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Cognitive and Sensory Profiles in Patients with Epilepsy, Migraine, and Their Comorbidity: A Quantitative Study

Yuyan Hao
Xiangyang No.1 People's Hospital, Hubei University of Medicine
Fan Zhang
Xiangyang No.1 People's Hospital, Hubei University of Medicine
Zhen Li
Xiangyang No.1 People's Hospital, Hubei University of Medicine
Jun Han
Xiangyang No.1 People's Hospital, Hubei University of Medicine
Wenmin Feng
Xiangyang No.1 People's Hospital, Hubei University of Medicine
Yanjie Zhou
Renmin Hospital of Wuhan University
Li Huang
yush2283@163.com

Xiangyang No.1 People's Hospital, Hubei University of Medicine

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Cognitive and Sensory Profiles in Patients with Epilepsy, Migraine, and Their Comorbidity: A Quantitative Study

Yuyan Hao, Fan Zhang, Zhen Li, Jun Han, Wenmin Feng, Yanjie Zhou, Li Huang
Corresponding author:
Li Huang, Email: yush2283@163.com
Yanjie Zhou, Email: yanjiezhou@whu.edu.cn

Affiliations:
Department of Neurology, Xiangyang No.1 People's Hospital, Hubei University of Medicine, Xiangyang, 441000.
Department of Neurology, Renmin Hospital of Wuhan University, Wuhan University, 99 Zhangzhidong Road, Wuhan 430060, China.

Abstract

Background: Epilepsy and migraine are highly comorbid neurological disorders with shared pathophysiological features. However, their combined impact on cognitive, emotional, and sensory processing remains insufficiently characterized. This study aimed to quantitatively compare these domains across patients with epilepsy, migraine, their comorbidity, and healthy controls.

Methods: The study recruited 27 patients with epilepsy, 27 with migraine, 20 with comorbid epilepsy and migraine, and 25 healthy controls. Cognitive function, anxiety, and depression were assessed using the Montreal Cognitive Assessment (MoCA), Self-Rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS), respectively. Disease-specific scales were also administered. Sensory function was evaluated by measuring the pain perception threshold (PPT) with von Frey filaments and by quantifying the current perception threshold (CPT) and pain tolerance threshold (PTT) using a Neurometer® at 2000 Hz (Aβ fibers), 250 Hz (Aδ fibers), and 5 Hz (C fibers).

Results: All patient groups showed significantly lower MoCA scores and higher SAS/SDS scores compared to controls (all $P < 0.05$). The comorbidity group had the most pronounced cognitive deficits, particularly in attention, executive function, and visuospatial memory. While PPT and CPT did not differ between groups, PTT was significantly reduced in all patient groups at 250 Hz and 5 Hz (all $P < 0.05$), with the

comorbidity group also showing lower PTT at 2000 Hz. Correlation analyses revealed positive associations between VAS score and headache attack duration, as well as between both MIDAS and HIT-6 scores and VAS score. LSSS score positively correlated with seizure duration. MoCA score positively correlated with both headache attack duration and HIT-6 score.

Conclusion: Patients with epilepsy, migraine, or their comorbidity exhibit significant cognitive and emotional impairments, with comorbid patients demonstrating additive deficits. The broad reduction in pain tolerance implicates shared sensory processing abnormalities and central sensitization as a potential mechanism linking the two disorders. These results support an integrated clinical approach that targets cognitive, emotional, and sensory dysfunction.

Key words: Epilepsy; Comorbidity; Migraine; Pain perception threshold; Current perception threshold; Pain tolerance threshold

Introduction

Epilepsy and migraine are among the most prevalent neurological disorders worldwide, posing substantial personal, social, and economic burdens. Epilepsy affects millions of individuals globally and is associated with significant disability, increased mortality, and reduced quality of life[1]. Similarly, migraine is a leading cause of years lived with disability, especially among young and middle-aged adults, imposing considerable direct and indirect costs[2]. Both conditions frequently impair daily functioning across cognitive, occupational, and social domains. Notably, epilepsy and migraine co-occur far more often than expected by chance. A population-based prospective study has demonstrated that the prevalence of migraine in patients with epilepsy is notably high, with a reported range of 8% to 23%[3]. This frequent comorbidity suggests shared underlying mechanisms. Pathophysiological overlaps include neuronal hyperexcitability, cortical spreading depression-like phenomena, and dysregulation of excitatory-inhibitory balance[4]. Genetic studies further support a common etiology, exemplified by familial hemiplegic migraine syndromes in which single-gene mutations can cause both migraine and epilepsy[5]. The fact that several antiseizure medications, such as valproate and topiramate, are also effective in preventing migraine further highlights their shared pathological pathways[6].

Pain is a complex sensory experience mediated by specific peripheral nerve fibers. Nociceptive signals are transmitted from cutaneous receptors to the cortex via two

primary types of afferent fibers: myelinated Aδ fibers, which conduct rapidly and elicit sharp, acute "first" pain, and unmyelinated C fibers, responsible for slower, dull, and prolonged "second" pain. These fibers are densely distributed within the trigeminal nerve and dorsal root ganglia, forming the anatomical basis of pain transmission[7]. Migraine attacks are characterized by the activation and sensitization of the trigeminal neurovascular system, which triggers not only headache but also a constellation of accompanying symptoms[8]. These include hypersensitivity to visual, auditory, and olfactory stimuli, cognitive impairments such as reduced responsiveness, emotional disturbances like irritability, and abnormal cutaneous allodynia. This symptom profile reflects a state of heightened overall sensitivity to sensory input[9]. Clinical, electrophysiological, and neuroimaging studies have consistently shown that migraine patients exhibit increased sensitivity to noxious stimuli both during and between attacks[10-12]. Nonetheless, findings regarding sensory sensitivity in migraine remain inconsistent, with some studies reporting no significant alterations[13]. In epilepsy, alterations in sensory processing have been less systematically studied. Although some clinical reports exist, most indicate no significant difference in pain sensitivity between epilepsy subjects and healthy controls[14, 15].

Despite these overlapping features, a direct comparison of cognitive, emotional, and sensory profiles in patients with epilepsy, migraine, and their comorbidity is still lacking. This is particularly true for profiles mediated by different nerve-fiber types (Aβ, Aδ, C). Furthermore, it remains unclear whether such sensory alterations correlate with clinical characteristics, or how the two conditions interact to affect cognition and emotion in comorbid patients. Based on the above researches, this study was designed to: (1) quantify and compare cognitive performance, emotional symptoms, and sensory thresholds in patients with epilepsy, migraine, and their comorbidity versus healthy controls; (2) evaluate whether sensory processing abnormalities differ according to fiber-type-specific pathways; and (3) explore whether comorbid patients show additive deficits. To address these aims, we performed comprehensive clinical and neuroelectrophysiological assessments. These included quantifying the pain perception threshold, analyzing sensory disturbances, and evaluating cognitive impairment, anxiety, and depression.

Methods

1. Participants

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Renmin Hospital of Wuhan University. A total of 99 participants were enrolled: 27 patients with epilepsy, 27 with migraine, 20 with comorbid epilepsy and migraine, and 25 age-, sex-, and education-matched healthy controls (HCs) recruited from the Physical Examination Center of the same hospital. In the present study, no differentiation was made between the subtypes of epilepsy and migraine. All cases that fulfilled the established diagnostic criteria were eligible for inclusion in this research. All patients were in a stable, mid-disease stage, right-handed, and without major neurological deficits. Exclusion criteria included illiteracy, brain injury, diabetes, heavy alcohol use, stroke, spinal cord or peripheral neuropathy, or other conditions that could affect cognition or somatosensory function. Prior to the initiation of the study, all participants were fully informed of the study protocol, purpose, potential risks, and benefits, and provided written informed consent with their signature.

2. Diagnostic Criteria

Patients were included in this study if they met one of the following two sets of diagnostic criteria: either the clinical diagnostic criteria for migraine as specified in the *International Classification of Headache Disorders (ICHD-3)* formulated by the International Headache Society (IHS), or the diagnostic criteria for epilepsy as established in the *2017 Classification of Epileptic Seizures and Epilepsies* issued by the International League Against Epilepsy (ILAE). Notably the criteria for comorbidity between epilepsy and migraine require greater attention, and such criteria should be consistent with the diagnostic standards for both epilepsy and migraine.

3. Procedure

All clinical scale assessments and sensory threshold measurements were conducted by a trained researcher who was blinded to the participant's group allocation. This blinding procedure was implemented to minimize assessment bias.

3.1 Disease Characteristic-Associated Scale

Migraine severity and impact were evaluated with the Visual Analogue Scale (VAS), Migraine Disability Assessment Scale (MIDAS), Headache Impact Test (HIT-6), and the Allodynia Symptom Checklist (ASC-12). Epilepsy severity and quality of life was assessed using the Liverpool Seizure Severity Scale 2.0 (LSSS 2.0).

3.2 Cognitive Functions and Mood States Assessment

Global cognitive function was assessed using the Montreal Cognitive Assessment

(MoCA), a widely adopted instrument that evaluates visuospatial ability, attention, language, memory, executive function, calculation, and orientation. Visuospatial construction and recall were measured with the Rey–Osterrieth Complex Figure test (ROCF), which includes both copy and delayed recall trials. Processing speed was evaluated via the Digital Symbol Substitution Test (DSST). Symptoms of anxiety and depression were quantified using the Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS), respectively.

3.3 Sensory Threshold Assessment

The pain perception threshold (PPT) was assessed using calibrated von Frey hairs (Touch-Test™ Sensory Evaluators, North Coast Medical, USA)[16]. Stimuli were applied to two standardized sites: the bilateral forehead (trigeminal V1 region) and the dorsal hand (C7 dermatome). The PPT was defined as the minimum filament pressure at which the participant first reported pain. At each site, the measurement was repeated three times with a 5-minute interval between trials, and the final PPT was calculated as the mean of the three recordings.

Current Perception Thresholds (CPT) and Pain Tolerance Thresholds (PTT) were determined using the Neurometer® CPT machine[17]. This equipment is a neuroselective transcutaneous electrical stimulator capable of generating sine-wave stimulation at frequencies of 2000 Hz, 250 Hz, and 5 Hz, with a current intensity ranging from 0 to 9.99 mA. Existing researches have demonstrated that specific stimulation frequencies selectively activate distinct nerve fiber types: 5 Hz frequency correlates with the function of C-polymodal fibers, as evaluated through quantitative thermal and pain sensation measurements. In contrast, 250 Hz and 2000 Hz are associated with Aδ and Aβ fibers, respectively. These correlations are supported by quantitative sensory and neurophysiological testing.

The procedure for CPT determination is as follows: First, the stimulus intensity is gradually increased from 0 to a maximum of 9.99 mA until the subject reports detecting a sensation in the vicinity of the electrode placement site. Subsequently, the stimulus is turned off and re-administered at progressively decreasing intensities until the sensation is no longer detected, with the intensity variation controlled within a range of 0.10 mA. Following this preliminary step, the subjects proceed to the "Automated Forced Choice CPT Determination Mode" to obtain the actual CPT measurements. During this mode, the subject is presented with a series of forced-choice tests, and the process continues until a sufficient number of consistent

responses are recorded. The final CPT value is then displayed on the device screen. For the measurement of PTT, participants self-administered electrical stimulation by holding a button that increased the current intensity in predefined steps. They were instructed to release the button immediately when the sensation became intolerable, at which point the displayed intensity was recorded as the PTT. The pain test is equipped with a protective mode, in which the system is preconfigured with a maximum intensity threshold. Once the stimulation intensity reaches this threshold, the system automatically ceases stimulation to ensure subject safety. CPT was evaluated bilaterally at the forehead (trigeminal V1) and the index fingers (C7 dermatome). For safety reasons, PTT was assessed only at the index fingers.

4. Statistical Analysis

The data were analyzed utilizing the SPSS statistical software package (version 25; SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation ($\bar{x} \pm s$). In contrast, graphical representations were constructed based on the mean and standard error of the mean (SEM). Prior to conducting further analyses, normality tests were performed for each group of data. For data that conformed to a normal distribution, multivariate analysis of covariance (ANCOVA) was employed to analyze each independent variable, with post-hoc multiple comparisons conducted using the LSD-t test. For data deviating from a normal distribution, non-parametric rank sum tests were utilized. With regard to correlation analysis, Pearson product-moment correlation analysis was adopted for normally distributed data, whereas Spearman rank correlation analysis was applied to non-normally distributed data. All statistical analyses were performed at a 95% confidence interval, with a *P*-value of less than 0.05 considered to indicate statistical significance.

Results

1. Sample Characteristics

This study enrolled a total of 27 patients diagnosed with epilepsy, 27 patients diagnosed with migraine, and 20 patients diagnosed with comorbid epilepsy and migraine. In addition, 25 HCs were recruited as the control group during the same study period. Table 1 presents the demographic and clinical characteristics of the four groups. No statistically significant differences were observed among the four groups in terms of age, gender and education level. With regard to disease characteristics, no significant statistical differences were found between the comorbidity group and the

epilepsy group (Fig. 1A-1D). However, in comparison with the migraine group, the comorbidity group exhibited lower scores in headache duration (Fig. 1G), VAS (Fig. 1H), MIDAS (Fig. 1I) and HIT-6(Fig. 1J).

Table 1 Demographic and clinical characteristics of the study population

	HCs (n=25)	Epilepsy (n=27)	Migraine (n=27)	Comorbidity (n=20)	*P*
Age(years)	32.40±11.965	30.89±13.885	36.74±11.967	32.90±14.704	0.409
Gender (Male/Female)	11/14	11/16	9/18	7/13	0.853
Education level(years)	13.84±4.616	12.44±2.940	13.81±3.282	12.15±3.216	0.222
The course of migraine disease (years)	-	-	9.48±8.271	8.30±12.699	0.701
Frequency of headache attacks (per month)	-	-	4.33±4.500	3.71±6.421	0.697
Duration of headache attack (hours)	-	-	20.07±18.187	8.75±6.646	0.005**
VAS	-	-	6.85±1.634	5.05±2.089	0.003**
MIDAS	-	-	22.59±32.135	6.30±8.355	0.017*
HIT-6	-	-	64.70±6.503	53.70±14.382	0.001**
ASC-12	-	-	3.11±3.203	2.20±1.824	0.260
The course of epilepsy disease (years)	-	8.06±9.358	-	10.75±14.175	0.437
Frequency of epileptic seizures (per month)	-	1.30±1.586	-	2.56±6.606	0.347
Duration of seizure (minutes)	-	3.15±1.870	-	3.27±1.775	0.830
LSSS2.0	-	11.04±9.184	-	15.25±9.503	0.132

HCs, healthy controls. VAS, the Visual Analogue Scale. MIDAS, Migraine Disability Assessment Scale. HIT-6, Headache Impact Test. ASC-12, the Allodynia Symptom Checklist. LSSS 2.0, the Liverpool Seizure Severity Scale 2.0. Mean ±SD. multivariate analysis of covariance (ANCOVA). *$P < 0.05$; **$P < 0.01$.

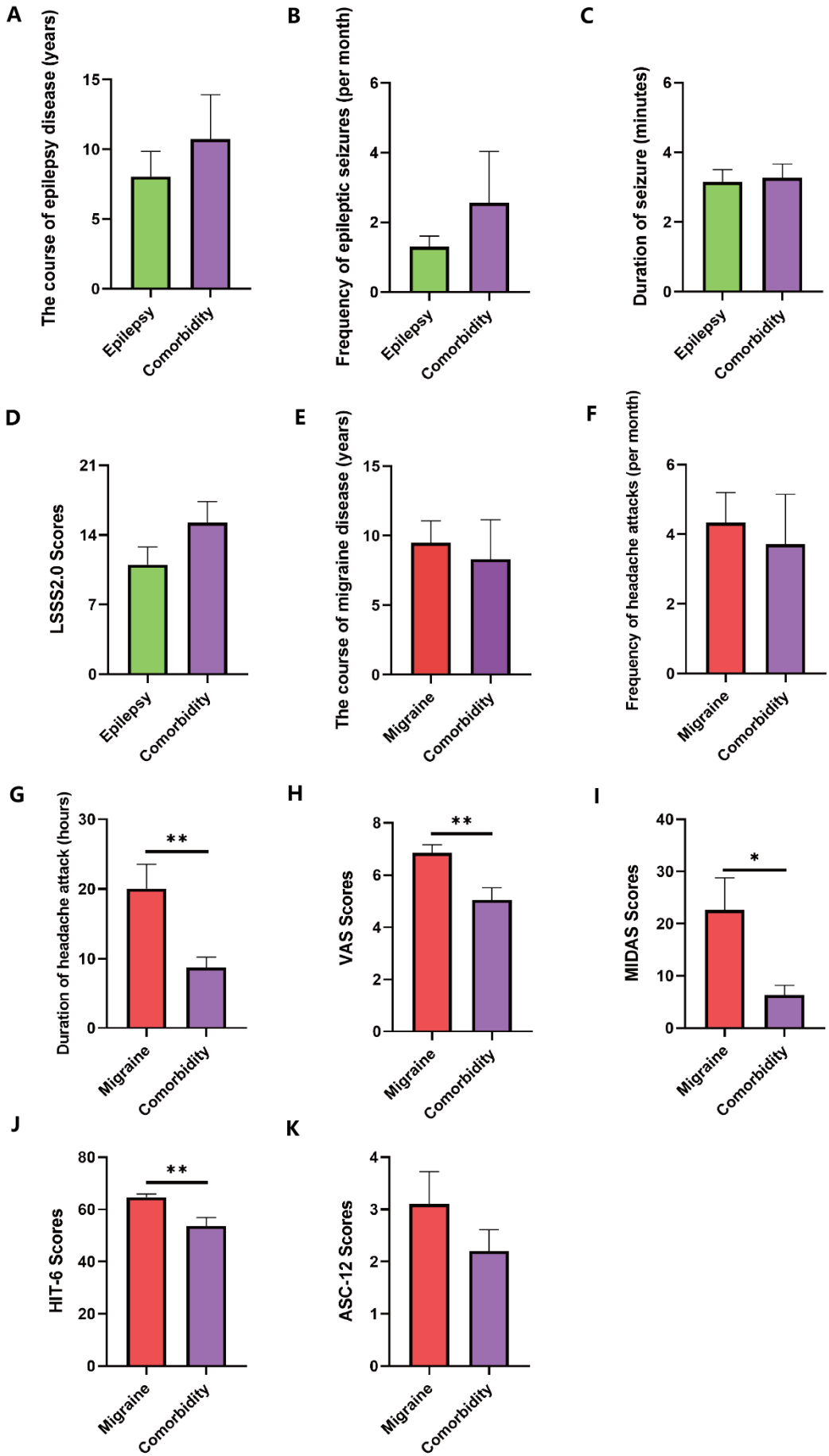

A
The course of epilepsy disease (years)
15
10
5
0
Epilepsy
Comorbidity
B
Frequency of epileptic seizures (per month)
6
4
2
0
Epilepsy
Comorbidity
C
Duration of seizure (minutes)
6
4
2
0
Epilepsy
Comorbidity
D
LSSS2.0 Scores
21
14
7
0
Epilepsy
Comorbidity
E
The course of migraine disease (years)
15
10
5
0
Migraine
Comorbidity
F
Frequency of headache attacks (per month)
6
4
2
0
Migraine
Comorbidity
G
Duration of headache attack (hours)
30
20
10
0
**
Migraine
Comorbidity
H
VAS Scores
8
6
4
2
0
**
Migraine
Comorbidity
I
MIDAS Scores
40
30
20
10
0
*
Migraine
Comorbidity
J
HIT-6 Scores
80
60
40
20
0
**
Migraine
Comorbidity
K
ASC-12 Scores
4
3
2
1
0
Migraine
Comorbidity

Figure 1 VAS, the Visual Analogue Scale. MIDAS, Migraine Disability Assessment Scale. HIT-6, Headache Impact Test. ASC-12, the Allodynia Symptom Checklist. LSSS 2.0, the Liverpool Seizure Severity Scale 2.0. **A, B, C** Comparison of the seizure course, attack frequency and duration between the epilepsy group and the comorbidity group. **D** Comparison of the LSSS scores between the epilepsy group and the comorbidity group. **E, F, G** Comparison of the headache course, attack frequency and duration between the migraine group and the comorbidity group. **H, I, J, K** Comparison of the VAS, MIDAS, HIT-6, and ASC-12 scores between the migraine group and the comorbidity group. Mean ± SEM; multivariate analysis of covariance (ANCOVA). $*P < 0.05$; $**P < 0.01$.

2.Cognitive and Mood Testing

The mean scores of participants on the MoCA, DSST, ROCF, SAS and SDS are summarized in Tables 2.1. Table 2.2 presents the specific measurement values of each sub-scale in the MoCA for the research subjects. And if the overall *P*-value of the relevant indicators exhibits a statistically significant difference, the specific *P*-values corresponding to pairwise inter-group comparisons will be detailed in the table. The same rule applies to the content presented below.

All three patient groups exhibited significant lower scores in MoCA scale, with a particularly notable statistical difference observed between the comorbidity group and the migraine group (Fig. 2A). In the specific subscales of the MoCA, compared with the control group:

- The migraine group showed significantly lower scores in the domains of language, executive function, and memory;
- The epilepsy group demonstrated worse symptoms in terms of visuospatial function, attention, executive function, and memory;
- The comorbidity group exhibited a diminished capacity in visuospatial function, attention, language, executive function, calculation, and memory.

Furthermore, the comorbid group scored significantly lower in attention and memory than the migraine-only group, and in visuospatial and executive function compared to both the migraine and epilepsy groups (Fig. 2B). On visuospatial memory tests, the comorbid group scored lower than controls on the ROCF-copy task, while all patient groups showed reduced performance on the ROCF-recall and the Digital Symbol Substitution Test (DSST) (Fig. 2C, 2D). The comorbid group also performed worse on the ROCF-copy and DSST relative to the migraine group.

On the emotional assessment scale, scores on the SAS were elevated across all patient groups compared to controls (Fig. 2E). Regarding the SDS scores, the epilepsy group and the comorbidity group exhibited notably higher scores than controls. Furthermore, in the inter-group comparisons among the disease groups, the SDS score of the comorbidity group was statistically higher than that of the migraine-only group (Fig.

2F).

Table 2.1 Intergroup comparison of cognitive and emotional-related scales

	MoCA	ROCF-copy	ROCF-recall	DSST	SAS	SDS
HCs(n=25)	26.92±2.886	33.52±2.771	20.12±5.325	68.92±11.726	25.80±3.304	28.12±4.737
Epilepsy (n=27)	21.67±5.015	30.74±6.801	12.43±8.226	51.96±14.960	32.41±7.667	33.04±9.784
Migraine (n=27)	23.63±3.152	32.48±2.874	12.15±6.087	57.81±16.019	34.00±8.557	31.70±9.707
Comorbidity(n=20)	19.35±4.133	27.15±7.271	9.80±4.775	47.40±14.887	37.90±8.491	37.75±7.718
P value	0.000**	0.001**	0.000**	0.000**	0.000**	0.003**
HCs vs. Epilepsy	0.000**	0.304	0.000**	0.000**	0.001**	0.036*
HCs vs. Migraine	0.002**	0.719	0.000**	0.007**	0.000**	0.125
HCs vs. Comorbidity	0.000**	0.007**	0.000**	0.000**	0.000**	0.000**
Comorbidity vs. Migraine	0.003**	0.029*	0.213	0.017*	0.561	0.016*
Comorbidity vs. Epilepsy	0.432	0.444	0.165	0.289	0.156	0.058

HCs, healthy controls. MoCA, the Montreal Cognitive Assessment. ROCF, the Rey–Osterrieth Complex Figure test. DSST, the Digital Symbol Substitution Test. SAS, the Self-Rating Anxiety Scale. SDS, the Self-Rating Depression Scale. Mean ±SD. multivariate analysis of covariance (ANCOVA). *$P < 0.05$; **$P < 0.01$.

Table 2.2 Intergroup comparison of the MoCA sub-scales

	Visuospatial functions	Attention	Language	Executive functions	Calculation	Memory	Orientation
HCs(n=25)	3.24±0.970	2.84±0.374	5.92±0.400	6.60±1.658	2.76±0.597	3.40±1.443	5.88±0.440
Epilepsy (n=27)	2.48±1.051	2.30±0.775	5.26±0.859	5.33±2.000	2.11±1.121	2.11±1.219	5.41±1.338
Migraine (n=27)	2.70±1.137	2.44±0.641	5.26±0.859	5.56±1.601	2.15±0.989	2.52±1.051	5.78±0.577
Comorbidity(n=20)	1.85±0.988	1.85±0.988	4.75±0.786	3.65±1.814	2.05±0.945	1.75±1.020	5.60±0.940
P value	0.000**	0.000**	0.000**	0.000**	0.032*	0.000**	0.249
HCs vs. Epilepsy	0.010**	0.014*	0.017*	0.012*	0.070	0.000**	-
HCs vs. Migraine	0.067	0.052	0.006**	0.037(b)*	0.054	0.010**	-
HCs vs. Comorbidity	0.000**	0.000**	0.000**	0.000(c)**	0.038*	0.000**	-
Comorbidity vs. Migraine	0.007**	0.006**	0.221	0.000(d)**	1.000	0.033*	-
Comorbidity vs. Epilepsy	0.043*	0.052	0.412	0.002(e)**	1.000	0.311	-

HCs, healthy controls. Mean ±SD. multivariate analysis of covariance (ANCOVA). *$P < 0.05$; **$P < 0.01$.

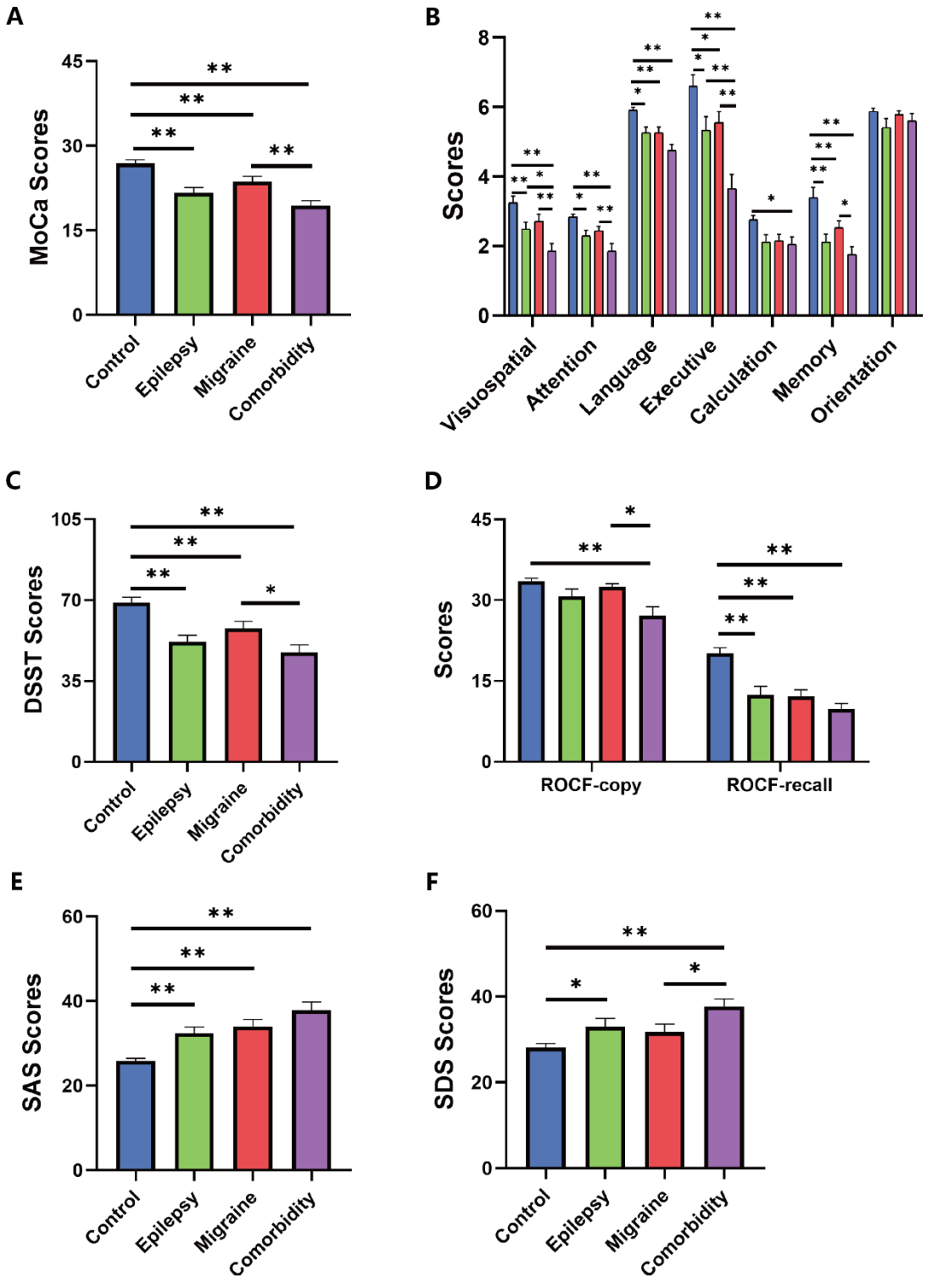


Figure 2 MoCA, the Montreal Cognitive Assessment. ROCF, the Rey–Osterrieth Complex Figure test. DSST, the Digital Symbol Substitution Test. SAS, the Self-Rating Anxiety Scale. SDS, the Self-Rating Depression Scale. **A** Comparison of Moca scale scores among the four groups. **B** Comparison of Moca sub-scale scores among the four groups. **C, D, E, F** Comparison of DSST, ROCF, SAS and SDS scale scores among the four groups. Mean ± SEM; multivariate analysis of covariance (ANCOVA). *$P < 0.05$; **$P < 0.01$.

3. Pain and sensory sensitivity

Mean values for pain perception threshold (PPT), current perception threshold (CPT), and pain tolerance threshold (PTT) are shown in Table 3. No statistically significant difference was observed between the left and right sides across the four groups. Compared with healthy controls, none of the patient groups showed significant differences in PPT or CPT at any tested site or frequency. In contrast, pain tolerance thresholds were markedly altered. At the C7 dermatome, PTT values were significantly lower in all patient groups at 250 Hz and 5 Hz compared to controls. Furthermore, the comorbid group exhibited significantly reduced PTT at 2000 Hz relative to both controls and the other patient groups (Fig. 3A–3K).

Table 3 Intergroup comparison of PPT, CPT and PTT

	PPT	CPT			PTT		
		2000HZ	250HZ	5HZ	2000HZ	250HZ	5HZ
HCs(n=25)							
V1 Left side	5.33±0.232	145.88±34.383	55.84±25.113	41.60±15.567	-	-	-
V1 Right side	5.33±0.228	134.20±27.429	48.12±21.394	35.64±14.029	-	-	-
C7 Left side	5.67±0.272	165.16±48.780	62.32±21.313	47.12±20.268	17.00±3.149	13.72±4.148	20.36±5.773
C7 Right side	5.69±0.292	179.44±54.673	74.16±32.695	51.84±19.976	17.44±3.216	13.92±4.142	21.16±5.145
Epilepsy (n=27)							
V1 Left side	5.33±0.253	136.15±46.259	61.22±23.052	39.44±15.356	-	-	-
V1 Right side	5.30±0.260	134.19±55.544	58.15±25.662	38.93±17.169	-	-	-
C7 Left side	5.71±0.313	166.07±34.555	60.85±18.089	47.59±13.720	15.56±3.786	10.11±3.534	15.67±4.852
C7 Right side	5.74±0.358	166.19±50.811	64.56±31.060	50.15±21.136	15.78±3.974	10.15±4.045	15.56±4.627
Migraine (n=27)							
V1 Left side	5.30±0.199	132.89±39.315	57.94±30.775	41.56±28.836	-	-	-
V1 Right side	5.28±0.204	117.19±32.881	46.89±20.991	38.15±20.471	-	-	-
C7 Left side	5.68±0.306	166.26±35.917	59.07±20.436	46.00±13.159	15.41±2.978	9.22±2.455	15.52±5.892
C7 Right side	5.65±0.314	161.78±41.230	63.93±18.535	45.63±15.599	15.70±3.561	10.00±3.282	16.04±6.016
Comorbidity(n=20)							
V1 Left side	5.26±0.2612	131.75±39.236	47.35±22.022	35.80±15.433	-	-	-
V1 Right side	5.27±0.268	116.15±41.051	45.55±17.996	29.55±14.627	-	-	-
C7 Left side	5.67±0.401	180.25±57.641	64.95±26.732	49.80±15.467	12.55±5.052	8.50±4.236	14.65±5.659
C7 Right side	5.67±0.382	171.10±57.867	60.35±26.599	46.40±14.218	13.10±4.678	8.45±4.571	13.55±4.785
P value (V1 Left side)	0.765	0.605	0.323	0.750	-	-	-
P value (V1 Right side)	0.817	0.218	0.160	0.254	-	-	-
P value (C7 Left side)	0.955	0.636	0.820	0.878	0.002**	0.000**	0.002**
HCs vs. Epilepsy	-	-	-	-	0.167	0.000**	0.003**
HCs vs. Migraine	-	-	-	-	0.128	0.000**	0.002**
HCs vs. Comorbidity	-	-	-	-	0.000**	0.000**	0.001**
Comorbidity vs. Migraine	-	-	-	-	0.011*	0.499	0.579
Comorbidity vs. Epilepsy	-	-	-	-	0.008**	0.133	0.536

P value (C7 Right side)	0.816	0.637	0.365	0.573	0.004**	0.000**	0.000**
HCs vs. Epilepsy	-	-	-	-	0.123	0.001**	0.000**
HCs vs. Migraine	-	-	-	-	0.107	0.001**	0.001**
HCs vs. Comorbidity	-	-	-	-	0.000**	0.000**	0.000**
Comorbidity vs. Migraine	-	-	-	-	0.024*	0.191	0.108
Comorbidity vs. Epilepsy	-	-	-	-	0.020*	0.153	0.194

HCs, healthy controls. V1, The first branch of the trigeminal nerve. C7, the seventh cervical nerve. PPT, the pain perception threshold. CPT, the current perception threshold. PTT, the pain tolerance threshold. Mean ±SD. multivariate analysis of covariance (ANCOVA). *$P < 0.05$; **$P < 0.01$.

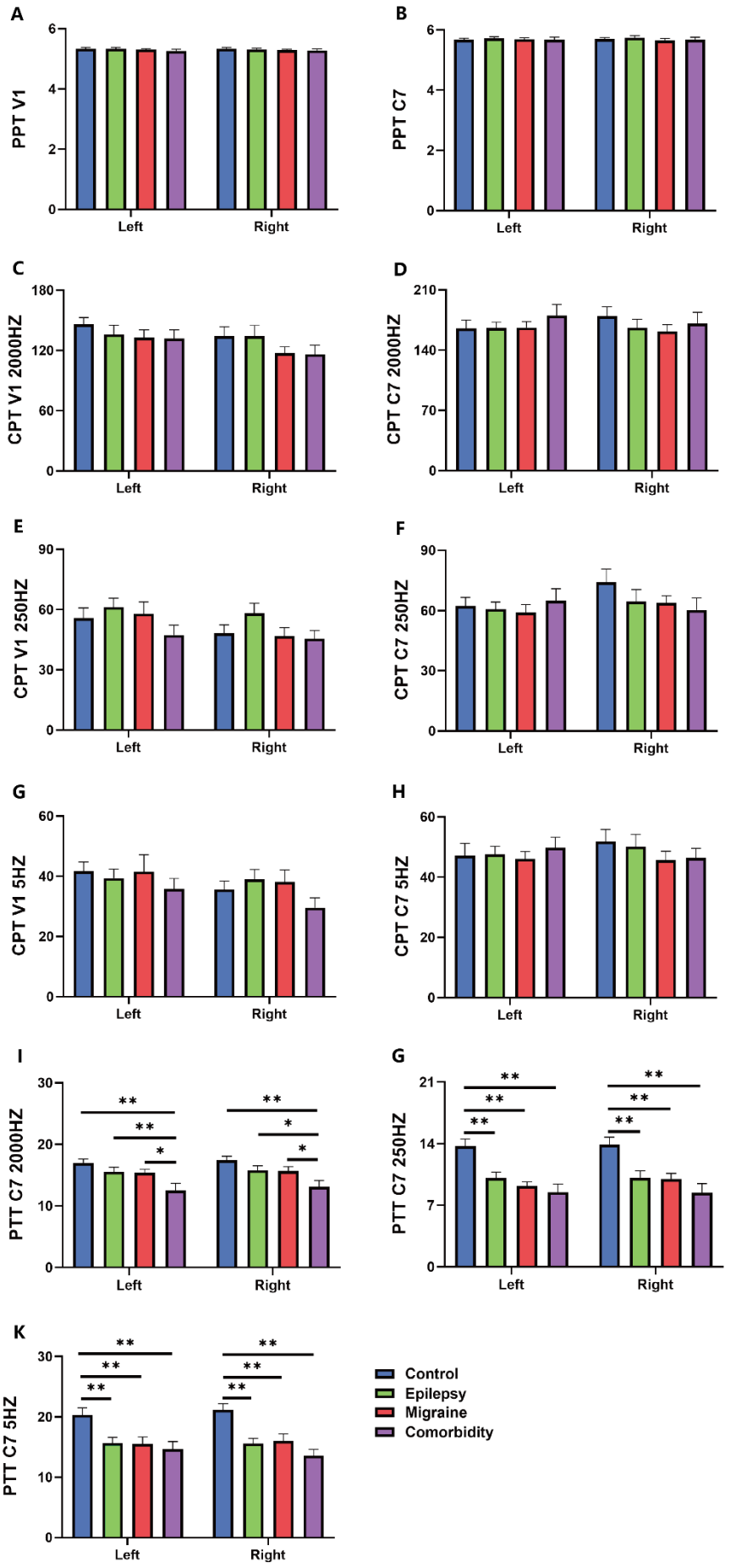

A
PPT V1
B
PPT C7
C
CPT V1 2000HZ
D
CPT C7 2000HZ
E
CPT V1 250HZ
F
CPT C7 250HZ
G
CPT V1 5HZ
H
CPT C7 5HZ
I
PTT C7 2000HZ
G
PTT C7 250HZ
K
PTT C7 5HZ
Left
Right
Control
Epilepsy
Migraine
Comorbidity

Figure 3 V1, The first branch of the trigeminal nerve. C7, the seventh cervical nerve. PPT, the pain perception threshold. CPT, the current perception threshold. PTT, the pain tolerance threshold. **A, B** Comparison of PPT values measured in the V1 and C7 regions. **C, D** Comparison of CPT values measured at a 2000Hz current frequency in the V1 and C7 regions. **E, F** Comparison of CPT values measured at a 250Hz current frequency in the V1 and C7 regions. **G, H** Comparison of CPT values measured at a 5Hz current frequency in the V1 and C7 regions. **I, J, K** Comparison of PPT values measured at different current frequencies (2000Hz, 250Hz, 5Hz) in the C7 region. Mean ± SEM; multivariate analysis of covariance (ANCOVA). **P* < 0.05; ***P* < 0.01.

4. Relation analysis

Correlation analyses were carried out between the headache-related scales, epilepsy-related scales and the corresponding clinical characteristics of headache/epilepsy (including pain intensity, frequency of headache/epileptic seizures, duration of headache/epileptic episodes, and total course of headache/epilepsy), respectively. Our research findings indicated that with regard to disease-related characteristics, the VAS score exhibited a positive correlation with the duration of headache attack (Fig. 4D), while both the MIDAS scores (Fig. 4B) and the HIT-6 scores (Fig. 4A) were positively correlated with the VAS scores. Additionally, the LSSS score showed a positive correlation with the duration of seizure (Fig. 4C). In terms of cognitive function, the MoCA scores were found to be positively correlated with both the HIT-6 scores (Fig. 4E) and the duration of headache attack (Fig. 4F). Additionally, correlation analyses were conducted between the values of PPT, CPT, and PTT and the aforementioned disease characteristics (i.e., pain intensity, frequency of headache/epileptic seizures, duration of headache/epileptic episodes, and total course of headache/epilepsy). Nonethless, no statistically significant correlation was observed in this set of analyses.

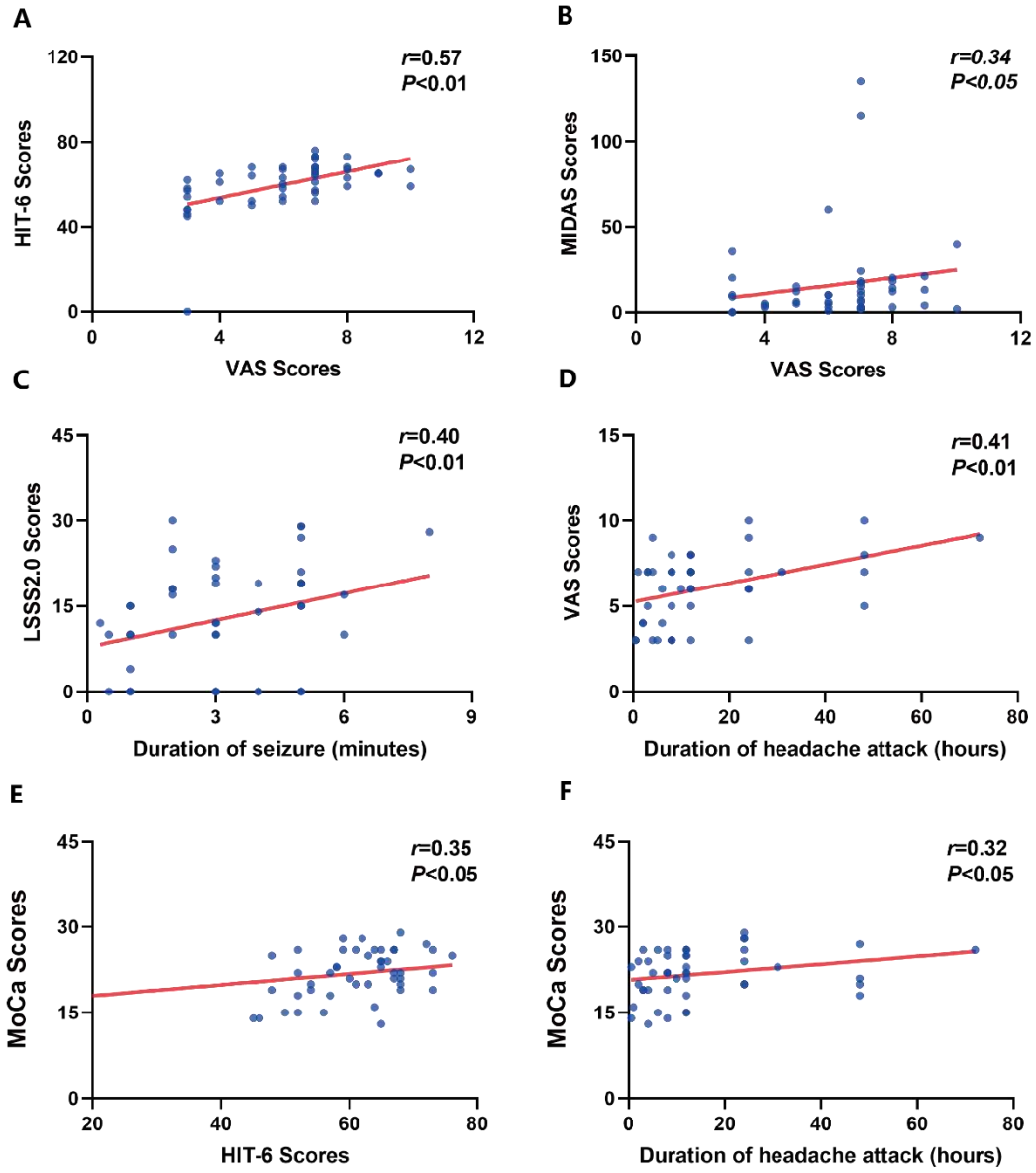


Figure 4 VAS, the Visual Analogue Scale. MIDAS, Migraine Disability Assessment Scale. HIT-6, Headache Impact Test. LSSS 2.0, the Liverpool Seizure Severity Scale 2.0. MoCA, the Montreal Cognitive Assessment. **A** the correlation analysis of VAS scores and HIT-6 scores during headache attack. **B** the correlation analysis of VAS scores and MIDAS scores during headache attack. **C** the correlation analysis of seizure duration and LSSS scores. **D** the correlation analysis of headache attack duration and VAS scores. **E** the correlation analysis of HIT-6 scores and MoCA scores. **E** the correlation analysis of the headache attack duration and MoCA scores. Spearman rank correlation analysis. *$P < 0.05$; **$P < 0.01$.

Discussion

This study provides a comparative analysis of cognitive, emotional, and sensory profiles in patients with epilepsy, migraine, and their comorbidity. Our findings reveal distinct and additive impairments in the comorbid group, alongside evidence of altered sensory processing shared across all patient groups.

Disease Characteristics and Comorbidity Impact

The findings of this study demonstrate that in patients with epilepsy complicated by migraine, no statistically significant difference was observed in epilepsy-related characteristics between those with the comorbidity and patients with epilepsy alone. Nevertheless, previous studies have suggested that the prognosis of patients with comorbid epilepsy and migraine is relatively poorer[18]. The divergence observed in the research conclusions may be ascribed to variations in methodological approaches: the current study adopted a cross-sectional comparative research design, whereas previous studies employed prospective follow-up methodologies. In addition, variations in patient inclusion criteria, research technical routes, and the definition of observation indicators may also serve as critical factors contributing to the inconsistent conclusions between the two types of studies. It is noteworthy that previous studies have confirmed that when epilepsy and migraine coexist, the headache symptoms of most patients are significantly alleviated compared with those with migraine alone. This finding is highly consistent with the conclusions drawn from the present study. The reduction in headache burden can be partially explained by the preventive effects of various antiepileptic drugs commonly administered to this patient population (e.g., topiramate, sodium valproate), which can achieve the dual therapeutic effects of epilepsy control and migraine prevention in patients with this comorbidity[19-21]. It should be emphasized that this study did not stratify or differentiate patients with the comorbidity based on the type of antiepileptic drugs used. This factor may have impacted the accuracy of the research conclusions and constitutes one of the limitations of the present study. Correlation analysis of disease characteristics indicated that the duration of epileptic seizures is positively associated with the severity of epilepsy; the duration of headache episodes shows a positive correlation with the VAS score; furthermore, a higher VAS score is accompanied by increased disability and greater adverse impacts on daily life resulting from headaches.

Additive Effect on Cognitive Impairment

Most patients with epilepsy are prone to cognitive impairments. A large body of research has demonstrated that the longer the duration of epileptic seizures, the more severe the damage to brain tissue, which in turn leads to poorer cognitive function[22]. Long-term chronic epilepsy may result in secondary neuronal loss and metabolic dysfunction[23]. Consistent with prior evidence, patients with epilepsy showed significantly lower MoCA scores than controls, most notably in visuospatial

function, attention, language, executive function, and memory. They also performed worse on the ROCF memory subset and the DSST. The impact of pain on cognitive function manifests as a multifaceted phenomenon. Patients with chronic pain typically exhibit impairments in multiple memory domains, including spatial memory, working memory, recognition memory, and episodic memory[24]. In comparison to the healthy control group, migraine patients achieved significantly lower scores in the MoCA. This score reduction was particularly prominent in the domains of language, executive function, and memory. Additionally, migraine patients also achieved lower scores in the ROCF memory subtest and the DSST. Collectively, the results derived from different assessment scales consistently indicate a decline in the cognitive level of migraine patients. However, patients with comorbidities demonstrate an additive detrimental effect. In comparison with those diagnosed with epilepsy alone or migraine in isolation, this cohort yields lower scores on certain cognitive assessment scales, which indicates a more severe degree of cognitive impairment. In the correlation analysis, a higher pain score and a longer duration of pain were found to be positively associated with more severe functional impairment. Consequently, scientific and standardized pain management plays a pivotal role in improving the prognosis of migraine patients.

Distinct Patterns of Emotional Comorbidity

Emotional disturbances were prevalent but distinct across groups. While all patient groups reported elevated anxiety, significant depression scores were specific to the epilepsy and comorbid groups. The particularly high depression scores in the comorbid group, exceeding those in migraine-only patients. Notably, anxiety and depression may not only present as independent comorbidities but also constitute accompanying symptoms of migraine attacks or epileptic seizures. In numerous research studies, the social prognosis of epilepsy patients has been shown to be less favorable than their clinical prognosis. Consequently, it is insufficient to regard epilepsy solely as a neurological disorder. Therefore, implementing measures to prevent and mitigate the stigma faced by epilepsy patients is of great significance for reducing the incidence of depression and improving the overall prognosis of these patients[25]. Anxiety and emotional symptoms have been recognized as the most prominent mental health comorbidities associated with migraine, exerting a substantial impact on the disease's prevalence, prognosis, treatment efficacy, and clinical outcomes[26]. In the present study, the SAS scores of migraine patients were

significantly higher than those of the normal control group, whereas no statistically significant difference was observed in the SDS scores. This finding provides direct evidence for the presence of anxiety symptoms in this patient population. Clinically, the accurate detection of anxiety symptoms and the implementation of both pharmacological and non-pharmacological interventions targeting these symptoms may contribute to improvements in headache severity and patient quality of life. Patients with comorbidities exhibited significantly higher scores compared to those with epilepsy alone or migraine alone, which indicates that the impact of underlying emotional factors is more pronounced. Our findings are largely consistent with the results of prior relevant studies.

Sensory Abnormalities and Central Sensitization: Mechanistic Insights

Most patients with migraines report symptoms of somatic sensory sensitization, such as increased pain after exposure to light, or abnormal skin pain symptoms (pain caused by non-harmful stimuli, such as combing hair or wearing glasses, is a relatively easy-to-identify sign of central sensitization)[27]. This study used the ASC-12 to observe this phenomenon, and among the migraine and epilepsy comorbid migraine patients enrolled in the study, each patient had more or less one or several items on the checklist.

In the present study, no statistically significant changes were observed in the PPT and CPT values of the migraine group when compared with the control group. As the CPT value is an indicator of sensory sensitivity, this result suggests that the sensory sensitivity of patients during the interictal period is comparable to that of normal individuals. It has been established in existing research that when the painless CPT test yields normal results, the PTT test may provide more valuable diagnostic information. On this basis, the research team further measured the PTT values of the subjects. Notably, the PTT values of bilateral C7 segments at frequencies of 250Hz and 5Hz in the patient group were significantly lower than those in the control group, with the difference reaching statistical significance. This finding implies that patients with migraine may exhibit abnormal sensory input associated with Aδ fibers and small C fibers. Given that the PTT test reflects pain sensitivity, the observed reduction in PTT values indicates the presence of hyperalgesia in migraine patients. Furthermore, the abnormal sensory input mediated by Aδ fibers and small C fibers may be closely associated with the occurrence of pain episodes in migraine patients.

Migraine patients were detected to have central sensitization and hyperalgesia through

the abnormal pain scale. Then, does central sensitization exist in epilepsy patients? This study was the first to evaluate the pain and sensory sensitivity of various afferent fibers in epilepsy patients. Our study found that, regardless of whether there was pain or not, epilepsy patients showed lower PTT than the healthy control group during bilateral C7 tests at 250Hz and 5Hz, suggesting that the pain tolerance of epilepsy patients was lower than that of the control group. This result was basically consistent with the test results of migraine patients, suggesting that epilepsy may have central sensitization and hyperalgesia like migraine, and may also be one of the reasons why the headache incidence of epilepsy patients is higher than that of other diseases. There was no significant statistical difference in PPT and CPT between epilepsy patients with co-morbid migraine and the control group. However, the pain tolerance thresholds of bilateral C7 at 2000Hz, 250Hz, and 5Hz were lower than those of the control group, suggesting that the co-morbid patients have harmful abnormalities in sensory input dependent on Aδ fibers and small C fibers (conveying pain sensation) and harmless abnormalities in sensory input dependent on Aβ fibers (conveying touch-pressure sensation). The abnormality in sensory input of Aδ fibers and small C fibers may be related to the existence of epilepsy pain; this is of great significance for studying the central sensitization and its co-morbidity mechanism of migraine and epilepsy.

In the present study, no statistically significant differences in PPT and CPT values were observed among the four groups. This finding is inconsistent with the previously reported regarding somatic sensory sensitization. Several factors may contribute to this discrepancy. First, it may be attributed to the sensitivity characteristics of Von Frey Hairs fibers and the Neurometer® CPT instrument, as the detection performance of such tools can directly influence the measurement results of pain thresholds. Second, the test time window selected in this study may also be a relevant factor: seizures in patients with epilepsy exhibit high unpredictability, making it challenging to align the examination with specific disease phases. Notably, the data collection of the present study was conducted during the interictal period (i.e., the interval between consecutive seizures).

Clinical Implications and Future Directions

These findings advocate for an integrated clinical approach. Assessment of comorbid patients should routinely include cognitive and mood evaluation, as these domains are disproportionately affected. The sensory profile observed, particularly the reduced

pain tolerance, suggests that pain modulation circuits are a relevant therapeutic target in both disorders. Future longitudinal studies are needed to clarify causal relationships, determine whether the sensory abnormalities are state or trait markers, and explore the efficacy of interventions aimed at modulating central sensitization (e.g., certain pharmacotherapies or neuromodulation) in improving both sensory and cognitive-affective outcomes.

Limitations

This study has several limitations. Its cross-sectional design precludes causal inferences. The sample size, though adequate for initial comparisons, may limit the detection of subtler effects. Assessments were conducted during the interictal period, which may not capture dynamic changes during or immediately after attacks. Furthermore, the potential confounding effects of specific medications, although partially controlled for by patient status, could not be fully isolated.

Conclusions

In conclusion, patients with comorbid epilepsy and migraine experience additive deficits in cognition and affect, alongside evidence of shared central sensitization manifested as reduced pain tolerance across multiple sensory fiber types. These results underscore the complexity of the epilepsy-migraine comorbidity, extending beyond simple co-occurrence to interactive effects on brain function. Recognizing and addressing these multidimensional impairments is crucial for optimizing the management and quality of life of affected individuals.

Declarations

Abbreviations

MoCA, Montreal cognitive assessment

SAS, Self-rating anxiety scales

SDS, Self-rating depression scale

PPT, Pain tolerance thresholds

CPT, Current perception thresholds

PTT, Pain tolerance thresholds

MIDAS, Migraine disability assessment scale

HIT-6, Headache impact test-6

VAS, Visual analog score

ASC-12, Allodynia symptom checklist-12

LSSS2.0, Liverpool seizure severity scale2.0

ROCF, Rey-osterrieth complex figure Test

DSST, Digit symbol substitution test

HCs, healthy controls

V1, The first branch of the trigeminal nerve

C7, the seventh cervical nerve

SD, standard deviation

SEM, error of the mean

Ethics approval and consent to participate

All participants or their guardians were informed of the study and gave their consent by signing the informed consent form. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Renmin Hospital of Wuhan University (WDRY2022-K108). Our trial was registered in the Chinese Clinical Trial Registry (ChiCTR) with the registration number 2200065174, and the registration date was October 30, 2022(Retrospectively registered).

Consent for publication

Not Applicable.

Availability of data and materials

This study included articles which are available via PubMed. All information analysed in this study was collected in a dataset and this is available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

The thesis was authored by Yuyan Hao. Fan Zhang, Zhen Li, Jun Han, and Wenmin Feng contributed to data collection. Yanjie Zhou and Li Huang offered assistance in the thesis writing process.

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