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## Severe amnesia following bilateral medial temporal lobe damage occurring on two distinct occasions

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**Abstract** A comprehensive neuropsychological assessment was performed on a 38-year-old woman with drug-resistant right temporal lobe epilepsy before temporal lobectomy, during a 2-year follow-up period, and approximately 3 years after surgery when she developed a malignant glioma in the left medial temporal lobe (MTL). Both before and after epilepsy surgery, memory function was normal. When the tumour was discovered, the patient suffered from severe retrograde and anterograde amnesia, whereas working memory and the other cognitive abilities were preserved. Compared with other cases of bilateral temporal lesion, this case is peculiar because the damage occurred on two distinct occasions. It suggests that only one MTL can allow normal memory function, or can take over the function normally subserved by a dysfunctional contralateral MTL when the dysfunction is marked and prolonged, such as in chronic epilepsy.

**Key words** Memory • Neuropsychological tests • Epilepsy surgery • Global amnesia • Temporal lobe epilepsy • Brain tumour

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### Introduction

Global amnesia is characterised by a severe loss of memory with relatively preserved cognitive abilities. It has been associated with selective damage to several brain regions, including the hippocampus, the mammillar bodies, the dorsal medial nucleus of the thalamus, the fornix and the pathways connecting them [1, 2]. Among the structures involved in this circuit, the medial temporal lobe (MTL) has been most frequently reported as bilaterally damaged in patients with global amnesia [3]. In almost all these patients the damage occurred on a single occasion, and it was due to various factors such as viral infections, anoxia, ischaemia, head injuries, surgery, etc. In this paper, we report the case of a young woman who underwent a right temporal lobectomy for medically refractory temporal lobe epilepsy (TLE) with an excellent seizure and neuropsychological outcome, who approximately 3 years later presented with a neoplastic lesion involving primarily the left MTL structures and rapidly developed severe global amnesia.

Due to its peculiarities, this case might also contribute to shed light on the issue of the possible contralateral reorganisation of memory processes subserved by the MTL structures chronically involved in epileptogenesis. Although the left and right MTLs are primarily involved in processing different types of material-specific information (i.e., verbal and visuospatial), their functions are at least partially bilaterally distributed, and they may present an ipsilateral or contralateral reorganisation [4]. While the literature on epilepsy surgery shows that patients undergoing surgical removal of one MTL can live without substantial memory impairment, less is known about how memory systems reorganise over the course of the illness and after surgery.

### Case report

Mrs. M.V. was a right-handed, 38-year-old female who was referred to our Epilepsy Surgery Unit for medically refrac-

tory partial seizures occurring since age 18. She was the product of an uncomplicated full-term pregnancy and delivery. She had no history of other medical illnesses including CNS infections, febrile convulsions or head injuries. The family history was negative for seizure disorders and other neurological or psychiatric diseases.

At 18 years of age, she began to notice brief paroxysmal episodes characterised by psycho-experiential symptoms (derealisation, depersonalisation, *déjà vu*) followed by rising epigastric sensation, fear, tachycardia and then behavioural arrest with loss of consciousness, oro-alimentary and right gestual automatisms. These episodes occurred weekly, lasted 1–2 min, and were followed by postictal confusion without apparent dysphasia. Many courses of various antiepileptic drugs were tried, without substantial improvement.

At the age of 38 the patient underwent a comprehensive presurgical protocol including neuropsychological and psychiatric assessment, magnetic resonance imaging (MRI) and video-EEG monitoring. Details about this protocol have been reported elsewhere [5]. The neuropsychological battery included several memory tests exploring verbal and visuospatial memory [6], as well as the WAIS-R, the Trail Making A and B, the Rey-Osterrieth Complex Figure Copy, the Benton Judgement of Line Orientation (Form H) and Raven's Coloured Progressive Matrices.

At admission, the neurological examination was unremarkable. Neuropsychological testing revealed a normal

IQ and no detectable cognitive deficits, as summarised in Table 1. A brain MRI (1.5-T Magnet) showed a small lesion in the right anterior mid-basal neocortical (T4 gyrus) temporal region (about 3 cm from the pole) compatible with a cavernous angioma. Video-EEG monitoring (Telefactor Corp, W. Conshohocken, PA) revealed irregular theta slowing and frequent spikes in the right anterior temporal regions. During the complex partial seizures recorded, the EEG showed a brief right anterotemporal focal flattening followed by 7 Hz rhythmic theta intermixed with a 2.5 Hz delta activity over the right temporal regions spreading over the ipsilateral suprasylvian regions. Based on anatomo-electro-clinical correlations, right TLE was diagnosed, with a likely early involvement of MTL structures in epileptic discharge. Consequently, a right lesionectomy plus corticectomy including MTL structures was offered and performed. Pathological examination of the lesion confirmed the diagnosis of cavernous angioma.

Regular follow-up visits were carried out 1, 12 and 24 months after surgery. Given that no seizures or auras were reported, after the third visit medication was gradually discontinued, with no subsequent seizure recurrences. The neuropsychological assessment was repeated 12 and 24 months after surgery and showed no substantial modifications, as reported in Table 1.

About 3 years after the intervention, she came again to our attention complaining of depression and continuously worsening memory difficulties. Clinical examination

**Table 1** Scores on neuropsychological tests over time

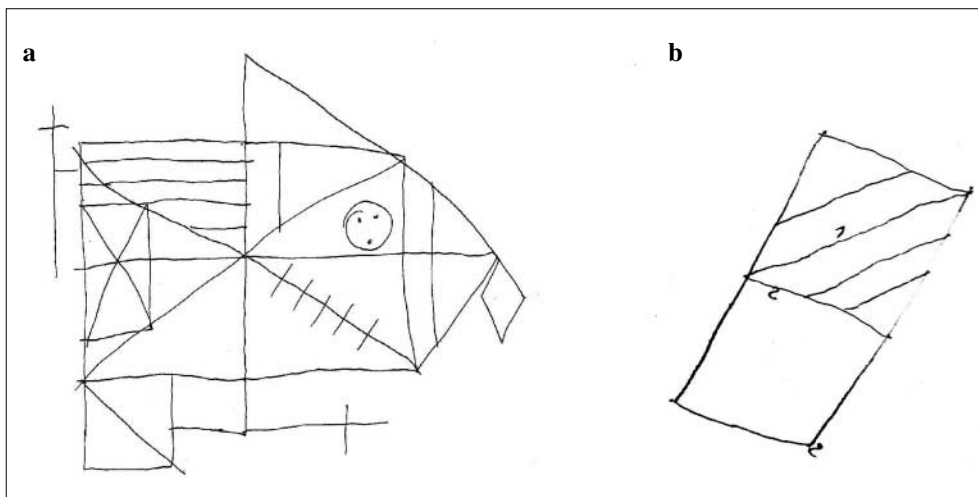
Neuropsychological tests	Presurgical evaluation for epilepsy surgery	One year after right temporal lobectomy	Two years after right temporal lobectomy	After about 3 years when a left medial temporal malignant glioma was discovered	One month after left temporal lesionectomy
WAIS					
VIQ	104	109	104	No	No
PIQ	97	95	113		
GIQ	100	102	109		
Trail making A	25"	22"	26"	24"	23"
Trail making B	67"	40"	58"	68"	65"
B-A	42"	18"	32"	44"	42"
Phonemic fluency	30	29	35	18	20
RAVLT					
Immediate recall	45.2	45.2	38.4	14.8	9.8
Delayed recall	10.2	10.1	9.1	0	0
Story recall					
Immediate recall	6.3	6.1	6.3	0	0
Delayed recall	5.7	6.1	6.1	0	0
Digit Span	5.5	5.5	5.5	4.5	4.5
Corsi Test	3.75	5.75	4.75	4.75	4.75
Figure of Rey					
Copy	34.1	34.1	33.4	34.4	34.4
Immediate recall	18.4	13.4	16.7	2.7	0
Delayed recall	15.1	11.1	17.4	0	0
Benton Test-Judgment of Line Orientation	30	30	30	30	30
Coloured Progressive Matrices of Raven	34	32.5	33.5	33	32.5

revealed very severe retrograde amnesia, with a lack of memory for public events, famous people and autobiographic information extending for decades. She was unable to recognise her neurologist, who had treated her for many years, and she was even unaware that she had suffered from epilepsy and had been surgically treated. Also, she did not remember why she had just been hospitalised. While the patient was able to recall the names of her two children, she was unaware of being married and did not know her husband's name. Nevertheless, she knew her date of birth and was able to recall some events that occurred in infancy and adolescence. Aside from the very severe memory disturbance, her neurological examination was unremarkable. In order to reduce the patient's burden, the neuropsychological evaluation was slightly shortened as compared with previous assessments. Intellectual abilities were assessed with Raven's Coloured Progressive Matrices only, while language (i.e., naming and comprehension) was not specifically tested as the clinical examination revealed no substantial impairment. As summarised in Table 1, the neuropsychological evaluation showed a severe impairment of long-term memory for both visuospatial and verbal information (e.g.,

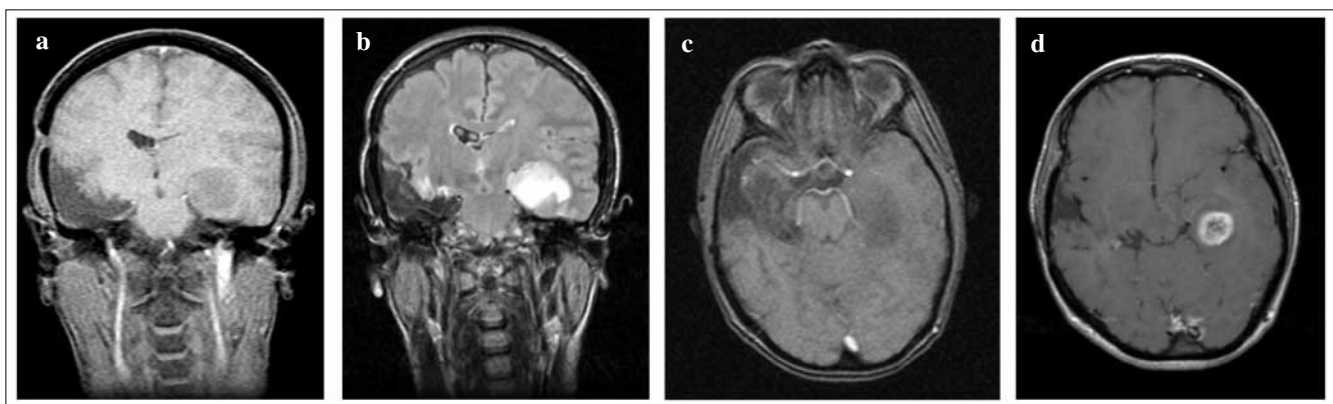
Fig. 1). On the contrary, working memory and attention were not compromised, and the sensory-motor, intellectual, perceptual abilities and constructive praxes were also well preserved. The anterograde memory performance was so severely compromised that already after a few minutes the patient did not even remember that she had been administered a task. For this reason, tests of recognition memory were deemed unnecessary and were not carried out.

Apart from findings related to previous right temporal lobectomy, brain MRI revealed a contrast-enhanced mass lesion involving the left hippocampus and parahippocampal gyrus, sparing their anterior portion (Fig. 2). Given that severe amnesia was already present and that there was a high risk of uncal herniation, the patient was offered surgery. Both she and her family gave their written informed consent to perform a left temporal lesionectomy. Pathological examination of the excised tissue showed a high-grade glioblastoma.

After surgery, the patient became mildly hypersexual with a slight worsening of her amnesia confirmed by a further neuropsychological evaluation performed 1 month after the operation (Table 1). The postoperative brain MRI



**Fig. 1a,b** Complex figure of Rey-Osterrieth: (a) copy; (b) immediate recall



**Fig. 2** Magnetic resonance of the brain. T1 (a) and T2-FLAIR (b) weighted coronal images, and T1 (c) and gadolinium T1 (d) axial images, showing findings related to previous right temporal lobectomy and tumour in medial left temporal lobe

showed the complete surgical removal of the left temporal lesion with disappearance of perilesional oedema. The patient survived for a further 13 months, during which she received chemotherapy and radiation therapy.

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## Discussion

Global amnesic syndrome is not rare, and it is well known that working memory is spared in patients with bilateral MTL lesions. However, this case is peculiar because the damage to right and left MTL structures occurred on two separate occasions. First, right temporal lobectomy was performed for intractable epilepsy, then three years later a malignant brain tumour damaged the left hippocampus and the parahippocampal cortex. This unfolding of events over time made it possible for us to document optimal memory function following unilateral MTL damage. This suggests that only one MTL can allow normal memory function, or can take over the function normally subserved by a dysfunctional contralateral MTL when this dysfunction is marked and prolonged, such as in chronic TLE.

Several cases of amnesia in conjunction with bilateral hippocampal damage have been reported and recently reviewed [3]. Our finding of retrograde and anterograde memory deficits with relatively spared cognitive abilities is consistent with previous observations on patients with bilateral lesions involving the hippocampal formation and the parahippocampal gyrus, with varying degrees of involvement of the extramedial temporal cortex. Although we serially performed a comprehensive neuropsychological assessment, we cannot solve the many controversies that still exist regarding hippocampal amnesia, such as the effect of lesion size, and the nature and degree of the anterograde and retrograde memory impairment.

It is largely accepted that when the left hemisphere is dominant, the left and right MTL systems are involved in the processing of different types of material-specific information. In fact, verbal and visuospatial memory deficits may be observed after surgery in the left and the right hemisphere, respectively, although deficits in visuospatial memory are often difficult to bring to light. However, in spite of this putative specialisation, the finding that left hemispheric patients tend to suffer combined non-verbal and verbal problems more often than right hemispheric patients [7] suggests that the left MTL plays a particularly important role in memory function. This putative dominant role of the left MTL might help explain why our patient continued to show optimal memory function after the first operation. Given that memory function was basically intact after right temporal lobectomy and that it declined rapidly to the degree of severe amnesia during the growth of a left MTL tumour three years later, either a contralateral memory reorganisation or an atypical memory lateralisation preceding the onset of epilepsy can be invoked as possible explanations.

While it is not possible for us to rule out either of these explanations, we believe that the first one is more likely, because epilepsy dated back at least 20 years and the right MTL function had probably been so compromised by the frequent ictal and interictal epileptiform discharges as to promote contralateral memory reorganisation.

In contrast to language function, plasticity and reorganisation of memory function in epilepsy have been less well investigated. Nevertheless, some findings suggest that memory reorganisation in the contralateral MTL can actually occur. For instance, differences in verbal memory deficits after left anterior temporal lobectomy in patients with early and late onset of epilepsy suggest a relationship between early onset of epilepsy and reorganisation of memory functions [4]. The findings of a recent fMRI study also suggest memory reorganisation in the contralateral temporal lobe. In this study [8], patients with left TLE showed greater verbal encoding activation in the right MTL, whereas those with right TLE showed greater non-verbal encoding activation in the left MTL. Moreover, another study suggested that MTL structures, being phylogenetically older, provide less material-specific functions, which tend to be bilaterally distributed, as compared with neocortical lateral structures [9].

While future work will be necessary to address the many issues that this paper has left open, our case report, due to its peculiarities, might contribute to increase the understanding of memory system reorganisation processes over the course of epilepsy.

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**Sommario** *L'argomento della riorganizzazione delle funzioni mnesiche nelle strutture temporo-mesiali contralaterali al focolaio epilettogeno è ancora controverso. Riportiamo il caso di una donna di 38 anni affetta da epilessia temporale destra sintomatica di angioma cavernoso, sottoposta a valutazione neuropsicologica prima dell'esecuzione dell'intervento neurochirurgico di lobectomia temporale destra, durante un periodo di follow-up di circa due anni e circa 3 anni dopo la chirurgia, quando sviluppava un glioma maligno a carico delle strutture temporali di sinistra. Al momento della valutazione prechirurgica relativa al primo intervento e nei successivi due anni di follow-up le funzioni mnesiche della paziente risultavano normali. Alla diagnosi del tumore temporale sinistro, la paziente presentava una amnesia retro-anterograda severa, mentre la memoria di lavoro e le restanti funzioni cognitive erano normali. Rispetto ai casi di lesioni bilaterali a carico delle strutture temporali, il caso da noi riportato appare peculiare, in quanto il danno si è verificato in due distinte occasioni. I dati neuropsicologici suggeriscono che le strutture temporo-mesiali di un unico emisfero possono consentire un funzionamento mnesico normale oppure che le funzioni mnesiche sottese da strutture temporo-mesiali coinvolte nel focolaio epilettogeno possono riorganizzarsi nelle omolo-*

*ghe strutture controlaterali quando la disfunzione indotta dall'epilessia è sufficientemente cronica e grave.*

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