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# **Hidden objective memory deficits behind subjective memory complaints in temporal lobe epilepsy**

Béatrice Lemesle, Emmanuel J. Barbeau, Emilie Milongo Rigal, Marie Denuelle, Luc Valton, Jérémie Pariente, and Jonathan Curot

**Abstract**

**Objective:** To test the hypothesis that temporal lobe epilepsy (TLE) patients with *subjective* initial memory complaints (not confirmed by an objective standard assessment) and various phenotypes also show *objective* very long-term memory deficit with accelerated long-term forgetting, we tested TLE patients with two surprise memory tests after 3 weeks: (1) the standard Free and Cued Selective Reminding Test (FCSRT), and (2) Epireal, a new test specifically designed to capture more ecological aspects of autobiographical memory.

**Methods:** 47 TLE patients (12 hippocampal sclerosis, 12 amygdala enlargement, 11 extensive lesions, 12 normal MRI) who complained about their memory, but for whom the standard neuropsychological assessment did not reveal any memory impairment after a standard delay of 20 min, underwent two surprise memory tests after three weeks. They were compared to 35 healthy control subjects.

**Results:** After 3 weeks, FCSRT and Epireal recall scores were significantly lower in patients than in controls ( $p < 0.001$ ). There was no significant correlation between FCSRT and Epireal scores ( $p = 0.99$ ). Seventy-six percent of TLE patients had objective impairment on at least one of these very long-term memory tests, regardless of the existence and type of lesion or response to antiseizure medication. Easily applicable, Epireal had a higher effect size, detected deficits in 28 % more patients, and is a useful addition to the standard workup.

**Conclusion:** Assessing long-term memory should be broadened to a wide spectrum of TLE patients with a memory complaint, regardless of the epileptic syndrome, and associated with a lesion or not. This could lead to rethinking TLE nosology associated with memory.

**Glossary:**

EEG: Electroencephalogram

FCSRT: Free and Cued Selective Reminding Test

QAM: Self-assessment memory questionnaire (Questionnaire d'autoévaluation de la mémoire)

STAI: State-Trait Anxiety Inventory

TEA: Transient epileptic amnesia

TLE: Temporal lobe epilepsy

yr.: year

**Introduction**

More than fifty percent of epilepsy patients complain that their memory function moderately or severely limits their daily functioning.<sup>1</sup> Even if their complaints are taken seriously, i.e., they lead to a neuropsychological evaluation, they may not be confirmed, leading to the idea that the patient may have a purely *subjective* complaint related to, for example, anxiousness or neuroticism<sup>2</sup>. This conclusion may be reinforced by the notion that some antiseizure medication may impair memory efficiency<sup>3-5</sup> and that, consequently, subjective memory impairment should not be taken too seriously.

Very long-term memory assessment, usually limited to specific autobiographical memory complaints, can, however, reveal accelerated long-term forgetting (ALF, normal learning of new information but accelerated forgetting of that information over subsequent days or weeks). ALF is particularly observed in transient epileptic amnesia (TEA, a syndrome primarily characterized by seizures with dense transient amnesia, in which there is also a high prevalence of interictal accelerated long-term forgetting and retrograde memory deficits)<sup>6,7</sup>.

However, it is unclear whether or not other TLE patients<sup>2,8</sup> not particularly suggestive of TEA<sup>6,7</sup>, with different phenotypes (such as syndromes related to hippocampal sclerosis, amygdala enlargement, etc.) also suffer from interictal accelerated long-term forgetting.

To test the hypothesis that these TLE patients with *subjective* memory complaint do, in fact, have an *objective* very long-term memory deficit related to accelerated long-term forgetting, 47 TLE patients who had a general complaint about their memory but for whom the standard neuropsychological assessment did not reveal memory impairment after a standard delay of 20 minutes, underwent two surprise memory tests after three weeks. One test, the Free and Cued Selective Reminding Test (FCSRT), was standard and adapted for very long-term assessment. The other, Epireal, was a new test specifically designed to capture more naturalistic components of autobiographical memory, such as episodes and recollection. We thought that the combination of both tests would be needed to reveal if some patients showed accelerated long-term forgetting. Their performance was compared to that of 35 matched healthy control subjects.

## **Methods**

### **Participants**

Patients suffering from focal TLE were recruited between 2015 and 2017. Inclusion criteria were: (1) TLE diagnosis confirmed by an epileptologist (MD, LV, JC) (see below); (2) spontaneous and recurrent interictal memory complaints, including autobiographical memory complaint – related to personal events, with poor sensitivity to cueing, and confirmed by a family member - to capture specific rather than vague or attentional complaints. The assessment of this complaint was based on the clinical interview performed by the MD in charge of the patient; (3) absence of objective memory impairment after standard neuropsychological assessment (score considered normal, i.e., within 2 standard deviations of

age-matched norms to the FCSRT<sup>9</sup> at 20-minute delayed free and cued recall); (4) MMSE score >25.

Patients were recruited from the epilepsy unit and the cognitive neurology departments of Toulouse University Hospital. All participants shared common features with a consistent diagnosis after several years of follow-up: epileptic seizures suggestive of TLE and recurrent spontaneous autobiographical memory complaints throughout follow-up. If epilepsy was the reason why most patients were referred to the epilepsy unit, TEA was initially diagnosed for some of the five patients referred to the cognitive department. However, this diagnosis was revised during evolution because follow-up demonstrated that they could not be limited to the strict definition of TEA<sup>6,7</sup> and these patients were managed like any other patient with TLE afterward.

Patients were matched (for age, gender, hand laterality, and socio-cultural level) with healthy control subjects recruited on a voluntary basis. Control subjects had no chronic diseases and no cognitive complaints. All participants underwent the same neuropsychological evaluation.

### **Temporal lobe epilepsy diagnosis**

TLE diagnosis associated the repetition of clinically stereotyped seizures whose semiology was highly suggestive of a temporal lobe origin [i.e., repeated seizures including one or several initial symptoms such as experiential phenomena (transitory mental states, sensory and memory illusions such as déjà-vu, reminiscences or dreamy-state)], oral automatisms (e.g., swallowing, chewing), epigastric feelings, fear, transient amnesia, partial impairment of memory, loss of contact, language disorders or verbal automatisms (such as repetition of phrases or understandable words, onomatopoeia, humming),<sup>10</sup> with epileptic activity (EEG abnormalities) on at least one scalp EEG recording suggesting a temporal lobe

origin (seizure(s) and/or interictal epileptic discharges and/or focal sharp theta slowing, located over one or both temporal lobes). Each patient underwent a 1.5 or 3 Tesla brain MRI for etiological diagnosis, including at least 3DT1, T2, FLAIR, and spin echo T2 sequences. Each patient also had several hours of scalp EEG recordings during wake and sleep periods throughout follow-up (except 3 patients, who only had several scalp EEGs awake). When no seizure was recorded on EEG data, the laterality of the hypothetical onset of seizures was based on congruent seizure semiology, location of MRI lesion, and epileptic activities.

### **Memory complaint rating**

The magnitude of the memory complaint was assessed using the reduced (20 questions out of 64) version of the QAM (memory self-evaluation questionnaire).<sup>11</sup> This questionnaire concerns places, persons, and facts of personal life. It had been validated previously as reliable for testing autobiographical memory, rather than measuring some aspects of attention that might interfere with the memory complaint. We selected the most relevant questions to specifically assess the status of anterograde memory and shorten the length of the clinical assessment.

### **Initial and three-week neuropsychological assessment**

A standard neuropsychological evaluation was performed during two sessions of equal length, separated by a 3-week interval (Table 1, details of the standard tests presented in the Results section). Among other tests, the standard French version of the FCSRT<sup>9</sup>, a verbal memory test consisting of learning 16 words, was administered during the first neuropsychological meeting and only participants with normal scores were included in the full study and tested 3 weeks later (Figure 1). The FCSRT is an explicit verbal memory test consisting of a first encoding stage where 4 sets of 4 words are learned and then recalled

immediately. It is then followed by three consecutive stages of free and cued recall during which subjects have to learn the 16 words; the target words are provided if subjects do not recall them. A delayed stage of free and cued recall is performed after 20 minutes.

Psychiatric scales were also proposed to all subjects to assess the levels of mood disturbance (Beck depression inventory), anxiety (State-Trait Anxiety Inventory STAI Y-A), and motivation (Starkstein motivation scale), which could bias neuropsychological performances.<sup>12</sup>

### **Long-term memory assessment at 3 weeks**

Both the free and cued recall parts of the FCSRT were administered by surprise again after three weeks (i.e., the subjects were not informed during the first meeting that they would be retested later on FCSRT words). As participants had normal performances on the FCSRT at the initial assessment, and as this test consists of three sequences of learning and recalling a list of words, this test is over-rehearsed and cannot be considered ecological. Learning is not incidental and does not allow assessment of all the components of episodic memory (“what”, “where”, “when” and sense of agency).<sup>13</sup>

Autobiographical memory is multisensory, usually learned incidentally and, in its episodic form, not repeated. Therefore, we designed a more naturalistic test, Epireal, which we expected would be more sensitive. The general idea of Epireal is to incidentally introduce eight standardized real-life mini-events during the neuropsychological assessment (for example, the subject is asked to give the examiner a green binder located on a chair behind him), and to test three weeks later if subjects remembered these events (illustration of mini-events in Figure 1; details in eFigure 1 & eTable 1). The eight mini-events were chosen according to the following constraints: events usable by the largest number of clinicians, not requiring constraints of place, time, or expensive material, and strict control of the encoding



conditions, so that all subjects experienced a similar multisensory situation. All subjects experienced the same mini-events in the same order. Subjects were not informed that they would subsequently be questioned on these mini-events. To facilitate the whole procedure, it was simply explained that the neuropsychological tests would be administered in two sessions separated by three weeks. Recall of these mini-events was not tested during the first neuropsychological assessment.

During the second neuropsychological assessment, three weeks later, participants were interviewed on the mini-events that had happened and asked to recall them as precisely as possible, as if reliving the moment. This explicit instruction implies a conscious recollection of the memory and a mental re-experience of the event, key components of episodic memory retrieval.<sup>13</sup> Different components of memory were assessed. 1) Sense of agency during retrieval, related to feelings of action, causality, and self-consciousness, i.e., if the participant thinks he/she was an actor or a spectator of the mini-event<sup>13,14</sup> (note that in this study, this was assessed objectively and not subjectively). A response “actor” or “spectator” was considered correct (agency performances) if the subject was indeed an actor (e.g., he himself took the binder) or spectator of the event (e.g., the phone is ringing, the patient does not act on it). 2) “where” context (e.g., on the chair behind the patient). 3) “when” context (e.g., at which moment of the initial evaluation).

A free recall phase was first performed, followed by a cued one. Retrieval of the eight mini-events was rated on 39 [content (what) = 22 max., spatial context (where) = 8 max., temporal features (when) = 9 max.] We added free and cued recall scores to obtain a *total score* for each memory test.

### **Statistical analyses**

Performances on the different cognitive tests were analyzed by repeated-measures multivariate analysis of variance (MANOVA) with factors of group (patients and controls)

and patients' clinical features within the patient groups (i.e., lesion, no lesion, etc.) across the different cognitive tests. A p-value  $<0.05$  was considered significant. We calculated effect size between groups using Cohen's  $d$  (effect size was considered weak between 0.2 and 0.5, medium between 0.5 and 0.8, and high above 0.8). All statistics, such as MANOVAs and Pearson correlations, were performed using *RStudio* and the *scipy.stats* Python library.

### **Standard Protocol Approvals, Registrations, and Patient Consent**

All participants provided written informed consent to take part in this study. The inclusion of patients and use of clinical data in this study was performed in the framework of an ethics authorization by the Toulouse University Hospital ('MR004 n°2020-140').

### **Data Availability Statement**

Anonymized data will be shared by request from any qualified investigator.

## **Results**

### **Subjects' demographic and clinical features**

Forty-seven patients (24 males, 3 left-handed) matched the inclusion criteria: 42 patients were recruited from the epilepsy unit and 5 from the cognitive neurology departments of Toulouse University Hospital. Thirty-five matched healthy control subjects (23 males, 3 left-handed) were recruited. Main demographic characteristics did not differ significantly between patients and controls (Table 1). MRI profiles of TLE were different across patients and were divided into four groups: hippocampal sclerosis (isolated or only associated with lesions related to mesial temporal sclerosis), amygdala enlargement<sup>15</sup> (without any visible hippocampal lesions), extensive temporal lesion (e.g. glial tumor, autoimmune encephalitis sequelae, arteriovenous malformations, etc.) and no lesion (Figure 2, Table 1). Details about

epileptic features for each patient are available individually in eTable 2. No patient was taking medication with known amnesic effects, except one (patient 29 took benzodiazepine as part of his usual treatment). Four patients took antidepressant medication. Epilepsy duration was heterogeneous across patients (mean duration: 10.7 years  $\pm$  7.3; Table 1). Fourteen (29.8%) patients matched the International League Against Epilepsy definition for pharmacoresistance.<sup>16</sup> Mean number of antiseizure medications per patient was 1.54  $\pm$  0.56 (Table 1). The standard neuropsychological and psychiatric evaluation of patients and control subjects is presented in Table 2.

### **Memory complaint and standard memory evaluation (initial evaluation)**

Memory complaint differed significantly between patients and controls as expected (QAM test;  $F(1, 79)=39.7$ ,  $p<0.001$ ), (Figure 3A and Table 1). Because it was an inclusion criterion, performance on the verbal test FCSRT did not differ between patients and controls, either for total (free + cued) immediate recall scores ( $F(1, 79)=0.1$ ,  $p>0.05$ ) or for total delayed (20 minutes) recall scores ( $F(1, 79)=0.6$ ;  $p>0.05$ ) (Figure 3B, maximum performance possible on the FCSRT = 16). Of note, the performance of the patients was slightly lower than that of controls ( $F(1, 79)=4.3$ ,  $p=0.039$ ) on the delayed free recall (20 minutes). The patients also repeated significantly more words they had already recalled ( $F(1, 79)=10.5$ ,  $p=0.001$ ). However, patients' individual scores remained within normal range ( $>-2$  SD from the mean of age-matched norms). The learning curves of the two groups superimpose for all four stages of recall, indicating that learning is very similar between the two groups at standard delays (eFigure 2).

### **Very long-term memory evaluation (assessment at three weeks)**

After three weeks, FCSRT scores were significantly lower in patients than in controls, both for free ( $F(1, 79)=25.2, p<0.001$ ) and total recall ( $F(1, 79)=27.5, p<0.001$ ) (Table 1, Figure 3C). Performance on the Epireal test was likewise significantly lower in patients than in controls, both for free ( $F(1, 79)=39.6, p<0.001$ ) and total recall ( $F(1, 79)=29.0, p<0.001$ ). There was no significant correlation between memory complaint (QAM scores) and FCSRT ( $r=0.01, p=0.37$ ) or Epireal total scores ( $r=-0.24, p=0.09$ ). Interestingly, there was no significant correlation between the FCSRT and Epireal total recall scores, either ( $r=0.00, p=0.99$ ).

We calculated the proportion of patients showing impairment on the two memory tests using a cut-off below the 5<sup>th</sup> percentile of control subjects. Impairment was seen in 48.9% of patients on the FCSRT versus 59.6% on the Epireal. Interestingly, 13 (27.7%) patients had deficits only on Epireal scores, 8 (17.0%) only on FCSRT scores, and 15 (31.9%) on both. Overall, 76.6% were impaired on the long-term memory tests. By contrast, eleven (23.4%) patients did not fail either test. Impairment on one or the other test did not depend on the type of lesion (Figure 4). There was no difference in delayed free and total recall scores in the Epireal or FCSRT after 3 weeks according to the MRI profiles (all  $p > 0.25$ ).

Considering detailed scores on Epireal, retrieval scores of “where” contextual information, “when,” and content were all significantly lower in patients than in controls (Table 2). Agency performances were also significantly lower in patients than in controls (spectator: ( $F(1, 79)=23.8, p<0.001$ ), actor: ( $F(1, 79)=13.35, p<0.001$ )).

### **No influence of lesion type on memory complaint and objective memory deficits**

Surprisingly, memory complaint was not significantly different between patients with or without a lesion. After three weeks, free and total recall scores on the Epireal and FCSRT were likewise not significantly different between patients with and without a lesion.

Moreover, it did not differ significantly according to the laterality of the seizure origin.

Within-patient group analyses are provided in eTable 3.

### **Relation with the severity of epilepsy and psychiatric scales**

Memory complaint or recall on the FCSRT or Epireal did not depend on the duration of epilepsy, or pharmacoresistance, or the number of drugs taken (eTable 3). The frequency of seizures significantly affected memory complaints ( $F(2,44)=4.5$ ,  $p=0.01$ ). However, the frequency of seizures did not significantly affect Epireal scores, either on free recall ( $F(2,44)=1.4$ ,  $p=0.24$ ) or the total score ( $F(2,44)=1.8$ ,  $p=0.17$ ). Nor did it influence performance on the FCSRT on either free ( $F(2,44)=0.6$ ,  $p=0.54$ ) or total recall ( $F(2,44)=1.8$ ,  $p=0.17$ ; eTable 3). No correlation was found between the STAI ( $p=0.71$ ), Beck depression inventory ( $p=0.24$ ), or motivation scale ( $p=0.68$ ) with Epireal total scores after 3 weeks. Likewise, no significant correlation was found between the QAM and either the Beck depression inventory ( $p=0.53$ ) or the STAI ( $p = 0.06$ ). However, a significant correlation between the QAM and the motivation scale ( $r=0.40$ ,  $p=0.005$ ) was found.

We also performed complementary analyses to assess whether the group of patients who did not show an objective impairment at three weeks also showed a specific neuropsychological or lesional pattern. We did not however, observe any statistical difference between this subgroup of patients and the other patients.

### **Discussion**

About 75% of a broad population of patients with TLE with initial subjective memory complaint were found to have objective memory impairment after three weeks, whether they

had a brain lesion or not and regardless of the type of lesion and response to antiseizure medication.

The majority of TLE patients showed significant impairment after 3 weeks, regardless of the type of memoranda (list of words or real-life events) and the retrieval modality (free or cued), despite showing no impairment over a standard delay of 20 min. Such a pattern suggests normal learning and retention of information over relatively brief delays, but accelerated long-term forgetting in this TLE population with initial subjective complaint.<sup>17-19</sup> Even cued recall was impaired after three weeks, suggesting genuine memory impairment that could not simply be explained by effortful or strategic difficulties.<sup>20,21</sup> Therefore, these results are consistent with a complaint dominated by anterograde *very long-term* memory difficulties and provide new evidence that initial “subjective” memory impairment should not be too rapidly dismissed and instead should be taken very seriously.

Such an observation may have a significant impact on the management of TLE patients. Most of them are first referred to epilepsy units for recurrent seizures, not for memory disorders, while they also complain about their long-term memory. Clinicians are trained first and foremost to analyze symptoms to make an accurate diagnosis as fast as possible. In this process, the complaints expressed by patients play a critical role because they help practitioners to know what symptoms to look for or to verify whether the complaint matches the symptoms, suggesting that they have correctly pinpointed the disease. Complaints in epilepsy – especially when dealing with subjective symptoms – have, however, a particular status because of the important proportion of psychogenic forms of seizures. Psychogenic non-epileptic seizures represent about 30% of cases in epilepsy centers<sup>22</sup> and combine heterogeneous subjective phenomena.<sup>23</sup> This may lead to a certain skepticism regarding complaints that cannot be confirmed by objective assessment.

One special type of subjective memory complaint has, nevertheless, attracted attention recently. Some patients have specific complaints about forgetting full episodes or details of events of their life, specifically concerning autobiographical information.<sup>17,24</sup> These patients usually have a normal memory evaluation when assessed in a standard manner, i.e., 20 to 60 minutes after encoding the memoranda. Their complaint was therefore initially considered subjective. It is only after special procedures were designed, allowing memory assessment after longer delays of 1 to 8 weeks, that it was observed that some of these patients had *objective* memory difficulties in the form of rapid forgetting or consolidation difficulties (accelerated long-term forgetting).<sup>25-27</sup> A high prevalence of accelerated long-term forgetting and autobiographical amnesia is especially noticed in TEA,<sup>6,7</sup> although controversies exist regarding the homogeneity of these patients and the mechanisms behind this rapid forgetting.

However, as TEA becomes better known, very long-term delay memory assessment (>1 week) has so far usually been proposed to patients with both ictal amnesia at the forefront of clinical phenotype and interictal complaints of autobiographical memory. In these cases, ictal and interictal memory disorders are the key symptoms guiding referral in consultation. Therefore, one question remains unanswered in this context. It remains unclear whether or not other epileptic patients, with both *subjective* memory complaints not particularly suggestive of TEA and an ictal semiology encompassing a series of non-memory symptoms, also show *objective* very long-term memory impairment. By demonstrating objective accelerated long-term forgetting in patients after 3 weeks belonging to the wider TLE spectrum, the results of our study should lead to rethinking the nosology of TLE syndromes associated with memory disorders, in particular to discussing the relevance of TEA as a syndrome on its own.

This study offers additional evidence for widespread, very long-term memory difficulties in epilepsy, as previously shown in subjective complaints.<sup>27</sup> However, our results also shed light on the structural basis of accelerated long-term forgetting. Unlike most

previous reports on TEA<sup>6,7</sup>, we selected a wide spectrum of TLE patients, in which memory complaint was the main common point. Otherwise, patient etiologies and lesions were highly heterogeneous. Importantly, these difficulties were also evidenced when the MRI was normal and did not vary depending on the type of lesion (hippocampal sclerosis, amygdala enlargement, or extensive temporal lesion). This is an important piece of information, suggesting that the same level of attention must be paid to a memory complaint regardless of the epileptic syndrome, and associated with a lesion or not. It is necessary to go further than data suggesting that a hippocampal lesion in focal epilepsies is the main predictor of accelerated long-term forgetting, but which do not take into account the patient's complaint and its autobiographical components.<sup>28</sup> Consequently, verifying long-term (a delay exceeding 3 weeks in the present study) memory must not be limited to TEA but should be proposed to a broad epileptic population with TLE, including those with no visible lesion on brain imagery or in epileptic contexts considered more benign.

Memory complaint was originally and has largely been described in the aging population, as a symptom that could precede mild cognitive impairment<sup>29</sup> and has been related to subjective self-perceived cognitive decline among apparently cognitively normal individuals.<sup>30</sup> It is associated with an increased risk of Alzheimer's disease.<sup>31</sup> Cortical atrophy,<sup>32</sup> white matter degeneration<sup>33</sup>, and altered connectivity in resting-state networks<sup>34</sup> have been observed in patients with memory complaint. In these cases, memory complaint may reflect an early symptom of amyloid  $\beta$ -related pathology.<sup>35</sup> In parallel, recent studies suggest that accelerated long-term forgetting might be a sensitive marker of very early Alzheimer's disease.<sup>36</sup>

In epileptic patients, such links between memory complaint and neural tissue or connectivity damages remain to be demonstrated. Preeminent hypotheses to explain memory complaint in the epileptic population have been: (1) influence of depressive mood,



psychological distress, and disturbance of attentional functions,<sup>37</sup> (2) interference of medication on memory processes,<sup>38</sup> and (3) role of interictal epileptic discharges, especially during sleep.<sup>39,40</sup> The first and second hypotheses lack evidence or are supported by inconsistent or scarce results.<sup>41</sup> Our results do not corroborate these two hypotheses. There was no correlation with self-questionnaires assessing motivation, depression, or anxiety, which is in agreement with previous studies that found no correlation between the Hospital Anxiety and Depression Scale and very long-term memory performance.<sup>25</sup> We also did not notice any difference due to the number of antiseizure medications. In addition, only one patient used to take potential amnesic drugs. The impact of multiple antiseizure medications has been suggested in TLE patients for the onset of accelerated long-term forgetting.<sup>42</sup> However, this has not been observed in other TLE cohorts.<sup>43</sup> The hypothesis of the influence of medication is even more questionable when memory complaint often precedes its introduction.

Although our results are insufficient to speak for the third hypothesis (i.e., role of interictal epileptic discharges), they suggest specific memory consolidation impairment and not a bias of memory tests due to psychiatric symptoms or other psychotropic drugs known to influence cognitive scores. Future works should combine these memory tests with electrophysiological recordings during wake and sleep to determine the influence of interictal epileptic discharges on memory complaint and consolidation processes. Indeed, one of the major observations of our work is the absence of significant differences between patients with or without a lesion or among lesion types, regardless of the response to antiseizure medication and the frequency of seizures. With the caveat that an underestimation of the frequency of seizures and asymptomatic seizures<sup>39</sup> cannot be excluded, we can hypothesize that alterations of connectivity in a widespread long-term memory network (overlapping core medial and lateral temporal nodes) related to epileptic abnormalities, rather than lesions, may impact

consolidation processes. Such a hypothesis would match several recent observations: reduced resting state functional connectivity correlated with accelerated long-term forgetting,<sup>44</sup> consolidation impairment correlated with activation of interictal hippocampal epileptic discharges during sleep in TLE<sup>39</sup> and with a pathological coupling of cortical spindles with hippocampal interictal epileptic discharges in animals.<sup>40</sup>

The requirement for two meetings at three-week intervals initially appears time-consuming and difficult to schedule. However, the possibility of interleaving an ecological task as in Epireal and the option to divide the assessment into two, counterbalances this apparent limitation. The evaluation is usually exhaustive, at least in a substantial portion of epileptic patients.<sup>45</sup> Therefore, the global duration of the assessment is not significantly longer with tests like Epireal.

In this study, we also introduced a new test, Epireal, on the grounds that it was more ecological (i.e., relied on more sensory modalities and had a clearer episodic structure and personal relevance than usual word lists) and could provide a richer assessment of autobiographical episodic memory. The effect size was higher for Epireal than for the word list. It also detected memory deficits in more patients. Interestingly, it also clearly revealed the episodic nature of the long-term memory deficit in that both the “where” and “when” components were impaired, as well as the point of view (actor vs. spectator) of the patients when they recalled the Epireal episodes. Such a test also reveals that memory difficulties are not limited to the verbal modality. It is also particularly interesting to note that performance on the Epireal test did not correlate at all with the FCSRT, suggesting that it captures different aspects of memory. It is important to note that impaired autobiographical episodic memory has already been largely documented in patients with TLE, though regarding retrograde memory<sup>24,46,47</sup>. In contrast, Epireal assesses the ability to form new long-term memories, i.e., anterograde episodic memory, which is virtually never done as part of the neuropsychological

assessment because of the lack of adequate tools (see, however, <sup>26,48-50</sup>). Compared to other ecological and multidimensional tests, like the Extended Rivermead behavioural memory test or tests using the concept of mini-events that have influenced the creation of Epireal,<sup>e1</sup> Epireal is embedded incidentally in the course of neuropsychological assessment. It also allows analyses of different components of the memory that can participate in the deficit such as content, sense of agency, or what/where context. In this sense, a test like Epireal, which was well tolerated by the patients, may be a useful addition to the standard neuropsychological workup.

Intriguingly, we failed to identify objective memory deficits in 23 % of patients. We were not able to find a specific neuropsychological or lesional factor that would make these patients specific compared to the rest of the group. Future work should aim at clarifying the origin of the complaint of these patients.

Pragmatically, however, combining this new ecological tool with the classical FCSRT allows objective accelerated long-term forgetting to be revealed in 27.7% more epileptic patients with memory complaint. Overall, about 75% of the patients were impaired on one or both tests. Thus, the addition of a test like Epireal is not a simple binary alternative within the available neuropsychological arsenal, but a complementary tool with the ability to screen and detect objective long-term memory consolidation difficulties in more patients.

## **Conclusion**

The results of this study highlight that memory difficulties in epilepsy are very likely to be more heterogeneous than expected. Overall, qualifying a memory complaint as “subjective” should be done cautiously, or even avoided, as it may lead to an inappropriate diagnosis, insufficient therapeutic evaluation, or stigmatization. Generalizing long-term

detection of memory disorders may be a goal easily achievable using a two-stage neuropsychological assessment and appropriate tools such as the ones used in this study. Further work should focus on connectivity alteration of long-term memory deficits in conjunction with wake and sleep EEG for interictal analyses linked to neuropsychological assessment.

**Ethical publication statement**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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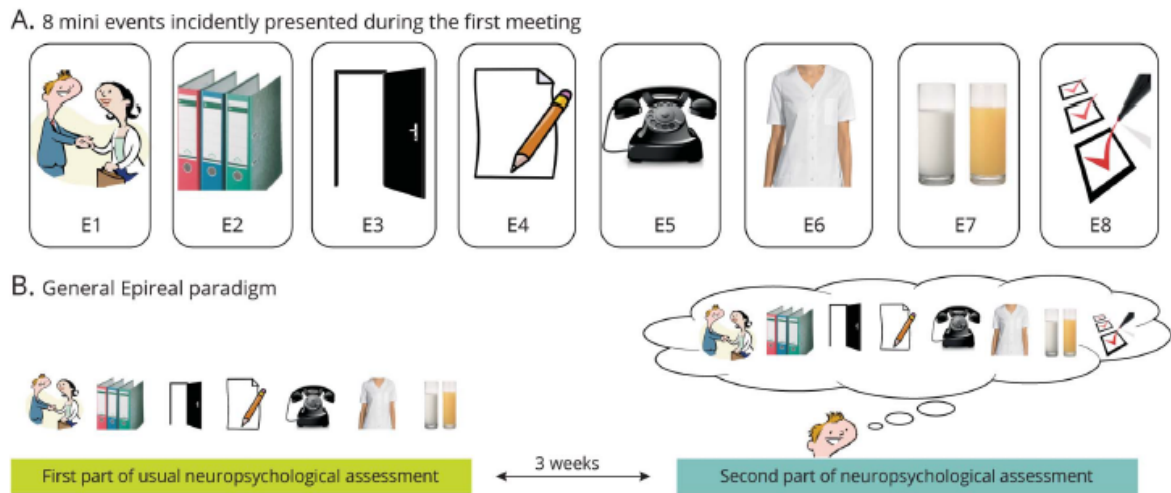


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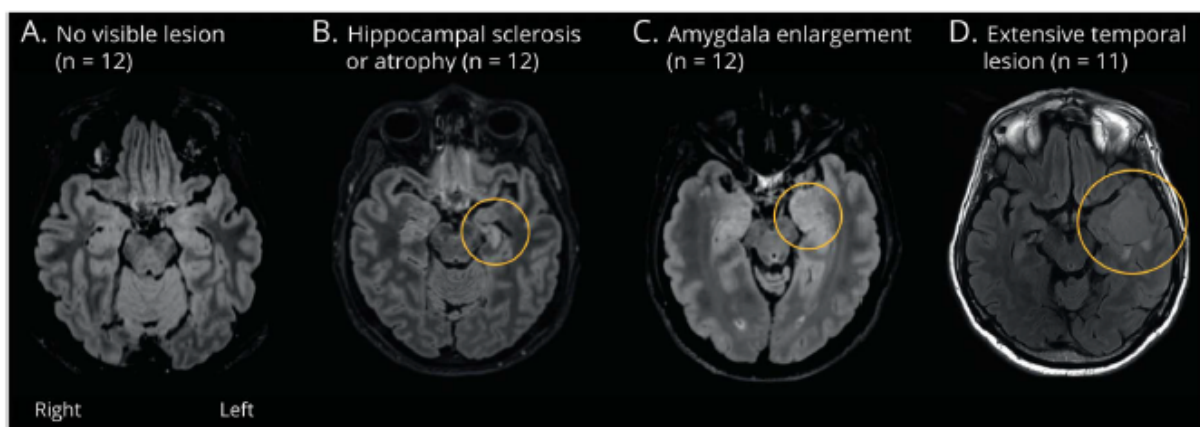
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## Figure legend



### Figure 1:

Epireal test. A – 8 mini-events are interleaved with standard neuropsychological tests during the first meeting and incidently presented (details of these mini-events are provided in eFigure 1). B – General Epireal paradigm. Participants are asked to recall these mini-events after 3 weeks.

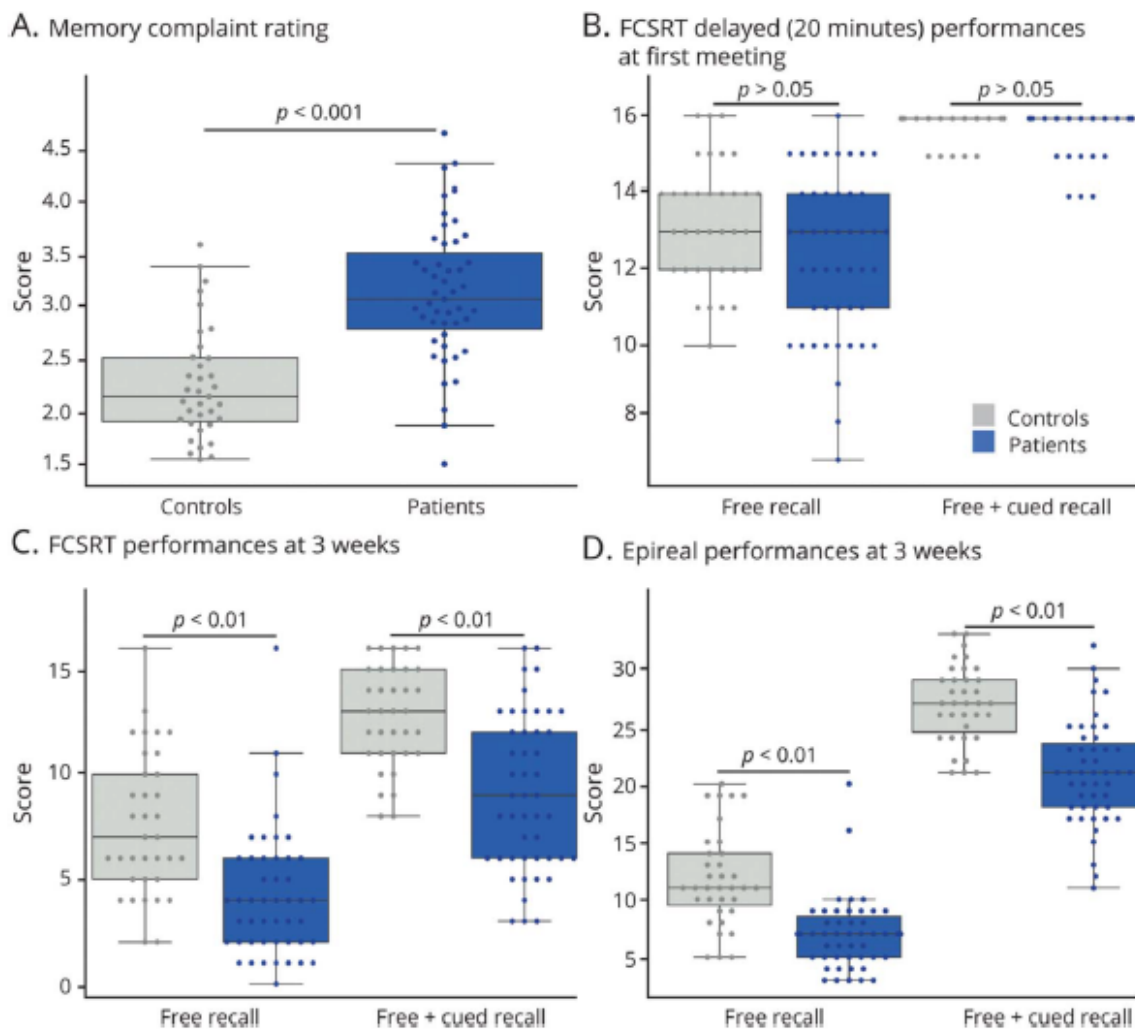


### Figure 2:

Four MRI profiles across patients (T2 FLAIR, axial slices).

A - No lesion visible on MRI (12 patients); B - Lesion clearly centered on the hippocampus (hippocampal sclerosis (HS) or more largely hippocampal atrophy; 12 patients). Example of

left anterior hippocampal sclerosis. C - Amygdala enlargement<sup>15</sup> without any other visible lesion (12 patients). Example of left enlargement of the amygdala (higher volume and slight hyperintensity of the left compared to the right). No lesion visible on the left hippocampus or on the contralateral temporal lobe. D - Extensive temporal lesion (11 patients). Example of an astrocytoma located in the anterior and basal left temporal lobe.

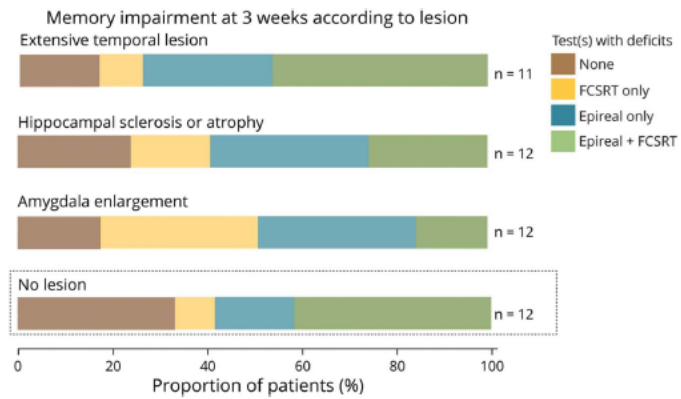


**Figure 3:**

Memory complaint, FCSRT scores, and Epireal scores in patients and controls.

A – Memory complaint assessed by the QAM. The QAM was used secondarily to quantify the complaint. B – Delayed FCSRT scores (free recall and total free+cued recall) after 20 minutes. No difference was observed between patients and controls. C – FCSRT scores after a

3-week interval. Scores were significantly lower in patients than in controls. D – Epireal scores after 3 weeks. Scores were significantly lower in patients than in controls.



**Figure 4:**

Proportions of patients failing the FCSRT and/or Epireal tests according to their MRI profile.

**Table 1:** Control subjects' and patients' clinical and demographic characteristics.

<b>Control subjects' and patients' clinical and demographic characteristics</b>			
	<b>Patients (n=47)</b>	<b>Control subjects (n=35)</b>	<b>P</b>
<b>Age (year, mean, SD)</b>	46.6 +/- 16	48.9 +/- 15.2	0.51
<b>Gender</b>	24M	23M	0.63
<b>Level of education (years, mean, SD)</b>	13.06 (+/-3.3)	13.37 (+/- 2.3)	0.64
<b>Handedness</b>	3L	3L	0.71
<b>Patient's clinical profile</b>			
<b>Location of seizure origin</b>	<b>Unilateral</b>	10R, 14L	
	<b>Bilateral</b>	3	
	<b>Uncertain</b>	19	
<b>Duration of epilepsy*</b> (no. patients) [mean (sd): 10.8 (10.5) yr]	<b>≥11 yr</b>	1	
	<b>≥6-10 yr</b>	15	
	<b>≥1-5 yr</b>	16	
<b>Frequency of seizures*</b> (no. patients)	<b>&lt;1/yr</b>	18	
	<b>≥1/yr</b>	17	
	<b>≥1/m</b>	10	
	<b>≥1/w</b>	1	
	<b>1/d</b>	0	
<b>Lesion type</b> (no. patients)	<b>No lesion</b>	12	
	<b>Hippocampal sclerosis</b>	12	
	<b>Amygdala enlargement</b>	12	
	<b>Extensive temporal lesion</b>	11 (autoimmune encephalitis sequelae (3); herpetic encephalitis sequelae (1); cavernoma (3); arteriovenous malformation (1); astrocytoma (1); cortical abnormality with meningoencephalocles (1); trauma sequelae (1))	
<b>Medical treatment</b> (no. patients)	<b>None</b>	3	
	<b>1 antiseizure medication</b>	27	
	<b>2 antiseizure medications</b>	15	
	<b>3 antiseizure medications</b>	2	

*M: Male; L: left; R: right; SD: standard deviation. \*Details per patient are available in*

*Supplementary Material eTable 3 and eTable 3. The frequency of seizures was self-estimated by patients.*

**Table 2:** Memory complaint, memory scores, standard neuropsychological tests, psychiatric scales in patients and control subjects.

Test ( <i>maximum score</i> )	Patients' mean score (SD)	Control subjects' mean score (SD)	P	Cohen's d
<b>Subjective memory complaint</b>				
QAM (6)	3.1 (0.6)	2.3 (0.5)	<0.001**	1.17
<b>Memory tests – Meeting 1<sup>ϕ</sup></b>				
FCSRT delayed free recall (16)	12.3 (2.1)	13.2 (1.5)	0.039 *	0.46
FCSRT delayed free + cued recall <sup>9</sup> (16)	15.8 (0.5)	15.8 (0.3)	0.42	-
<b>Memory tests – Meeting 2</b>				
FCSRT free recall (16)	4.2 (3.0)	7.6 (3.3)	<0.001**	0.94
FCSRT total recall (16)	9.1 (3.6)	12.7 (2.3)	<0.001**	0.99
Epireal free recall (39)	7.0 (3.1)	11.8 (4.1)	<0.001**	1.11
Epireal total recall (39)	21.0 (4.5)	26.9 (3.3)	<0.001**	1.18
Epireal contextualization - “where” (8) - “when” (9)	5.4 (1.6) 6.5 (1.8)	6.6 (1.1) 7.7 (1)	<0.001** <0.001**	0.82 0.79
Epireal content details - “what” (22)	16.9 (2.8)	19.0 (1.9)	<0.001**	0.74
Epireal retrieval agency - spectator (8) - actor (31)	4.2 (1.9) 24.5 (4)	5.6 (1.3) 27.9 (2.2)	<0.001** <0.001**	0.74 0.89
<b>Standard neuropsychological tests</b>				
TMT-B <sup>s</sup> (seconds)	76.9 (34.2)	84.2 (52.9)	0.45	-
WAIS digit symbol (133)	67.7 (17.1)	74.3 (16.4)	0.03*	0.37
Fluency letter	22.1 (6.8)	26 (7.6)	0.02*	0.52
Fluency animals	28.2 (7.7)	31.6 (7.3)	0.02*	0.43
Confrontation naming	39.5 (0.8)	39.4 (1.5)	0.55	-
<b>Psychiatric scales</b>				
Beck depression inventory (39)	5.8 (4.1)	1.6 (1.9)	<0.001**	1.05
STAI (80)	37 (9.5)	29.4 (7.5)	<0.001**	0.79
Starkstein scale (42)	11.4 (5)	9.5 (3.5)	0.03*	0.41



<sup>φ</sup> *The cued recall test is only for words that were not initially recalled in the free recall trial.*

*The two modes of recall (free and cued) allow distinguishing between disorders of storage and retrieval processes.*

## Supplementary material legend

### eFigure 1:

Details of the mini-events and Epireal procedure.

During the second meeting after 3 weeks, the participant waits in the same waiting room as before meeting 1. No spatial or temporal clue about meeting 1 is given to the participant during meeting 2. None of the objects used during meeting 1 remain during meeting 2 to avoid influencing recall. The examiner asks the participant to recall every detail that he/she can of meeting 1 (content, spatial and temporal context, order of events, agency). This free recall phase is subsequently completed by cued recall if the participant failed to retrieve part or all of an event.

### eFigure 2:

Line graphs for the free recall and total (free+delayed) recall on the FCSRT for patients and controls.

The curves of the two groups superimpose for all four stages of recall, indicating that the learning curves of the two groups are very similar at standard delays.

### eTable 1:

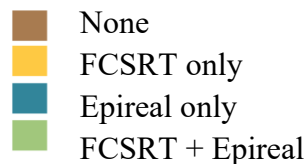
Example of scoring a mini-event.

Example of event 5: During his/her absence, the examiner makes a phone call so that a phone rings twice in the office (each time 4 rings, 1-minute interval between them). The examiner has to count 1 point for each right answer, for free recall, cued recall, and recognition. Please note that the “Recognition score” was not considered in the results presented in this study, to allow a strict comparison between Epireal and FCSRT.

**eTable 2:**

Clinical epileptic features and details of patients. Patients are sorted according to memory test scores.

Test(s) with deficits after 3 weeks:



AE: Enlargement of the amygdala; CBZ: Carbamazepine, ESL: Eslicarbazepine, GBT: Gabapentin, LMT: Lamotrigine, LVT: Levetiracetam, OXC: Oxcarbazepine, VPA: Sodium valproate, ZNS: Zonisamide; B: Bilateral; HS: Hippocampal sclerosis; IEDs: Interictal epileptic discharges; STS: Sharp transient and slow activities; L: Left; R: Right; U: Uncertain; yr.: years

**eTable 3:**

Memory complaint rating and memory performances at 3 weeks, according to epileptic clinical features. Numbers in parentheses indicate the number of patients included in the analyses.

\*  $DF=1, 45$  \*\*  $DF=3, 43$  \*\*\* $DF=2, 44$ .

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