

1 **Title**

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

3 **Authors**

4 Israel Contador^{1,a}, Abraham Sánchez^{2,a}, Michael D. Kopelman³, Jesús González de la
5 Aleja⁴, & Pablo Ruisoto⁵

6 *1. Department of Basic Psychology, Psychobiology and Methodology of Behavioral*
7 *Sciences, University of Salamanca. Spain.*

8 *2. Basque Center of Cognition, Brain and Language (BCBL), Donostia-San Sebastian,*
9 *Spain.*

10 *3. King's College London, Institute of Psychiatry, Psychology, & Neuroscience, London, UK.*

11 *4. University Hospital "12 de Octubre", Madrid, Spain.*

12 *5. Department of Health Sciences, Public University of Navarre, Spain.*

13 **Corresponding authors:**

14 ^aIsrael Contador. Facultad de Psicología. Departamento de Psicología Básica,
15 Psicobiología y Metodología de las Ciencias del Comportamiento. Universidad de
16 Salamanca. Avenida de la Merced, 109-131. 37005, Salamanca, Spain.

17 ^aAbraham Sánchez. Basque Center of Cognition, Brain and Language (BCBL),
18 Donostia-San Sebastian. Mikeletegi Pasealekua, 69, 20009 Donostia, Gipuzkoa.

19 **Word Count:** 5870 words, 2 tables; 2 figures.

20

1 **HIGHLIGHTS**

2 • There was no evidence of accelerated forgetting over longer delays (days or weeks)
3 in well controlled (no seizures recurrence) temporal lobe epilepsy patients.

4 • Temporal Lobe Epilepsy patients showed faster forgetting of verbal information
5 after 10 minutes of exposure.

6 • These findings are consistent with an impairment of early (rather than late)
7 consolidation processes.

8

1 **ABSTRACT**

2 **Objective.** The main goal of the study was to analyse differences in the forgetting
3 rates of Temporal Lobe Epilepsy (TLE) patients at different intervals (30 seconds, 10
4 minutes, 1 day and 1 week) compared with those of healthy controls. A secondary aim
5 of this research was to provide an assessment of the relationship between clinical
6 epilepsy-related variables and forgetting rates in TLE patients. **Method.** The sample
7 was composed of 14 TLE patients and 14 healthy matched controls. All participants
8 underwent a full standardised neuropsychological assessment including general
9 intelligence, executive functioning, memory, language and other variables, such as
10 depression, anxiety or everyday memory failures. Two specific memory tasks,
11 consisting of cued recall of 4 short stories and 4 routes, were carried out at four different
12 intervals. **Results.** There was a significant difference between groups at 10-min interval
13 on the stories task, with the TLE group displaying greater forgetting than healthy
14 controls. None of the other intervals on either task showed significant group differences.
15 No differences were found when controlling for clinical epilepsy-related variables.

16 **Conclusion.** Forgetting of verbal information at 10 minutes was greater in patients with
17 TLE compared with controls, but accelerated longer term forgetting was not found. This
18 study suggests that a late consolidation process is not necessarily impaired in TLE
19 patients.

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

22

23

1 **1. Introduction**

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

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

1 patients, for both visual and verbal information (Muhlert et al., 2011; Tramoni et al.,
2 2011; Wilkinson et al., 2012). This pattern of forgetting of episodic memories has been
3 called accelerated long-term forgetting (acronym ‘ALF’), which suggests a dual process
4 of memory consolidation: normal consolidation of information over earlier intervals
5 with impaired late consolidation (Blake, 2000; Muhlert et al., 2011; Tramoni et al.,
6 2011).

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

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

1 term remains unclear (Butler et al., 2009; Cassel et al., 2016; Ricci et al., 2015;
2 Wilkinson et al., 2012). Finally, although antiepileptic medication (AEDs) can have
3 beneficial effects on memory performance (Jansari et al., 2010; Midorikawa &
4 Kawamura, 2008; O'Connor et al., 1997), other studies suggest that greater use of
5 AEDs adversely affect forgetting rates at early delays (Butler et al., 2009; Jokeit et al.,
6 2005; Motamedi & Meador, 2003). A further group of studies has not found any
7 relationship between AEDs and memory function (Fitzgerald et al., 2013; Miller et al.,
8 2017).

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

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

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

14 **2. Method**

15 *2.1 Participants*

16 In this study, 14 patients with TLE (mean age= 41.43, 11 women, 3 men) were
17 selected from the Epilepsy Unit (Neurology Service) of a University Hospital depending
18 on the National Health System (Madrid, Spain). It is important to note that sample sizes
19 are frequently small in TLE studies, and our sample falls within the 50% central
20 distribution of the sample sizes on this topic. Out of 34 articles on forgetting in TLE,
21 75% assessed samples of fewer than 25 patients, with considerable variability among
22 studies (see figure 1s and table 1s, supplementary material).

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

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

1 2.2 *Materials*

2 2.2.1 *Neuropsychological assessment.*

3 All participants underwent a full standardized neuropsychological assessment.

4 According to recommendations by Elliott, Isaac, & Muhlert (2014), there should be no
5 dissimilarities in standardised measures across the groups in order to ensure that
6 differences in memory performance at long term intervals are not influenced by memory
7 difficulties at shorter delays or by baseline differences in other cognitive functions. For
8 general intelligence assessment, we employed the vocabulary, similarities, block design
9 and matrix reasoning tasks from the Wechsler Adult Intelligence Scale-Third Edition
10 (Wechsler, 1997a). The Hayling and Brixton tests were used as measures of executive
11 functioning (Burgess & Shallice, 1997). Immediate and delayed verbal memory were
12 assessed using Word List tasks from the Wechsler Memory Scale-Third Edition, and
13 immediate and delayed visual memory were assessed with the Visual Reproduction
14 subtest (Wechsler, 1997b). A 30-item brief version of the Boston Naming Test was used
15 for language assessment (BNT) (Kaplan et al., 1983). For autobiographical memory
16 evaluation, the Autobiographical Memory Interview was used (AMI) (Kopelman et al.,
17 1990). Other self-administered questionnaires, such as the Memory Failures for
18 Everyday questionnaire (MFE) (Cornish, 2000), Beck Depression Inventory (BDI)
19 (Beck et al., 1996), and Beck Anxiety Inventory (BAI) (Beck et al., 1988) were used to
20 assess everyday memory failures, depression, and anxiety symptoms, respectively.

21 2.2.2 *Long-Term forgetting assessment.*

22 In order to assess forgetting, cued recall tasks were employed at four delay intervals
23 (30 seconds, 10 minutes, 1 day and 1 week). The method was similar to other studies

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

16 2.2.2.1 *Story task.*

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

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

7 2.2.2.2 *Route task.*

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

21 2.3 *Procedure*

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

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

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

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

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

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

13 [INSERT FIGURE 1]

14 2.4 Statistical analysis

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

$$20 \quad n_A = (\sigma_A^2 + \sigma_B^2/\kappa) \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\mu_A - \mu_B} \right)^2$$

21 where μ_A is the mean in group A; μ_B is the mean in group B; σ_A is standard
22 deviation in Group "A"; σ_B is the standard deviation in Group "B"; κ is the matching
23 ratio; α is Type I error (meaning $1 - \alpha$ is confidence level); and β is Type II error

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

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

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

22 **3. Results**

23 *3.1 Clinical, Neuropsychological, and Demographic Variables*

1 Table 1 depicts the demographic and clinical variables of the patient sample (age of
2 onset, duration of the illness, seizure type, medication, laterality of the epileptic activity
3 focus and neuroimaging outcome). A majority of the participants were women (79%)
4 with a mean age of $41.43 \pm$ years ($SD = 14.28$). The mean age of onset was 24.43 ($SD =$
5 10.61), and the mean duration of the illness was 17.35 years ($SD = 12.45$).

6 Patients showed a combination of complex and simple partial seizures, and 5 out of
7 14 patients also had secondary generalized tonic-clonic seizures. Eight out of the 14
8 participants showed normal MRI, only 4 out of 14 showed signs of MTS, and 2 showed
9 hippocampi atrophy according to the clinical reports provided by the neuro-radiologist.
10 All patients had been seizure-free for 3 months prior to the beginning of the study.
11 Moreover, the majority (9 out of 14) of the patients had not any seizures for 6 months.

12 [INSERT TABLE 1]

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

21 [INSERT TABLE 2]

22 3.2 *Forgetting: Verbal and Visual Information*

1 Figure 2 depicts mean raw scores on both experimental tasks across all delay
2 intervals compared across the groups. On these memory tasks, the groups did not differ
3 significantly at the first delay interval (30 seconds) in the recall of stories (TLE =
4 16.71 ± 1.43 ; Control = 17.07 ± 2.43 ; $t = -0.47$, $p = .640$; $g = .178$) or routes (TLE =
5 16.21 ± 2.36 ; Control = 15.21 ± 2.39 ; $t = 1.113$, $p = .275$; $g = .420$). Thus, it can be stated
6 that they were “matched” in acquisition of the information. All participants reached the
7 60% criterion (stories and routes) after one presentation and multiple trials of materials
8 were not necessary.

9 [INSERT FIGURE 2]

10 Moreover, as can be seen, the forgetting curves were similar for both groups, after
11 being matched at the initial interval. In other words, mean change scores (MCS) did not
12 differ significantly across the intervals, except between the 30 second and the 10-minute
13 delay on the stories task. The effect size for this interval was large. Thus, the TLE group
14 showed faster forgetting of verbal information at the 10-minute interval (TLE =
15 2.86 ± 2.98 ; Control = -0.64 ± 4.24 ; $t = 2.527$, $p = .017$; $g = .955$), but there were no
16 significant differences at the 1-day (TLE = 7.14 ± 6.09 ; Control = 4.29 ± 4.48 ; $t = 1.414$, p
17 = $.169$; $g = .534$) or 1-week intervals (TLE = 13.14 ± 3.35 ; Control = 10.93 ± 5.39 ; $t =$
18 1.231 , $p = .229$; $g = .465$). For visuo-spatial information, there were no differences in
19 forgetting at any delays: both groups displayed similar forgetting rates across all
20 intervals, with no significant differences at the 10-minute (TLE = 1.93 ± 2.79 ; Control =
21 -0.07 ± 3.17 ; $t = 1.771$, $p = .088$; $g = .669$), 1-day (TLE = 6.50 ± 2.93 ; Control =
22 4.36 ± 3.82 ; $t = 1.667$, $p = .107$; $g = .630$) or 1-week intervals (TLE = 8.93 ± 3.69 ; Control
23 = 7.43 ± 3.59 ; $t = 1.090$, $p = .285$; $g = .412$).

1 It should also be noted that the correlation between forgetting rates on the WMS
2 word list (free recall) and the story task (cued recall at 10 minutes) was not significant (r
3 $=-0.187$, $p = 0.340$). No significant Spearman's correlations were found between age
4 and forgetting rates (MCS) of the story (10-min: $r = -0.134$, $p = .646$; 1-day: $r = 0.300$, p
5 $= .295$; 1 week: $r = 0.506$, $p = .064$), or between age and route forgetting (10-min: $r = -$
6 0.288 , $p = .317$; 1-day: $r = 0.154$, $p = .599$; 1 week: $r = -0.356$, $p = .210$) at different
7 intervals. Likewise, no significant correlations were found between illness duration and
8 forgetting rates of the story (10-min: $r = 0.140$, $p = .633$; 1-day: $r = 0.105$, $p = .719$; 1
9 week: $r = .363$, $p = .200$), or between illness duration and route forgetting (10-min: $r =$
10 0.050 , $p = .862$; 1-day: $r = 0.258$, $p = .371$; 1 week: $r = 0.134$, $p = .646$) at different
11 intervals. Finally, correlations between forgetting rates (stories/routes) and number of
12 epileptic seizures (during the last year) were not significant (all p values $>.10$).

13 3.3 *Epilepsy-Related Variables Analysis*

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

20 3.3.1 *Presence/absence of hippocampal abnormalities.*

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

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

3 For the forgetting of stories, there was a significant main effect of delay ($F_{2,24} =$
4 20.164 , $p < .001$), but no main effect of group ($F_{1,12} = 0.733$, $p = .409$), nor a significant
5 delay by group interaction ($F_{2,24} = 0.406$, $p = .671$). For routes, there was a significant
6 main effect of delay ($F_{2,24} = 31.861$, $p < .001$), but no significant main effect of group
7 ($F_{1,12} = 0.023$, $p = .881$). There was no significant delay by group interaction ($F_{2,24} =$
8 2.117 , $p = .142$).

9 3.3.2 *Laterality of seizure focus.*

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

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

19 3.3.3 *Anti-epileptic medication.*

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

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

6 **4. Discussion**

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

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

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

8 There are aspects of method that may explain the heterogeneity of the results in TLE
9 patients (Cassel & Kopelman, 2019; Elliott et al., 2014). For instance, the use of free
10 recall tasks can lead to a floor effect, whereas ceiling effects may easily emerge with the
11 use of recognition tasks, masking accelerated forgetting (Elliott et al., 2014). In our
12 study, memory was assessed using cued questions, which allowed us generally to avoid
13 both ceiling and floor effects, although, as shown in Fig 3s, these effects were
14 observable in some individual participants. Moreover, we used four different delay
15 intervals to monitor the time-period over which accelerated forgetting might occur. As
16 proposed by Baddeley, Atkinson, Kemp, and Allen (Baddeley et al., 2018), multiple test
17 designs seem to be necessary to detect accelerated forgetting, in contrast to repeated
18 testing within individuals. Some studies have found accelerated long-term forgetting
19 using two delayed intervals (from 30 min/1 hour up to 1 or several weeks) (Blake, 2000;
20 Gascoigne et al., 2019; Helmstaedter et al., 2018; Narayanan et al., 2012; Savage et al.,
21 2017; Tramoni et al., 2011; Wilkinson et al., 2012). However, it can be argued that
22 forgetting across initial or early delays might be underestimated in these studies if they
23 have not used any testing between the two intervals (Cassel & Kopelman, 2019). In fact,

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

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

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

1 which have shown accelerated forgetting on recall tasks (pictures and words) within 10
2 or 20 minutes, after matching for initial memory performance (Green & Kopelman,
3 2002; Isaac & Mayes, 1999a, 1999b; Kopelman & Stanhope, 1997).

4 In the present study, we need to acknowledge that moderate effect sizes (range: .41-.53)
5 were reached for verbal and visuospatial material at longer delays (1 day, 1 week), even
6 though these differences were not statistically significant. Moreover, at these longer
7 delays, memory was assessed by phone, whereas the context at earlier intervals (30
8 seconds and 10 minutes) was the same (i.e., laboratory room) for all participants. It
9 might have been the case that the healthy controls experienced a context-dependent
10 advantage at 10 minutes, relative to the TLE group, which was absent at the longer
11 delays. However, context effects may not be as robust as sometimes thought, especially
12 when memory items are not properly perceived as a part of the environment or are
13 interactively processed with the environment (Fernández & Glenberg, 1985; Eich,
14 1985). Moreover, only 6 of our TLE participants showed hippocampal abnormalities,
15 which might have affected their context-dependent memory.

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

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

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

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

3 **5. Conclusion**

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

19 **Funding sources and authors statements**

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

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

9 **Conflict of Interest**

10 The authors declare that they have no conflict of interest.

11 **Acknowledgements**

12 We thank Patricia Alzola and Anneli Cassel for their collaboration in obtaining the pilot
13 data. We acknowledge Prof. Félix Bermejo and Prof. Robin Morris for their help at the
14 inception of the study. Finally, the authors especially thank the cooperation of all
15 participants in this research.

16 **6. References**

- 17 Atherton, K. E., Filippini, N., Zeman, A. Z. J., Nobre, A. C., & Butler, C. R. (2019).
18 Encoding-related brain activity and accelerated forgetting in transient epileptic
19 amnesia. *Cortex*, *110*, 127–140. <https://doi.org/10.1016/j.cortex.2018.04.015>
- 20 Audrain, S., & McAndrews, M. P. (2018). Cognitive and functional correlates of
21 accelerated long-term forgetting in temporal lobe epilepsy. *Cortex*, *110*, 101–
22 114. <https://doi.org/10.1016/j.cortex.2018.03.022>

- 1 Baddeley, A., Atkinson, A., Kemp, S., & Allen, R. (2018). The problem of detecting
2 long-term forgetting: Evidence from the Crimes Test and the Four Doors Test.
3 *Cortex*, *110*, 69–79. <https://doi.org/10.1016/j.cortex.2018.01.017>
- 4 Barnett, A. J., Park, M. T. M., Pipitone, J., Chakravarty, M. M., & McAndrews, M. P.
5 (2015). Functional and Structural Correlates of Memory in Patients with Mesial
6 Temporal Lobe Epilepsy. *Frontiers in Neurology*, *6*.
7 <https://doi.org/10.3389/fneur.2015.00103>
- 8 Beck, A. T., Brown, G., Epstein, N., & Steer, R. A. (1988). An Inventory for Measuring
9 Clinical Anxiety: Psychometric Properties. *Journal of Consulting and Clinical*
10 *Psychology*, *56*(6), 893–897.
- 11 Beck, A. T., Steer, R. A., & Brown, G. (1996). *Manual for the Beck Depression*
12 *Inventory-II*. Psychological Corporation.
- 13 Bell, B. D. (2006). WMS-III logical memory performance after a two-week delay in
14 temporal lobe epilepsy and control groups. *Journal of Clinical and Experimental*
15 *Neuropsychology*, *28*(8), 1435–1443.
- 16 Bell, B. D., Fine, J., Dow, C., Seidenberg, M., & Hermann, B. P. (2005). Temporal lobe
17 epilepsy and the selective reminding test: The conventional 30-minute delay
18 suffices. *Psychological Assessment*, *17*(1), 103.
- 19 Blake, R. V. (2000). Accelerated forgetting in patients with epilepsy: Evidence for an
20 impairment in memory consolidation. *Brain*, *123*(3), 472–483.
21 <https://doi.org/10.1093/brain/123.3.472>
- 22 Blume, W. T. (2003). Diagnosis and management of epilepsy. *Canadian Medical*
23 *Association Journal*, *168*(4), 441–448.
- 24 Burgess, P., & Shallice, T. (1997). *The Hayling and Brixton Tests. Test manual*. Thames
25 Valley Test Company.

- 1 Butler, C. R., Bhaduri, A., Acosta-Cabronero, J., Nestor, P. J., Kapur, N., Graham, K.
2 S., Hodges, J. R., & Zeman, A. Z. (2009). Transient epileptic amnesia: Regional
3 brain atrophy and its relationship to memory deficits. *Brain*, *132*(2), 357–368.
4 <https://doi.org/10.1093/brain/awn336>
- 5 Butler, C. R., Gilboa, A., & Miller, L. (2019). Accelerated long-term forgetting. *Cortex*,
6 *110*, 1–4. <https://doi.org/10.1016/j.cortex.2018.12.009>
- 7 Butler, C. R., van Erp, W., Bhaduri, A., Hammers, A., Heckemann, R., & Zeman, A.
8 (2013). Magnetic resonance volumetry reveals focal brain atrophy in transient
9 epileptic amnesia. *Epilepsy & Behavior*, *28*(3), 363–369.
10 <https://doi.org/10.1016/j.yebeh.2013.05.018>
- 11 Cassel, A., & Kopelman, M. D. (2019). Have we forgotten about forgetting? A critical
12 review of ‘accelerated long-term forgetting’ in temporal lobe epilepsy. *Cortex*,
13 *110*, 141–149. <https://doi.org/10.1016/j.cortex.2017.12.012>
- 14 Cassel, A., Morris, R., Koutroumanidis, M., & Kopelman, M. D. (2016). Forgetting in
15 temporal lobe epilepsy: When does it become accelerated? *Cortex*, *78*, 70–84.
16 <https://doi.org/10.1016/j.cortex.2016.02.005>
- 17 Contador, I., Sánchez, A., Kopelman, M. D., & González de la Aleja, J. (2017). Long-
18 term forgetting in temporal lobe epilepsy: Is this phenomenon a norm? *Epilepsy*
19 *& Behavior*, *77*, 30–32. <https://doi.org/10.1016/j.yebeh.2017.09.020>
- 20 Coras, R., Pauli, E., Li, J., Schwarz, M., Rössler, K., Buchfelder, M., Hamer, H., Stefan,
21 H., & Blumcke, I. (2014). Differential influence of hippocampal subfields to
22 memory formation: Insights from patients with temporal lobe epilepsy. *Brain*,
23 *137*(7), 1945–1957. <https://doi.org/10.1093/brain/awu100>

- 1 Cornish, I. M. (2000). Factor structure of the Everyday Memory Questionnaire. *British*
2 *Journal of Psychology*, *91*(3), 427–438.
3 <https://doi.org/10.1348/000712600161916>
- 4 Deak, M. C., Stickgold, R., Pietras, A. C., Nelson, A. P., & Bubrick, E. J. (2011). The
5 role of sleep in forgetting in temporal lobe epilepsy: A pilot study. *Epilepsy &*
6 *Behavior*, *21*(4), 462–466. <https://doi.org/10.1016/j.yebeh.2011.04.061>
- 7 Dewar, M., Hoefeijzers, S., Zeman, A., Butler, C., & Della Sala, S. (2015). Impaired
8 picture recognition in transient epileptic amnesia. *Epilepsy & Behavior*, *42*, 107–
9 116. <https://doi.org/10.1016/j.yebeh.2014.10.032>
- 10 Eich, E. (1985). Context, memory, and integrated item/context imagery. *Journal of*
11 *Experimental Psychology: Learning, Memory, and Cognition*, *11*(4), 764–770.
- 12 Elliott, G., Isaac, C. L., & Muhlert, N. (2014). Measuring forgetting: A critical review
13 of accelerated long-term forgetting studies. *Cortex*, *54*, 16–32.
14 <https://doi.org/10.1016/j.cortex.2014.02.001>
- 15 Fernández, A., & Glenberg, A. M. (1985). Changing environmental context does not
16 reliably affect memory. *Memory & Cognition*, *13*, 333-345.
- 17 Fitzgerald, Z., Mohamed, A., Ricci, M., Thayer, Z., & Miller, L. (2013). Accelerated
18 long-term forgetting: A newly identified memory impairment in epilepsy.
19 *Journal of Clinical Neuroscience*, *20*(11), 1486–1491.
20 <https://doi.org/10.1016/j.jocn.2013.04.037>
- 21 Gascoigne, M. B., Smith, M. L., Barton, B., Webster, R., Gill, D., & Lah, S. (2014).
22 Accelerated long-term forgetting in children with temporal lobe epilepsy.
23 *Neuropsychologia*, *59*, 93–102.
24 <https://doi.org/10.1016/j.neuropsychologia.2014.04.012>

- 1 Gascoigne, M. B., Smith, M. L., Barton, B., Webster, R., Gill, D., & Lah, S. (2019).
2 Accelerated long-term forgetting and behavioural difficulties in children with
3 epilepsy. *Cortex*, *110*, 92–100. <https://doi.org/10.1016/j.cortex.2018.03.021>
- 4 Giovagnoli, A. R., Casazza, M., & Avanzini, G. (1995). Visual Learning on a Selective
5 Reminding Procedure and Delayed Recall in Patients with Temporal Lobe
6 Epilepsy. *Epilepsia*, *36*(7), 704–711. [https://doi.org/10.1111/j.1528-](https://doi.org/10.1111/j.1528-1157.1995.tb01050.x)
7 [1157.1995.tb01050.x](https://doi.org/10.1111/j.1528-1157.1995.tb01050.x)
- 8 Green, R. E., & Kopelman, M. D. (2002). Contribution of Recollection and Familiarity
9 Judgements to Rate of Forgetting in Organic Amnesia. *Cortex*, *38*(2), 161–178.
10 [https://doi.org/10.1016/S0010-9452\(08\)70648-8](https://doi.org/10.1016/S0010-9452(08)70648-8)
- 11 Helmstaedter, C., Winter, B., Melzer, N., Lohmann, H., & Witt, J.-A. (2018).
12 Accelerated long-term forgetting in focal epilepsies with special consideration
13 given to patients with diagnosed and suspected limbic encephalitis. *Cortex*, *110*,
14 58–68. <https://doi.org/10.1016/j.cortex.2018.01.003>
- 15 Hoefeijzers, S., Dewar, M., Della Sala, S., Butler, C., & Zeman, A. (2015). Accelerated
16 long-term forgetting can become apparent within 3–8 hours of wakefulness in
17 patients with transient epileptic amnesia. *Neuropsychology*, *29*(1), 117–125.
18 <https://doi.org/10.1037/neu0000114>
- 19 Howard, C. E., Andrés, P., Broks, P., Noad, R., Sadler, M., Coker, D., & Mazzoni, G.
20 (2010). Memory, metamemory and their dissociation in temporal lobe epilepsy.
21 *Neuropsychologia*, *48*(4), 921–932.
22 <https://doi.org/10.1016/j.neuropsychologia.2009.11.011>
- 23 Isaac, C. L., & Mayes, A. R. (1999a). Rate of Forgetting in Amnesia: I. Recall and
24 Recognition of Prose. *Journal of Experimental Psychology: Learning, Memory*
25 *and Cognition*, *25*(4), 942–962.

- 1 Isaac, C. L., & Mayes, A. R. (1999b). Rate of Forgetting in Amnesia: II. Recall and
2 recognition of word lists at different levels of organization. *Journal of*
3 *Experimental Psychology: Learning, Memory and Cognition*, 25(4), 963–977.
- 4 Jansari, A. S., Davis, K., McGibbon, T., Firminger, S., & Kapur, N. (2010). When
5 “long-term memory” no longer means “forever”: Analysis of accelerated long-
6 term forgetting in a patient with temporal lobe epilepsy. *Neuropsychologia*,
7 48(6), 1707–1715. <https://doi.org/10.1016/j.neuropsychologia.2010.02.018>
- 8 Jokeit, H., Krämer, G., & Ebner, A. (2005). Do antiepileptic drugs accelerate
9 forgetting? *Epilepsy & Behavior*, 6(3), 430–432.
10 <https://doi.org/10.1016/j.yebeh.2004.12.012>
- 11 Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test (BNT):*
12 *Manual, (2nd edition)*. Lea and Fabiger.
- 13 Kopelman, M. D. (2000). Focal retrograde amnesia and the attribution of causality: An
14 exceptionally critical view. *Cognitive Neuropsychology*, 17(7), 585–621.
15 <https://doi.org/10.1080/026432900750002172>
- 16 Kopelman, M. D., & Stanhope, N. (1997). *Rates of forgetting in organic amnesia*
17 *following temporal lobe, diencephalic, or frontal lobe lesions*. 11(3), 343.
- 18 Kopelman, M. D., Wilson, B. A., & Baddeley, A. (1990). *Autobiographical memory*
19 *inventory*. Thames Valley Test Company.
- 20 Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative
21 science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, 4.
22 <https://doi.org/10.3389/fpsyg.2013.00863>
- 23 Mayes, A. R., Hunkin, N. M., Isaac, C., & Muhlert, N. (2018). Are there distinct forms
24 of accelerated forgetting and, if so, why? *Cortex*, 110, 115–126.
25 <https://doi.org/10.1016/j.cortex.2018.04.005>

- 1 Midorikawa, A., & Kawamura, M. (2008). Recovery of Long-Term Anterograde
2 Amnesia, but Not Retrograde Amnesia, after Initiation of an Anti-Epileptic Drug
3 in a Case of Transient Epileptic Amnesia. *Neurocase*, *13*(5–6), 385–389.
4 <https://doi.org/10.1080/13554790701851536>
- 5 Miller, L. A., Mothakunnel, A., Flanagan, E., Nikpour, A., & Thayer, Z. (2017).
6 Accelerated Long Term Forgetting in patients with focal seizures: Incidence rate
7 and contributing factors. *Epilepsy & Behavior*, *72*, 108–113.
8 <https://doi.org/10.1016/j.yebeh.2017.04.039>
- 9 Motamedi, G., & Meador, K. (2003). Epilepsy and cognition. *Epilepsy & Behavior*, *4*,
10 25–38. <https://doi.org/10.1016/j.yebeh.2003.07.004>
- 11 Mueller, S. G., Laxer, K. D., Scanlon, C., Garcia, P., McMullen, W. J., Loring, D. W.,
12 Meador, K. J., & Weiner, M. W. (2012). Different structural correlates for verbal
13 memory impairment in temporal lobe epilepsy with and without mesial temporal
14 lobe sclerosis. *Human Brain Mapping*, *33*(2), 489–499.
15 <https://doi.org/10.1002/hbm.21226>
- 16 Muhlert, N., Grünewald, R. A., Hunkin, N. M., Reuber, M., Howell, S., Reynders, H.,
17 & Isaac, C. L. (2011). Accelerated long-term forgetting in temporal lobe but not
18 idiopathic generalised epilepsy. *Neuropsychologia*, *49*(9), 2417–2426.
19 <https://doi.org/10.1016/j.neuropsychologia.2011.04.018>
- 20 Narayanan, J., Duncan, R., Greene, J., Leach, J.-P., Razvi, S., McLean, J., & Evans, J. J.
21 (2012). Accelerated long-term forgetting in temporal lobe epilepsy: Verbal,
22 nonverbal and autobiographical memory. *Epilepsy & Behavior*, *25*(4), 622–630.
23 <https://doi.org/10.1016/j.yebeh.2012.06.038>
- 24 O'Connor, M., Sieggreen, M. A., Ahern, G., Schomer, D., & Mesulam, M. (1997).
25 Accelerated Forgetting in Association with Temporal Lobe Epilepsy and

- 1 Paraneoplastic Encephalitis. *Brain and Cognition*, 35(1), 71–84.
2 <https://doi.org/10.1006/brcg.1997.0928>
- 3 Ricci, M., Mohamed, A., Savage, G., & Miller, L. A. (2015). Disruption of learning and
4 long-term retention of prose passages in patients with focal epilepsy. *Epilepsy &*
5 *Behavior*, 51, 104–111. <https://doi.org/10.1016/j.yebeh.2015.06.016>
- 6 Savage, S., Hoefjeziers, S., Milton, F., Streatfield, C., Dewar, M., & Zeman, A. (2017).
7 The evolution of accelerated long-term forgetting: Evidence from the TIME
8 study. *Cortex*, 110, 16–36. <https://doi.org/10.1016/j.cortex.2017.09.007>
- 9 Shao, J., Wang, H., & Chow, S. C. (2008). *Sample size calculations in clinical research*.
10 Chapman & Hall/CRC.
- 11 Staley, K. J., & Dudek, F. E. (2006). Interictal Spikes and Epileptogenesis. *Epilepsy*
12 *Currents*, 6(6), 199–202. <https://doi.org/10.1111/j.1535-7511.2006.00145.x>
- 13 Stamate, A., Logie, R. H., Baddeley, A. D., & Della Sala, S. (2020). Forgetting in
14 Alzheimer’s disease: Is it fast? Is it affected by repeated retrieval?
15 *Neuropsychologia*, 138, 107351.
16 <https://doi.org/10.1016/j.neuropsychologia.2020.107351>
- 17 Tramoni, E., Felician, O., Barbeau, E. J., Guedj, E., Guye, M., Bartolomei, F., &
18 Ceccaldi, M. (2011). Long-term consolidation of declarative memory: Insight
19 from temporal lobe epilepsy. *Brain*, 134(3), 816–831.
20 <https://doi.org/10.1093/brain/awr002>
- 21 Tramoni-Negre, E., Lambert, I., Bartolomei, F., & Felician, O. (2017). Long-term
22 memory deficits in temporal lobe epilepsy. *Revue Neurologique*, 173(7–8), 490–
23 497. <https://doi.org/10.1016/j.neurol.2017.06.011>
- 24 Visser, M., Forn, C., Gómez-Ibáñez, A., Rosell-Negre, P., Villanueva, V., & Ávila, C.
25 (2018). Accelerated long-term forgetting in resected and seizure-free temporal

- 1 lobe epilepsy patients. *Cortex*, *110*, 80–91.
2 <https://doi.org/10.1016/j.cortex.2018.02.017>
- 3 Voltzenlogel, V., Vignal, J.-P., Hirsch, E., & Manning, L. (2014). The influence of
4 seizure frequency on anterograde and remote memory in mesial temporal lobe
5 epilepsy. *Seizure*, *23*(9), 792–798. <https://doi.org/10.1016/j.seizure.2014.06.013>
- 6 Wechsler, D. (1997a). *WAIS-III*. Psychological Corporation.
- 7 Wechsler, D. (1997b). *Wechsler memory scale (WMS-III)*. Psychological Corporation.
- 8 Wilkinson, H., Holdstock, J. S., Baker, G., Herbert, A., Clague, F., & Downes, J. J.
9 (2012). Long-term accelerated forgetting of verbal and non-verbal information
10 in temporal lobe epilepsy. *Cortex*, *48*(3), 317–332.
11 <https://doi.org/10.1016/j.cortex.2011.01.002>
- 12 World Health Organization. (2019). *Epilepsy*. [https://www.who.int/news-room/fact-](https://www.who.int/news-room/fact-sheets/detail/epilepsy)
13 [sheets/detail/epilepsy](https://www.who.int/news-room/fact-sheets/detail/epilepsy)
- 14 Zeman, A., Butler, C., Muhlert, N., & Milton, F. (2013). Novel forms of forgetting in
15 temporal lobe epilepsy. *Epilepsy & Behavior*, *26*(3), 335–342.
16 <https://doi.org/10.1016/j.yebeh.2012.09.030>

1

2

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/χ^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±5.58	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

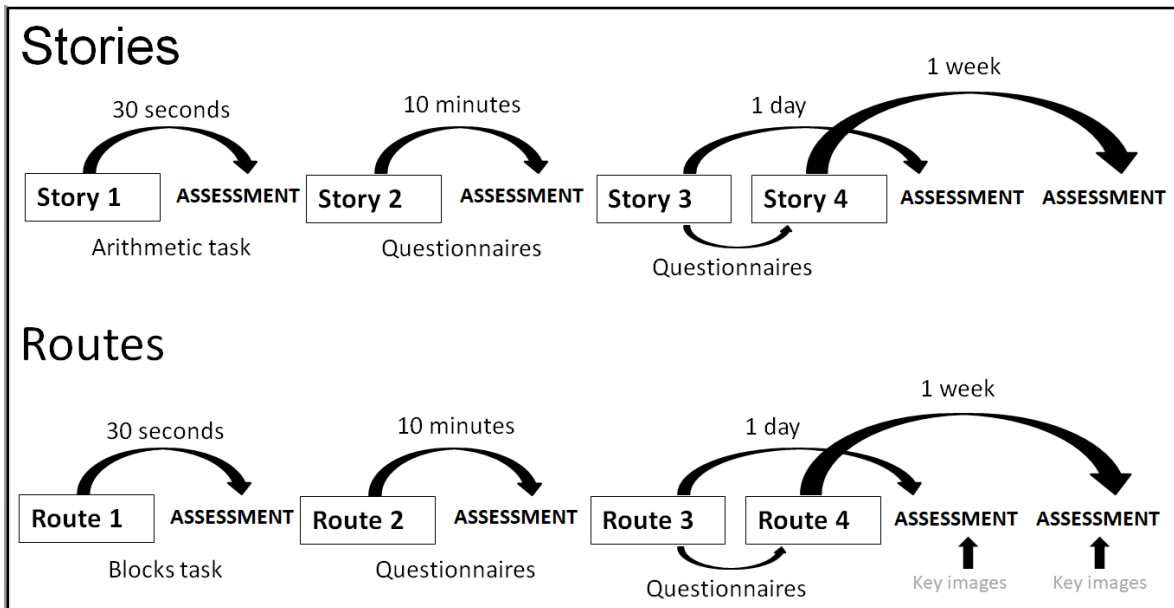


Figure 1. Long-term forgetting assessment procedure.

Stories

Routes

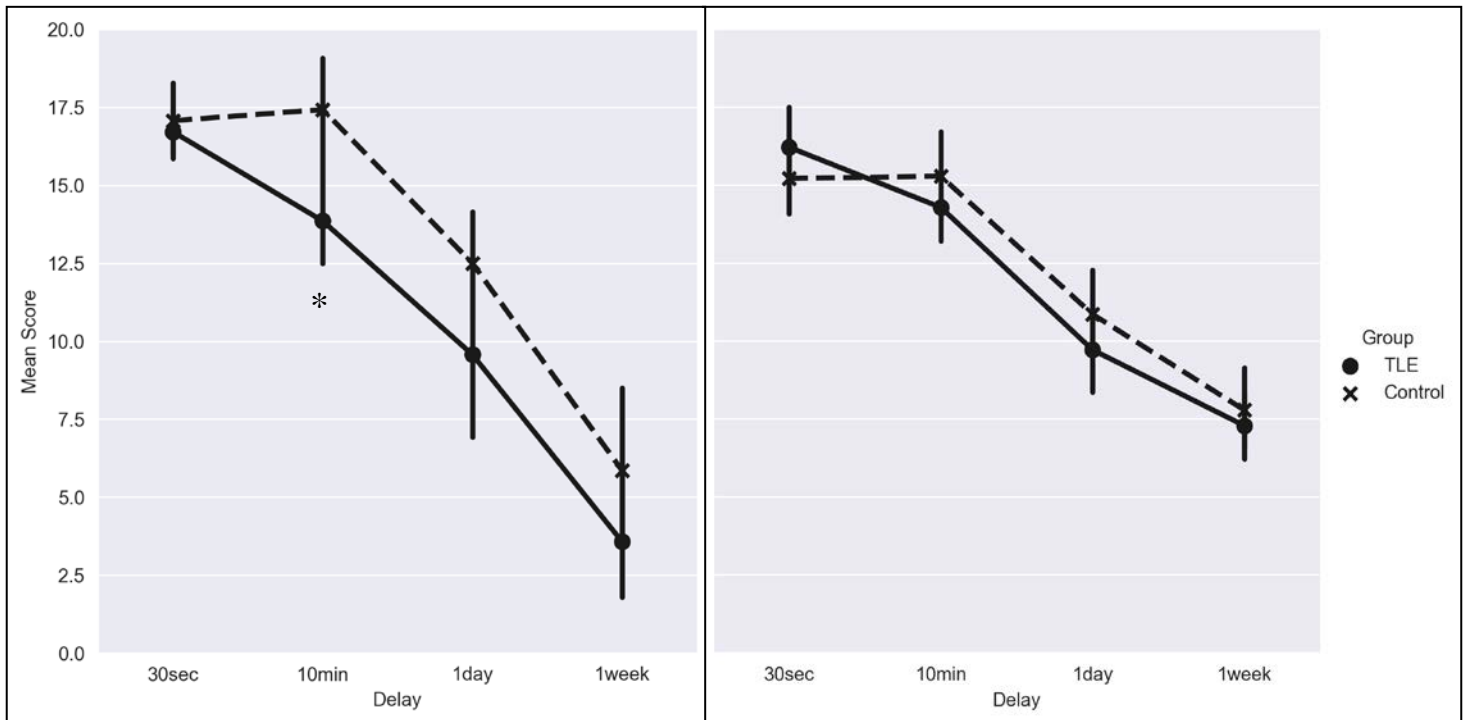


Figure 2. Long-term forgetting tasks' (stories and routes) mean raw scores by group. Error bars depict 95% confidence intervals. The asterisk (*) indicates intervals that reached significant differences between the groups.

SUPPLEMENTARY MATERIAL

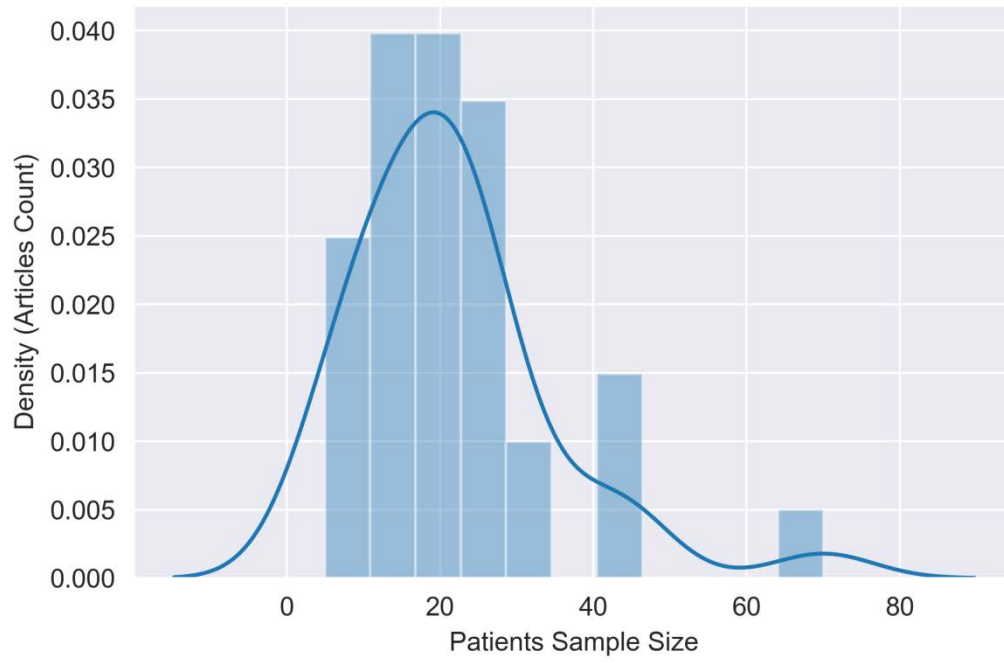


Fig 1s. Sample sizes distribution of 34 articles on forgetting in TLE.

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

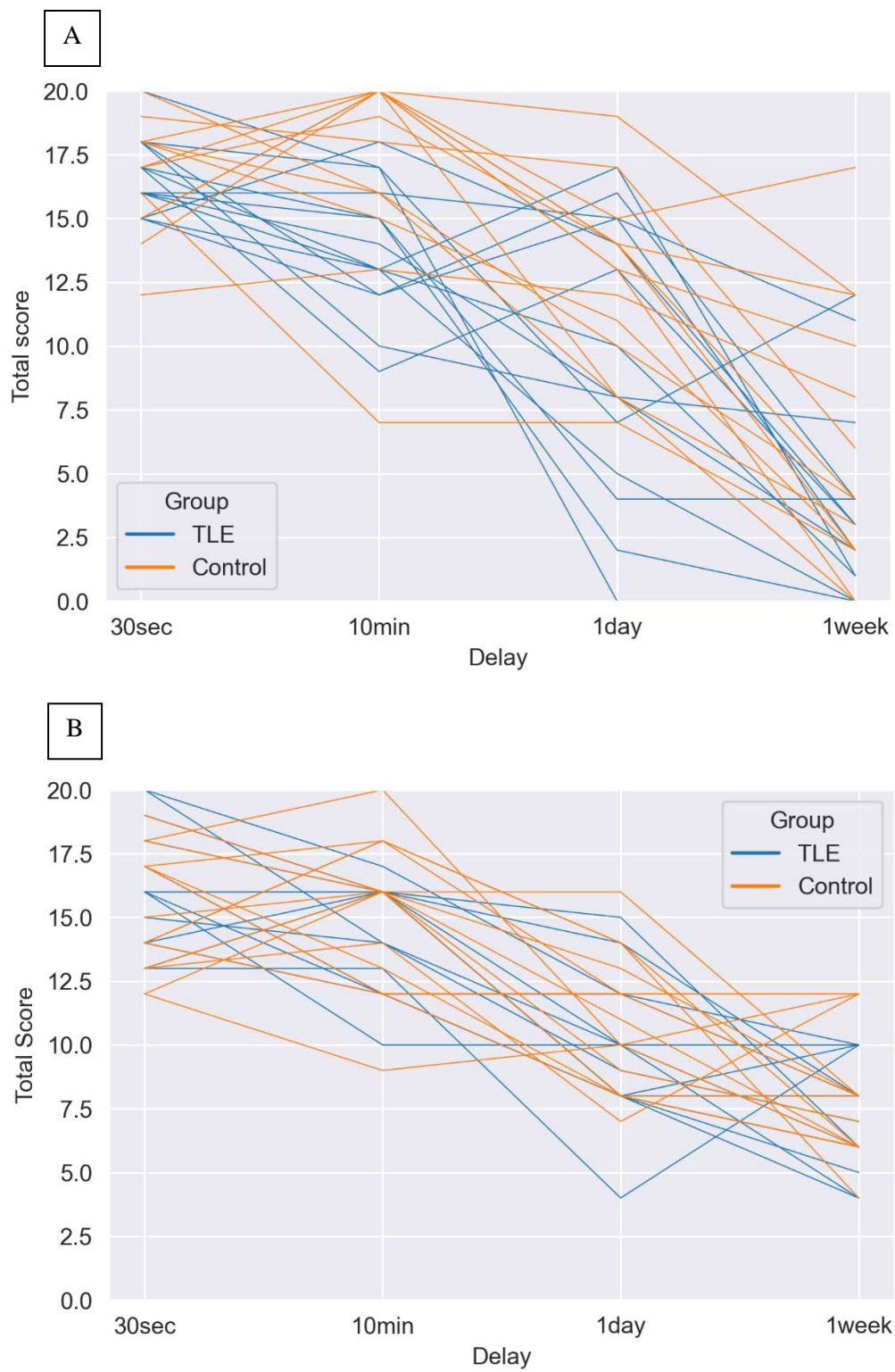


Fig 3s. Individual performance in memory tasks. A) Story task. B) Route task.