Research Article

Executive Functions in Chronic Mesial Temporal Lobe Epilepsy

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There is no consensus as to whether mesial temporal lobe epilepsy (MTLE) leads to executive function deficits. In this study, we adopted an extensive neuropsychological test battery and assessed different executive functions in chronic, unilateral MTLE. Performance of MTLE patients was compared with that of healthy peers and with normative data. Several MTLE patients had scores below cut-off or below the 10th percentile of normative data. Scores of the whole patient group were overall in the average range of normative data. Relative to controls, MTLE patients performed poorly in tests of working memory, cognitive flexibility, categorical verbal fluency, set-shifting, categorization, and planning. These findings raise an important methodological issue as they suggest that executive function deficits in chronic MTLE may be individually variable and that their assessment should include different tests. Deficits in chronic MTLE are not limited to temporal lobe functions, such as memory, but may extend to extra temporal cognitive domains, such as executive functions.

1. Introduction

Mesial temporal lobe epilepsy (MTLE) is possibly the most frequent form of epilepsy [1] and is associated with overt or subtle structural abnormalities in the hippocampus, parahippocampal gyrus, and amygdala [2]. Recent investigations have suggested that functional and structural abnormalities in MTLE may extend beyond the temporal lobes. Volume reduction has been observed in extratemporal areas such as thalamus, caudate nuclei, lenticular nuclei, corpus callosum, and frontal lobes (for a review, see [3]). Alterations of frontotemporal white matter tracts [4] and of neurotransmitter systems [5] have also been reported. Metabolic changes have been observed not only in mesial and lateral temporal areas, but also in the prefrontal cortex [6] and in subcortical structures [7, 8]. Thalamus, basal ganglia, and frontal lobes are part of corticosubcortical circuits that are involved in the regulation of motor functions, behavior, and cognitive functions such as set-shifting, planning, and inhibitory control [9, 10]. As increasing evidence points to

functional and structural alterations of these corticosubcortical circuits, it may be expected that MTLE patients experience executive function deficits.

The term "executive functions" refers to high-order cognitive functions which allow adaptation to nonroutine situations such as novel, conflicting, or complex tasks [11, 12]. Planning, set-shifting, strategic behavior, response initiation, and response inhibition are some of the cognitive functions that may be listed under this umbrella term. Executive function deficits are often found in association with frontal lobe damage [13, 14]. However, recent neuropsychological investigations as well as neuroimaging studies have pointed to a distributed brain network, which encompasses frontal areas as well as posterior areas (e.g., parietal association areas: [15]; cerebellum: [16]) and subcortical structures (e.g., basal ganglia: [17]; thalamus: [18]). Executive function deficits may be found in a large number of neurological pathologies, in diffuse brain damage, and in focal brain damage [11, 12]. Single-case analyses of brain-damaged patients have shown that executive function deficits may have different

clinical manifestations and that performance on executive function tests may be dissociated with deficits observed on some tests and not on others [11, 12]. Executive function deficits may have important consequences on the patient's autonomy and severely compromise the quality of life. Given the multicomponent aspect of executive functioning, its systematic assessment needs to cover several cognitive processes.

Chronic MTLE may affect cognitive and emotional processing [19–21]. Compared with healthy controls, MTLE patients often show reduced episodic memory and difficulties in learning new information [22, 23]. Recent studies have also reported difficulties in decision making [24, 25]. There are mixed results regarding executive functioning in chronic MTLE. Some studies have reported reduced performance for MTLE patients as compared with controls [26–28]; others have found no relevant differences [22, 24]. As, in most studies, only a single test or a very short test battery has been used to assess executive functioning in MTLE, it may be possible that deficits have been overlooked in some cases. Also, no specific assessment of different executive functions has been done.

Studies that have used the Wisconsin Card Sorting Task (WCST) [42] have found significant differences between MTLE patients and controls, pointing to abstraction, categorization, and set-shifting deficits in MTLE (e.g., [24, 26–28]; see also [43]). Studies that have screened for deficits in working memory [22, 24], inhibitory control [24, 28], verbal fluency [22, 28], or cognitive flexibility [22, 24] have obtained heterogeneous findings, making it difficult to conclude whether and to what extent MTLE patients present executive function deficits. Inconsistent findings have also been reported with regard to the effect of seizure lateralization. Giovagnoli [26] found that patients with left-sided MTLE are more impaired than patients with right-sided MTLE on the WCST, whereas Corcoran and Upton [28, 44] reported the opposite pattern of results. Other investigations found no significant effect of seizure lateralization on executive functioning [22, 45].

This study aimed at investigating executive functioning in a group of chronic, unilateral MTLE patients. Differently from previous studies, we used an extensive battery of neuropsychological tests and assessed different aspects of executive functioning (verbal attention, verbal working memory, psychomotor speed, cognitive flexibility, verbal fluency, set-shifting, categorization, inhibition, and planning). In this study, we compared performance of MTLE patients with that of healthy peers as well as with normative data. In separate analyses, we also controlled for possible effects of seizure lateralization (left-sided MTLE versus right-sided MTLE), structural abnormality (hippocampus versus amygdala), and antiepileptic drug therapy (AED), which has been documented to significantly affect cognitive performance [46–49]. A correlation analysis also examined the association of executive function performance with age at seizure onset and epilepsy duration.

Following previous reports on deficits of TLE patients in single executive function tests, we expected the MTLE patients to perform poorly relative to the healthy controls in the more comprehensive neuropsychological test battery. As epilepsy in the dominant hemisphere may have detrimental effects on language processing, we also expected the left-sided MTLE patients to perform poorly relative to the right-sided MTLE patients on verbal fluency tests. Finally, we hypothesized that executive function deficits are enhanced in the patients with the earlier onset epilepsy and the longer disease duration.

2. Methods

2.1. Participants. We examined prospectively 28 consecutive patients with unilateral MTLE (12 women). (Patients also performed tasks of decision making; these results are described in [25].) Patients had pharmacoresistant, focal epilepsy and were candidates for epilepsy surgery (age at seizure onset: mean 21.5 ± 14.5 years; disease duration: mean 18.2 ± 15.2 years). Patients underwent a detailed clinical and neurological examination including prolonged video-EEG monitoring, high-resolution MRI, interictal SPECT or PET, and a neuropsychological examination. They were seizure-free for at least 48 hours before the neuropsychological testing. Twenty-six patients were right hander [50]; two were ambidextrous (only right-hander patients were taken into consideration in the analysis of the effect of seizure lateralization).

Patients underwent a high-resolution 1.5-Tesla MRI with T1-weighted spin echo and gradient echo 3D multiplanar reconstruction images (with and without intravenous contrast application), axial and coronal T2-weighted turbospin echo, T1 inversion recovery, T2-weighted fast fluid attenuated inversion recovery (FLAIR), and diffusion-weighted sequences. Coronal T2-weighted and FLAIR slices extended 1–3 mm. Axial images were acquired with an angle parallel to the long axis of the hippocampus. All but three MRI scans were visually evaluated by two independent raters (G. K., F. K.) who were familiar with the radiological analysis of the temporal lobe structures and were blinded to diagnosis. Three patients underwent MRI outside our institution following the above-mentioned protocol. For these three patients, we obtained a detailed written description of the mesial temporal structures. Agreement was achieved in all but two cases (agreement: 93%). A third rater (E.T.) who was blinded to diagnosis was consulted to resolve these two cases. MRI revealed a clear unilateral abnormality in the left mesial temporal lobe in 17 patients (LMTLE) and a clear unilateral abnormality in the right mesial temporal lobe in 11 patients (RMTLE). Hippocampal abnormality was found in 10 patients (hippocampus group = MTLE-HC), amygdala abnormality in 11 patients (corpus amygdaloideum group = MTLE-CA), and abnormalities affecting both structures in 7 patients (see Figure 1 for examples of MRI features for the three groups). The MTLE-HC group included patients with MRI features of *hippocampal sclerosis* (atrophic hippocampus with missing internal three-layer architecture and increased signal in T2 and FLAIR sequences) and *hippocampal dysplasia* (hippocampus with distorted anatomy, with blurring of white/grey matter interface, and increased signal in T2 and FLAIR sequences). Amygdala was regarded as *dysplastic* if it

(a) Patient AJ (MTLE-HC group)   (b) Patient PE (MTLE-CA group)   (c) Patient WE (MTLE-HC+CA group)
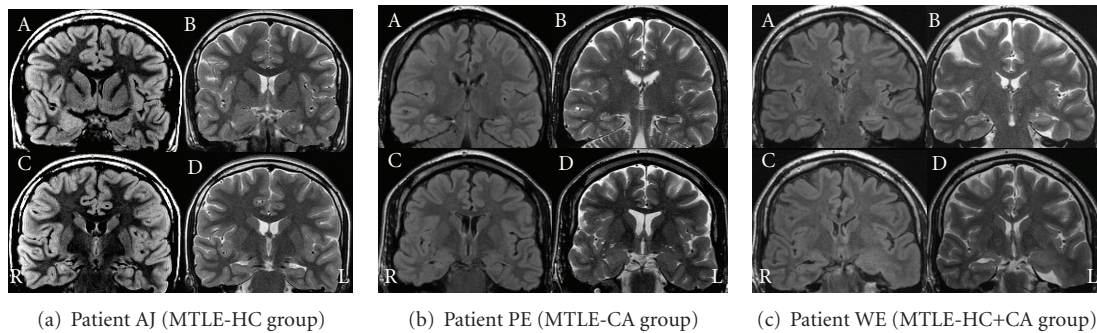
FIGURE 1: Examples of MRI features for the MTLE-HC group (a), the MTLE-CA group (b), and the MTLE-HC+CA group (c). (a) Upper row: (A) FLAIR and (B) T2-weighted coronal images showing on the right side enlarged amygdala with increased MR signal in FLAIR and T2-weighted sequences (dysplastic amygdala). Lower row: (C) FLAIR and (D) T2-weighted coronal images showing normal hippocampus; R: right hemisphere; L: left hemisphere. (b) Upper row: (A) FLAIR and (B) T2-weighted coronal images showing on the right side atrophic hippocampus with increased MR signal in FLAIR and T2-weighted sequences (hippocampal sclerosis). Lower row: (C) FLAIR and (D) T2-weighted coronal images showing normal amygdala; R: right hemisphere; L: left hemisphere. (c) Upper row: (A) FLAIR and (B) T2-weighted coronal images showing on the left side dysplastic hippocampus with increased MR signal in FLAIR and T2-weighted sequences. Lower row: (C) FLAIR and (D) T2-weighted coronal images showing on the left side enlarged amygdala with increased MR signal in FLAIR and T2-weighted sequences (dysplastic amygdala); R: right hemisphere; L: left hemisphere.

was larger than the contralateral side, if increased signal in T2 and FLAIR sequences was observed, or both.

Fifteen patients received antiepileptic drug monotherapy (carbamazepine, oxcarbazepine, lamotrigine, and levetiracetam); 13 patients were on polytherapy (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproate, zonisamide; AED daily doses and serum levels are reported for each patient in Table 4). The serum level was measured within one day from the neuropsychological examination in 24/28 patients (86%); in the remaining cases, the serum level refers to the closest previous measurement (deviation from the day of the neuropsychological examination: 17 to 44 days). All but one patient had serum levels within standards. The patient with the serum level for one antiepileptic drug slightly above the normal range did not manifest signs of intoxication. Also, neuropsychological performance did not differ between this patient and the patient group.

Twenty healthy volunteers (15 women) participated in the study. They were recruited from the personnel of the Innsbruck Medical University. Exclusion criteria for participation were history of stroke, head trauma, psychiatric disorder, substance abuse, or neurological disorders which may compromise cognition. Healthy participants and MTLE patients were comparable in age (controls: mean 36.0 ± 13.0 years; MTLE patients: mean 40.3 ± 11.3 years) and education (controls: mean 11.4 ± 1.6 years; MTLE patients: mean 10.6 ± 1.7 years). The present study was approved by the local ethics committee. Informed consent was obtained from all participants.

2.2. Neuropsychological Assessment. MTLE patients completed tests of verbal memory (learning, free recall, and recognition—Münchner Gedächtnistest, MGT) [33], nonverbal memory (subtest of the Visueller und Verbaler Merkfähigkeitstest, VVM) [34], vocabulary [29], numeracy [30, 31], mental complex calculation [32], and executive

functions (verbal attention and verbal working memory—digit span tests of the Wechsler Memory Scale-Revised, WMS-R [36]; psychomotor speed and cognitive flexibility—Trail Making Test-A and B, TMT-A and B [37]; categorical verbal fluency, phonological verbal fluency, and verbal fluency with alternating categories—subtests of the Regensburger Wortflüssigkeitstest, RWT [38]; planning and problem solving—Planungstest [41]; abstraction and categorization—WCST [39]; inhibitory control—Go-NoGo task adapted from [40]). MTLE patients also responded to a questionnaire on anxiety and depression (Hospital Anxiety and Depression Scale-Deutsche Version, HADS-D) [35]. Controls were tested on vocabulary, numeracy, mental complex calculation, and executive functions. The numeracy test assesses basic probability and mathematical concept understanding [30, 31].

2.3. Statistical Analysis. Data did not satisfy assumptions of a normal distribution. Therefore, group differences were analyzed through nonparametric methods (Kruskal-Wallis H-test, Mann-Whitney U-test). Significance was set at $\alpha = .05$.

A Spearman-rank correlation analysis was carried out for the MTLE group between executive function scores, age at seizure onset, and epilepsy duration. The following executive function variables were entered into the analysis: completed categories (WCST), perseverative errors (WCST), digit span backward (WMS-R), correct NoGo trials (Go-NoGo task), sec in the TMT-B, total number of moves (Planungstest), categorical verbal fluency (RWT), and verbal fluency with alternating categories (set-shifting, RWT). Applying Bonferroni correction for multiple correlations, significance was set at $\alpha = .003$.

3. Results

3.1. Comparison with Normative Data. Median scores of healthy controls were in the average range of normative data

TABLE 1: Medians for scores in neuropsychological background tests as a function of group.

	Max. score	MTLE patients Mdn	Healthy controls Mdn	P value	Patients deviating from norms (n/N)	(%)
Vocabulary [29]	37	28.5	31.0	**.010**	0/28[1]	0
Numeracy [30, 31]	11	8.0*	9.0	**.004**	15/28[2]	54
Mental complex calculation [32]	24	11.0	14.0	**.044**	0/23[3]	0
Verbal memory (MGT) [33]						
Learning (5. trial)	16	13.0	—	—	5/27[4]	19
Immediate free recall	16	10.0	—	—	11/27[4]	41
Delayed free recall	16	12.0	—	—	9/27[4]	33
Recognition (corrected score)	16	15.0	—	—	8/27[4]	30
Nonverbal memory, immediate free recall (VVM) [34]	31	18.0	—	—	6/25[4]	24
Anxiety (HADS-D) [35]	21	6.0	—	—	5/28[5]	18
Depression (HADS-D) [35]	21	2.0	—	—	2/28[5]	7
Digit span forward (WMS-R) [36]	12	7.0	7.5	.069	7/28[4]	25
Digit span backward (WMS-R) [36]	12	6.0	7.0	**.013**	8/28[4]	29
Psychomotor speed (TMT-A) [37]		28.5	28.0	.379	3/28[4]	11
Cognitive flexibility (TMT-B) [37]		77.0	55.5	**.007**	12/28[4]	43
Categorical verbal fluency (RWT) [38]		23.5	27.0	**.027**	8/28[4]	29
Phonological verbal fluency (RWT) [38]		7.0	9.0	.080	12/27[4]	44
Set-shifting (RWT) [38]		14.0	16.0	**.004**	2/28[4]	7
Categorization (WCST) [39]						
Completed categories	5	2.5	4.0	**.010**	7/28[4]	25
Perseverative errors		10.0	6.0	**.011**	10/28[4]	36
Go-NoGo task (adapted from [40])						
Correct Go-trials	100	98.9	100.0	**.038**	2/28[4]	7
Correct NoGo-trials	100	83.3	80.0	.892	3/28[4]	11
Planning (Planungstest) [41]						
Total number of moves		36.0	34.0	**.009**	2/28[4]	7
Errors		0.0	0.0	—	1/28[4]	4

Note: Group comparisons were carried out by means of Mann-Whitney U-test. Significance was set at $\alpha = .05$.
MTLE: mesial temporal lobe epilepsy; Mdn: Median; ([1]): cut-off IQ 85; ([2]): cut-off median 9; ([3]): cut-off 5; ([4]): cut-off 10th percentile; ([5]): cut-off 10; (*): slightly below cut-off; (—): not available.

in all tests (Tables 1 and 2). The MTLE patients' median score in the numeracy test was below cut-off. In other tests, the MTLE patients' median scores were in the average range of normative data. The evaluation of individual scores revealed several patients with performance below cut-off or below the 10th percentile of normative data (4–54%; Tables 1 and 2). Regarding the executive function tests, 7 patients (25%) performed below the 10th percentile of normative data in 5-to-8 measures; 19 patients (68%) performed below the 10th percentile in 1-to-3 measures. Only two patients showed a normal performance in all measures.

3.2. Comparison of MTLE Patients with Healthy Controls.
Performance of MTLE patients was compared with that of healthy controls by means of Mann-Whitney U-test. Group differences were significant in several neuropsychological measures. MTLE patients obtained slightly lower vocabulary scores, numeracy scores, and mental complex calculation scores than controls (Table 1). Relative to controls, MTLE patients also performed poorly in tests of verbal working memory, cognitive flexibility, categorical verbal fluency, set-shifting, categorization, and planning (Table 1). A significant group difference was also found in the Go-NoGo task. MTLE patients responded less accurately than controls to Go trials; groups did not differ from each other in NoGo trials. There were no significant group differences in tests of verbal attention, psychomotor speed, and phonological verbal fluency (Table 1).

3.3. Effect of Seizure Lateralization

3.3.1. Comparison with Normative Data.
RMTLE patients had a median score slightly below cut off in the numeracy test and a median score slightly below the 10th percentile

TABLE 2: Medians for demographic information and scores in neuropsychological background tests as a function of seizure lateralization.

	Max. score	LMTLE patients (n = 16)	RMTLE patients (n = 10)	P value
		Mdn	Mdn	
Age (years)		46.0	35.5	.076
Education (years)		10.0	10.0	.075
Age at disease onset (years)		20.5	17.0	—
Disease duration (years)		11.5	14.0	—
Vocabulary [29]	37	27.0	29.0	.057
Numeracy [30, 31]	11	8.5*	7.5*	**.014**
Mental complex calculation [32]	24	11.5	9.0	**.034**
Verbal memory (MGT) [33]				
Learning (5. trial)	16	13.0	15.0	—
Immediate free recall	16	9.5*	13.0	—
Delayed free recall	16	12.0	14.0	—
Recognition (corrected score)	16	15.0	14.0	—
Nonverbal memory, immediate free recall (VVM) [34]	31	17.5	17.0	—
Anxiety (HADS-D) [35]	21	5.5	7.0	—
Depression (HADS-D) [35]	21	4.5	2.0	—
Digit span forward (WMS-R) [36]	12	7.0	6.0	.079
Digit span backward (WMS-R) [36]	12	5.5	5.5	**.047**
Psychomotor speed (TMT-A) [37]		29.5	24.5	.691
Cognitive flexibility (TMT-B) [37]		78.0	73.5	**.018**
Categorical verbal fluency (RWT) [38]		22.5	27.0	.056
Phonological verbal fluency (RWT) [38]		5.0*	8.0	**.012**
Set-shifting (RWT) [38]		13.5	15.0	**.011**
Categorization (WCST) [39]				
Completed categories	5	3.5	2.0*	**.027**
Perseverative errors		10.0	10.0	**.032**
Go-NoGo task (adapted from [40])				
Correct Go-trials	100	98.9	98.9	.059
Correct NoGo-trials	100	83.3	98.6	.878
Planning (Planungstest) [41]				
Total number of moves		35.5	36.0	**.029**
Errors		0.0	0.0	—

Note: Group comparisons between LMTLE patients, RMTLE patients, and healthy controls were carried out by means of Kruskal-Wallis H-test. Significance was set at $\alpha = .05$.
LMTLE: left-sided mesial temporal lobe epilepsy; RMTLE: right-sided mesial temporal lobe epilepsy; Mdn: Median; (*): slightly below cut-off or below the 10th percentile of normative data; (—): not available.

in the WCST (Table 2). LMTLE patients had a median score slightly below cut off in the numeracy test and a median score slightly below the 10th percentile in the verbal memory test (immediate free recall) and the phonological verbal fluency test (Table 2). In other tests, the median scores of both groups were in the average range of normative data.

3.3.2. Comparison with Healthy Controls. We performed group comparisons by means of Kruskal-Wallis H-tests. As indicated in Table 2, results were significant in tests of numeracy, mental complex calculation, verbal working memory, cognitive flexibility, phonological verbal fluency, set-shifting, categorization, and planning. Two-by-two comparisons were carried out by means of Mann-Whitney U-tests. LMTLE patients obtained lower scores than RMTLE patients in the phonological verbal fluency test ($z = -2.06$, $P = .041$); other differences between the patient groups were not significant. Relative to healthy controls, LMTLE patients performed poorly in tests of cognitive flexibility ($z = -2.68$, $P = .007$), phonological verbal fluency ($z = -2.81$, $P = .004$), set-shifting ($z = -3.01$, $P = .002$), categorization (completed categories: $z = -2.35$, $P = .019$; perseverative errors: $z = -2.46$, $P = .014$), and planning ($z = -2.16$, $P = .033$). RMTLE patients obtained lower scores than healthy

TABLE 3: Medians for demographic information and scores in neuropsychological background tests as a function of structural abnormality.

	Max. score	MTLE-HC patients ($n = 10$)	MTLE-CA patients ($n = 11$)	P value
		Mdn	Mdn	
Age (years)		47.0	34.0	**.017**
Education (years)		9.5	10.0	**.001**
Age at disease onset (years)		17.5	15.0	—
Disease duration (years)		30.5	6.0	—
Vocabulary [29]	37	25.0	29.0	**.030**
Numeracy [30, 31]	11	7.0*	8.0*	.059
Mental complex calculation [32]	24	9.0	12.5	.310
Verbal memory (MGT) [33]				
Learning (5. trial)	16	12.0	14.0	—
Immediate free recall	16	6.5*	13.0	—
Delayed free recall	16	8.5*	14.0	—
Recognition (corrected score)	16	12.0*	16.0	—
Nonverbal memory, immediate free recall (VVM) [34]	31	16.0	21.0	—
Anxiety (HADS-D) [35]	21	9.5	6.0	—
Depression (HADS-D) [35]	21	3.5	2.0	—
Digit span forward (WMS-R) [36]	12	6.0	7.0	.128
Digit span backward (WMS-R) [36]	12	5.0	6.0	**.031**
Psychomotor speed (TMT-A) [37]		33.0	27.0	.866
Cognitive flexibility (TMT-B) [37]		80.5	71.0	.078
Categorical verbal fluency (RWT) [38]		20.0	27.0	.326
Phonological verbal fluency (RWT) [38]		8.0	8.0	.746
Set-shifting (RWT) [38]		13.0	14.0	.187
Categorization (WCST) [39]				
Completed categories	5	1.0*	4.0	**.014**
Perseverative errors		17.5*	9.0	**.047**
Go-NoGo task (adapted from [40])				
Correct Go-trials	100	98.3	98.9	.646
Correct NoGo-trials	100	73.3*	86.7	.205
Planning (Planungstest) [41]				
Total number of moves		36.0	36.0	.416
Errors		0.0	0.0	—

Note: Group comparisons between MTLE-HC patients, MTLE-CA patients, and healthy controls were carried out on residualized dependent variables by means of Kruskal-Wallis H-test. Significance was set at $\alpha = .05$.
MTLE-HC: patients with hippocampal abnormalities; MTLE-CA: patients with abnormalities in the corpus amygdaloideum; Mdn: Median; (*): slightly below cut-off or below the 10th percentile of normative data; (—): not available.

controls in tests of numeracy ($z = -2.86$, $P = .005$), mental complex calculation ($z = -2.30$, $P = .019$), verbal working memory ($z = -2.33$, $P = .022$), categorization (completed categories: $z = -2.15$, $P = .035$), and planning ($z = -2.24$, $P = .028$). Other differences between patient groups and healthy controls were not significant.

3.3.3. Further Comparisons between RMTLE Patients and LMTLE Patients.
Mann-Whitney U-tests indicated that RMTLE patients and LMTLE patients were comparable in terms of age at seizure onset and epilepsy duration. There

were also no significant group differences in tests of verbal memory, nonverbal memory, anxiety, and depression.

3.4. Effect of Structural Abnormality

3.4.1. Comparison with Normative Data. MTLE-CA patients scored slightly below cut-off in the numeracy test (Table 3). MTLE-HC patients scored below cut-off in the numeracy test and below the 10th percentile in tests of verbal memory, categorization, and inhibitory control (Table 3). Other median scores were in the average range of normative data for both patient groups.

3.4.2. Comparison with Healthy Controls. As the MTLE-HC patients were older and had less education than both the healthy controls and the MTLE-CA patients, we residualized age and education on the dependent variables and then used these measures in the analysis. Group comparisons were performed by means of Kruskal-Wallis *H*-tests. There were significant group differences in tests of vocabulary, verbal working memory, and categorization (Table 3). MTLE-HC patients obtained lower scores than MTLE-CA patients in the WCST (completed categories: $z = -1.97$, $P = .051$). Relative to healthy controls, MTLE-HC patients performed poorly in tests of vocabulary ($z = -1.98$, $P = .005$), verbal working memory ($z = -2.68$, $P = .006$), and categorization (completed categories: $z = -2.75$, $P = .005$; perseverative errors: $z = -2.48$, $P = .012$). Differences between MTLE-CA patients and healthy controls were not significant.

3.4.3. Further Comparisons between MTLE-HC Patients and MTLE-CA Patients. As indicated by Mann-Whitney *U*-test, MTLE-HC patients and MTLE-CA patients had comparable age at seizure onset. The MTLE-HC group had longer epilepsy duration than the MTLE-CA group ($z = -2.44$, $P = .012$). Differences between MTLE-HC patients and MTLE-CA patients in tests of verbal memory, nonverbal memory, anxiety, and depression were not significant when residualized scores were submitted to Mann-Whitney *U*-tests.

3.5. Effect of Antiepileptic Drug Therapy. Patients on monotherapy and patients on polytherapy had comparable scores in all demographic, clinical, and neuropsychological measures (Mann-Whitney *U*-tests, all $P > .05$). The comparison of individual scores with the patient group distribution indicated that five patients had an outlier performance—that is, below 2.5 SD from the group mean—in some memory and executive function measures. Outlier cases were evenly distributed between the monotherapy group and the polytherapy group (see Table 4).

3.6. Correlation Analysis. There was a significant correlation between epilepsy duration and performance on the WCST (completed categories, $r = -.581$, $P = .002$). The longer the disease duration, the poorer the performance. No significant correlation was found between age at seizure onset and performance on executive function tests. (An exploratory analysis indicated that performance on nonexecutive function tests (vocabulary, memory, and complex numerical processing) directly correlated with performance on executive function tests. However, these results did not survive Bonferroni correction for multiple correlations. Neither performance on executive function tests nor performance on nonexecutive function tests correlated with anxiety and depression scores.)

4. Discussion

This study used an extensive neuropsychological test battery and assessed several aspects of executive functioning in chronic, unilateral MTLE patients. Performance of a carefully selected group of pharmacoresistant MTLE patients, who were candidates for epilepsy surgery, was compared with that of healthy peers as well as with normative data. Possible effects of seizure lateralization, structural abnormality, antiepileptic drug therapy, age at seizure onset, and epilepsy duration were also analyzed.

Results indicated that both the MTLE group and the healthy control group had median scores in the average range of normative data. However, there were significant group differences in several executive function measures. Relative to healthy peers, MTLE patients performed poorly in tests of verbal working memory, cognitive flexibility, categorical verbal fluency, set-shifting, categorization, planning, and inhibitory control. They performed comparably to healthy controls in tests of verbal attention, psychomotor speed, and phonological verbal fluency. The evaluation of individual scores corroborated the results of these group comparisons. Several patients had scores below cut-off or below the 10th percentile of normative data. Also, almost one-third of the patients had impairments in 5-to-8 measures of executive functioning; two thirds had impairments in 1-to-3 measures. These findings raise an important methodological issue as they suggest that executive function deficits in chronic MTLE may be individually variable and that their assessment needs to include different tests. We suggest the use of an extensive neuropsychological test battery which assesses different aspects of executive functioning (e.g., working memory, cognitive flexibility, categorization, inhibitory control, and planning). As shown by this study, the use of a single task (e.g., Go-NoGo) is not sufficient for the detection of executive function deficits which may be highly specific.

As a correlation analysis indicated, performance of MTLE patients on the WCST inversely correlated with epilepsy duration. Similar results were described by Kim et al. [27], whereas Martin et al. [43] found no association between performance on the WCST and epilepsy duration or age at seizure onset. Black et al. [45] tested working memory and executive functions in a large group of TLE patients (the majority of patients had mesial temporal lobe epilepsy). Results showed that age at seizure onset and seizure frequency, which significantly correlated with epilepsy duration, were significant predictors of the patients' impairments. In this study, MTLE patients had intractable epilepsy, and epilepsy duration ranged from few months to several years. As the brain suffers for longer time from the epileptic discharges [51], it seems likely that the cognitive deficits were more pronounced in the MTLE patients with the longer disease duration.

The negative effect of epilepsy duration on cognition may be related not only to the effect of the epileptic seizures themselves, but also to other factors including the long-term antiepileptic drug therapy. All commonly used antiepileptic drugs seem to have some behavioral and cognitive effects, with the patients on polytherapy being on average more affected than the patients on monotherapy [46–49]. For example, phenytoin, phenobarbital, and valproate have been related to decline in attention and psychomotor speed (for a review, see [48]); also, patients taking topiramate have been found to perform poorly on verbal fluency [52]

Table 4: Individual daily dose and serum level of the antiepileptic drug therapy.

Patient code	Gender	Age	Education	AED daily dose (mg)	AED serum level (μg/ml)	Outlier
P 1	m	35	10	PGB 600, PB 150	PGB 6.3, PB 11.1	
P 2	m	34	10	LEV 2000, PHE 200	LEV 9.2, PHE 3.2	
P 3	f	46	10	LTG 150, LEV 2000	LTG 2.0, LEV 27.4	a
P 4	f	48	9	LTG 400, PRM 500, ZNS 200	LTG 9.5, PB 12.0, PRM 10.4, ZNS 18.6	b, c, d
P 5	m	49	9	CBZ RD 1050	CBZ 3.8, CBZ Epoxid 0.6	
P 6	f	44	12	CBZ RD 600	CBZ 7.7	
P 7	m	46	10	CBZ 300	CBZ 3.4	
P 8	m	20	13	OXC 900	OXC 0.4, 10-OH-Carbazepin 24.6	
P 9	m	44	10	OXC 900, LEV 3000	OXC 0.2, 10-OH-Carbazepin 13.2, LEV 27.0	
P 10	f	46	10	LEV 3000	LEV 47.9	e
P 11	m	37	13	CBZ 300	CBZ 0.0	
P 12	m	33	13	CBZ RD 1200	CBZ 7.9	
P 13	m	59	10	CBZ RD 200	CBZ 1.7, CBZ Epoxid 0.1	d, f
P 14	m	51	9	CBZ RD 1200, TPM 250	CBZ 10.1, TPM 4.5	
P 15	f	24	10	CBZ 750	CBZ 8.6	a
P 16	f	54	9	LEV 1500	LEV 28.8	
P 17	m	58	10	CBZ RD 800, ZNS 200	CBZ 10.1, CBZ Epoxid 1.2, ZNS 5.4	
P 18	f	50	9	LEV 2000	LEV 32	
P 19	f	18	12	LEV 3000, VPA RD 1250, ZNS 300	LEV 70.3, VPA 111.7, ZNS 22.4	
P 20	m	38	10	LTG 300, PHE 200	LTG 3.9, PHE 5.4	
P 21	f	36	10	LTG 200	LTG 10.7	
P 22	m	24	16	LEV 3000, PGB 300	LEV 43.8, PGB 3.9	
P 23	m	29	10	LEV 3000, PHE 400	LEV 27.5, PHE 19.9	
P 24	f	35	13	CBZ RD 600	CBZ 5.8	
P 25	m	57	10	CBZ RD 400, LEV 3000	CBZ 5.4, CBZ Epoxid 0.9, LEV 38.2	
P 26	m	43	10	LEV 4000, OXC 2100	LEV 23.8, OXC 0.0, 10-OH-Carbazepin 24.3	
P 27	f	30	10	LEV 1000	LEV 3.4	
P 28	f	40	9	CBZ RD 1400	CBZ 12.2	

AED: antiepileptic drug; m: male; f: female; CBZ: carbamazepine; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHE: phenytoin; PGB: pregabalin; PRM: primidone; TPM: topiramate; VPA: valproate; ZNS: zonisamide; a: outlier performance in planning (total number of moves or errors, Planungstest); b: outlier performance in categorical verbal fluency (animals/min, RWT); c: outlier performance in categorization (perseverative errors, WCST); d: outlier performance in verbal memory (recognition, MGT); e: outlier performance in verbal attention (digit span forward, WMS-R); f: outlier performance in inhibitory control (correct NoGo trials, Go-NoGo task).

and categorization [27]. Compared with older antiepileptic drugs, some of the new antiepileptic drugs have fewer negative effects on cognition [46, 48]. In this study, we found that only few patients had an outlier performance relative to performance of the whole patient group. None of the medications seemed to have stronger effects on cognition than others. Also, there were no differences between patients on monotherapy and patients on polytherapy in any memory or executive function measure. Although we cannot exclude the possibility that small group differences between patients on monotherapy and patients on polytherapy have been missed because of the small sample group, these findings may suggest that the antiepileptic drug therapy had no relevant effect on the executive function performance of MTLE patients in this study.

Results of the comparison of left-sided MTLE patients with right-sided MTLE patients showed no relevant group differences with the only exception of a verbal fluency measure. Relative to right-sided MTLE patients, left-sided MTLE patients performed poorly in a phonological verbal fluency test. These results are in line with other investigations, which suggest no severe effect of seizure lateralization on executive functioning [22, 43, 45]. For example, Tudesco et al. [22] tested MTLE patients with unilateral hippocampal sclerosis. Comparably to this study, they found that left-sided MTLE patients differed from right-sided MTLE patients in verbal fluency tests, but not in working memory and set-shifting tests.

There are competing hypotheses in the literature as to the underlying mechanisms of executive function deficits in MTLE. A first hypothesis (nociferous cortex hypothesis) [53] proposes that executive function deficits in MTLE result from the propagation of the epileptic discharges from the temporal lobe epileptic focus to the frontal lobes. There are white matter tracts connecting the temporal lobes with the frontal lobes [54, 55], and the epileptic discharges may propagate

through these projections. According to a second hypothesis (*hippocampal contribution* hypothesis) [28], executive function deficits in MTLE are related to dysfunction of the hippocampus. Specifically, as the hippocampus is involved in the retrieval of information from short-term memory, in the formation of memory associations, and in learning new information, the MTLE patients' impairments in working memory tasks as well as in other executive function tasks, such as the WCST, that rely on such processes would result from dysfunction of the hippocampus. Finally, increasing evidence [3] points to the implication of extratemporal functional and structural brain abnormalities—for example, damage to frontosubcortical circuits, volume loss, or metabolic changes in extratemporal regions—in the executive function disorders of TLE patients. Our study design does not allow us to precisely define the impact of these different factors on executive function performance. Although an exploratory analysis indicated that patients with hippocampal abnormalities (MTLE-HC) scored lower than patients with amygdala abnormalities (MTLE-CA) and healthy controls in the WCST, we may not exclude the possibility that different factors—propagation of epileptic discharges, dysfunction of mesial temporal structures, and extratemporal brain modifications—contributed to the executive function disorders of MTLE patients in this study. Other investigation methods—for example, functional magnetic resonance imaging, voxel-based morphometry, or diffusion tensor imaging—have to be employed, together with neuropsychological testing, to address this question.

One could ask whether there is a specific pattern in the executive function deficits of MTLE patients. Miyake et al. [56] used a latent variable analysis to investigate how executive functions relate to each other. Results indicated that functions such as updating, shifting, and inhibition are clearly separable, but that they are not completely independent from each other and seem to share some common processes. Miyake et al. [56] proposed that the *central executive* component of working memory [57] is a feasible candidate to account for some of the commonality underlying different executive functions [56, 58]. The central executive is an attentional control system, which allocates resources and coordinates and monitors short-term storage processes as well as more general processes [59]. Several executive function tests clearly load on central executive resources, as they require the maintenance of goal and content information, the manipulation of memory representations, or the suppression of irrelevant information. In this study, MTLE patients had difficulties in particular in the tests that put high demands on attentional control resources (e.g., WCST, planning test, and verbal fluency test with alternating categories), whereas they performed relatively well in the less demanding tests (e.g., digit span forward, TMT-A).

In sum, this study indicates that deficits in chronic MTLE are not limited to temporal lobe functions, such as memory, but may extend to extratemporal cognitive domains. Patients with chronic, pharmacoresistant MTLE have executive function deficits, and these deficits are individually variable. Executive functions such as cognitive flexibility, planning, and inhibitory control are essential in everyday life. It is thus possible that MTLE patients experience difficulties in everyday functioning, in particular in those situations that are unknown and require rapid adaptation or flexible problem solving. This study adds to the characterization of cognitive deficits in MTLE and suggests the use of a comprehensive assessment battery in the individual neuropsychological diagnosis.

Acknowledgments

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