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ORIGINAL RESEARCH

Impaired Cognitive Abilities in Siblings of Patients with Temporal Lobe Epilepsy

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Purpose: Patients with temporal lobe epilepsy (TLE) are at high risk of cognitive impairment. In addition to persistent seizures and antiepileptic drugs (AEDs), genetic factors also play an important role in the progression of cognitive deficits in TLE patients. Defining a cognitive endophenotype for TLE can provide information on the risk of cognitive impairment in patients. This study investigated the cognitive endophenotype of TLE by comparing neuropsychological function between patients with TLE, their unaffected siblings, and healthy control subjects.

Patients and Methods: A total of 46 patients with TLE, 26 siblings, and 33 control subjects were recruited. Cognitive function (ie, general cognition, short- and long-term memory, attention, visuospatial and executive functions, and working memory) was assessed with a battery of neuropsychological tests. Differences between groups were evaluated by analysis of covariance, with age and years of education as covariates. The Kruskal–Wallis test was used to evaluate data that did not satisfy the homogeneity of variance assumption. Pairwise comparisons were adjusted by Bonferroni correction, with a significance threshold of $P<0.05$.

Results: Patients with TLE showed deficits in the information test ($P<0.001$), arithmetic test ($P=0.003$), digit symbol substitution test ($P=0.001$), block design test (BDT; $P=0.005$), and backward digit span test ($P=0.001$) and took a longer time to complete the Hayling test Part A ($P=0.011$) compared to controls. Left TLE patients tended to have worse executive function test scores than right TLE patients. The siblings of TLE patients showed deficits in the BDT ($P=0.006$, Bonferroni-corrected) relative to controls.

Conclusion: Patients with TLE exhibit cognitive impairment. Executive function is worse in patients with left TLE than in those with right TLE. Siblings show impaired visuospatial function relative to controls. Thus, cognitive deficits in TLE patients have a genetic component and are independent of seizures or AED use.

Keywords: temporal lobe epilepsy, cognitive impairment, endophenotype

Introduction

Temporal lobe epilepsy (TLE) is the most common type of focal refractory epilepsy in adults.[1] Evidence from recent genetic studies indicates that TLE has higher heritability than was previously assumed.[2–4] The contribution of genetic factors to the pathology of TLE has been demonstrated by familial and twin studies.[5–7] However, the genetic mechanisms underlying sporadic TLE are not fully understood.[8–11] A genome-wide association study of sporadic TLE has implicated the sodium channel gene cluster on chromosome 2q24.3.[12] Some studies have identified tyrosine receptor kinase B gene variants in patients with TLE,[11,13]

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while another showed that the variants were associated with depressive disorder in this patient population.[14] Thus, TLE and associated cognitive dysfunction develops as a result of a combination of genetic and environmental factors.

Patients with TLE usually exhibit cognitive impairment[15,16] such as deficits in attention; verbal, nonverbal memory, and working memory; executive function; and spatial visualization.[17–19] Deficits in attention and executive function were recorded in up to 70% of untreated adult patients with new-onset epilepsy.[20] Multiple factors can cause cognitive impairment including genes, antiepileptic drugs (AEDs), recurrent seizures, and lesions in the temporal lobe.[21] The extent to which genetic factors contribute to cognitive dysfunction remains unknown. To this end, examining the endophenotype of TLE patients—which is more closely related to genotype than to phenotype—can clarify the role of genetics in the pathogenesis of TLE by identifying candidate phenotypic traits for genetic mapping. An endophenotype is defined by the following criteria: (1) independent of the prevalence of the disease in the population; (2) stable (ie, does not change with disease recurrence or remission); (3) heritable; and (4) more prevalent in the family of the affected individual than in the general population.[22]

Endophenotypes have been investigated in relation to psychiatric disorders[23–27] and certain types of epilepsy such as idiopathic generalized epilepsy.[28,29] Recent studies suggest that TLE patients have structural endophenotypes[30–32] that distinguish them from healthy control subjects. Although there have been many studies of cognitive impairment in TLE,[33,34] there is no consensus on the classification of cognitive phenotype.

The present study was carried out in order to identify potential phenotypic biomarkers that can be useful for future genetic analyses of cognitive impairment in TLE. To this end, we compared cognitive ability in TLE patients, their unaffected siblings, and healthy control subjects using a battery of neuropsychological tests.

Patients and Methods

Subjects

A total of 46 TLE patients were recruited at Xiangya Hospital of Central South University (Hunan Province, China). The clinical diagnosis of TLE was made by veteran epileptologists based on seizure symptoms, video-electroencephalography, and brain magnetic resonance imaging (MRI) scans[35] according to International League Against Epilepsy criteria.[36,37] There are 3 seizure types associated with TLE: (1) focal aware seizure, in which consciousness is typically maintained during the seizure; (2) focal impaired awareness seizure, which is accompanied by epigastric and autonomic auras and déjà vu; and (3) focal-to-bilateral tonic–clonic seizure, in which abnormal epileptic discharges occur in the temporal lobe during the ictal or interictal period. There were no other MRI abnormalities except for hippocampal sclerosis (HS), and patients were able to communicate with the psychiatrists until they fully understood the questionnaires.

Patients' asymptomatic siblings and healthy volunteers matched to the patients in terms of age and sex were also included in the study. We excluded siblings with a history of illicit drug abuse or encephalitis that could affect cognition and interfere with the test results, as well as those with a history of suspected seizures or other injuries or who failed to complete the neuropsychological tests. In total, 26 of the 46 patients (male, n=9) had a sibling who was included in the study. The 33 healthy control subjects (male, n=14) had no family history of neurologic, psychiatric, or genetic disorders. We performed power analyses to ensure that the sample size was adequate to show intergroup differences.

All participants were right-handed and underwent electroencephalography (EEG) tests and brain MRI scans. All of the control subjects and siblings had normal EEG and brain MRI data, except 1 sibling (4%) with abnormal EEG findings (slightly suspicious epileptiform discharges with maximums in the frontal and temporal lobes) and 1 (4%) with visible HS.

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Xiangya Hospital of Central South University. All participants provided written, informed consent for access to their medical records (containing demographic and clinical information).

Neuropsychological Tests

All participants were evaluated with the following neuropsychological tests.

(1)Mini-Mental State Examination (MMSE). This questionnaire assesses mental state and general cognition including registration, attention, calculation, recall, language, ability to follow simple commands, and orientation, with a total score of 30 points.[38]

(2)Arithmetic test in the Chinese revision of the Wechsler Adult Intelligence Scale (WAIS-RC). The test evaluates quantitative reasoning and attention abilities,

which are components of working memory.[39] There are 14 arithmetic problems, and the subject is required to answer the questions orally within a limited time.

(3)Information test in the WAIS-RC. This test includes 29 general knowledge questions that evaluate long-term memory.

(4)Forward digit span test (FDST) and backward digit span test (BDST) in the WAIS-RC. These tests evaluate attention, short-term memory, and working memory. In the tests, a sequence of numbers is shown to the subject, who is asked to repeat it forward or backward.[40]

(5)Digit symbol substitution test (DSST) in the WAIS-RC. The test evaluates attention, short-term memory, psychomotor speed, and executive function.[41] The subject is required to transcribe a digit-symbol code using a key within 90 s.

(6)Block design test (BDT) in the WAIS-RC. This test evaluates visuospatial construction, speed of execution, perceptual integration, and planning capacity. Subjects are required to assemble red and white blocks in a specified pattern within the specified time.[42]

(7)The Hayling test. This test evaluates response initiation and suppression speed, which are both components of executive function.[41,43] The test consists of 2 sets of 15 sentences with a phrase missing in each sentence. In Part A, the examiner reads each sentence out loud and the subject must complete the sentence with a logical phrase. In Part B, the subject completes a sentence with a nonsense phrase. The completion time for Hayling test Part A (Hayling-A time) and Part B (Hayling-B time) were measured in the present study to evaluate response initiation and suppression speeds, respectively.

(8)Trail making test (TMT). This test evaluates attention and executive function. The subject is required to connect a sequence of consecutive targets on a sheet of paper as quickly as possible. There are 2 parts to the test: in part A, the targets are 25 numbers (1, 2, 3, etc.) that the subject must connect in sequential order; in part B, the subject must alternate between numbers and letters (1, A, 2, B, etc.). We used the time taken to complete part B of the test (TMT-B time) as a measure of visual scanning and graphomotor speeds.

(9)Verbal fluency test (VFT, animal naming). This test evaluates verbal ability by requiring the subject to name as many different animal names as possible in 1 min.[44]

Each test had uniform and reliable scoring criteria, and the whole battery took approximately 50 min to complete.

Statistical Analysis

Statistical analyses were carried out with SPSS v25.0 (IBM, Armonk, NY, USA). Analysis of variance was used to compare years of education and age and the chi-squared test was used to compare the sex ratio between groups. The MMSE score was used as a measure of the general cognitive ability of the participants. Levene's test was used to detect homogeneity of variances; based on the result, we performed analysis of covariance (ANCOVA) with years of education and age as covariates or the Kruskal–Wallis nonparametric test (for the arithmetic test, TMT-B time, and BDT only). If the main analysis indicated significant intergroup differences, pairwise post hoc comparisons were carried out to identify the cause in the ANCOVA or Kruskal–Wallis nonparametric test. All comparative analyses were adjusted with the Bonferroni correction. We also performed a subgroup analysis of participants with left and right TLE as well as a correlation analysis between patients' performance in neuropsychological tests and factors that may have confounded the results such as seizure frequency, history of focal to bilateral tonic–clonic seizure, number of AEDs, and duration of seizures. The significance threshold for all analyses was $P<0.05$ (2-sided P values).

Results

Characteristics of the Study Population

The groups were similar in terms of age ($F_{2101}=2.4$, $P=0.1$), years of education ($F_{2101}=1.1$, $P=0.3$), and sex ratio ($\chi^2=0.6$, $P=0.7$). The demographic and clinical characteristics of the study population are shown in Tables 1 and 2.

In the general cognitive assessment with the MMSE, the score of TLE patients was 1.59 points lower than that of the control group ($P=0.016$). The detailed results of neuropsychological tests are shown in Table 3. The main group analysis revealed significant differences between groups in most tests except for TMT-B time. In pairwise comparisons, patients with TLE (n=46) showed deficits in the information test, arithmetic test, BDST, DSST, BDT, and Hayling-A time. Meanwhile, their siblings (n=26) showed deficits in the BDT. That is, both patients and siblings showed significant differences in BDT scores relative to the control group, with patients showing poorer performance. After excluding the 20 patients without siblings that participated in the study, the difference in

Table 1 Demographic and Clinical Characteristics of the Study Population

Characteristics	Value
Mean age of onset (range), years	15.55 (10.0, 21.3)
Mean duration of seizures (range), years	10 (4.5, 17.3)
Frequency of seizures	
Multiple daily	4 (8.7)
Daily	3 (6.5)
Weekly	12 (26.1)
Monthly	16 (34.8)
Annually	10 (21.7)
Less than annually	1 (2.2)
Personal history	
FS	8 (17.4)
Number of AEDs	
1	33 (71.8)
2	10 (21.7)
3	3 (6.5)
TLE lateralization	
Left	20 (43.5)
Right	26 (56.5)
MRI	
HS	14 (30.4)

Note: Values are shown as n (%) unless otherwise indicated.
Abbreviations: AED, antiepileptic drug; FS, febrile seizure; HS, hippocampal sclerosis; MRI, magnetic resonance imaging; TLE, temporal lobe epilepsy.

performance on the BDT remained significant (P=0.002, patients vs controls; P=0.008, siblings vs controls).

Subgroup Analyses

An additional analysis was carried out for left and right TLE patient subgroups. There was no statistically significant difference between left TLE patients (n=20) or their siblings (n=11) and control subjects (n=33) in terms of age (patients, P=0.9; siblings, P=0.3), years of education (patients, P=0.1; siblings, P=0.2), and sex ratio (patients, P=0.7; siblings, P=0.6). There was no difference in age between right TLE patients (n=26) or their siblings (n=15) and control subjects (both P=0.6). There was no difference between right TLE patients or their siblings and controls in terms of years of education (patients, P=0.5; siblings, P=0.5) or sex ratio (patients, P=0.6; siblings, P=0.5).

The mean scores for each test by group and the main group analyses and pairwise post hoc comparative analyses of the left and right TLE subgroups are shown in Tables 4 and 5, respectively. The main group effects in the information and arithmetic tests, FDST, BDST, DSST, BDT, TMT-B time, and Hayling-A and -B times differed significantly between left TLE patients, their siblings, and control subjects. In pairwise post hoc comparisons, patients with left TLE had worse performance in the arithmetic test, Hayling-A time, TMT-B time, DSST, and BDT relative to controls, whereas deficits were only observed in the siblings in the BDT. The main group effects in the information and arithmetic tests, FDST, BDST, DSST, VFT, BDT, and Hayling-A and -B times differed significantly between right TLE patients, their siblings, and controls. Patients with right TLE (n=26) showed deficits in the information and arithmetic tests, BDST, DSST, and Hayling-A time. The siblings showed comparable performance to controls in all tests.

The left TLE subgroup showed worse performance in most of the neuropsychological tests than right TLE patients, especially in those evaluating executive function (including visuospatial function tests) such as Hayling-A time (left TLE patients vs controls, P=0.009; right TLE patients vs controls, P=0.045) and TMT-B time (left TLE patients vs controls, P=0.043; right TLE patients vs controls, P=0.3). A correlation analysis showed that the performance of TLE patients in the BDT was not correlated with duration of seizures in years (r=−0.2, P=0.3), seizure frequency (r=−0.2, P=0.1), number of AEDs (r=0.01, P=0.9), or history of secondary generalized seizures (r=−0.08, P=0.5).

Discussion

This is the first study investigating cognitive function in the unaffected siblings of TLE patients. The patients showed

Table 2 Sociodemographic Characteristics of the Study Population by Group

	Patients (n=46)			Sibling (n=26)	Control (n=33)
	TLE (n=46)	Left TLE (n=20)	Right TLE (n=26)		
Male sex	20 (43.5%)	7 (35.0%)	13 (50.0%)	9 (34.6%)	14 (42.4%)
Age	28.5±8.8	32.8±8.7	25.2±7.4	32.3±10.4	33.2±11.8
Years of education	11.0±3.3	11.2±3.4	12.3±3.2	11.8±3.1	12.8±3.2

Abbreviation: TLE, temporal lobe epilepsy.

Table 3 Average Test Scores for Each Group and Intergroup Comparisons

Neuropsychological Measure	Group			Main Group Comparisons		Sibling vs Control	Patient vs Control
	Patient (n=46)	Sibling (n=26)	Control (n=33)	F	P	P	P
Information	11.4 (4.8)	13.1 (5.2)	16.5 (6.01)	25.5	<0.001	0.1	<0.001
Arithmetic	10.1 (3.7)	10.9 (3.8)	12.7 (2.7)	–	0.004	0.1	0.003
DSST	51.9 (17.2)	54.7 (16.4)	63.4 (20.0)	15.0	<0.001	0.2	0.001
VFT	15.7 (6.6)	15.3 (4.8)	16.3 (5.6)	2.9	0.025	1.0	1.0
Hayling-A time	146.4 (73.3)	137.8 (61.0)	102.8 (61.0)	7.2	<0.001	0.2	0.011
Hayling-B time	188.3 (71.8)	208.8 (71.7)	169.9 (78.4)	11.2	<0.001	0.1	0.3
TMT-B time	2.7 (2.0)	2.3 (1.3)	2.7 (1.3)	–	0.1	–	–
BDT	31.5 (10.4)	30.6 (10.1)	38.9 (8.4)	–	0.001	0.006	0.005
FDST	6.9 (1.9)	8.0 (1.9)	7.7 (1.5)	5.4	0.001	0.9	0.2
BDST	4.0 (1.5)	5.0 (1.5)	5.4 (1.9)	9.2	<0.001	1.0	0.001

Note: Data are shown as mean score (standard deviation).
Abbreviations: BDST, backward digit span test; BDT, block design test; DSST, digit symbol substitution test; FDST, forward digit span test; Hayling-A time, time taken to complete Hayling test Part A; Hayling-B time, time taken to complete Hayling test Part B; TLE, temporal lobe epilepsy; TMT-B time, time taken to complete the trail making test Part B; VFT, verbal fluency test.

Table 4 Subgroup Analyses of Left TLE

Neuropsychological Measure	Group		Main Group Comparisons		Sibling vs Control	Patient vs Control
	Left TLE Patients (n=20)	Siblings (n=11)	F	P	P	P
Information	12.8 (5.4)	13.0 (4.1)	20.2	<0.001	0.9	0.2
Arithmetic	9.8 (3.5)	11.3 (3.8)	6.4	<0.001	1.0	0.032
DSST	47.7 (15.9)	50.7 (19.0)	–	0.011	0.2	0.016
VFT	17.3 (8.9)	15.7 (4.2)	2.3	0.1	1.0	0.7
Hayling-A time	157.1 (81.0)	129.0 (31.6)	–	0.005	1.0	0.009
Hayling-B time	207.3 (75.3)	224.6 (68.8)	10.1	<0.001	0.4	0.3
TMT-B time	155.6 (85.8)	115.6 (71.1)	–	0.048	0.5	0.043
BDT	30.1 (8.7)	27.8 (9.4)	–	0.001	0.005	0.006
FDST	7.0 (1.6)	7.6 (2.0)	3.8	0.008	1.0	0.6
BDST	4.3 (1.7)	5.2 (1.9)	5.7	0.001	1.0	0.2

Note: Data are shown as mean score (standard deviation) of main group comparisons and pairwise post hoc comparisons of left TLE patients, their siblings, and control subjects.
Abbreviations: BDST, backward digit span test; BDT, block design test; DSST, digit symbol substitution test; FDST, forward digit span test; Hayling-A time, time taken to complete Hayling test Part A; Hayling-B time, time taken to complete Hayling test Part B; TLE, temporal lobe epilepsy; TMT-B time, time taken to complete the trail making test Part B; VFT, verbal fluency test.

extensive cognitive deficits in both long- and short-term memory, attention, working memory, executive function, and visuospatial function, which is consistent with previous findings.[45,46] The unaffected siblings had never experienced seizures, were not medicated, and were asymptomatic, but nonetheless showed impaired visuospatial function similar to patients, suggesting that these deficits have a genetic component and are independent of seizures or AED use.

Cognitive impairment in TLE patients reflects the dysfunction of temporal and frontal cortices. A study of 54 TLE patients and 28 controls examined by diffusion tensor imaging (DTI) and neuropsychological tests found that working memory performance was correlated with the frontoparietal network and contralateral temporal lobe.[47] Hippocampal−thalamic connections and the prefrontal cortex have been implicated in executive function in TLE patients.[48,49] A recent brain MRI study that included pooled data of 2149 individuals with epilepsy found reductions in thalamic volume and cortical thickness in the temporal and frontal lobes of TLE patients.[50] This can

Table 5 Subgroup Analyses of Right TLE

Neuropsychological Measure	Group		Main Group Comparisons		Sibling vs Control	Patient vs Control
	Right TLE Patients (n=26)	Siblings (n=15)	F	P	P	P
Information	10.3 (4.2)	13.1 (5.2)	20.4	<0.001	0.1	<0.001
Arithmetic	10.3 (3.8)	10.6 (3.9)	–	0.022	0.2	0.030
DSST	55.1 (17.7)	57.7 (14.0)	12.7	<0.001	0.7	0.046
VFT	14.4 (3.9)	15.0 (5.3)	3.1	0.020	1.0	0.6
Hayling-A time	138.3 (67.2)	144.3 (76.4)	–	0.015	0.1	0.045
Hayling-B time	173.7 (66.7)	197.2 (73.8)	8.2	<0.001	0.4	1.0
TMT-B time	128.5 (85.3)	133.8 (97.2)	–	0.5	–	–
BDT	32.7 (11.6)	32.6 (10.5)	18.0	<0.001	0.2	0.1
FDST	6.7 (2.1)	8.3 (1.9)	4.5	0.003	0.7	0.2
BDST	3.9 (1.4)	4.9 (1.1)	–	0.004	1.0	0.006

Note: Data are shown as mean score (standard deviation) of main group comparisons and pairwise post hoc comparisons of right TLE patients, their siblings, and control subjects.

Abbreviations: BDST, backward digit span test; BDT, block design test; DSST, digit symbol substitution test; FDST, forward digit span test; Hayling-A time, time taken to complete Hayling test Part A; Hayling-B time, time taken to complete Hayling test Part B; TLE, temporal lobe epilepsy; TMT-B time, time taken to complete the trail making test Part B; VFT, verbal fluency test.

explain our finding that TLE patients showed cognitive impairment in both the frontal and temporal lobes, which may result from damage in remote brain regions away from the epileptogenic focus.

Anterograde memory function is associated with the temporal lobe. In this study, we assessed short-term memory recall with the Montreal Cognitive Assessment (MoCA), DSST, FDST, BDST, short-term memory (registration) subtest, and recall subtest of the MMSE (Supplementary Table 1). TLE patients showed cognitive deficits in neuropsychological tests of anterograde memory including the DSST, BDST, recall task subtest of the MMSE, and MoCA, whereas no differences relative to control subjects were observed in the FDST or the short-term memory (registration) subtest of the MMSE. These results highlight the complexity of cognitive impairment in TLE patients.

The BDT assesses visuospatial construction, speed of execution, perceptual integration, and planning capacity,[51] which involve the frontal, temporal, and parietal lobes along with the visual cortex and cerebellum.[52] There are several neuropsychological tests for evaluating visuospatial function, as a single test cannot cover all of the subcomponents.[53] The 2 hemispheres play different roles in visuospatial information processing;[54] besides, the memory, execution, and visuospatial subsets of the BDT should all be separately considered when using tests for cognitive assessments. A previous investigation of 374 patients found that average left hemisphere thickness in patients was related to their performance on the BDT,[55] while another study showed that left hippocampal atrophy in TLE patients was associated with visuospatial deficits.[56] However, how these anatomic abnormalities contribute to cognitive impairment remains to be determined.

In the exploratory analysis of right TLE patients and their siblings, the former showed obvious deficits in long-term and working memory, visuospatial function, and response initiation speed, whereas the cognitive performance of their siblings was comparable to that of controls. A DTI study revealed that white matter in patients with right TLE was less impacted by seizures than that in patients with left TLE, and was less likely to involve bilateral alterations.[47] Patients with right TLE also showed less extensive structural damage compared to left TLE patients.[50] The right temporal lobe is more closely related to emotional recognition[57,58] and social cognition,[59–62] which we did not evaluate. In our study, right TLE patients had higher scores in certain neuropsychological tests than left TLE patients, and their siblings did not demonstrate cognitive deficits, is in accord with previous researches.

This study had limitations. Firstly, as it was a cross-sectional study the subjects were not repeatedly tested at different time points, which would be useful for examining the progression of cognitive changes in TLE patients. On the other hand, we carried out post hoc analyses to exclude selection bias resulting from the small number of HS

patients in our study and determined that there were no significant differences between patients with vs those without HS or between their siblings in any of the neuropsychological tests, which is consistent with previous findings that TLE with and without HS are on the same pathologic continuum.[63–65] Thus, the inclusion of both TLE patients with and those without HS along with their siblings enhances the generalizability of our findings.

Conclusion

The results of our study demonstrate that impaired visuospatial function is an endophenotype of TLE that is observed in both patients and their unaffected siblings. This neuropsychological indicator is relatively stable and measurable and provides a link between genetic and phenotypic aspects of cognitive impairment in TLE, as well as providing insight into the possible underlying mechanisms. Moreover, our data suggest that the more extensive cognitive impairment in TLE patients compared to their siblings is the combined effect of genetic factors and epileptic activity.

Abbreviations

AED, antiepileptic drug; ANCOVA, analysis of covariance; BDST, backward digit span test; BDT, block design test; DSST, digit symbol substitution test; DTI, diffusion tensor imaging; EEG, electroencephalography; FDST, forward digit span test; HS, hippocampal sclerosis; MMSE, Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI, magnetic resonance imaging; TLE, temporal lobe epilepsy; TMT, trail making test; VFT, verbal fluency test; WAIS-RC, Chinese revision of the Wechsler Adult Intelligence Scale.

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Disclosure

The authors report no conflicts of interest in this work.

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