).
MOCA: The Montreal Cognitive Assessment, ***MMSE:*** The Mini-Mental State Examination, ***n:*** number of patients, ***SD:*** Standard Deviation Significantly different (*$p < 0.05$) from persons with migraine and healthy controls.

Table 5
Correlation between MOCA scores and hippocampal subfields in the whole group.

			1	2	3	4	5	6	7	8	9	10	11	12	13
1	**MOCA**	r													
		p													
2	**CONN imported values**	r	-,277**												
	cluster rest_L_CA_3	p	,008												
3	**+36 + 18 + 38**	r	-,169	,661**											
	rest_L_HATA	p	,112	,000											
4	**−54 -60 + 30**	r	-,191	,195	,263*										
	rest_L_HATA	p	,071	,065	,012										
5	**−2 + 28 + 36**	r	-,192	,232*	,386**	,356**									
	rest_L_HATA	p	,070	,027	,000	,001									
6	**+46 -56 + 46**	r	-,142	,470**	,654**	,142	,308**								
	rest_L_HATA	p	,181	,000	,000	,181	,003								
7	**+38 -84 + 6**	r	,235*	-,357**	-,262*	-,359**	-,211*	-,276**							
	rest_L_fimbria	p	,026	,001	,013	,001	,046	,008							
8	**−10 -98 + 6**	r	,238*	-,454**	-,316**	-,149	-,220*	-,282**	,675**						
	rest_L_fimbria	p	,024	,000	,002	,160	,037	,007	,000						
9	**+52 + 16 −34**	r	,207	-,431**	-,365**	-,287**	-,318**	-,214*	,247*	,317**					
	rest_L_fimbria	p	,051	,000	,000	,006	,002	,043	,019	,002					
10	**−42 + 18 −24**	r	,264*	-,364**	-,293**	-,276**	-,227*	-,333**	,404**	,440**	,683**				
	rest_L_fimbria	p	,012	,000	,005	,009	,032	,001	,000	,000	,000				
11	**+22 −12 −12**	r	,273**	-,327**	-,330**	-,308**	-,232*	-,323**	,363**	,208*	,326**	,334**			
	rest_R_CA_3′	p	,009	,002	,002	,003	,028	,002	,000	,049	,002	,001			
12	**+46 + 6 −14**	r	,344**	-,355**	-,215*	-,238*	-,145	-,198	,345**	,272**	,188	,277**	,466**		
	rest_R_CA_3	p	,001	,001	,042	,024	,174	,062	,001	,010	,076	,009	,000		
13	**+40 + 26 −6**	r	,191	-,451**	-,327**	-,202	-,120	-,158	,242*	,271**	,305**	,225*	,359**	,438**	
	rest_R_HP_tail	p	,071	,000	,002	,056	,260	,136	,021	,010	,003	,034	,001	,000	
14	**−36 + 14 −6**	r	,266*	-,344**	-,432**	-,359**	-,183	-,239*	,396**	,314**	,217*	,322**	,325**	,417**	,550**
	rest_R_HP_tail	p	,011	,001	,000	,001	,084	,023	,000	,003	,040	,002	,002	,000	,000

r: Spearman's rho, Correlation Coefficient.
MOCA: The Montreal Cognitive Assessment, ***MMSE:*** The Mini-Mental State Examination.
** p: Correlation is significant at the 0.01 level (2-tailed).
* p: Correlation is significant at the 0.05 level (2-tailed).

between the migraine group and controls.

Table 3 illustrates significant demographic and clinical differences among three groups: MO (Group 1), MA (Group 2), and Healthy Controls (HC, Group 3). The age variable did not show statistically significant differences across groups (ANOVA $F = 1.539$, $p = 0.22$), indicating similar age distributions.

In terms of education years, MO and HC showed a significant difference ($p < 0.001$), with the healthy control group having a higher education level on average. Group MA and HC also displayed a marginally significant difference in education ($p = 0.052$), while no significant difference was observed between MO and MA ($p = 0.966$). The overall one-way ANOVA analysis confirmed a significant difference in education levels among the groups ($F = 9.313$, $p < 0.001$).

For cognitive assessments, the MOCA scores did not differ significantly between MO and MA. However, MO and HC ($p < 0.001$), as well as MA and HC ($p = 0.01$), showed significant differences, with the control group scoring higher than both migraine groups. Similarly, MMSE scores were higher in controls than MO ($p = 0.01$) and MA ($p =$

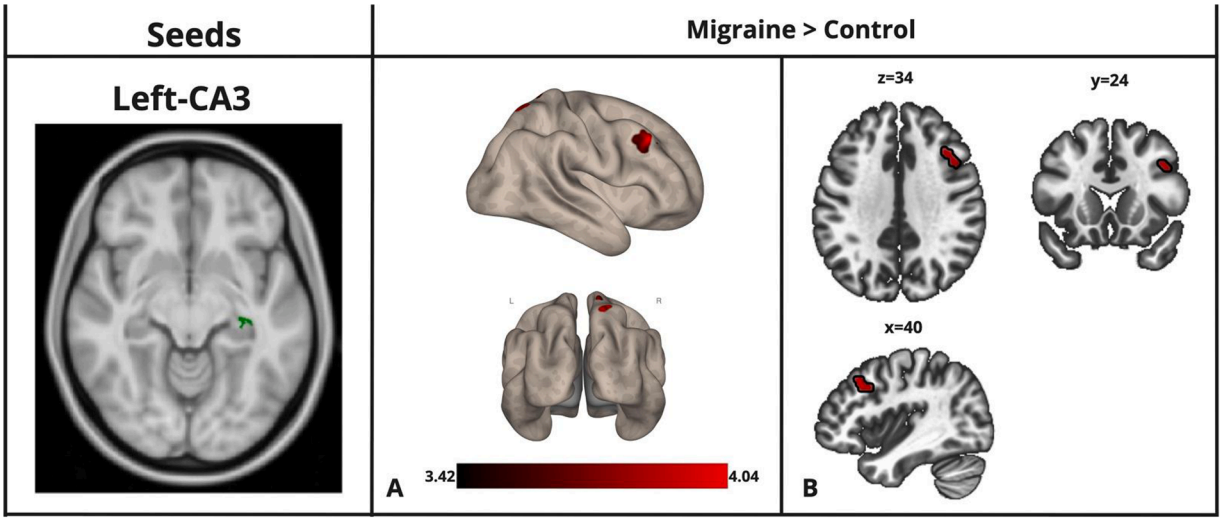


Fig. 2. The seed-based connectivity results of the left-CA3 (Migraine>Control).
The left-CA3, in the migraine group, exhibited higher connectivity to the right MFG compared to the healthy controls (A1-B1). The red patches indicate an increase in functional connectivity in the migraine group. The color bars present the t-statistics. (p-values indicate differences in functional connectivity between groups by one-way analyses of co-variance $p < 0.001$ voxels and p-FWE<0.05 at cluster level with a minimum of 30 voxels for each cluster). The regions depicted on brain maps are described in Table 6. Abbreviation: MFG, middle frontal cortex.

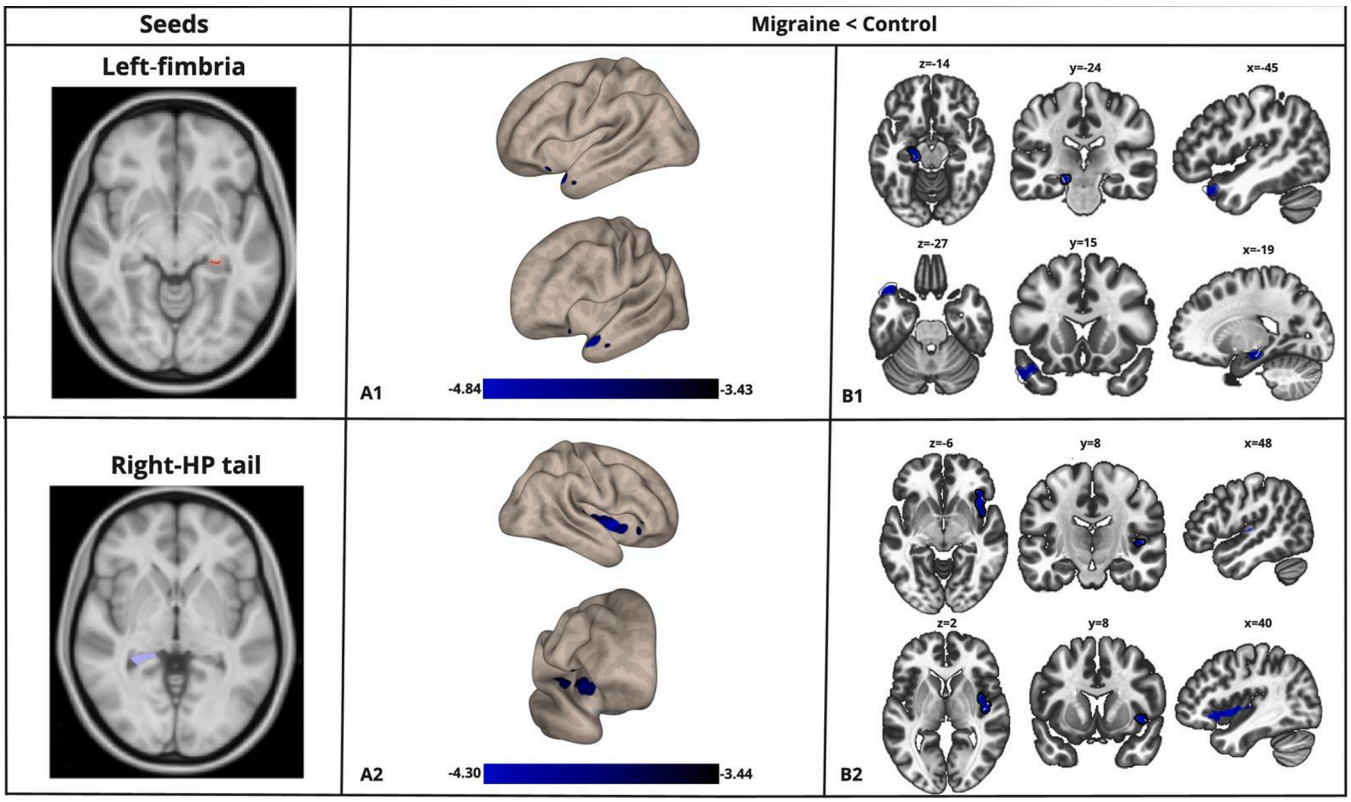


Fig. 3. The seed-based FC results of the left-fimbria, and the right-hippocampal tail (Migraine<Control).
In this seed-based connectivity analysis, the left fimbria and right HP-tail reveal intriguing connectivity patterns. Notably, the left fimbria in the migraine group exhibits reduced connectivity to the bilateral occipital cortex and temporal pole (A1-B1). Furthermore, the right HP-tail shows diminished connectivity to the bilateral frontal orbital and insular cortex (A2-B2). Areas of reduced connectivity are highlighted in blue, representing significant functional differences in the migraine group. The color bars denote t-statistics, and statistical significance is set at $p < 0.001$ voxels and p-FWE <0.05 at the cluster level, with a minimum cluster size of 30 voxels. The regions depicted on brain maps are described in Table 6.

0.023).

Gender distribution was another area of significant difference, particularly between MO and HC ($\chi^2 = 19.3, p < 0.001$) and between MA and HC ($\chi^2 = 11.2$, $p < 0.001$), with a higher female proportion in migraine groups compared to controls. Pearson Chi-Square tests confirmed a significant difference in gender composition across groups ($\chi^2 = 23.6$, $p < 0.001$).

These results indicate that the healthy control group had higher education and cognitive scores, while the migraine groups, with a predominantly female composition, exhibited lower cognitive test scores.

Table 4 compares right hippocampal volume measurements between migraine patients and healthy controls, revealing significant differences in specific hippocampal subregions. The findings suggest that migraines are associated with smaller volumes in several right hippocampal regions, including the CA1 head ($p = 0.006$), HATA ($p < 0.001$), whole hippocampal head ($p = 0.003$), and whole hippocampus ($p < 0.001$). The volume reductions in these areas may have implications for understanding the structural impact of migraines on brain anatomy.

The analysis in Table 5 reveals correlations between MOCA scores and hippocampal subfields across various coordinates. Significant correlations were observed between MOCA scores and several subfields, including the left CA3, left fimbria, right CA3, and right HP tail. These findings imply that specific areas within the hippocampus may be associated with cognitive function, as measured by MOCA scores, indicating their potential role in supporting cognition.

3.1. *Between-group differences in the functional connectivity of the hippocampal subfields*

After education years were added as a covariate into the second-level functional analysis, the left CA3, left fimbria, and right hippocampal (HP)-tail in the migraine group exhibited significant functional connectivity differences between migraine group and healthy controls (Figs. 2–4 and Table 6). The left CA3 exhibited higher connectivity with the right middle frontal gyrus (MFG) ($t = 5.71$ and p-FWE=0.021), right lateral occipital cortex, and right superior parietal lobule ($t = 4.95$ and p-FWE=0.028) in the migraine group (Table 6), (Figs. 2A, B and Fig. 4A). In contrast, the left fimbria and the right HP-tail in the migraine group exhibited lower functional connectivity compared to the controls (Fig. 3). The left fimbria exhibited lower connectivity to the left temporal pole (t=−6.82, p-FWE<0.001) and the left hippocampus (t=−5.89, p-FWE=0.040) in the migraine group (Figs. 3 A1–B1, Fig. 4B, and Table 6). Additionally, the right HP-tail exhibited decreased connectivity with the right insular orbital cortex, right Heschl's gyrus, and the right frontal orbital cortex (t=−5.24 p-FWE<0.001) (Table 6) (Figs. 3 A2-B2 and Fig. 4C).

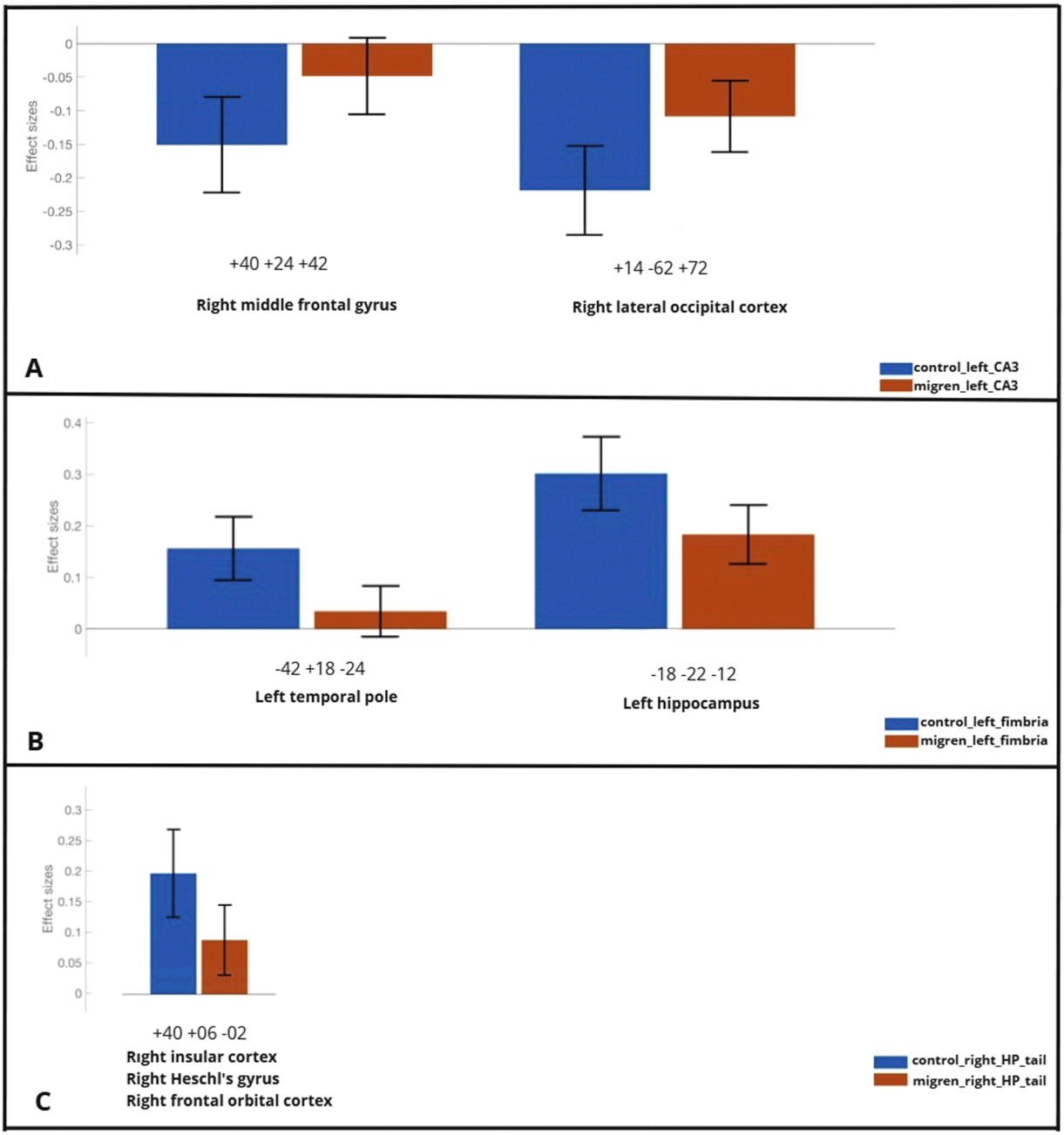


Fig. 4. Effect size of ROIs showing functional connectivity differences between Migraine and Control groups
The effect sizes (Fisher z-transformed correlation coefficients) are shown for both groups: the red bars represent the migraine group, and the blue bars represent the control group. The effect size reflects the strength of functional connectivity in ROIs, which shows significant connectivity differences between the two groups. Panels A, B, and C represent the left CA3, left fimbria, right HP-tail seeds, respectively. The coordinates on the x-axis correspond to the peak MNI coordinates (from Table 6), related to the ROIs that exhibited functional connectivity differences between the two groups. Regions below the coordinates show connectivity differences in the related seeds.

Table 6
Functional connectivity differences between the two groups. Seeds exhibiting functional connectivity differences between the two groups. While the left CA3 show increased connectivity; left fimbria and the right hippocampal-tail connectivity were decreased in the migraineurs. The p-value assesses the difference between groups using one-way analyses of covariance.

Seeds	Regions	MNI coordinates	size	t-max	*p*-value
Migraine > HC					
Left CA3	Right middle frontal gyrus	40 24 42	126	4.95	0.021097*
	Right lateral occipital cortex	14 −62 72	68	5.07	0.028527*
Migraine < HC					
Left fimbria	Left temporal pole	−42 18 −24	150	−6.82	0.004416*
	Left hippocampus	−18 −22 −12	42	−5.69	0.040813*
Right hippocampal tail	Right insular cortex Right Heschl's gyrus Right frontal orbital cortex	40 06 −02	299	−5.24	0.000097*

HC: healthy controls.
* $p < 0.001$ voxel and P-FWE < 0.05 at the cluster level.

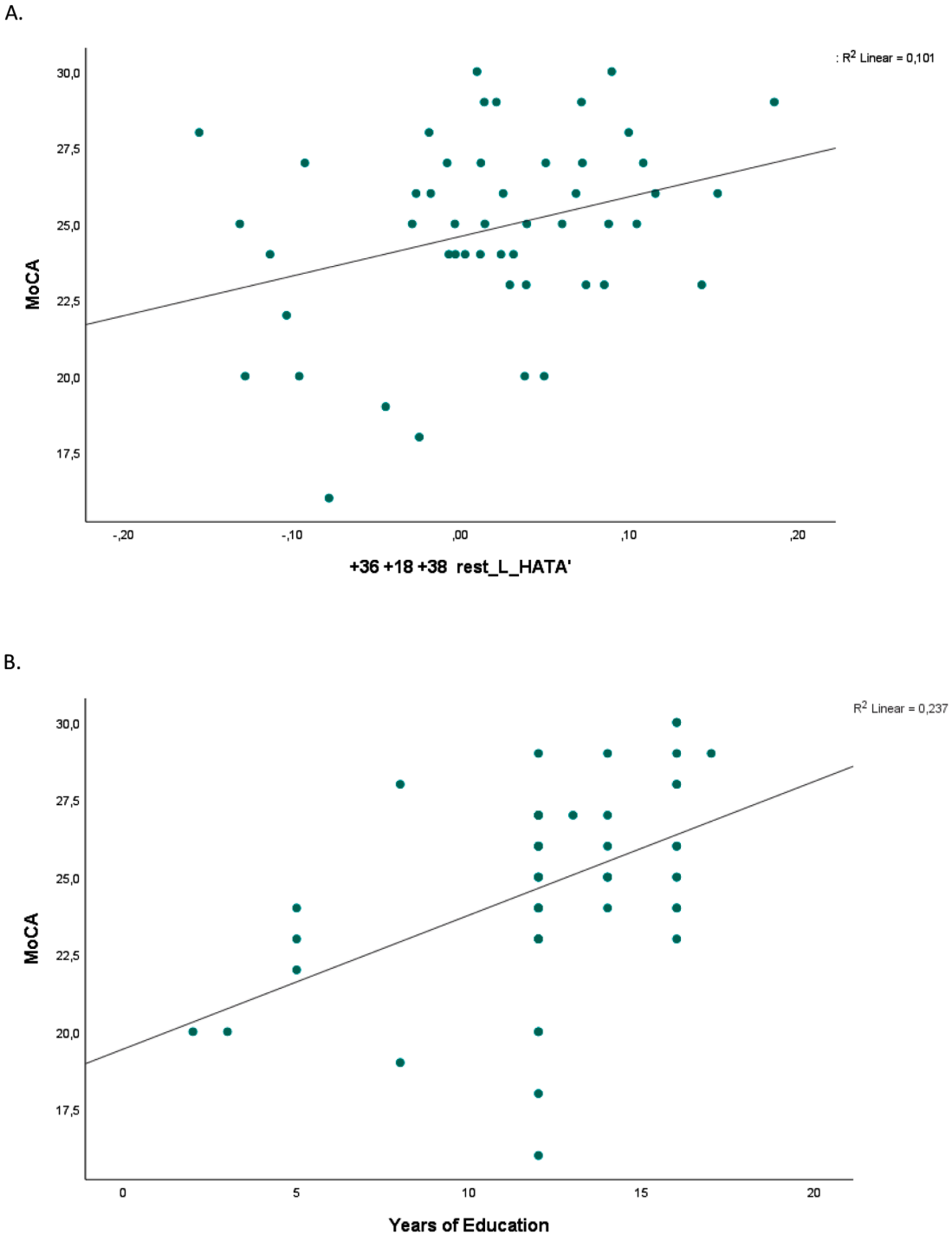
3.2. Regression analysis of functional connectivity

Multiple linear regression was calculated to predict MOCA scores based on radiological parameters, age, and education in the migraine group. In univariate linear regression analyses, Left_HATA +36 + 18 + 38 (β=0.317; 95 % CI, 1.611–24.457; $p = 0.026$) and education (β=0.487; 95 % CI, 0.660–0.205; $p < 0.001$) were significant predictors for MOCA. Multivariable linear regression analysis adjusted for age and education showed that the MOCA was significantly related to Left_HATA +36 + 18 + 38 (β=0.530; 95 % CI, 6.139–37.261; $p = 0.008$) and education (β: 0.572; 95 % CI, 0.248–0.777; $p < 0.001$) (Supp. Table 1).

In the Stepwise method, Left_HATA +36 + 18 + 38 (β:0.295; 95 % CI, 6.139–37.261; $p = 0.019$) and education (β: 0.491; 95 % CI, 0.221–0.657; $p < 0.001$) remained as significant predictive values (Supp. Table 2 and Graphic 2).

4. Discussion

The findings of this study revealed significant differences between patients with migraine and healthy controls in the volumes and resting



Graphic 2. Scatter plots showing the significantly associated variables with Montreal Cognitive Assessment (MoCA) in stepwise model. A) The connectivity of Left HATA (+36 +18 +38) increased with MoCA score (p=0.019, B=0.295, %95 CI [0.221–0.657]) and B) the MoCA score significantly increased with years of education (p<0.001, B=0.491, %95 CI [2.109–22.051]).

state functional connectivity (rsFC) of the hippocampal subfields. Our findings of higher functional connectivity between the hippocampal subfield (CA3) and the MFG, as well as with the lateral occipital cortex, in the patients' group are consistent with previous studies suggesting a hyperconnectivity pattern in cognitive impairment (Cera et al., 2019; Han et al., 2022), which is evident even in patients without dementia. This has been also mechanistically confirmed in Association-Sequence Network (ASN) model of episodic memory (Han et al., 2009; Kim and Lee, 2023), indicating the role of compensatory functional mechanisms in age-related cognitive decline.

Also, studies (Hu et al., 2023; Lo Buono et al., 2017; J. Zhang et al., 2016) suggested an increased connectivity pattern including right rostral anterior cingulate cortex, prefrontal cortex, orbitofrontal cortex, supplementary motor area, and also overlapping with our findings. These study results align well the findings showing that polysynaptic hippocampal-cortical connections (Morgado-Bernal, 2011; Poppenk et al., 2013) also involve some specific associations between fimbrial and frontal temporal and occipital regions (Bubb et al., 2017; Morgado-Bernal, 2011; Poppenk et al., 2013) that play a critical role in high cognitive functions (Amoroso et al., 2018; Fornito et al., 2004; Han et al., 2009) and found to be altered in patients with AD (Anand and Dhikav, 2012) also suggesting our findings of altered functional connectivity between these aforementioned regions. To be more specific our findings of lower functional connectivity between the left hippocampal fimbria and hippocampus and temporal cortex, as well as the reduced connection between the HP with the frontal, temporal, and insular cortex, are thus also consistent with previous studies mentioned above.

Some studies revealed that altered hippocampal volumes in migraine (Chong et al., 2017; Hubbard et al., 2014) with specifically indicating the role of pain frequency on hippocampal plasticity (Yu et al., 2021), structure (J. Liu et al., 2013), and connectivity (Gao et al., 2016; Tomasi et al., 2013) which was also confirmed for specific regions we observed (Maleki et al., 2013; Wei et al., 2020). Nevertheless, the influence of the hippocampus on cognitive functions, brain connectivity and structure could not be delineated in the studies mentioned above, which may provide novel insight into the cognitive basis of migraine, To the best of our knowledge, only one study conducted by Tsai et al., showed altered structural integrity within hippocampal subdivisions, in the pathophysiology of subjective cognitive impairment and migraine (Tsai et al., 2023).

Our finding of altered network activity between the fimbria and frontal cortex is particularly interesting with its proven role in retrieving memories through a direct pathway. This is suggested with several animal and human studies (Cohen et al., 1999; M. Zhang et al., 2020) and its consistent with previous research suggesting that the rMFG plays a crucial role in attention, awareness, and mental flexibility (Cohen et al., 1999) through its role in converging the dorsolateral frontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) (Gu et al., 2022). Based on this, it is not unreasonable to assume that abnormal CA3-MFG connectivity may be related to the lack of concentration and cognitive dysfunction experienced by patients with migraine. Also, our findings of altered frontal connectivity align with recent literature showing that migraine patients with ictal episodes exhibited greater activation of the frontal regions during executing a working memory test (Ruiz-Tagle et al., 2024). This is in line with previous studies showing a significant effect of pain on brain function (Afridi et al., 2005; Coppola et al., 2016) that was associated with altered cognition and cognition-related brain activity in acute migraine patients (Coppola et al., 2016; Mathur et al., 2015). These findings align with the previous healthy data showing that decreased functional connectivity between the anterior hippocampus and medial prefrontal cortex (mPFC) indicates successful memory encoding (Tessitore et al., 2015). We have shown that the left fimbria and right HP-tail showed considerably different connectivity features compared to the control group, which aligns with recent data showing altered intrahippocampal connectivity in mild cognitive impairment. However, to the best of our knowledge no specific study evaluated the connection between fimbria and HP tail in headache patients with cognitive impairment (Won et al., 2021). Furthermore, abnormal MFG connectivity in migraines with and without aura has been shown in the absence of clinically relevant cognitive deficits (Tessitore et al., 2015).

Our research extends the fMRI findings of Buono et al., who demonstrated alteration in the DMN, higher connectivity in the left angular gyrus, left supramarginal gyrus, right precentral gyrus, right postcentral gyrus, and right insular cortex in patients with migraine experiencing aura, which is suggesting that pain has a widespread impact on brain function due to its modifying effect on the complex brain networks that is a process beyond pain perception (Lo Buono et al., 2017). It should also be noted that we demonstrated a specific statistically significant association between hippocampal connectivity changes and impaired cognition MOCA scores, which is a unique relationship found between impaired cognition and specific dynamic hippocampal changes reported for the first time in this original study. Based on these findings, it appears plausible to hypothesize that compensatory higher activity between the MFG and hippocampal subfields may further explain the lower cognitive functions, as described in our recent research (Velioglu et al., 2023) and the previous studies cited above.

The hippocampal subfield volumes of the migraine patients in this study were significantly lower than those of the healthy controls (Table 4). Also, we found a significant correlation between impaired cognitive scores and hippocampal connectivity (Table 5). It may, therefore, be concluded that the abnormal connection between hippocampal subfields and cognitive regions may constitute the main cause of migraine patients' low cognition (Vos de Wael et al., 2018; Zhu et al., 2021). Interestingly, cognitive scores were associated with the connectivity of the right fimbria and the CA3 region, which is consistent with previous studies of the role of impaired hippocampal connectivity in neurodegenerative conditions (Thompson et al., 2008; Voineskos et al., 2015; Zhang et al., 2020). The role of CA3 has also been confirmed in a recent study by Petrusic et al., showing decreased CA3 vol in migraine patients compared to controls (Petrušić et al., 2024). To the best of our knowledge, there is no specific study that evaluated a special role of the hippocampus in cognitive impairment in migraine patients. Therefore, considering the essential role of CA3 in episodic memory formation, it is not unreasonable to assume its undeniable role in cognitive impairment in migraine patients, which has been suggested by our present results.

To summarize, all the above findings demonstrate that the hippocampus has unique functions and connections with migraine-related cognitive impairment. Moreover, the abnormal connectivity between hippocampal subfields and other brain regions causes a series of cognitive symptoms in patients with migraine. More importantly, following the correlation analysis, we are more than ever convinced that each hippocampal subfield plays a critical role in cognitive functioning (Table 5).

Our findings are consistent with earlier functional and structural migraine research demonstrating cognitive deterioration in sufferers (Lo Buono et al., 2017; Rocca et al., 2006; Tessitore et al., 2015). However, as previously mentioned, despite being among the most robust research in this field, these studies did not evaluate the cognitive correlates of migraine and yielded conflicting results regarding the role of the hippocampus in pain memory (Russo et al., 2017). Furthermore, those results were insufficient to distinguish the role of the hippocampus in cognition from a pain-related catastrophizing process. Nonetheless, these studies helped elaborate a general framework of structural and functional brain changes in migraine pathophysiology by stressing the relevance of hippocampus and migraine duration in determining the prognosis of migraine cases, which our investigation also confirmed with observed hippocampal alterations which are co-activated with DMN and can be functionally considered in episodic memory processing and cognition (Menon, 2023; Smallwood et al., 2021). Our findings suggest that migraine, independent of chronicity and pain severity/intensity or aura status, is crucial in determining cognitive function and hippocampal connections.

A good example is a recent publication by Wen et al., who reported in the Rotterdam Study that migraines with aura are associated with better cognitive functions (Wen et al., 2016). That finding is consistent with our results showing that migraine patients with aura did not exhibit significantly impaired cognitive functions compared to migraine patients without aura. Several studies indicate that individuals experiencing migraine with aura may exhibit more pronounced cognitive deficits, particularly in sustained attention and processing speed (Hooker and Raskin, 1986; Martins and Cunha e Sa, 1999). However, this is a controversial topic that is worth discussing. During migraine attacks, several other studies reported the reversed pattern. For instance, La Buono et al. showed comparable cognitive scores on fluency and memory tasks between migraine patients (both with and without aura) and non-migraineurs. However, some considerable connectivity differences were observed in the left angular gyrus, left supramarginal gyrus, right precentral gyrus, right postcentral gyrus, and right insular cortex between migraine patients with and without aura (Lo Buono et al., 2017). From a clinical point of view, this is also suggested by a large population study by Gaist et al. showing that migraine or one of the migraine subtypes did not differ from those of non-migraineurs in any of the cognitive tests (Gaist et al., 2005).

However, our finding of decreased cognitive functions in migraine patients compared to the controls is compatible with a recent meta-analysis involving more than 3000 migraine patients, indicating lower general cognitive and language function in migraine and suggesting that the condition is associated with an increased risk of all-cause dementia, vascular dementia, and AD (Gu et al., 2022). Since migraine is a more significant risk factor for cardiovascular and cerebrovascular events or structural abnormalities in the brain than in healthy individuals (Chiang et al., 2021; Kurth et al., 2020; Peng et al., 2017), it is tempting to conclude that possible hypoperfusion deficits and related functional and structural changes may be responsible for cognitive changes in patients with the condition.

This study also has a number of limitations. First, the samples used included Turkish citizens only, and future research might usefully be combined with more extensive data from different ethnicities. Second, we did not explore the impact of gender differences on the hippocampus, and greater attention should be paid to such differences in future research. Third, it is difficult to deny the theoretical link between migraine with aura and dementia based on our findings alone. The impact of aura on dementia should, therefore, be re-investigated with an accurate evaluation of migraine aura. Despite these limitations, the main strength of this study is that the findings did correlate with cognitive scores. Critical structural alterations and the abnormal connectivity between the hippocampal subfields and other brain regions may, therefore, be used as a biomarker for migraine with cognitive impairment.

In conclusion, our findings demonstrated significant structural and rsFC differences between different hippocampal subfields, emphasizing the role of the hippocampus in migraine-related cognitive impairment, suggesting its role as a valuable cognitive biomarker to support the diagnosis and treatment of migraine and future research into the condition.

Plain language summary

Our study found significant differences in hippocampal subfields, highlighting the hippocampus's role as a cognitive biomarker in migraine-related impairment, aiding diagnosis and treatment.

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Ethical statement

Approval for the study was granted by the Alanya University ethical committee (Ethical report number 16,072,023/289).

CRediT authorship contribution statement

Seyda Cankaya: Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Behcet Ayyildiz:** Software, Methodology, Formal analysis. **Dila Sayman:** Investigation, Data curation. **Umutcan Duran:** Investigation, Data curation. **Dogukan Ucak:** Investigation, Formal analysis. **Ramazan Karaca:** Investigation, Data curation. **Sevilay Ayyildiz:** Methodology, Formal analysis. **Ece Ozdemir Oktem:** Investigation. **Hatice Lakadamyalı:** Supervision, Formal analysis. **Ceyhun Sayman:** Investigation. **Ahmet Ozsimsek:** Investigation. **Ali Yalçınkaya:** Methodology. **Lutfu Hanoglu:** Supervision, Conceptualization. **Halil Aziz Velioglu:** Methodology, Formal analysis. **Burak Yulug:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120961.

Data availability

Data will be made available on request.

References

Afridi, S.K., Giffin, N.J., Kaube, H., Friston, K.J., Ward, N.S., Frackowiak, R.S., Goadsby, P.J., 2005. A positron emission tomographic study in spontaneous migraine. Arch. Neurol. 62 (8), 1270–1275.

Amoroso, N., La Rocca, M., Bruno, S., Maggipinto, T., Monaco, A., Bellotti, R., Tangaro, S., 2018. Multiplex networks for early diagnosis of Alzheimer's disease. Front. Aging Neurosci. 10, 365.

Anand, K.S., Dhikav, V., 2012. Hippocampus in health and disease: an overview. Ann. Indian Acad. Neurol. 15 (4), 239–246.

Baars, M.A., Van Boxtel, M.P., Jolles, J., 2010. Migraine does not affect cognitive decline: results from the Maastricht aging study. Headache: J. Head and Face Pain 50 (2), 176–184.

Beaty, R.E., Benedek, M., Barry Kaufman, S., Silvia, P.J., 2015. Default and executive network coupling supports creative idea production. Sci. Rep. 5 (1), 10964.

Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37 (1), 90–101.

Braun, U., Schäfer, A., Walter, H., Erk, S., Romanczuk-Seiferth, N., Haddad, L., Tost, H., 2015. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proc. Natl. Acad. Sci. 112 (37), 11678–11683.

Bubb, E.J., Kinnavane, L., Aggleton, J.P., 2017. Hippocampal–diencephalic–cingulate networks for memory and emotion: an anatomical guide. Brain and Neurosc. Adv. 1, 2398212817723443.

Cees De Groot, J., De Leeuw, F.E., Oudkerk, M., Van Gijn, J., Hofman, A., Jolles, J., Breteler, M.M., 2000. Cerebral white matter lesions and cognitive function: the Rotterdam Scan Study. Annals of Neurol.: Official J. Am. Neurol. Assoc. Child Neurol. Society 47 (2), 145–151.

Cera, N., Esposito, R., Cieri, F., Tartaro, A., 2019. Altered cingulate cortex functional connectivity in normal aging and mild cognitive impairment. Front. Neurosci. 13, 857.

Chiang, M.-C., Dumitrascu, O.M., Chhabra, N., Chiang, C.-C., 2021. Migraine with visual aura and the risk of stroke-a narrative review. J. Stroke Cerebrovascul. Diseases 30 (11), 106067.

Chong, C.D., Dumkrieger, G.M., Schwedt, T.J., 2017. Structural co-variance patterns in migraine: a cross-sectional study exploring the role of the hippocampus. Headache: J. Head and Face Pain 57 (10), 1522–1531.

Cohen, N.J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., Nash, C., 1999. Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. Hippocampus 9 (1), 83–98.

Coppola, G., Di Renzo, A., Tinelli, E., Di Lorenzo, C., Di Lorenzo, G., Parisi, V., Pierelli, F., 2016. Thalamo-cortical network activity during spontaneous migraine attacks. Neurology 87 (20), 2154–2160.
Faul, F., Erdfelder, E., Buchner, A., Lang, A.-G., 2009. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behav. Res. Methods 41, 1149–1160.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12 (3), 189–198.
Fornito, A., Yücel, M., Wood, S., Stuart, G.W., Buchanan, J.-A., Proffitt, T., Pantelis, C., 2004. Individual differences in anterior cingulate/paracingulate morphology are related to executive functions in healthy males. Cereb. Cortex 14 (4), 424–431.
Gaist, D., Pedersen, L., Madsen, C., Tsiropoulos, I., Bak, S., Sindrup, S., Christensen, K., 2005. Long-term effects of migraine on cognitive function: a population-based study of Danish twins. Neurology 64 (4), 600–607.
Gao, Q., Xu, F., Jiang, C., Chen, Z., Chen, H., Liao, H., Zhao, L., 2016. Decreased functional connectivity density in pain-related brain regions of female migraine patients without aura. Brain Res. 1632, 73–81.
Gil-Gouveia, R., Martins, I.P., 2019. Cognition and cognitive impairment in migraine. Curr. Pain Headache Rep. 23, 1–10.
Gu, L., Wang, Y., Shu, H., 2022. Association between migraine and cognitive impairment. J. Headache Pain. 23 (1), 88.
Han, S.D., Bangen, K.J., Bondi, M.W., 2009. Functional magnetic resonance imaging of compensatory neural recruitment in aging and risk for Alzheimer's disease: review and recommendations. Dement. Geriatr. Cogn. Disord. 27 (1), 1–10.
Han, S.D., Fleischman, D.A., Yu, L., Poole, V., Lamar, M., Kim, N., Barnes, L.L., 2022. Cognitive decline and hippocampal functional connectivity within older Black adults. Hum. Brain Mapp. 43 (16), 5044–5052.
Hooker, W.D., Raskin, N.H., 1986. Neuropsychologic alterations in classic and common migraine. Arch. Neurol. 43 (7), 709–712.
Hu, S., Hao, Z., Li, M., Zhao, M., Wen, J., Gao, Y., Jia, X., 2023. Resting-state abnormalities in functional connectivity of the default mode network in migraine: a meta-analysis. Front. Neurosci. 17, 1136790.
Hubbard, C.S., Khan, S.A., Keaser, M.L., Mathur, V.A., Goyal, M., Seminowicz, D.A., 2014. Altered brain structure and function correlate with disease severity and pain catastrophizing in migraine patients. eNeuro 1 (1).
IBM Corp. Released, 2017. IBM SPSS Statistics for Windows, Version 25.0. IBM Corp., Armonk, NY.
Iglesias, J.E., Augustinack, J.C., Nguyen, K., Player, C.M., Player, A., Wright, M., Wald, L. L., 2015. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. Neuroimage 115, 117–137.
Islamoska, S., Hansen, Å.M., Wang, H.-X., Garde, A.H., Andersen, P.K., Garde, E., Nabe-Nielsen, K., 2020. Mid-to late-life migraine diagnoses and risk of dementia: a national register-based follow-up study. J. Headache. Pain. 21, 1–12.
Jiang, W., Liang, G.-H., Li, J.-A., Yu, P., Dong, M., 2022. Migraine and the risk of dementia: a meta-analysis and systematic review. Aging Clin. Exp. Res. 34 (6), 1237–1246.
Keskinoglu, P., Ucku, R., Yener, G., Yaka, E., Kurt, P., Tunca, Z., 2009. Reliability and validity of revised Turkish version of Mini Mental State Examination (rMMSE-T) in community-dwelling educated and uneducated elderly. Int. J. Geriatr. Psychiatry 24 (11), 1242–1250.
Kim, J.S., Lee, S.A., 2023. Hippocampal orchestration of associative and sequential memory networks for episodic retrieval. Cell Rep. (8), 42.
Kurth, T., Rist, P.M., Ridker, P.M., Kotler, G., Bubes, V., Buring, J.E., 2020. Association of migraine with aura and other risk factors with incident cardiovascular disease in women. JAMA 323 (22), 2281–2289.
Lee, S.-Y., Lim, J.-S., Oh, D.J., Kong, I.G., Choi, H.G., 2019. Increased risk of neurodegenerative dementia in women with migraines: a nested case–control study using a national sample cohort. Medicine (Baltimore). 98 (7), e14467.
Liu, J., Lan, L., Li, G., Yan, X., Nan, J., Xiong, S., Liang, F., 2013. Migraine-related gray matter and white matter changes at a 1-year follow-up evaluation. J. Pain 14 (12), 1703–1708.
Liu, Z., Xiao, X., Zhang, K., Zhao, Q., Cao, X., Li, C., Sahakian, B.J., 2019. Dynamic brain network changes in resting-state reflect neuroplasticity: molecular and cognitive evidence. Biorxiv, 695122.
Lo Buono, V., Bonanno, L., Corallo, F., Pisani, L.R., Lo Presti, R., Grugno, R., Marino, S., 2017. Functional connectivity and cognitive impairment in migraine with and without aura. J. Headache Pain. 18, 1–6.
Maleki, N., Becerra, L., Brawn, J., McEwen, B., Burstein, R., Borsook, D., 2013. Common hippocampal structural and functional changes in migraine. Brain Struct. Function 218, 903–912.
Maleki, N., Gollub, R.L., 2016. What have we learned from brain functional connectivity studies in migraine headache? Headache: J. Head and Face Pain 56 (3), 453–461.
Martins, I., Cunha e Sa, M., 1999. Loss of topographic memory and prosopagnosia during migraine aura. Cephalalgia 19 (9), 841–843.
Mathur, V.A., Khan, S.A., Keaser, M.L., Hubbard, C.S., Goyal, M., Seminowicz, D.A., 2015. Altered cognition-related brain activity and interactions with acute pain in migraine. NeuroImage: Clinical 7, 347–358.
Mazaika, P.K., Hoeft, F., Glover, G.H., Reiss, A.L., 2009. Methods and software for fMRI analysis of clinical subjects. Neuroimage 47, S58.
Menon, V., 2023. 20 years of the default mode network: a review and synthesis. Neuron 111 (16), 2469–2487.
Morgado-Bernal, I., 2011. Learning and memory consolidation: linking molecular and behavioral data. Neuroscience 176, 12–19.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53 (4), 695–699.
Ozdilek, B., Kenangil, G., 2014. Validation of the Turkish Version of the Montreal Cognitive Assessment Scale (MoCA-TR) in patients with Parkinson's disease. Clin. Neuropsychol. 28 (2), 333–343.
Peng, K.-P., Chen, Y.-T., Fuh, J.-L., Tang, C.-H., Wang, S.-J., 2017. Migraine and incidence of ischemic stroke: a nationwide population-based study. Cephalalgia 37 (4), 327–335.
Petrušić, I., Radović, M., Daković, M., Radojičić, A., Coppola, G., 2024. Subsegmentation of the hippocampus in subgroups of migraine with aura patients: advanced structural neuroimaging study. J. Headache Pain. 25 (1), 1–10.
Poppenk, J., Evensmoen, H.R., Moscovitch, M., Nadel, L., 2013. Long-axis specialization of the human hippocampus. Trends Cogn. Sci. (Regul. Ed.) 17 (5), 230–240.
Preis, M.A., Schmidt-Samoa, C., Dechent, P., Kroener-Herwig, B., 2013. The effects of prior pain experience on neural correlates of empathy for pain: an fMRI study. PAIN® 154 (3), 411–418.
Ren, Y., Nguyen, V.T., Sonkusare, S., Lv, J., Pang, T., Guo, L., Guo, C.C., 2018. Effective connectivity of the anterior hippocampus predicts recollection confidence during natural memory retrieval. Nat. Commun. 9 (1), 4875.
Rocca, M.A., Ceccarelli, A., Falini, A., Colombo, B., Tortorella, P., Bernasconi, L., Filippi, M., 2006. Brain gray matter changes in migraine patients with T2-visible lesions: a 3-T MRI study. Stroke 37 (7), 1765–1770.
Ruiz-Tagle, A., Figueiredo, P., Pinto, J., Vilela, P., Martins, I.P., Gil-Gouveia, R., 2024. Working memory during spontaneous migraine attacks: an fMRI study. Neurolog. Sci. 45 (3), 1201–1208.
Russo, A., Silvestro, M., Tedeschi, G., Tessitore, A., 2017. Physiopathology of migraine: what have we learned from functional imaging? Curr. Neurol. Neurosci. Rep. 17, 1–11.
Shine, J.M., Bissett, P.G., Bell, P.T., Koyejo, O., Balsters, J.H., Gorgolewski, K.J., Poldrack, R.A., 2016. The dynamics of functional brain networks: integrated network states during cognitive task performance. Neuron 92 (2), 544–554.
Smallwood, J., Bernhardt, B.C., Leech, R., Bzdok, D., Jefferies, E., Margulies, D.S., 2021. The default mode network in cognition: a topographical perspective. Nat. Rev. Neurosci. 22 (8), 503–513.
Society, H.C.C.o.t.I.H., 2013. The international classification of headache disorders, (beta version). Cephalalgia 33 (9), 629–808.
Stark, C.E., Squire, L.R., 2000. Functional magnetic resonance imaging (fMRI) activity in the hippocampal region during recognition memory. J. Neurosci. 20 (20), 7776–7781.
Tang, L., Pruitt, P.J., Yu, Q., Homayouni, R., Daugherty, A.M., Damoiseaux, J.S., Ofen, N., 2020. Differential functional connectivity in anterior and posterior hippocampus supporting the development of memory formation. Front Hum Neurosci 14, 204.
Taya, F., Dimitriadis, S.I., Dragomir, A., Lim, J., Sun, Y., Wong, K.F., Bezerianos, A., 2018. Fronto-parietal subnetworks flexibility compensates for cognitive decline due to mental fatigue. Hum. Brain Mapp. 39 (9), 3528–3545.
Tessitore, A., Russo, A., Conte, F., Giordano, A., De Stefano, M., Lavorgna, L., Tedeschi, G., 2015. Abnormal connectivity within executive resting-state network in migraine with aura. Headache: J. Head and Face Pain 55 (6), 794–805.
Thompson, C.L., Pathak, S.D., Jeromin, A., Ng, L.L., MacPherson, C.R., Mortrud, M.T., Bernard, A., 2008. Genomic anatomy of the hippocampus. Neuron 60 (6), 1010–1021.
Tomasi, D., Wang, G.-J., Volkow, N.D., 2013. Energetic cost of brain functional connectivity. Proc. Natl. Acad. Sci. 110 (33), 13642–13647.
Tsai, C.-L., Chou, K.-H., Lee, P.-L., Liang, C.-S., Kuo, C.-Y., Lin, G.-Y., Yang, F.-C., 2023. Shared alterations in hippocampal structural covariance in subjective cognitive decline and migraine. Front. Aging Neurosci. 15, 1191991.
Varangis, E., Habeck, C.G., Razlighi, Q.R., Stern, Y., 2019. The effect of aging on resting state connectivity of predefined networks in the brain. Front. Aging Neurosci. 11, 234.
Velioglu, H.A., Ayyildiz, B., Ayyildiz, S., Sutcubasi, B., Hanoglu, L., Bayraktaroglu, Z., Yulug, B., 2023. A structural and resting-state functional connectivity investigation of the pulvinar in elderly individuals and Alzheimer's disease patients. Alzheimer's & dementia 19 (7), 2774–2789.
Viviano, R.P., Raz, N., Yuan, P., Damoiseaux, J.S., 2017. Associations between dynamic functional connectivity and age, metabolic risk, and cognitive performance. Neurobiol. Aging 59, 135–143.
Voineskos, A.N., Winterburn, J.L., Felsky, D., Pipitone, J., Rajji, T.K., Mulsant, B.H., Chakravarty, M.M., 2015. Hippocampal (subfield) volume and shape in relation to cognitive performance across the adult lifespan. Hum. Brain Mapp. 36 (8), 3020–3037.
Vos de Wael, R., Larivière, S., Caldairou, B., Hong, S.-J., Margulies, D.S., Jefferies, E., Bernhardt, B.C., 2018. Anatomical and microstructural determinants of hippocampal subfield functional connectome embedding. Proc. Natl. Acad. Sci. 115 (40), 10154–10159.
Vuralli, D., Ayata, C., Bolay, H., 2018. Cognitive dysfunction and migraine. J. Headache Pain 19 (1), 109.
Wei, H.-L., Chen, J., Chen, Y.-C., Yu, Y.-S., Zhou, G.-P., Qu, L.-J., Zhang, H., 2020. Impaired functional connectivity of limbic system in migraine without aura. Brain Imaging Behav 14, 1805–1814.
Wen, K., Nguyen, N., Hofman, A., Ikram, M., Franco, O., 2016. Migraine is associated with better cognition in the middle-aged and elderly: the Rotterdam Study. Eur. J. Neurol. 23 (10), 1510–1516.

Whitlock, E.L., Diaz-Ramirez, L.G., Glymour, M.M., Boscardin, W.J., Covinsky, K.E., Smith, A.K., 2017. Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. JAMA Intern Med 177 (8), 1146–1153.
Won, J., Callow, D.D., Pena, G.S., Jordan, L.S., Arnold-Nedimala, N.A., Nielson, K.A., Smith, J.C., 2021. Hippocampal functional connectivity and memory performance after exercise intervention in older adults with mild cognitive impairment. J. Alzheimer's Disease 82 (3), 1015–1031.
Xu, Z.-G., Xu, J.-J., Chen, Y.-C., Hu, J., Wu, Y., Xue, Y., 2021. Aberrant cerebral blood flow in tinnitus patients with migraine: a perfusion functional MRI study. J. Headache Pain 22 (1), 61.
Yu, Y., Zhao, H., Dai, L., Su, Y., Wang, X., Chen, C., Hu, C., 2021. Headache frequency associates with brain microstructure changes in patients with migraine without aura. Brain Imaging Behav 15, 60–67.
Zeng, H., Jin, Y., Wu, Q., Pan, D., Xu, F., Zhao, Y., Kong, W., 2022. EEG-FCV: an EEG-based functional connectivity visualization framework for cognitive state evaluation. Front Psychiatry 13, 928781.
Zhang, J., Su, J., Wang, M., Zhao, Y., Yao, Q., Zhang, Q., Li, G.-F., 2016. Increased default mode network connectivity and increased regional homogeneity in migraineurs without aura. J. Headache Pain 17, 1–9.
Zhang, M., Liu, Y., Hu, G., Kang, L., Ran, Y., Su, M., Yu, S., 2020. Cognitive impairment in a classical rat model of chronic migraine may be due to alterations in hippocampal synaptic plasticity and N-methyl-D-aspartate receptor subunits. Mol Pain 16, 1744806920959582.
Zhao, W., Zhao, L., Chang, X., Lu, X., Tu, Y., 2023. Elevated dementia risk, cognitive decline, and hippocampal atrophy in multisite chronic pain. Proc. Natl. Acad. Sci. 120 (9), e2215192120.
Zheng, F., Cui, D., Zhang, L., Zhang, S., Zhao, Y., Liu, X., Shi, L., 2018. The volume of hippocampal subfields in relation to decline of memory recall across the adult lifespan. Front. Aging Neurosci. 10, 320.
Zhu, Y., Dai, L., Zhao, H., Ji, B., Yu, Y., Dai, H., Ke, J., 2021. Alterations in effective connectivity of the hippocampus in migraine without aura. J. Pain Res. 3333–3343.