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Abstract

Transient epileptic amnesia (TEA) is an epileptic syndrome characterized by recurrent, brief episodes of amnesia. Patients with TEA often complain of interictal (between attacks) retention deficits, characterised by an 'evaporation' of memories for recent events over days to weeks. Clinical tests of anterograde memory often fail to corroborate these complaints as TEA patients commonly perform within the normal range after the standard 10-30-minute delay period. Modified laboratory tests that include a 1-3 week delay period frequently reveal clear evidence of 'accelerated long-term forgetting' (ALF). However, they are not used routinely and lack ecological validity. In the present study we examined whether 'real-life' ALF can be captured via a controlled incidental memory test in TEA patients. To this end, the experimenter told 27 TEA patients and 32 controls a well-rehearsed amusing story, apparently as a way of making light conversation before starting a set of research experiments. Without prior warning, the experimenter subsequently probed the participants' memory of this story via tests of free recall and forced choice recognition after 30 minutes or 1 week. After 30 minutes retention was comparable in TEA patients and controls. After 1 week TEA patients retained significantly less story material than controls, and significant ALF was revealed in the TEA patients in the recognition test. Our data show that ALF in a 'real-life' situation can occur even when standard memory tests indicate normal memory function. Moreover, our data suggest that incidental memory tests can capture real-life ALF, and that forced-choice recognition tests might be more sensitive than free recall tests for the detection of real-life ALF.

1. Introduction

Transient Epileptic Amnesia (TEA) is characterised by brief, recurrent episodes of amnesia occurring as a result of epilepsy. During these episodes, episodic memory is impaired, while other cognitive functions remain intact (Zeman & Butler, 2010). TEA is regarded as a subtype of temporal lobe epilepsy (TLE) on the basis of its clinical features, EEG and neuroimaging findings (Butler et al., 2007; Butler & Zeman, 2008b; Lapenta et al., 2014; Mosbah et al., 2014; Zeman & Butler, 2010). In addition to interictal (between attacks) deficits of remote autobiographical (Butler et al., 2007; Manes, Hodges, Graham, & Zeman, 2001; Milton et al., 2010) and topographical memory (Butler et al., 2007), almost half (44%) of patients with TEA describe interictal deficits in the longer-term retention of recently acquired memories (Butler et al., 2007; Hoefeijzers, Dewar, Della Sala, Zeman, & Butler, 2013; Manes, Graham, Zeman, de Luján Calcagno, & Hodges, 2005; Muhlert, Milton, Butler, Kapur, & Zeman, 2010). This interictal retention deficit, which often persists after successful treatment of the epileptic attacks with anticonvulsants (Zeman & Butler, 2010), can be as disturbing for patients as the occasional, brief amnesic episodes caused by seizures (Butler & Zeman, 2008b). Patients with TEA describe this interictal retention deficit as an 'evaporation' of memories for recent events (Butler & Zeman, 2008b). Specifically, they tend to complain of a rapid fading of recent everyday events such as activities, conversations, films or books, over a matter of days to weeks. For example, Butler and Zeman (2008a) reported the case of a university lecturer who was able to discuss the merits of a film a day after watching it. However, he had no recollection of the film one week later.

As these patients' performance on standard, i.e. 30-min, tests of anterograde memory function is commonly within the normal range (e.g., Butler & Zeman, 2008b; Mendes, 2002; Zeman, Boniface, & Hodges, 1998; Zeman & Butler, 2010) their memory complaints may not to be considered further by clinicians. However, systematic assessment of their memory

via laboratory tests over longer (1-3 week) delays has provided clear evidence of an accelerated fading of their memory over days to weeks - a clinical phenomenon termed 'accelerated long-term forgetting' (ALF) (Butler et al., 2007; Hoefeijzers et al., 2013; Muhlert et al., 2010; Zeman & Butler, 2010). ALF has also been reported in patients with other types of temporal lobe epilepsy (TLE; e.g., Blake, Wroe, Breen, & McCarthy, 2000; Jansari, Davis, McGibbon, Firminger, & Kapur, 2010; Kapur et al., 1997; Kemp, Illman, Moulin, & Baddeley, 2012; Lah, Mohamed, Thayer, Miller, & Diamond, 2014; Lucchelli & Spinnler, 1998; Martin et al., 1991; Mayes et al., 2003; McGibbon & Jansari, 2013; O'Connor, Sieggreen, Ahern, Schomer, & Mesulam, 1997; Ricci, Mohamed, Savage, & Miller, 2015; Wilkinson et al., 2012; for an exception, see Giovagnoli, Casazza, & Avanzini, 1995).

In cases where ALF is examined clinically or for research purposes, laboratory tests are usually employed. Although such tests allow for tight experimental control and comparisons within and between groups, they differ from the patients' real-life experiences in several ways. Firstly, these tests typically probe a patient's memory for somewhat artificial materials such as wordlists or abstract designs (e.g., Butler et al., 2007; Lah et al., 2014). Secondly, these tests typically involve multiple learning trials (i.e., repetitions), so as to allow for the adequate comparison of forgetting curves across participants (e.g., Hoefeijzers et al., 2013). Thirdly, these tests invariably employ an 'intentional' encoding method, whereby participants are aware, at the point of learning/encoding, that they are undergoing clinical assessment/are part of a research study, and in particular, that their memory for the material will be probed subsequently. Notwithstanding such tests' capacity to detect deficits in longer-term retention, these artificial factors could result in an over- or underestimation of a patient's long-term forgetting in day-to-day life. This calls for measures that can capture long-term forgetting in real-life contexts whilst retaining objectivity and experimental control.

To our knowledge, only a handful of published studies report real-life memory testing over extended delays in patients with TLE (Helmstaedter, Hauff, & Elger, 1998; Muhlert et al., 2010; Narayanan et al., 2012; Ricci, Mohamed, Savage, Boserio, & Miller, 2015; Tramoni et al., 2011), and only one of these studies (Muhlert et al., 2010) focused on TEA specifically. Muhlert et al. (2010) devised a test to probe TEA patients' long-term memory for a recently experienced real-life event, e.g. a visit to a castle or museum. Each participant's experienced event was recorded with a SenseCam, a camera that automatically captures images of events. By using these event images as memory cues, the authors were able to demonstrate ALF for real-life stimuli in their TEA patients. However, it is likely that their research participants were aware that the visits were part of a research study; hence memory encoding could have been intentional rather than incidental. Intentional encoding might influence subsequent recall performance differently than incidental encoding (Kuhnert et al., 2013). Importantly, this effect of "knowing to be tested" is a manipulation associated with laboratory testing that does not often occur during memory formation in every-day life situations (Helmstaedter et al., 1998). Indeed, real-life encoding is often incidental.

A small number of studies has investigated the long-term retention of *incidentally encoded* information in TLE patients. Helmstaedter et al. (1998) probed participants' memory for incidentally encoded events occurring during a standard neuropsychological examination a week before. They found that performance on this real-life incidental memory test was significantly poorer in the TLE patients than controls. However, it is unclear whether these findings pertain to ALF as Helmstaedter et al. (1998) did not assess memory for the real-life events after a standard (30-min) delay. Therefore, it is unclear whether or not the poorer 1-week memory of the real-life events in their TLE patients represented ALF or an earlier memory deficit that was carried over to the 1-week delay.

Tentative evidence for ALF for incidentally encoded information in TLE comes from a neat study by Tramoni et al. (2011) who did assess memory both after a standard and long delay. They invited 5 TLE patients and 5 controls 'for coffee at the hospital cafeteria'. Unbeknownst to the participants, this coffee break involved a structured protocol involving a chain of episodes. Memory for these episodes was subsequently tested after 1 hour and 6 weeks. On both test occasions, participants were asked to recall these coffee break events in as much detail as possible, followed by a two-alternative forced-choice questionnaire made up of 15 questions. While there was no significant group difference after 1 hour on the recall or recognition test, the TLE patients performed significantly poorer than the controls on both tests after 6 weeks. Although this response pattern is indicative of ALF, the authors did not in fact report group differences in the forgetting rates over the 1-hour to 6-week interval. Moreover, both groups performed at ceiling after 1 hour, which complicates the assessment of ALF due to potential masked group differences at this baseline.

Narayanan et al. (2012) conducted a similar study to examine the retention of incidentally learned real-life information in TLE patients and controls, and they did report a group comparison of forgetting rates. In their study, a second experimenter, who was part of the plot, "interrupted" the participant's testing session and started a well-rehearsed conversation between the experimenters about a car that was parked outside the building and still had its lights on. Memory for the interrupting event (e.g., verbal content, facial features) was tested after 30 minutes and 4 weeks in the form of a free recall test. The 4-week free recall test was followed by a 3-alternative forced-choice recognition test consisting of 6 questions. While there was no significant group difference after 30 minutes, the TLE patients performed significantly poorer than the controls after 4 weeks, both on the free recall test and the recognition test. However, the rate of forgetting between these two test points did not differ significantly between the TLE patients and controls, i.e. no (significant) ALF was

observed in the patient group. Given small sample sizes and medium-large effect sizes, the authors suggest that the lack of significance might have been due to low power.

A recent study by Ricci et al. (2015) suggests that in TLE ALF for incidentally encoded real-life material might be detected only in patients with hippocampal lesions. They assessed retention of a 90-minute autobiographical experience (consisting of 14 tests, 3 questionnaires and 5 staged events) after 30-minutes, 24 hours and 4 days using a recall and forced-choice recognition testing. On the recall test, ALF was observed over the 30-minute – 24 hour delay interval in TLE patients with hippocampal lesions but not in TLE patients without hippocampal lesions or patients with extratemporal epilepsy. Moreover, no ALF was revealed over the 24 hour – 4 day delay interval. However, as acknowledged by the authors, repeated testing at multiple test times could have boosted memory retention at later tests, thereby masking ALF over longer delays and in some patients.

Notwithstanding several limitations, including the lack of evidence for significant ALF, the above studies suggest that ALF in TLE might be detectable via real-life incidental memory tests. However, it has not yet been established whether or not *real-life ALF* can be captured via controlled incidental memory tests in *TEA patients*.

We examined this in the present study via a real-life incidental memory test in TEA patients with complaints of ALF as well as in matched controls. Shortly after arriving, the experimenter told participants a well-rehearsed amusing story, apparently as a way of making light conversation before starting a set of actual research experiments (reported in part in Hoefeijzers, Dewar, Della Sala, Butler, & Zeman, 2015 and Dewar, Hoefeijzers, Zeman, Butler, & Della Sala, 2015). Without prior warning, the experimenter subsequently probed the participants' memory of this story via tests of free recall and forced choice recognition after 30 minutes or 1 week.

2. Materials and methods

2.1. Participants

2.1.1. TEA patients and controls overall

A total of 27 TEA patients with complaints of ALF and 32 controls took part in this study. All patients met the diagnostic criteria for TEA (Zeman et al., 1998): (i) a history of recurrent, witnessed episodes of transient amnesia; (ii) intact cognitive functions (aside from memory) during typical episodes, as judged by a reliable witness; and (iii) evidence for a diagnosis of epilepsy based on one or more of the following: epileptiform abnormalities on EEG, concurrent onset of other clinical features of epilepsy (such as lip smacking or olfactory hallucinations), or clear-cut response to anticonvulsant therapy. All patients were on anticonvulsant monotherapy, and, at the time of testing, had been free from overt seizures for at least six months. All participants spoke English as their first language and had no symptoms of psychiatric disturbance.

The TEA patients and controls were closely matched for age ($t(40.543)= 0.666$, $p = .509$, r = .10) and relatively closely matched for education, although the number of years spent in education was significantly higher in the controls than the TEA patients ($t(57)= -2.152$, $p = 0.036$, r = .27) (see Table 1). All TEA patients and controls underwent neuropsychological screening (see Table 1): the National Adult Reading Test (NART; Nelson, 1982) and the Wechsler Abbreviated Scale of Intelligence (WASI) similarities and matrix reasoning subtests (Wechsler, 1999) were used to assess general intelligence. The Wechsler Memory Scale–III (WMS-III) logical memory test (immediate and 30-min delayed recall and 30-min delayed recognition of Story A only; Wechsler, 1997) and delayed recall of

the Rey–Osterrieth complex-figure test (Osterrieth & Rey, 1944) were used as anterograde memory measures. The copy of the Rey–Osterrieth complex-figure test also was applied as a measure of visuospatial perception. A test of verbal fluency, the FAS letter fluency test (Spreen & Benton, 1977; Tombaugh, Kozak, & Rees, 1999) was used to examine executive function. Mood was assessed using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Lastly, all but one of the TEA patients completed two subjective memory questionnaires devised by our research team, the first focusing on forgetting (maximum total score = 27) and the second on very long-term-memory (maximum total score = 52) (see supplementary file 1 and 2).

The demographics and standard neuropsychological test performance of the TEA patients and controls are provided in Table 1 (see left columns). The control group significantly outperformed the TEA patient group on the WMS-III Logical memory delayed recall test ($t(57)= -2.634$, $p < 0.05$, r = .33), resulting in significantly higher % retention scores ($t(42.198)= -2.223$, $p < 0.05$, r = .32). Although relatively low, the HADS depression score of the TEA patient group was significantly higher than that of the control group ($t(57)= 2.661$, $p < 0.05$, r = .33).

<<INSERT TABLE 1 HERE>>

2.1.2 TEA patients and controls within the 30-minute and 1-week test groups

Each TEA patient and control was randomly allocated to one of two test time groups: a *30-minute test group*, and a *1-week test group*. The participants in these two groups took part in separate larger-scale research projects, both of which included the incidental memory test, but with different delay periods (30 minutes vs. 1 week). The inclusion and exclusion criteria were identical for TEA patients in these two groups. The 1-week test group consisted of 16

TEA patients and 16 controls. The 30-min test group consisted of 11 TEA patients[1] and 16 controls. Table 1 (right columns) provides the demographics and standard neuropsychological test performance of the TEA patients and controls within these two test groups. The 30-minute and 1-week test groups had comparable demographics and neuropsychological test scores, except for the following: in the 1-week test group the NART-predicted Verbal IQ scores were significantly higher for the controls compared to the TEA patients ($t(30)= -2.144$, $p < 0.05$, r = .37), and the HADS depression scores were significantly higher for the TEA patients compared to the controls ($t(30)= 3.028$, $p < 0.01$, r = .48). The WMS-III Logical memory delayed recall test scores did not differ significantly between the TEA patients and controls in either the 30-minute test group or the 1-week test group. However, the p-values approached significance (30-minute test group, $t(25)= -1.913$, $p = 0.067$, r = .36; 1-week test group, $t(30)= -1.938$, $p = 0.062$, r = .33) as expected given the significant differences between TEA patients and controls overall (see above and Table 1). The 1-week test group was significantly older than the 30-minute test group ($t(57)= -3.093$, $p < 0.01$, r = .38), and this was the case for both participant groups (TEA patients: $t(25)= -2.262$, $p < 0.05$, r = .41); controls: $t(30)= -2.062$, $p < 0.05$, r = .35). Unfortunately, we were unable to match the test groups for age via equal allocation of ages to the two test groups, because we collected the data for the two test groups one year apart (as part of two separate research projects). Lastly, the male/female ratio of the patient and control groups was not matched (TEA 20M / 7F; Controls 14M/18F) because TEA is more common amongst men (Zeman & Butler, 2010), and patients' spouses were, where possible, used as controls so that the experimenter's story could be learned under identical circumstances.

[1] A larger overall study included both TEA and TLE patients in the 30-minute group, resulting in a group of 11 TEA patients and 5 TLE patients. However, as the current study focused on ALF in TEA, we included only the TEA patients in the current data set.

The study was approved by the National Health Service (NHS) Scotland A Research Ethics Committee and by the Psychology Research Ethics Committee of the University of Edinburgh. Informed consent was obtained for the overall research study from each participant according to the Declaration of Helsinki and subsequent updates (World Medical Association, 2001).

2.2. Procedure and materials

The experiment consisted of an encoding phase and a memory test phase, which were separated either by 30 minutes or 1 week.

2.2.1. Encoding phase

As the core purpose of this experiment was to investigate forgetting of *incidentally encoded* information, it was important that participants were not aware that they were participating in an experiment at the time of 'encoding'. To this end we ran this experiment prior to a 'real' research study that participants had volunteered to take part in (reported in part in Hoefeijzers et al., 2015 and Dewar et al., 2015). Prior to commencement of the 'real' research study the experimenter (SH) followed a set "introductory talk" protocol, during which he first introduced himself, then spoke casually about his former and current research, which naturally led to him telling an apparently casual but well-rehearsed entertaining story about an event that occurred prior to testing a participant in his first PhD study. The story consisted of 51 story points (see Supplementary file 3 for a full transcript). All participants then completed the first session of the 'real' experiment, which consisted of a wordlist learning paradigm.

2.2.2. Memory Test phase

Story retention was probed without warning, either 30 minutes after story encoding (30-min test group) or one week after story encoding (1-week test group). All assessments were carried out in person. We probed memory at the two time points *between-subjects* so as to avoid repeated testing - which can protect against forgetting (Jansari et al., 2010; Roediger & Butler, 2011). In both test groups story retention was assessed first via free recall, and subsequently via a 5-alternative forced-choice recognition test.

During the ***Free recall test*** participants were asked to try to recall the experimenter's story in as much detail as possible. There was no time limit, and participants were asked to indicate when they had finished. Participants' recalled stories were recorded via dictaphone and later transcribed for scoring.

During the ***5-alternative forced-choice recognition test*** participants had to answer 13 questions about the experimenter's story. For each question, the participant had to indicate which *one* of five potential answers was correct. Some of the foils were similar to the correct answer or included material relevant to other parts of the study, so as to make the test sufficiently challenging. Participants were told about this explicitly to ensure that they would select the answer that provided the most specific answer to each question.

After completing the memory tests all participants were asked (i) whether they had suspected that the experimenter's story had been part of the experiment, and (ii) whether they thought that they would be asked to remember the story at a later point.

It is of note that 8/16 controls in the 30-minute group and 7/16 controls in the 1-week test group were the patients' spouses. In these cases the patient and matched control encoded the experimenter's story under identical conditions (i.e., together at the same time), and their story memory was tested on the same occasion, albeit separately (one after the other).

2.3. Test scoring

2.3.1. Free recall test

For each participant we computed the number of story points correctly recalled (out of 51 total points – see Supplementary file 3). Only story points that were recalled verbatim or close synonyms were scored as correct. We then computed a proportion correct score by dividing the number of story points correctly recalled by the participant by 51.

2.3.2. 5-alternative forced-choice recognition test.

For each participant we computed the number of correct answers in the forced-choice-recognition test (out of 13 answers – see Supplementary file 4). We then computed a proportion score by dividing the number of correct answers by 13.

2.4. Statistical analysis

We applied a univariate ANOVA with between subject factors "test-delay group" (30-minute test versus 1-week test) and "participant group" (TEA patients versus controls). In addition, planned comparisons (via independent T-tests) were run to compare (i) the TEA patients versus the controls at each of the test times separately, and (ii) the 30-minute test group versus the 1-week test group within the TEA group and control group separately. These analyses were conducted for both the story recall test and 5-alternative forced-choice recognition test. ANCOVAs with covariates, "HADS-depression score", "NART-predicted verbal IQ", "age", "education", and "gender" were run to examine the effect of participant group (TEA patients versus controls) and test delay (30-minute and 1-week test) on free recall and forced-choice test performance when controlling for the subtle group differences for these 5 non –memory variables (reported in 2.1 *Participants*). Pearson correlations were applied to correlate performance on the incidental memory task with performance on the

standard memory tests of the neuropsychological test battery (i.e., the WMS-III logical memory story delayed recall and recognition score and the Rey-figure delayed recall score).

The Greenhouse–Geisser correction for nonsphericity was applied if the sphericity assumption was violated (according to the Mauchly's test of sphericity). Moreover, independent T-tests assuming unequal variances were applied if the assumption of equal variances was violated (according to the Levene's test for equality of variance). Effect sizes for the ANOVAs were determined using partial η^2, where 0.14 is a large effect (Stevens, 2002). Effect sizes for the T-tests were determined using *r*. The alpha level was set to 0.05 for all analyses.

3. Results

3.1 Post-experiment questioning

Post-experimental questioning revealed that although some participants had wondered why the experimenter was telling his story in such detail, no participants suspected that the story was part of the experiment, and all participants were surprised to be asked about the story subsequently. These data indicate that story encoding was indeed incidental, as planned.

3.2 Story recall test

Figure 1 shows delayed recall performance for the incidentally encoded story after 30 minutes and 1 week in the TEA patients and controls.

Overall, the TEA patients recalled significantly fewer story points than the controls ($F(1,55) = 4.748$, $p < 0.05$, $\eta 2p = .079$). Moreover, overall the 1-week test group recalled significantly fewer story points than the 30-minute test group ($F(1, 55) = 65.078$, $p < 0.001$, $\eta 2p = .542$).

However, there was no significant interaction between participant group and test group F(1, 55) = 1.663, p = 0.203, η2 p= .029). Planned comparisons revealed that in both TEA patients and controls the 1-week test group recalled significantly fewer story points than the 30-minute test group (TEA group: t(25)= 6.150, p < 0.001, r = .78; controls: t(30) = 5.167, p < 0.001, r = .69). Moreover, whereas the proportion of recalled story points did not differ significantly between TEA patients and controls at the 30-minute test (t(25) = -0.573, p = 0.572, r = .11), the TEA patients recalled significantly fewer story points than the controls at the 1-week test (t(30) = -2.696, p < 0.05, r = .44).

3.2. Story recognition test

Figure 2 shows recognition performance for the incidentally encoded story after 30 minutes and 1 week in the TEA patients and controls.

<<INSERT FIGURES 1 AND 2 HERE>>

Overall, the TEA performed significantly poorer than the controls on the recognition test (F(1,55) = 7.931, p < 0.01, η2p= .126). Moreover, overall, the 1-week test group performed significantly poorer than the 30-minute test group on the recognition test (F(1, 55) = 78.785, p < 0.001, η2p= .589). There was a significant interaction between the participant group and the test time group (F(1, 55) = 5.489, p < 0.05, η2p= .091). Planned comparisons revealed that in both TEA patients and controls the 1-week test group performed significantly poorer than the 30-minute test group (TEA patients: t(24.058) = 8.485, p < 0.001, r = .87.; controls: t(30) = 4.828, p < 0.001, r = .66.) Moreover, whereas recognition performance did not differ significantly between the TEA patients and controls at the 30-minute test (t(25) = -0.365, p = 0.718, r = .07), the TEA patients' recognition performance was significantly poorer than that

of the controls at the 1-week test (t(30) = -3.517, p = 0.001, r = .54).

3.3. Ceiling/floor effects

None of the TEA patients or controls in the 30-minute test group performed at floor (i.e., proportion score of 0) or ceiling (i.e., proportion score of 1) in the free recall test. Five of the TEA patients and two of the controls in the 1-week test group did not recall any story points in the free recall test (i.e., proportion score of 0). However, even when these 7 participants were excluded, free recall remained significantly lower in the TEA patients than the controls in the 1-week test group ($M_{patients}$ = 0.16±0.08, $M_{controls}$ = 0.25±0.10; t(23) = -2.436, $p < 0.05$, r = .45). Likewise, the participant group x test group interaction remained non-significant (F(1, 48) = 1.013, p = 0.319, η^2_p= .021).

Three controls in the 30-minute test group correctly answered all 13 multiple-choice questions (i.e., proportion score of 1). Their exclusion did not alter the recognition test findings (a significant participant group x test group interaction: F(1,52) = 8.039, $p < 0.01$, η^2_p= .134; no significant difference between the TEA patients and controls in the 30-minute test group: $M_{patients}$ = 0.85±0.08, $M_{controls}$ = 0.83±0.11; t(22) = 0.438, p = 0.666, r = .09). None of the TEA patients or controls performed at floor or ceiling at the 1-week forced-choice recognition test.

3.4. HADS, NART-IQ, age, education, gender and performance on the incidental memory test

3.4.1. HADS-depression

The HADS-depression scores were significantly higher for the TEA patients than for the controls across the study (t(57) = 2.661, p = 0.01, r = .33) as well as in the 1-week test group specifically (t(30)= 3.028, p < 0.01, r = .48). Inclusion of the HADS-depression score as a covariate in the incidental story free recall and recognition analyses had an effect on the free recall task only: (i) the main effect of participant group (TEA patients vs. controls) in the free recall test was now no longer significant (F(1,54) = 3.308, p = 0.075, η^2_p= .058), and (ii) the difference in free recall between the TEA patients and controls in the 1-week test group was now no longer significant (F(1,29) = 3.465, p = 0.073, η^2_p= .107). No other findings changed.

3.4.2. NART-predicted verbal IQ

The NART-predicted Verbal IQ scores were significantly higher for the controls than for the TEA patients in the 1-week test group (t(30)= -2.188, p < 0.05, r = .37). Inclusion of the NART-predicted verbal IQ as a covariate in the incidental story free recall and recognition analyses had only a minor effect, in as much as the main effect of participant group (TEA patients vs. controls) in the free recall test was now no longer significant (F(1,52) = 3.931, p = 0.053, η^2_p= .070. No other findings changed.

3.4.3. Age

The participants in the 1-week test group were significantly older than the participants in the 30-minute test group ($M_{30\text{-min}}$ = 62.59±8.67, $M_{1\text{-week}}$ = 68.31±5.40; t(57)=-3.093, p < 0.01, r = .38), and this was the case for both participant groups (TEA patients: t(21.980)= -2.265, p < 0.05, r = .44); controls: t(30)= -2.062, p < 0.05, r = .35). However, inclusion of age as a covariate in the incidental story free recall and recognition analyses had no effect on the main findings.

3.4.4. Years of education

Years of education was significantly higher in the controls than the TEA patients ($t(57)= -2.152$, $p < 0.05$, r = .27) (see Table 1). Inclusion of years of education as a covariate in the incidental story free recall and recognition analyses had only a minor effect, in as much as the main effect of participant group (TEA patients vs. controls) in the free recall test was now no longer significant ($F(1,54) = 2.504$, $p = 0.119$, $\eta^2_p = .044$. No other findings changed.

3.4.5. Gender

The gender ratio of our patient and control groups was not matched well due to the higher prevalence of TEA in mean and the recruitment of patients' spouses as controls, where possible. This resulted in more women in the control group than patient group (TEA 20M/7F; Controls 14M/18F). Given a recent finding by Miller, Flanagan, Mothakunnel, Mohamed, & Thayer (2015) of sex differences in some aspects of verbal memory we included gender as a covariate in the incidental story free recall and recognition analyses. This had only an effect on the free recall task. The main effect of participant group (TEA patients vs. controls) in the free recall test was now no longer significant ($F(1,54) = 3.254$, $p = 0.077$, $\eta 2p = .057$). Nevertheless, the difference in free recall between the TEA patients and controls in the 1-week test group remained significant ($F(1,29) = 4.641$, $p = 0.040$, $\eta 2p = .138$). As before, there was no significant difference in free recall in the 30-minute test group ($F(1,24) = 1.138$, $p = 0.297$, $\eta 2p = .045$). No other findings changed.

3.4.6. Potential combination effects of depression, verbal IQ, age, education and gender

Although we found minimal contributions of HADS-depression, NART-IQ, age, education, and gender we acknowledge that they may have had an effect in combination. To examine this possibility, we re-ran our univariate analyses and planned comparisons with all five

factors included as covariates. Our main finding held: the TEA group continued to demonstrate significant ALF in the recognition test. Specifically, although we no longer observed a significant main effect of Group in the recognition test ($F(1,48) = 2.357$, $p = 0.131$, $\eta 2p = .047$), there remained a significant effect of Test delay ($F(1,48) = 59.814$, $p < 0.001$, $\eta 2p = .555$), and importantly, a significant Group x Test delay interaction in the recognition test ($F(1,48) = 4.923$, $p < 0.05$, $\eta 2p = .093$). Indeed, whereas recognition performance did not differ significantly between the TEA patients and controls at the 30-minute test ($F(1,18) = 0.024$, $p = 0.879$, $\eta 2p = .001$), the TEA patients' recognition performance was significantly more poorly than that of the controls at the 1-week test ($F(1,25) = 5.185$, $p < 0.05$, $\eta 2p = .172$).

In the free recall test the main effect of Test delay continued to be significant ($F(1,48) = 58.097$, $p < 0.001$, $\eta 2p = .548$). However, there was no longer a significant effect of Group ($F(1,48) = 0.797$, $p = 0.377$, $\eta 2p = .016$), and, as before, there was no significant Group x Test delay interaction ($F(1,48) = 1.184$, $p = 0.282$, $\eta 2p = .024$).

3.5. Correlations between the incidental test and standard memory tests

In the 30-minute test group performance on the incidental story free recall test did not correlate significantly with performance on the Rey-figure delayed recall test (TEA patients: $r = .258$, $p = .444$; controls: $r = .064$, $p = .814$) or the WMS-III logical memory story delayed test (TEA patients: $r = .510$, $p = .109$; controls: $r = .405$, $p = .120$). It is of note however that the r-values of the latter correlations were relatively large, and indeed inspection of the latter suggested that the correlations might not have reached significance due to the presence of some outliers within the small samples. Performance on the forced choice recognition test did not correlate significantly with performance on the WMS-III logical memory story recognition test (TEA patients: $r = .161$, $p = .636$; controls: $r = .147$, $p = .587$).

In the 1-week test group performance on the incidental story free recall test did not correlate significantly with performance on the Rey-figure delayed recall test (TEA patients: r = -.392, p = .134; controls: r = -.149, p = .583) or the WMS-III logical memory story delayed recall test (TEA patients: r = -.322, p = .224; controls: r = -.192, p = .477), and if anything such correlations were negative. Moreover, performance on the forced choice recognition test did not correlate significantly with performance on the WMS-III logical memory story recognition test (TEA patients: r = .114, p = .675; controls: r = -.384, p = .142).

4. Discussion

We were able to capture real-life ALF in TEA patients via a novel memory test, in which memory for an incidentally encoded story was probed via recall and forced choice recognition after 30 minutes or 1 week. Whereas the TEA patients and controls performed comparably in the 30-minute test, the TEA patients performed significantly more poorly than the controls in the 1-week test (see Figures 1 and 2). Moreover, the TEA patients demonstrated significant ALF in the recognition test, in as much as the drop in recognition performance between the 30-minute test and the 1-week test was significantly larger in the TEA patients than the controls. The equivalent interaction between participant group and test time group was not significant for the recall test. Since a significant participant group difference was observed in the 1-week test but not in the 30-minute test, it is likely that the non-significant interaction was the result of insufficient power. Moreover, the effect size of the participant group difference in the 1-week test was slightly higher for the recognition test than the free recall test. Therefore, it is possible that the recognition test was more sensitive to ALF than was the free recall test, at least with regards to memory for the incidentally encoded memory. Forced-choice recognition tests provide retrieval support, thus facilitating

retrieval of information that might not be recallable under free recall conditions. Like TEA patients, several controls (i.e., control 17, 26 and 27 – see Supplementary Table 1) struggled to freely recall details from the story after 1 week, resulting in very low scores on the 1-week free recall test (range = 0-0.04). However, the performance of these three controls improved somewhat when retrieval support was provided i.e. in the recognition test (range = 0.62-0.69). In contrast 4 of the 7 TEA patients (i.e., TEA 12, 18, 21 and 24 – see Supplementary table 1) who performed very poorly on free recall after 1 week (range = 0-0.04) continued to perform very poorly, even when provided with retrieval support (range = 0.23-0.39). Whereas the recognition test might have detected primarily storage/consolidation deficits, which are hypothesized to contribute to ALF (e.g., Hoefeijzers et al., 2015, 2013), the free recall test might have detected both storage/consolidation deficits and retrieval deficits, the latter of which can also occur as a result of 'normal' aging.

Our design does not permit a direct *within-subjects* investigation of forgetting over the 30-minute to 1-week interval. As discussed in the Methods, we opted for a between-subjects design in order to reduce potential contamination of 1-week performance by retrieval practice/rehearsal effects, which could have reduced 'true' ALF (Jansari et al., 2010). Notwithstanding the limitations of the between-subjects design, the 4 groups were comparable on the majority of cognitive and demographic measures (see Table 1). With the exception of a significant age difference (TEA 30-minute group < TEA 1-week group) the TEA patients in the 30-minute test time group and in the 1-week test time group did not differ significantly on any of the measures, including standard tests of immediate and delayed prose recall and our subjective memory questionnaires. The latter finding reduces the possibility that the difference between the 30-minute test and the 1-week test in the TEA group could have been the result of differences at baseline, although we note that this interpretation cannot be ruled out conclusively with the data to hand. Moreover, the few non-memory

measures for which differences were revealed between the test groups/participant groups across the study (HADS depression, NART-predicted verbal IQ, age, education and gender) had only negligible effects on the overall outcome of the study. Only depression appeared to account for some of the difference in 1-week recall between the TEA patients and controls, rendering this difference non-significant ($p = 0.073$). The impact of depression on long-term memory in epilepsy patients has been well documented in the literature. However, it does not seem to be the main underlying factor for ALF (e.g., Witt, Glöckner, & Helmstaedter, 2012). Indeed, the significant group differences and participant group x test group interaction (ALF) in our forced choice recognition test remained after controlling for depression. In fact, the finding of significant ALF in our TEA group in our forced choice recognition test held even after controlling for age, education, gender, depression and verbal IQ together. Therefore, it is very unlikely that the ALF observed here can be accounted for by a combined effect of these factors.

It is also unlikely that the ALF observed in our study can be explained away by higher rates of story rehearsal during the week in the 1-week test group controls than the 1-week test group TEA patients. No participants suspected that the story was part of the overall experiment that they were completing, and all participants were surprised to be asked about the story subsequently. Therefore, it is unlikely that participants tried to rehearse the story intentionally. Nonetheless, there is the possibility that patient and control couples spontaneously discussed the story after the experimenter left, and that doing so benefitted their memory, perhaps especially in the controls. If so, story retention would be expected to be higher for the participants who encoded the story together with their spouses than for participants who encoded the story alone. However, overall, there was no significant difference in 1-week free recall or 1-week recognition performance between participants who encoded the story with their spouses (7 TEA patients and 7 controls) or alone (9 TEA patients

and 9 controls), and this was also the case for the TEA patients and controls separately. Moreover, there were no significant interactions between group and encoding conditions (alone vs. with spouse).

Performance in the incidental memory test (1-week or 30-minute) was not associated significantly with performance in the (30-minute) delayed recall of the WMS-III logical memory test story or the Rey Figure, either in the patients or in the controls. However, the r-values and data hinted at a positive correlation between free recall in the 30-minute incidental memory test and free recall in the 30-minute WMS-III logical memory test. This finding suggests very tentatively that, at standard delays, our incidental memory test and the WMS-III logical memory test might have tapped into similar memory capacities/processes. The absence of significant correlations between the 30-minute WMS-III logical memory test and the 1-week incidental memory test is not too surprising, given the lack of correspondence between epilepsy patients' complaints of ALF and their performance on standard (30-minute) memory tests (e.g., Butler et al., 2009; Corcoran & Thompson, 1992).

Unfortunately, since this study was not designed for clinical purposes, we did not re-assess performance on the WMS-III logical memory test and the Rey-Figure test after a 1-week delay interval. Therefore, it cannot be determined whether or not incidental memory tests like ours should be used in preference to current 'standard' tests for capturing ALF. In order to draw such conclusions, carefully designed long-term forgetting studies are needed that allow for direct comparison of memory decline over extended delay intervals for incidentally-encoded real-life material and intentionally encoded 'standard' test material. Existing clinical assessment tests with extended delay norms (e.g. Miller et al., 2015) would be very useful for such experiments. Such studies would further elucidate to what extent

current laboratory tests are reliable measures of real-life ALF in patients with TEA. Finally, the story used in our study was appropriate within the context of our study as it was told by a young member of the team during informal conversation. However, we acknowledge that our story would not be appropriate for use by senior researchers or within clinical settings. Therefore, we recommend that the future studies proposed above implement more neutral stories that can be recounted naturally by researchers and clinicians alike.

We acknowledge that we did not include any objective measures of attention or stress, and that these potential covariates could affect retention/recognition performance in memory tests. However, given the high performance of both the TEA patients and controls in our forced-choice recognition test (see Figure 2) it is unlikely that our participants' performance was hampered by such factors. Nevertheless, future studies in this domain should consider including objective measures of attention and stress levels (e.g. cortisone levels, skin conductance) to rule-out such possibilities.

Conclusion

The present study suggests that incidental memory tests can capture real-life ALF in TEA, both via free recall and forced-choice recognition. However, forced-choice recognition tests might be more sensitive for the detection of real-life ALF because they provide retrieval support. In so doing, they might tap more specifically into the storage/consolidation deficits associated with ALF (Atherton, Nobre, Zeman, & Butler, 2014; Butler & Zeman, 2008b; Hoefeijzers et al., 2015, 2013; Muhlert et al., 2010; Tramoni et al., 2011; Zeman & Butler, 2010) rather than being 'contaminated' by additional retrieval deficits, which could affect free recall in TEA patients *and* some older controls alike. Finally, our study measuring real-life memory in TEA patients confirms the occurrence of ALF in a real-life situation, and that any complaints by a patient of a rapidly fading memory should be evaluated thoroughly via

an extended delay interval, even when standard memory tests indicate normal memory functioning.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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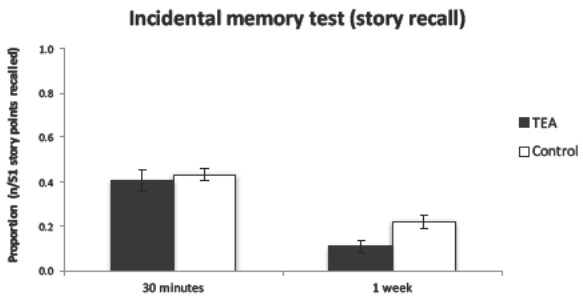
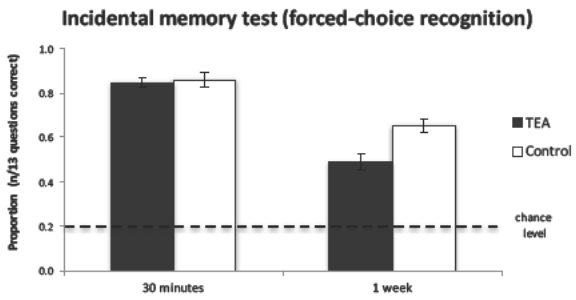
Figure captions:

Figure 1. Proportion of story points recalled (out of 51 story points) by TEA patients and controls after 30 minutes and 1 week. Error bars represent standard errors of the mean (SEM).

Figure 2. Proportion of multiple-choice questions correctly answered (out of 13 multiple-choice questions) by TEA patients and controls after 30 minutes and 1 week. The horizontal line depicts chance level (5 choices per question). Error bars represent standard errors of the mean (SEM).


Incidental memory test (story recall)
Proportion (n/51 story points recalled)
1.0
0.8
0.6
0.4
0.2
0.0
30 minutes
1 week
TEA
Control


Incidental memory test (forced-choice recognition)
Proportion (n/13 questions correct)
1.0
0.8
0.6
0.4
0.2
0.0
30 minutes
1 week
TEA
Control
chance level