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Preserved memory in temporal lobe epilepsy patients after surgery for low-grade tumour. A pilot study

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Abstract The objective was to carry out a pilot study exploring memory outcome in patients with temporal lobe epilepsy (TLE) and low-grade tumour. A prospective study using a competence-related memory assessment was carried out in the Laboratory of Neuropsychology, Epilepsy Center and Neurosurgical Department of the "C. Besta" National Neurological Institute in 24 TLE patients undergoing surgical resection for left (n=12) or right (n=12) low-grade tumours and 36 healthy subjects. Patients underwent mesial or lateral temporal lobe lesionectomy. Neuropsychological tests exploring verbal and visual short-term memory, learning, delayed recall and ability to control interference in memory were applied. Before and after surgery, significant verbal impairment was present in left TLE patients compared to controls and right TLE patients, and visual deficits were present in both groups compared to controls. After surgery, there was no significant decrease in mean verbal or visual memory scores related to the operated side. Some memory abilities subserved by the contralateral temporal lobe improved. Postoperative memory scores were related to preoperative scores, side of operation, age and education. In patients with TLE and low-grade tumour, temporal lobe surgery does not necessarily induce memory deficits. Improvement of memory abilities subserved by the unoperated temporal lobe may be expected.

Key words Memory • Learning • Temporal lobe epilepsy • Surgery • Low-grade tumour

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Introduction

The surgical treatment of patients with temporal lobe epilepsy (TLE) can induce a pattern of cognitive impairment affecting problem-solving, general intelligence, language, visual perception, learning and memory [1, 2]. Learning and memory are generally the most severely altered functions. Bilateral resection of the amygdala, hippocampus and anterior lateral cortex [3] or unilateral resection in the presence of pre-existing contralateral temporal lobe damage [4] usually induces global amnesia. Unilateral resection easily provokes material-specific learning and memory deficits: in left hemisphere dominant patients, left temporal lobe surgery often affects verbal functions [5–10], while right temporal lobe surgery may induce non-verbal deficits [6, 7, 11–14]. However, recent studies indicated that the mesial and lateral regions of the two temporal lobes are involved by different memory mechanisms [15–17] which, in TLE patients, may be affected irrespective of the verbal–non-verbal dichotomy [18–20].

Impairment of memory abilities subserved by the operated temporal lobe has been reported in 55% [21] to 100% of patients [9, 22, 23]. Cognitive functions sustained by other brain regions (contralateral temporal lobe, frontal lobe and posterior lateral cortex of operated temporal lobe) may improve [6, 22, 24, 25]. Factors such as clinical outcome, sex, age at testing, age at seizure onset, disease duration, severity of neuron loss in the removed tissue, preoperative memory performance, location and extent of surgery, duration of postoperative follow-up and antiepileptic drug treatment may all influence memory outcome [26, 27]. Furthermore, reorganisation of brain function also plays a role [28–30].

While the influence of such factors on memory outcome has been extensively investigated in patients with cryptogenic TLE, there is little data concerning lesional TLE, which represents a frequent condition of drug-resistant seizures [31]. In particular, it was documented that the degree of neuron loss in the resected tissue may predict memory outcome [10], but there is scarce information concerning memory outcome after surgery for low-grade tumours [22]. At the neuropsychological level, the variability of memory outcome after temporal lobe surgery across different studies may reflect discrepancies in the paradigm of assessment, which could exclude particular abilities [17] or restrict comparability of test results [8].

In brief, although different variables have been proven to predict memory outcome after surgery for cryptogenic TLE, in patients with TLE and low-grade tumour, memory prognosis is not so clear. Furthermore, a competence-related neuropsychological assessment should contribute to surpass the variability of memory results across patient groups. On these grounds, we carried out a pilot study in patients operated on for drug-resistant TLE and low-grade tumours. The specific aims were: (a) to determine postoperative memory changes, (b) to compare memory performance in relation to the side of the lesion and (c) to explore the variables determining postoperative memory scores.

Materials and methods

Subjects

Twenty-four TLE patients [32] with left (n=12) or right (n=12) temporal lobe lesions entered the study according to the following criteria: (a) epileptic seizures as onset symptom, (b) magnetic resonance imaging (MRI) showing a temporal lobe tumour without enhancement and mass effect and (c) absence of psychiatric disorders, intellectual and attention deficits. Seizures were recorded in six patients: their onset fitted with tumour location. Interictal electroencephalography (EEG) showed slow and epileptiform abnormalities in the temporal or temporofrontal regions on the side of the tumour (n=11), non-specific aspects (n=4) or bilateral asynchronous (n=1), frontal (n=1) or temporal contralateral abnormalities (n=1). Left and right TLE patients had similar age of seizure onset (Mann–Whitney test, U=48, p=0.16), disease duration (U=60.5, p=0.50), and preoperative seizure frequency (U=55.5, p=0.28). Patients and healthy controls (n=36) did not differ in age (Kruskall–Wallis one-way ANOVA, χ^2=1.64, p=0.43) or years of schooling (χ^2=2.92, p=0.23). All subjects were right-handed on the Edinburgh Inventory [33]. Table 1 summarises demographic and clinical characteristics of the subjects.

Two left and four right TLE patients underwent lesionectomy including T1, T2 and T3 neocortex and the temporal pole. Seven left and five right TLE patients underwent mesial lesionectomy including amygdala, hippocampus, uncus, parahippocampus, fusiform lobule and pyriform cortex. Three left and three right TLE patients underwent lateral plus mesial temporal cortectomy including the lesion. In no patient did MRI or pathological specimen reveal signs of hippocampal sclerosis; pathological findings included ganglioglioma (n=8), oligodendroglioma (n=5), fibrillary astrocytoma (n=3), DNET (n=2), pilocytic astrocytoma (n=2), xanthoastrocytoma (n=1), hamartoma (n=1), ependymoma (n=1) and subependymoma (n=1). Table 2 shows postoperative MRI aspects and clinical outcome assessed by Engel's outcome scale [34]. The interval between surgery and postoperative neuropsychological evaluation was similar in left and right patients (U=68.5, p=0.83). The clinical and MRI follow-up were contemporary to neuropsychological assessment, although all patients also underwent MRI soon after surgery.

Verbal neuropsychological tests

The verbal Selective Reminding Procedure (SRP) [35] evaluates the learning of a 10 two-syllable word list. The number of words recalled after the first presentation gives an index of short-term memory (STM); the sum of the words recalled in the following 17 trials without reminding, i.e., consistent long-term retrieval (CLTR), is the learning score [36].

Table 1 Demographic and clinical characteristics of the subjects

	Left TLE patients (n=12)	Right TLE patients (n=12)	Controls (n=36)
Age	34.25±11.12	31.66±10.09	36.61±10.66
Males/females	8/4	3/9	18/18
Schooling (years)	10.41±3.70	11.00±4.82	12.33±3.53
Age at disease onset	27.91±12.51	21.41±9.96	
Disease duration (years)	6.33±5.10	10.08±9.25	
Monthly preoperative seizure frequency	9.58±7.76	5.83±5.95	
Monthly postoperative seizure frequency	1.91±4.20	0.58±0.99	
Time of testing after surgery (months)	11.25±13.16	8.50±7.44	

Table 2 Clinical seizure outcome (Engel's Classes I–IV) and postoperative MRI findings

	Left TLE			Right TLE		
	Pts	Residual lesion	Seizure outcome	Pts	Residual lesion	Seizure outcome
Mesial lesionectomy	SA	Yes	IA	FS	No	IA
	CB	Yes	IA	MI	Yes	IA
	LA	No	IA	PL	No	IA
	CE	No	IIIA	NG	Yes	IC
	BS	Yes	IIB	AE	Yes	IA
	TM	No	IVB			
	LM	Yes	IB			
Lateral lesionectomy	MR	No	IA	TP	No	IA
	PA	No	IB	BR	No	IVA
				CM	No	ID
				SC	Yes	IA
Mesial plus lateral lesionectomy	NV	No	IA	MV	No	IA
	MS	Yes	IVA	ST	Yes	IA
	FA	No	IVB	DS	No	IB

Story Recall (SR) [37] requires immediate and delayed repetition of a short story, which is usually scored cumulatively; we used the delayed recall score obtained half an hour after the first presentation as an index of long-term memory.

The verbal Memory Distractor Test (MDT) evaluates ability to control interference effects in recalling 30 two-syllable words. It requires repetition immediately and after intervals of 5, 10, 15, 30 and 60 s, during which distractor activity takes place (counting backwards by threes) [38–40].

Visual neuropsychological tests

The visual SRP requires the learning of 10 abstract designs and is structured like the analogous verbal test, to give STM and CLTR scores [41].

The Rey Complex Figure (RCF) [42] requires the copying and reproduction after half an hour of an abstract picture, giving an index of visual long-term memory.

The visual MDT is structured like the analogous verbal test [39], requiring immediate or delayed recognition of 30 abstract designs.

Other neuropsychological tests

Raven's Coloured Progressive Matrices [43] and Attentive Matrices [44] assessed general intelligence and attention, respectively.

Data analysis

Following Hermann and Wyler [21], we considered that psychometric changes at least one standard deviation away from the initial patient scores were of clinical significance. On this basis, memory performance was judged improved, stable or worsened. Preoperative and postoperative patient scores were compared with control scores by separate non-parametric statistics (Kruskall–Wallis one-way ANOVA and post-hoc Mann–Whitney tests). Significance level was assessed as $p \leq 0.00063$, according to Bonferroni correction for eight pair-wise comparisons performed for each test measure at an overall alpha error of 0.05 for each factor. Preoperative and postoperative memory scores obtained by left and right TLE patients were compared by separate Wilcoxon tests. Separate regression analyses were used to assess associations of postoperative memory scores with preoperative scores and clinical variables (age of seizure onset, interval between surgery and postoperative evaluation, side of operation, location of resection – mesial, lateral and mesial plus lateral, clinical outcome – absence *vs.* persistence of seizures, age and education). To do this, separate factor analyses of postoperative and preoperative memory scores were computed ; factor loadings were attributed to different neuropsychological factors if they were greater than 0.4.

Results

Clinical seizure outcome [34] was satisfactory in most patients (16 patients in Engel class A, of which five left and eight right TLE patients were seizure-free) (Table 2). In patients with seizure persistence, postoperative seizure frequency compared to preoperative frequency significantly decreased in left (Wilcoxon test, $z=-2.93$, $p=0.003$) and right TLE patients ($z=-2.70$, $p=0.006$). Table 3 shows the percentages of patients who had postoperative memory changes of clinical significance [21]. Table 4 shows mean preoperative and postoperative test scores.

Table 3 Percentages of stable, impaired and improved patients according to learning and memory score changes

Tests	Left TLE patients			Right TLE patients		
	Unchanged (%)	Impaired (%)	Improved (%)	Unchanged (%)	Impaired (%)	Improved (%)
Verbal tests						
Word learning	59	33	8	50	8	42
Short Story	92	8	–	50	16	34
Distractor Test	67	8	25	58	8	34
Visual tests						
Design learning	67	8	25	83	17	–
Rey Figure	83	–	17	84	–	16
Distractor Test	66	–	34	84	–	16

Table 4 Mean (±SD) test scores obtained by patients and controls

	Left TLE		Right TLE		Controls
	Preoperative	Postoperative	Preoperative	Postoperative	
Raven's Matrices	31.75±3.13	32.08±2.64	31.58±4.94	32.08±2.64	32.08±4.50
Attentive Matrices	54.66±6.56	55.41±4.64	49.91±6.84	51.91±5.30	55.72±2.92
Verbal tests					
Short-term memory	5.50±1.83	5.16±1.80	4.91±1.50	5.91±1.24	5.89±1.49
Word learning	80.50±48.47	76.83±52.24	112.50±33.17	122.41±36.58	130.83±33.32
Short Story	8.50±3.65	8.41±2.99	15.66±5.67	15.16±6.35	18.41±4.51
Distractor Test	23.08±4.97	23.91±4.90	24.33±5.34	25.58±4.39	27.13±2.85
Visual tests					
Short-term memory	2.08±2.27	2.75±2.41	2.08±2.53	1.91±2.74	4.33±2.32
Design learning	105.58±48.23	120.16±31.66	100.75±43.72	92.25±45.23	29.88±27.14
Rey Figure	17.66±7.69	21.25±8.75	17.08±7.57	20.00±7.55	22.72±5.82
Distractor Test	22.08±4.92	25.25±4.24	3.16±3.97	23.50±4.68	26.27±2.17

Verbal neuropsychological tests

Patients and controls did not differ in terms of preoperative STM (χ^2=3.57, p=0.16). Kruskall–Wallis one-way ANOVA showed significant differences in preoperative CLTR (χ^2=10.58, p=0.005), SR (χ^2=23.35, p<0.0001) and MDT scores (χ^2=8.56, p=0.01). Post-hoc Mann–Whitney tests revealed that left TLE patients were impaired compared to controls in CLTR (U=82.5, p=0.001), SR (U=30, p<0.0001) and MDT (U=97.5, p=0.004), and compared to right TLE patients in SR (U=13, p=0.0006).

After surgery, there were no differences in STM scores (χ^2=1.6, p=0.44). Significant differences were found in CLTR (χ^2=10.59, p=0.005) and SR (χ^2=24.70, p<0.0001), and Mann–Whitney tests showed that left TLE patients were impaired in CLTR (U=83.5, p=0.001) and SR (U=17, p<0.0001) compared to controls, and in CLTR (U=33, p=0.02) and SR (U=21.5, p=0.003) compared to right TLE patients.

In left TLE patients, separate Wilcoxon tests did not show any differences between preoperative and postoperative test scores (STM: z=–1.34, p=0.17; CLTR: z=–0.59, p=0.55; SR: z=–0.36, p=0.71; MDT: z=–1.26, p=0.20). Likewise, no difference was found in right TLE patients (STM: z=–1.61, p=0.10; CLTR: z=–1, p=0.31; SR: z=–0.11, p=0.90; MDT: z=–1.26, p=0.21).

Visual neuropsychological tests

Preoperative comparisons showed differences in STM (χ^2=12.60. p=0.001), RCF (χ^2=7.43, p=0.02) and MDT scores (χ^2=10.34, p=0.005), and no difference in CLTR (χ^2=4.25, p=0.12). Left TLE patients were impaired in STM (U=98, p=0.004), RCF (U=128, p=0.03) and MDT (U=107.5, p=0.009) compared to controls. Right TLE patients were impaired in STM (U=101, p=0.005), RCF (U=124, p=0.02) and MDT (U=113.5, p=0.01) compared to controls. No difference was found between the two patient groups.

After surgery, between-group difference was found in STM (χ^2=10.67, *p*=0.004) and Mann–Whitney test showed that right TLE patients were impaired compared to controls (*U*=93, *p*=0.003). Between-group differences in RCF (χ^2=1.19, *p*=0.55) and MDT (χ^2=3.01, *p*=0.22) disappeared.

In left TLE patients, postoperative MDT scores increased compared to preoperative scores (*z*=–2.20, *p*=0.02), while no change was found in STM (*z*=–1.52, *p*=0.12), CLTR (*z*=–1.40, *p*=0.16) and RCF (*z*=–1.71, *p*=0.08). In right TLE patients, there was no change in STM (*z*=–0.13, *p*=0.89), CLTR (*z*=–0.73, *p*=0.46), RCF (*z*=–0.28, *p*=0.78) and MDT scores (*z*=–0.41, *p*=0.68).

Other neuropsychological tests

Kruskall–Wallis one-way ANOVA showed no difference between patients and controls in terms of general intelligence (as expressed by Raven’s Coloured Progressive Matrices) during the preoperative (χ^2=2.76, *p*=0.25) or postoperative evaluation (χ^2=0.91, *p*=0.63). Attentive Matrices scores were different during the preoperative evaluation (χ^2=7.33, *p*=0.02) due to lower scores in right TLE patients compared to controls (*U*=101.5, *p*=0.006); the difference disappeared after surgery (χ^2=3.74, *p*=0.15).

Determinants of postoperative memory

Separate factor analyses of preoperative and postoperative memory scores obtained by TLE patients provided two factors: Visual Memory and Verbal Memory (Table 5). Postoperative Visual Memory was associated with preoperative Visual Memory, side of tumour and education. Postoperative Verbal Memory was associated with preoperative Verbal Memory, side of tumour, education, age and age of seizure onset (Table 6).

Table 5 Factor structure of the memory battery

	Preoperative factors		Postoperative factors	
	Visual Memory	Verbal Memory	Visual Memory	Verbal Memory
Short-term Memory	0.88		0.82	
Design Learning	0.58		0.85	
Rey Figure	0.58		0.87	
Distractor Test	0.82		0.76	
Short-term Memory		0.45		0.72
Word Learning		0.89		0.82
Short Story		0.92		0.87
Distractor Test		0.57		0.71

Table 6 Regression analyses of postoperative memory factors

	Postoperative Visual Memory			Postoperative Verbal Memory		
	R^2	*F*	*p*	R^2	*F*	*p*
Preoperative Visual Memory	0.42	15.85	0.0006	0.03	0.64	0.43
Preoperative Verbal Memory	0.007	0.16	0.69	0.59	31.98	<0.0001
Age of seizure onset	0.03	0.60	0.44	0.29	9.10	0.006
Disease duration	0.03	0.65	0.43	0.0002	0.004	0.94
Age	0.09	2.22	0.15	0.34	11.47	0.002
Education	0.22	6.33	0.02	0.19	5.19	0.03
Side of tumour	0.16	4.13	0.05	0.38	13.34	0.001
Location of resection	0.01	0.27	0.61	0.003	0.06	0.81
Postoperative interval	0.12	3.11	0.09	0.004	0.09	0.76
Clinical outcome	0.06	1.43	0.24	0.05	1.07	0.31

Discussion

Consistent with the opinion that verbal tests can predict the side of epileptic focus [8], we found that patients with TLE and low-grade tumour on the left side had significant verbal memory deficits with respect to healthy subjects and patients with right TLE and tumour. Verbal tests exploring long-term memory and recall after interference proved to be more accurate in picking up deficits than STM tests, and delayed verbal recall (as expressed by SR) significantly discriminated left TLE with respect to right TLE. Conversely, there was no difference between left and right TLE patients in visual memory tests, possibly due to the fact that most visual items can be verbalised and may involve encoding functions of both temporal lobes [45].

In most patients, postoperative learning and memory performance subserved by the operated temporal lobe remained unchanged, and mean postoperative scores for all tests were not significantly lower than preoperative scores. On the other hand, in many patients there was postoperative improvement in memory abilities subserved by the unoperated temporal lobe, as expressed by individual changes and increase of mean test scores (e.g., STM, RCF and MDT scores in left TLE patients). The fact that the resected tissue was a tumour possibly played a role in determining the satisfactory memory outcome in our patients, in line with previous documentation that the surgical removal of pathological tissue induces less severe memory deficits than the removal of normal tissue [10, 46–49]. Our findings are also consistent with previous indications that selective temporal lobe resection induces less memory deficits than extensive resection [50] and is often accompanied by improvement in memory [51, 52] and other cognitive functions [6, 25, 53]. In particular, the improvement of memory abilities subserved by the unoperated temporal lobe extends the results of studies concerning lesionectomy for temporal lobe tumour [22], anterior temporal lobectomy [6, 24, 54], amygdalo-hippocampectomy [25] and corticoamygdalectomy [53]. Milner [55] suggested that postoperative cognitive improvement reflects non-specific enhancement of brain function, in keeping with the fact that intelligence improves following temporal lobe resection [24, 54]. A more specific explanation is that the reduction of discharges propagated from the epileptic region to contralateral temporal lobe areas, via the anterior commissure and corpus callosum, allows the improvement of memory functioning [24].

Our results show that, in TLE associated with low-grade brain tumour, preoperative memory performance is the main predictor of postoperative performance, even though side of resection, age, education and age of disease onset were also proven to predict memory outcome. The relation we found between postoperative and preoperative memory factors indicates that higher preoperative performance may be associated with better outcome than low preoperative performance. This confirms the idea that preoperative neuropsychological evaluation can to some extent predict outcome (as expressed by the adequacy model hypothesis) [26], although other studies reported the greatest risk for memory loss in patients with the most intact memory functions [14, 28, 29, 56, 57]. In our patients, the positive relation between postoperative and preoperative performance was possibly related to the nature of the lesion (i.e., low-grade tumour), whose long biological history may allow cognitive compensatory mechanisms, as well as to patients' young age and good education [29, 56].

As regards the age of seizure onset, we found better postoperative performance in patients with late onset than in those with early onset, arguing that a late onset may permit long-lasting normal cognitive functioning with greater chance of memory recovery after circumscribed brain damage. By contrast, previous studies described minor memory loss in patients with early onset [28]. In that case, the long-standing disruption of brain activity due to seizures can result in reorganisation of brain functions and development of compensatory abilities, preventing the deficits expected as a consequence of surgery [56].

Usually, patients who achieve good seizure control have milder postoperative memory deficits than those who continue to have frequent postoperative seizures [24, 29]. In our patients, despite a significant clinical improvement, memory outcome was not related to seizure outcome. It may be that, in patients with TLE and low-grade tumour, the role played by clinical outcome is surpassed by other factors (e.g., persistent drug therapy, subclinical epileptic discharges, age, education).

Learning and memory impairment or improvement are usually significant in the first postoperative month [27], while improvement can slowly continue successively [29]. In our cases, the postoperative reassessment was carried out after the acute postoperative period (at a mean interval of 11 months in left TLE patients and eight months in right TLE patients), when memory changes became mild, and this may explain the lack of relation between postoperative memory abilities and the duration of postoperative interval.

In conclusion, our study shows that, in selected TLE patients, the resection of a low-grade tumour does not necessarily induce serious memory loss and may allow improvement of memory abilities subserved by contralateral temporal lobe regions. Memory outcome is related to different variables, the most important of which is preoperative memory functioning. These preliminary findings suggest a distinction of memory prognosis in patients with TLE and low-grade tumour with respect to patients with drug-resistant cryptogenic TLE, as well as implications of a competence-related paradigm of memory assessment.

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