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Remote memory deficits in transient epileptic amnesia

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Transient epileptic amnesia is a form of temporal lobe epilepsy in which sufferers often complain of irretrievable loss of remote memories. We used a broad range of memory tests to clarify the extent and nature of the remote memory deficits in patients with transient epileptic amnesia. Performance on standard tests of anterograde memory was normal. In contrast, there was a severe impairment of memory for autobiographical events extending across the entire lifespan, providing evidence for the occurrence of 'focal retrograde amnesia' in transient epileptic amnesia. There was a milder impairment of personal semantic memory, most pronounced for midlife years. There were limited deficits of public semantic memory for recent decades. These results may reflect subtle structural pathology in the medial temporal lobes or the effects of the propagation of epileptiform activity through the network of brain regions responsible for long-term memory, or a combination of these two mechanisms.

Introduction

Memory complaints are common among people with epilepsy (Corcoran and Thompson, 1992), especially among patients with temporal lobe epilepsy in which key structures involved in processing memories, including the hippocampus, are directly involved by seizure activity (Butler and Zeman, 2008a). However, whilst there is extensive evidence for anterograde memory deficits in temporal lobe epilepsy, relatively few studies have investigated remote memory (Noulhiane et al., 2007; Butler and Zeman, 2008a). Nevertheless, remote memory deficits can have considerable

impact on psychological well-being and are sometimes the presenting feature of patients with temporal lobe epilepsy (Gallassi, 2006).

Remote memory is multi-faceted, comprising memories that were encoded in the relatively distant past, arbitrarily defined as over one year ago (Kapur, 1999; Butler and Zeman, 2008a). Remote memory has episodic and semantic components. Episodic memory is typically autobiographical, involving the recollection of personally experienced events and allowing 'mental time travel' into the past, or 'autonoetic awareness' (Tulving, 1985). Semantic memory enables the recollection of declarative facts

and includes personal (e.g. where one went to school) and public (e.g. knowledge about famous people) components.

The relative impairment of episodic and semantic memory by neurological disorders has implications for theories of long-term memory. The 'standard model' of memory consolidation (e.g. Squire, 1992) proposes that both episodic and semantic information becomes independent of the hippocampus after consolidation. Hippocampal damage should, therefore, lead to a temporal gradient for both episodic and semantic information with greater sparing of remote than recent information. In contrast, Multiple Trace Theory (e.g. Moscovitch et al., 2005) suggests that semantic but not episodic memory becomes independent of the hippocampus over time. According to Multiple Trace Theory, medial temporal lobe damage should lead to a temporally extended impairment of episodic memory; for semantic memory, Multiple Trace Theory, like the consolidation model, predicts a standard temporal gradient. Examination of patients with medial temporal lobe damage has produced mixed results; some studies favour the standard consolidation model (e.g. Bayley et al., 2005; Kirwan et al., 2008), and others Multiple Trace Theory (e.g. Steinvorth et al., 2005; Poreh et al., 2006; Rosenbaum et al., 2008).

Previous studies have confirmed the occurrence of remote memory deficits in temporal lobe epilepsy but have differed on their precise nature. Some studies have revealed an impairment of autobiographical memory throughout the entire life span (e.g. Viskontas et al., 2000; Noulhiane et al., 2007), whereas in others the deficit extends back as little as 5 years (Kapur et al., 1997). Viskontas et al. (2000) found autobiographical memory deficits with intact personal semantics, while others have reported deficits in both autobiographical memory and semantic memory for public events with intact personal semantic memory (Lucchelli and Spinnler, 1998; Voltzenlogel et al., 2006) or disproportionate loss of public semantics compared to autobiographical memory (Barr et al., 1990; Manning et al., 2005). This evidence is consistent with the dissociations observed between components of remote memory in other contexts (e.g. O'Connor et al., 1992; Graham and Hodges, 1997) suggesting there is at least partial independence between these processes (Kapur, 1999). This suggestion converges with neuroimaging evidence that shows neural overlap between components of remote memory as well as unique contributions corresponding to the specific properties of the retrieved memories (e.g. Graham et al., 2003; Levine et al., 2004; Svoboda et al., 2006; Burianova and Grady, 2007).

Transient epileptic amnesia (TEA) is a form of temporal lobe epilepsy in which approximately two thirds of patients spontaneously complain of persistent interictal remote memory impairment (Zeman et al., 1998; Butler et al., 2007; for a review see Butler and Zeman, 2008a). In TEA, which typically starts in late middle-age, the main and sometimes only manifestation of the seizure is a period of amnesia, usually lasting less than one hour, during which other cognitive functions remain intact. The ictal amnesia may be predominantly anterograde, predominantly retrograde or both anterograde and retrograde. Attacks are frequent, often occur on waking and typically respond promptly to modest doses of anticonvulsants. Manual volumetry revealed subtle (~8%) but significant hippocampal body atrophy in a group of patients with TEA (Butler et al., 2009), and a detailed single case

study indicated that the epileptic focus lay in the medial temporal lobe (Butler et al., 2008b). In addition to the remote memory impairment, around half of patients complain of accelerated forgetting of recently acquired information (Manes et al., 2005; Butler et al., 2007; see Butler and Zeman, 2008a for a review).

Previous studies in TEA have confirmed the existence of autobiographical memory loss extending back over several decades (Manes et al., 2001, 2005; Butler et al., 2007; Butler and Zeman, 2008b). However, these studies leave several questions unanswered. First, whilst the memory deficits appear greater for more recent memories (Manes, 2005; Butler et al., 2007), the extent of the remote memory loss is unclear, as previous studies have not directly examined memory for childhood and early adult events (Manes et al., 2005; Butler et al., 2007). Second, tests used to assess autobiographical memory to date, based on the Autobiographical Memory Interview (Kopelman et al., 1989), may not have identified the full extent of the impairment (cf. Levine et al., 2002). Third, there have been conflicting reports on the involvement of personal semantic memory (Manes et al., 2001; Butler et al., 2007) and limited investigation, to date, of public semantic memory in TEA (Butler and Zeman, 2008a).

This study addresses these unanswered questions, using a broad range of memory tests in a group of 14 patients with TEA and 12 matched control participants. In the assessment of autobiographical memory we used the Autobiographical Interview (Levine et al., 2002), which provides a more sensitive measure than previous instruments.

We included a battery of anterograde memory tests to assess whether the remote memory loss occurring in TEA is a form of 'focal retrograde amnesia' or a manifestation of more global memory loss. Focal retrograde amnesia is defined as a selective loss of some or all forms of retrograde memory in the absence of anterograde memory impairment. Reports of focal retrograde amnesia have given rise to controversy, often revolving around the possible role of neuropsychiatric factors and the presence of subtle anterograde memory deficits (Kopelman, 2000, 2002; see Kapur, 2000). However, previous work has suggested that focal retrograde amnesia may occur in patients with TEA (Manes et al., 2005), and in some other neurological contexts (discussed more fully below).

In summary, we used a range of tests of anterograde and retrograde memory to define the nature of the remote memory deficit in TEA. We aimed to answer the following questions: (i) what is the extent and nature of the autobiographical memory loss?; (ii) is there impairment of personal semantic and public semantic memory?; and (iii) is there evidence for focal retrograde amnesia?

Materials and methods

Participants

Fourteen patients were recruited from around the United Kingdom via The Impairment of Memory in Epilepsy (TIME) Project (Butler et al., 2007) over the course of approximately 12 months. Patients had been diagnosed with TEA using Zeman et al.'s (1998) diagnostic

criteria: (i) a history of recurrent witnessed episodes of transient amnesia; (ii) cognitive functions other than memory judged to be intact during typical episodes by a reliable witness; and (iii) evidence for a diagnosis of epilepsy based on one or more of the following: epileptiform abnormalities on electroencephalography, the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations), or a clear-cut response to anticonvulsant therapy. Patients were invited to take part if they reported autobiographical memory problems and if they had previously expressed an interest in taking part in future research. All patients were taking anticonvulsant medication at the time of testing. These had abolished the amnestic attacks and patients had all been seizure free for at least 18 months prior to testing. Since cessation of the attacks, participants reported that there had been no discernible improvement in their memory problems. The clinical characteristics of the TEA for each participant are presented in Table 1. The majority of the patients had brief (<1 h), frequent attacks typical of those previously described in TEA (Butler and Zeman, 2008a). Two patients with more prolonged attacks (6 and 11), and two patients with low numbers of attacks (11 and 13) nevertheless satisfied the diagnostic criteria outlined above. Patients varied in the number of seizures reported, which is likely to be related to differences in time to diagnosis. Thirteen of the 14 patients had undergone an MRI scan. No major structural pathology was detected in any case. Twelve age and education-matched, neurologically normal control subjects were recruited. This study was approved by the Multicentre Research Ethics Committee, United Kingdom (MREC 03/10/77). Participants gave written, informed consent.

Neuropsychological profile

Standard neuropsychological tests were used to assess general intelligence (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), memory for famous faces (Graded Faces Test; Thompson *et al.,* 2002), language (Graded Naming Test; McKenna and Warrington, 1980), and executive functioning (letter and category fluency; Wisconsin Card Sorting Test; Kongs *et al.,* 2000; and the Trail Test). Depression and anxiety was measured using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). Media exposure, an important influence on public semantic memory, was also assessed (Kapur *et al.,* 1999).

Anterograde memory tests

Anterograde memory was measured using the Logical Memory Test (immediate and 30 min delayed recall and recognition test of a prose passage; Wechsler, 1999), the Rey-Osterrieth complex figure (copy and 30 min delayed recall; Osterrieth and Rey, 1944); word and face recognition on the Warrington Recognition Memory Test (Warrington, 1984) and the Paired Associates Learning Test (PAL; CANTAB).

Remote autobiographical memory

Autobiographical Interview

The Autobiographical Interview (Levine *et al.,* 2002) was conducted to provide a fine-grained assessment of autobiographical memory performance across the life-span. Administration and scoring was according to standard procedures (Levine *et al.,* 2002). Participants recalled a unique autobiographical episode, lasting less than half a day, which was specific in time and place for each decade in their life. For analysis, memories were divided into five life periods: childhood (4–9), youth (10–19), young adult (20–29), middle-age (30 to the most recent decade), and the most recent decade. Due to variation in the age of participants, the number of events incorporated into the middle-age period varied but was the same across groups.

Two levels of retrieval support were provided initially. During recall, participants spontaneously described an event. After recall, if participants had not provided a detailed account, a general probe consisting of non-specific questions (e.g. can you provide more details?) was conducted. In the specific probe, participants were asked more detailed, semi-structured questions designed to extract additional contextual information. The specific probe was administered after the recall and general probe conditions had been completed for all the memories. Participants rated events for personal significance on a scale of 1 (no importance) to 6 (great importance).

Table 1 Clinical characteristics of the patients with TEA

ID	Sex	Year of onset	Age at onset	Number of attacks	First to last attack (months)	Duration of attack	Amnesia on waking?	Treatment response	Other features sometimes present	ALF
1	M	1990	52	60	24	16–30 min	Yes	Complete	Autom/unresp	Yes
2	M	2002	72	18	21	16–30 min	Yes	Complete	Olf hall/autom	No
3	M	2002	59	7	6	31–59 min	No	Complete	Olf hall/autom	No
4	M	2003	54	6	12	31–59 min	Yes	Complete	Autom/unresp	Yes
5	F	2001	66	50	18	6–15 min	Yes	Complete	Olf hall	No
6	M	1994	59	6	6	2–24 h	Yes	Complete	Autom/unresp	No
7	F	2000	66	36	18	16–30 min	Yes	Complete	Pure amnesia	No
8	F	2003	45	5	7	16–30 min	Yes	Complete	Olf hall	No
9	F	1993	52	60	139	16–30 min	No	Complete	Pure amnesia	Yes
10	M	2002	56	8	16	31–59 min	Yes	Complete	Olf hall	No
11	M	2003	71	2	3	2–24 h	Yes	Complete	Olf hall	No
12	M	2000	75	15	43	31–59 min	Yes	Complete	Pure amnesia	Yes
13	F	2003	66	4	2	31–59 min	Yes	Complete	Olf hall	No
14	M	2004	52	10 (circa)	18 (circa)	16–30 min	Yes	Complete	Olf hall/GTC	Yes

Autom = automatisms; unresp = brief period of unresponsiveness; Olf hall = olfactory hallucinations; GTC = generalized tonic-clinic seizures; ALF = patients who subjectively reported symptomatic accelerated long–term forgetting.

The interview was audio-recorded and transcribed for scoring. Narratives were segmented into details which were defined as a unique occurrence, observation, or thought (Levine *et al.,* 2002). Details were classified as 'internal' or 'external'. Internal details were episodic information specific to the main event and were classified into event, place, time, perceptual, and emotion/thought details. External details included information not directly related to the event. These were classified as semantic (factual information or extended events) and 'other' (e.g. metacognitive statements, editorializing and inferences). Specific contextual information, not related to the main event, was scored as external detail. Repetition of information was scored but not included as external details.

Additionally, qualitative ratings were assigned to each memory (Levine *et al.,* 2002). The time, place, perceptual, and emotion/thought sub-categories were rated on a scale from 0 (no information pertaining to that sub-category) to 3 (specific, rich detail relating to the sub-category). Episodic richness was scored on a scale from 0–6 to account for its greater importance. A time integration measure (on a 0–3 scale) assessed the integration of the episode into a larger time scale. The ratings summed to 21.

We were unable to verify the accuracy of the memories systematically. Where possible, we requested verification from spouses: they confirmed the accuracy of the memories in all instances. The interviews for all participants were analysed by one scorer (F.M.). A second scorer (N.M.) analysed a subset of the memories (27%). Both scorers had undergone extensive training in the scoring method as described in the Autobiographical Interview Scoring Manual and Levine *et al.* (2002). Coefficients showed that agreement between scorers was high for the qualitative score (0.86), and for internal (0.96) and external details (0.95).

Crovitz Interview

A modified version of the Crovitz Interview (Crovitz and Schiffman, 1974), based on that used by Hodges and Ward (1989), was administered. Participants supplied a memory of a personally experienced event connected with 1 of 10 high frequency nouns (e.g. table, ship) and named the decade when the event occurred. Responses were scored on a 0–3 scale (as in Hodges and Ward, 1989). A score of 3 was given for a memory specific in time and place that was rich in detail; 2 was given for a personal memory not specific in time and place; 1 was given to a vague memory with no specific personal involvement; and 0 for no response or for a generic, semantic response. Memories were divided into four periods: childhood (up to 10), youth (11–19), adulthood (20 to the most recent decade), and the most recent decade. All responses were scored by two scorers (F.M. and a blind scorer, A.S.). Agreement between scorers was high (0.96).

Personal semantic memory

Participants were asked six questions about personal facts for each decade. Questions included names of friends, home addresses, jobs and family events (developed by D.P.; for a related test see Viskontas *et al.,* 2000). Questions were scored out of 3 (0 = no details; 3 = three pieces of relevant information), making a maximum score of 18 for each decade. As for the Autobiographical Interview, at analysis, memories were divided into five periods: childhood (up to 9), youth (10–19), young adult (20–29), middle-age (30 to the most recent decade), and the most recent decade.

Public semantic memory

Dead-or-Alive Test

In the Dead-or-Alive Test (Kapur *et al.,* 1992; updated by D.P.), participants were given the names of 75 famous people (e.g. John F. Kennedy and Tony Blair) and answered whether the person was dead (58 people) or alive (17 people). The decade of death was evenly distributed from the 1960's to the current decade. If participants believed the person was dead, they were asked in what decade the person had died, and the cause of death (e.g. natural, murder).

Famous Events Test

The Famous Events Test (Graham *et al.,* 1998; updated by D.P.) consisted of 82 real events (e.g. The Suez Crisis), evenly distributed across the period 1930–2005, and 71 fictitious events (e.g. 'The Edinburgh Castle Fire'). Real and fictitious events were interleaved. For events that participants recognized, they assigned a decade and gave details. Two points were assigned to a clear and detailed description of the event, one point if some details were provided, and 0 points for no correct information.

Famous Faces Test

The Famous Faces Test (Hodges and Graham, 1998; updated by D.P.), comprising 70 famous people (e.g. politicians and sports persons), was used. A famous face was presented together with three non-famous faces. Participants had to identify, name and give details about the famous person. Two points were awarded for a clear and accurate description, one point for partial information, and 0 points for no correct information.

New Words Acquisition Test

The New Words Acquisition Test (developed by D.P.) consisted of 42 words (e.g. A-Bomb, WiFi) that had entered common usage within the last 60 years (for a related test, see Kopelman *et al.,* 2009). Knowledge of word meaning was assessed in recall, followed by a recognition test. In recall, words were presented individually and participants provided a definition. Two points were awarded for a clear and accurate definition, 1 point for a partially correct answer, and 0 points for an incorrect response. In the recognition test, the correct definition was provided together with three additional plausible, but incorrect, definitions.

Results

Standard neuropsychology

Neuropsychological results are shown in Table 2. The following analyses were conducted with independent samples *t*-tests. Groups were matched for age ($P = 0.43$) and IQ ($P = 0.40$). There was no difference between groups in the Trail Test ($P = 0.19$), the Wisconsin Card Sorting Test ($P = 0.76$), or the letter ($P = 0.90$) and category ($P = 0.60$) verbal fluency tasks. Groups also did not differ in the graded faces ($P = 0.92$) or graded naming ($P = 0.85$) tasks. On the Hospital Anxiety and Depression Scale, patients reported significantly elevated anxiety ($P = 0.01$) and a non-significant trend for increased depression ($P = 0.07$). Although patients had a higher score than controls on the media exposure test, this was not significant ($P = 0.21$).

Table 2 Demographic and neuropsychological profile of patients with TEA and control participants

	TEA group (n = 14) Mean (SD)	Control group (n = 12) Mean (SD)	P-value
Age, years	67.7 (9.15)	64.58 (10.54)	0.43
Full scale IQ	123.43 (11.36)	119.33 (13.07)	0.40
Executive function scores			
Wisconsin Card Sorting Test	3.00 (1.41)	2.82 (1.47)	0.76
Categories completed			
Letter Fluency (words/3 min)	42.93 (16.89)	43.67 (13.36)	0.90
Category Fluency (words/ min)	19.14 (4.94)	18.00 (6.15)	0.60
Trail Test (B-A) (s)	50.35 (46.27)	80.04 (65.17)	0.19
Semantic memory scores			
Graded Faces (60)	43.85 (8.28)	44.18 (6.87)	0.92
Graded Naming (30)	23.46 (2.90)	23.73 (4.08)	0.85
Hospital Anxiety and Depression Scale scores (max score)			
Anxiety Score (21)	8.00 (4.84)	3.58 (2.97)	0.01
Depression Score (21)	3.93 (2.76)	2.00 (2.45)	0.07
Media exposure (30)	16.36 (2.65)	14.42 (4.89)	0.21

Anterograde memory

Anterograde memory results are shown in Table 3. There were no significant differences between groups on the immediate, delayed, or recognition versions of the logical memory test (all $Ps>0.4$), and no differences on the copy or delayed recall tests of the Rey–Osterrieth complex figure (all $P > 0.80$). Performance was also matched on the Warrington Recognition Faces and Words Tests (all $P > 0.3$), and the Paired Associates Learning Test ($P = 0.17$).

Autobiographical memory

Autobiographical interview

Recall

The mean number of internal and external details at the recall stage were analysed in a 2 (Group) × 2 (Detail type) × 5 (Time period) ANOVA. There was an effect of Detail type [$F(1,24) = 7.09$, $P = 0.014$] indicating the greater production of external than internal details, but no effect of Group [$F(1,24) = 0.40$, $P = 0.53$] or Time [$F(4,96) = 0.63$, $P = 0.64$]. No interactions were significant ($P > 0.3$).

A separate ANOVA for internal details (Fig. 1A) alone revealed no effect of Group [$F(1,24) = 2.34$, $P = 0.14$], Time [$F(4,96) = 1.82$, $P = 0.13$] and no Group × Time interaction [$F(4,96) = 0.21$, $P = 0.89$]. For external details (Fig. 1B) alone, there were no significant effects (all $F < 0.90$, $P > 0.8$).

A 2 (Group) × 5 (Time) ANOVA for the recall qualitative ratings (Fig. 1C) revealed a significant effect of Time [$F(4,96) = 3.76$, $P = 0.007$] but no interaction between Time and Group [$F(4,96) = 0.60$, $P = 0.67$]. There was a main effect of Group [$F(1,24) = 8.2$, $P = 0.009$] with controls scoring higher than patients. T-tests revealed a significant difference between Groups for all time periods ($P < 0.05$), except for childhood ($P = 0.13$).

Specific probe

The number of internal (Fig. 2A) and external (Fig. 2B) details across all three retrieval conditions (recall, general probe, specific

probe) were analysed in a 2 (Group) × 2 (Detail type) × 5 (Time period) ANOVA. There was an effect of Group [$F(1,24) = 20.54$, $P < 0.001$] indicating that patients produced significantly fewer Details (internal and external) than controls; an effect of Detail type [$F(1,24) = 10.90$, $P < 0.005$] with more external than internal details; but no Detail type × Group interaction [$F(1,24) = 0.80$, $P = 0.38$]. There was no effect of Time [$F(4,96) = 1.31$, $P = 0.12$] but there was an interaction between Detail type and Time [$F(4,96), = 2.56$, $P < 0.05$] The remaining interactions were not significant (all $F < 1.2$, $P > 0.3$).

A separate analysis of internal details showed a significant effect of Group [$F(1,24) = 50.86$, $P < 0.001$] indicating that patients produced fewer internal Details than controls. The Time × Group interaction was not significant [$F(4,96) = 1.53$, $P > 0.2$] but there was a significant effect of Time [$F(4,96) = 8.45$, $P = 0.001$] indicating that more details were recalled for recent than remote memories. T-tests revealed that control participants recalled more internal Details than patients for all Time periods ($P < 0.01$).

For external Details, there was no effect of Time [$F(4,96) = 0.18$, $P > 0.9$] no interaction between Time and Group [$F(4,96) = 0.83$, $P > 0.5$] but there was an effect of Group [$F(1,24) = 4.79$, $P = 0.039$] indicating that controls produced more external Details than patients. T-tests revealed that controls produced more external Details than patients for the youth and recent Time periods ($P < 0.05$), but not for the childhood, young adult and middle-age periods ($P > 0.1$).

Internal Details were partitioned into different types of contextual information to provide a more fine-grained analysis concerning the type of information impaired (Fig. 2C). T-tests indicated that patients produced fewer Details than controls for the event, place, time, perceptual and thought/emotion sub-categories ($P < 0.02$).

The mean qualitative ratings for patients and controls across time are shown in Fig. 2D. There was a significant effect of Time [$F(4,96) = 12.91$, $P < 0.001$] indicating that scores were higher for recent than remote events, but no interaction between Group and Time [$F(1,24) = 0.96$, $P = 0.43$]. There was a significant effect of Group [$F(1,24) = 28.86$, $P < 0.001$] with controls

Table 3 Performance on anterograde memory tests for patients with TEA and controls

| Anterograde memory scores (max score)	TEA group Mean (SD)	Control group Mean (SD)	P-value
Episodic memory scores			
Story recall immediate (25)	14.00 (1.88)	13.67 (5.25)	0.83
Story recall delayed (25)	12.21 (2.33)	11.75 (4.97)	0.76
Story recognition (15)	12.86 (1.70)	12.33 (2.10)	0.49
Visuospatial perception scores			
Rey Complex Figure Copy (36)	33.14 (2.32)	32.96 (3.56)	0.88
Rey Complex Figure Delayed Recall (36)	16.89 (5.78)	16.71 (6.98)	0.94
Warrington Recognition Memory Test			
Word recognition (50)	48.00 (1.83)	46.73 (3.80)	0.54
Face recognition (50)	42.00 (3.81)	43.00 (3.98)	0.30
Paired Associates Learning (units)	−0.77 (1.85)	0.09 (0.80)	0.17
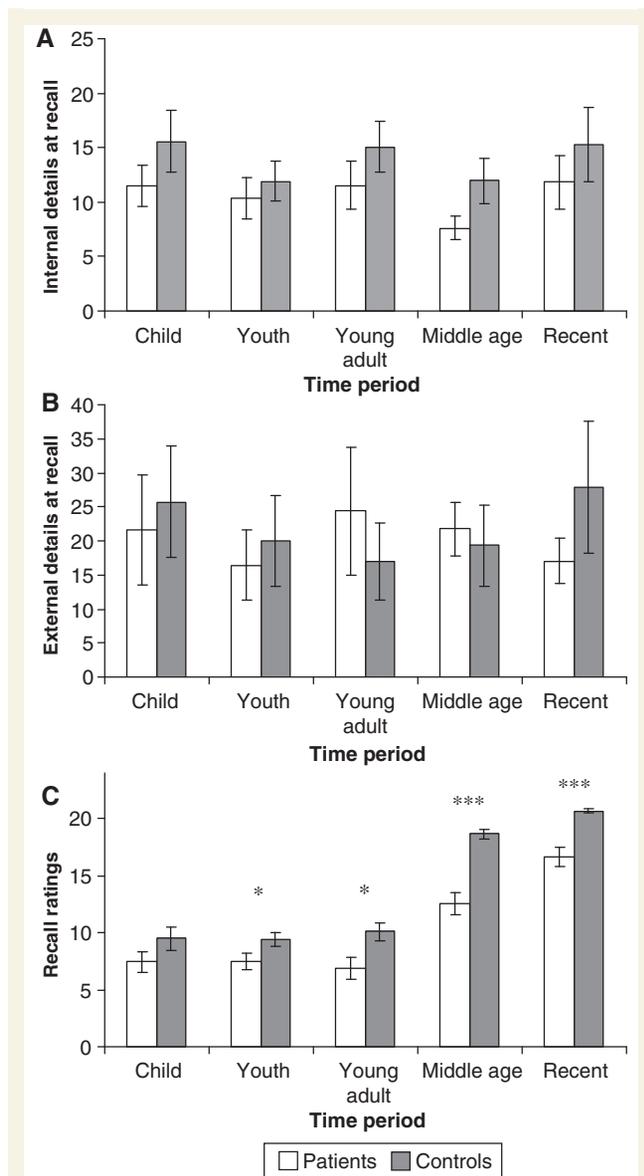
Figure 1 (**A**) Mean number of internal details recalled for each time period at recall; (**B**) mean number of external details recalled for each time period at recall; (**C**) mean rating (out of 21) for each time period at recall. *$P < 0.05$; ***$P < 0.005$.

scoring higher than patients. *T*-tests indicated that controls scored significantly higher than patients for all Time periods ($P < 0.01$).

A post-memory retrieval rating indicated that there was no difference between patients (mean = 3.14, SD = 1.19) and controls (mean = 3.46, SD = 0.72) in the personal significance of the memories [$t(24) = 0.81$, $P = 0.43$].

Crovitz Test

The memories provided by controls (mean = 26.50, SD = 2.07) scored significantly higher than those produced by patients (mean = 20.64, SD = 4.67) [$t(24) = 4.01$, $P = 0.001$]. An ANOVA (Time × Group) assessed differences between patients and controls in the distribution of memories over time (Fig. 3). This yielded a significant effect of time [$F(3,72) = 12.82$, $P < 0.001$] indicating a bias toward retrieving more recent memories. There was a significant interaction between Time period and Group [$F(3,72) = 24.69$, $P = 0.031$]. Pairwise comparisons indicated that patients retrieved significantly fewer memories than controls from the youth period ($P < 0.05$) but produced more from the most recent period, although this effect missed significance ($P = 0.053$).

Personal semantic memory

Figure 4 shows personal semantic memory performance across time for both groups. An ANOVA (Time period × Group) revealed an effect of Group [$F(1,24) = 9.50$, $P = 0.005$] indicating that patients recalled significantly fewer personal semantic details than controls. There was a marginally significant effect of Time [$F(4,96) = 2.47$, $P = 0.05$] but no interaction between Time and Group [$F(4,96) = 1.89$, $P = 0.12$]. *T*-tests revealed that controls recalled significantly more personal semantic details than patients for the middle-age period ($P = 0.002$); the remaining periods were not significant ($P > 0.1$).

Public semantic tests

Dead-or-Alive Test

Table 4 shows the mean performance for patients and controls in the Dead-or-Alive Test measures. *T*-tests revealed that controls
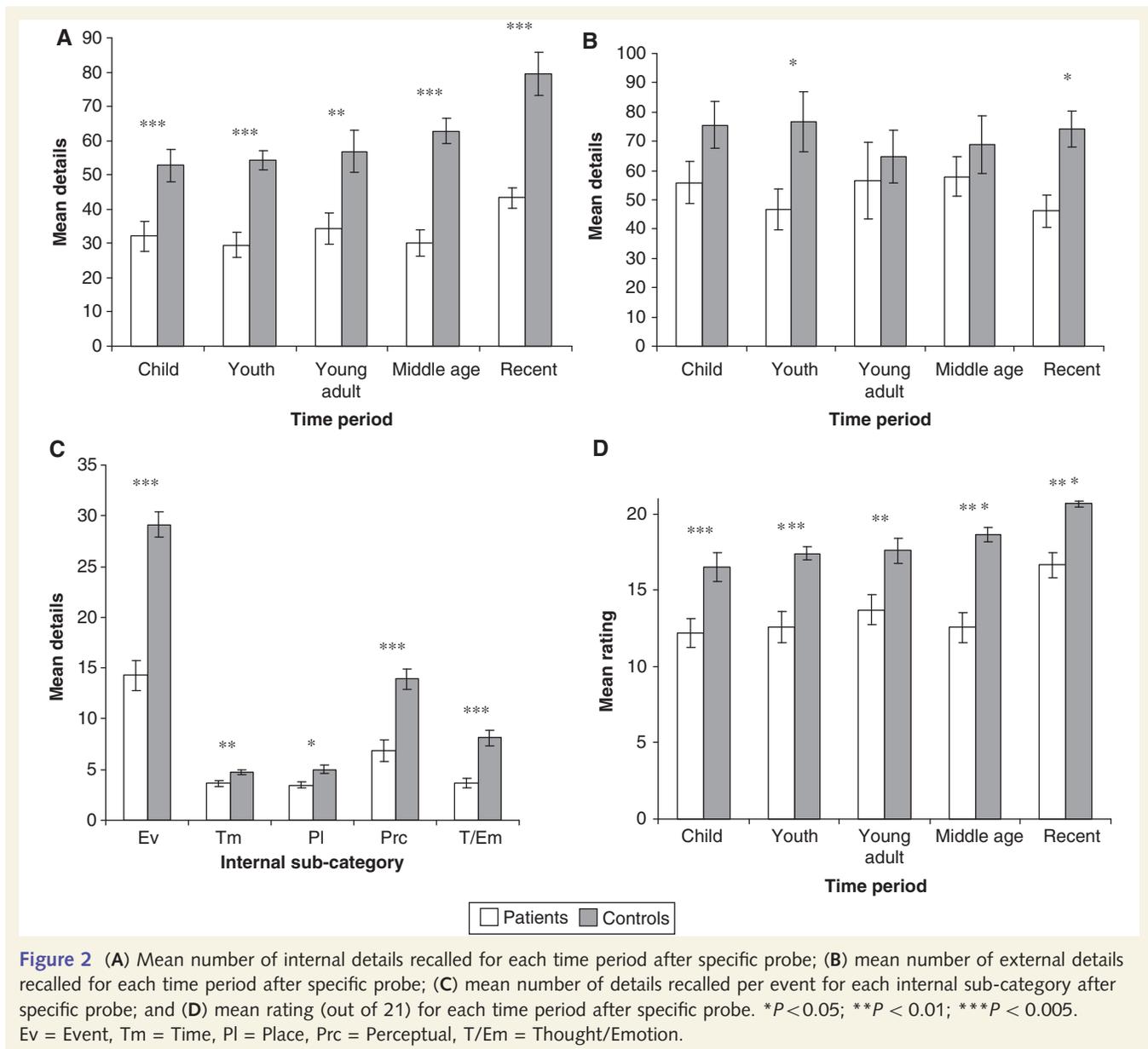
Figure 2 (**A**) Mean number of internal details recalled for each time period after specific probe; (**B**) mean number of external details recalled for each time period after specific probe; (**C**) mean number of details recalled per event for each internal sub-category after specific probe; and (**D**) mean rating (out of 21) for each time period after specific probe. *$P<0.05$; **$P < 0.01$; ***$P < 0.005$. Ev = Event, Tm = Time, Pl = Place, Prc = Perceptual, T/Em = Thought/Emotion.

were more accurate than patients at the dead-or-alive [$t(24) = 2.42$, $P = 0.02$] and cause of death judgements [$t(24) = 2.63$, $P = 0.015$]. There was a trend for controls to date the cause of death more accurately than patients, although this missed significance [$t(24) = 2.01$, $P = 0.055$].

Famous people were grouped according to the decade in which they died to provide a fine-grained assessment of the effect of time on performance. For the dead-or-alive judgement (Fig. 5A), an ANOVA (Time × Group) revealed a significant effect of Time [$F(4,96) = 14.61$, $P < 0.001$]; the effect of Group narrowly missed significance [$F(1,24) = 3.93$, $P = 0.059$]. There was an interaction between Time and Group [$F(4,96) = 2.92$, $P = 0.025$]. Pairwise comparisons assessing this interaction showed that participants were impaired relative to controls for the 1990s and 2000s ($P < 0.02$), but not for the 1960s, 1970s and 1980s ($P > 0 .25$).

For the cause of death judgement (Fig. 5B), there was a significant effect of Time [$F(4,96) = 6.90$, $P < 0.001$] and Group

[$F(1,24) = 5.79$, $P = 0.02$]. The interaction between Time and Group was significant [$F(4,96) = 2.97$, $P = 0.02$]. Comparisons revealed patients were impaired for the 1990s and 2000s ($P<0.02$) but not for the 1960s, 1970s and 1980s ($P > 0.2$).

Analysis of the decade of death judgement (Fig. 5C) yielded an effect of Time [$F(4,96) = 6.40$, $P < 0.001$] and a non-significant trend for controls to score higher than patients [$F(1,24) = 3.10$, $P = 0.09$]. There was a significant interaction between Time and Group [$F(4,96) = 3.88$, $P < 0.01$] with patients impaired for the 1980s and 2000s ($P < 0.05$), but not for the 1960s, 1970s and 1990's ($P > 0.2$).

Famous Events Test

Mean performance is displayed in Table 4. There was no difference between patients and controls in the recognition of famous events [Correct Hits—False Positives; $t(24) = 0.72$, $P = 0.48$], naming the decade in which the event occurred [$t(24) = 0.69$,
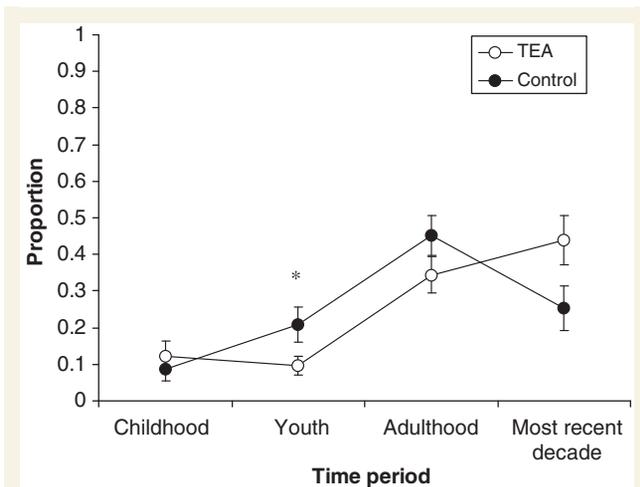
Figure 3 Mean distribution over time of autobiographical memories recalled in Crovitz Interview. *$P < 0.05$.
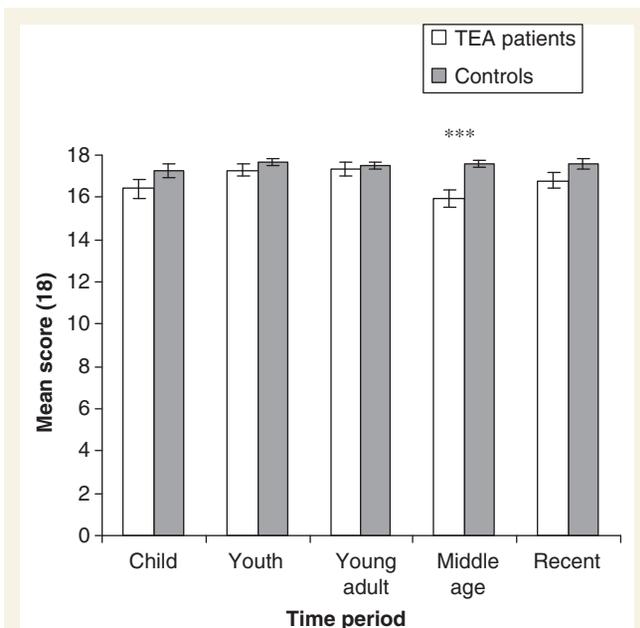

Figure 4 Mean score on the personal semantic test for each time period. ***$P < 0.005$.

$P = 0.50$], or in providing details about the events [$t(24) = 1.33$, $P = 0.20$].

Events were segmented according to the decade in which they took place to assess the effect of Time on performance. For recognition accuracy (Fig. 6A), an ANOVA (Time × Group) yielded a significant effect of Time [$F(7,168) = 8.71$, $P < 0.001$], but no effect of Group [$F(1,24) = 0.47$, $P > 0.5$]. There was a significant interaction, however, between Time and Group [$F(7,168) = 3.62$, $P = 0.001$]. Comparisons indicated that patients were impaired relative to controls for the most recent decade ($P < 0.001$), but not for the other decades ($P > 0.1$).

For dating the event (Fig. 6B), there was a significant effect of Time [$F(7,168) = 5.03$, $P < 0.001$] but not of Group

$[F(1,24) = 0.53$, $P > 0.40$] and no interaction [$F(7,168) = 1.26$, $P > 0.25$].

For event details (Fig. 6C), there was a significant effect of Time [$F(7,168) = 7.74$, $P < 0.001$] but not of Group [$F(1,24) = 1.51$, $P > 0.20$]. There was a significant interaction between Time and Group [$F(7,168) = 4.10$, $P < 0.01$], with patients impaired relative to controls for the 1980s, 1990s and 2000s ($P < 0.05$), but not for the more remote decades ($P > 0.2$).

Famous Faces Test

The mean scores for the Famous Faces Test are presented in Table 4. There was no difference between groups in the recognition of famous faces [$t(24) = 0.11$, $P = 0.91$], naming the famous face [$t(24) = 0 .11$, $P = 0.92$], or in providing details about the person [$t(24) = 0.09$, $P = 0.93$].

New Words Acquisition Test

Table 4 shows the mean scores on the New Words Acquisition Test. There was no difference between groups in either the recall [$t(24) = 0.30$, $P = 0.77$] or recognition tests [$t(24) = 0.73$, $P = 0.47$].

Discussion

This study examined whether patients with TEA demonstrated impairments for: (i) episodic autobiographical memory; (ii) personal semantic memory; (iii) public semantic memory; and (iv) anterograde memory. The main findings are discussed below.

Episodic autobiographical memory

We tested autobiographical memory for specific events using two well-established tests, the Autobiographical Interview (Levine et al., 2002) and the Crovitz Interview (Crovitz and Schiffman, 1974). Consistent with previous studies (e.g. Manes et al., 2005; Butler et al., 2007), we observed marked impairments of autobiographical memory for patients with TEA on both tests. At recall in the Autobiographical Interview, the deficits reached significance for the qualitative rating but not for the number of internal details produced; however, the summed score across all three retrieval conditions revealed marked deficits on both measures. This demonstrates the greater sensitivity that the specific probe condition provides relative to recall in isolation. Indeed, the specific probe provided the first evidence that autobiographical memory deficits in TEA extend across the entire life span. Furthermore, patients did not demonstrate a standard temporal gradient (Ribot, 1882), with greater sparing of more remote memories. Instead, both patients and controls recalled more details for recent than remote memories. This result is complemented by the finding from the Crovitz Interview that participants tended to produce memories from the most recent decade. This was more marked for patients than controls, again suggesting that there is no differential sparing of remote memories in TEA.

Using the Autobiographical Interview, we divided the internal details into different sub-categories of contextual details to clarify the type of information that was impaired. Participants

Table 4 Performance on public semantic memory tests for patients with TEA and controls

Public semantic memory scores	TEA group proportion correct (SD)	Control group proportion correct (SD)	P-value
Dead or Alive Test			
Dead/alive	0.75 (0.14)	0.86 (0.08)	0.020
Cause of death	0.64 (0.15)	0.78 (0.11)	0.015
Dating death	0.30 (0.10)	0.38 (0.12)	0.055
Famous Events Test			
Recognition	0.58 (0.06)	0.64 (0.15)	0.48
Decade	0.35 (0.10)	0.39 (0.17)	0.50
Details	0.48 (0.09)	0.56 (0.19)	0.20
Famous Faces Test			
Recognition	0.83 (0.11)	0.84 (0.09)	0.91
Naming	0.55 (0.20)	0.56 (0.21)	0.92
Details	0.68 (0.18)	0.69 (0.18)	0.93
New Words Acquisition Test			
Recall	0.71 (0.14)	0.73 (0.15)	0.77
Recognition	0.90 (0.05)	0.88 (0.07)	0.47

demonstrated impairments for event, time, place, perceptual and emotion/thought details, indicating widespread deficits of different contextual information rather than the isolated loss of selective types of information.
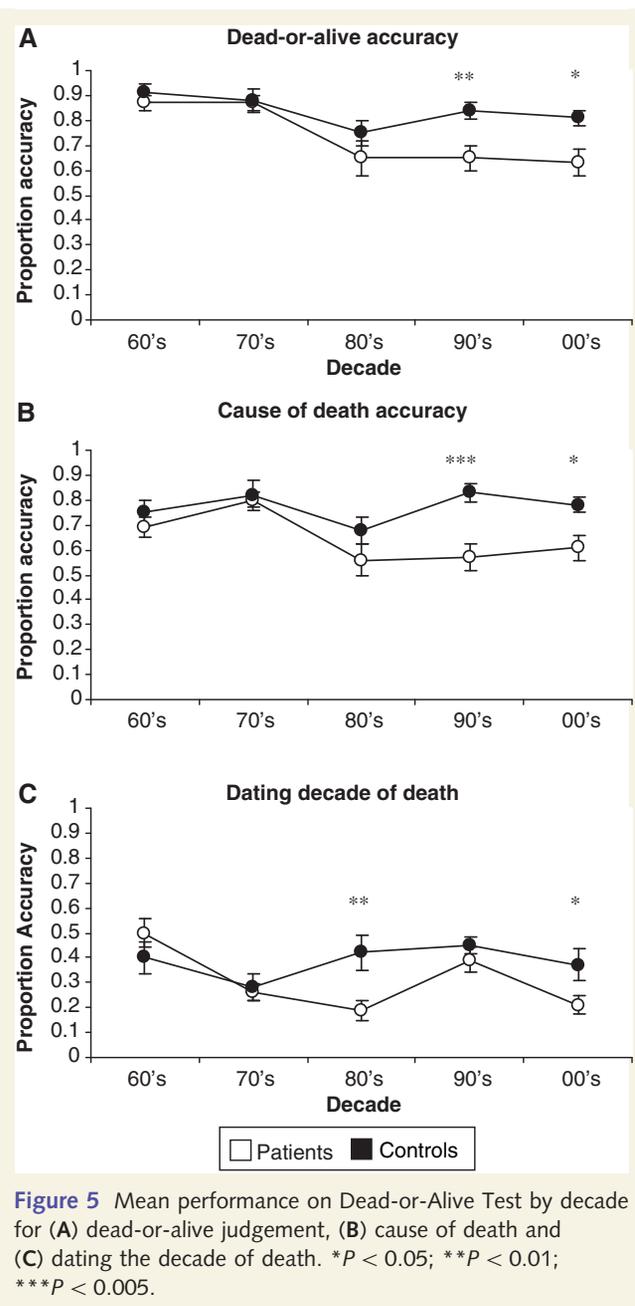
Compared to controls, patients retrieved fewer external details, which largely reflect recall of semantic information (McKinnon *et al.*, 2006). This effect, however, reached significance only for the youth and recent time periods.

Personal semantic memory

We found a significant overall impairment in personal semantic memory. This appeared mild compared to episodic autobiographical memory deficits, and was only significant for the middle-age period. Unlike Butler *et al.* (2007), we found no significant deficit for the most recent time period, although there was a near significant trend in this direction. There were no significant differences between groups for the childhood and youth time periods, although again there was a trend for patients to score lower than controls. One caveat is that performance was generally high for both patients and controls, raising the possibility that a ceiling effect might have reduced our ability to identify more subtle deficits. Nevertheless, our results provide clear evidence for some impairment in personal semantic memory, most pronounced for the middle-age period.

Public semantic memory

Deficits in public semantic memory were more selective than autobiographical memory impairments. Patients showed overall impairments on the Dead-or-Alive Test, but not for the Famous Events, Famous Faces and New Words Acquisition Tests. However, when performance was demarcated into time periods for the Dead-or-Alive and Famous Events Tests, there was evidence for a temporal gradient, with impaired performance relative to controls on recent decades but unimpaired knowledge for more

Figure 5 Mean performance on Dead-or-Alive Test by decade for (**A**) dead-or-alive judgement, (**B**) cause of death and (**C**) dating the decade of death. $*P < 0.05$; $**P < 0.01$; $***P < 0.005$.

remote decades. It is unclear why the Dead-or-Alive Test, but not the other tests produced an overall impairment. One explanation is that the Dead-or-Alive Test taps episodic event memory more than other tests of public knowledge, since the death of a personality is usually a discrete event, with relevant media exposure often limited to a few days or a few weeks. Related to this, it has been demonstrated that autobiographical significance facilitates performance on a semantic test of famous people in healthy participants (Westmacott and Moscovitch, 2003; see also Manns *et al.*, 2003), but this benefit was not apparent in a group of patients with medial temporal lobe damage (Westmacott *et al.*, 2003). Nevertheless, regardless of the reason for our finding, this study provides the first demonstration, in a group of patients with TEA, of impairments in public semantic memory; and it points to the sensitivity of the Dead-or-Alive Test as a measure of
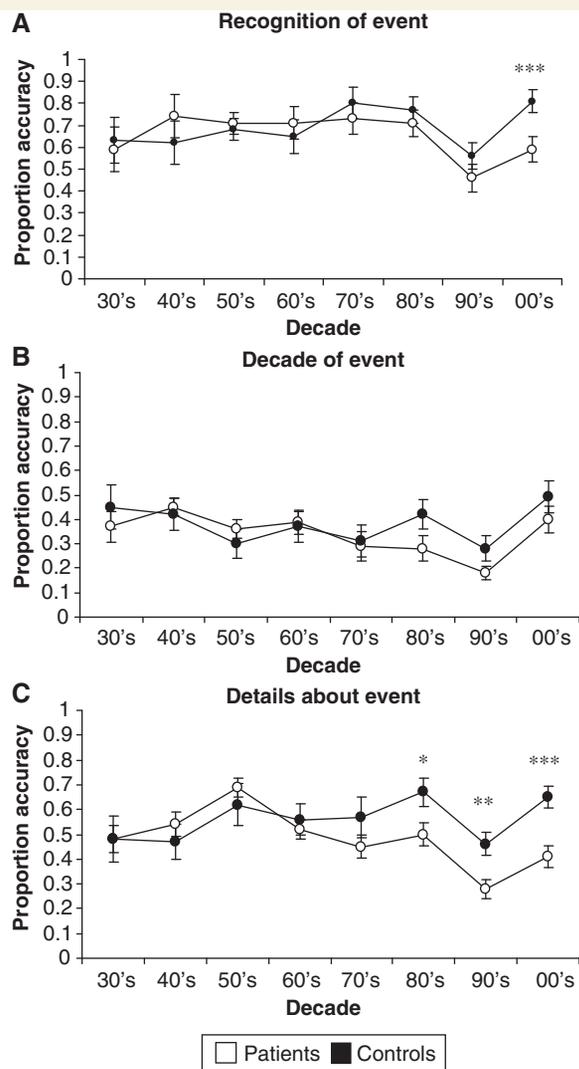
Figure 6 Mean performance on Famous Events Test for (**A**) recognition of event, (**B**) decade of event and (**C**) details about event. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$.

remote memory. Furthermore, the lack of significant difference between patients and controls on the Media Exposure Test (Kapur et al., 1999) suggests that the deficits cannot be attributed to this factor.

Do patients with TEA exhibit 'focal retrograde amnesia'?

In contrast to the remote memory deficits, there was no evidence for impairment on a range of anterograde memory tests. Furthermore, the fact that autobiographical memory deficits stretched back to childhood, many decades prior to any report of memory difficulties, together with anecdotal evidence for the loss of previously salient memories, suggests that the remote memory deficits are unlikely to be due to an impairment of memory encoding by seizure-related activity (Kopelman, 2000). The distinctive profile of memory loss indicates that the remote memory deficits detected here constitute a distinctive form of

'focal retrograde amnesia' as the term is generally understood—an inability to retrieve memories that have been successfully acquired in the past, in the absence of any deficit on standard tests of anterograde memory. Focal retrograde amnesia has been described previously in the context of cerebral vasculitis (Evans et al., 2003), pathology in vicinity of the uncinate fasciculus (Levine et al., 1998), posterior cerebral pathology affecting visual imagery (Rubin and Greenberg, 1998) and psychogenic or functional amnesia (Kopelman, 2000; Krichevsky et al., 2004).

However, normal performance on standard tests does not guarantee that anterograde memory is normal in all respects. In previous work (Butler et al., 2007), we demonstrated that some patients with TEA exhibit 'accelerated long-term forgetting'; excessive loss of recently acquired memories over periods—from 24 h to several weeks—longer than those normally used in standard tests. Five out of fourteen patients studied here reported this symptom (Table 1). Without further investigation, we cannot rule out the possibility that other patients would show some form of accelerated forgetting or that the group as a whole would demonstrate an impairment. Nevertheless, the lifelong extent of the autobiographical memory impairment revealed in this study, the loss of remote memories that had previously been accessible according to patients and informants, and the recent symptomatic onset of both retrograde amnesia and accelerated forgetting (around the time of the onset of the epilepsy), suggest that it is unlikely that this non-standard form of anterograde memory impairment provides the only or main explanation for the remote memory loss demonstrated here.

The pathogenesis of remote memory impairment in transient epileptic amnesia

There is evidence from functional imaging of widespread changes within the autobiographical memory network in patients with temporal lobe epilepsy. Addis et al. (2007), using functional MRI, showed that relative to controls, there was reduced activation in the hippocampus, prefrontal cortex, temporal poles and the lateral parietal cortex, together with decreased connectivity between the left hippocampus and other areas of the autobiographical network such as the medial prefrontal cortex. It remains uncertain whether these functional changes are the cumulative result of repeated epileptiform activity within the network, or of structural changes within the system.

Thus, the remote memory loss observed here may be the result of repeated clinical and/or subclinical activity propagating from the medial temporal lobe through the neocortical 'autobiographical memory network', resetting synaptic weights and thereby disrupting the distributed representations on which autobiographical memories are thought to depend (Butler and Zeman, 2008a; for a similar explanation, see Gallassi et al., 1988). Gallassi (2006) and Mendes (2002) have similarly proposed that memory deficits in TEA may be the result of epileptic discharges involving the hippocampus and mesial temporal lobes. This proposal has received some support from work with animals. Specifically, spatial navigation studies with rats have shown that kindling of seizures

by electrical stimulation in regions of the hippocampus (e.g. CA1) can result in remote memory deficits (Gilbert *et al.,* 1996) and that these impairments persist after kindling was discontinued (Lopes Da Silva *et al.,* 1986; for related work, see Leung *et al.,* 1990; Arkhipov, *et al.,* 2008).

An explanation along these lines is compatible with the 'standard model' of memory consolidation (e.g. Squire, 1992; Squire and Bayley, 2007) in which the medial temporal lobes are thought to play a temporary role in episodic memory storage, pending their transfer, via a 'slow' learning system, to neocortical representation. However, according to this explanation, due to the widespread neural overlap between the semantic and episodic memory systems (e.g. Levine *et al.,* 2004; Burianova and Grady, 2007), one might have expected the episodic and semantic memory deficits to be more closely related than we observed.

Alternatively, the subtle structural pathology apparent in the hippocampus in patients with TEA (Butler *et al.,* 2009) could underlie the remote memory loss reported here. This explanation would not be consistent with the standard model of memory consolidation, but is in keeping with the major rival theory, Multiple Trace Theory (e.g. Nadel and Moscovitch, 2001; Moscovitch *et al.,* 2005; Rosenbaum *et al.,* 2008), which proposes that episodic memories remain dependent on the medial temporal lobes throughout the lifetime, with a gradual accumulation of 'multiple traces' over time as a result of cycles of conscious or unconscious memory rehearsal. The temporally extended episodic memory deficits we observed, together with the restricted, temporally graded semantic memory impairment is consistent with Multiple Trace Theory and is similar to that previously observed in numerous patients with medial temporal lobe damage (e.g. Viskontas *et al.,* 2000; Moscovitch *et al.,* 2005; Steinvorth *et al.,* 2005; Poreh *et al.,* 2006; Rosenbaum *et al.,* 2008; but see Bayley *et al.,* 2005; Kirwan *et al.,* 2008).

These alternative explanations make competing predictions that can be tested in future work: the first, 'physiological', explanation predicts progressive depletion of autobiographical memories in patients with continuing clinical or subclinical epileptiform activity. The second, 'structural', explanation predicts a positive correlation between the extent of hippocampal pathology and the extent of autobiographical memory loss. This has, however, not been detected to date (Butler *et al.,* 2009).

Conclusions

This study used a broad range of memory tests to investigate remote memory deficits in TEA. The most severe deficits were observed for autobiographical memory: patients showed substantial deficits across the entire lifespan, involving all elements of episodic memory. There was an overall impairment of personal semantic knowledge, most pronounced for the middle-age time period. There were subtle deficits for public semantic memory, although this appeared relatively restricted, and more pronounced for recent than remote knowledge. In contrast to the diverse range of remote memory deficits, anterograde memory was unimpaired, providing evidence for focal retrograde amnesia in TEA.

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