**Title**

# Accelerated Forgetting in Temporal Lobe Epilepsy: When Does it Occur?

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## HIGHLIGHTS

- There was no evidence of accelerated forgetting over longer delays (days or weeks) in well controlled (no seizures recurrence) temporal lobe epilepsy patients.
- Temporal Lobe Epilepsy patients showed faster forgetting of verbal information after 10 minutes of exposure.
- These findings are consistent with an impairment of early (rather than late) consolidation processes.

**ABSTRACT**

**Objective.** The main goal of the study was to analyse differences in the forgetting rates of Temporal Lobe Epilepsy (TLE) patients at different intervals (30 seconds, 10 minutes, 1 day and 1 week) compared with those of healthy controls. A secondary aim of this research was to provide an assessment of the relationship between clinical epilepsy-related variables and forgetting rates in TLE patients. **Method.** The sample was composed of 14 TLE patients and 14 healthy matched controls. All participants underwent a full standardised neuropsychological assessment including general intelligence, executive functioning, memory, language and other variables, such as depression, anxiety or everyday memory failures. Two specific memory tasks, consisting of cued recall of 4 short stories and 4 routes, were carried out at four different intervals. **Results.** There was a significant difference between groups at 10-min interval on the stories task, with the TLE group displaying greater forgetting than healthy controls. None of the other intervals on either task showed significant group differences. No differences were found when controlling for clinical epilepsy-related variables. **Conclusion.** Forgetting of verbal information at 10 minutes was greater in patients with TLE compared with controls, but accelerated longer term forgetting was not found. This study suggests that a late consolidation process is not necessarily impaired in TLE patients.

**Keywords:** Accelerated long-term forgetting; Temporal Lobe Epilepsy; Memory consolidation; Forgetting.

## 1. Introduction

Epilepsy constitutes one of the most common neurological disorders in the general population (World Health Organization, 2019). Temporal Lobe Epilepsy (TLE) is the most common focal epileptic syndrome and it is frequently associated with cognitive impairment, particularly with memory disorders (Blume, 2003). This syndrome is characterized by recurrent seizures generated in temporal lobe regions, including the hippocampi (Barnett et al., 2015), although its clinical manifestations between patients can be very heterogeneous. The presence of hippocampal atrophy in these patients, sometimes associated with mesial-temporal sclerosis (MTS; Mueller et al., 2012), may be extensive across the hippocampal regions or only limited to an isolated region (e.g., CA1), leading to differing degrees of memory impairment (Coras et al., 2014; Mueller et al., 2012). In addition, there may be variable degrees of lateralization of atrophy and/or epileptic activity across different patients (Barnett et al., 2015), which alter the manifestations of cognitive impairment in TLE (Audrain & McAndrews, 2018; Barnett et al., 2015; Coras et al., 2014; Helmstaedter et al., 2018; Mueller et al., 2012; Visser et al., 2018).

Memory complaints can be a common symptom among patients with TLE, even when they display a normal performance on standardised memory tests (Narayanan et al., 2012; Tramoni-Negre et al., 2017). In cases where rapid forgetting is reported, this may be attributable to an acquisition problem or to disruption of early consolidation (Kopelman, 2000; Cassel et al., 2016). In other cases, TLE patients appear to retain information normally over short intervals (up to 1 hour), but then they lose it after longer (days or weeks) periods of time (Mayes et al., 2018). Indeed, some studies have found evidence of a higher rate of forgetting after such longer periods among TLE

patients, for both visual and verbal information (Muhlert et al., 2011; Tramoni et al., 2011; Wilkinson et al., 2012). This pattern of forgetting of episodic memories has been called accelerated long-term forgetting (acronym 'ALF'), which suggests a dual process of memory consolidation: normal consolidation of information over earlier intervals with impaired late consolidation (Blake, 2000; Muhlert et al., 2011; Tramoni et al., 2011).

However, findings in this literature are controversial. Some studies have failed to find accelerated forgetting in TLE patients occurring at the longer term (Bell, 2006; Bell et al., 2005; Contador et al., 2017; Howard et al., 2010). One study found that left-TLE patients forgot visual information similarly to controls, whereas the forgetting of right-TLE patients was faster than that of left-TLE and controls for this type of material (Giovagnoli et al., 1995). However, other evidence showed ALF for verbal material in left- TLE but not right-TLE patients (Blake et al. 2000). These findings could lead to the conclusion that accelerated forgetting over long delays is not necessarily a feature in TLE patients, and is dependent upon other factors such as epilepsy-related clinical variables (Muhlert et al., 2011; Voltzenlogel et al., 2014) or aspects of testing technique (Cassel & Kopelman, 2019; Elliott et al., 2014; Muhlert et al., 2011).

The existing literature on the role of clinical variables in accelerated forgetting has also given rise to controversies. For instance, some authors have found an important effect of laterality of epileptic focus or structural abnormalities on accelerated forgetting (Atherton et al., 2019; Gascoigne et al., 2014; Ricci et al., 2015), whereas others have not (Audrain & McAndrews, 2018; Cassel et al., 2016; Visser et al., 2018). Moreover, while it is clear that hippocampal pathology is relevant to explaining early memory deficits observed in TLE, the role of this structure on forgetting occurring at the longer

term remains unclear (Butler et al., 2009; Cassel et al., 2016; Ricci et al., 2015; Wilkinson et al., 2012). Finally, although antiepileptic medication (AEDs) can have beneficial effects on memory performance (Jansari et al., 2010; Midorikawa & Kawamura, 2008; O'Connor et al., 1997), other studies suggest that greater use of AEDs adversely affect forgetting rates at early delays (Butler et al., 2009; Jokeit et al., 2005; Motamedi & Meador, 2003). A further group of studies has not found any relationship between AEDs and memory function (Fitzgerald et al., 2013; Miller et al., 2017).

There is no consensus about the neurocognitive mechanisms underlying accelerated forgetting over long delays (Butler et al., 2019; Mayes et al., 2018). It has frequently been assumed that an impairment of late consolidation best explains the phenomenon (Tramoni et al., 2011; Tramoni-Negre et al., 2017; Wilkinson et al., 2012). However, there is some evidence indicating that this might not be the case (see Cassel & Kopelman 2019). An impairment of early consolidation may be contributing in those cases where the accelerated forgetting only becomes statistically significant at later test delays: even when forgetting curves appear to diverge at a late delay, it is still possible that the forgetting commenced earlier (Cassel et al., 2016). Interestingly, Hoefeijzers et al. (2015) reported that accelerated forgetting became apparent at earlier intervals (3-8 hours) in patients with Transient Epileptic Amnesia (TEA), a subsyndrome of TLE, as opposed to the later delays commonly used to assess long-term forgetting in these patients (i.e., at 1-day or 1-week). Accelerated forgetting may be particularly widespread among people with TEA, affecting nearly half of the patients with this condition in some studies (Zeman, Butler, Muhlert, & Milton, 2013). In brief, the assumption that late impairment in consolidation underlies accelerated forgetting over

longer periods in TLE remains controversial (Cassel and Kopelman, 2019; Contador et al., 2017).

The main aim of the present study was to examine patterns of forgetting rates in TLE patients compared with those in healthy control subjects at different time-intervals. The prevailing perspective in the scientific literature suggests that accelerated forgetting can occur specifically at longer intervals (1 day to 1 week) in TLE patients. However, we hypothesise that accelerated forgetting, if it occurs, will always be characterised by forgetting at shorter delays (up to 10 minutes), irrespective of whether any later forgetting (1 day to 1 week) also occurs. A secondary aim was to provide an assessment of the relationship between forgetting rates in TLE patients and clinical epilepsy-related variables in these groups. To this end, we examined the presence/absence of hippocampal abnormalities, laterality of seizure focus, and the number of anti-epileptic medications.

## 2. Method

### *2.1 Participants*

In this study, 14 patients with TLE (mean age= 41.43, 11 women, 3 men) were selected from the Epilepsy Unit (Neurology Service) of a University Hospital depending on the National Health System (Madrid, Spain). It is important to note that sample sizes are frequently small in TLE studies, and our sample falls within the 50% central distribution of the sample sizes on this topic. Out of 34 articles on forgetting in TLE, 75% assessed samples of fewer than 25 patients, with considerable variability among studies (see figure 1s and table 1s, supplementary material).

All patients were diagnosed by expert neurologists, and met the diagnostic criteria for TLE, based on medical history (seizures with typical symptoms suggesting temporal lobe origin) and video-electroencephalogram. They underwent a full neurological examination and 1.5T magnetic resonance imaging (MRI). All images were reported by expert neuro-radiologists, who were asked to identify medial-temporal structural abnormalities (either MTS or hippocampal atrophy) and to exclude other diseases that might underlie seizure disorders. The diagnosis protocol included standard interictal EEG recordings. All patients underwent several EEG records that included routine video-EEG and at least one sleep-deprived EEG test. When necessary, 24-hour ambulatory EEG or prolonged video-EEG was performed. Patients were not weaned off medication prior to the recording. Laterality of seizures was determined according to these EEG findings, reported by two neurologists with expertise in epilepsy. All patients showed evidence of anterior temporal spikes and/or sharp waves with maximal voltage in the anterior temporal regions during video EEG recordings. Written informed consent was obtained from all patients before enrolment in the study, and the protocol was approved by the bioethics committee of the University Hospital “12 de Octubre”.

All selected patients had seizures that were well controlled by medication (i.e., not manifesting recurrent seizures). Patients with cranial injury history or neurological or medical disorders, other than epilepsy, were excluded from the study. Psychiatric disorders and substance or alcohol abuse were also exclusion criteria. In addition, 14 matched (age, gender, education, intelligence) healthy control participants were recruited (mean age=33.07, 10 women, 4 men). Any control participant reporting subjective memory complaints was excluded.

## *2.2 Materials*

### *2.2.1 Neuropsychological assessment.*

All participants underwent a full standardized neuropsychological assessment. According to recommendations by Elliott, Isaac, & Muhlert (2014), there should be no dissimilarities in standardised measures across the groups in order to ensure that differences in memory performance at long term intervals are not influenced by memory difficulties at shorter delays or by baseline differences in other cognitive functions. For general intelligence assessment, we employed the vocabulary, similarities, block design and matrix reasoning tasks from the Wechsler Adult Intelligence Scale-Third Edition (Wechsler, 1997a). The Hayling and Brixton tests were used as measures of executive functioning (Burgess & Shallice, 1997). Immediate and delayed verbal memory were assessed using Word List tasks from the Wechsler Memory Scale-Third Edition, and immediate and delayed visual memory were assessed with the Visual Reproduction subtest (Wechsler, 1997b). A 30-item brief version of the Boston Naming Test was used for language assessment (BNT) (Kaplan et al., 1983). For autobiographical memory evaluation, the Autobiographical Memory Interview was used (AMI) (Kopelman et al., 1990). Other self-administered questionnaires, such as the Memory Failures for Everyday questionnaire (MFE) (Cornish, 2000), Beck Depression Inventory (BDI) (Beck et al., 1996), and Beck Anxiety Inventory (BAI) (Beck et al., 1988) were used to assess everyday memory failures, depression, and anxiety symptoms, respectively.

### *2.2.2 Long-Term forgetting assessment.*

In order to assess forgetting, cued recall tasks were employed at four delay intervals (30 seconds, 10 minutes, 1 day and 1 week). The method was similar to other studies

which have been published elsewhere (Cassel et al., 2016; Contador et al., 2017). These were designed using principles outlined in previous literature on accelerated forgetting with regard to: matching group characteristics, use of several delay intervals, analysis of visual and verbal material, matching of initial learning, prevention of overlearning and rehearsal, and avoidance of ceiling and floor effects (Baddeley et al., 2018; Cassel & Kopelman, 2019; Elliott et al., 2014). Two initial pilot studies were carried out for comparable versions of the material (stories and routes) in English and Spanish language (Cassel et al., 2016; Contador et al., 2017). After completing this initial pilotting, minor changes were introduced in the materials to ensure that no ceiling or floor effects were observed, that a 60% learning criterion was achieved, and that the different stories and routes were of equivalent difficulty. Further pilotting in normal controls (N = 20) confirmed that the individual stories and routes were equally memorable (pairwise comparisons) at 30 seconds interval (all p-values >.10). In addition, a counterbalanced order was followed for the presentation of verbal and visual materials.

*2.2.2.1 Story task.*

Participants were asked to attend to 4 brief stories (A-D) read by the examiner. Each story was composed of 10 chunks to remember (see an example in the supplementary material), which were scored individually from 0 to 2 points, giving 1 point for partially correct answers and 2 for fully correct answers. One point was given for answers close to the target (e.g., the participant said “a boy” instead of “a teenager”), whereas 2 points were given for the completely correct answer. Story recall was assessed at four time intervals (after 30 seconds, 10 minutes, 1 day and 1 week), using a different story at each delay, and asking questions about key items of information (What was the

departure time?). A simple arithmetic interference task (subtracting 3s from 100) was used during the 30-second interval to avoid simple rehearsal. Each story could be easily identified by the participants because the instructions stated that the stories contained different characters and the questionnaire for each story began with a cued question about the main character (e.g., who planned the boat trip?; see the example story in the supplemental material).

*2.2.2.2 Route task.*

Two urban circuits, video-recorded from the front of a car, were used for testing visual memory. Both circuits were divided into 2 parts, providing 4 routes (A1, A2, B1 and B2). Each route was assessed using 10 chunks of information, of which 5 referred to directions taken by the car (e.g., right vs. left) and the other 5 referred to other elements (e.g., buildings, traffic signals) of the environment (see figure 2s, supplementary material). Each component of information was scored from 0 to 2, similar to the stories, using key questions. Following the same procedure as in the story task, a different route (out of 4 possible) was presented at each delay interval. Thus, we assessed recall on the route task both by a series of two-option forced-choice spatial decisions and cued recall of landmarks passed in the video (after each spatial decision). A simple visuo-constructive task from WAIS-III block design was used as an interference task during the 30-second interval: participants were asked to build any of the figures that they had completed in the previous standardized assessment.

## *2.3 Procedure*

After neurological investigations to make the diagnosis had been completed, a comprehensive neuropsychological assessment was administered in two sections: a

standardized assessment and the experimental memory tests (stories and routes). Between these two sections, participants were given a brief break in order to avoid information overload. The total duration of the assessment was approximately 2 hours and 30 minutes.

For the story recall test, the examiner read each story aloud, following a counterbalanced order. Different stories were read at each delay interval. During the 30-second interval, the arithmetic distractor task was used before participants were asked the cued questions about the story. No significant differences were found between the groups at the 30-second delay ($p > .10$) for the levels of cued recall learning (see results section), with 60% correct recall as the minimum criterion to reach. If this criterion was not attained, the material was re-presented, and cued-recall tested again until the criterion was reached. Nevertheless, none of the participants required further presentations of the material, indicating that, in these mildly memory-affected cases, learning/encoding of new information was preserved. Self-reported questionnaires (BDI, BAI, MFE, AMI) were used during the 10-minute interval.

A similar procedure was followed during the routes task. Videos were shown on a laptop, using the same counterbalanced order and making 5 pauses at key moments/images (e.g., crossroads) to encode directions and specific elements of the scene. At this time, participants were asked simple questions concerning possible directions to be taken and specific characteristics of one element of the scene (i.e., what is the colour of this panel?). Then at each delay interval, key images at each pause in the videos were shown again to ask the cued questions. The learning criterion was also 60% at the 30-second delay interval, similar to the verbal task. The block design distractor

task was used during the 30–second interval, and questionnaires (BDI, BAI, MFE, AMI) were used during the 10-minute delay.

All participants were phoned after 1 day (including a night of sleep) and 1 week in order to complete the delayed memory tasks. Participants were aware that they would be phoned to answer questions about the stories and routes. To prevent information rehearsal, participants did not know what story/route that they had to remember and the materials were sent just before the long-term assessment (1 day and 1 week). For the routes test, key images were sent via email during the phone interview, so that participants could see the key moments related to the cued question. None of the assessments was carried out during a postictal phase. In fact, no seizures were reported by any participant during the assessment period. Figure 1 depicts the procedure to assess verbal (stories) and visual (routes) forgetting.

[INSERT FIGURE 1]

### *2.4 Statistical analysis*

All statistical analyses were carried out using SPSS version 24. We conducted a power calculation in order to determine the desirable sample size (Shao et al., 2008). This calculation was based on previous reports in TLE, where significant accelerated forgetting at the longer term was found, and means and standard deviations were given (Narayanan et al., 2012; Visser et al., 2018). The following formula was used:

$$n_A = \left(\sigma_A^2 + \sigma_B^2/\kappa\right)\left(\frac{z_{1-\alpha} + z_{1-\beta}}{\mu_A - \mu_B}\right)^2$$

where $\mu A$ is the mean in group A; $\mu B$ is the mean in group B; $\sigma A$ is standard deviation in Group "A"; $\sigma B$ is the standard deviation in Group "B"; κ is the matching ratio; $\alpha$ is Type I error (meaning $1-\alpha$ is confidence level); and $\beta$ is Type II error

(meaning $1-\beta$ is power). Z is the critical value of the normal distribution at the required confidence level. The estimated sample size ranged from 13 to 17 patients giving a statistical power of 80% and an α of 5%.

In our study, means and standard deviations (SD) were calculated for demographic and neuropsychological data. In general, demographic, neuropsychological and forgetting data fitted a normal distribution, according to the Shapiro-Wilk test. Consequently, t-tests were used to check for differences in scores between the groups. However, for some isolated variables that did not fulfil normality criteria, non-parametric (Kruskal-Wallis) tests were also used to avoid Type I errors (false positive). In addition, in view of the group sizes and the heterogeneity of certain variables, Spearman correlation coefficients were calculated between age, the duration of illness, the number of seizures (last year) and forgetting rates (WMS, immediate and delayed measures, and the cued recall tasks).

Mean Change Scores (MCS) were calculated for the estimation of forgetting rates in both groups. These scores were obtained from the difference between the first interval (30 seconds) and the later delays both on stories and routes tasks. A mixed repeated-measures ANOVA was carried out for the assessment of interaction effects regarding clinical variables (between-subject factor) and the delay interval (within-subject factor). Given the size of the sample, Hedge's *g* was calculated to estimate the effect sizes of the MCS between multiple test points over time. These were interpreted as small (d = 0.2), medium (d = 0.5) or large (d = 0.8) (Lakens, 2013). Significance levels were set at $p < .05$.

## 3. Results

### *3.1 Clinical, Neuropsychological, and Demographic Variables*

Table 1 depicts the demographic and clinical variables of the patient sample (age of onset, duration of the illness, seizure type, medication, laterality of the epileptic activity focus and neuroimaging outcome). A majority of the participants were women (79%) with a mean age of 41.43± years (SD = 14.28). The mean age of onset was 24.43 (SD = 10.61), and the mean duration of the illness was 17.35 years (SD = 12.45).

Patients showed a combination of complex and simple partial seizures, and 5 out of 14 patients also had secondary generalized tonic-clonic seizures. Eight out of the 14 participants showed normal MRI, only 4 out of 14 showed signs of MTS, and 2 showed hippocampi atrophy according to the clinical reports provided by the neuro-radiologist. All patients had been seizure-free for 3 months prior to the beginning of the study. Moreover, the majority (9 out of 14) of the patients had not any seizures for 6 months.

[INSERT TABLE 1]

As shown in Table 2, there were no significant differences in demographic or neuropsychological variables when the two groups were compared, except that the TLE group performed worse than the healthy controls at immediate visual reproduction on the WMS-III ($p = .049$), word list recognition on the WMS-III ($p = 0.031$), and the Brixton test ($p = 0.006$). No significant differences were found on forgetting rates of WMS-III, verbal ($p = 0.977$) and non-verbal material ($p = 0.474$), between the groups. Importantly, both TLE and control scores on all the neuropsychological tests were within the normal range of normative data.

[INSERT TABLE 2]

### *3.2 Forgetting: Verbal and Visual Information*

Figure 2 depicts mean raw scores on both experimental tasks across all delay intervals compared across the groups. On these memory tasks, the groups did not differ significantly at the first delay interval (30 seconds) in the recall of stories (TLE = 16.71±1.43; Control = 17.07±2.43; t = -0.47, p = .640; g = .178) or routes (TLE = 16.21±2.36; Control = 15.21±2.39; t = 1.113, p = .275; g = .420). Thus, it can be stated that they were "matched" in acquisition of the information. All participants reached the 60% criterion (stories and routes) after one presentation and multiple trials of materials were not necessary.

[INSERT FIGURE 2]

Moreover, as can be seen, the forgetting curves were similar for both groups, after being matched at the initial interval. In other words, mean change scores (MCS) did not differ significantly across the intervals, except between the 30 second and the 10-minute delay on the stories task. The effect size for this interval was large. Thus, the TLE group showed faster forgetting of verbal information at the 10–minute interval (TLE = 2.86±2.98; Control = -0.64±4.24; t = 2.527, p = .017; g = .955), but there were no significant differences at the 1-day (TLE = 7.14±6.09; Control = 4.29±4.48; t = 1.414, p = .169; g = .534) or 1-week intervals (TLE =13.14±3.35; Control = 10.93±5.39; t = 1.231, p = .229; g = .465). For visuo-spatial information, there were no differences in forgetting at any delays: both groups displayed similar forgetting rates across all intervals, with no significant differences at the 10-minute (TLE = 1.93±2.79; Control = -0.07±3.17; t = 1.771, p = .088; g = .669), 1-day (TLE = 6.50±2.93; Control = 4.36±3.82; t = 1.667, p = .107; g = .630) or 1-week intervals (TLE = 8.93±3.69; Control = 7.43±3.59; t = 1.090, p = .285; g = .412).

It should also be noted that the correlation between forgetting rates on the WMS word list (free recall) and the story task (cued recall at 10 minutes) was not significant (r =-0.187, p = 0.340). No significant Spearman's correlations were found between age and forgetting rates (MCS) of the story (10-min: r = -0.134, p = .646; 1-day: r = 0.300, p = .295; 1 week: r = 0.506, p = .064), or between age and route forgetting (10-min: r = -0.288, p = .317; 1-day: r = 0.154, p = .599; 1 week: r = -0.356, p = .210) at different intervals. Likewise, no significant correlations were found between illness duration and forgetting rates of the story (10-min: r = 0.140, p = .633; 1-day: r = 0.105, p = .719; 1 week: r = .363, p = .200), or between illness duration and route forgetting (10-min: r = 0.050, p = .862; 1-day: r = 0.258, p = .371; 1 week: r = 0.134, p = .646) at different intervals. Finally, correlations between forgetting rates (stories/routes) and number of epileptic seizures (during the last year) were not significant (all p values >.10).

### *3.3 Epilepsy-Related Variables Analysis*

For the assessment of the epilepsy-related variables, the TLE patients were divided into groups based on: (a) the presence/absence of hippocampal abnormalities, (b) laterality of epileptic focus and (c) the number of epileptic medications. As we were interested in analysing the influence of these clinical variables on forgetting rates, special attention was paid both to the between-group factor and its interaction with the within-subject factor (i.e., group by delay interaction).

#### *3.3.1 Presence/absence of hippocampal abnormalities.*

Participants with TLE were divided into two groups: 6 TLE patients having hippocampal abnormalities and 8 TLE patients without recognised hippocampal

abnormalities. There were no differences between these two groups in terms of demographics or neuropsychological performance.

For the forgetting of stories, there was a significant main effect of delay ($F_{2, 24}$ = 20.164, p <.001), but no main effect of group ($F_{1,12}$= 0.733, p= .409), nor a significant delay by group interaction ($F_{2,24=}$ 0.406, p= .671). For routes, there was a significant main effect of delay ($F_{2,24}$=31.861, p<.001), but no significant main effect of group ($F_{1,12}$=0.023, p= .881). There was no significant delay by group interaction ($F_{2,24}$= 2.117, p= .142).

### *3.3.2 Laterality of seizure focus.*

Patients were divided into two groups: 8 TLE patients with left-sided seizure focus and 5 TLE patients with right-sided seizure focus. One patient was excluded from the analyses because the scalp EEG failed to detect clear laterality. These groups did not differ significantly in demographic and cognitive variables.

For stories, there was a significant main effect of delay ($F_{2,24}$= 48.942, p<.001), but no main effect of group ($F_{1,12}$= 1.848, p= .178) and no significant delay by group interaction ($F_{2,24}$= 0.565, p= .689). For routes, there was a main effect of delay ($F_{2,24}$=40.057, p<.001), but no main effect of group ($F_{1,12}$= 2.166, p= .136) and no significant delay by group interaction ($F_{2,24}$= 0.230, p= .920).

### *3.3.3 Anti-epileptic medication.*

Patients with TLE were divided into two groups: 9 patients were taking monotherapy (only 1 anti-epileptic drug) and 5 TLE patients were taking polytherapy (more than 1 anti-epileptic drug). These two groups were similar with regard to demographic and cognitive variables.

For stories, there was a significant main effect of delay ($F_{2,24}$= 49.850, p<.001) but no main effect of group ($F_{1,12}$ =2.226, p= .129) and no significant delay by group interaction ($F_{2,24}$= 0.352, p= .841). For routes, there was a significant main effect of delay ($F_{2,24}$= 39.847, p<.001), but no main effect of group ($F_{1,12}$= 1.829, p= .181) and no significant delay by group interaction ($F_{2,24}$= 0.515, p=.725).

## 4. Discussion

It has been argued that accelerated forgetting over long delays is a feature of TLE. Studies have indicated that TLE patients correctly retained information over short delays (from 30 seconds to 30 minutes), but then rapidly lost it over longer periods (after 1 week up to 8 weeks) of time (Blake, 2000; Muhlert et al., 2011; Narayanan et al., 2012; Tramoni et al., 2011; Wilkinson et al., 2012). However, there is increasing evidence that this pattern of forgetting is not such a common feature in this syndrome. In the present study, TLE patients did not show accelerated forgetting at 1-day or 1-week when compared with healthy controls. Other studies have also failed to find accelerated long-term forgetting in TLE patients (Bell, 2006; Bell et al., 2005; Cassel et al., 2016; Contador et al., 2017; Giovagnoli et al., 1995; Howard et al., 2010), thereby challenging the notion that TLE is usually characterised by delayed memory deficits. Interestingly, similar findings to the present were recently reported in Alzheimer's dementia (Stamate et al., 2020).

Several factors might account for the absence of accelerated forgetting over long delays. Firstly, patients in this study were well controlled by antiepileptic medication and were not manifesting recurrent seizures. The anti-epileptic medication may also have ameliorated underlying abnormal interictal electrical activity. Both these effects may have benefitted neural processes involved in the acquisition, consolidation and retrieval of

memories (Staley & Dudek, 2006; Tramoni et al., 2011). Secondly, the TLE patients assessed here were relatively mild cases, who displayed normal performance on standard neuropsychological measures. Consequently, they needed only one presentation of the experimental material to reach the learning criterion. However, it is noteworthy that some studies have found an accelerated rate of forgetting at longer-term delays in patients, who also demonstrated only subtle symptomatology and a good response to treatment (Atherton et al., 2019; Butler et al., 2013; Savage et al., 2017).

There are aspects of method that may explain the heterogeneity of the results in TLE patients (Cassel & Kopelman, 2019; Elliott et al., 2014). For instance, the use of free recall tasks can lead to a floor effect, whereas ceiling effects may easily emerge with the use of recognition tasks, masking accelerated forgetting (Elliott et al., 2014). In our study, memory was assessed using cued questions, which allowed us generally to avoid both ceiling and floor effects, although, as shown in Fig 3s, these effects were observable in some individual participants. Moreover, we used four different delay intervals to monitor the time-period over which accelerated forgetting might occur. As proposed by Baddeley, Atkinson, Kemp, and Allen (Baddeley et al., 2018), multiple test designs seem to be necessary to detect accelerated forgetting, in contrast to repeated testing within individuals. Some studies have found accelerated long-term forgetting using two delayed intervals (from 30 min/1 hour up to 1 or several weeks) (Blake, 2000; Gascoigne et al., 2019; Helmstaedter et al., 2018; Narayanan et al., 2012; Savage et al., 2017; Tramoni et al., 2011; Wilkinson et al., 2012). However, it can be argued that forgetting across initial or early delays might be underestimated in these studies if they have not used any testing between the two intervals (Cassel & Kopelman, 2019). In fact,

other studies have found earlier accelerated forgetting in TLE, when shorter delay intervals were employed (Audrain & McAndrews, 2018; Deak et al., 2011).

In our secondary analyses, we did not find any relationship between clinical epilepsy-related variables and forgetting in TLE. It is interesting to note that we did not find a significant effect of laterality on forgetting. This is consistent with some other findings in the literature (Audrain & McAndrews, 2018; Visser et al., 2018). Furthermore, neither hippocampal abnormalities (Wilkinson et al., 2012), nor the number of anti-epileptic medications (Fitzgerald et al., 2013; Miller et al., 2017) influenced forgetting in our sample. Our results in this regard should be interpreted cautiously, because of the small size of our clinical sample and because other authors have found an association between these variables and memory performance. Nevertheless, this finding suggests that there is heterogeneity in TLE patients, and emphasises that individual variability must be taken into account.

Faster forgetting of verbal information at a short delay (10 minutes) was found in this study, with a large effect size (.955). Such forgetting was not found on standard tests of the WMS-III, which could mean that our cued recall test has higher sensitivity for detecting subtle early memory impairment. Our finding contrasts with that of Cassel et al. (2016), who found that TLE patients showed faster forgetting of visuospatial information in the first 10 minutes after learning, whereas forgetting of verbal material was not significantly different at this delay. This discrepancy might be explained by the left predominance of the epileptic activity displayed by the patients in our sample, compared with those of Cassel et al. (2016). Importantly, both studies showed that faster forgetting can be detected within 10 minutes of learning. Thus, our findings are consistent with those of non-epileptic amnesic patients with temporal lobe pathology,

which have shown accelerated forgetting on recall tasks (pictures and words) within 10 or 20 minutes, after matching for initial memory performance (Green & Kopelman, 2002; Isaac & Mayes, 1999a, 1999b; Kopelman & Stanhope, 1997).

In the present study, we need to acknowledge that moderate effect sizes (range: .41-.53) were reached for verbal and visuospatial material at longer delays (1 day, 1 week), even though these differences were not statistically significant. Moreover, at these longer delays, memory was assessed by phone, whereas the context at earlier intervals (30 seconds and 10 minutes) was the same (i.e., laboratory room) for all participants. It might have been the case that the healthy controls experienced a context-dependent advantage at 10 minutes, relative to the TLE group, which was absent at the longer delays. However, context effects may not be as robust as sometimes thought, especially when memory items are not properly perceived as a part of the environment or are interactively processed with the environment (Fernández & Glenberg, 1985; Eich, 1985). Moreover, only 6 of our TLE participants showed hippocampal abnormalities, which might have affected their context-dependent memory.

It has been previously argued that poor encoding and impairments in early consolidation might underlie accelerated forgetting occurring at later delays (Cassel et al., 2016; Dewar et al., 2015). Our study shows that differences in forgetting can emerge at an early delay (up to 10 minutes), but we did not find significant differences at longer delays. Our findings could be interpreted as consistent with a dual process of memory consolidation, whereby early consolidation mechanisms are impaired in TLE patients but later consolidation mechanisms remain preserved. However, the standard deviation is largest in the TLE group at the 1-day interval, suggesting variability in forgetting in TLE patients between 10 mins and 24 hours. Moreover, despite the absence of

statistically significant differences between TLE patients and controls, we cannot rule out that the late consolidation process is also impaired in some individual cases, given that the effect sizes on forgetting rates are medium for later intervals. In any case, the individual profile (Fig 3s.) confirms that forgetting patterns in the TLE group are heterogeneous.

Some limitations of the current study should be mentioned. Although a power calculation indicated that our sample size was sufficient to reveal significant differences, the possibility that a larger sample might have produced more significant differences (particularly at long-term delays) cannot be excluded. However, previous studies investigating accelerated forgetting in epilepsy have typically ranged in sample size from 11 to 28 patients (see Table 1s and Figure 1s in Supplementary Material). It is noteworthy that several studies with comparable sample sizes to ours have found accelerated forgetting in TLE (Atherton et al., 2019; Muhlert et al., 2011), whereas others with considerably larger samples have failed to find such a pattern (Bell, 2006; Bell et al., 2005). Secondly, we used only cued recall (and forced-choice) measures to assess forgetting at the longer delays. Thirdly, because we employed strict criteria for the selection of participants, our sample might not be fully representative of TLE patients, due to the heterogeneity of this condition (in terms of age of onset, clinical severity of symptoms, prognosis and response to treatment). Finally, a clinical standard magnetic field of 1.5T (MRI) was used for the diagnostic process. It has been shown that scanners with higher resolution (≥3T) have improved sensitivity for detecting temporal lobe abnormalities, but their use is not currently extended in clinical practice. Strengths of the manuscript include having a well-matched control sample, testing for

differences in verbal and visual memory, and avoiding repeated testing of the same materials.

## 5. Conclusion

In conclusion, our findings support the notion that accelerated forgetting of verbal material may be found at short delays (10 minutes), suggestive of a problem in early consolidation in TLE. However, we did not obtain evidence of accelerated long-term forgetting for verbal material. There were no differences in forgetting for non-verbal material at any interval. Clinical variables such as the presence or absence of hippocampal abnormalities, laterality of the epileptic activity focus, or number of anti-epileptic medications, did not appear to influence forgetting rates in this study. It is possible that well-controlled epilepsy, and the good response to anti-epileptic medication, may be related to the absence of memory deficits at longer intervals. Overall, it appears that forgetting is not necessarily accelerated in TLE after long delays, and forgetting patterns in TLE may vary across individual patients. The use of cued recall tasks is a promising approach to measuring forgetting reliably at later intervals, avoiding ceiling and floor effects. In the future, new methods of assessing forgetting at different intervals should be explored, and it would be desirable to investigate larger samples with diverse clinical characteristics.

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This study was partially supported by a post-doc fellowship (JC 2011-0012) from the Spanish Ministry of Education. We have reported how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the

study (see methods). The conditions of the ethics approval do not permit public archiving of the study data. This information will be made available to researchers upon request. They should contact the lead author, following completion of a data sharing agreement and the approval by the ethics committee. No part of the study procedures or analyses was pre-registered prior to the research being conducted. Detailed examples of the experimental stimuli are available in supplementary material. Copyright restrictions prevent public archiving of the neuropsychological tests and questionnaires used in this study, which can be obtained from copyright holders (see cited references).

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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**TABLES**

Table 1. Demographic and clinical variables

| ID | Age | Gender | Onset (Age) | Duration | Seizure types | Seizure frequency (last year) | Medication | Laterality (EEG) | MRI |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 21 | M | 12 | 9 | SPS; CPS | 2 | OXC;ZNS | L | Normal |
| 2 | 19 | F | 14 | 5 | SPS; CPS | 0 | OXC | R | R HCA A |
| 3 | 28 | M | 15 | 13 | SPS; GTCS | 0 | CBZ | L | Normal |
| 4 | 27 | F | 26 | 1 | SPS; GTCS | 2 | LAM | L | Normal |
| 5 | 56 | F | 53 | 3 | SPS; CPS | 2 | ESL | L | Normal |
| 6 | 56 | M | 21 | 35 | SPS; CPS; GTCS | 4 | PMD;CBZ | R | R MTS |
| 7 | 50 | F | 30 | 20 | SPS; CPS | 0 | LEV | L | Normal |
| 8 | 51 | F | 21 | 30 | SPS; CPS; GTCS | 0 | CBZ; LEV | L | Normal |
| 9 | 42 | F | 31 | 11 | SPS; CPS; GTCS | 4 | ZNS | R | R MTS |
| 10 | 48 | F | 32 | 16 | CPS; GTCS | 0 | CBZ | R>L | L HCA A |
| 11 | 52 | F | 16 | 36 | CPS; GTCS | 1 | LEV | R | R MTS |
| 12 | 59 | F | 34 | 25 | SPS; CPS | 5 | LCM;LEV | L | Normal |
| 13 | 25 | F | 23 | 2 | SPS; CPS; GTCS | 2 | ESL;LEV | L | Normal |
| 14 | 46 | F | 23 | 23 | SPS; CPS; GTCS | 0 | LEV | L | L MTS |

Index: A = Atrophy, CBZ = Carbamazepine, CPS = Complex Partial Seizures, ESL = Eslicarbazepine, F = Female, GTCS = Generalised Tonic-Clonic Seizures, HCA = Hippocampus Atrophy, L = Left, LAM = Lamotrigine, LCM = Lacosamide, LEV = Levetiracetam, M = Male, MTS = Medial Temporal Sclerosis, OXC = Oxcarbazepine, R = Right, SPS = Simple Partial Seizures, ZNS = Zonisamide

Table 2. Demographic and neuropsychological outcomes comparison by group

| **Test** | **TLE (n=14)** M (SD) | **Control (n=14)** M (SD) | **t/$\chi^2$** | **p** |
|---|---|---|---|---|
| Age | 41.43±14.29 | 33.07±13.19 | 1.608 | .119 |
| Gender (n; Male: Female) | 3:11 | 4:10 | | |
| Education (years) | 16.64±3.93 | 18.43±3.01 | -1.349 | .188 |
| Intelligence (WAIS-III) | | | | |
| Similarities | 23.86±4.91 | 26.93±3.95 | -1.822 | .079 |
| Vocabulary | 49.86±9.08 | 52.79±5.98 | -1.008 | .322 |
| Block design | 41.00±11.38 | 48.79±11.01 | -1.839 | .077 |
| Matrix reasoning | 18.57±4.51 | 20.86±3.86 | -1.439 | .162 |
| Memory (WMS-III) | | | | |
| Word list | | | | |
| Free recall- I | 37.29±4.81 | 37.00±3.88 | -1.061 | .298 |
| Free recall -II | 9.43±3.19 | 9.93±1.98 | -.701 | .488 |
| Recognition | 23.79±.58 | 22.50±2.03 | -2.280 | .031* |
| Designs | | | | |
| Free recall- I | 87.57±11.03 | 95.07±8.02 | -2.057 | .049* |
| Free recall -II | 72.21±22.14 | 81.50±19.23 | -1.184 | .246 |
| Recognition | 45.50±2.34 | 46.29±2.23 | -.907 | .372 |
| Language (BNT) | 26.71±2.61 | 28.14±1.61 | -1.740 | .093 |
| Executive function | | | | |
| Hayling test | 17.71±1.49 | 17.71±1.90 | .000 | 1.00 |
| Brixton test (mistakes) | 13.07±3.69 | 8.43±5.54 | 2.971 | .006* |
| Autobiographical memory (AMI) | | | | |
| Childhood | 18.46±2.44 | 18.50±2.49 | -.038 | .969 |
| Early adulthood | 19.21±2.12 | 20.14±1.06 | -1.465 | .154 |
| Recent years | 19.82±1.55 | 19.86±1.84 | -.055 | .956 |
| Total | 57.50±4.11 | 58.57±4.31 | -.672 | .506 |
| Questionnaires | | | | |
| Anxiety (BAI) | 8.21±8.99 | 7.79±5.39 | .152 | .879 |
| Depression (BDI) | 12.64±8.33 | 8.93±6.58 | 1.308 | .202 |
| Memory failure (MFE) | 48.64±16.93 | 46.21±6.81 | .497 | .622 |

M = Mean; SD = Standard deviation; *p<.05

## FIGURES

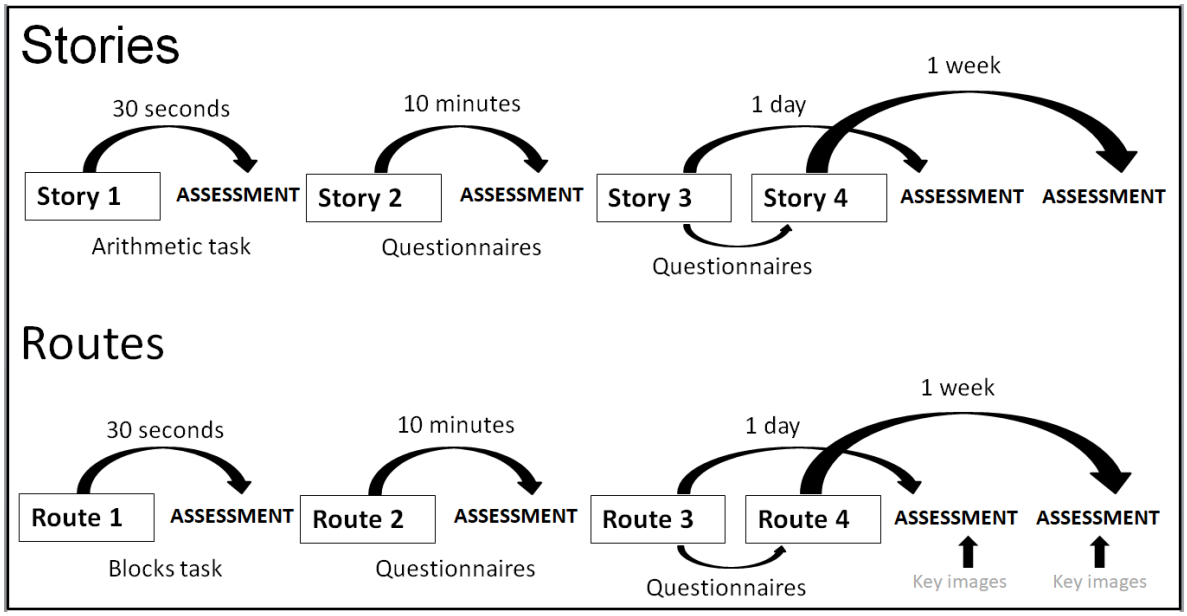


Figure 1. Long-term forgetting assessment procedure.

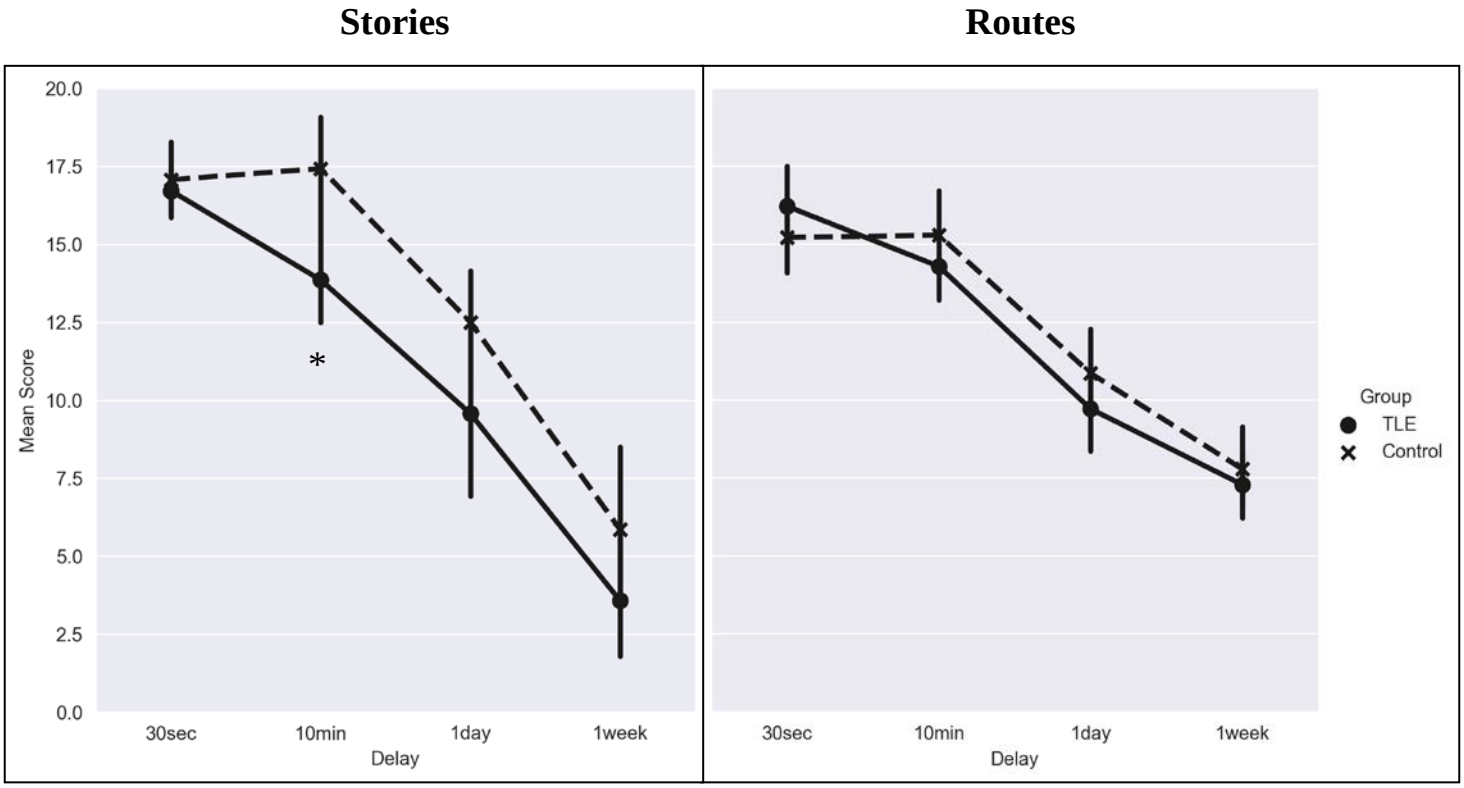


Figure 2. Long-term forgetting tasks' (stories and routes) mean raw scores by group. Error bars depict 95% confidence intervals. The asterisk (*) indicates intervals that reached significant differences between the groups.

**SUPPLEMENTARY MATERIAL**

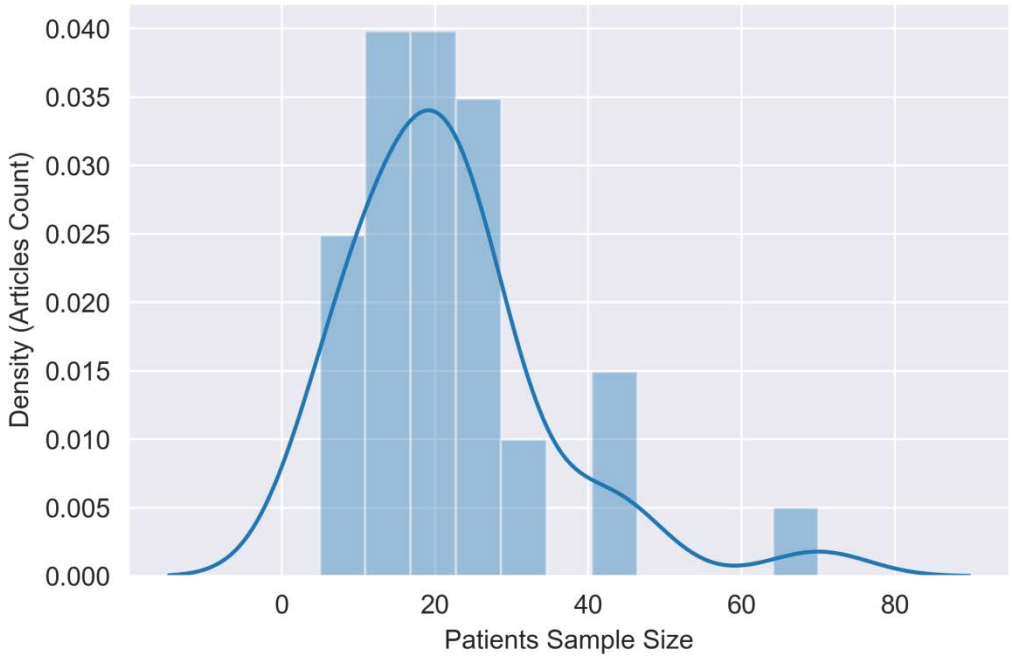


Fig 1s. Sample sizes distribution of 34 articles on forgetting in TLE.

Table 3s. Sample characteristics of 34 articles on for getting in TLE.

| Author and year | Target Sample | Patients n | Mean Age | Female % | Matched to controls |
|---|---|---|---|---|---|
| (Visser et al., 2018) | TLE | 30 | 41.3 | 50% | Yes |
| (Helmstaedter et al., 2018) | TLE | 32 | 43 | 55.5% | No |
| (Audrain & McAndrews, 2018) | TLE | 23 | 37.17 | 34.8% | Partial |
| (Atherton, Filippini, Zeman, Nobre, & Butler, 2018) | TEA | 15 | 67.73 | 20% | Yes |
| (Gascoigne et al., 2018) | TLE | 20 | 11.3 | 50% | Partial |
| (Savage et al., 2017) | TEA | 14 | 78.3 | 35.7% | Partial |
| (Miller, Mothakunnel, Flanagan, Nikpour, & Thayer, 2017) | TLE | 44 | 42.5 | 50% | Yes |
| (Hoefeijzers, Zeman, Della Sala, & Dewar, 2017) | TEA | 27 | 66.44 | 25.9% | Partial |
| (Contador et al., 2017) | TLE/TEA | 5 | 24.4 | 60% | Yes |
| (Cassel et al., 2016) | TLE | 18 | 39.33 | 50% | Yes |
| (Ricci, Mohamed, Savage, & Miller, 2015) | TLE | 22 | 39 | N/A | Yes |
| (Ricci, Mohamed, Savage, Boserio, & Miller, 2015) | TLE | 21 | 39 | N/A | Yes |
| (Hoefeijzers, Dewar, Della Sala, Butler, & Zeman, 2015) | TEA | 11 | 69.82 | 9% | Yes |
| (Dewar, Hoefeijzers, Zeman, Butler, & Della Sala, 2015) | TEA | 16 | 69.63 | 25% | Partial |
| (Lah, Mohamed, Thayer, Miller, & Diamond, 2014) | TLE | 23 | 44.81 | 60.9% | Partial |
| (Gascoigne et al., 2014) | TLE | 23 | 12.5 | 56.5% | Partial |
| (Evans, Elliott, Reynders, & Isaac, 2014) | TLE | 7 | 39.71 | 57.1% | Yes |
| (Atherton, Nobre, Zeman, & Butler, 2014) | TEA | 11 | 67.73 | 9% | Partial |
| (Hoefeijzers, Dewar, Della Sala, Zeman, & Butler, 2013) | TEA | 17 | 65.47 | 47.1% | Yes |
| (Wilkinson et al., 2012) | TLE | 27 | 36.54 | N/A | Yes |

| Author and year | Target Sample | Patients n | Mean Age | Female % | Matched to controls |
|---|---|---|---|---|---|
| (Narayanan et al., 2012) | TLE | 14 | 33.57 | 64.3% | Yes |
| (C. Butler, Kapur, Zeman, Weller, & Connelly, 2012) | TEA | 22 | 68.4 | 45.4% | Yes |
| (Barkas et al., 2012) | TLE | 23 | 47.79 | 56.5% | Partial |
| (Tramoni et al., 2011) | TLE | 5 | 42.6 | 20% | Partial |
| (Muhlert et al., 2011) | TLE | 14 | 46.4 | 71.4% | Yes |
| (Deak, Stickgold, Pietras, Nelson, & Bubrick, 2011) | TLE | 7 | 44 | N/A | Yes |
| (Muhlert, Milton, Butler, Kapur, & Zeman, 2010) | TEA | 11 | 68.6 | 9% | Partial |
| (C. R. Butler et al., 2009) | TEA | 22 | 66.4 | 45.4% | Yes |
| (Mameniskiene, Jatuzis, Kaubrys, & Budrys, 2006) | TLE | 70 | 33.3 | 58.6% | Partial |
| (Bengner et al., 2006) | TLE | 44 | 42.08 | 54.5% | Partial |
| (Bell, 2006) | TLE | 25 | 39 | 60% | Partial |
| (Manes, Graham, Zeman, de Lujan Calcagno, & Hodges, 2005) | TEA | 7 | 65 | 14.3% | Partial |
| (Bell et al., 2005) | TLE | 42 | 36.88 | N/A | Partial |
| (Blake, 2000) | TLE | 21 | 33.76 | 66.7% | No |

N/A= Not reported; Partial = patients and controls were matched only in some features, but not in others (depending on the article).

## EXAMPLE OF THE STIMULI

**Story task.** [Spanish version]. */Un adolescente/ iba a realizar un /viaje en barco/ desde /Cádiz/ a las /12.15/. /El viento era fuerte/ y navegaban muy cerca de /otra embarcación/. Para evitar el colapso, el capitán /cambió la dirección/, pero /golpearon con una roca/ y el /motor se averió/.*

[English translation. */A teenager/ had planned a /boat trip/ from /Cadiz/ at /12.15 p.m/. /The wind was strong/, and they were navigating very close /to another vessel/. To avoid a collision, /the captain/ changed the direction/, but they /hit a rock/, and the /engine broke down/*].

**Routes**

Figure 2s. Example of the stimuli in the route task

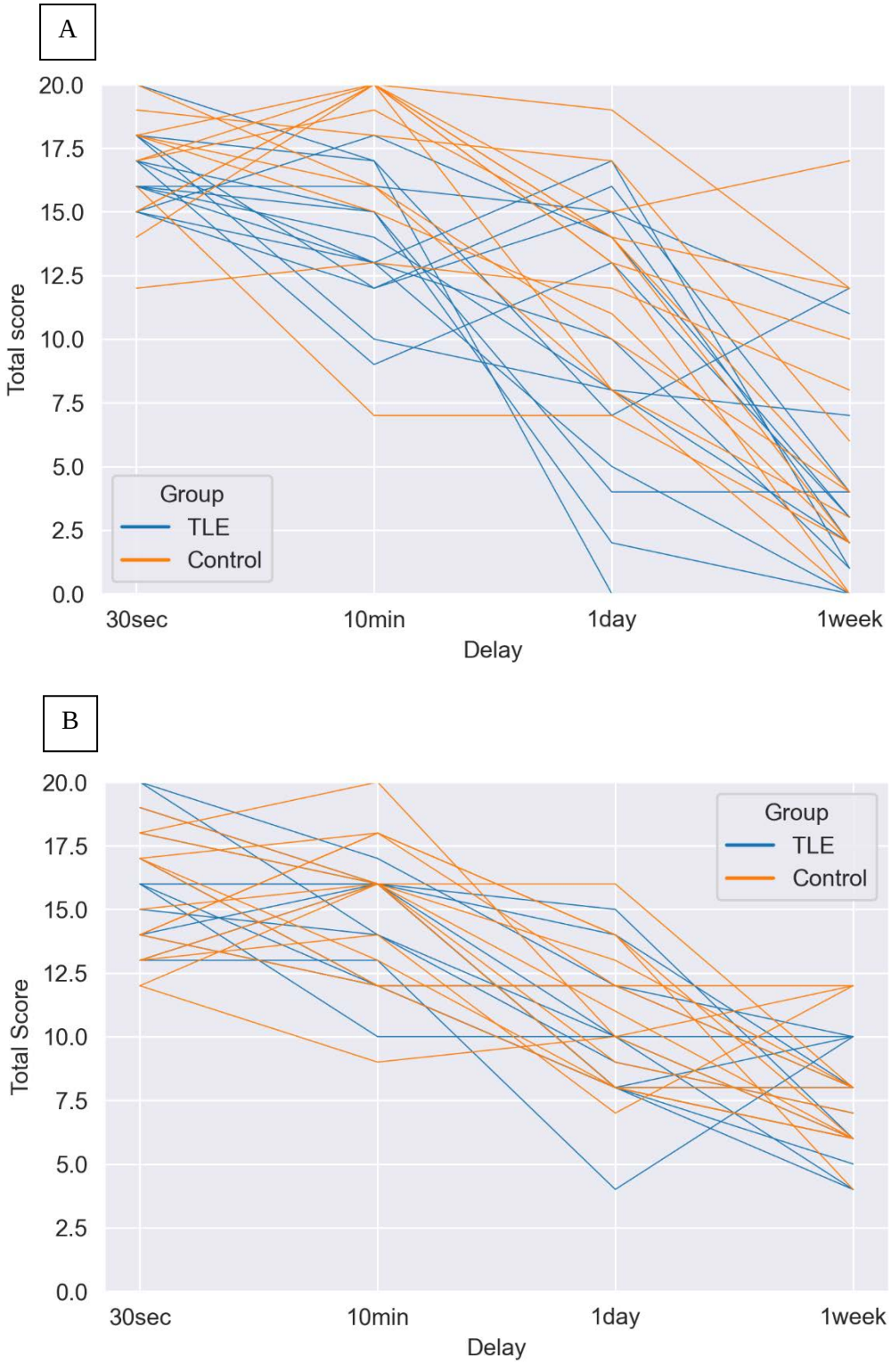


Fig 3s. Individual performance in memory tasks. A) Story task. B) Route task.