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Long-term consolidation of declarative memory: insight from temporal lobe epilepsy

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Several experiments carried out with a subset of patients with temporal lobe epilepsy have demonstrated normal memory performance at standard delays of recall (i.e. minutes to hours) but impaired performance over longer delays (i.e. days or weeks), suggesting altered long-term consolidation mechanisms. These mechanisms were specifically investigated in a group of five adult-onset pharmaco-sensitive patients with temporal lobe epilepsy, exhibiting severe episodic memory complaints despite normal performance at standardized memory assessment. In a first experiment, the magnitude of autobiographical memory loss was evaluated using retrograde personal memory tasks based on verbal and visual cues. In both conditions, results showed an unusual U-shaped pattern of personal memory impairment, encompassing most of the patients' life, sparing however, periods of the childhood, early adulthood and past several weeks. This profile was suggestive of a long-term consolidation impairment of personal episodes, adequately consolidated over 'short-term' delays but gradually forgotten thereafter. Therefore, in a subsequent experiment, patients were submitted to a protocol specifically devised to investigate short and long-term consolidation of contextually-bound experiences (episodic memory) and context-free information (semantic knowledge and single-items). In the short term (1 h), performance at both contextually-free and contextually-bound memory tasks was intact. After a 6-week delay, however, contextually-bound memory performance was impaired while contextually-free memory performance remained preserved. This effect was independent of task difficulty and the modality of retrieval (recall and recognition). Neuroimaging studies revealed the presence of mild metabolic changes within medial temporal lobe structures. Taken together, these results show the existence of different consolidation systems within declarative memory. They suggest that mild medial temporal lobe dysfunction can impede the building and stabilization of episodic memories but leaves long-term semantic and single-items mnemonic traces intact.

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Abbreviations: WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale

Introduction

The hypothesis that new memories consolidate slowly over time was proposed a century ago (Müller and Pilzecker, 1900), and remains a leading topic in memory research (McGaugh, 2000). In modern consolidation theory, it is assumed that new memories are initially labile before undergoing a series of processes that render the memory representations progressively more stable. These processes are generally referred to as memory consolidation. Most research in the realm of memory consolidation focuses on time-dependent neural systems, and cellular and molecular mechanisms enabling lasting memories. In contrast, the possibility that different material may undergo separate consolidation processes has received little investigation.

Declarative memory is comprised of memory for personal experiences (episodic memory) and for facts and concepts (semantic memory) (Tulving, 1972; Kinsbourne and Wood, 1975; Nadel and Moscovitch, 1997; Moscovitch *et al.*, 2006). One influential view of memory organization considers declarative memory as a unitary process that is dependent on the medial temporal lobe region, a set of interconnected structures comprising the hippocampus and underlying entorhinal, perirhinal and parahippocampal cortices (Squire *et al.*, 2007). An alternative view is the possibility of a hierarchical functional segregation within medial temporal lobe structures, with episodic memory depending primarily on the hippocampus and context-free semantic memory depending primarily on the underlying cortices (Mishkin *et al.*, 1997, 1998). Accordingly, subhippocampal cortices receive their input from cortical sensory areas and convey information to the hippocampus situated at the top of the hierarchy, to form the complex associations that characterize episodic memory. Subhippocampal cortices, however, may be sufficient, even in the absence of the hippocampus, to support the less complex associations required for the factual information that characterizes semantic memory (Mishkin *et al.*, 1997, 1998). Within this theoretical framework, it is unclear whether semantic and episodic memories are consolidated similarly or follow separate pathways.

In recent years, there has been growing interest in a subset of patients with temporal lobe epilepsy displaying normal, or above normal, performance at standard delays of recall (i.e. ~30 min) but impaired performance over longer periods of retention (i.e. days or weeks), suggesting an alteration of consolidation memory mechanisms (Kapur *et al.*, 1997; Blake *et al.*, 2000; Butler and Zeman, 2008). This memory loss has been particularly studied in the spectrum of transient epileptic amnesia, a subtype of temporal lobe epilepsy in which memory deficit is the core symptom of ictal and interictal manifestations (Kapur and Markowitsch, 1990; Kapur, 1993; Zeman *et al.*, 1998; Manes *et al.*, 2005; Butler *et al.*, 2007; Butler and Zeman, 2008; Milton *et al.*, 2010). In this syndrome, patients typically present with transient amnesic episodes and most of them also disclose accelerating forgetting rate and an isolated autobiographical memory deficit contrasting with the preservation of semantic memories (Manes *et al.*, 2005; Butler *et al.*, 2007; Butler and Zeman, 2008; Milton *et al.*, 2010). In such patients, autobiographical memory deficit could be interpreted as an anterograde memory problem caused by accelerated rate of forgetting. Then, these patients would present selective long-term consolidation deficit for autobiographical memories.

In the present study, we conducted an in-depth evaluation of a subgroup of patients with temporal lobe epilepsy with a pattern of memory loss suggestive of a long-term consolidation deficit. Patients were all suffering from adult onset pharmaco-sensitive temporal lobe epilepsy with or without past transient amnesic episodes, exhibited memory complaint of gradually and permanently forgetting autobiographical memory contrasting with normal performance at standardized memory assessment. To clarify the putative relationship of memory disturbances with clinical seizures, we specifically focused on a subset of subjects with temporal lobe epilepsy, with complete remission of clinical seizures under anti-epileptic medication.

The first aim of this study was to document objectively their complaints in assessing their ability to recall personal past episodes. Second, we tested the hypothesis that this difficulty stems from a long-term consolidation disturbance selectively affecting new episodic memories. In order to test this hypothesis, we devised a neuropsychological protocol evaluating consolidation at immediate, 1-h and 6-week delays of different types of information: context-rich (episodic and spatial) and context-free (semantic factual and single-items) memories. Taken as a whole, our results suggest that context-rich and context-free memories follow separate consolidation pathways. In addition, metabolic neuroimaging study based on MRI and ^{18}F-fluorodeoxyglucose PET methods showed metabolic changes within the medial temporal lobe. These results are discussed in light of current models of memory organization, which favour the view of a segregated functional organization within medial temporal lobe structures.

Patients and methods

Case descriptions

Five patients (mean age = 42.6 years; SD = 9.3 years) were selected from a large cohort of subjects evaluated in our memory clinic, according to the following criteria: (i) adult onset partial complex seizures; (ii) full remission of seizures for at least 1 year under anti-epileptic drugs prior to testing; (iii) unusual complaint of gradually forgetting personal episodes; (iv) intact cognitive functioning including general knowledge and performance to standardized memory assessment; and (v) temporal lobe epileptiform abnormalities prominently evidenced during sleep recording on scalp EEG. All provided full consent to follow the testing procedure. One reported acute episodes of isolated memory loss as depicted in transient epileptic amnesia (Zeman *et al.*, 1998). The other four exhibited various features of complex partial seizures as observed in the temporal lobe epilepsy spectrum.

Table 1 Demographic and clinical characteristics of the five patients

	Patient C.P.	Patient M.R.	Patient J.H.	Patient T.B.	Patient M.C.
Sex	Female	Male	Male	Male	Male
Age (years)	37	52	52	31	41
Education (years)	17	17	10	17	20
Memory complaint					
Estimated date of onset	1990	1995	2002	2000	2000
Characteristics of forgotten memories:					
Personal life episodes	X	X	X	X	X
Salient holiday episodes	X	X	X	X	X
Routes	X		X		
Epilepsy					
First epileptic seizure	1991	1997	2006	2005	2005
Aura	No	No	No	No	'Déjà vu', anxiety, amnesia
SGTCS	Yes	Yes	No	Yes	No
Complex partial seizures	Yes	Yes	Yes	No	Yes
Nocturnal predominance	Yes	Yes	No	Yes	No
Anti-epileptic treatment	Carbamazepine	Carbamazepine	Lamotrigine	Sodium valproate	Levetiracetam
Treatment response	Complete	Complete	Complete	Complete	Complete
Neurological examination	Normal	Normal	Normal	Normal	Normal
CT-scan	Normal	Normal	Normal	Normal	Normal
Standard EEG	Normal	Normal	BSW	BSW	Normal
Sleep EEG	Spikes Left temporal electrodes	Spikes Right temporal electrodes	Spikes Right temporal electrodes	Spikes Left and right temporal electrodes	Spikes Left and right temporal electrodes

Complete = complete cessation of epileptic seizures; SGTCS = secondary generalized tonic-clonic seizures; BSW = bitemporal sharp waves.

Patients reported marked disturbances in recollecting details of salient episodes of their life, such as weddings, birthdays or trips experienced in recent years. Accordingly, episodes were not forgotten at the moment, but gradually over a period of several weeks. Moreover, they were complaining of difficulties recognizing familiar places and finding their way in unfamiliar environments. Complaints were confirmed by close relatives and colleagues. Interestingly, the memory complaint of the five patients had preceded the clinical manifestation of epilepsy. Despite this apparent handicap, they were fully capable of carrying out their professional duties, most at a high level of responsibility, indicating the preservation of some general cognitive abilities. Patients' characteristics are provided in Table 1.

Two patients (Patients C.P. and M.R.) had a history of reactive depression due to the respective death of their mother and niece. They were transiently treated with Paroxetine® 5 (Patient C.P.) and 10 (Patient M.C.) years, respectively, before the onset of their memory complaint. Overall, patients had no history of psychiatric disorder and substance abuse. Moreover, no significant differences were detected between the patient group and control subjects on the depression and anxiety ratings of the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). Neurological examination and CT scan of the brain were entirely normal for all patients. Brain scanning was performed using a 1.5 T Magnetom Vision Plus magnetic resonance imager (Siemens, Erlangen, Germany) with morphological 3D T_1-weighted magnetization prepared rapid gradient echo sequences. Images were also obtained in the coronal plane for T_2 and fluid-attenuated inversion-recovery. MRI scan showed no evidence of abnormal brain signal, including in the hippocampal structures, in three patients (Patients C.P., M.R. and T.B.). Right hippocampal sclerosis and left hippocampal dysplasia were found in Patients J.H. and M.C., respectively.

The main characteristics of epilepsy and EEG findings are indicated in Table 1. Epilepsy began in all the patients during adulthood (range 18–50). No familial history of epilepsy and personal history of febrile seizure were reported. Three patients had secondary generalized seizures during sleep. Four out of five patients also presented with diurnal partial complex seizures with automatisms, confusion and amnesia. Only one patient (Patient M.C.), reported auras suggestive of internal temporal lobe onset ('déjà vu' and anxiety). Video-EEG recordings of partial complex seizures were available in only one patient (Patient C.P.). Standard EEG recordings and/or sleep EEG in all patients found spikes over the temporal regions (left side in one, right in two and bilateral in two). In the five cases, sleep EEG showed an activation of spiking during slow wave sleep. Monotherapy by standard anti-epileptic drugs was begun at variable delay after epilepsy onset. A clear-cut response was obtained however, and none had a seizure over the past year (mean = 20.4 months; SD = 10). Nevertheless, despite the complete cessation of clinical epileptic seizures, patients kept complaining of forgetting personal life episodes.

General neuropsychological assessment

The cognitive abilities of the patients were assessed using a series of standardized neuropsychological tests (Table 2). Performance was evaluated by comparison with standard published norms.

Patients' mean IQ was above average (mean patients' IQ = 115; SD = 10.36) (standard mean = 100; SD = 15). They obtained high scores at all the Wechsler Adult Intelligent Scale (WAIS)-III subtests (Wechsler, 2000). They also showed above average abilities in the various aspects of memory assessed by the Wechsler Memory Scale (WMS)-III subtests (Wechsler, 2001). Their mean general delayed

Table 2 Performances of the five patients on standard neuropsychological examination

Tests	Patient C.P.	Patient M.R.	Patient J.H.	Patient T.B.	Patient M.C.
Intelligence scale (WAIS-III)					
Verbal IQ[a]	130	119	95	119	130
Performance IQ[a]	95	102	103	127	108
Full scale IQ[a]	116	112	99	125	123
Memory scale (WMS-III)					
Working memory index[a]	100	117	139	108	117
Visual delayed index[a]	106	94	109	127	100
Auditory delayed index[a]	127	110	132	127	119
General delayed memory[a]	121	101	134	133	113
Executive/attentional skills					
Copy of the Rey Osterreich figure (36)	36	35	36	36	36
WAIS-III similarities subtest[b]	14	13	9	12	14
WAIS-III matrix reasoning subtest[b]	11	9	12	15	13
Trail making (time in s)					
Part A	20	37	37	22	25
Part B	43	91	71	44	68
Word fluency					
Letter	28	34	27	19	19
Category	46	49	36	32	27
Wisconsin card sorting test					
Categories (6)	6	6	6	6	6
Perseverative errors	4	0	0	0	0
Set loss	0	0	0	1	1
Stroop interference procedure (time in s)					
Interference	93	101	86	80	103
WAIS-III digit span subtest[b]	12	14	8	14	15
Standard anterograde memory assessment					
RL/RI-16					
Free delayed recall (16)	14	12	10	16	13
Total (free + cued) delayed recall (16)	16	16	16	16	16
Recognition (48)	48	48	48	48	48
Delayed recall of the Rey Osterreich figure (36)	16,5	21	24,5	34	26,5
California verbal learning Test					
Free recalls 1-5 list A (80)	72	48	56	65	75
Free recall interfering list B (16)	9	6	7	8	9
Free recall list A (16)	14	14	15	16	16
Delayed free recall list A (16)	15	12	16	16	16
Autobiographical memory interview					
Personal semantic (63)	59	54	60	61	63
Autobiographical incidents (27)	16[c]	16[c]	23	23	13[d]
Language/semantic abilities					
Pyramid and Palm Tree Test (52)	52	50	51	52	52
Picture naming (80)	80	80	80	80	80
WAIS-III Information subtest[b]	14	10	8	11	18
WAIS-III Comprehension subtest[b]	16	14	8	12	12
WAIS-III Vocabulary subtest[b]	16	15	7	14	17
Visual abilities					
Benton face perception (54)	49	47	45	52	47
Benton line orientation (30)	29	28	24	30	26
Praxis (29)	29	29	29	29	29

Numbers in brackets in the first column refer to maximum scores.
Scaled scores:
a m = 100 ± 15.
b m = 10 ± 3.
c Borderline.
d Abnormal, according to previously published cut-off scores.

memory score was 120.4 (SD = 13.9) (standard mean = 100; SD = 15). Language, praxis and visuoperceptive skills were all normal. Assessment of executive skills showed preservation of set shifting and reasoning abilities, and no sensitivity to interference. Anterograde memory performances, as assessed with the RL/RI-16, a French version of the Free and Cued Selective Reminding Test (Grober *et al.*, 1988; Van Der Linden, 2004), the California Verbal Learning Test (Delis, 1987) and the Rey-Osterrieth Figure (Rey, 1959) were well above average. Semantic knowledge was assessed using Wechsler Adult Intelligent Scale-III vocabulary, information and comprehension subtests, a standardized French picture naming task (DO80) (Deloche and Hannequin, 1997), a semantic matching task (the Pyramid-Palm Trees Test) (Howard and Patterson, 1992) and word fluency tasks (Cardebat *et al.*, 1990). Results showed a preservation of semantic knowledge in all patients.

A standard autobiographical memory test, the autobiographical memory interview (Kopelman *et al.*, 1990), was administered as an initial assessment. This test measures memory for personal semantic and autobiographical incidents in a short-answer format. The results showed that the five patients were within the normal range for the personal semantic subtest. However, while Patients J.H. and T.B. were also within the normal range for the autobiographical incident subtest, Patients C.P., M.R. and M.C., respectively scored in the 'abnormal' range, according to previously published cut-off scores (Table 2).

To summarize, despite the magnitude of the patients' memory complaint, no significant impairment was demonstrated throughout standardized assessment in most aspects of the neuropsychological screening battery. The only deficits concerned the evocation of details of personal events in Patients C.P., M.R. and M.C.

In order to assess the common and main characteristic of the patients' complaint (i.e. a patchy retrograde amnesia for personal events extending many years into their past), and its potential mechanism (i.e. a gradual forgetting of episodes over a period of several weeks), patients were then examined with experimental retrograde and long term anterograde memory procedures within the course of six sessions. Patients' performances were compared with those obtained by control subjects who gave informed consent before undertaking the study.

Methods

Personal retrograde memory assessment

Recollection of past personal episodes was experimentally evaluated in patients and a group of age-matched control subjects ($n = 15$, mean age = 42.33 years; SD = 9.62 years) using two semi-structured questionnaires, based on verbal (TEMPau task, Piolino *et al.*, 2000, 2009) and visual personal cues, respectively (test of familiar photographs, Manes *et al.*, 2001; Gilboa *et al.*, 2004; Joubert *et al.*, 2004) (for details of procedures, see online Supplementary Material). These tests assess the recall of strictly episodic memories via the Remember/Know (R/K) paradigm (Tulving, 1985; Gardiner, 1988). Four to five periods of life were investigated, depending on the patients' age. For each examined period, episodes were cued with four verbal topics (eight for the recent period) or five personal photographs. For the recent period assessment, the familiar photographs task specifically investigated events that occurred during the last month, while the TEMPau task focused on eight events that have occurred in the past year, including six in the past month. A recollection score was calculated for each period that included only the specific detailed memories for which a maximum score of 4 on an episodic scale had been obtained (Piolino *et al.*, 2000). Responses were systematically validated by a reliable relative.

Because of the small size of the patients' group, non-parametric statistics were used. Mann–Whitney U-tests were carried out to examine the influence of Group (patients versus control subjects) as a between-subject factor on memory scores.

Long-term anterograde memory assessment

A neuropsychological protocol was devised to evaluate short-term and long-term retention of different information types, context-rich (episodic) and context-free. For these two information types, participants were subjected to a similar experimental protocol: (i) immediate recall and (ii) short- (1 h) and long-term (6 weeks) delayed recall, each of these recalls being followed by a forced-choice recognition procedure. For each recognition test, different distractor sets were used at 3 min, 1 h and 6 week delays.

Episodic memory tasks

Episodic memory refers to contextually-bound experiences that occurred at a specific time and place. Episodic memory tasks were then based on contextual information and included (i) two complex stories, in which words are linked together within a narrative context; (ii) two route learning tasks (in virtual and real environments, respectively) (Barbeau *et al.*, 2006), in which places are linked together by the temporal and spatial context (navigation route) and (iii) the memorization of a chain of episodes occurring at specific time and place under closely controlled experimental conditions (Barbeau *et al.*, 2006; Tramoni *et al.*, 2009).

For story learning, patients and control subjects ($n = 15$, mean age = 42.33 years; SD = 9.62 years) were required to listen to two stories from the Logical Memory subtest of the Wechsler Memory Scale-III (Wechsler, 2001). Recall was assessed immediately afterwards, and 1 h and 6 weeks later. One point was awarded for each item correctly recalled (total score of 50). Recognition was then tested at 3 min, 1 h and 6 weeks delay in a two forced-choice procedure using 15 questions for each story (total score of 30).

For route learning in virtual and real environments, patients and control subjects ($n = 15$, mean age = 42 years; SD = 9.01 years) had to learn two routes, each containing 15 decision points. The first route was video-recorded from the front of a moving car (length = 4 km, duration = 6 min), while the second consisted of a circuit within the hospital (length = 267 m, duration = ~5 min). Participants were shown the route once before the evaluation began. They then had to choose, at each decision point, the correct direction out of two possible alternatives. The trials were repeated for each participant until 90% accuracy was attained. One hour and 6 weeks later, participants were asked to recall the route (direction at each decision point) with as much detail as possible. The percentage of directions correctly recalled was calculated (recall score). Participants then had to look at/follow the same itinerary again and choose the right direction at each decision point; the percentage of correctly recognized directions was then calculated (recognition score).

For the memorization of a chain of episodes (Tramoni *et al.*, 2009), participants (patients and their spouses, $n = 5$, mean age = 39.8 years; SD = 9.12 years) were told that in order to thank them, the examiner wished to invite them for coffee at the hospital cafeteria. Underlying this apparently informal invitation was an experimental procedure involving a series of episodes that subjects underwent without being aware that they would subsequently be questioned about them (Supplementary Material). One hour as well as 6 weeks later, participants were asked to recall these events in as much detail as possible, as if they were reliving them (the circumstances, what they did and

felt, where, how and with whom the scene took place). The episodicity of the recall was scored on a 5 point scale (Piolino *et al.*, 2000) (recall score). Then participants had to select the right answer in a two-alternative forced-choice questionnaire (15 items, e.g. recognition at 1 h: 'Were we sitting next to the door or at the back of the cafeteria?'; at 6 weeks: 'Were we sitting next to the checkout or next to the door?') (recognition score).

Mann–Whitney U-tests were carried out to examine the influence of Group (patients versus control subjects) as a between-subject factor on recall and recognition scores.

Context-free memory tasks

The following procedures were based on 'context-free' material, in which participants were required to recall or recognize information without necessarily re-experiencing the context of learning. They included a semantic task, which consisted of a list of 15 facts unknown to participants and control subjects, and five recognition memory tests based on single-item stimuli (Barbeau *et al.*, 2005, 2006) (controls: $n = 15$, mean age = 41.86 years; SD = 9.08 years). The term of single-item refers to concrete or abstract concepts that are not embedded in a context (as opposed to a word in a story, or a landmark within a route), but processed as a single component (Mayes and Roberts, 2001; Turriziani *et al.*, 2004). Single-item recognition memory tasks are therefore usually solved without referring to the context of learning, in contrast with contextually-bound episodic memory tasks.

The five single-item recognition memory tests were based on a large variety of stimuli (words, places, doors and faces), learning (incidental and explicit) and recognition (yes/no, forced choice with one or more distractors) procedures (for details of procedures, see online Supplementary Material). Words were selected from the Brulex database (Content *et al.*, 1990) and were matched for frequency and length. Doors were selected from a subtest of the Doors and People Battery (Baddeley, 1994), and faces from the face recognition subtest of the Wechsler Memory Scale-III (Wechsler, 2001). Both tests were adapted so that trial-unique distracters could be used at the different time-points. Performance on the recognition tests was calculated as the number of correct answers (hits + correctly rejected items) expressed as a percentage of all answers.

A list of 15 new facts—all unknown to participants (e.g. 'Ulan Bator is the capital of Mongolia')—was presented orally until the subject reached 90% accuracy at free recall. Recall and recognition of the correct answer among three proposals were then tested at 3 min, 1 h and 6 weeks delay. Mann–Whitney U-tests were carried out to examine the influence of Group (patients versus control subjects) as a between-subject factor on recall and recognition scores.

Difficulty of tests

To study task-difficulty effect, a difficulty index was computed for each test (Holdstock *et al.*, 2002). This index, expressed as percentage, is calculated from the mean recognition score of the control subjects and indicates where a control subject's mean score stands between chance and a perfect score. The following equation was used: Difficulty = $(s–c)/(p–c)$ where s is the control subject's mean score, c is chance performance and p is a perfect score. A high score indicates an easy test.

Mann–Whitney U-tests were carried out to examine the effect of Test (episodic versus context-free) as a between-subject factor on the difficulty index.

Positron emission tomography

Brain metabolism was studied with ^{18}F-fluorodeoxyglucose in each patient using an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukesha, WI, USA), with 6.2 axial resolution, allowing 47 contiguous transverse sections of 3.27 mm thickness. ^{18}F-fluorodeoxyglucose (150 MBq) was injected intravenously in an awake and resting state, with eyes closed, in a quiet environment. Image acquisition started 30 min after injection and ended 15 min later. Images were reconstructed using ordered subsets expectation maximization algorithm, with five iterations and 32 subsets, and corrected for attenuation using CT transmission scan.

Findings were compared at group level with the PET scans of 14 healthy volunteers, acquired with the same camera, under the same conditions (mean age = 44.2 years; SD = 16.8 years, not different from patients; $P = 0.89$, Mann–Whitney U-test). Informed consent was obtained from all subjects. The protocol was approved by the local ethics committee and conformed to the Declaration of Helsinki on human investigation.

The PET images were converted from the DICOM to the Analyze format using the software MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html), then transferred to the software SPM2 (Welcome Department of Cognitive Neurology, University College, London, UK). The data were standardized onto the Montreal Neurological Institute atlas by using a 12-parameter affine transformation, followed by non-linear transformations and a trilinear interpolation. The dimensions of the resulting voxel were $2 \times 2 \times 2$ mm. The images were then smoothed with a Gaussian filter (12 mm full width at half-maximum) to blur individual variations in gyral anatomy and to increase signal-to-noise ratio. The resulting PET images were divided by their individual vermis fluoroderoxyglucose uptake value to control for individual variations in global PET measures (Guedj *et al.*, 2010). The vermis has been selected as being a preserved area. The individual vermis value was obtained for each subject using the 'Anatomical ROIs Analysis' toolbox of SPM2 allowing the automatic extraction of the labellized region mean value from the Anatomical Automatic Labelling atlas (Tzourio-Mazoyer *et al.*, 2002).

Significant hypometabolisms were analysed in patients in comparison with healthy subjects, using ANCOVA statistical model and age as nuisance variable. The SPM maps were thresholded to $P = 0.01$ and corrected for extent to 20 voxels. Cluster values were extracted and MNI coordinates converted into Talairach coordinates using Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html). Mann–Whitney U-test was performed to confirm significance of cluster values obtained.

Magnetic resonance spectroscopy imaging

To assess cerebral changes, we used proton magnetic resonance spectroscopy imaging because of its known sensitivity in detecting metabolic abnormalities in epileptic patients (Guye *et al.*, 2002).

Magnetic resonance spectroscopy imaging results from patients were compared with those obtained from 12 control subjects (mean age = 29 years; range 21–34 years) using a 1.5 T Magnetom Vision Plus magnetic resonance scanner (Siemens, Erlangen, Germany). Metabolic exploration was carried out using ^{1}H-magnetic resonance spectroscopy imaging, with the acquisition of a slice in the bihippocampal plane centred on the hippocampus, using an acquisition-weighted, hamming shape 2D-SE pulse sequence (echo time = 136 ms, repetition time = 1500 ms, 15 mm slice thickness, field of view 240 mm, 21×21 encoding steps leading to 524 free induction

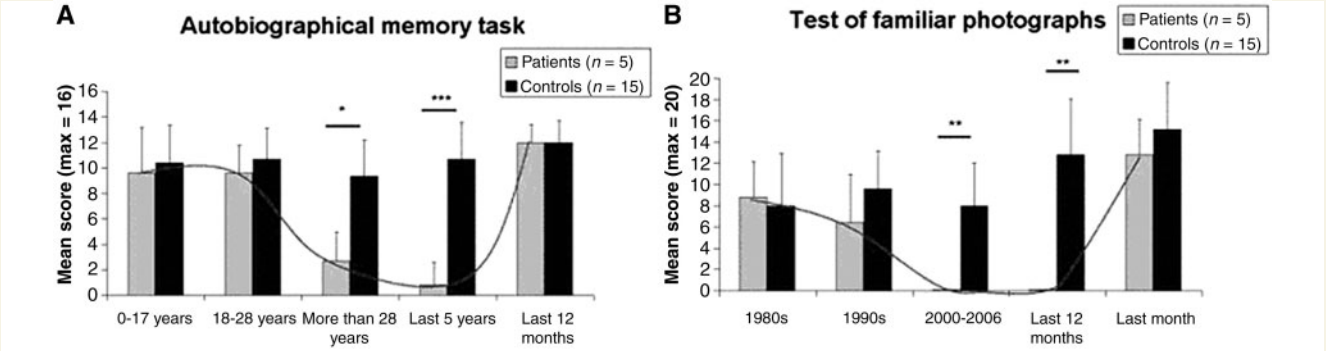

Figure 1 Mean recollection score in the two groups of participants as a function of time in response to a semi-structured questionnaire based on personal verbal (**A**) and visual (**B**) cues. Planned comparisons to illustrate the Group effect for each period are indicated in the figure. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. (Bars indicate the standard error of the mean).

decays acquired in 12 min), designed in-house. Spatial resolution was defined as the width of the spatial response function at 64% of the maximum. This definition yielded a spatial resolution of 5.7 mm and a quasi-cylindrical voxel. Prior to the procedure, eight regions of interest, including limbic (i.e. one anterior and one posterior hippocampal region of interest in each hemisphere) and neocortical structures (i.e. one medial occipital and one lateral temporo-occipital region of interest in each hemisphere), were selected. Peak areas for N-acetylaspartate, choline and creatine in each region of interest were quantified using an automatic AMARES algorithm. The N-acetylaspartate/(choline + creatine) ratio was used as a metabolic index reflecting the relative concentration of N-acetylaspartate in the selected regions of interest. We then used a Mann–Whitney U-test to compare N-acetylaspartate/(choline + creatine) ratios from patients and controls for each region of interest.

Results

Personal retrograde memory assessment

Results demonstrated a preservation in the recollection of episodes experienced during the childhood, early adulthood and recent weeks, but a significant loss in the last 5–10 years ($P < 0.05$) (Fig. 1A and B). For the recent period, the spared episodes had occurred mainly in the several weeks prior to assessment, in agreement with patients' reports. This autobiographical memory alteration was characterized by an unusual U-shaped gradient present in each patient.

In summary, the two experimental procedures developed to assess autobiographical memory with verbal and visual cues yielded an unusual U-shaped gradient objectivizing the patient's complaint of gradually forgetting personal episodes. Surprisingly, patients could easily recollect episodes experienced during the past several weeks but not those experienced 5–10 years ago. One possible explanation to account for this peculiar pattern of memory loss could be a long-term consolidation impairment for personal episodes adequately consolidated over delays of weeks but gradually and permanently forgotten after several months. Thus, this apparently 'retrograde' autobiographical memory deficit could be the result of a selective 'anterograde' long-term consolidation impairment of episodic information. This hypothesis was evaluated in the following section.

Long-term anterograde memory assessment

Episodic memory tasks

While no significant difference was found between the two groups in recall and recognition scores at the 1-h time point, a Group effect was found for all tasks and for the two recall and recognition scores at the 6-week time point ($P < 0.01$) (Fig. 2).

In summary, while patients could recollect with details stories, new routes and successive events experienced 1 h before, performance was significantly altered at six-week delay regardless of the modality of retrieval (recall and recognition).

Context-free memory tasks

No significant difference was found between the two groups on the recognition scores at 1 h ($P = 0.209$) and at 6-week delay ($P = 0.901$) (Fig. 3).

For single-item recognition memory tasks, performance of patients always remained well above the level of chance alone and manipulation of any variables of the recognition tasks that rendered the procedure harder (longer delay before recognition, recognition among several distractors) did not impede patients' performance in comparison with controls. In addition, patients could learn, retrieve and recognize new facts after a long delay as accurately as controls.

In summary, long-term anterograde memory assessment showed that patients displayed preserved abilities to encode, consolidate and recollect stories, routes, a chain of episodes along with single items and learning of new facts one hour later. Six weeks later however, a dissociation was observed in the patients group: their performances were comparable with those obtained by controls for single-item memory and learning of new facts, but they were unable to recall and recognize stories, routes and a chain of episodes. This dissociation is displayed in Fig. 4. There

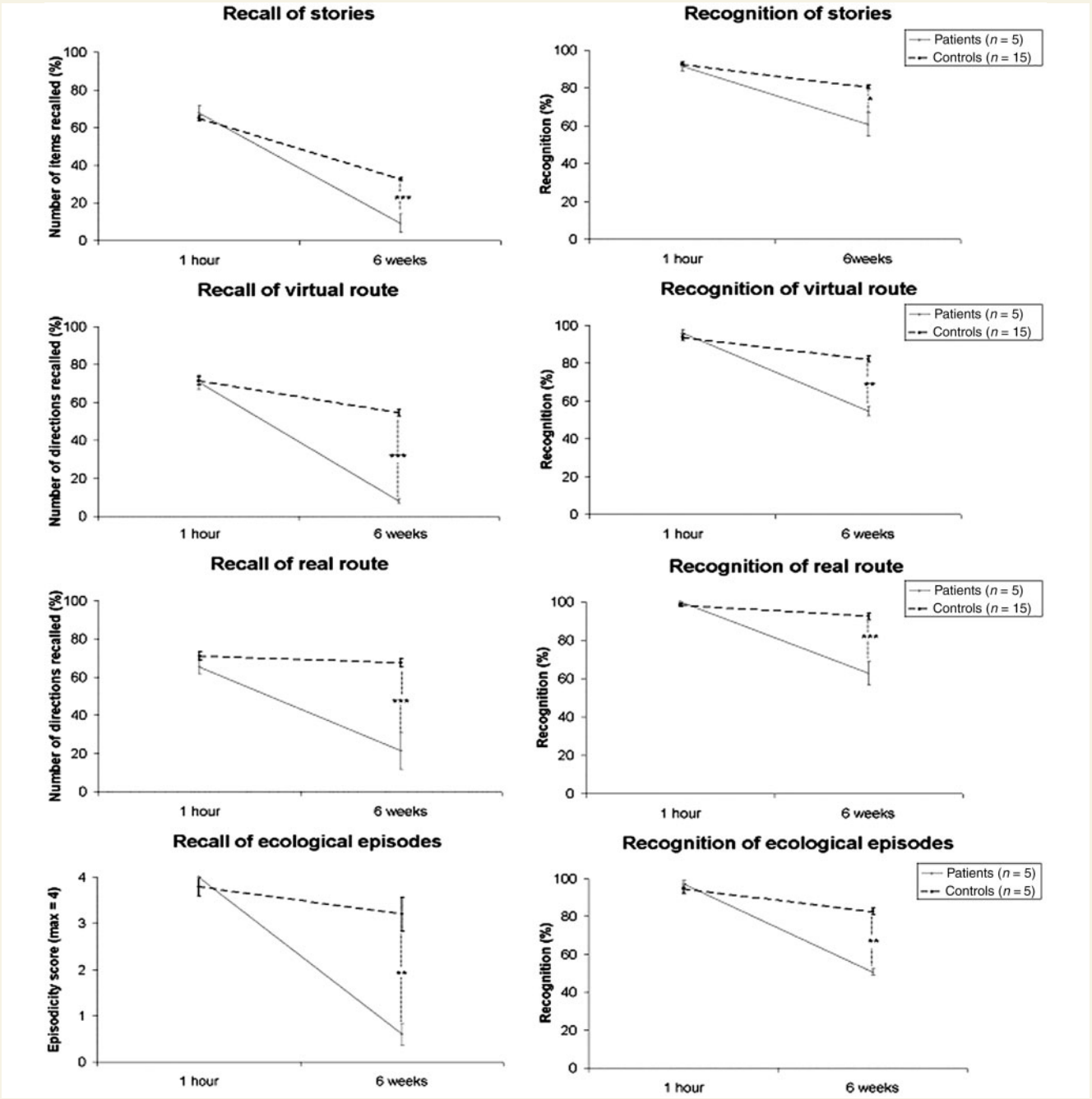

Figure 2 Recall and recognition scores obtained for four tests assessing episodic memory in the two groups of participants, as a function of delay after the learning phase. Planned comparisons to illustrate the Group effect for each period are indicated in the figure. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. (Bars indicate the standard error of the mean).

is no difference between episodic and context-free information recognition z-scores at 1-h delay ($P = 0.663$) but a significant difference at the 6-week delay ($P < 0.001$).

Difficulty of tests

No significant effect of test type on the difficulty index was observed at the 1-h time point. Furthermore, episodic tasks were easier overall than context-free tasks at the 6-week time point, although the difference just failed to reach significance ($P = 0.067$) (Table 3).

The impact of repeated exposure to stimuli was also evaluated. At encoding, stimuli were presented only once in all procedures, except for the two route and the new fact learning tasks (presented until 90% accuracy was reached). For these latter, no difference was seen between the number of presentations made to patients and to controls, or between the three different tasks within the patient group ($P = 0.151$).

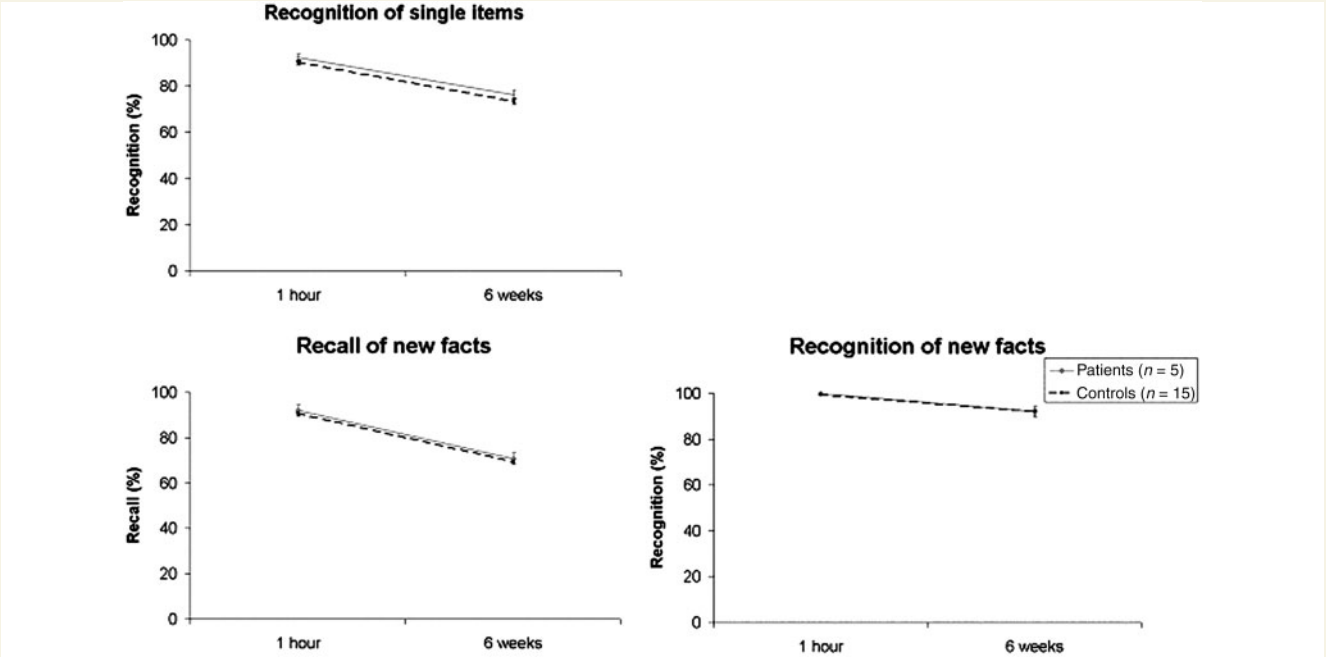

Figure 3 Recall and recognition scores for the six tests assessing context-free memory in the two groups of participants as a function of delay after the learning phase. (Bars indicate the standard error of the mean).

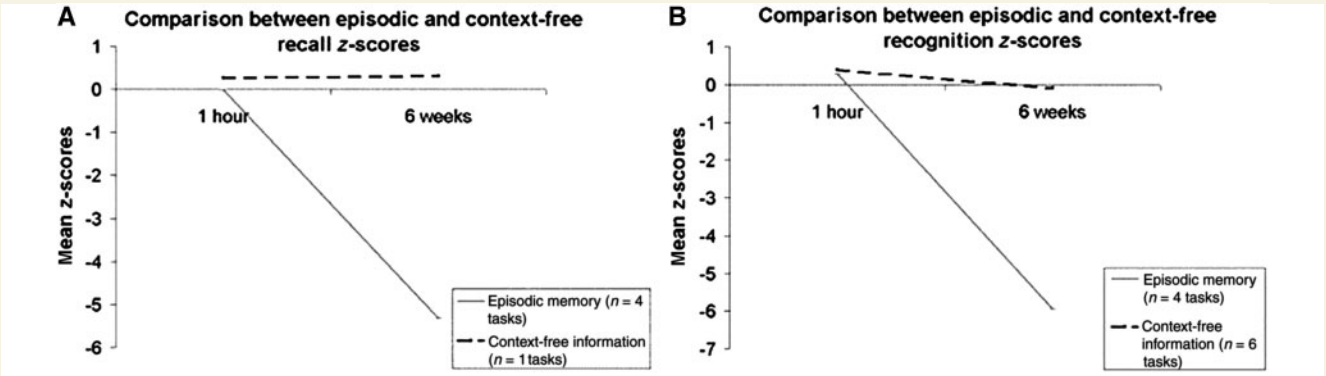

Figure 4 Mean Recall (**A**) and Recognition (**B**) *z*-scores in episodic and context-free memory tests.

Positron emission tomography

In comparison with healthy subjects, patients exhibited significant right temporal hypometabolism, involving polar cortex (Brodmann area 38) and uncus (a medial temporal lobe structure formed by the ventral-medial portion of the amygdala and the head of the hippocampus) (Talairach coordinates of the local maxima: 32, 8, −31; *t*-score = 3.23; $k = 85$; $P < 0.01$, Mann–Whitney U-test; Fig. 5). No other cortical hypometabolism was found elsewhere.

Magnetic resonance spectroscopy imaging

A significant decrease in the N-acetylaspartate/(choline + creatine) ratio was seen in patients in only two regions of interest that included the anterior ($P < 0.05$) and posterior ($P < 0.001$) right hippocampus (Mann–Whitney U-test) (Fig. 6).

In summary, in comparison with control subjects, group analyses showed metabolic changes within the right medial temporal lobe, including the hippocampal formation, as suggested by decreased fixation of the radiotracer on PET scan study, and neuronal loss or dysfunction reflected by a decrease in the N-acetylaspartate/(choline + creatine) ratio on magnetic resonance spectroscopy imaging. Together with individual analysis of structural brain MRI, which revealed abnormal hippocampal signals in two out of five patients, neuroimaging studies suggest the existence of mild hippocampal dysfunction in our patients' group.

Discussion

This study investigated the mechanisms of memory impairment in patients with adult-onset pharmaco-sensitive temporal lobe epilepsy with vivid episodic memory complaints, contrasting with

Table 3 Percentage score of difficulty for each test at the 1-h and 6-week time points

	1 h	6 weeks	
Episodic memory tests			
Learning of stories	96.44	84.88	
Route learning in a virtual environment	89.32	65.36	
Route learning in a real environment	84.88	60.88	
Chain of episodes	95.99	82.03	
Mean ± SD	91.65 ± 5.56	73.28 ± 11.93	$P = 0.067$
Context-free tasks			
Two-alternative forced-choice recognition of words	76.94	57.76	
Two-alternative forced-choice recognition of topographical scenes	82.22	60.44	
Four-alternative forced-choice recognition of doors	76.88	52.00	
Yes-no recognition of faces	80.36	41.48	
Yes-no recognition of words	96.24	47.92	
New facts	99.1	84	
Mean ± SD	85.29 ± 9.84	57.26 ± 14.76	$P = 0.067$

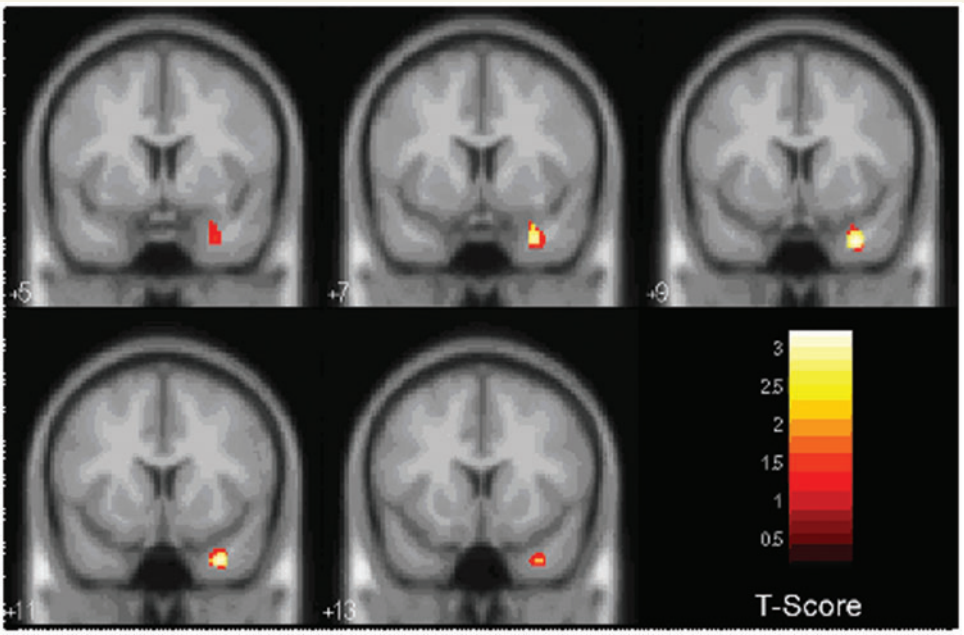

Figure 5 Anatomical localization of significant ^{18}F-fluorodeoxyglucose PET hypometabolism in patients. In comparison with healthy subjects, patients exhibited significant right temporal hypometabolism, involving polar cortex (Brodmann area 38) and uncus (Talairach coordinates of the local maxima: 32, 8, −31; *t*-score = 3.23; $k = 85$; $P = 0.0055$, Mann–Whitney U-test). The cluster is projected onto coronal sections of a normal MRI set, spatially normalized into the standard SPM2 template. The right hemisphere is to the right.

normal (or above normal) performance at standardized memory assessment. The main neuropsychological findings are 2-fold: (i) the demonstration of a U-shaped autobiographical memory loss of periods encompassing most adult life, sparing however, the childhood, early adulthood and several recent weeks and (ii) the demonstration of a clearcut dissociation between long-term consolidation of context-free material (single items and factual information) and context rich information (episodic memory). In addition, individual structural brain study and group metabolic neuroimaging studies indicated the presence of mild changes within the medial temporal lobe including the hippocampus.

Patients' impairment in the context of temporal lobe epilepsy

The present findings are close to those reported in a form of temporal lobe epilepsy with a particularly intimate association with memory, transient epileptic amnesia, where most patients present an accelerated rate of forgetting and a retrograde memory deficit affecting specifically autobiographical memory (Kapur and Markowitsch, 1990; Zeman *et al.*, 1998; Manes *et al.*, 2005; Butler *et al.*, 2007; Butler and Zeman, 2008; Milton *et al.*, 2010).

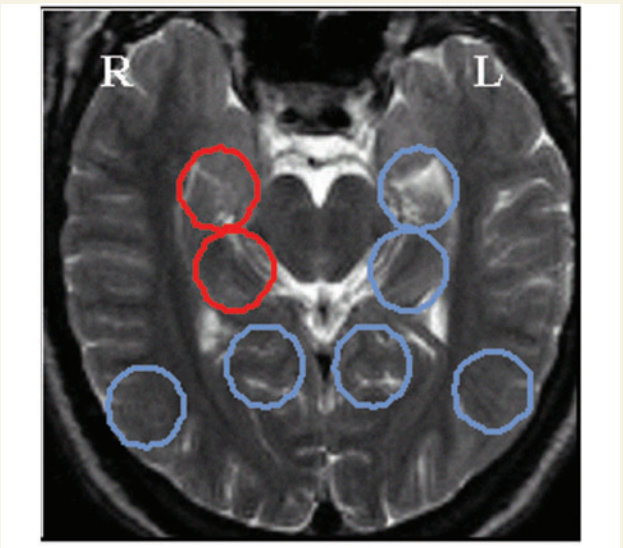

Figure 6 Magnetic resonance spectroscopic imaging data. Red circles indicate abnormally low N-acetylaspartate/(choline + creatine) ratios and blue circles indicate normal ratios. A significant decrease was seen in the anterior and posterior right hippocampus. L = left; R = right.

In a study assessing long-term memory performance in a large group of patients with transient epileptic amnesia, an accelerated rate of forgetting in the recall of a words list and complex drawings was evident after a 3-week delay in about half of patients (Butler *et al.*, 2007). Here, we extend these findings to show that in some patients with temporal lobe epilepsy, this effect can be specific to one declarative memory kind, namely context-rich episodic memory. Patients were impaired at the long-term recall/recognition of stories, in which elements (words) are linked together by the narrative content of the story. They were also impaired at the long-term recall/recognition of two spatial memory tasks, in which different places are linked together by the spatial and temporal constraints of the navigation route. Finally, patients were also impaired at the long-term recall/recognition of a chain of events embedded in a spatial and temporal context, specifically designed to evaluate the episodic content of information retrieval (Tramoni *et al.*, 2009). In contrast, long-term consolidation of new facts and single items was fully preserved. Patients were submitted to a list of 15 facts unknown to participants and their performance at long-term recall/recognition was flawless. Their long-term performance at five recognition memory tests based on single-item stimuli (including paired forced-choice recognition of topographical landmarks such as doors) was also similar to that obtained by controls. In summary, patients' impairment was consistent independent of the modality of retrieval (recall/recognition), but appeared 'material specific', selectively involving the long-term consolidation of context-rich information that requires the establishment of complex relationships among elements, events and places. In contrast, long-term consolidation of context-free information, such as new facts and single-items, remained preserved.

Several studies on patients with transient epileptic amnesia have also focused on their remote memory abilities. A U-shaped retrograde autobiographical memory deficit has been depicted in Patient RG (Manes *et al.*, 2001), with a sparing of extreme life periods (childhood, early adulthood and recent past weeks), as found in the present study. In a subsequent group study however, using other procedures of autobiographical memory assessment [Autobiographical Interview, (Levine *et al.*, 2002); Crovitz Interview, (Crovitz and Schiffman, 1974)], Milton and colleagues (2010) have demonstrated a severe impairment of memory for autobiographical events extending across the entire lifespan in patients with transient epileptic amnesia. These findings slightly differ from those reported here, in particular with regard to the extreme life periods. One possibility is that the procedures we used were not sensitive enough to pinpoint a moderate impairment in remote and recent periods. However, the TEMPau paradigm is considered a sensitive tool for exploring strictly episodic autobiographical memory in patients with temporal lobe epilepsy (Noulhiane *et al.*, 2007). In contrast to the Autobiographical Interview, this procedure relies on a specific mode of subjective experience accompanying the retrieval of memory, in the form of a first-person perspective (Tulving, 2004). Another difference lies in the fact that the Autobiographical Interview assesses only one specific event for each time period, as opposed to four events (and eight in the most recent period) in the TEMPau task (Supplementary Material). Regarding the recent period, it is noteworthy to mention that the TEMPau task requires participants to recollect events from eight different time periods, including six in the past several weeks (last summer, Christmas or New Year's day, last month, last week, last week-end, 2 days ago, yesterday and today). Thus, the apparent preservation of patients' performance for the previous 12 months period mainly reflects the preservation of performance for the last several weeks. This point is also illustrated by the results of the familiar photographs task, in which patients' performance was altered for pictures representing events that had occurred in the last 12 months, but preserved for those illustrative of the last month period. These findings are in full accordance with the patients' complaint of a gradual loss of personal events over several weeks, but also with their long-term memory impairment at episodic tasks, which is experimentally evidenced at the 6-week endpoint. With regard to the most remote period, it is possible that the patients reported herein suffer from a milder form of temporal lobe epilepsy, and that episodic memory traces acquired during brain development have partially resisted to disorganization by recurrent seizures or epileptiform activities.

Overall, the patients depicted in the present study share several similarities with transient epileptic amnesia, including adult-onset pharmaco-sensitive temporal lobe epilepsy, within normal range memory functioning at standard evaluation delays, an accelerated forgetting rate of declarative memory combined with a retrograde autobiographical memory deficit, and evidence for medial temporal lobe changes on brain imaging (Butler *et al.*, 2009). However, their retrograde amnesia displays a slightly different profile. In addition, a history of recurrent witnessed episodes of transient amnesia, the main criterion for transient epileptic amnesia, was absent in most patients of our series (4/5). Thus, while the patients described herein could be placed within the transient epileptic amnesia spectrum, the main clinical expression

of seizures is lacking, suggesting that our patients endorse a slightly different profile than usually encountered in this syndrome.

Patients' impairment in light of memory organization models

The dissociation reported herein could be discussed within the framework of so-called dual-process models. According to Mishkin and colleagues (1997, 1998), 'context-rich' memory such as memory for episodic events could be dissociated from 'context-free' memory such as semantic memory. Beyond their respective differences, other groups have elaborated similar hierarchical models of memory. For Eichenbaum and colleagues (2007), information is first memorized in an inflexible manner at the single-item level. This stage is also critical for paired-associate tasks within the same modality when the relation between the items is inflexible and can be stored as a single item equivalent. In this model, it is thought that flexible relations between items are established in a subsequent stage, in particular when they are spatially or temporally discontiguous, or when transitivity across items is required (Wallenstein *et al.*, 1998). Aggleton and Brown (1999) also provide evidence for a distinction between two memory systems, one being crucial for familiarity judgements, while the other is thought to be critical for episodic and spatial memory. Although these models significantly differ in many aspects, all converge on the notion that memory for single items and context-free information could be dissociated from memory for complex material and context-rich episodes.

This pattern of memory impairment is reminiscent of some previously reported amnesic syndromes (Vargha-Khadem *et al.*, 1997; Mayes *et al.*, 2004; Barbeau *et al.*, 2005). In particular, three adolescents who suffered from early hippocampal damage have shown impaired spatial, temporal and autobiographical memory but, despite their severe amnesia, were able to attend regular school and acquire a substantial amount of new semantic knowledge (Vargha-Khadem *et al.*, 1997; Baddeley *et al.*, 2001; Spiers *et al.*, 2001). In formal assessment, recall of context-rich memory such as stories and autobiographical and spatial memory were severely impaired. In contrast, single-item recognition tasks based on a large set of material type (including paired forced-choice recognition of topographical scenes) was fully preserved. Similar patterns of impairment were further reported following selective hippocampal insult at an adult age (Holdstock *et al.*, 2002; Barbeau *et al.*, 2005; Holdstock, 2005; Taylor *et al.*, 2007; Bird and Burgess, 2008). The reverse dissociation has also been described in Patient M.S. (Barbeau *et al.*, 2006), a subject with subhippocampal lesions and severe deficits in tests of recognition and recall of single-items, but preserved performance at spatial and episodic memory tasks. A similar dissociation within the verbal memory domain has also been reported in Patient N.B. following surgical resection of a subhippocampal epileptic focus, which spared however the hippocampal formation (Bowles *et al.*, 2007). In the present study however, the memory deficit is not apparent during the initial learning stages but appears later, several weeks after successful encoding, pointing to impaired long-term consolidation mechanisms. Together with previous neuropsychological studies, the present findings indicate that contextually-bound experiences and context-free information, including factual knowledge, are partly dissociable, during the earliest but also the latest steps of the consolidation process. Consequently, they suggest that consolidation of episodic memory on the one hand and semantic memory on the other hand are, at least partly, subserved by distinct neural systems.

Although there is a form of agreement that the anatomical components of the medial temporal lobe make distinct contributions to memory function, the mechanisms by which the labour is divided remains debated (Eichenbaum *et al.*, 2007; Mayes *et al.*, 2007; Squire *et al.*, 2007). In the framework of dual-process models, episodic and semantic memories are subserved by different brain structures, semantic memory depending on extra-hippocampal areas and episodic and spatial memory relying on hippocampal formations (Mishkin *et al.*, 1997; Vargha-Khadem *et al.*, 1997; Spiers *et al.*, 2001; Mayes *et al.*, 2004; Barbeau *et al.*, 2005; Winters *et al.*, 2008). However, direct evidence for hippocampal lesion is lacking in most of our patient series. Only two patients displayed structural hippocampal changes on brain MRI (hippocampal sclerosis in Patient J.H.; focal hippocampal dysplasia in Patient M.C.). Nonetheless, medial temporal lobe dysfunction encompassing the hippocampus was suggested by abnormal metabolic profile on MRI and PET group studies. Within dual-process models, these findings could suggest that basic sensory memory functions subserved by extra-hippocampal structures are sufficient for entry and consolidation of information within the semantic system, but not within the episodic one, which requires the long-term binding of this sensory information normally provided by the hippocampus situated at the top of the hierarchical system. In other words, hippocampal dysfunction impedes the long-term stabilization of episodic memory traces but leaves intact long-term retention of semantic information, which involves putatively intact extra-hippocampal structures.

Here, metabolic studies revealed changes within the right medial temporal lobe structure. Thus, it could be argued that the observed dissociation between episodic and semantic memories reflects in fact this asymmetry, episodic memories being multi-modal and spatial, and likely mediated by the right or both hemispheres, whereas the semantic memories, mainly concerned with verbal material, would be primarily mediated by the left hemisphere. We, however, believe this hypothesis unlikely as performance at recall/recognition of verbal memory tasks such as the Logical Memory subtest of the Wechsler Memory Scale-III (Wechsler, 2001) was found to be impaired at the 6-week delay, and performance at non-verbal memory tasks such as picture recognition tasks was comparable to controls at the same delay. In addition, we believe this laterality effect should not be over-estimated, considering that, in our patients, structural and sleep EEG abnormalities, when evidenced, involved either the left, right or both temporal lobes and more generally, temporal lobe epilepsy often produces functional changes within both medial temporal lobe structures (Williamson *et al.*, 1993). Thus, the observed dissociation reported here can hardly be formulated within a left-verbal-preserved/right-non-verbal-altered framework, but rather within a model that takes into account the contextual aspects of the learned material (Winocur *et al.*, 2010).

To our knowledge, such dissociation in the long-term consolidation of episodic and semantic memory has never formally been documented in the human. As mentioned above, Butler and colleagues (2007) have assessed word lists and complex drawings consolidation in a group of patients with transient epileptic amnesia and demonstrated an accelerated forgetting over a several week-delay. In contrast, Bayley *et al.* (2008) have studied long term consolidation of single-item memory in a group of patients with large medial temporal lobe lesions. Based on recognition procedures using a wide range of stimuli (such as faces, objects and words), they evidenced residual memory traces of information encoded up to 10 months before (Bayley *et al.*, 2008). More stringent evidence supporting the idea that the long-term storage of episodic and semantic memory relies on distinct cortical networks are derived from animal studies (Ross and Eichenbaum, 2006). Rats with hippocampal lesions exhibit severe deficit on spatial/contextual memory over several weeks (Clark *et al.*, 2005; Winocur *et al.*, 2005, 2009), contrasting with a preservation of long-term memory that is not embedded in a specific context (Tse *et al.*, 2007). In contrast, rats with perirhinal lesion exhibit long-term consolidation deficit of the object memory trace that supports object recognition memory (Winters and Bussey, 2005).

All patients also displayed a dense and extended retrograde episodic autobiographical amnesia that covers most of their adult life, sparing however, their childhood and early adulthood periods. Interestingly, neither the 'standard model' of memory consolidation (Squire and Alvarez, 1995) nor the Multiple Trace Theory (Moscovitch and Nadel, 1998) can fully account for this U-shaped gradient of memory loss. Indeed, according to the 'standard model' of memory consolidation, hippocampal damage should lead to a temporal gradient with greater sparing of remote than recent information (Squire and Bayley, 2007). But remote and recent information were found spared to a similar extent in our study. In contrast, Multiple Trace Theory suggests that episodic memory remains dependent of the hippocampus over time (Moscovitch *et al.*, 2006). Thus, patients should have a deficit in episodic autobiographical memory for all time periods (Milton *et al.*, 2010). We found no impairment across all lifetime periods using a test that assessed strictly episodic autobiographical memory (Piolino *et al.*, 2009). A possibility is that episodic memory traces acquired during brain development are structurally more stable, requiring less reactivation later on to be accessible, subsequently being less prone to disorganization in the case of hippocampal dysfunction. Finally, this remote episodic information may remain partly available under a less integrated, schematic version, which recollection endorses sufficient narrative details to obtain normal performance on autobiographical testing. Winocur and colleagues (2010) have recently proposed that memory undergoes a series of transformation over time. Accordingly, when initially formed, memory is assumed to be episodic and context-bound, and remains dependent on the hippocampus for as long as it is available. With time and experience, a hippocampal memory supports the development, in neocortex, of a schematic version which retains the gist of the original memory, but few of its contextual details.

Relationships between impaired consolidation and epilepsy

The phenomenon reported here challenges the traditional models of memory that assume information has reached long-term memory once it has been stored for longer than few minutes (Kapur *et al.*, 1997; Jansari *et al.*, 2010). Rather, it indicates that memories have an extended period of vulnerability during which they undergo a process of slow consolidation before reaching long-term/permanent storage (Horn *et al.*, 1981; Blake *et al.*, 2000). In the same view, several data indicate that reactivation of a memory trace can induce an additional labile phase that requires an active process to stabilize memory (Misanin *et al.*, 1968). This process, termed as reconsolidation, is hypothesized to be an important component of long-term memory processing (Nader, 2003; Dudai, 2006; Tronson and Taylor, 2007). In a recent study, Jansari and colleagues (2010) showed in a patient with temporal lobe epilepsy the protective effect of repeatedly recalling/reactivating the information on memory traces. Then, in a closely controlled experimental setting, repeated reactivation can lead to the stabilization of long-term memory traces. However, and as suggested by our results, when information rehearsal does not occur, contextually bound material remains vulnerable during a several-week period and eventually fades, despite successful initial encoding.

A key question that remains unanswered concerns the mechanism by which epileptic activity interferes with memory consolidation processes. The responsibility of recurrent seizures to account for long-term consolidation impairment has been raised by several authors. This hypothesis is highly plausible in those cases of severe, pharmaco-resistant temporal lobe epilepsy awaiting resective surgery (Viskontas *et al.*, 2000). Here however, all patients have been free of clinical seizure for the past year (20 months on average). An alternative hypothesis is that ongoing subclinical epileptiform activity (Holmes and Lenck-Santini, 2006; Zangaladze *et al.*, 2008) within the hippocampal formation impedes the chain of molecular and cellular events that participate to the building and stabilization of episodic representations (McGaugh, 2000). In support of this hypothesis, activation of epileptic spikes on EEG recording and seizures prominently occurred during sleep in all patients. A large body of evidence supports the role of slow wave sleep in memory consolidation processes (Stickgold, 2005; Takashima *et al.*, 2006; Gais *et al.*, 2007; Rauchs *et al.*, 2008). Thus, alteration of sleep-related memory consolidation may be a potential mechanism to account for the observed memory deficits in our patient group, which would deserve further investigation.

Finally, all patients included in the present study exhibited memory impairments in the setting of pharmaco-sensitive temporal lobe epilepsy, with or without a past history of transient amnestic episodes. The term of 'interictal epileptic episodic amnesia' could tentatively be proposed to account for this peculiar pattern of memory disorder, occurring in subjects with a history of adult onset pharmaco-sensitive temporal lobe epilepsy, memory complaint of gradually forgetting autobiographical memory contrasting with normal performance at standardized memory assessment. In contrast with 'transient epileptic amnesia', this descriptive

terminology does not put the emphasis on the acute memory disturbance and its putative relationship to seizures, but rather on the non-ictal and long-standing aspects of the deficit, and the episodic nature of the forgotten material. Interictal epileptic episodic amnesia may provide a potentially valuable model for studying the functional impact of subictal epileptiform activities on neural networks involved in the building and stabilization of episodic memory traces, and may help shading some light into some of the mechanisms underlying memory consolidation processes.

Conclusion

We report on a series of patients with adult-onset pharmaco-sensitive temporal lobe epilepsy, and episodic memory complaints contrasting with normal performance at standardized memory assessment. In-depth neuropsychological evaluation demonstrated a retrograde autobiographical amnesia covering most adult life, along with a clear-cut dissociation between long-term consolidation of episodic anterograde memory and context-free material including semantic knowledge. Together with neuroimaging metabolic data, our results may suggest that hippocampal dysfunction impedes consolidation of episodic memory but leaves intact semantic memory, in the line of models that posit a segregated functional organization within medial temporal lobe structures. They also suggest that episodic memory consolidation deficits underlie some of the memory disturbances observed in the setting of temporal lobe epilepsy. The term of 'interictal epileptic episodic amnesia' could tentatively be proposed to qualify this pattern of memory loss, occurring in the setting of adult onset temporal lobe epilepsy, and despite full remission of clinical seizures under anti-epileptic treatment.

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Supplementary material

Supplementary material is available at *Brain* online.

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Supplementary Materials and Methods

Autobiographical memory tasks

TEMPau task (Piolino et al., 2000)

Method : Participants are first given precise instructions to recall personal events from different time periods which occurred only once, at a particular place and date, and lasted several minutes or hours but nevermore than a day. Four or five periods of life (P1: childhood up to 17 years ; P2: 18-28 years ; P3: more than 28 years; P4: last 5 years excluding the last year; P5: last year) were investigated according to the patients age. P3 was therefore investigated only in MR, JH and MC. In each of the periods examined, except for the last one, four topics were investigated (a meeting or an event linked to a person, a school or professional event, a trip or a journey and a family event). Eight questions were asked about the most recent period, in chronological order (last summer, Christmas or New Year's day, last month, last week, last week-end, two days ago, yesterday, today). For each event recalled, the subjects had to indicate the subjective states of conscious awareness (remembering, simply knowing or guessing) associated with retrieval of the episode.

Scoring: Each event is scored on a 5-point episodic scale (from 0 to 4) which takes into account the specificity of the content (i.e. single or repeated event), the spatiotemporal situation, and more especially the presence of internal details (i.e. perceptions, thoughts, feelings). Two main total scores are recorded per lifetime period examined: (a) an overall score, which includes all the memories (both specific and generic) and corresponds to the classic episodic memory score used in the Autobiographical Memory Interview (Kopelman et al., 1989) and (b) an episodic score, which only includes specific and detailed memories scoring 4 (max = 16).

Test of familiar photographs

The experimental stimuli consisted of 25 coloured photographs of specific personal events experienced by the subjects. Photographs were collected with the help of family members who were asked to select pictures that had not been recently viewed by the participant. Five periods [P1:1980-1990; P2: 1990-2000; P3: 2000-2006; P4: last 12 months - except for the last month; P5: last month] were investigated with five photographs of personal events corresponding to each period.

The 25 pictures were presented one by one in random order and the subjects were asked to recollect and re-live a specific episode that occurred during the depicted event. They were required to describe this episode with as many details as they could (e.g. “can you tell us a specific event that happened at the wedding?”). Episodes were scored on a 5 points scale (from 0 to 4) for specificity and richness of detail, as in the scoring of the TEMPau task. We calculated for each subject a score for each time period (max = 20).

Episodic memory tests

Memorization of a chain of episodes

First the subject and the examiner took the elevator to the ground floor. Next they went to the news stand because the examiner explained that he had to buy the local daily paper for the waiting room. Then they went to the cafeteria, where the examiner ordered and paid for the coffees and teas. While having their drink, a conversation took place between the examiner and the participant, during which the examiner led the conversation by asking a set of questions about the last movie seen, the last holidays, the participant’s occupation and its place of birth. Afterwards, they visited the nearby children’s hospital, from where they could see the helicopter platform. They then took the elevator back to the department, stopped by the secretary’s office to hand in the daily paper and went on to the examiner’s office.

Single-item recognition memory tests

Two-alternative forced-choice recognition of words

192 words were selected from the Brulex database (Content et al., 1990) and were matched for frequency and length. During the encoding phase, subjects were asked to consecutively look at 48 words and to count the number of syllables with a time limit of 4 seconds. Three minutes after an interfering task, a forced-choice recognition task was completed with a first set of 48 distractors (Set 1). Each target was shown simultaneously with a distractor, presented in equal proportion on either the left or the right side of the sheet, and the subject was asked to recognise the target. Without prior warning, a second and third recognition tasks were conducted one hour and 6 weeks later with different sets of distractors (Set 2 and 3). Each subject’s performance was expressed as a percentage of correct answers (level of chance: 50%, recognition of all targets:100%).

Two-alternative forced-choice recognition of topographical scenes

120 photographed places (buildings, streets, squares…) were presented to participants who had to count the number of the main components composing the scene with a time limit of 4 seconds. Three minutes after an interfering task, a forced-choice recognition task was completed with a first set of 30 distractors (Set 1). Each target was shown simultaneously with a distractor, presented in equal proportion on either the left or the right side of the sheet, and the subject was asked to recognise the target. Without prior warning, a second and recognition tasks were conducted one hour and 6 weeks later with different sets of distractors (Set 2 and 3). Each subject's performance was expressed as a percentage of correct answers (level of chance: 50%, recognition of all targets:100%).

Four-alternative forced-choice recognition of doors

100 doors were selected from the Doors'test (Baddeley et al., 1994). During the encoding phase, subjects were asked to consecutively look at 10 doors and to memorize them. Each target was presented until the subject acknowledged having encoded the stimulus, with a time limit of 4 seconds. Three minutes later, a forced-choice recognition task was completed with a first set of 30 distractors (Set 1). Each target was shown simultaneously with three distractors in randomized position and the subject was asked to recognise the target. Without prior warning, a second and third recognition tasks were conducted one hour and 6 weeks later with different sets of distractors (Set 2 and 3). Each subject's performance was expressed as a percentage of correct answers (level of chance: 25%, recognition of all targets:100%).

Yes-no recognition of faces

72 faces were selected from the face recognition subtest of the Wechsler Memory Scale-III (Wechsler, 2001). During the encoding phase, subjects were asked to consecutively look at 18 faces and to memorize them. Each target was presented until the subject acknowledged having encoded the stimulus, with a time limit of 4 seconds. Three minutes later, a forced-choice recognition task was completed with a first set of 18 distractors (Set 1). Targets and distractors are presented one by one in a random order and the subject was asked to recognise the target. Without prior warning, a second and third recognition tasks were conducted one hour and 6 weeks later with different sets of distractors (Set 2 and 3). Each subject's performance was expressed as a percentage of correct answers (level of chance: 50%, recognition of all targets:100%).

Yes-no recognition of words

128 words were selected from the Brulex database (Content et al., 1990) and were matched for frequency and length. This recognition test was administrated three months after the two-alternative forced-choice recognition of words to avoid effect of interference.

During the encoding phase, subjects were asked to consecutively look at 32 words and to memorize them. Each target was presented until the subject acknowledged having encoded the stimulus, with a time limit of 4 seconds. Three minutes later, a forced-choice recognition task was completed with a first set of 32 distractors (Set 1). Targets and distractors are presented one by one in a random order and the subject was asked to recognise the target. Without prior warning, a second and third recognition tasks were conducted one hour and 6 weeks later with different sets of distractors (Set 2 and 3). Each subject's performance was expressed as a percentage of correct answers (level of chance: 50%, recognition of all targets:100%).