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CAROLINA BARRETO RODRIGUES GONÇALVES

Presurgical Evaluation of Memory Function in Epilepsy Patients

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Trabalho realizado sob a orientação de:

PROFESSORA DOUTORA MARIA ISABEL JACINTO SANTANA

DOUTORA ANA RITA DE BRITO MACHADO

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Presurgical Evaluation of Memory Function in Epilepsy Patients

Carolina Barreto Rodrigues Gonçalves[1]

Professora Doutora Maria Isabel Jacinto Santana[1, 2]

Doutora Ana Rita de Brito Machado[2]

[1] Faculdade De Medicina, Universidade De Coimbra, Portugal

[2] Serviço de Neurologia do Centro Hospitalar e Universitário do Hospital de Coimbra

Carolina Barreto Rodrigues Gonçalves
carolinabrgoncalves@hotmail.com

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Abstract

Introduction: Temporal lobe epilepsy is the most common form of refractory focal epilepsy and can be treated with resection of the seizure onset zone. Surgery carries a risk of memory impairment and patients undergo preoperative evaluation to determine the location of seizure onset zone and predict postoperative memory decline. It has not been established which specific methods are the most accurate for this purpose. Neuropsychological assessment can contribute to the lateralization of seizure focus and risk prediction. Functional magnetic resonance imaging (fMRI) can localize or lateralize memory and predict its postoperative decline. However, a standardized fMRI memory paradigm does not yet exist.

Objectives: Our aim was to compare the performance in a memory fMRI paradigm with results obtained from neuropsychological testing, considering the epileptic focus lateralization determined by video-EEG and structural MRI in patients with temporal lobe epilepsy proposed for surgical treatment.

Methods: Ten epilepsy patients with refractory temporal lobe epilepsy underwent a presurgical evaluation protocol, including structural MRI, video-EEG, neuropsychological assessment, and an experimental word-recognition fMRI paradigm. The fMRI determined the lateralization index (LI) of verbal memory.

Results: Three of the ten studied patients presented a clear right lateralization of verbal memory, two had a borderline score and five showed left lateralization. We compared these results with the ones obtained from the other tests. The LI confirmed the lateralization of verbal memory in the cases in which there were discrepancies between said tests, determining whether patients could be proposed for surgery. We found that the performance in the fMRI paradigm correlated significantly with several verbal memory and language tasks in the neuropsychological evaluation. There was also an unexpected correlation with a visual memory test, although this test can be easily verbalized.

Conclusions: Our study was too small for definitive conclusions. However, it seems that this fMRI paradigm can be used to reliably determine verbal memory lateralization within the context of pre-surgical evaluation of temporal lobe epilepsy. We propose a larger study comparing healthy controls and patients with epilepsy to test this paradigm and confirm our results.

Keywords: epilepsy; fMRI; verbal memory.

Resumo

Introdução: A epilepsia do lobo temporal é a forma mais comum de epilepsia focal refractária e pode ser tratada com a ressecção da zona do foco epiléptico. A cirurgia acarreta o risco de perda de memória e os doentes são submetidos a uma avaliação pré-operatória para determinar a localização do foco epiléptico e prever a diminuição pós-operatória da memória. Não está estabelecido quais os métodos mais precisos para este objectivo. A avaliação neuropsicológica pode contribuir para a lateralização do foco epiléptico e para a previsão do risco. A ressonância magnética funcional (fMRI) consegue localizar ou lateralizar a memória e prever a sua diminuição pós-operatória. Contudo, ainda não existe um paradigma de fMRI da memória padronizado.

Objectivos: O nosso objectivo foi comparar o desempenho no paradigma da fMRI da memória com os resultados obtidos na avaliação neuropsicológica tendo em conta a lateralização do foco epiléptico determinada pelo vídeo-EEG e pela ressonância magnética estrutural em doentes com epilepsia do lobo temporal propostos para cirurgia.

Métodos: Dez doentes com epilepsia do lobo temporal refractária foram submetidos a protocolo de avaliação pré-operatória que incluía ressonância magnética estrutural, vídeo-EEG, avaliação neuropsicológica e um paradigma experimental de fMRI da memória. A fMRI determinou o índice de lateralização da memória verbal.

Resultados: Três dos dez doentes estudados apresentavam uma clara lateralização da memória verbal à direita, dois tinham um índice em valores limite e cinco mostravam lateralização à esquerda. Comparámos estes resultados com os obtidos nos outros exames complementares. O índice de lateralização confirmou a lateralização da memória verbal nos casos em que havia discrepâncias entre os exames complementares, determinando se os doentes poderiam ser propostos para cirurgia. Observámos que o desempenho no paradigma de fMRI se correlacionava significativamente com vários dos testes de memória verbal e linguagem da avaliação neuropsicológica. Havia também uma correlação inesperada com um teste de memória verbal, embora este teste possa ser facilmente verbalizado.

Conclusões: O nosso estudo foi demasiado pequeno para conclusões definitivas. Não obstante, parece que este paradigma de fMRI pode ser usado para determinar com confiança a lateralização da memória verbal na avaliação pré-operatória de doentes com epilepsia do lobo temporal. Propomos um estudo mais alargado comparando controlos saudáveis com doentes com epilepsia para testar este paradigma e confirmar os nossos resultados.

Introduction

Epilepsy is a chronic neurological disorder with a prevalence of up to 1% in the general population (1, 2). One-third of patients have pharmacoresistant epilepsy, and, of these, over two-thirds have focal epilepsy (1, 3). Temporal lobe epilepsy is the most common form of focal epilepsy (2, 4). Refractory temporal lobe epilepsy may be treated with surgical removal of seizure onset zone with a success rate between 60 and 80% (3-8). The temporal lobe and hippocampus play an important role in memory encoding and, therefore, memory impairment is common in these patients both before and as a consequence of surgery (2, 5, 8). Verbal and visual memories are affected differently. Verbal memory is more affected by focal epilepsy and consequent surgery on speech-dominant hemisphere (7). Visual memory is affected after surgery on the nondominant hemisphere, although less consistently (4, 8). As such, it is essential to perform a complete preoperative patient evaluation that includes a detailed clinical history, electrophysiologic testing (EEG), neuroimaging (MRI) and neuropsychological testing. The main objectives of this evaluation are to determine the seizure onset zone localization with the greatest precision, to investigate possible associated lesions, and to predict postoperative cognitive decline. Importantly, this preoperative assessment provides information regarding indication for surgery and potential associated postoperative clinical risks (4).

The prediction of postoperative memory decline can be based on neuropsychological testing, functional MRI (fMRI) or on invasive methods, such as the intracarotid sodium amobarbital procedure (Wada test), a test more rarely used in recent years (4, 6, 9). Currently, there is not a clear consensus on which specific methods are the most accurate to predict postoperative memory decline. Neuropsychological testing can identify a selective visual or verbal memory deficit, thus contributing to the lateralization of seizure focus. Also, characterization and quantification of such deficit is a functional prognostic indicator of postoperative memory decline (4, 9). The Wada test implies the performance of a cerebral angiography with the risks associated with an invasive procedure. It is an exam with limitations on reproducibility and that can have false positives. In the last decade, clinical indications for performing the Wada test have considerably decreased, mostly due to the emergence of non-invasive methods of functional cortical mapping, such as fMRI (2, 6, 9-12).

fMRI is a non-invasive technique that can be used to localize or lateralize important brain functions and predict postoperative outcome of such functions, such as language and verbal and visual memories, regardless of the type of lesion or side of epileptic focus (4, 5, 13, 14). fMRI can also determine localization or lateralization of dysfunction, which might indicate a functional deficit area or the seizure onset zone (5, 12). Currently, it is the method of election for language localization. The Wada test can be used to lateralize language, but not localize, a clear advantage of fMRI. Regarding memory, the capacity of the Wada test to predict postoperative memory decline is controversial (9). As such, recent work has focused on the research of fMRI paradigms for the study of verbal and visual memory. Material-specific encoding paradigms that mainly activate the speech-dominant (verbal) and nondominant (visual) hemispheres have been investigated to predict memory decline after epilepsy surgery (7). Several studies have investigated absolute rather than asymmetric activations using language lateralization index (LI) within the medial temporal lobe (MTL) with mixed results (15, 16). To date, the majority of studies has only investigated lateralization of absolute activations within the MTL (11, 14, 17). Recently, it has been demonstrated that frontal and temporal activations are involved in verbal memory formation, suggesting that preoperative extratemporal activations may play a role in predicting verbal memory decline after epilepsy surgery (7, 18). The problem remains that there is not a standardized fMRI memory paradigm established (2, 5, 10). Different studies use different approaches and tasks (5, 8, 9). Depending on the type of memory the task requires, the areas of activation in fMRI will vary. fMRI's predictive value varies with different protocols (5). The heterogenicity in these studies is one of the reasons why there is not a consensus on which methods are better predictors of postoperative memory decline (4). However, recent evidence has concluded that the combination of fMRI, side of epileptic focus and preoperative verbal memory score correctly predicted verbal memory decline in 90% of patients, while the Wada test was not able to predict changes in either verbal or nonverbal memory (13).

The present work aims to compare the performance on neuropsychological testing with the results of the application of a memory fMRI paradigm. This will allow in the future to propose a memory fMRI method within the protocol of presurgical epilepsy evaluation for predicting postsurgical memory decline in individual patients.

Methods

Subjects

We enrolled ten consecutive patients with medically refractory epilepsy undergoing presurgical evaluation at the Neurology Department at Coimbra Hospital and University Centre (CHUC). The median age of this group is 40 years, ranging from 21 to 53 years, and six patients were males. All patients were native Portuguese speakers and were under anti-epileptic pharmacological treatment. Per protocol, they perform clinical and neuropsychological assessments, prolonged ictal and interictal EEG-video, structural MRI and functional MRI. Handedness was determined using the Edinburgh Handedness Inventory (19) and the Finger Tapping and Grooved Pegboard tests and 9 in 10 patients were classified as right-handed.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Commission of Faculty of Medicine of the University of Coimbra. Written informed consent was obtained from all patients.

Neuropsychological testing

All patients underwent a standardized cognitive assessment, including the Montreal Cognitive Assessment (MoCA) and the Clock Drawing Test (CDT) as screening tools as well as the Battery for Neuropsychological Assessment of Adults with Epilepsy (20), which is a comprehensive battery composed by several instruments that assess various cognitive functions: The Wechsler Memory Scale (WMS) (21); visual attention and processing were assessed with the Toulouse-Piéron Test (22), the Stroop Color-Word Test (23), and the Trail Making Tests A and B (24); visuospatial skills were assessed with the Judgement of Line Orientation test (25) and copying tasks (cube, house, and flower); Luria's graphomotor sequences (26) assessed task switching; language was assessed using the Token Test (27), a naming task (food items and animal names), and a writing task in the form of a letter; non-verbal reasoning was assessed using Raven's Progressive Matrices (28). All tests were adapted and validated for the Portuguese population.

From this battery and for this specific study, we selected tests that evaluate different modalities of memory, namely the Digit Span and Mental Control subtests of the WMS to assess short-term memory, Trail Making Tests A and B for working memory and the immediate and delayed recall of the Associate Learning subtests, Logical Memory and Visual Reproduction (WMS) that assess episodic memory. We also considered the Token Test as an instrument of evaluation of complex verbal comprehension and, therefore, as an indication of patients' language performance.

Magnetic resonance data acquisition

We used a 3T Siemens TimTrio MRI scanner. Gradient-echo echoplanar images provided blood oxygen level-dependent contrast. Each volume comprised 52 contiguous oblique axial slices, slice thickness 2.5 mm, field of view (FOV) 24 cm, matrix 96 x 96 and in-plane resolution 2.5 mm x 2.5 mm.

Echo time (TE) was 25 ms and repetition time (TR) was 2.75 s. The field of view was positioned to cover the temporal and frontal lobes with the slices aligned with the long axis of the hippocampus.

Memory encoding paradigm

A total of 100 concrete nouns were visually presented. The words were presented for 3 seconds each in 30-second blocks of 10 words, followed by 15-second crosshair fixation. A 3-second interval between stimuli differed from the repetition time of 2.75 seconds, introducing jitter and ensuring random sampling. Patients were told to memorize the words for later recall testing. For the deep encoding task, patients had to deem each item pleasant/unpleasant using a joystick. In the recognition task after scanning, patients were shown the previous 100 words mixed with 50 new words. Each word was indicated as recognized/not-recognized using a button box. True positives, false positives and recognition accuracy (true positives – false positives) were calculated based on patients' answers.

VBM data analysis

The T1 weighted images were processed using SPM8 (Statistical Parametric Mapping) version (http://www.fil.ion.ucl.ac.uk/), in order to perform Voxel-Based Morphometry (VBM) analyses. Every scan was aligned, normalized into standard anatomical space and smoothed with an 8-mm full-width at half maximum Gaussian kernel.

We used an event-related design to compare encoding-related responses to individual stimuli that were subsequently remembered. For each subject, delta functions of words recognized were convolved with the canonical hemodynamic response and its temporal derivate.

Using the WFU PickAtlas in SPM8, we produced an anatomical mask incorporating frontal and medial temporal lobes (amygdala, parahippocampal gyrus, hippocampus, middle and inferior frontal gyri). A bootstrap method was used to calculate the Verbal Memory Lateralization Index (LI) within the frontotemporal mask in all patients using the SPM8. A LI of ≥ 0.5 or ≤ 0.5 was deemed strongly left- or right-lateralized, respectively.

Data analysis

The statistical analysis of demographic and clinical results was performed by using IBM SPSS Statistics, version 23.0. Exploratory correlations with LI, true positives, false positives and recognition accuracy were investigated using a Spearman's rank correlation coefficient.

Results

Demographic and clinical data

As observed in Table 1, the age of onset of epilepsy ranged from 7 months to 29 years (mean: 16.0) and the duration of disease ranged from 8 to 51 years (mean: 21.9). All patients were receiving two or more antiepileptic drugs. Prolonged interictal and ictal EEG-video revealed different paroxysmal activity patterns: left temporal (4), right temporal (3), right occipital and frontotemporal (1), bilateral frontotemporal (1), and left frontotemporal (1). Structural MRI demonstrated different structural lesions at seizure onset zone: left mesial sclerosis (2), bilateral mesial sclerosis (2), right mesial sclerosis (2), left temporal heterotopia (1), right occipital heterotopia (1), left temporal post-surgical residual dysembryoplastic neuroepithelial tumor (DNET) (1). No structural defects were observed in one patient with left temporal paroxysmal activity. All but two patients had concordant findings in the EEG-video and structural MRI (patients 4 and 7). Patient 4 presented bilateral mesial sclerosis on neuroimaging but only showed right temporal paroxysmal activity and patient 7 had no evident lesions on MRI but showed left temporal paroxysmal activity.

Neuropsychological performance

The results of the standardized cognitive tests used to assess the 10 epilepsy patients are shown in Table 2. On the MoCA, patients scored an average of 19.3 points (range: 13 to 26). The Clock Drawing Test averaged at 15 points (range: 6 to 18). In the Digit Span task, patients repeated, on average, 5.3 digits (range: 3 to 7) in direct order and repeated, on average, 3.5 digits (range: 2 to 5) in inverse order. The Mental Control test averaged at 5.4 points (range: 3 to 7), but Patient 2 had not performed this task. Patients took an average of 49.2 seconds (range: 22 to 109) to complete the Trail Making Test A and made no errors. In the Trail Making Test B, patients needed an average of 163.2 seconds (range: 79 to 355) to complete it and made an average 1.2 mistakes (range: 0 to 3). The Associative Learning test had an average score of 14.75 points (range: 7.5 to 20.5) in the immediate recall and an average score of 8.7 (range: 6.5 to 10) in the delayed recall. In the Logical Memory test, patients scored, on average, 7.1 points (range: 2.5 to 14) on the immediate recall and 5.15 points (range: 1 to 12) on the delayed recall. The Visual Reproduction test had an average score of 12.8 points (range: 9 to 15) on the immediate recall and an average score of 10.1 points (5 to 14) on the delayed recall. In the Token Test, patients scored an average of 20.65 points (range: 17.5 to 22). The Naming task averaged at 27 words (range: 19 to 30).

Six patients presented scores in the Logical Memory test (both immediate and delayed recall) of more than one negative standard deviation. Another patient only had such a score in the delayed recall of the test. These results point to defects in verbal memory.

In the Visual Reproduction test, only one patient had a negative standard deviation higher than one, in the delayed recall. Nevertheless, this patient’s score in the immediate recall was of more than one positive standard deviation.

Table 1 - Patients demographic and clinical characteristics

Subject	Age (years)	Gender	Handedness	Education	Age of disease onset (years)	Duration of disease (years)	Seizure classification	Seizure frequency (per month)	EEG	MRI	Antiepileptic treatment (mg/day)
1	38	M	Right	9	18	20	Focal onset with impaired awareness	2-3	right occipital and frontotemporal PA	right occipital subcortical focal heterotopia	VPA 3000 ZNS 300
2	53	F	Right	4	20	33	Focal automatisms with impaired awareness	1-2	left temporal PA	left temporal subcortical focal heterotopia	ZNS 300 ESL 800 LTG 300 PRP 3
3	52	M	Right	6	7 (months)	51	Focal onset impaired awareness and generalized tonic-clonic	4	left temporal PA	left mesial sclerosis	CBZ 1200 VPA 1500 ZNS 300
4	23	M	Left	12	15	8	Focal onset with impaired awareness and generalized tonic-clonic	1	right temporal PA	bilateral mesial sclerosis	LTG 200 CBZ 1200
5	39	F	Right	7	29	10	Generalized tonic-clonic generalized atypical absence	16-36	bilateral temporal and frontal PA	bilateral mesial sclerosis	MCB 450 LTG 250 VPA 2000
6	48	M	Right	11	29	19	Focal onset with impaired awareness	3	left fronto-temporal PA	left mesial sclerosis	CBZ 1400 VPA 1500 LVT 2500
7	42	F	Right	9	14	28	Focal onset with impaired awareness	8	left temporal PA	No structural defects	ZNS 300 ESL 800
8	21	F	Right	12	3	18	Focal automatisms with awareness	8-12	right temporal PA	right mesial sclerosis	LVT 2500 CBZ 800
9	32	M	Right	9	10	22	Focal automatisms with impaired awareness	4	right temporal PA	right mesial sclerosis	VPA 2000 LCS 400 LVT 2000 PRP 6
10	31	M	Right	9	21	10	Focal automatisms with impaired awareness	2	left temporal PA	left temporal residual DNET	ESL 1600 VPA 500

Characteristics of the patient group were age, gender, handedness, education, age of disease onset, duration of disease, seizure classification, seizure frequency, EEG, MRI, and antiepileptic treatment. CBZ = carbamazepine; DNET = dysembryoplastic neuroepithelial tumor; EEG = electroencephalography; ESL = eslicarbazepine acetate; F = female; LCS = Lacosamide; LTG = Lamotrigine; LVT = levetiracetam; M = male; MCB = Moclobemide; MRI = magnetic resonance imaging; PA = paroxysmal activity; PRP = Perampanel; VPA = valproic acid; ZNS = Zonisamide.

Table 2 - Neuropsychological data for the 10 patients

Subject	MoCA	CDT	DS (Dir.)	Z score	DS (Inv.)	Z score	MC	Z score	TMT A (seconds /errors)	Z score	TMT B (seconds/ errors)	Z score	AL (I)	Z score	AL (D)	Z score	LM (I)	Z score	LM (D)	Z score	VR (I)	Z score	VR (D)	Z score	Token Test	Z score	Naming	Classification (pattern of deficits)
1	17/30	14	3	-1.96	3	-0.87	3	-2.01	62"/0	-1,62	178"/0	-1,89	10	-2,26	6,5	-2,73	5	-1,73	3	-1,96	13	0,77	13	0,75	19,5/22	-1,13	21/30	left neocortical
2	13/30	14	4	-0.92	4	-0.16	N/A	N/A	109"/0	-4.19	295"/1	-3.87	7,5	-1,36	7,5	-2.45	4	-1,45	2,5	-2.18	9	1,48	7,5	-0.62	20/22	0,8	19/30	left neocortical and mesial
3	19/30	16	5	-0.08	3	-1.21	7	0.46	76"/0	-1.99	355"/3	-5.12	11	-1,6	8	-1.47	7	-1,97	5,5	-1.18	13	2,23	13	1.27	19,5/22	0,16	30/30	left neocortical and mesial
4	26/30	17	6	-0.21	5	-0.22	4	-1.79	32"/0	1,04	79"/1	-0,02	17	-1,19	9,5	-1,78	11,5	-0,21	10,5	-0,2	14	0,73	11	-0,74	21,5/22	-1,06	30/30	normal
5	17/30	6	7	0.88	4	-0.26	6	-0.39	34"/0	0,81	173"/3	-1,32	17,5	0,59	10	0,93	3	-2,34	3	-2,02	12	0,84	7,5	-0,62	21,5/22	0,53	24/30	normal
6	20/30	16	6	-0.06	5	0.29	7	0	22"/0	1,25	79"/1	-0,04	18,5	0,28	8,5	-1,65	10,5	-0,35	7	-0,97	14	0,49	10,5	-0,56	21,5/22	0,53	28/30	left mesial
7	17/30	15	4	-1.25	2	-1.49	7	0.16	50"/0	-0,26	166"/2	-1,17	17	0,46	8,5	-1,1	8	-0,62	5,5	-1,18	11	0,43	8,5	-0,28	17,5/22	0,2	28/30	left mesial
8	23/30	17	7	0.55	4	-1.01	6	-0.25	30"/0	1,24	81"/0	-0,11	20,5	0,92	10	0,39	14	0,64	12	0,25	14	0,73	14	0,82	22/22	0,46	30/30	normal
9	19/30	16	5	-0.54	3	-0.87	4	-1.47	47"/0	-0,17	134"/1	-0,65	9,5	-2,42	9	-0,3	5,5	-1,55	1	-2,64	15	1,48	5	-1,38	22/22	0,75	30/30	bilateral mesial
10	22/30	18	6	0.17	2	-1.49	5	-0.93	30"/0	1,48	92"/0	0,53	19	0,53	9,5	0,18	2,5	-2,62	1,5	-2,47	13	0,77	11	0,22	21,5/22	0,38	30/30	left mesial

AL = associative learning; CDT = clock drawing test; D = delayed; Dir. = direct; DS = digit span; I = immediate; Inv. = inverse; LM = logical memory; MC =mental control; MoCA = Montreal cognitive assessment; N/A = not available; TMT = trail making test; VR = visual reproduction.

Neuropsychological assessment allowed us to obtain a classification of each individual patient dysfunction pattern: left mesial (3), left neocortical and mesial (2), left neocortical (1), and bilateral mesial (1). Three patients showed no cognitive dysfunction, according to this evaluation.

fMRI memory paradigm data

Table 3 - Results of the fMRI memory paradigm

Subject	LI	Words Remembered	False Positives	Recognition accuracy
1	0,72	56	5	51
2	0,54	56	16	40
3	0,32	65	12	53
4	0,75	92	3	89
5	0,67	75	35	40
6	0,41	79	7	72
7	0,052	53	18	35
8	0,79	94	11	83
9	0,95	93	13	80
10	0,54	92	31	61

LI = lateralization index; Recognition accuracy = Words Remembered – False Positives

According to the results presented in table 3, 5/10 patients had a LI clearly indicative of left hemisphere dominance; in 2 patients the LI may be considered borderline; 3 had right lateralization of verbal memory. During the word recognition task, patients remembered an average of 75.5 words (range: 53 to 94), but there was an average of 15.1 of false positives (range: 3 to 35). The recognition accuracy, calculated as words remembered - false positives, averaged at 60.4 (range: 35 to 89).

Overall assessment

Table 4 - Patient assessments

Subject	EEG	Structural MRI	Neuropsychological assessment	LI
1	right occipital and frontotemporal PA	right occipital subcortical focal heterotopia	left neocortical pattern	0.72
2	left temporal PA	left temporal subcortical focal heterotopia	left neocortical and mesial pattern	0.54
3	left temporal PA	left mesial sclerosis	left neocortical and mesial pattern	0.32
4	right temporal PA	bilateral mesial sclerosis	Normal	0.75
5	bilateral fronto-temporal PA	bilateral mesial sclerosis	Normal	0.67
6	left fronto-temporal PA	left mesial sclerosis	Left mesial pattern	0.41
7	left temporal PA	No structural defects	Left mesial pattern	0.052
8	right temporal PA	right mesial sclerosis	Normal	0.79
9	right temporal PA	right mesial sclerosis	bilateral mesial pattern	0.95
10	left temporal PA	left temporal DNET remainder	Left mesial pattern	0.54

The preoperative patient evaluation included structural MRI, EEG, neuropsychological assessment and calculation of verbal memory lateralization index using fMRI. DNET = dysembryoplastic neuroepithelial tumor; EEG = electroencephalography; LI = lateralization index; MRI = magnetic resonance imaging; PA = paroxysmal activity

When comparing the results of the different preoperative assessments, we found that they were entirely concordant in some cases while showing some discrepancies in others.

The LI demonstrated that three patients (patients 3, 6, and 7) had right lateralization of verbal memory. In these patients, the structural MRI, EEG and neuropsychological assessment all pointed to dysfunction on the left hemisphere. Therefore, the LI confirmed the dysfunction on the left hemisphere observed in the other exams.

Patients 2 and 10 both presented a LI of 0.54, which may be considered a borderline score. Both these patients showed left lesion and paroxysmal activity, along with a pattern of left dysfunction on the neuropsychological evaluation.

Three patients (4, 5 and 8) showed a high left LI as well as right paroxysmal activity, but the neuropsychological evaluation was normal. Patients 4 and 5 presented bilateral mesial sclerosis while patient 8 had right mesial sclerosis.

Finally, patients 1 and 9 both showed lesion and paroxysmal activity on the right hemisphere. The LI was congruent with the structural MRI and the EEG, but the neuropsychological evaluation diverged from these tests.

Exploratory correlations with results of fMRI memory paradigm

Table 5 - Correlations of lateralization index

	Lateralization Index	
	ρ	p
Words remembered	0.697	p<0.05
Token Test	0.748	p<0.05

ρ = Spearman's rank correlation coefficient; p = p-value

Table 6 - Correlations of words remembered (performance during the memory paradigm)

	Words remembered	
	ρ	p
MoCA	0.793	p<0.01
CDT	0.705	p<0.05
Token Test	0.940	p<0.001
Visual Memory (immediate)	0.813	p<0.01
Associative Learning (delayed)	0.708	p<0.05
Naming	0.725	p<0.05
TMT-A	-0.682	p<0.05
TMT-B	-0.657	p<0.05

ρ = Spearman's rank correlation coefficient; p = p-value

Table 7 - Correlations of false positives (intrusions/confabulations)

	False positives	
	ρ	p
Logical Memory (immediate)	-0.673	p<0.05

ρ = Spearman's rank correlation coefficient; p = p-value

Table 8 - Correlations of recognition accuracy

	Recognition accuracy	
	ρ	p
MoCA	0.889	p<0.001
CDT	0.765	p<0.01
Visual Reproduction (immediate)	0.904	p<0.001
Naming	0.722	p<0.05
TMT-B	-0.707	p<0.05
Token Test	0.735	p<0.05

ρ = Spearman's rank correlation coefficient; p = p-value

We found that the LI correlated significantly with the number of words remembered during the fMRI paradigm and with the performance on the Token test. There was a significant correlation between the number of words remembered and the performances on the MoCA, Clock Drawing Test, Token test, Visual Memory (immediate), Associate Learning (delayed), and the Naming task, as well as an inverse correlation with the Trail Making Tests A and B. The number of false positives correlated inversely with the performance on the Logical Memory (immediate) test. The recognition accuracy had a significant correlation with the performances on the MoCA, Clock Drawing Test, the Visual Reproduction (immediate), the Naming task, and the Token Test, and presented an inverse correlation with the Trail Making Test B.

Discussion

This study was developed in patients proposed for surgery whose controversial presurgical evaluation limited surgical indication. From the start, these were complex patients, and this study will be important to pave the way for the use of this fMRI memory paradigm to compensate for the difficulty in performing the Wada test.

In that line, we observed that the LI obtained from the fMRI paradigm demonstrated right lateralization of verbal memory in three patients (patients 3, 6 and 7) who also showed lesions and paroxysmal activity on the left hemisphere in addition to a neuropsychological pattern of left temporal dysfunction. Thus, the LI confirmed the localization of epileptic focus evidenced by the MRI, EEG, and neuropsychological assessment. It also showed that the right temporal lobe was intact and compensating for the dysfunction of the left hippocampus. Therefore, left hippocampal resection could be performed safely without major memory sequelae.

Two patients (patients 2 and 10) presented a contradictory result between the LI and what was found on structural MRI, EEG, and neuropsychological evaluation. All these three tests pointed to left dysfunction, yet the patients had a LI of 0.54. Nonetheless, if we consider these LI results as borderline scores, indicative of left dysfunction as well, the index could corroborate once again the concordance between the other exams, supporting that left hippocampectomy is adequate for these patients.

The right lateralization of verbal memory presented in these five patients (patients 2, 3, 6, 7 and 10), instead of the classic left hemisphere lateralization, may result from functional reorganization away from seizure onset zone, as suggested by previous works. However, this would be a somewhat inadequate reorganization as neuropsychological dysfunction was still present in two of those patients (17, 29-31).

All the other patients presented strong left lateralization of verbal memory. Of these, three patients exhibited right paroxysmal activity and a normal neuropsychological assessment (patients 4, 5 and 8) Hence, the LI confirmed the integrity of the left hippocampus suggested by the neuropsychological evaluation, thus showing that these patients could undergo right hippocampal resection.

In the remaining two patients (patients 1 and 9), we observed a discrepancy between the neuropsychological assessment and LI results, in which the index (left lateralization) was congruent with the right localization of the epileptic focus demonstrated by the EEG and the structural MRI. In these cases, the LI is of greater value, indicating that the patients may be considered surgical candidates for right hippocampectomy.

Epilepsy surgery is associated with a risk of postsurgical memory decline. As such, it is vital to determine the location/dominance of cognitive functions. The accurate localization of these functions would allow for a precise prediction of memory decline in the cases of ambiguous location or overlap of function and dysfunction to carefully weigh the risks and benefits. In our study, the paradigm used allowed us to recommend most of the patients for surgery with greater confidence of a high probability of successful epilepsy treatment and a low risk of verbal memory decline. However, we also observed that the proposed score (0.50) of the verbal memory lateralization index may not be the most adequate. In fact, the fMRI paradigm used in this study was based on one idealized for a different population (7) and there is no evidence that it can be applied without adaptations to our population and culture.

When analyzing our fMRI paradigm according to neuropsychological performance, we found a predictable correlation between the LI and the number of words remembered. Likewise, we observed a correlation with the Token test, which assesses language, as it is a task of complex verbal comprehension. There was also an expected correlation between the performance on the verbal memory task performed in the MRI and neuropsychological tasks of high verbal coefficient (comprehension, naming, and word retrieval). However, we also found a less predictable correlation with a visual memory test, which can be explained by a verbal mechanism of encoding instead of a visual one as proposed by others (32, 33). There was also an inverse correlation with the Trail Making Tests A and B (both evaluating working memory and visual attention), which might be due to such tests also recruiting verbal functions, but this should be confirmed by studies with a larger sample. The false positives of the recall task had a predictable inverse correlation with the immediate recall in the Logical Memory subtest, as the later evaluates verbal memory and the former presents wrong recognitions. These results seem to suggest that the fMRI memory paradigm correlates with the neuropsychological testing of verbal memory and that it might be, therefore, appropriate for studying activations during encoding tasks to determine the precise location of verbal memory in future studies.

Our study had several limitations. The sample was small and heterogeneous so that there were numerous variables that could play a role in the final results. Further, larger studies, particularly comparing epilepsy patients and healthy controls, are needed to confirm these results and to establish the ideal score of the LI to use in our population and culture.

In conclusion, these preliminary results suggest that the LI paradigm should be considered to integrate a pre-surgical temporal lobe epilepsy protocol contributing to a successful epilepsy treatment and a low risk of verbal memory decline.

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