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Research Paper

Evaluation of Cognitive Impairment in Refractory Temporal Lobe Epilepsy Patients Concerning Structural Brain Lesions

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ABSTRACT

Introduction: Temporal lobe epilepsy (TLE) is the most prevalent form of drug-resistant epilepsy with concurrent cognitive impairment. Prevention, earlier diagnosis, and personalized management of cognitive deficits in TLE require more understanding of underlying structural and functional brain Ialterations. No study has evaluated the performance of TLE patients in different cognitive domains based on their structural brain lesions.

Methods: In this study, 69 refractory TLE patients underwent magnetic resonance imaging (MRI) epilepsy protocol and several neuropsychological tests, consisting of the Wechsler adult intelligence scale-revised, Rey-Osterrieth complex figure test, verbal fluency test, digit span test, spatial span test, Wechsler memory scale-III, design fluency test, Rey visual design learning test, auditory-verbal learning test, and trail making test. MRI findings were classified into the following groups: Focal cortical dysplasia, gliosis, atrophy, mesial temporal sclerosis (MTS), tumor, vascular malformation, and other lesions or normal. Results of neuropsychological tests were compared between MRI groups using a generalized linear model with gamma distribution and log link.

Results: Patients with MTS showed better performance in general intellectual functioning, working memory, attentional span, and auditory-verbal learning compared to patients with non-MTS MRI lesions. Atrophy and focal cortical dysplasia had the largest differences from MTS.

Conclusion: Cognitive performance of refractory TLE patients varies concerning structural brain alterations. Further neuroimaging studies of TLE lead to prevention and more accurate management of cognitive decline in clinical settings.

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Highlights

- Cognitive status in temporal lobe epilepsy (TLE) varies concerning structural brain alterations.
- Patients with mesial temporal sclerosis (MTS) show better cognitive performance than those with non-MTS lesions.
- Among non-MTS findings, patients with atrophy have more severe cognitive deficits.

Plain Language Summary

Temporal lobe epilepsy (TLE) is the most common form of epilepsy which does not respond to anti-seizure drugs and needs surgery of the brain lesions. One of the most important issues of TLE patients is their cognitive impairment. Cognition refers to the mental processes for thinking, understanding, and perception of the environment such as attention, memory, learning, language, etc. Prevention, earlier diagnosis, and treatment of cognitive deficits in TLE patients need more understanding of their brain changes. No study has evaluated the cognition of TLE patients in detail based on their brain lesions. In this study, 69 drug-resistant TLE patients have undergone brain magnetic resonance imaging (MRI) and several neuropsychological tests that assess cognition, consisting of the Wechsler adult intelligence scale-revised, Rey-Osterrieth complex figure test, verbal fluency test, digit span test, spatial span test, Wechsler memory scale-III, design fluency test, Rey visual design learning test, auditory-verbal learning test, and trail making test. MRI findings were classified into the following groups based on the type of brain lesion by an expert: Focal cortical dysplasia, gliosis, atrophy, mesial temporal sclerosis (MTS), tumor, vascular malformation, and other lesions or normal. Results of neuropsychological tests were compared between MRI groups using appropriate statistical methods. Patients with MTS, as the most common lesion in TLE, showed better results compared to patients with lesions other than MTS in intelligence, memory, attention, and learning tests. Patients with atrophy and focal cortical dysplasia had the largest differences from those with MTS. These results suggest that the cognitive performance of drug-resistant TLE patients is different based on their structural brain changes. As imaging, in particular brain MRI, is the most available technique in the clinic for the assessment of epilepsy, further brain imaging studies can lead to prevention and better management of cognitive decline in TLE.

1. Introduction

Epilepsy as a neurological disorder causing a prominent global burden has a mortality rate of at least twice as high as the normal population and a variety of psychosocial sequels (Devinsky et al., 2018). Despite extensive research in the field, more than one-third of epilepsy patients are still refractory to anti-seizure drugs (ASDs), associated with a higher risk of irreversible injuries and comorbidities. Although further epidemiologic studies on epilepsy are warranted, certainly temporal lobe epilepsy (TLE) accounts for the most drug-resistant cases and surgery candidates among all epilepsy types (Téllez-Zenteno & Hernández-Ronquillo, 2012). TLE was formerly defined based on clinical features and the origin of seizures - temporal lobe-without considering diagnostic methods including magnetic resonance imaging (MRI) and electroencephalography (Ong, 2019). However, based on the recent classification of epilepsies developed by the International League Against Epilepsy (ILAE), etiology, comorbidities, and quality of life should also be considered (Scheffer et al., 2017). Accordingly, cognitive impairment, reported as the most important comorbidity by patients, has attracted more attention in TLE research recently (Fisher et al., 2000).

Different cognitive domains including attention, memory, learning, language, executive functions, and social cognition are impaired in TLE (Bell et al., 2011). However, the underlying pathophysiology has been partially understood so far. Considering the important role of the temporal lobe in higher cognitive functions, there are various hypotheses about the origin of cognitive impairment in TLE (Chauvière, 2020a); Recurrent seizures, structural alterations and reorganizations, the deficit of excitatory-inhibitory balance in functional networks, epileptogenesis, interictal and postictal brain activities, impairment of synaptic plasticity, and ASDs all have been proposed as potential causes based on animal models and human studies (Chauvière, 2020b). Further understanding of the structural and functional neural basis of TLE results in the prevention and more accurate management of cognitive impairment in patients. Neuroimaging ex-

periments have discovered some correlations between brain areas and cognitive performance in TLE (Allone et al., 2017). Lateralization of epilepsy has been a frequently-reported finding (Bostock et al., 2017); for example, left TLE patients had more problems with verbal span in working memory and executive function tests, whereas right TLE ones showed visuospatial deficits and lower scores in auditory naming tasks and assessment of theory of mind (Rastogi et al., 2014). A few studies have found that patients with mesial temporal sclerosis (MTS), as the most common MRI lesion in refractory TLE, had more errors and lower scores in tests of executive functions than other TLE patients (Rastogi et al., 2014). However, no study has compared other structural MRI lesions in TLE with each other and for other cognitive domains. Despite a paradigm shift from defining an epileptogenic zone to more complex epileptic networks and increasing use of diffusion tensor and functional imaging, conventional MRI is still the most available imaging technique in clinical settings (Jehi, 2018). Thus, in this article, we aim to compare cognitive performance between TLE patients based on their structural brain MRI lesions.

2. Materials and Methods

This is a cross-sectional study involving patients with refractory TLE who were admitted to Ayatollah Kashani and Milad Hospitals in Isfahan City, Iran, between March 2018 and September 2019. The patients were diagnosed with TLE based on clinical findings and long-term monitoring and were candidates for surgery due to drug resistance. All demographic, neuropsychological, and imaging data were gathered concerning confidentiality. Sixty-nine patients fulfilled the ILAE definition of drug resistance (Kwan et al., 2009), underwent MRI protocol for epilepsy, and had no history of brain surgery or other neurologic or psychiatric disorder. MRI findings were classified by an expert in the field as follows: Normal, focal cortical dysplasia (FCD), gliosis, atrophy, MTS, tumor, vascular malformation, and others. In addition, neuropsychological tests, described below, were applied and interpreted by a skilled psychologist and neuropsychiatrist, respectively.

To assess intellectual functioning in general, the Wechsler adult intelligence scale-revised (WAIS-R) test was obtained (Kaufman, 1983). Total intelligence quotient (IQ) score, verbal and practical IQ subscores, as well as their subscales (information, comprehension, arithmetic, digit span, similarities, and vocabulary-picture arrangement, picture completion, block design, object assembly, and digit symbol), were calculated and demographically corrected for each patient. Rey-Osterrieth complex figure (ROCF) test examines visuo-constructional abilities, spatial planning, and memory (Rey, 1941). Copy, immediate recall, and delayed recall after one and 30 minutes were scored through the ROCF (Osterrieth, 1944). A recognition trial was used at the end as well. The verbal fluency test (VFT) evaluates the ability to produce fluent speech in special categories (semantic fluency) by particular letters (phonemic fluency) (Malek et al., 2013). VFT total score is the average of items named in each part. Wechsler memory scale-III (WMS-III) is still a widely used tool for the assessment of memory abilities (San Antonio, 1997). WMS-III overall score comes from eight indices achieved by the performance in different tests (auditory immediate, visual immediate, immediate memory, auditory delayed, visual delayed, auditory recognition delayed, general memory, and working memory). Digit span and spatial span tests measure attentional capacity by giving increasing amounts of verbal or visual information to participants and asking them to repeat what they have grasped (Lezak et al., 2012). Performance is summarized in a total score which consists of maximum correct repeats in forward and backward sections. In trail making test (TMT), participant connects numbers and alphabets based on an order to each other as fast as possible (Reitan, 1958). The time of each part is an indicator of executive function and divided attention. Auditory-verbal learning test (AVLT) is a measure of learning and memory by repeating a list of remembered words in five consecutive trials and after a distraction caused by the presentation of another list, in addition to recalling the first list after a delay, and recognition of all heard words at the end (Boake, 2000). Each trial results in a total number of correct, false, and preserved answers. Rey visual design learning test (RVDLT) assesses learning of non-verbal information. In this test, 15 simple geometric forms are shown in five trials and the participant is asked to draw what he/she remembers after each trial and after a delay time. The test ends with a recognition trial and the total number of correct, false, and preserved answers are recorded for each trial (Strauss et al., 2006). The design fluency test evaluates cognitive flexibility and the ability to draw visual patterns fluently. In three sections, the participant draws a maximum number of shapes with four straight lines in small squares containing dots. In each section they are allowed to use specific types of dots and several non-repetitive and repetitive shapes drawn are calculated separately (Lezak et al., 2012). General and specific aspects of quality of life in TLE patients were evaluated through a quality-of-life inventory for epilepsy-31 (QOLIE-31). Overall scores and subscores (seizure worry, overall quality of life, emotional well-being, energy and

fatigue, cognitive functioning, medication effect, and social functioning) were noted for each patient. Also, to assess depression, the Beck depression inventory-II (BDI-II) was applied (Ghassemzadeh et al., 2005).

Descriptive parameters including Mean±SD, in addition to the Kruskal-Wallis test (KWT) and generalized linear model with gamma distribution and log link (GLM), were administered for analysis through MATLAB software, version R2016a (MathWorks Inc., Natick, Massachusetts, USA) and IBM SPSS software, version 24 statistics for Windows (IBM Corp., USA). P<0.05 was statistically significant.

3. Results

Demographic and clinical characteristics of enrolled TLE patients are shown for each classified structural MRI lesion (Table 1). Fifty-eight percent of participants (40 patients) had MTS, while each of the other MRI lesions accounted for one to nine percent of the sample population. One patient had cavernous angioma as vascular malformation. Three of five patients with tumoral lesions were already diagnosed with dysembryoplastic neuroepithelial tumors. Two participants had small vessel disease and brain cysts which were classified as other lesions.

Results of formerly described psychological and neuropsychological tests are presented in detail (Table 2). As data did not follow the normal distribution, KWT was used to compare different groups of MRI lesions. Two significant differences were found; the WAIS-R vocabulary score was significantly lower in FCD than MTS group (P=0.0462), and the normal group showed lower results in the QOLIE-31 medication effect than the gliosis group (P=0.0161).

By classifying all lesions into non-MTS and MTS groups and comparing results using KWT, the following scores were shown to be significantly lower for non-MTS lesions: WAIS-R comprehension (P=0.0365), WAIS-R digit span (P=0.0092), WAIS-R picture completion (P=0.0119), WMS-III working memory (P=0.0175), digit span test (P=0.008), AVLT total acquisition (P=0.0252), and design fluency test non-repetitive (p=0.0473). To consider the effect of the aforementioned demographic and clinical characteristics on cognitive performance, GLM was applied. Total and practical IQ, WAIS-R arithmetic, WAIS-R picture arrangement, WAIS-R object assembly, and spatial span test scores were added to the design fluency test non-repetitive was removed from the previous list (Figure 1).

GLM was used to compare each lesion in a non-MTS group with MTS as the reference. The effect of the epileptogenic zone on the result of each test was also evaluated considering the right zone as the reference. Patients with atrophy had significantly lower scores in the following WAIS-R subscales: Total IQ (P=0.000), verbal (P=0.000), practical (P=0.038), information (P=0.023), comprehension (P=0.000), arithmetic (P=0.000), digit span (P=0.000), vocabulary (P=0.000), picture arrangement (P=0.01), picture completion (P=0.000), block design (P=0.001), object assembly (P=0.003), and digit symbol (P=0.004). The normal group in WAIS-R practical (P=0.038), picture completion (P=0.001), and object assembly (P=0.041), FCD group in WAIS-R comprehension (P=0.008), arithmetic (P=0.033), vocabulary (P=0.000), picture arrangement (P=0.014), and picture completion (P=0.001) performed significantly worse than MTS group. Patients whose zone of epilepsy was bilateral showed lower scores in WIAS-R picture arrangement (P=0.019), picture completion (P=0.038), and object assembly (P=0.008) than right TLE patients. In addition, left TLE acquired significantly higher scores than right TLE in the WAIS-R digit span (P=0.046). In the ROCF test, patients with atrophy had lower cognitive performance than MTS in copy (P=0.000), immediate (P=0.013), delayed recall after 1 (P=0.013), and 30-minute (P=0) subscales. The gliosis group also showed significantly lower scores in copy part (P=0.041). Patients with tumoral lesions had a significant negative mean differences in total scores on the verbal fluency test (P=0.022). Comparing WMS-III, patients with atrophy gained lower scores in auditory immediate (P=0.013), visual immediate (P=0.002), immediate memory (P=0.004), and working memory (P=0.006). FCD cases performed worse in immediate memory (P=0.012), general memory (P=0.022), and working memory (P=0.047) in addition to the normal group which had significantly lower scores in the auditory recognition delayed subscale (P=0.048). In digit span (P=0.000) and spatial span (P=0.02) tests, the atrophy group manifested worse performance. Gliosis (P=0.006) and tumor (P=0.013) groups were similar to the atrophy group in the spatial span test. Moreover, patients with bilateral epileptogenic zone had weaker performance in this test than right TLE patients (P=0.016). In TMT part A, atrophy (P=0.022) and FCD (P=0.002) got worse results but other MRI lesions (P=0.019) and left TLE (P=0.017) got better results. Evaluating AVLT, it was revealed that atrophy (P=0.021) and gliosis (P=0.036) had lower significant total acquisition but only atrophy was worse in delayed recall (P=0.038). In RVLT, FCD (P=0.009) and atrophy (P=0.003) groups showed significantly lower scores in the total acquisition, and the tumor group was worse in correct recognition compared to MTS (P=0.035). Non-repetitive part of the design fluency test also represented the signifi-

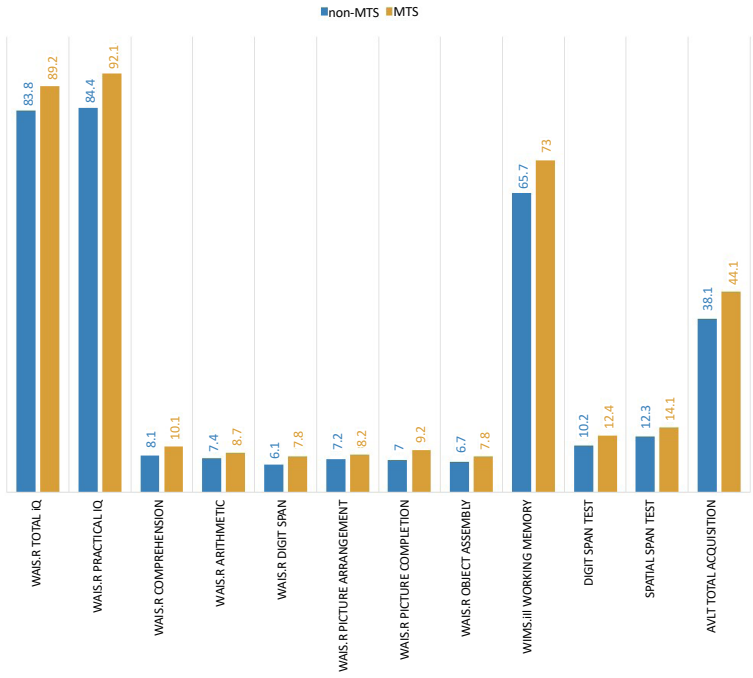

Figure 1. Significant differences of cognitive performance between refractory TLE patients with MTS and non-MTS MRI lesions using GLM with gamma distribution and log link

Mean score of following tests' subscales are showed separately for two groups (MTS and non-MTS) above each bar. P of comparison between two groups are written in parenthesis here: WAIS-R total IQ (P=0.01), WAIS-R practical IQ (P=0.002), WAIS-R comprehension (P=0.005), WAIS-R arithmetic (P=0.013), WAIS-R digit span (P=0.003), WAIS-R picture arrangement (P=0.013), WAIS-R picture completion (P=0), WAIS-R object assembly (P=0.001), WMS-III working memory (P=0.028), digit span test total score (P=0.028), spatial span test total score (P=0.012), AVLT total acquisition (P=0.011). Non-significant differences are not shown.

Abbreviations: TLE: Temporal lobe epilepsy; MTS: Mesial temporal sclerosis; MRI: Magnetic resonance imaging; GLM: Generalized linear model; WAIS-R: Wechsler adult intelligence scale-revised; IQ: Intelligence quotient; WMS-III: Wechsler memory scale-III; AVLT: Auditory-verbal learning test.

cantly lower performance of the atrophy group (P=0.001). Furthermore, obtained from psychological questionnaires, patients with other MRI lesions had significantly lower scores of BDI-II (P=0.009), the FCD group had less seizure worry (P=0.014), the normal group had less energy and fatigue (P=0.037), and gliosis group was less affected by medication than MTS group in QOLIE-31 (P=0.047).

4. Discussion

The preliminary analysis, comparing the cognitive performance of refractory TLE patients between different MRI lesions by KWT, showed one borderline cognitive difference and a significant dissimilarity in one of the QOLIE-31 subscales (Table 2). The sample sizes of groups were unequal and the MTS group accounted for a large portion of patients (Table 1). Hence, we put data from non-MTS lesions in a single group and repeated the analysis. This classification had also practical benefits, as MTS is the most common brain lesion in TLE and is readily determined in clinical settings. All acquired significant differences in the previous step were confirmed by GLM except one that had already a borderline P. Accordingly, the data suggest that TLE patients with lesions other than MTS perform significantly worse than those with MTS in general intellectual functioning, working memory, attentional span, and auditory-verbal learning (Figure 1). More detailed data on differences between MRI findings and epileptogenic zones using GLM revealed that among non-MTS lesions, atrophy, and FCD group are differentiated from the MTS group in more cognitive domains (Figure 2). Gliosis, normal, tumor, and others are the next lesions, respectively. Left TLE patients showed better performance in TMT and digit span test, while patients with bilateral epileptogenic zone were worse in spatial span test, WAIS-R picture completion, picture arrangement, and object assembly subscales compared to right TLE.

Table 1. Demographic and clinical characteristics of enrolled refractory TLE patients classified based on brain MRI findings

Characteristic		Mean±SD/No. (%)							
		NL	FCD	Gliosis	Atrophy	MTS	Tumor	VM	Others
Age (y)		35.3±8.9	34.7±9.9	27.2±8.8	25.7±8.3	25.2±7.3	23.6±17.4	15±0	41±29.7
Gender	Male	5(83.3)	2(40)	4(66.7)	3(75)	23(57.5)	5(100)	0	1(50)
	Female	1(16.7)	3(60)	2(33.3)	1(25)	17(42.5)	0	1(100)	1(50)
Education	Non-academic	4(66.7)	5(100)	5(83.3)	3(75)	29(72.5)	4(80)	1(100)	2(100)
	Academic	2(33.3)	0	1(16.7)	1(25)	11(27.5)	1(20)	0	0
Seizure onset (y)		22.2±14.5	2.8±2.7	10.8±8.3	9±7	9.3±8	7.3±5.8	2±0	21±8.5
Seizure frequency (w)		2±4	7.2±0.4	3.6±4.0	3.8±4.2	2.1±3.3	2.3±3.2	0.1±0	4±5.6
Zone of epilepsy	Right	3(50)	2(40)	0	1(25)	17(42.5)	3(60)	1(100)	0
	Left	2(33.3)	3(60)	5(83.3)	3(75)	21(52.5)	2(40)	0	1(50)
	Bilateral	0	0	1(16.7)	0	2(5)	0	0	0
	Not recognized	1(16.7)	0	0	0	0	0	0	1(50)
Total		6(9)	5(7)	6(9)	4(6)	40(58)	5(7)	1(1)	2(3)

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Abbreviations: TLE: Temporal lobe epilepsy; MRI: Magnetic resonance imaging; NL: Normal; FCD: Focal cortical dysplasia; MTS: Mesial temporal sclerosis; VM: Vascular malformation; SD: Standard deviation.

Supporting our results about the atrophy group, decreased volume of grey and white matter, as a quantitative marker for atrophy, has shown significant association with immediate and delayed memory impairment, lower IQ, and weaker executive functions in previous studies (Oyegbile et al., 2006). MTS was suggested as a related factor to the severity of working memory impairment based on a functional connectivity model and MRI volumetric analysis, but our data showed significantly worse working memory in a non-MTS group than MTS group (Rastogi et al., 2014). Moreover, evaluating patients' executive functions using the modified Wisconsin card sorting test (MWCST) and VFT has shown that the MTS group had lower scores and more errors in MWCST than the non-MTS group and vice versa for VFT (Corcoran & Upton, 1993; Giovagnoli, 2001). The inconsistency with our results might be due to the overestimation of MWCST in the assessment of executive functions and the lower population of the non-MTS group in VFT (Rzezak et al., 2009). As far as we know, there are no other studies evaluating the cognitive performance of TLE patients based on different types of structural brain MRI lesions.

Former studies have found the role of the left hemisphere in the reorganization of memory regardless of verbal and non-verbal form, and also severe memory deficits of left TLE, particularly in verbal working memory (Allone et al., 2017). According to our results, although the significantly better performance of left TLE patients in the digit span test is against this lateralization, total and verbal subscores of WMS-III followed the trend. However, none of the mean differences were statistically considerable. Increased connectivity between the hippocampus and thalamus was associated with executive dysfunction particularly in right TLE and for TMT (Dinkelacker et al., 2015). It is compatible with the lower performance of right TLE patients in this study in TMT. Marked alertness deficit among attentional networks was revealed in right TLE in comparison to left TLE patients (Liu et al., 2016), which is by the significant positive mean difference in the digit span test in our results.

Table 2. Psychological and neuropsychological tests' results classified based on brain MRI findings

Test	Result	Mean±SEM							
		NL	FCD	Gliosis	Atrophy	MTS	Tumor	VM*	Others
WAIS-R	Total IQ score	88.3±4.6	71±2.8	90.2±9.3	67.2±4.5	89.2±2.2	92±5	-	97.5±5.5
	Verbal IQ	88.3±3.5	73.2±2.8	90.8±8	69.7±3	87.7±1.8	90.7±4.1	-	90.5±2.5
	Practical IQ	88.3±3.5	73.2±2.8	90.8±8	69.7±3	92.1±2.8	90.7±4.1	-	90.5±2.5
	Information	9.2±1.3	6.7±0.6	8.8±1.9	6.2±1.2	9.7±0.6	9±1.2	-	11.5±0.5
	Comprehension	8.3±1.1	5±0.8	10.5±1.9	5.5±1.8	10.1±0.6	9±0.9	-	10.5±1.5
	Arithmetic	9.2±1	5±0.7	9.2±1.6	5±0.4	8.7±0.4	7.3±0.5	-	7±1
	Digit span	6.8±0.5	5±0.7	7±1.4	4.2±1.6	7.8±0.4	6±0	-	7±0
	Vocabulary	7.8±0.7	2.2±0.7	7.5±1.6	3±0.6	7.5±0.4	8.3±0.9	-	8.5±1.5
	Similarities	5.3±0.6	5±0.4	6.7±0.9	5±0.7	7.2±0.6	6.5±1.6	-	7±0
	Picture arrangement	8±0.4	4.5±1.1	8.7±2.2	5±1.1	8.2±0.5	7.3±0.7	-	10.5±1.5
	Picture completion	7.7±1.1	4.2±0.4	8.3±1.7	4.7±1.4	9.2±0.5	8.3±1	-	9.5
	Block design	11.2±2.1	7.5±1.3	9.3±1.6	5.5±1.5	10.8±0.5	11±1.2	-	11.5±0.5
	Object assembly	7.2±1.2	5±0.7	7.5±1.7	5±1.6	7.8±0.5	7±1.9	-	9.5±2.5
	Digit symbol	5.2±0.9	5.2±1.2	5.2±1.6	3±0.7	5.5±0.4	4.7±0.3	-	5.5±0.5
ROCFT	Copy score	26.7±4.8	22.2±3.9	20.5±4.5	10±5.2	25.1±1.3	23.4±3.6	14±0	17.7±2.2
	Immediate recall	15.9±3.9	15.9±2.9	12.1±3.2	6.4±2.7	11.3±1.1	6.8±1.9	9±0	14.2±2.7
	Delayed recall after 1 min	14.2±3.4	13.6±2.9	11±3.4	6±3.9	11.2±1.2	12.8±6.5	10±0	13.7±2.2
	Delayed recall after 30 min	13.8±3.7	12.5±2.5	9.9±3.4	4.5±3	10.4±1.1	7.7±1.4	11.5±0	11.2±2.7
	Recognition total correct	18.2±0.5	14.7±1.2	16.8±1.7	15±1.1	16±0.5	16±1.1	14±0	20±3
VFT	Total score	10.3±1.1	7.4±1	10.9±1.5	7.3±2.1	10.3±0.4	7.1±1.8	12±0	10.5±0.8
WMS-III	Total score	74.1±3.31	62.8±3.4	85.3±12.5	65.7±3.5	78.9±2.7	83.9±15.8	112±0	87.4±4.4
	Auditory immediate	70.2±4.2	60.5±1.3	89.8±13.4	59±0	80.8±3.2	96.5±19.9	131±0	90.5±5.5
	Visual immediate	103.7±6.7	106±2.8	97.7±8.9	75.3±9.4	100.5±3.1	91±20.2	109±0	91.5±20.5
	Immediate memory	85.8±4.6	60.5±1.3	90±13.4	62.7±3.2	87.3±3.3	93.5±21.8	123±0	89.5±15.5
	Auditory delayed	67.2±5.7	59.2±0.2	87.5±14.7	59±0	77.4±3.6	91±15.2	128±0	97.5±3.5
	Visual delayed	78.2±6.4	83.7±11.4	83.2±9.7	78.3±16.7	80.3±2.8	78.5±8.5	104±0	91±1
	Auditory recognition delayed	64.7±5.2	66±6.3	81.2±11.4	59±0	70.2±2.7	65±3.8	65±0	82.5±20.5
	General memory	91.3±3.7	63.7±3.4	89.2±15.1	77±15.6	90.7±4	94.5±20.5	127±0	112.5±7.5
	Working memory	71.3±4.7	62±2.7	64.7±1.8	59±0	73±2.2	64.5±3.5	74±0	66.5±7.5
DST	Total score	10.5±0.6	8.6±0.8	10.8±1.7	6.7±2.3	12.4±0.6	10.8±1.4	19±0	12.5±2.5
SST	Total score	16.3±1.7	12.2±0.7	10.8±2.1	10.2±1.6	14.1±0.6	9.6±2	16±0	14.5±2.5

Test	Result	Mean±SEM							
		NL	FCD	Gliosis	Atrophy	MTS	Tumor	VM*	Others
TMT	Part A score	49.2±2.5	101.8±11.6	62.2±8.1	85.7±12.3	64.6±6.5	56.8±8.7	53±0	37±15
	Part B score	153.5±25.9	164.5±19.3	151.6±19.8	165±0	141.1±6.6	145±6.3	107±0	148±50
AVLT	Total acquisition	41±3.4	33.5±2.7	39.3±8.3	32.2±2.3	44.1±1.7	38.8±3	53±0	38±2
	Amount learned in trials	4.3±1.4	4.2±1	3.5±1	3±0.8	4±0.3	5.4±1	6±0	5.5±1.5
	Delayed recall	7.3±0.9	5±1.3	6.8±1.9	3.7±0.8	6.4±0.5	4.8±1.2	9±0	7.5±1.5
	Proactive interference	0.7±1.2	0±0.4	1±0.5	1.5±0.6	0.7±0.3	-0.2±0.8	0±0	-0.5±1.5
	Retroactive interference	2±1.1	2.7±1.3	1.2±0.7	1.7±1.5	2.3±0.3	4.8±1.7	0±0	0±3
	Correct recognition	31.3±5.8	31±6.1	34.5±5.1	29.7±1.7	36.5±1.4	39.2±3.5	45±0	32.5±9.5
RVDLT	Total acquisition	21.8±4.4	14.6±2.4	32±9.1	12.5±2.2	23.1±1.8	16.2±2.1	16±0	34.5±0.5
	Amount learned in trials	2.3±1.2	2.8±0.7	4±0.9	0.7±0.8	2.7±0.4	2±0.6	3±0	5±3
	Delayed recall	4.8±1.2	4.6±1	8.2±1.8	3.2±1	5.1±0.4	3.8±0.4	5±0	7.5±0.5
	Correct recognition	6.3±0.4	4.8±0.6	5.8±0.8	4.5±1	5.9±0.3	4.4±0.9	7±0	6.5±0.5
DFT	Total non-repetitive shapes	17.5±3.3	12.8±3.2	17.2±2.6	5.5±2.2	17.5±1.4	14±3.9	12±0	5.5±4.5
	Total repetitive shapes	15.5±4	6.8±1.8	13.6±5.7	8.2±3.2	9.6±1.2	11.4±3.7	21±0	4±0
BDI-II	Total score	12.3±6.8	15.8±4.4	11.2±4.1	17.2±7.9	11.1±1.4	13.2±8	44±0	6.5±1.5
QO-LIE-31	Total score	42.5±1.5	41.6±6.8	43.8±1.7	39.5±4.4	46.7±1.8	46.4±9.1	-	57.5±11.5
	Seizure worry	39.7±4.2	30±1.71	48.3±6	41.7±3.2	45±1.7	39±4.4	-	54±8
	The overall quality of life	53±2.6	40.7±6.1	49±5	42±8.3	49.7±2.2	45.5±14.2	-	49.5±6.5
	Emotional well-being	47.8±6.6	40.7±8.1	55.7±5.1	45.7±9.8	50.5±2.4	49.5±11.1	-	51±8
	Energy and fatigue	44.7±6.2	46.7±4.7	42.5±6	42±6.8	51.4±2.5	59±7.6	-	54.5±2.5
	Cognitive functioning	51.3±5.3	45±4.7	51.5±5.2	42.7±3.9	54.2±2.3	50±10.1	-	56.5±8.5
	Medication effect	40.7±3.6	44.2±5.3	58.3±2.6	45.7±6.5	47.5±2	45±1.3	-	54.5±7.5
	Social functioning	40.3±4.6	37.2±5.7	45.5±2	37.3±2.4	46.9±2.5	36.5±6.6	-	51.5±3.5

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Abbreviations: MRI: Magnetic resonance imaging; NL: Normal; FCD: Focal cortical dysplasia; MTS: Mesial temporal sclerosis; VM: Vascular malformation; SEM: Standard error of the Mean; WAIS-R: Wechsler adult intelligence scale-revised; ROCFT: Rey-Osterrieth complex figure test; VFT: Verbal fluency test; WMS-III: Wechsler memory scale-III; DST: Digit span test; SST: Spatial span test; TMT: Trail making test; AVLT: Auditory-verbal learning test; RVDLT: Rey visual design learning test; DF: Design fluency test; BDI-II: Beck depression inventory-II; QOLIE-31: Quality of life inventory for epilepsy-31; IQ: Intelligence quotient; Min: Minute.

*There was one patient in this group that had not performed WAIS-R and QOLIE-31 tests: There is the sign (-) in the table in case of missing data.

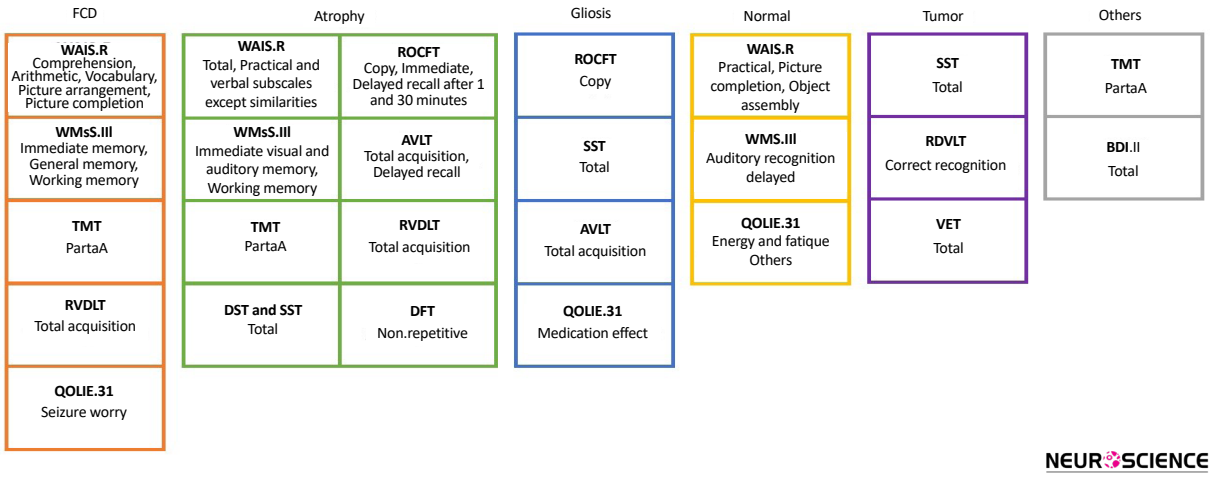

Figure 2. Significant differences of cognitive performance between refractory TLE patients based on structural brain MRI lesions using GLM with gamma distribution and log link considering MTS as the reference

Each box contains the name of the test in bold and its subscales in italic font; The score of patients with specified type of non-MTS lesion above the boxes in these subscales, were significantly different from those with MTS.

Abbreviations: TLE: Temporal lobe epilepsy; MRI: Resonance imaging; GLM: Generalized linear model; MTS: Mesial temporal sclerosis; FCD: Focal cortical dysplasia; WAIS-R: Wechsler adult intelligence scale-revised; WMS-III: Wechsler memory scale-III; TMT: Trail making test; RDVLT: Rey visual design learning test; QOLIE-31: Quality of life inventory for epilepsy-31; DST: Digit span test; SST: Spatial span test; ROCFT: Rey-Osterrieth complex figure test; AVLT: Auditory-verbal learning test; DFT: Design fluency test; VFT: Verbal fluency test; BDI-II: Beck depression inventory-II.

The main limitation of our study was the number of patients in each MRI lesion group. Despite using GLM to consider the effect of demographic and clinical characteristics, a larger matched sample population results in stronger models and more reliable results. Furthermore, in each group of MRI lesions, more detailed classification could be done based on the lesion (e.g. for tumor and vascular malformation) and more accurate location (e.g. for gliosis and atrophy). More clinical data such as drug history and seizure semiology in addition to more model effects such as interaction between main effects could be added to the analysis in case of larger populations. Here, we enrolled refractory TLE patients, as neuropsychological tests are still mostly used for surgery candidates rather than patients who are routinely followed up. Preventing cognitive decline in TLE by cognitive rehabilitation, earlier diagnosis, and better management of cognitive impairment in clinical settings, require large multi-center studies involving patients in earlier stages of disease and non-refractory TLE patients as well.

5. Conclusion

The cognitive performance of refractory TLE patients varies based on structural brain alterations. Non-MTS patients seem to be worse than MTS ones in general intellectual functioning, working memory, attentional span, and auditory-verbal learning. FCD and atrophy are differentiated from MTS in more cognitive domains. Further structural and functional neuroimaging studies of TLE result in the prevention and more accurate management of cognitive impairment in clinical practice.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethical Committee of Isfahan University of Medical Sciences (Code: IR.MUI.MED.REC.1399.852) and as it was retrospective containing no interventions, informed consent was waived.

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Authors' contributions

Conceptualization, supervision and funding acquisition: Jafar Mehvari Habibabadi; Methodology: Farinaz Tabibian and Jafar Mehvari Habibabadi; Software and formal analysis: Farinaz Tabibian and Mohammad Reza Maracy; Investigation and resources: Hossein Kahnouji, Mahtab Rahimi and Maryam Rezaei; Writing the original draft: Farinaz Tabibian; Review & editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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