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Cognitive impairment and drug responsiveness in mesial temporal lobe epilepsy☆

Sibel Celiker Uslu [a], Burcu Yuksel [b,*], Betul Tekin [c], Hande Sariahmetoglu [d], Dilek Atakli [d]

[a] Samsun Training and Research Hospital Neurology Department, İlkadım, 55090 Samsun, Turkey
[b] Antalya Training and Research Hospital, Neurology Department, Muratpasa, 07050 Antalya, Turkey
[c] Rumeli Hospital Neurology Department, Kucukcekmece, 34295 Istanbul, Turkey
[d] Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Neurology Department, Bakirkoy, 34147 Istanbul, Turkey

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ABSTRACT

Objectives: Mesial temporal lobe epilepsy (MTLE) is the most common form of partial epilepsies. Seizures of MTLE with hippocampal sclerosis (MTLE-HS) are typically resistant to antiepileptic drug (AED) therapy. Although memory disturbances in patients with MTLE-HS are expected, verbal attention and frontal lobe functions may also be impaired. We aimed to examine the relationship between the clinical features and cognitive functions of patients by comparing cognitive test scores of patients with MTLE with few seizures (drug-responsive group) and those with frequent seizures (pharmacoresistant group).
Methods: Seventy-nine patients with MTLE-HS and 30 healthy controls were enrolled. Thirty-four patients were accepted as the drug-responsive group (DrG), and 45 patients were included in the pharmacoresistant group (PRG). Tests evaluating attention, memory, and executive functions were performed on all participants.
Results: Forty-nine (62%) female and 30 (38%) male patients with MTLE-HS, and 14 (46.7%) female and 16 (53.3%) male controls participated in the study. The mean age of the patients and controls was 33.53 ± 9.60 (range, 18–57) years and 35.90 ± 7.98 (range, 18–56) years, respectively. Both the DrG and PRG showed poorer performances in tests evaluating memory and frontal lobe functions when compared with the control group (CG). Additionally, attention test results were significantly worse in the PRG than in the DrG.
Conclusion: It is reasonable to say that increased seizure frequency is the main causative factor of verbal attention deficit due to the poorer attention test results in the PRG. Poor performances in memory and frontal lobe function tests of all patients with MTLE-HS emphasized the importance of the mutual connection between the temporal lobe and prefrontal cortices.

1. Introduction

The most common underlying pathophysiology in temporal lobe epilepsy (TLE) is hippocampal sclerosis (HS), and this situation causes a special clinical syndrome called mesial temporal lobe epilepsy (MTLE), which is the most common form of partial epilepsies; MTLE is typically resistant to antiepileptic drug (AED) therapy. However, the causal relation between HS and the development of MTLE is not yet clearly understood. Furthermore, the disease course may differ from one patient to another. Some studies have shown seizure control in 20–25% of patients receiving AEDs and surgical outcomes for seizure freedom in patients with mesial temporal sclerosis ranges from 70% to 90% [1]. A small group of patients with infrequent seizures can be maintained on optimal doses, and seizures may even stop in the meantime [2–4]. However, except this small portion of patients with good seizure control, most of the patients are considered intractable and candidates for surgery [5,6]. It is not yet understood that why some patients have intractable seizures while others respond well to medical treatment.

An important finding in patients with MTLE-HS is memory deficits. In some studies, impairment of verbal memory was demonstrated in patients with left-sided HS; however, nonverbal memory deficits were not seen in patients with right-sided HS [7–9]. Verbal memory decline and naming difficulties in left-sided surgery and visual memory decline in right- and left-sided surgeries are the most prominent losses [10]. Barr et al. suggested that right temporal lobe dysfunction may provide a focal disruption to a specific system responsible for pattern recognition and object identification [11]. In addition with these findings, Glikmann-Johnston et al. stated that lateralization of spatial memory was influenced by task-specific factors, the object location task was the one most expected to reveal right-lateralized effect. Ability to navigate, learn, and recall objects and locations and draw a plan of the

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* Corresponding author.
E-mail address: dr.byuksel@gmail.com (B. Yuksel).

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environment was related to the integrity of both the right and left mesial temporal lobes in TLE [12].

In recent years, volumetric studies have provided a new opportunity to identify the functional adequacy of the structure. Increased left hippocampal activity on functional magnetic resonance imaging (fMRI) in individuals with left TLE or increased right hippocampal activity in patients with right TLE was associated with better presurgery memory performance. However, multiple methodological issues still remain to be solved [13–15].

Using quantitative magnetic resonance imaging (MRI) tools, voxel-based morphometric techniques, and diffusion tensor imaging techniques, structural abnormalities were seen to extend beyond the epileptogenic hippocampus. Cortical, subcortical, and cerebellar regions and their direct and indirect connectivity have shown to be affected. The extension of these structural abnormalities might contribute to probability of seizure freedom after epilepsy surgery [16].

In concert with the extensive anatomical abnormalities, although MTLE preferentially affects memory functions, it also affects other domains of cognitive functioning. Riley et al. demonstrated that altered connectivity between caudate and dorsal prefrontal cortex in TLE is associated with impaired performance in working memory, attention, and executive functioning [17]. Meador reported that increased frequency of seizures in patients with MTLE caused significant worsening of attention function [18]. Similarly, Ozkara et al. found significantly lower attention test results in the PRG. They stated that increased frequency of seizures caused significant worsening of attention function [19]. Because of mutual connections between the temporal lobe and prefrontal cortices, verbal attention and frontal lobe functions could be impaired. Another theory is that the memory deficit may alter the results of tests assessing frontal function [20,21]. History of secondarily generalized seizures in patients with MTLE may also affect frontal lobe functions. Besides the underlying pathology of HS, cognitive decline was also found to be associated with seizure frequency, seizure onset at an early age, adverse effects of AEDs, and duration of the disease [22,23].

The aim of this study was to compare patients with drug-responsive MTLE and patients with drug-resistant MTLE in terms of memory, attention, and executive functions. We believed that this would lead us to understand if memory disorders are related to underlying hippocampal pathology or medically resistant seizures. As a second aim, we also evaluated attention and executive functions between the groups to see if seizure frequency or connections between the temporal lobe and prefrontal cortices could affect the other domains of cognitive functions.

2. Material and methods

This study was approved by local ethics committee, and all patients with MTLE-HS and healthy control participants gave written informed consent.

2.1. Participants

A total of 79 patients with MTLE-HS, whose diagnoses were according to their seizure history, electroencephalography (EEG), neuropsychological tests, and MRI findings, and 30 healthy controls were enrolled in the study. The demographic features and clinical characteristics (age, sex, education level, age of onset and duration of the disease, history of febrile convulsions, family history of epilepsy, consanguineous marriage, seizure type, and AED usage) of the patients were recorded.

Patients with MTLE-HS were divided into two groups; 34 patients under the treatment of a maximum of two AEDs with less than or equal to two complex partial seizures per month or less than two secondarily generalized seizures per year were accepted as the drug-responsive group (DrG), and 45 patients who were excluded from the above-mentioned drug-responsiveness criteria were accepted as the pharmacoresistant group (PRG). Patients who were followed up for at least one year by the same epileptologist were included to the study. All patients have interictal or ictal EEG abnormalities relevant to TLE and their HS was detected by MRI scan with atrophy on T1W and signal increase on T2W images. All tests were conducted before surgery in the PRG. Thirty age-, sex-, and education level-matched healthy controls were included. Controls were mostly selected from relatives of patients, or they were community controls.

Tests were performed to reveal all aspects of cognitive functioning; mainly attention, memory, and executive functions, and were applied to all participants (both patients and healthy volunteers). The tests performed were as follows: *Verbal Memory-Recall, Recognition, Total Learning-Tests* (*VMT*) (with short-term memory, maximum and total learning, recall, recognition, and total recall for verbal memory), *Wechsler Memory Scale* (*WMS*) (with immediate recall, delayed recall, recognition, and total score for visual memory), *Wechsler Memory Scale* (*WMS*) *story subtest* (with immediate recall, delayed recall) for verbal and logical memories, *Digit Span Test* (with attention, reverse attention, and total attention scores for verbal attention), *Stroop test* (with 1st and 5th card times, mistake, and correction for executive functions), *verbal fluency* and *verbal fluency with alternating categories test* (semantic fluency with animals per minute, word pairs per minute, perseverations, and switching errors for executive functions).

Exclusion criteria were as follows: i) mental retardation, ii) younger than 18 years of age, iii) less than primary school education, iv) presence of additional systemic diseases and depression, v) illicit drug abuse, vi) presence of generalized tonic–clonic or complex partial seizure one week prior to the study, vii) previous surgical history for MTLE-HS, vii) bilateral HS, viii) lesions other than HS on MRI.

2.2. Data analysis

The collected data were analyzed using Number Cruncher Statistical System (NCSS) 2007 & Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA). Descriptive statistics were used for sociodemographic and clinical variables. The relationships between various parameters were analyzed using Student's *t*-test, and the categorical variables of the patients and controls were determined using the Mann–Whitney *U* test. The Chi-square and Fisher's exact test were used for comparisons between qualitative data. Values of $p < 0.05$ were considered as statistically significant.

3. Results

Forty-nine (62%) female and 30 (38%) male patients with MTLE-HS, and 14 (46.7%) female and 16 (53.3%) male controls participated in the study. The mean age of the patients and controls was 33.53 ± 9.60 (range, 18–57) years and 35.90 ± 7.98 (range, 18–56) years, respectively. The mean age of seizure onset was 15.17 ± 10.17 (range, 1–45) years. There were no significant differences between the patients and controls in terms of age, sex, and education level ($p > 0.05$) (Table 1). The age of onset of the disease in the DrG was higher than in the PRG; the difference was statistically significant ($p = 0.001$) (Table 2).

3.1. Cognitive test results

3.1.1. Memory test results

Concerning the verbal memory test, short-term memory did not differ between the patients and controls ($p > 0.05$); however, other memory test scores were significantly lower in patients than in controls ($p = 0.001$). The maximum learning score (maximum number of learned words) in the verbal memory test was statistically significantly higher in the DrG than in the PRG ($p = 0.001$). Patients in the PRG had significantly worse logical memory scores ($p = 0.001$) than patients in the DrG.

For the visual memory tests, immediate and delayed recall and recognition tests were found to be statistically worse in the patient group

Table 1
Demographic and clinical data of the patient and control groups.

	Patients n = 79 (%)	Controls n = 30 (%)	p
Age (years)	33.53 ± 9.60 (18–57)	35.90 ± 7.98 (18–56)	0.23
Sex			
• female	49 (62)	14 (46.7)	0.14
• male	30 (38)	16 (53.3)	
Education			
• primary school	56 (70.88)	21 (70)	
• high school	17 (21.51)	6 (20)	0.82
• university	6 (7.61)	3 (10)	
Age at onset of epilepsy (year)	15.17 ± 10.17 (1–45)	–	
Duration of epilepsy (years)	18.96 ± 8.58 (2–42)	–	
History of febrile seizure	49 (62.0)	–	
Epilepsy in family	14 (17.7)	–	
Consanguineous marriage	16 (20.2)	–	
Side			
• Right HS	40 (50.6)	–	
• Left HS	39 (49.4)		

than in the controls ($p = 0.001$), and there were no significant differences between the DrG and PRG.

3.1.2. Attention test results

For the verbal attention test, the scores of PRG were significantly lower than those of the DrG and controls ($p = 0.001$).

3.1.3. Executive functions

There were no significant differences between drug responsiveness and executive functions ($p > 0.05$). However, patients showed worse performance in the Stroop test and in verbal fluency with alternating categories; the scores of animal and fruit/human counts were significantly lower in patients than in the controls ($p < 0.05$) (Table 3).

3.2. Duration of the disease and cognitive test results

The longer the disease duration the worse the performance in attention, verbal memory (especially learning phase), visual memory, and logical memory was found ($p < 0.05$). There was a negative correlation between disease duration and the Stroop test or verbal fluency with the alternating categories test; however, there was no significant difference in the verbal fluency test ($p > 0.05$) (Table 4).

Eventually, although statistically significant difference was found between DrG and PRG in maximum learning score of the verbal memory test and logical memory scores, *Digit Span Test* evaluating attention had the largest effect size for separating the groups PRG and DrG. We also compared DrG with PRG in the left temporal lobe for verbal memory and attention and in the right temporal lobe for visual memory and attention. We found significant differences ($p < 0.05$) only in attention test results between the DrG and PRG in the left temporal lobe and scores were lower in the PRG.

Table 2
Clinical data of the drug-responsive group and pharmacoresistant group.

	DrG (n = 34)	PRG (n = 45)	p
Age at onset of epilepsy	20.74 ± 11.28 (20.00)	10.97 ± 6.79 (11.00)	[a]0.001**
Duration of epilepsy	16.79 ± 9.26 (15.50)	20.60 ± 7.73 (20.00)	[a]0.042*
Side			[b]0.999
Right HS	17 (50.0)	23 (51.1)	
Left HS	17 (50.0)	22 (48.9)	
History of febrile seizure	23 (67.6)	26 (57.8)	[b]0.509
Epilepsy in family	7 (20.6)	7 (15.6)	[b]0.778
Consanguineous Marriage	6 (17.6)	10 (22.2)	[b]0.827

DrG: Drug-responsive group; PRG: Pharmacoresistant group.
Significant differences are shown in bold and italics.
[a] Mann–Whitney *U* test.
[b] Yates's continuity correction test.
* $p < 0.05$.
** $p < 0.01$.

4. Discussion

Temporal lobe epilepsy is the most common form of drug-resistant focal epilepsy in adults, and it is associated with cognitive impairment. Patients with TLE exhibit memory disturbances and show decline in speeded psychomotor processing, executive functions, and naming [24,25]. More common cognitive morbidity is supposed to be seen in patients with MTLE rather than in patients with other TLEs [26].

In our study, when we examined the demographic features and clinical characteristics of the patients such as age, sex, education level, localization of the disease, history of febrile seizures, family history of epilepsy, and consanguineous marriage, there was no significant difference between the DrG and PRG. The factors associated with poor prognosis were young age at onset of epilepsy and long duration of disease. Sanchez et al.'s study included 110 patients with MTLE and the presence of early onset of seizures was found to be a poor prognostic factor [27]. Similarly, Aguglia et al. stated that, in 424 patients with MTLE, age at onset of seizures was significantly higher in patients with a good prognosis. Other factors, including sex, family history of epilepsy or febrile seizures, perinatal asphyxia, febrile seizures, and interictal EEG abnormalities were not associated with prognosis [28]. Kim et al. found that early onset of seizures, history of febrile seizures, and epileptiform discharges on EEG were associated with poor prognosis [29]. In contrast with these studies, Andrade-Valença et al. reported no association between age of onset and prognosis [4].

Although MTLE preferentially affects memory functions, it also affects other domains of cognitive functioning. Thus, we evaluated attention and executive functions besides memory. In our study, the scores of verbal attention tests in the PRG were significantly lower than in the DrG and controls. According to our results, we suggest that the prognosis of the disease and increased frequency of seizures might affect attention and sustained attention. Similarly, Meador et al. reported that increased frequency of seizures in patients with MTLE caused significant worsening of attention function [18]. Ozkara et al. compared DrG (n = 18) with PRG (n = 95), a total of 113 patients with MTLE in terms of attention, and they found significantly lower attention test results in the PRG. They stated that increased frequency of seizures caused significant worsening of attention function [19].

Verbal and visual memory results showed that learning in patients with MTLE was insufficient and delayed. Moreover, there might be an issue in consolidation of long-term memory or recall. We found no significant differences between the DrG and PRG concerning verbal and visual memory except for maximum number of learned words. According to this result, we considered that DrG learned more words than PRG, but they all could not transfer the words to the long-term memory. Furthermore, in our opinion the maximum number of learned words might be affected by decreased attention and sustained attention in PRG. The results of our study were consistent with the results from recent studies. According to Luiz et al., lower memory performances were found in 87 patients with MTLE-HS than in controls, and the decrease was considered to be related to HS [30]. Ozkara et al. reported a decrease in verbal and visual memory performances in 113 patients with MTLE-HS; however, there was no significant difference between the DrG and PRG concerning memory functions. They concluded that memory impairment in patients with MTLE-HS was permanent and might be related to the direct effect of HS itself [19]. In contrast with these results, Voltzenlogel et al. evaluated patients based on seizure frequency. Long-term memory impairment, especially recall function, was found more affected in patients with increased seizure frequency than in patients with fewer seizures. Attention, executive functions, and intelligence quotient (IQ) did not differ significantly between these two

Table 3
Cognitive test scores of the patient and control group.

			DrG (n = 34)	PRG (n = 45)	Control (n = 30)	DrG-PRG	DrG-Control	PRG-Control
VERBAL ATTENTION	DST	Attention	5.00 ± 1.44	4.44 ± 0.81	5.40 ± 1.33	0.105	*0.109*	***0.001*** **
		Reverse attention	3.91 ± 1.19	3.24 ± 1.05	4.27 ± 1.23	**0.014** *	*0.213*	***0.001*** **
		Total attention	8.91 ± 2.44	7.69 ± 1.66	9.67 ± 2.41	**0.027** *	*0.103*	***0.001*** **
MEMORY TEST	VMPT	STM	5.41 ± 1.56	5.36 ± 1.51	6.07 ± 1.41	0.808	*0.075*	*0.099*
		Repeat count	9.56 ± 1.78	9.78 ± 0.79	8.03 ± 2.14	0.111	***0.004*** **	***0.001*** **
		MLS	13.15 ± 2.00	11.73 ± 2.1	14.70 ± 0.60	**0.005** **	***0.001*** **	***0.001*** **
		Recall	10.38 ± 3.46	9.69 ± 2.98	13.80 ± 1.21	0.342	***0.001*** **	***0.001*** **
		Recognition	3.94 ± 2.86	4.69 ± 2.44	1.17 ± 1.23	0.214	***0.001*** **	***0.001*** **
		Recall + recognition	14.32 ± 1.15	14.38 ± 1.23	14.97 ± 0.18	0.494	***0.001*** **	***0.005*** **
		TLS	103.24 ± 17.93	96.47 ± 18.34	119.30 ± 13.25	0.105	***0.001*** **	***0.001*** **
	WMS Visual	Immediate recall	8.74 ± 3.21	8.78 ± 2.77	11.53 ± 1.98	0.950	***0.001*** **	***0.001*** **
		Delayed recall	6.88 ± 3.79	6.91 ± 3.28	10.60 ± 2.70	0.971	***0.001*** **	***0.001*** **
		Recognition	2.50 ± 1.21	2.07 ± 1.05	3.23 ± 0.94	0.101	***0.013*** *	***0.001*** **
	WMS-LM	Immediate recall	8.97 ± 3.40	7.20 ± 4.04	12.73 ± 2.97	**0.016** *	***0.001*** **	***0.001*** **
		Delayed recall	7.21 ± 3.67	5.42 ± 4.21	10.97 ± 3.42	**0.023** *	***0.001*** **	***0.001*** **
EXECUTIVE FUNCTIONS	Stroop	Stroop 1st card time (second)	13.29 ± 3.41	13.89 ± 4.83	10.33 ± 2.81	*0.750*	***0.001*** **	***0.001*** **
		Stroop 5th card time (second)	44.85 ± 34.06	41 ± 20.97	30.87 ± 11.86	*0.960*	*0.052*	***0.031*** *
		Stroop error	1.32 ± 2.16	1.13 ± 2.11	0.53 ± 0.68	*0.496*	*0.272*	*0.790*
		Corrected error	1.47 ± 1.42	1.6 ± 1.51	0.97 ± 1.10	*0.763*	*0.165*	*0.073*
	Verbal Fluency	Animal count	16.41 ± 5.01	15.11 ± 4.77	20.17 ± 4.92	*0.244*	***0.004*** **	***0.001*** **
		Animal perseveration	0.24 ± 0.55	0.40 ± 0.75	0.53 ± 0.82	*0.324*	*0.118*	*0.474*
		Alternating categories (Fruit/Human count)	7.21 ± 1.75	6.44 ± 1.90	8.73 ± 1.93	*0.072*	*0.072*	***0.002*** **
		Fruit/Human (Perseveration)	0.44 ± 0.56	0.82 ± 1.23	0.37 ± 0.72	*0.332*	*0.304*	*0.080*
		Fruit/Human (inability to change category)	0.18 ± 0.39	0.13 ± 0.50	0.17 ± 0.38	*0.272*	*0.967*	*0.310*

DST: Digit Span Test; VMPT: Verbal Memory Processing Test; WMS_LM: Wechsler Memory Scale Story Subtest; WMS_Visual: Wechsler Memory Scale Visual Memory Subtest; STM: Short-term memory; MLS: Maximum learning score; TLS: Total learning score.
Significant differences are shown in bold and italics.
* $p < 0.05$.
** $p < 0.01$.

Table 4
Duration of the disease and cognitive functions.

	n = 79	Duration of the disease	
		R	[e]P
VERBAL ATTENTION	Attention	−0.248	**0.028** *
	Reverse attention	−0.419	**0.001** **
	Total attention	−0.389	**0.001** **
MEMORY	VMPT-STM	−0.059	**0.607**
	VMPT-Repeat count	0.379	**0.001** **
	VMPT-MLS	−0.294	**0.008** **
	VMPT-Recall	−0.077	[f]**0.499**
	VMPT-Recognition	0.061	[f]**0.592**
	VMPT-Recall + Recognition	−0.156	**0.169**
	VMPT-TLS	−0.201	[f]**0.076**
	WMS_Visual-Immediate recall	−0.274	[f]**0.015** *
	WMS_Visual-Delayed recall	−0.288	[f]**0.010** *
	WMS_Visual-Recognition	−0.297	**0.008** **
	WMS_LM-Immediate recall	−0.342	**0.002** **
	WMS_LM-Delayed recall	−0.274	**0.015** *
EXECUTIVE FUNCTIONS	Stroop 1	0.306	**0.006** **
	Stroop 5	0.281	**0.012** *
	Stroop error	0.036	**0.755**
	Stroop corrected error	0.015	**0.896**
	Verbal fluency (Animal count)	−0.203	[f]**0.073**
	Verbal fluency (Animal perseveration)	−0.041	**0.722**
	Alternating categories (F/H count)	−0.243	[f]**0.031**
	F/H Perseveration	−0.109	**0.338**
	F/H Inability to change category	−0.141	**0.215**

VMPT: Verbal Memory Processing Test; WMS_LM: Wechsler Memory Scale Story Subtest; WMS_Visual: Wechsler Memory Scale Visual Memory Subtest; STM: Short-term memory; MLS: Maximum learning score; TLS: Total learning score; F/H: Fruit/Human.
Significant differences are shown in bold and italics.
[e] r = Spearman's Correlation Coefficient.
[f] r = Pearson Correlation Coefficient.
* $p < 0.05$.
** $p < 0.01$.

groups [31]. Lopez et al. compared groups of good seizure control and poor seizure control in terms of cognitive functions, and there were no significant difference between the two groups concerning attention; visual, verbal, and logical memory; and executive functions [32]. In our study, short-term and long-term logical memory losses were more significant in patients in the PRG than in those in the DrG. With these results, we considered that the affected sustained attention function while reading stories to the PRG could be because of seizure frequency and that might affect the logical memory test results. Helmstaedter et al. established a strong correlation between logical memory and attention, language function, and vocabulary in 81 patients with epilepsy [33].

In our study, patients showed worse performance in verbal fluency with alternating categories and the Stroop test. There were no significant differences in drug responsiveness and executive functions between the patients and controls. These results showed that mental set shifting and recall functions were significantly affected in patients than controls. Two hypotheses have been investigated for demonstrating the underlying process of executive system dysfunction in MTLE. The first hypothesis is that the epileptogenic cortex adversely affects the extratemporal regions, which mediate executive system abilities [34–36]. The second hypothesis is that the human hippocampi are directly involved in the mediation of some executive system functions and performance deficits, and therefore, this situation is directly attributable to hippocampal pathology [37]. Tuchscherer et al. determined significantly poorer performance in the Stroop, Trails B, and verbal fluency tests, which are commonly used measures of executive functions [38]. Zamarian et al. found that a PRG of patients with MTLE performed poorly in tests of executive functions [39]. Other studies showed no difference between patients with MTLE and controls regarding executive functions [40,41]. The different results of these studies for evaluating executive functions might be accounted for by the use of different test batteries.

In some studies, the longer the disease duration the worse the performance in memory and other cognitive functions could be seen in patients with MTLE [42–45]. Our study showed worse performance in attention, verbal memory (especially the learning phase), visual memory, and logical memory as disease duration increased. Rauch et al. followed up 8 nonsurgical patients with intractable epilepsy for 12.8 years and a progressive decline was observed in verbal and visual memory scores [46]. Similarly, Fuerst et al. noted that patients with continuing seizures had a decline in hippocampal volume and that medically refractory patients had progressive hippocampal atrophy. Consequently, impairment in memory performances could be seen [47]. In contrast with these studies, Helmstaedter et al. showed no significant difference in memory tests during long-term follow-up in patients with drug-responsive MTLE who had fewer seizures [22].

We also compared DrG with PRG in the left temporal lobe for verbal memory and attention and in the right temporal lobe for visual memory and attention. We only found significant differences in attention test results between the DrG and PRG in the left temporal lobe. According to this result, we thought that seizure frequency affected the attention function, and this function mostly related to the left hemisphere. Studies demonstrated that anatomical abnormalities in MTLE were not limited to the epileptogenic hippocampus. In addition to gray matter abnormalities, aberrant white matter tracts and connections are present in chronic TLE. Some studies found an association between left-hemisphere seizure focus and attention deficits in children and adults [48–50]. Our results were consistent with these studies.

Our study has some limitations. Some other tests could have been added to show the difference in cognitive functions between right- and left-sided epilepsies in both the PRG and DrG. After surgery in the PRG, all these tests could have been used to show improvement or recovery. The patients who were not willing to undergo surgery could be tested prospectively. A long-term evaluation of these patients would allow us to follow the alterations over time.

In conclusion, MTLE is the most common form of drug-resistant focal epilepsy in adults, and it is associated with cognitive impairment. Impairment was examined in all parts of cognitive functioning including memory, attention, and executive functions. Impairment of memory functions in patients with MTLE-HS is a well-known and expected clinical feature. The main reason of impairment in attention was considered to be the increased seizure frequency, and memory dysfunction was thought to be related to the underlying hippocampal pathology. Furthermore, worse performance in executive functions was determined in all patient groups, and this finding might support the mutual connection between the temporal lobe and prefrontal cortices. We hope that our study will cast light for future research of neuropsychological outcomes in temporal lobe epilepsies.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

[1] Kumlien E, Doss RC, Gates JR. Treatment outcome in patients with mesial temporal sclerosis. Seizure 2002;11(7):413–7.
[2] Kobayashi E, Lopes-Cendes I, Guerreiro CA, Sousa SC, Guerreiro MM, Cendes F. Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy. Neurology 2001;56(2):166–72.
[3] Stephan LJ, Kwan P, Brodie MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? Epilepsia Mar 2001;42(3):357–62.
[4] Andrade-Valença LP, Valença MM, Ribeiro LT, Matos AL, Sales LV, Velasco TR, et al. Clinical and neuroimaging features of good and poor seizure control in patients with mesial temporal lobe epilepsy and hippocampal atrophy. Epilepsia 2003;44(6):807–14.
[5] van Paesschen W, Duncan JS, Stevens JM, Connelly A. Etiology and early prognosis of newly diagnosed partial seizures in adults: a quantitative hippocampal MRI study. Neurology Sep 1997;49(3):753–7.
[6] Murakami N, Ohno S, Oka E, Tanaka A. Mesial temporal lobe epilepsy in childhood. Epilepsia 1996;37(Suppl. 3):52–6.
[7] Helmstaedter C. Neuropsychological aspects of epilepsy surgery. Epilepsy Behav Feb 2004;5(Suppl. 1):S45–55.
[8] Delaney RC, Rosen AJ, Mattson RH, Novelly RA. Memory function in focal epilepsy: a comparison of non-surgical, unilateral temporal lobe and frontal lobe samples. Cortex 1980 Mar;16(1):103–17.
[9] Loring DW. Neuropsychological evaluation in epilepsy surgery. Epilepsia 1997;38(Suppl. 4):S18–23.
[10] Sherman EM, Wiebe S, Fay-McClymont TB, Tellez-Zenteno J, Metcalfe A, Hernandez-Ronquillo L, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. Epilepsia May 2011;52(5):857–69. https://doi.org/10.1111/j.1528-1167.2011.03022.x [Epub 2011 Mar 22].
[11] Barr WB. Examining the right temporal lobe's role in nonverbal memory. Brain Cogn Oct 1997;35(1):26–41.
[12] Glikmann-Johnston Y, Saling MM, Chen J, Cooper KA, Beare RJ, Reutens DC. Structural and functional correlates of unilateral mesial temporal lobe spatial memory impairment. Brain 2008;131:3006–18.
[13] Bonelli SB, Powell RH, Yogarajah M, Samson RS, Symms MR, Thompson PJ, et al. Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. Brain 2010;133:1186–99.
[14] Binder JR. Functional MRI is a valid noninvasive alternative to Wada testing. Epilepsy Behav 2010;20(2):214–22. https://doi.org/10.1016/j.yebeh.2010.08.004.
[15] Binder JR, Swanson SJ, Sabsevitz DS, Hammeke TA, Raghavan M, Mueller WM. A comparison of two fMRI methods for predicting verbal memory decline after left temporal lobectomy: language lateralization versus hippocampal activation asymmetry. Epilepsia 2010;51:618–26.
[16] Bell B, Lin J, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 2011;7:154–64. https://doi.org/10.1038/nrneurol.2011.3 [published online 8 February 2011].
[17] Riley JD, Moore S, Cramer SC, Lin JJ. Caudate atrophy and impaired frontostriatal connections are linked to executive dysfunction in temporal lobe epilepsy. Epilepsy Behav 2011;21:80–7.
[18] Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002;58(8 Suppl 5):S21–6.
[19] Ozkara C, Hanoğlu L, Keskinkiliç C, Yeni N, Aysal F, Uzan M, et al. Memory in patients with drug-responsive mesial temporal lobe epilepsy and hippocampal sclerosis. Epilepsia 2004;45(11):1392–6.
[20] Kim CH, Lee SA, Yoo HJ, Kang JK, Lee JK. Executive performance on the Wisconsin Card Sorting Test in mesial temporal lobe epilepsy. Eur Neurol 2007;57(1):39–46 [Epub 2006 Nov 14].
[21] Oddo S, Solis P, Consalvo D, Seoane E, Giagante B, D'Alessio L, et al. Postoperative neuropsychological outcome in patients with mesial temporal lobe epilepsy in Argentina. Epilepsy Res Treat 2012;2012:370351. https://doi.org/10.1155/2012/370351 [Epub 2011 Nov 22].
[22] Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 2003;54(4):425–32.
[23] Jokeit H, Seitz RJ, Markowitsch HJ, Neumann N, Witte OW, Ebner A. Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. Brain 1997;120(Pt 12):2283–94.
[24] Dodrill CB. Neuropsychological effects of seizures. Epilepsy Behav 2004;5(Suppl. 1):S21–4.
[25] Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, et al. Cognitive prognosis in chronic temporal lobe epilepsy. Ann Neurol 2006;60(1):80–7.
[26] Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Arch Neurol 1997;54(4):369–76.
[27] Sànchez J, Centanaro M, Solís J, Delgado F, Yépez L. Factors predicting the outcome following medical treatment of mesial temporal epilepsy with hippocampal sclerosis. Seizure 2014;23(6):448–53.
[28] Aguglia U, Beghi E, Labate A, Condino F, Cianci V, Mumoli L, et al. Age at onset predicts good seizure outcome in sporadic non-lesional and mesial temporal sclerosis based temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2011;82(5):555–9.
[29] Kim WJ, Park SC, Lee SJ, Lee JH, Kim JY, Lee BI, et al. The prognosis for control of seizures with medications in patients with MRI evidence for mesial temporal sclerosis. Epilepsia 1999;40(3):290–3.
[30] Castro LH, Silva LC, Adda CC, Banaskiwitz NH, Xavier AB, Jorge CL, et al. Low prevalence but high specificity of material-specific memory impairment in epilepsy associated with hippocampal sclerosis. Epilepsia 2013;54(10):1735–42.
[31] Voltzenlogel V, Vignal JP, Hirsch E, Manning L. The influence of seizure frequency on anterograde and remote memory in mesial temporal lobe epilepsy. Seizure 2014;23(9):792–8.
[32] Grau-Lopez L, Jimenez M, Ciurans J, Caceres C, Becerra JL. Importance of neuropsychological and clinical features to predict seizure control in medically treated patients with mesial temporal epilepsy and hippocampal sclerosis. Epilepsy Behav 2017;69:121–5.
[33] Helmstaedter C, Wietzke J, Lutz MT. Unique and shared validity of the "Wechsler logical memory test", the "California verbal learning test", and the "verbal learning and memory test" in patients with epilepsy. Epilepsy Res 2009;87(2–3):203–12.
[34] Hermann B, Seidenberg M. Executive system dysfunction in temporal lobe epilepsy: effects of nociferous cortex versus hippocampal pathology. J Clin Exp Neuropsychol Dec 1995;17(6):809.

[35] Barbas H. Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. Brain Res Bull 2000;52(5):319–30.
[36] Colnat-Coulbois S, Mok K, Klein D, Pénicaud S, Tanriverdi T, Olivier A. Tractography of the amygdala and hippocampus: anatomical study and application to selective amygdalohippocampectomy. J Neurosurg 2010;113(6):1135–43.
[37] Corcoran R, Upton D. A role for the hippocampus in card sorting? Cortex 1993;29 (2):293–304.
[38] Tuchscherer V, Seidenberg M, Pulsipher D, Lancaster M, Guidotti L, Hermann B. Extrahippocampal integrity in temporal lobe epilepsy and cognition: thalamus and executive functioning. Epilepsy Behav 2010;17(4):478–82.
[39] Zamarian L, Trinka E, Bonatti E, Kuchukhidze G, Bodner T, Benke T, et al. Executive functions in chronic mesial temporal lobe epilepsy. Epilepsy Res Treat 2011; 2011:596174.
[40] Tudesco Ide S, Vaz LJ, Mantoan MA, Belzunces E, Noffs MH, Caboclo LO, et al. Assessment of working memory in patients with mesial temporal lobe epilepsy associated with unilateral hippocampal sclerosis. Epilepsy Behav 2010;18(3):223–8.
[41] Labudda K, Frigge K, Horstmann S, Aengenendt J, Woermann FG, Ebner A, et al. Decision making in patients with temporal lobe epilepsy. Neuropsychologia 2009;47: 50–8.
[42] Jokeit H, Ebner A. Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. J Neurol Neurosurg Psychiatry 1999;67(1):44–50.
[43] Elmstaedter C. Effects of chronic epilepsy on declarative memory systems. Prog Brain Res 2002;135:439–53.
[44] Jokeit H, Ebner A. Effects of chronic epilepsy on intellectual functions. Prog Brain Res 2002;135:455–63.
[45] Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. Prog Brain Res 2002;135:429–38.
[46] Rausch R, Kraemer S, Pietras CJ, Le M, Vickrey BG, Passaro EA. Early and late cognitive changes following temporal lobe surgery for epilepsy. Neurology 25 2003;60(6): 951–9.
[47] Fuerst D, Shah J, Shah A, Watson C. Hippocampal sclerosis is a progressive disorder: a longitudinal volumetric MRI study. Ann Neurol 2003;53(3):413–6.
[48] D'Alessandro P, Piccirilli M, Tiacci C, Ibba A, Maiotti M, Sciarma T, et al. Neuropsychological features of benign partial epilepsy in children. Ital J Neurol Sci 1990;11: 265–9.
[49] McDonald CR, Delis DC, Norman MA, Wetter SR, Tecoma ES, Iragui VJ. Response inhibition and set shifting in patients with frontal lobe epilepsy or temporal lobe epilepsy. Epilepsy Behav 2005;7:438–46.
[50] Gascoigne MB, Smith ML, Barton B, Webster R, Gill D, Lah S. Attention deficits in children with epilepsy: preliminary findings. Epilepsy Behav 2017;67:7–12. https://doi.org/10.1016/j.yebeh.2016.11.013.