



# Memory consolidation and the hippocampus: further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia

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## Abstract

Studies of autobiographical memory in semantic dementia have found relative preservation of memories for recent rather than remote events. As semantic dementia is associated with progressive atrophy to temporal neocortex, with early asymmetric sparing of the hippocampus, this neuropsychological pattern suggests that the hippocampal complex plays a role in the acquisition and retrieval of recent memories, but is not necessary for the recall of older episodic events. In an alternative view of memory consolidation, however, the hippocampus plays a role in the retrieval of all autobiographical memories, regardless of the age of the memory [Curr. Opin. Neurobiol. 7(1997)217]. This 'multiple trace theory' predicts that patients with semantic dementia should show no effects of time in their autobiographical recall. In this article, we ask whether it is possible to reconcile the data from semantic dementia with the multiple trace theory by investigating whether the time-dependent pattern of autobiographical retrieval seen in the disease is due to (i) patients showing this effect being exceptional in their presentation; and/or (ii) patients with semantic dementia exhibiting impaired strategic retrieval from concomitant frontal damage. A series of experiments in patients with semantic dementia, the frontal variant of frontotemporal dementia and Alzheimer's disease clearly demonstrates that neither of these two factors can explain the documented effect of time seen in semantic dementia. Nonetheless, we discuss how damage to semantic knowledge could result in an autobiographical memory deficit and suggest that data from semantic dementia may be consistent with both views of hippocampal involvement in long-term memory. © 2002 Elsevier Science Ltd. All rights reserved.

**Keywords:** Episodic memory; Retrograde amnesia; Semantic memory; Temporal gradients; Strategic retrieval; Frontal lobes

## 1. Introduction

A number of investigations have found that patients with semantic dementia, the temporal lobe variant of frontotemporal dementia, who present with focal atrophy to the neocortex in the context of early sparing of the hippocampal complex, showed effects of time on tests of remote memory, with better preservation of episodic events and semantic facts from very recent life compared with other time-periods [22,24,28,39,84]. It has been proposed that this data offers support for the standard model of memory consolidation in which the

hippocampal complex (i.e. the hippocampus, subiculum, parahippocampal gyrus/entorhinal cortex) plays a critical role in the acquisition and initial retrieval of episodic and semantic memories<sup>1</sup>. The interpretation of these results has been challenged, however, by other researchers, notably Nadel and Moscovitch [65,66,71], who pointed out that other factors, such as strategic

<sup>1</sup> It should be noted that while most researchers argue that medial temporal lobe structures play a key role in the acquisition of new episodic memories, controversy still exists regarding the exact functions of the hippocampus proper (including the dentate gyrus and subiculum) versus the entorhinal and perirhinal cortex [68,87,89]. For the purposes of this article, we will refer to the hippocampal complex (including all aforementioned medial temporal lobe regions) with the caveat that there is accruing evidence for separate learning systems within the medial temporal lobe.

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retrieval deficits due to accompanying frontal lobe pathology, could be resulting in the reverse effect of time. In this article, we addressed empirically two of the issues raised by Moscovitch and Nadel [66], as well as considering in the discussion other possible explanations which have yet to be tested.

## 2. Frontotemporal dementia

Frontotemporal dementia (FTD) is the term currently applied to a number of syndromes in which patients present with degeneration of the frontal and/or temporal lobes (previously referred to as Pick's disease, [41]). The two principle subtypes of FTD—reflecting the major locus of pathology, predominantly frontal versus temporal—have different behavioural and cognitive profiles [44]. In the frontal variant of FTD (fvFTD), frontal lobe pathology predominantly affects the orbitomedial cortex causing changes in behaviour and personality; most notably apathy, loss of empathy or emotional warmth, impulsivity, disinhibition, change in dietary preference and stereotyped or ritualistic behaviours [6,63]. The patients show increasing problems with planning and organising activities, a pattern which has been attributed to impairments in goal-setting and attainment, as well as mental flexibility and set-shifting [31,32]. Rahman et al. [78] found that a group of eight patients with fvFTD showed deficits on the reversal stage of a visual discrimination learning paradigm and increased risk-taking behaviour, a pattern which the authors attributed to dysfunction in orbitomedial frontal cortex. Notably, however, the patients showed little impairment on tests sensitive to damage in dorsolateral prefrontal cortex, such as spatial working memory. Perry and Hodges [77] confirmed that patients with fvFTD could be differentiated from patients with other neurodegenerative conditions by their poorer performance on tests of attention and executive function. Episodic memory was also impaired, although to a lesser degree than the deficit seen in a group with early dementia of the Alzheimer type. Critically, the preservation of semantic memory in the context of impaired executive function in the fvFTD group was the converse to that found in patients with the temporal variant of FTD (also termed semantic dementia, the label we will adopt for the rest of this paper). This result suggests that there are at least two sub-types of frontotemporal dementia and that the patients at the frontal versus temporal ends of the spectrum can be clearly differentiated at a neuropsychological level. It is worth noting, however, that there are cases who present with a more mixed profile of frontal and temporal lobe dysfunction and that over time, all patients eventually show evidence of both frontal and temporal involvement.

Turning to semantic dementia, the predominant cognitive feature is a progressive deterioration of semantic knowledge about people, objects, facts and word meanings. Patients perform poorly on neuropsychological tests dependent upon conceptual information, such as picture naming, category fluency (i.e. generating as many exemplars from a semantic category as possible in one minute), word-picture matching, defining concepts in response to their names or pictures and sorting picture or words according to pre-specified criteria (e.g. electrical versus non-electrical). The deficit is also evident on non-verbal tests of semantic knowledge, such as selecting the correct colour for a black-and-white line drawing (e.g. red for a heart; black or brown for a gorilla), drawing animals or objects from memory [8], sound-picture matching [7], demonstrating the use of objects [36] and selecting which of two pictures (fir tree or palm tree) goes best with a pyramid (Pyramid and Palm Trees Test [46]). By contrast, patients show little impairment, even at relatively late stages of the disease, on tests of phonology and syntax, visuospatial skills and working memory [7,43,76].

Recent neuroradiological studies have found convincing support for the view that anterior and inferior areas of the temporal lobe are affected early in semantic dementia and that this profile is different from other neurodegenerative conditions that affect long-term memory, such as Alzheimer's disease [9,21,34,38,67,83]. With respect to medial temporal lobe regions, there is accruing evidence that the hippocampi and parahippocampal gyri are involved at later stages in the disease [82,9,21].

## 3. Remote memory in semantic dementia

While one of the five characteristics of semantic dementia proposed by Hodges et al. [43] was relatively preserved autobiographical and day-to-day (episodic) memory, more recent studies have revealed a more complex, and theoretically interesting, pattern. Snowden et al. [84] and Graham and Hodges [24] described the performance of patients with semantic dementia on the Autobiographical Memory Interview (AMI [54]). Unlike amnesic patients, who often show better recall of distant memories compared with more recent personal events, patients with semantic dementia showed the opposite pattern: better recall of recent memories compared with those from childhood and early adulthood.

A single case-study, described by Graham and Hodges [24] investigated autobiographical memory in semantic dementia in more detail. The patient, AM, was asked to retrieve autobiographical memories related to the same 15 words in each of four time-periods spanning the whole of his life. AM's memories from the

five years prior to testing were qualitatively better than the memories he produced for the other three time-periods, which spanned a total of 60 years of his life. More specifically, AM showed clear evidence of a ‘step-like’ pattern of performance on this test, as opposed to a temporal gradient extending back in time. In two subsequent studies, Graham and colleagues demonstrated that a similar effect of time is evident on tests of remote memory for famous events [28] and famous people [39]. Likewise the study by Snowden et al. [84] demonstrated that patients with semantic dementia possessed significantly better knowledge of British decimal coins in current usage (e.g. 50 pence) than of pre-decimal coins (e.g. a half crown or shilling), which went out of use in the early 1970s. Patients with Alzheimer’s disease were as good, if not better, at providing knowledge on the pre-decimal examples compared with the decimal coins (although see [90]).

#### 4. Models of memory consolidation

##### 4.1. The standard model of memory consolidation

The results from these studies have been interpreted by the authors as support for a view in which the hippocampal complex and the temporal neocortex play separate, but complementary, roles in the acquisition and maintenance of long-term memories [1,24,25,39,56,60,69,79,85,86]. More specifically, the hippocampal complex helps bind together activated neocortical components of a recently experienced event and is, therefore, initially critical for the retrieval of new memories. Over time, repeated reinstatement of these hippocampal-neocortical ensembles results in the formation of permanent connections between the neocortical regions activated by the experience. Eventually, therefore, retrieval of the event can become independent of the hippocampus.

The data from semantic dementia can be explained by this model of memory consolidation in the following way: advancing pathology in the temporal neocortex results in a progressive loss of long-term memories, both semantic and autobiographical, but sparing, at least early in the disease, of the hippocampal complex allows the encoding and subsequent retrieval of a recently experienced event. A patient with semantic dementia will, therefore, be able to encode new experiences, but increasingly poor consolidation of memories from the hippocampus to the neocortex, and the limited storage capacity of the hippocampus, means that the new representations will be relatively short lived [70].

The main support for the standard model of memory consolidation, before the data from semantic dementia were published, came from studies of patients with

amnesia after medial temporal lobe lesions or fornix damage [14,37,48,80,94]. The standard model predicts that selective hippocampal damage will result in a temporally-graded retrograde amnesia. For example, Reed and Squire [79] assessed the extent of retrograde amnesia in four patients: two of these cases were thought to have damage restricted to the hippocampal complex bilaterally, while the other two patients had additional temporal neocortical damage, as well as hippocampal pathology. The findings were in keeping with the standard model: the patients with selective hippocampal lesions showed limited retrograde amnesia, while the cases who had more extensive temporal lobe damage were found to have severe and pervasive deficits in the retrieval of autobiographical and semantic information. Reed and Squire concluded that retrograde amnesia can either be limited or extensive in time, depending upon whether the pathology is restricted to the hippocampus or extends to adjacent temporal neocortical regions.

##### 4.2. The multiple-trace model of memory consolidation

The lack of well-documented temporally-limited retrograde impairments in patients with bilateral hippocampal lesions lead Nadel and Moscovitch [71], to challenge the standard model of memory consolidation. These authors suggest that the hippocampus is necessary for the retrieval of episodic, autobiographical, memories for the whole of a person’s life. They note that many patients show a retrograde amnesia for autobiographical events which extends for as much as 25–40 years in the past [11,50,80,88,92]. In terms of animal studies of consolidation, Nadel and Moscovitch suggest that when the hippocampus is crucial for learning, as in remembering where a platform is located in a water maze or where food is stored in a radial arm maze, damage often results in a flat retrograde amnesia [4,10]. When the hippocampus is not critical for learning, as in object discrimination, no retrograde amnesia or a graded retrograde amnesia is typically documented [91,93]. The authors conclude that the animal literature is largely consistent with the neuropsychological case-reports and propose that a reformulation of the standard model is necessary in order to fully explain the research findings in the literature.

Turning to semantic dementia, Westmacott et al. [90] describe a study of autobiographical retrieval in a patient with semantic dementia (EL). EL’s autobiographical memory was assessed using a set of 50 family photographs evenly distributed across his lifetime. EL was asked to provide as much detail as possible about the events portrayed in the photographs, and a measure of episodic quality was created by scoring the memories for the presence of five criteria (e.g., sense of recognition, ‘I remember’; knowledge of temporal context

(year); knowledge of spatial/situational context (location); expression of emotion (smiling, laughing); and narrative structure (describing a sequence of events). In contrast to previous studies of autobiographical memory in semantic dementia, and consistent with the multiple-trace model, Wesmacott et al. found preserved autobiographical memory across the whole of the patient's lifetime. Notably, EL showed a temporal gradient when asked to name the people shown in the photographs, with better naming of people in the recent photographs compared with people included in photographs documenting more remote events.

Given the neuropsychological data from amnesia and semantic dementia, Nadel and Moscovitch [71] (also [65,66,72]) proposed instead that the hippocampal complex plays a permanent, as opposed to a temporary, role in the retrieval of episodic memories (the multiple trace theory). The initial stages of memory encoding are similar to that of the standard model: the separate neural components of a recently experienced memory are bound together by the hippocampal complex, creating a medial temporal-neocortical ensemble (i.e. the hippocampal complex acts as an indexer pinpointing the different neocortical areas that need to be activated to produce the full content of the event). According to the multiple trace model, the medial temporal units are necessary for retrieving the memory representation for as long as it exists, and that repeated retrieval of episodes results in the creation of recoded, highly related, traces within the hippocampal complex. The implications of the multiplicity of traces in the hippocampal complex is that older memories have more traces which are more widely distributed over the medial temporal lobe than younger memories.

It is noteworthy that Nadel and Moscovitch [71] propose that the role of the hippocampus in memory retrieval is specific to episodic, or autobiographical, events. Thus patients with severe bilateral hippocampal damage may show a flat gradient for past autobiographical memories, but a clear temporal gradient for remote semantic memory, such as knowledge of famous personalities. At present, it is unclear how this view maps onto theories about the role of hippocampal and perirhinal/entorhinal cortices in episodic and semantic learning, respectively, but it is important to distinguish between the permanent role of the hippocampus in the retrieval of autobiographical memories versus a more temporary, or perhaps weaker involvement, in the storage of semantic knowledge.

## 5. Semantic dementia and the multiple-trace model

While the multiple-trace model provides a compelling explanation for many of the contradictory results from the amnesic literature, it is unclear how this model

accounts for the reverse step pattern seen in semantic dementia on tests of remote memory [22] (although see Westmacott et al. [90]). A number of possible factors, two of which are summarised below, have been proposed by Moscovitch and Nadel [66].

### 5.1. AM: an exception to the rule?

Moscovitch and Nadel [66] note that, although there are reports of at least nine patients with semantic dementia who have shown a reverse temporal gradient on tests of autobiographical memory [24,84], only one patient has shown the theoretically important reverse step function with better recall of autobiographical memories for a short period of time (2 years in the case of AM reported in Graham and Hodges [24]). Moscovitch and Nadel quite reasonably note, therefore, that caution needs to be extended towards generalising from this particular case to all patients with semantic dementia, and from there towards rejecting the multiple trace model of memory consolidation.

### 5.2. Strategic retrieval deficits due to frontal damage

In Nadel and Moscovitch's original article [71], they suggest that a reverse step pattern might be obtained on tests of autobiographical memory if strategic retrieval processes, subserved by the frontal lobes, were malfunctioning or inoperative. While there is little empirical evidence that patients with fvFTD show such effects of time in their autobiographical retrieval [40], further work is necessary before dismissing this possibility completely.

## 6. Purpose of this study

The aims of the current study were, therefore, to address these two issues and to determine whether the data from semantic dementia is inconsistent with predictions from the multiple trace model. In four experiments, we show that (1) the data in semantic dementia is replicable across patients; and (2) that there is little evidence that the step-like pattern seen in semantic dementia is caused by strategic retrieval deficits.

## 7. Experiment 1a: testing autobiographical memory in semantic dementia using a detailed Crovitz test

### 7.1. Participant

Patient JH, aged 58 years old at the time of study, fulfilled both local and consensus criteria for semantic dementia [43,73] and has been the subject of previous reports [29,39]. At time of presentation, JH had a

Table 1  
General profiles and selected neuropsychological test scores for JH and DM, the subjects of experiment 1

Test (max.)	JH	DM <sup>a</sup>	Controls (S.D.)
Age	58	59–61	
Duration of illness	3 years	5 years	
Years education	10	20	
Mini-Mental State Examinations (30)	24	29	29 (0.9)
National Adult Reading Test Errors (50) <sup>b</sup>	46	21	10.9 (6.2)
Neuropsychiatric Inventory	3	9	
<i>Imaging</i>			
MRI	Bitemporal atrophy, L > R	L. polar temporal atrophy	
SPECT	L. temporal hypoperfusion	L. temporal hypoperfusion	
<i>Semantic memory</i>			
Category fluency (four living categories)	7	53	60.3 (12.6)
Graded Naming Test (30)	NT	17	
Picture Naming Battery (64)	11	61	> 62
Pyramids and palm trees-pictures (52)	33	46	51.2 (1.4)
<i>Visuospatial</i>			
Rey complex figure, copy (36)	31	34	34 (2.9)
<i>Episodic memory</i>			
Logical memory, imm. recall (23.5)	1.25	5	9.9 (3.9)
Rey complex figure, 30 min delayed recall (36)	12	26	15.2 (7.4)
<i>Phonology and syntax</i>			
Letter fluency (FAS)	12	53	45.2 (9.9)
Test for the reception of grammar (80)	67	78	78.8 (1.8)
<i>Executive</i>			
Wisconsin card sort test-categories (6)	NT	6	6

<sup>a</sup> Results taken from the last of the three sessions in the longitudinal study.

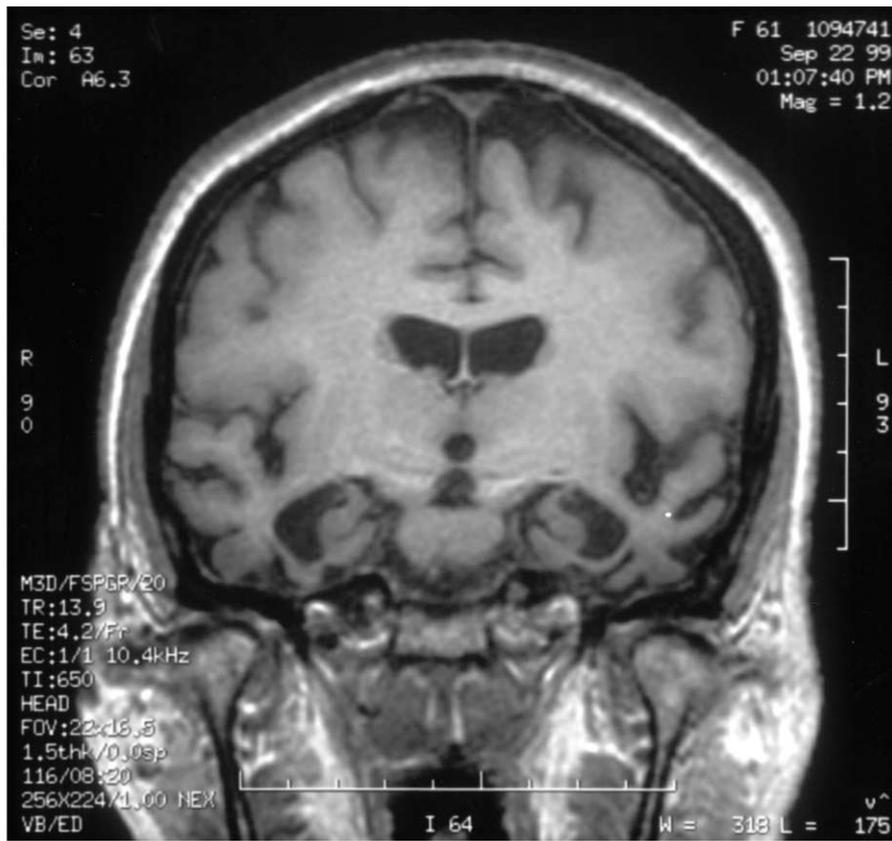
<sup>b</sup> Surface dyslexia is a feature of SD.

3-year history of word finding difficulties and comprehension impairment. Formal neuropsychological evaluation (see Table 1) revealed marked deficits on tests tapping semantic memory, such as category fluency for four living (animals, breeds of dog, birds and water creatures) categories [42] (7; controls:  $58.3 \pm 12.3$ ), picture naming (11; controls > 62), and the picture version of the pyramids and palm-trees test [46] (33; controls:  $51.2 \pm 1.4$ ). On letter fluency, JH's performance was impaired (12; controls  $44.6 \pm 10.2$ ), but less so than her category fluency. By contrast, JH's visuospatial skills and non-verbal anterograde memory were intact: she scored normally on both copy of the Rey complex figure [75] and recall after a 30-min delay. Using the Neuropsychiatric Inventory [13] as an index of behavioural problems due to possible frontal dysfunction, JH scored 3 out of a maximum of 144. Coronally-oriented magnetic resonance imaging (MRI) scans showed bitemporal atrophy without clinically apparent frontal involvement (see Fig. 1). A voxel-based morphometry study [67] had confirmed severe bilateral

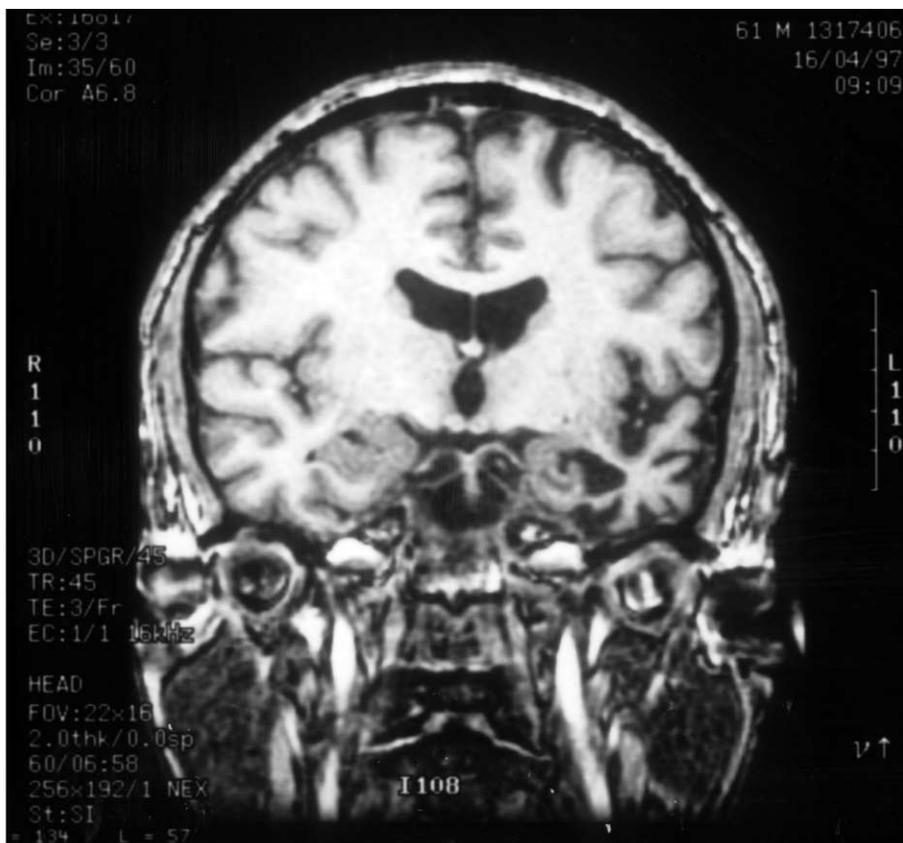
involvement of the anterior temporal lobes (left > right) together with a degree of ventromedial frontal atrophy; there was, however, no significant atrophy of the hippocampus or parahippocampal gyrus.

## 7.2. Method and scoring

A modified version of the Galton–Crovitz [12] technique was used, based on that described in Hodges and Ward [45] and Graham and Hodges [24]. JH was given 14 words (e.g. holiday, journey, and friend) and was asked to produce a detailed and specific autobiographical memory in response to each cue-word. The words were given in each of four time-periods spanning the whole of JH's life: 0–18, 19–39, 40–54 and 55–58 years of age. Memories were subsequently scored on a 5-point scale as described previously by Graham and Hodges [24]. Briefly the scores were: 0, do not know/not related to target word; 1, semantic facts related to the target word; 2, generic, poorly detailed episodic memory; 3, generic, richly detailed episodic memory; 4,



(a)



(b)

Fig. 1. Coronal T1-weighted volumetric MRI of (a) JH (experiment 1a); and (b) DM (experiment 1b).

specific in time, poorly detailed episodic memory; and 5, specific in time, richly detailed episodic memory. Memories were independently scored by two raters and a mean of the two scores calculated for each target item. JH's performance in each of the four time-periods was then compared with the data from the three controls described previously in Graham and Hodges [24]. The data were analysed using Friedman and Wilcoxon rank-sum tests.

### 7.3. Results

Fig. 2 summarises JH's performance over the four time periods in comparison to controls. A Friedman analysis showed that JH's performance on the Crovitz test was significantly affected by time period ( $X^2 = 7.6$ ,  $P = 0.05$ ) and using Wilcoxon rank-sum tests, confirmed this effect was related to the production of more detailed autobiographical memories in the most recent time-period (0–18 vs. 55–58:  $Z = 2.2$ ; 19–39 vs. 55–58:  $Z = 2.0$ ; 40–54 vs. 55–58:  $Z = 2.3$ , all significant at  $P < 0.05$ ). There were no significant differences between JH's performance on any of the other time-periods (0–18 vs. 19–39:  $Z = 0.05$ ,  $P = 0.96$ ; 0–18 vs. 40–54:  $Z = 0.13$ ,  $P = 0.89$ ; 19–39 vs. 40–54:  $Z = 0.35$ ,  $P = 0.72$ ). Statistical analyses reported in Graham and Hodges [24] found no significant effect of time in the quality of the control subjects' autobiographical memories.

Fig. 2 illustrates a further facet of JH's performance: despite performing significantly better on the most recent five years, her score on this time-period was still outside the control range. Wilcoxon rank-sum tests confirmed that JH was significantly impaired on all time-periods compared with the control subjects (0–18:  $Z = 3.2$ ,  $P < 0.01$ ; 19–39:  $Z = 3.2$ ,  $P < 0.01$ ; 40–54

(controls 40–59):  $Z = 2.8$ ,  $P < 0.01$ ; 55–58 (controls 60–65):  $Z = 2.2$ ,  $P < 0.05$ ).

## 8. Experiment 1b: longitudinal testing of autobiographical memory in a single case of semantic dementia

### 8.1. Participant

The second case, DM, an ex-surgeon (aged 59–61 years during the time of this study) first developed symptoms at the age of 56: he had experienced increasing difficulty producing the names for technical instruments related to his occupation. Over time, his word finding problems progressed from low frequency surgical items to everyday objects and he and his family reported increasing problems with language comprehension. Formal neuropsychology revealed more subtle deficits in word production than those seen in JH (see Table 1). On the Graded Naming Test [61] DM scored 17/30 (predicted score for similar background  $> 20$ ), although he showed a milder impairment on the picture naming test from the semantic battery [7] scoring 61/64 (controls  $> 62$ ) and on category fluency (53 for four categories; controls:  $60.3 \pm 12.6$ ). He made a greater number of errors on the National Adult Reading Test [74] than would have been expected given his educational level (21/50 errors). On the picture version of the Pyramid and Palm Trees Test, DM's level of performance was more than 3 standard deviations outside of the control range (46/52, controls  $51.2 \pm 1.4$ ), and he showed significant impairment on more stringent tests of conceptual knowledge, such as synonym judgement (see [26] for details). By contrast, DM's executive abilities, visuospatial skills and anterograde memory were normal: DM scored 53 on FAS letter fluency, managed six categories on the Wisconsin Card Sort Test [35]; scored 78/80 on the Test for the Reception of Grammar [3] and was able to copy (34/36) and recall (26/36) the Rey complex figure [75], as well as control subjects. DM, like JH, did not score significantly on the Neuropsychiatric Inventory [13].

MRI scanning revealed pathology restricted to the left temporal lobe, in particular the polar region (see Fig. 1). Voxel based morphometry confirmed changes in the left anterior temporal lobe with sparing of the right side and of medial temporal structures; a mild degree of left sided ventro-medial frontal atrophy was also detected [67]. 99Tc-HMPAO SPECT confirmed hypoperfusion in the left temporal lobe. DM has been involved in various studies conducted by our research group [28,39,82]. Of particular interest were investigations of how repeated exposure to verbal stimuli—DM practised at home with word dictionaries—can help arrest, at least initially, the progressive loss of vocabu-

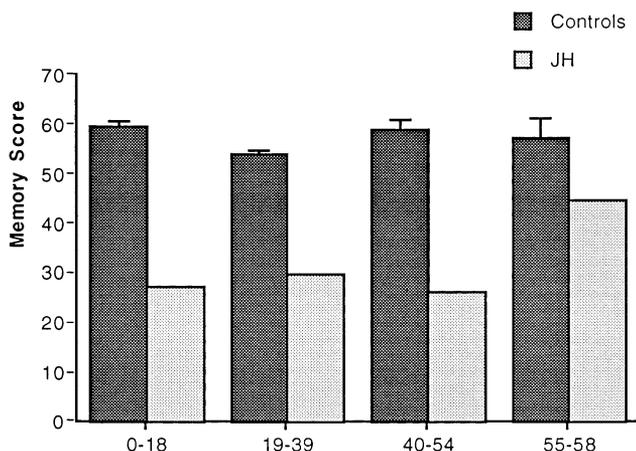


Fig. 2. JH's 4 time period Crovitz demonstrating relatively better autobiographical memory for the most recent time window in contrast to the previous three. Maximum score for each time period = 70 (see text for scoring system). Bars = standard error.

lary commonly seen in semantic dementia [26,27] providing support to the notion that explicit learning can take place in this condition.

## 8.2. Method

DM was administered the Autobiographical Memory Interview (AMI, [54]) on three separate occasions separated by twelve month intervals (years: 1995–1997). The AMI probes personal semantic (e.g. names of work colleagues) and autobiographical information (e.g. the first meeting of someone in your twenties) across three life periods: childhood, early adulthood, and recent life. As the questions in the recent life events in Kopelman et al.'s version of the test relate mainly to recent hospital attendances, we used a version modified by Greene et al. [30] which assesses events that are more likely to have occurred prior to any onset of pathology (e.g. an event from a funeral or wedding attended in the last five years). DM's responses on both sections were scored according to the criteria described in the AMI manual and to allow comparison across the three testing sessions the data are reported as *z*-scores. To create the *z*-scores, we compared DM's performance on the AMI with six control subjects, who were matched, as closely as possible to DM, for age and educational level (average age =  $65.8 \pm 9.17$ ; number of years education =  $14.7 \pm 2.9$ ).

## 8.3. Results

Fig. 3 shows the results from the longitudinal testing of DM on the AMI. Considering the personal semantic section first, the six control subjects scored close to ceiling,  $20.8 \pm 0.4$  (childhood),  $20.9 \pm 0.2$  (early adulthood) and  $20.6 \pm 0.5$  (recent life), presumably due to their high educational level. DM initially showed significant impairment on this component for both childhood and early adulthood, but was within 2 standard deviations of the control subjects for recent life. From the second testing session onwards, he showed increasing problems with this component for all three time-periods. On the autobiographical memory section, the controls again performed close to ceiling:  $8.3 \pm 1.2$  (childhood),  $8.5 \pm 0.6$  (early adulthood) and  $8.7 \pm 0.5$  (recent life). For the first two testing sessions, DM showed no significant impairment on any of the time periods other than early adulthood (testing session 2) compared with the control subjects. By 1997, however, his performance on both childhood and early adulthood was impaired as measured by *z*-scores of  $-3.6$  (childhood) and  $-6.4$  (early adulthood). By contrast, his ability to produce incidents from the recent period remained at the same level as 1995.

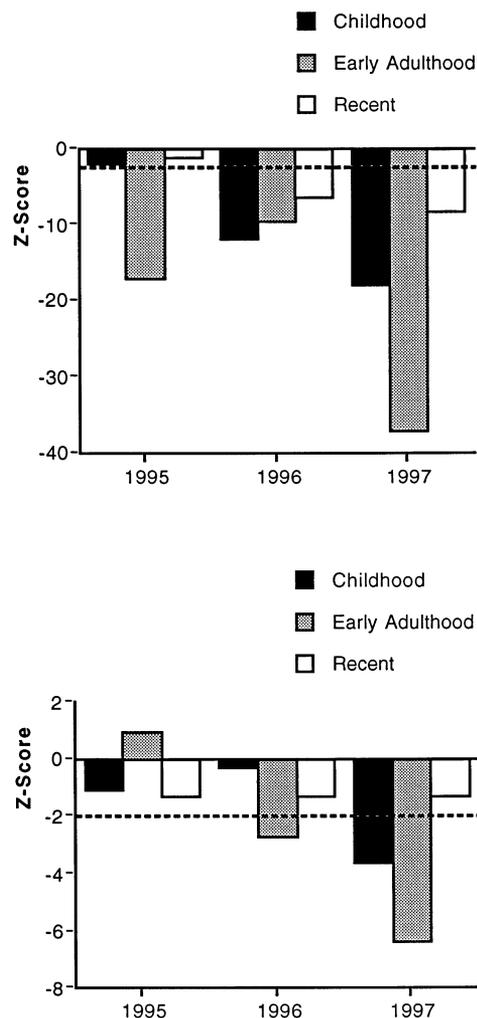


Fig. 3. Plot of D.M.'s performance (expressed as a *z*-score) on personal semantics (top) and autobiographical incidents sections of the AMI over the three testing sessions.

## 8.4. Experiment 1: discussion

At present, the claim that patients with semantic dementia show better retrieval of very recent memories compared with those from the distant past is based predominantly on the single case-report of patient AM [24]. In experiment 1a, we replicated this finding in another patient with semantic dementia, JH, and found a virtually identical pattern to that documented in AM. Both patients showed better preservation of recent autobiographical memories compared with those for the rest of their life, although it should be noted that the quality of JH's and AM's autobiographical memories was significantly impaired compared with controls in all time-periods.

In experiment 1b, we illustrate two further aspects of this neuropsychological phenomenon in a patient with semantic dementia, DM, who presented in the very earlier stages of the disease. On the autobiographical

component of the AMI, DM showed increasing problems over time with retrieval of episodic experiences from childhood and early adulthood. By contrast, his performance on the recent time-period was always within 2 standard deviations of the control group. Interestingly, DM showed a different pattern of performance on the personal semantic subsection of the AMI, with impairment noticeable in the childhood and early adulthood time-periods initially, and in all time-periods by 1997. In the Graham and Hodges [24] study, it was also found that patients with semantic dementia were impaired on the personal semantic component of the AMI regardless of time-period. In fact, DM's performance in 1997, while considerably poorer than the control subjects, was significantly better than the average of the six patients described in the original article. The impairment seen in semantic dementia on the personal semantic component of AMI is presumably caused by word-finding and comprehension difficulties, and is particularly obvious on the personal semantic component because many of the questions require production of names of people and addresses.

In summary, the findings from experiment 1 suggest that the pattern of performance on autobiographical memory described in patient AM [24], was not artefactual and that the evolution of pathology in semantic dementia may affect older autobiographical memories in advance of recently experienced episodes.

### **9. Frontal lobe lesions, strategic retrieval deficits and remote memory**

The aim of the next two experiments was to investigate whether the reverse step pattern observed in semantic dementia is due to defective strategic retrieval processes, which are thought to initiate, direct and order the search of episodic and semantic memory systems [58,64]. There is good evidence that semantic dementia represents the temporal variant of frontotemporal dementia (tvFTD): a high proportion of cases eventually develop the same behavioural changes as seen in patients with fvFTD [6] and voxel based morphometry techniques show a combination of ventromedial frontal and anterior temporal/amygdala atrophy in all cases of semantic dementia so far examined [67]. Given these facts, it is plausible that the reverse step function in semantic dementia is due to concomitant frontal pathology.

To date, the only reported study of autobiographical memory in fvFTD failed to find any evidence of a reverse temporal gradient on tests of remote memory and, with respect to autobiographical memory, commented that the patient's responses 'were lacking in specific detail and were often not time-specific.... All the datable responses (six out of 10) came from his

early life (1930s and 1940s)' [40] pp.825). One has to be cautious, however, about extrapolating from this single case as the patient also showed evidence of anterograde memory impairment, which may have been caused by hippocampal damage.

A more detailed study of the effect of non-progressive frontal lesions on autobiographical retrieval was carried out by Della Sala et al. [16] using the Autobiographical Memory Enquiry [5]. Della Sala et al. found that six out of 16 of the frontal patients examined were impaired on autobiographical retrieval, although they showed a trend towards producing fewer details from the most recent life time-period (late adulthood) compared with childhood and early adulthood. Mangels et al. [59] also investigated remote memory in patients with frontal lobe damage, although this study was based on tests of semantic rather than autobiographical memory, and included public events and famous faces tests. Like the other study, the patients showed an impairment on the retrieval of remote memory, but when this deficit was affected by time, it typically went in the opposite direction to that described in semantic dementia: for example, the patients showed better performance on the famous faces test for the 1940s and 1950s, with poorer performance on more recent decades.

The study of autobiographical memory retrieval in fvFTD is, therefore, extremely relevant to the controversy about autobiographical memory in semantic dementia, as it allows us to test the hypothesis that the reverse-step pattern of remote memory loss in semantic dementia may be due to concomitant frontal lobe damage.

## **10. Experiment 2**

### *10.1. Recruitment and diagnosis of the subjects used in experiment 2*

All patients were recruited from the Memory Clinic at Addenbrooke's Hospital in Cambridge, England with an informant-confirmed history of progressive cognitive change. The patients in the early stage of Alzheimer's disease fulfilled NINCDS-ARDA [62] criteria for probable or possible AD and, in particular, all showed progressive decline on new learning of both verbal and non-verbal material. The patients with semantic dementia met both local and consensus criteria for this variant of FTD [43,73] and were impaired, as measured by performance more than 2 standard deviations below matched control subjects, on tests tapping word production and conceptual knowledge (e.g. Graded Naming Test [61], category fluency, word-picture matching and the Pyramids and Palm Trees Test [46]). Significantly better performance was seen in other

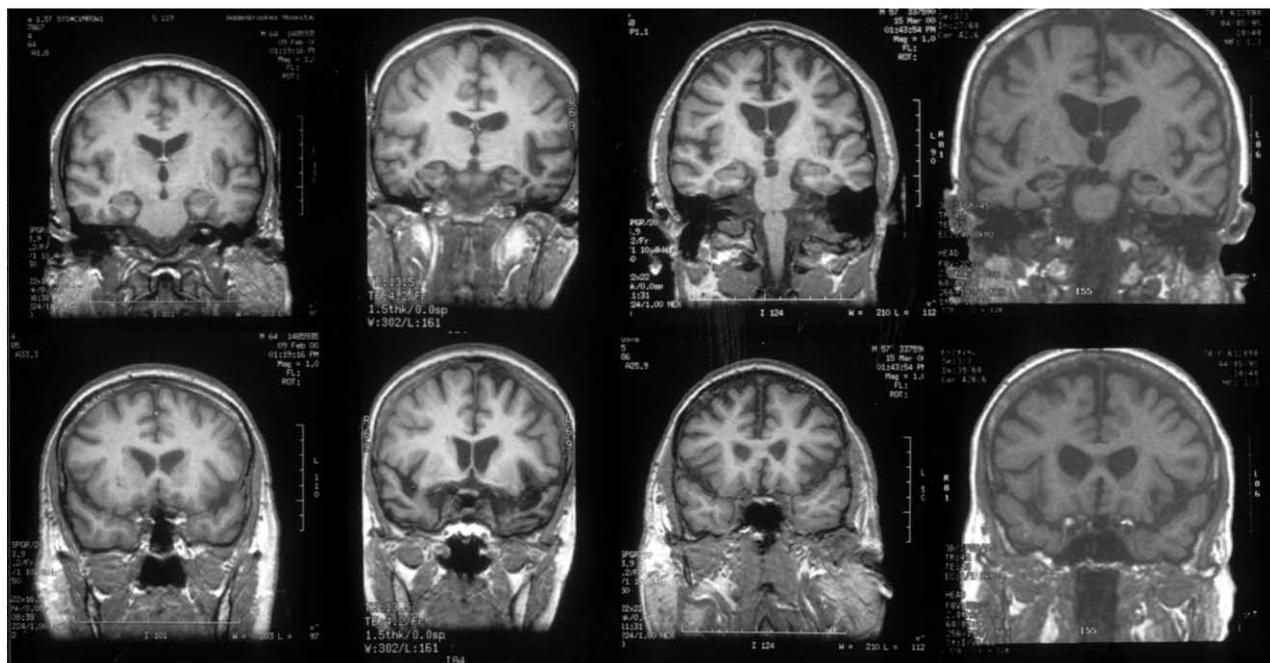


Fig. 4. Coronal T1-weighted MRI scans through the hippocampus (top panel) and temporal pole (bottom panel) in (from left to right) a normal control, aged 64 years; a semantic dementia subject, aged 67 years; a frontal variant frontotemporal dementia subject, aged 57 years; and an Alzheimer's disease subject, aged 78 years.

cognitive domains, such as visuospatial ability and anterograde memory. The fvFTD cases presented with the characteristic 'frontal' behavioural syndrome (e.g. disinhibition, impulsivity, stereotypic or ritualistic behaviours, change of food preference etc) as assessed both on clinical history and quantitatively using the Neuropsychiatric Inventory [13] and met consensus criteria for this variant of FTD [73]. To exclude any cases of fvFTD where there may have been significant coexistent temporal pathology, we excluded any patients who showed significant deficits on any tests included in Hodges' semantic battery [7]. In addition, as the aim of the experiment was to examine autobiographical memory, any patient who was known to confabulate was also excluded from the analyses. In order to determine whether subjects were confabulating, we asked family members, when possible, to confirm the correctness of the patients' responses.

Fig. 4 shows coronally oriented T1-weighted MRI scans from a patient with fvFTD, a patient with semantic dementia and a patient with early Alzheimer's disease at the level of the temporal pole and at the level of the body of the hippocampus. The fvFTD subject shows moderate symmetrical frontal lobe atrophy with relative preservation of the temporal lobes, while the SD subject shows asymmetric temporal atrophy (left worse than right<sup>2</sup>). In the AD subject there was a

degree of generalised cortical and moderate hippocampal atrophy.

## 11. Experiment 2a: a group study based on the AMI in Alzheimer's disease, semantic dementia and frontal variant frontotemporal dementia

### 11.1. Participants

A total of 36 participants took part in this experiment: nine with mild probable AD (six men and three women, mean age  $70.4 \pm 6.4$  years), nine patients with semantic dementia (four men and five women, mean age  $59.4 \pm 5.3$  years), nine with fvFTD (all men, mean age  $59.7 \pm 8.4$  years), and nine control participants (five men and four women, mean age  $59.8 \pm 7.0$  years). A one way analysis of variance (ANOVA) confirmed that there was a significant effect of age across the four groups ( $F(3, 23) = 5.6, P < 0.01$ ). Mann-Whitney analyses revealed that the patients with Alzheimer's disease were significantly older than all other participants (AD vs. control subjects:  $Z = 2.5, P < 0.05$ ; AD vs. SD:  $Z = 3.0, P < 0.01$ ; AD vs. fvFTD:  $Z = 2.5, P < 0.05$ ). There were no significant differences in age between the patients with semantic dementia, patients with fvFTD and the control subjects. Table 2 shows that the patient groups were matched for years of education (approximately 12 years in each group,  $F(2, 24) = 0.54, P = \text{ns}$ ) and duration of illness ( $F(2, 24) = 1.1, P = \text{ns}$ ), which ranged from  $4.3 \pm 1.7$  years (in the

<sup>2</sup> There was a degree of asymmetry in the temporal atrophy of all of the SD cases. All had prominent atrophy of the left temporal lobe. In 3/9 cases in experiment 2a and 3/6 cases in experiment 2b atrophy, however, was more severe on the right than the left.

Table 2  
Demographic and general psychometric data of groups in experiment 2a

	AD ( <i>n</i> = 9)	SD ( <i>n</i> = 9)	fvFTD ( <i>n</i> = 9)	Controls
Age	70.4 (6.4)	59.4 (5.3)	59.7 (8.4)	
Duration of illness	4.7 (1.3)	4.3 (1.7)	6.5 (5.4)	
Years education	12.6 (4.5)	12.2 (5.2)	12.8 (2.2)	
Clinical Dementia Rating Scale	0.94 (0.2)	0.93 (0.5)	0.81 (0.3)	
Mini-Mental State Examination (30)	22.7 (2.8)	21.5 (5.2)	27.4 (2.1)	29 (0.9) <sup>a</sup>
Neuropsychiatric Inventory	NT	NT	31 (16.7)	
<i>Semantic memory</i>				
Category fluency, four living	32.4 (14.6)	15.2 (15.1)	50 (13.7)	60.3 (12.6) <sup>a</sup>
Pyramid and palmtrees-pictures (52)	46.7 (4.6)	36.8 (9.3)	51.3 (0.9)	51.2 (1.4) <sup>a</sup>
<i>Visuospatial</i>				
Rey figure, copy (36)	25.2 (9.3)	32 (5.3)	34.9 (1.1)	34 (2.9) <sup>a</sup>
<i>Episodic memory</i>				
Logical memory, immediate	3.1 (2.1)	3.0 (1.4)	11.1 (4.5)	9.9 (3.9) <sup>a</sup>
Logical memory, delayed	0.1 (0.2)	1.5 (1.9)	7.3 (3.8)	7.8 (3.8) <sup>a</sup>
Rey figure (30 min recall)	2.6 (2.8)	10.3 (7.2)	18.4 (5.4)	15.2 (7.4) <sup>a</sup>
<i>Executive</i>				
Letter fluency (FAS)	31.6 (10.6)	20.7 (13.4)	26.9 (16.6)	45.2 (9.9) <sup>b</sup>
WCST categories (6)	NT	NT	5.1 (1.4)	6

<sup>a</sup> Data obtained from the control panel of the Cognition and Brain Sciences Unit, *n* = 31 volunteers, age = 68.5 ± 7.1;

<sup>b</sup> From the same control panel, *n* = 24 volunteers, age = 69.7 ± 7.8.

semantic dementia group) to 6.5 ± 5.4 years (fvFTD). On the Clinical Dementia Rating Scale [2], the patient groups showed equivalent scores, suggestive of mild dementia. On the MMSE [20], the patients with Alzheimer's disease and the group with semantic dementia were equally impaired with scores of 22.7 ± 2.8 and 21.5 ± 5.2, respectively. The fvFTD subjects score on the MMSE was marginally below that of neurologically healthy control subjects (27.4 ± 2.1; controls 29.2 ± 1.0). It should be noted, however, that this test is not designed to measure the behavioural symptoms which are the predominant feature of this type of dementia and, as such, is known to be insensitive to this diagnosis.

Table 2 also shows performance on a range of general neuropsychological tests in each of the three groups. The AD patients showed very severe impairment on all tests of new learning, scoring 2.6 ± 2.8 (out of a possible 36; control subjects, 15.2 ± 7.4) on delayed recall of the Rey figure [75]; and 0.1 ± 0.2 (control subjects, 7.8 ± 3.8) on delayed recall of a story. The group also showed a significant impairment on category and letter fluency, a mild deficit on the Pyramids and Palm Trees Test [46] and on their copying of the Rey figure. By contrast, the semantic dementia group showed a pervasive deficit on tests of word production (category fluency: 15.2 ± 15.1; controls 60.3 ± 12.6) and tests of semantic knowledge, such as the Pyramid and Palm Trees Test (36.8 ± 9.3; controls 51.2 ± 1.4).

Though the language comprehension deficit seen in the disease makes testing across other domains difficult in this group, they showed relatively preserved visuospatial skills (Rey figure copy: 32 ± 5.3) and non-verbal anterograde memory (Rey figure delayed recall: 10.3 ± 7.2). The fvFTD group performed well on many of the neuropsychological tests, although their mean score on the letter fluency (26.9 ± 16.6; controls 45.2 ± 9.9) was marginally lower than that of the Alzheimer group. On the Wisconsin Card Sorting Test [35] the group scored an average of 5.1 ± 1.4 categories (controls = 6). The most striking impairment seen in the fvFTD group was on the Neuropsychiatric Inventory [13] where the group scored 31 ± 16.7. If control subjects score on this test, they typically achieve only very minor endorsements of disinhibition, irritability and depression subscales.

## 12. Experiment 2a

### 12.1. Method

The three patient groups and the control subjects were administered the Autobiographical Memory Interview [30,54] as described above in experiment 1b. Overall results from the study were analysed using a 4 (groups: AD, semantic dementia, fvFTD and controls) by 3 (life periods: childhood, early adulthood, and recent life) mixed measure ANOVA. Analyses of each

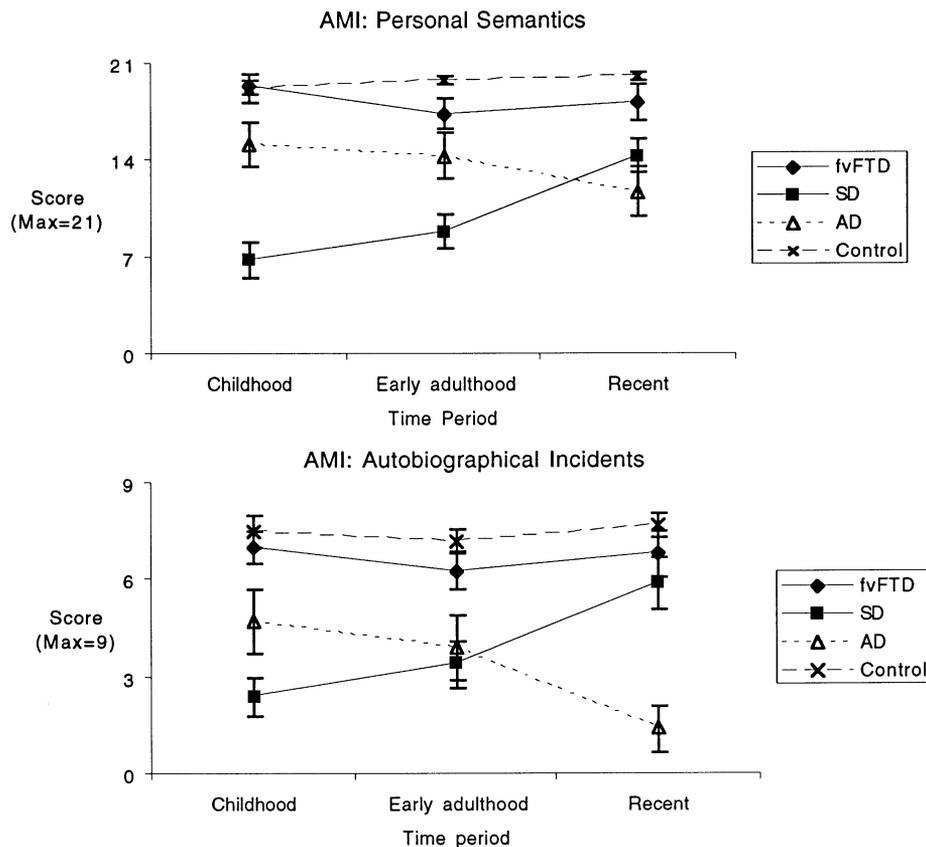


Fig. 5. Results of AMI group study (experiment 2a): personal semantics (top) and autobiographical incidents (bottom). Note that unlike the SD and AD groups, there is no evidence of a gradient in fvFTD in either section.

subject group's performance over the three time-periods were carried out using one-way repeated measure ANOVA's and differences between time-periods within a group studied using Mann–Whitney analyses.

## 12.2. Results

Fig. 5 shows the results for the personal semantic and autobiographical components of the AMI. In the personal semantic section, the ANOVA revealed a non-significant effect of time-period ( $F(2, 64) = 0.73, P = 0.49$ ), but a significant effect of group ( $F(3, 32) = 18.3, P < 0.001$ ). There was a significant time-period by group interaction ( $F(6, 64) = 8.2, P < 0.001$ ). In three of the groups (AD, fvFTD and control subjects), one way ANOVA's showed a non-significant difference between the three time-periods (AD:  $F(2, 24) = 1.0, P = 0.37$ ; fvFTD:  $F(2, 24) = 0.91, P = 0.41$ ; controls:  $F(2, 24) = 0.02, P = 0.98$ ). By contrast, a significant effect of time-period was found in the patients with semantic dementia ( $F(2, 24) = 11.4, P < 0.001$ ): Mann–Whitney analyses of the temporal effect showed that the performance of the patients with semantic dementia was significantly better on the most recent time-period com-

pared with childhood ( $Z = 3.1, P < 0.01$ ) and early adulthood ( $Z = 2.7, P < 0.01$ ); their performance on the childhood and early adulthood components, however, was equivalent ( $Z = 0.87, P = 0.38$ ).

For the autobiographical component of the AMI, see Fig. 5, there was also a highly significant main group effect ( $F(3, 32) = 13.6, P < 0.001$ ) but no effect of time-period ( $F(2, 64) = 0.37, P = 0.69$ ). There was, however, a significant interaction between time-period and group ( $F(6, 64) = 6.9, P < 0.001$ ). As described above for the personal semantic component, the only patient group to show a significant effect of time-period were the semantic dementia patients ( $F(2, 24) = 6.2, P < 0.01$ ). The other three groups, (AD, fvFTD and control participants) showed no effect of time ( $F(2, 24) = 2.3, P = 0.12$ ;  $F(2, 24) = 0.40, P = 0.67$ ;  $F(2, 24) = 0.92, P = 0.41$ , respectively). Mann–Whitney analyses revealed that the patients with semantic dementia scored more highly in the recent time-period compared with childhood ( $Z = 2.6, P < 0.01$ ) and early adulthood ( $Z = 2.1, P < 0.05$ ). There was no significant difference in performance between childhood and early adulthood ( $Z = 1.1, P = 2.6$ ).

Table 3  
Demographic and general psychometric data of groups experiment 2b

	AD	SD	fvFTD	Controls
Age	74.8 (5.1)	61.0 (4.0)	55.8 (7.5)	
Duration of illness	4.7 (2.3)	3.5 (2.3)	5.3 (2.3)	
Years education	11.8 (4.1)	10.3 (1.4)	13.2 (2.4)	
Clinical Dementia Rating Scale	1.1 (0.5)	1.0 (0.6)	0.9 (0.4)	
Mini-Mental State Examination (30)	23.7 (3.5)	22.0 (5.7)	28.3 (1.4)	29 (0.9) <sup>a</sup>
Neuropsychiatric Inventory	NT	NT	40 (18.0)	
<i>Semantic memory</i>				
Category fluency, four living	39.0 (22.3)	15.8 (15.8)	48.8 (15.1)	60.3 (12.6) <sup>a</sup>
Pyramid and palmtrees-pictures (52)	46.0 (4.8)	37.5 (12.0)	51.5 (0.8)	51.2 (1.4) <sup>a</sup>
<i>Visuospatial</i>				
Rey figure copy (36)	27.9 (5.0)	30.0 (5.5)	35.0 (1.3)	34 (2.9) <sup>a</sup>
<i>Episodic memory</i>				
Logical memory (immediate)	2.6 (1.9)	3.0 (1.2)	11.3 (2.5)	9.9 (3.9) <sup>a</sup>
Logical memory (delayed)	0.1 (0.1)	0.7 (0.5)	7.6 (3.0)	7.8 (3.8) <sup>a</sup>
Rey figure (30 min recall)	1.5 (2.6)	10.5 (9.5)	20.5 (5.2)	15.2 (7.4) <sup>a</sup>
<i>Executive</i>				
Letter fluency (FAS)	30.8 (20.2)	19.8 (10.1)	32.3 (17.6)	45.2 (9.9) <sup>b</sup>
WCST categories (6)	NT	NT	5.0 (1.6)	6

<sup>a</sup> Data obtained from the control panel of the Cognition and Brain Sciences Unit,  $n = 31$  volunteers, age =  $68.5 \pm 7.1$ .

<sup>b</sup> From the same control panel,  $n = 24$  volunteers, age =  $69.7 \pm 7.8$ .

### 13. Experiment 2b: performance on the free-recall Crovitz test in patients with Alzheimer's disease, semantic dementia and frontal variant FTD

#### 13.1. Participants

A total of 18 patients, six in the early stages of Alzheimer's disease (four males, two females, average age  $74.8 \pm 5.1$ ), six with semantic dementia (three males, three females, average age  $61.0 \pm 4.0$ ) and six with frontal variant FTD (all male, average age  $55.8 \pm 7.5$ ) and ten control subjects (five men and five women, average age  $65.4 \pm 4.6$ ) took part in experiment 2b. The same selection criteria as described for experiment 2a were applied to the patients in this study and as for the earlier study, there was no significant differences in duration of illness (AD:  $4.7 \pm 2.3$  years; SD:  $3.5 \pm 2.3$  years; fvFTD:  $5.3 \pm 2.3$ ;  $F(2, 15) = 0.99$ ,  $P = 0.39$ ) or years education (AD:  $11.8 \pm 4.1$ ; SD:  $10.3 \pm 1.4$ ; fvFTD:  $13.2 \pm 2.4$ ;  $F(2, 15) = 1.5$ ,  $P = 0.26$ ). There was, however, a significant effect of age across the three patient groups,  $F(2, 15) = 17.7$ ,  $P < 0.001$ : the AD patients were significantly older than the other two patient groups ( $Z = 2.9$ ,  $P < 0.01$ ). There was no significant difference in age between the patients with semantic dementia and the fvFTD group ( $Z = 1.1$ ,  $P = 0.26$ ). The overall pattern of performance on neuropsychological tests was similar in patients involved in this experiment to the groups described in experiment 2a (see Table 3): the AD patients showed marked deficits on tests of verbal and non-verbal memory, the semantic

dementia group on tests of semantic knowledge and the fvFTD patients on the Neuropsychiatric Inventory [13].

#### 13.2. Method

For this experiment, the three patient groups and control subjects were administered a free-recall version of the Crovitz test [12]. Participants were given 20 cue-words (e.g. train, book, car etc.) and asked to produce a detailed and time-specific autobiographical memory in response to each word. The memories could be from any time-period in the patient's life and, in order to elicit as much detail as possible, there was no time limit and participants were prompted if their response was poor. Prompts did not, however, provide the subject with example memories or cue the subject towards recalling an episode from any particular time-period. For example, the most commonly used prompts were, "Can you tell me more about that?" or "Can you be more specific?"

All the memories provided by the patients and control subjects were scored by two raters, one of whom was naive to the purpose of the experiment. The scoring system was based on that described in Graham and Hodges [24] (i.e. the same method as experiment 1a), in which a score of 0–5 is given depending upon whether the memory is detailed and describes a specific event. Once the memories had been scored by both raters, the memories were sorted into two groups: generic versus specific. A memory was considered a generic response if it could not be classified as the recollection of a single,

time-specific autobiographical experience. For example, the following memory produced to the word, 'train' is clearly a repeated event, "I used to take the train to work every morning at 07:30 hours". By contrast, the following, "For our summer holiday one year, we took the train to Blackpool. I remember we had to be up very early in the morning...", must have only happened once in the subject's life and can be accurately pinned down to a particular time and place in the past (the essence of episodic recall). As the aim of this study was to determine whether patients with different neurodegenerative conditions showed a preference for retrieving memories from the recent or distant past (at least compared with control subjects), we were interested in making sure that we compared only the responses that could be considered truly episodic in quality. For the purposes of the study, therefore, the generic memories were not analysed further.

To obtain a measure of the effect of time on the free-recall Crovitz task, the number of memories recalled from the first three decades of life was compared with the number recalled from the year prior to testing. These time periods were chosen so that we could maximise the possibility of finding effects of time in the patient groups. More specifically, that the patients with semantic dementia and fvFTD produced more recent memories than remote episodes, while the patients with Alzheimer's disease and the control subjects retrieved more from the remote time-period compared with the recent. A further advantage of this method of analysis, compared with inspecting the profile of memory production over time [19], is that patients of varying ages can be compared directly (e.g. patients in the early stages of AD, who are typically older, can be contrasted with patients with FTD, who are typically younger). Total number of specific memories recalled (irrespective of time period) was also analysed to ensure that there were no significant differences across group in the number of autobiographical memories.

### 13.3. Results

The control subjects produced  $17.7 \pm 0.7$  specific memories from 20 cue-words. By contrast, all patient groups produced fewer specific autobiographical memories and, therefore, more generic responses (see Fig. 6): fvFTD,  $13.0 \pm 3.8$ ; SD,  $10.5 \pm 3.4$ ; and AD,  $6.5 \pm 3.8$ . A one-way ANOVA confirmed that there was a significant difference in the number of memories produced by the groups ( $F(3, 24) = 19.8$ ,  $P < 0.001$ ). Mann-Whitney analyses confirmed that all three patient groups produced significantly fewer specific memories than the control subjects (all groups,  $Z = 3.2$ ,  $P < 0.001$ ). In terms of the patient groups, there was no significant difference in the number of memories produced by the fvFTD and semantic dementia patients ( $Z = 1.3$ ,  $P =$

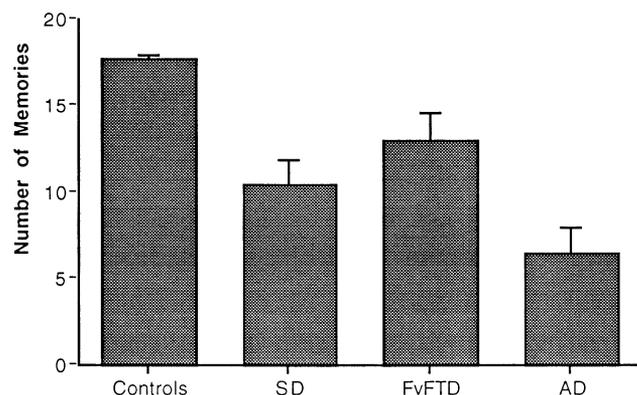


Fig. 6. Total number of specific memories produced by each group on the 20 item Crovitz test (experiment 2b): maximum score = 20.

0.17). The number of specific memories seen in the AD patients, however, was significantly fewer than the fvFTD group ( $Z = 2.4$ ,  $P < 0.05$ ) and showed a trend toward significance when contrasted with the semantic dementia patients ( $Z = 1.7$ ,  $P = 0.09$ ).

Fig. 7 shows the data analysed using our remote-recent index. More specifically, the number of memories dated to the last year prior to testing was subtracted from the number dated to the first three decades. A positive score means that more memories were produced for the older time-period, while a negative score represents an excess of memories from the previous year. The figure illustrates that the patients with semantic dementia produced more memories from the recent compared with the remote time-period (mean recent-remote index =  $-4.4 \pm 1.5$ ) compared with the other patient groups (fvFTD,  $4.3 \pm 1.9$ ; and AD,  $2.4 \pm 0.5$ ) and the control subjects (control subjects,  $4.3 \pm 1.7$ ). A one-way ANOVA, based on the number of memories produced in the recent time-period divided by the total

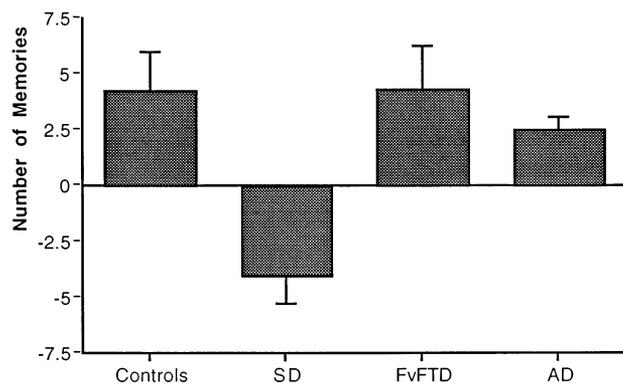


Fig. 7. Recent-remote memory index (experiment 2b). The number of memories produced from the previous year of each subject's life was tallied and then subtracted from those produced from the first 3 decades. The bars represent this remote/recent memory difference: a positive score indicates that more memories were produced from the remote time period while a negative score indicates more memories from the recent time period.

number of specific memories produced overall, was highly significant ( $F(3, 24) = 10.1$ ,  $P < 0.001$ ) and Mann–Whitney analyses confirmed that the semantic dementia group produced significantly more recent memories than the other groups (all comparisons,  $Z = 2.7$ ,  $P < 0.01$ ). By contrast, the fvFTD and the AD groups were not significantly different from each other ( $Z = 0.33$ ,  $P = 0.74$ ) or the control subjects (FTD vs. controls:  $Z = 0.88$ ,  $P = 0.38$ ; AD vs. controls:  $Z = 1.2$ ,  $P = 2.5$ ).

#### 13.4. Experiment 2: discussion

The results of experiment 2 were not consistent with Nadel and Moscovitch's [71] hypothesis that the reverse-step function seen on tests of autobiographical memory in semantic dementia is due to impaired strategic retrieval processes. On the AMI (experiment 2a), the frontal patients showed no evidence of a temporal gradient and their performance, as a group, did not differ from that of age-matched controls. It is possible, however, that the exceptionally good performance of the fvFTD patients in experiment 2a masked a reverse step function akin to that seen in semantic dementia. This explanation seems unlikely, however, as a subgroup of the frontal patients ( $n = 6$ ) tested in experiment 2a showed a significant problem with autobiographical retrieval in experiment 2b, producing fewer specific memories than control subjects.

The most important result from experiment 2b, however, relates to the memory difference score, in which the number of specific memories from the first three decades was compared with the number of specific memories from the year prior to testing. A positive value, reflecting the production of more memories in the earlier time-period compared with the most recent, was found in the fvFTD, early AD and control group. The opposite pattern is clearly documented in the semantic dementia patients, with significantly more memories produced in the recent time-period. It is noteworthy in this experiment, that the total number of memories produced (regardless of time period) for the semantic dementia and fvFTD groups was relatively similar, as well as significantly worse than controls.

It is important to note that the findings from experiment 2b do not contradict the view that damage to frontal lobe structures may cause some impairment to strategic retrieval per se [64], as the fvFTD patients did show an overall autobiographical memory deficit. It is difficult, however, to attribute a direct causal relationship between frontal damage, strategic retrieval deficits and poor autobiographical memory in this population as other symptoms of the frontal syndrome, such as apathy or impulsivity, may have contributed to

the poor performance on the test. Even if impaired strategic retrieval is the cause of the autobiographical deficit seen in fvFTD, however, experiment 2b reveals that this type of processing deficit does not necessarily result in better retrieval of recent memories compared with those from the more distant time-period.

In experiment 2, an AD group was included as an example of the prototypic amnesic syndrome associated with mesial temporal pathology. Although they scored better on remote, as opposed to recent, time periods of the AMI, this result did not reach statistical significance. The most striking feature of the AD group is their poor performance overall, when compared with fvFTD and SD, in experiment 2 making it difficult to draw strong conclusions from this group. The presence or absence of a significant gradient might depend critically upon the exact stage of disease and the number of patients studied (Section 14.7).

The results from our study, particularly from experiment 2b, are consistent with recent functional neuroimaging studies [58] and other investigations in non-progressive patients with frontal damage [16,40,59]: Della Sala et al. observed deficits that were either flat or typically in the opposite direction to that described in semantic dementia. A recent study which utilised the AMI in, among others, a group of subjects with large frontal lesions secondary to yttrium implants, used to treat intractable affective disorders, also found no effect of time-period [53]. Our investigations suggest, therefore, that while patients with progressive frontal lesions, like many with non-progressive pathology, may show problems with autobiographical retrieval, typically this pattern is not affected by the age of the memories. So, while it is plausible that strategic retrieval deficits due to frontal damage can result in autobiographical memory problems, the studies contradict the view that the memory deficit is significantly affected by the age of the memory.

## 14. General discussion

The experiments described in this article addressed two problems with the existing data on autobiographical memory in semantic dementia, namely (a) lack of replicability across patients; and (b) the possibility that the deficit documented in autobiographical memory is confounded by strategic retrieval difficulties. The results reveal that it is unlikely that either of these two factors is the sole explanation for the better preservation of recent memories, compared with more distant memories, in patients with semantic dementia.

A further issue raised by Moscovitch and Nadel [66], which was not tested here, is worth discussing. Both the AMI and Crovitz based tests are highly verbally de-

manding, in the sense that subjects are asked to produce and discuss personal events from their past. It is possible that the difficulties with language production and single-word comprehension seen early in semantic dementia could result in the poor performance seen on autobiographical memory tests (and even effects seen across time).

#### 14.1. *A linguistic deficit rather than a memory impairment?*

There are various levels at which linguistic problems could interfere with performance on autobiographical memory tests. First, the patient must be capable of understanding the cue that is being given by the experimenter in order to retrieve a suitable memory. In the AMI, different cues are provided in different time-periods (e.g. childhood-recall an incident while at secondary school; early adulthood-recall an incident from your wedding). Testing autobiographical memory in this way could, theoretically, result in a skewing of performance if a patient did not understand some cues, but was capable of comprehending others. In the detailed Crovitz test used in AM [24] and JH, however, the same words were given as cues in all time-periods. It is unlikely, therefore, that better performance on the recent time-period reflects poor comprehension of cue-words, as this would effect all time-periods equally.

It is clear, however, that restricted expressive vocabulary almost certainly had an impact on AM's and JH's ability to produce detailed autobiographical memories. Both patients showed a significant degree of impairment, at least compared with control subjects, across all time-periods, a pattern which must be related to their anomic difficulties. Despite this, AM and JH still showed better recall of recent personal events in the most recent time-period, an improvement which was related to the production of events with greater episodic quality, as measured by the transition from episodes which have frequently occurred (e.g. eating breakfast) to those that are unique (e.g. the time you broke your leg). This improvement in scores in the most recent time-period seems unlikely to be related to linguistic factors, unless the patients were using more and/or better vocabulary in the recent time-period.

This proposal does not mean, however, that testing patients with non-verbal stimuli, such as photographs, or using recognition memory-based tests would not improve overall autobiographical recall. Moscovitch and Nadel [66] and Westmacott et al. [90] provide some evidence in support of this view by describing a patient with semantic dementia who showed better retrieval of personal memories when tested with pictures compared

with verbal labels<sup>3</sup>. EL showed relatively good autobiographical retrieval for photographs regardless of the age of the event depicted in the photograph. It should be noted, however, that the criteria used to score the quality of the memories are likely to be relatively easily satisfied and are, therefore, not as stringent a measure of episodic memory as used in other studies [24]. For example, a patient could achieve a score of approximately 80% (EL averaged 90% across all time-periods) if the memory included the phrase, "I remember", mentions a season or year (which is possibly easily detected from the photograph), notes the ongoing activity (e.g., talking, playing sport etc., again often inferable from the photograph), and conveys an emotion, such as smiling or laughing (notably patients with semantic dementia are often overly garrulous in their emotional responses). The only measure, therefore, which seems truly difficult and epitomises autobiographical memory is 'narrative structure', whereby the patient has to describe a sequence of events. In their article, Westmacott et al. admit the limitations of their scoring scheme noting that, "Our point, however, is not to argue that EL's remote and recent verbal episodic memory is normal: we believe it is probably not. Rather, we wish to demonstrate that he retains a great deal of autobiographical memories of his remote past and, insofar as our assessment techniques permit us to judge, they are not abnormally less detailed than his recent memories".

Westmacott et al.'s [90] study illustrates that the method used to score episodic quality in tests of autobiographical memory can have a dramatic effect on the interpretation of the memory deficit. The degree of overall episodic memory impairment in semantic dementia remains unclear but we would maintain that Westmacott et al.'s use of a simple scoring system is likely to obscure any effect of time for at least two reasons. First, the lack of control data means that it is not possible to determine whether autobiographical memory is impaired from non-verbal cues; and second, the patient performed close to ceiling on all time-periods making it difficult to test for significant differences between recent and remote memories.

It is clear, therefore, that the issue of better non-verbal access to autobiographical memory in semantic dementia requires further investigation: to our know-

<sup>3</sup> As an aside, it is interesting to note that AM was also tested on autobiographical retrieval from family photographs. These photographs ( $n = 24$ ) came from different time periods in his life (e.g., weddings, holidays, visits from friends etc.), although time was not systematically manipulated. AM showed exceptionally poor recall of autobiographical incidents from these photographs; the only good memory related to a recent visit from two friends. This data, albeit anecdotal, contrasts with the pattern reported in the case of EL [90], suggesting that the benefit of providing non-verbal cues when testing autobiographical memory may not generalise across all patients with semantic dementia.

ledge there have been no systematic studies of autobiographical memory across modality in neuropsychological patients. The reasons for this are simple: it is extremely difficult to investigate a patient's autobiographical history using non-verbal cues, such as photographs, because it relies on access to family albums and to people who knew the patient both in childhood and in later life. Additionally, such studies are extremely time-consuming and serious problems arise in obtaining adequate control data. In other domains of memory, such as semantic memory, it is possible to investigate modality-specific deficits because the stimuli comprising the tests are not personally specific to each individual patient.

In light of Moscovitch and Nadel's data, it is useful to review briefly a recent study which investigated modality-specific semantic memory deficits in semantic dementia [55]. Nine patients were asked to define concrete concepts either from presentation of a picture of the concept or from its spoken name. The study found a significant concordance between performance, as measured by production of core definitions, on items presented as pictures and words. A more detailed investigation of the attributes produced to both pictures and words revealed that four out of seven patients with greater left temporal lobe damage than right produced significantly more correct information in response to pictures, but that all those patients with more right temporal lobe atrophy compared with left ( $n = 2$ ) produced more correct information in response to words. Looking at the individual patients, it is interesting to note that AM, the patient who showed poor autobiographical retrieval when cued with words or family photographs, was one of the patients who showed no significant advantage for words or pictures in the definitions task. Lambon Ralph et al.'s results suggest that we should be cautious when interpreting better performance on non-verbal, compared with verbal, tests; this pattern may not be evidence in support of normal access to autobiographical, or semantic, memory, and factors such as better recall in the recent time-period may still be evident regardless of modality of testing.

It is also important to specify exactly what is meant by non-verbal access to autobiographical memory. In Lambon Ralph et al.'s study [55], performance on words versus pictures of the same semantic concepts was compared. A similar test of autobiographical memory would be comparison of autobiographical retrieval to a cue word (e.g. wedding) compared with a picture of the concept (e.g. two unfamiliar people getting married). In the reports of Moscovitch and Nadel [66] and Westmacott et al. [90], their subject with semantic dementia was provided with familiar family photographs, some of which depicted events from the patient's past. The additional confound in this method is that the experimenter has provided a highly specific retrieval cue (the patient's own wedding), thereby reducing the difficulty

of the task (compared with other autobiographical memory tests) and aiding the patient's search for a suitable episodic event.

#### *14.2. Reconciling the data from semantic dementia with the multiple-trace model of memory consolidation?*

We have shown that none of the explanations proposed by Moscovitch and Nadel [66] seem to provide a plausible account for the reverse step function in semantic dementia. It is possible, however, to reconcile our data with the multiple-trace model of memory consolidation. Moscovitch and Nadel [66] suggest a plausible avenue based upon the suggestion by Rubin and Greenberg [81] that visual imagery plays a critical role in autobiographical recollection, and that damage to our store of visual information might result in a focal retrograde amnesia for personal events. More specifically, they suggest that the activation of an autobiographical experience proceeds in a cascade manner, noting that 'a train whistle activates the auditory cortex, which in turn activates a pattern of firing in visual cortex which may create the image of meeting someone at the train station' (p5413). According to this model of autobiographical recollection, the loss of one component of the representation, such as visual information, would result in an inability to activate other aspects of the memory. In support of this hypothesis, Rubin and Greenberg found that five of their eleven cases with damage to visual regions had a severe retrograde amnesia (most without a temporal gradient) with only mild to moderate anterograde deficits.

Moscovitch and Nadel [66] extended this theoretical view to semantic dementia proposing that semantic memory, like vision, is part of the network which comprises our past personal experiences and is critical to gaining access to the memory trace. Loss of semantic memory, therefore, may result in patients showing a similar pattern to that seen in the visual memory deficit amnesia cases described by Rubin and Greenberg. As clearly documented in AM [24] and now JH (experiment 1a), this neuropsychological prediction is strikingly accurate in patients with semantic dementia, who show a significant retrograde amnesia for most of their life (except the most recent two or so years) with no obvious temporal gradient.

#### *14.3. Does loss of semantic knowledge invariably lead to a deficit in autobiographical memory?*

The proposal outlined above predicts that it should be rare to find cases in the literature who show good autobiographical memory retrieval in the context of impaired semantic knowledge. There are, however, a few patients who seem contradictory to Nadel and Moscovitch's theory [15,17,18,33,51]. The opposite contrast,

preservation of conceptual knowledge in the context of retrograde autobiographical memory loss, is much more strongly documented [19,47,49,52,57].

De Renzi et al. [15] described a patient who suffered left posterior temporal lobe damage (including the hippocampus) after encephalitis. The subject, LP, showed a similar neuropsychological pattern of impairment to that seen in semantic dementia: deficits on tests tapping semantic memory (e.g. naming, word-picture matching, definitions to nouns, sorting at increasingly specific semantic levels etc.), with relatively better performance on visuoperceptual, problem-solving and syntactic tasks. Notably, however, she showed impairment on verbal and visual anterograde memory tests, although spatial learning was better. On remote semantic memory tests, such as producing information about famous people or events, she was poor. By contrast to this severe impairment to all aspects of semantic knowledge, LP showed good recall of personal events from prior to her disease. De Renzi et al. note that on a 20 item questionnaire about LP's past, "her responses were precise and circumstantial and never revealed uncertainty or contradicted what was reported by her relatives". They continued, "Her husband had noticed this discrepancy in memory function and was so amazed by it as to wonder whether she did not forget on purpose" (p587).

Kitchener and Hodges [51] reported a similar neuropsychological pattern in the context of progressive deterioration of the right temporal lobe. Their subject, VH, showed a profound deficit on tests of famous people and events, and to a lesser extent on tests of general semantic knowledge (in particular, naming, category fluency and the pictorial version of the Pyramid and Palm Trees Test [46]). Her autobiographical memory, however, was preserved and she could produce information about personally relevant events and people (a pattern similar to Kapur et al.'s [49] case).

These single-case studies reveal that retrieval of personal events from the past need not be significantly affected by a semantic memory deficit, a view which at first glance seems to conflict with Moscovitch and Nadel's [66] proposal about the cause of retrograde amnesia in semantic dementia. It is important to note, however, that LP and VH had only unilateral temporal lobe damage at time of testing: LP to the inferior and anterior part of the left temporal lobe, including the hippocampus and adjacent structures, VH to the right temporal lobe, not involving medial temporal regions, with milder involvement of the left. A recent study by Eslinger [17] clearly demonstrates that unilateral lesions of the temporal lobe result in significantly less impairment on the AMI [54] than bilateral temporal lobe lesions. Eslinger noted that, "Significant loss of autobiographical incidents...requires bilateral disruption of frontal and/or temporal mechanisms". (p494).

The data from semantic dementia seems consistent with this literature: many of the patients that have shown a significant impairment to autobiographical memory have had bilateral atrophy to the temporal lobes. The only patient who showed a much milder deficit and little evidence, at least initially, of the reverse step-like pattern, showed selective left temporal lobe damage [28]. It is clear that further work on memory consolidation will need to characterise the relationship between autobiographical memory deficits, conceptual knowledge and the neuroanatomical regions involved in memory acquisition and storage.

#### *14.4. The sting in the tail: what is the hippocampus doing in the multiple-trace model?*

There is one aspect of these explanations, particularly with reference to the multiple-trace model, which remains confusing. To explain the retrograde amnesia in semantic dementia, Moscovitch and Nadel [66] suggest that semantic memory is a critical component of autobiographical memory and is needed to gain access to older memory traces, which have a significant semantic component. As discussed above, this theoretical interpretation is based on Rubin and Greenberg's study [81] and the idea that an autobiographical memory is retrieved via a cascade method of activation (i.e. hearing the voice of a friend on the radio may activate a visual memory of the time you went punting with them and fell in the River Cam). Loss of one aspect of the memory (e.g. visual information or conceptual knowledge) breaks the chain of links and arrests the progression of the activation, resulting in poor autobiographical memory retrieval.

Turning to the multiple-trace model, however, Moscovitch and Nadel [66] note that, 'the medial temporal component (of the medial temporal-neocortical ensemble), which may provide the spatial context of the experience, acts as a pointer or index to the neocortical elements needed to provide the detailed content of the experience'. (p87). This view leads one to wonder why, even in circumstances where there is a loss of part of the chain linking all the components of an autobiographical experience (visual or semantic memory loss), the hippocampus is not able to activate the non-damaged parts of the episodic experience? In Rubin and Greenberg's paper, it is clear that the authors interpret their patients' memory problems in terms of the standard model, whereby the neocortically-based memory traces are hippocampally-independent. In the multiple-trace model, however, the hippocampus stores some aspects of the autobiographical memory and is necessary for recovering these events regardless of how long ago they were experienced.

Moscovitch (personal communication) suggests that Rubin and Greenberg's results, and additionally those

from semantic dementia, can be explained in terms of the multiple trace model, if one adopts the view that some types of information have preferential access to the hippocampal trace. Given that our autobiographical experiences are so strongly visual, it seems reasonable that a loss of visual representations would have a devastating impact on autobiographical memory regardless of which model of memory consolidation one chooses to believe. While this hypothesis explains visual memory-deficit amnesia [81], it is not clear how this view could be extended to semantic memory. Moscovitch and Nadel would have to propose that semantic knowledge, like visual information, also has preferential access to the hippocampal trace, a view which weakens the power of the model for explaining both types of memory deficit.

#### *14.5. Why do patients with semantic dementia show better recall of more recent memories compared with older memories?*

Moscovitch and Nadel [66] propose that the medial temporal regions, which are relatively spared early in the disease, allow the binding of new memory traces based on neocortical areas, perhaps subserving visual areas, which are not pathologically affected. Studies of visual recognition memory in semantic dementia seem to provide some evidence in support of this theory. Normal recognition memory has been documented in semantic dementia (for stimuli which are still known to the subject and for items which are no longer known) when the target item (e.g. a coloured picture of a familiar object) in a recognition memory test was identical to an item that had been seen previously at study [23,29]. Poor recognition memory was found, however, when a perceptual manipulation was introduced between study and test for 'unknown' items (e.g. a round-dial telephone was replaced with a push-button phone), but not for stimuli which were still known to the patient. These data suggest that patients with semantic dementia are able to maximise the use of perceptual information available at encoding, even in circumstances where the semantic knowledge they possess about a concept is severely impoverished. The relatively better performance seen on autobiographical memory tasks in the very recent time-period presumably reflects a similar mechanism.

#### *14.6. Semantic dementia and the standard model of memory consolidation: the same story?*

Having discussed how the multiple trace model can account for the remote memory data seen in patients with semantic dementia, it is interesting to reconsider these results in terms of the standard model of memory consolidation, which initially seemed to provide a better explanation for the phenomenon [24,84]. In this view, poor retrieval of older autobiographical experiences

reflects progressive damage to connections binding autobiographical memories within the neocortex, while the better preservation of recent events is due to binding of new experiences via undamaged areas within the neocortex. In some senses, therefore, closer inspection of the two models of memory consolidation, at least with respect to the data from semantic dementia, reveals very similar explanations for the pattern seen in the disease. If there is any significant differences in the way the models explain the data it seems to boil down to poor access to the memory trace [66] or loss of existing stored memories [22]. At present, it is not clear whether these subtle differences (i.e. access versus storage) will turn out to be theoretically important to the models and/or the interpretations of the researchers who have proposed them.

#### *14.7. Further questions*

Two additional issues were raised by our investigation. The first relates to whether patients with Alzheimer's disease show effects of time in autobiographical memory retrieval. In the original Graham and Hodges [24] paper, the patients with AD showed a significant effect of time, with better recall of more remote compared with recent memories. In experiment 2a, however, any advantage for childhood memories did not reach significance in our AD group. The presence or absence of a temporal gradient in AD is highly controversial, and theoretically relevant to the models of memory consolidation discussed here. Further studies in AD, which take into account disease heterogeneity, should be aimed at addressing this controversy.

The second, related, topic refers to the mapping between of neuroanatomical damage and cognitive deficits in humans. Recent investigations have found evidence of significant atrophy of medial temporal lobe regions in semantic dementia and AD [9,21,82]. Although the extent of atrophy in both patient groups was not large, and there was a more asymmetrical pattern in SD compared with AD, it was notable that the two patient populations showed similar levels of atrophy to the hippocampus [9,21]. If we are to believe that the cognitive patterns reported here for SD and AD are real, it remains to be solved, by proponents of both the standard and multiple trace models of memory consolidation, what role the hippocampus is truly playing in human memory.

## **15. Summary**

In this study, we have provided further evidence that patients with semantic dementia show better recall of very recent personal memories compared with those from the more distant past, replicating the data from Graham and Hodges [24]. We have also demonstrated that it is

unlikely that this effect of time on autobiographical memory is due to strategic retrieval deficits: a group of patients with fvFTD, with prefrontal cortex damage, showed no significant effects of time in their memory retrieval.

In Graham and Hodges' [24] paper, it was proposed that the 'step-like' performance seen on tests of autobiographical memory in semantic dementia is support for a model of memory consolidation in which the hippocampal complex plays a time-limited role in the acquisition and retrieval of recent memories. In the discussion here, however, we debate whether the data from semantic dementia can be accommodated by the model of memory consolidation proposed by Nadel and Moscovitch [71], and conclude that both theories invoke similar explanations, with subtle psychological differences, for both the poor retrieval of older autobiographical memories and the good acquisition of new episodes: a loss of semantic memory contributing to the former and good perceptual learning to the latter. Furthermore, we reviewed the literature on patients with preservation of autobiographical memory in the context of poor conceptual knowledge and find no evidence to date that is contradictory to the proposed explanation. At present, therefore, the data from semantic dementia are concordant with both models of memory consolidation and further studies in patients with semantic memory loss, and amnesia, are necessary before we can discard one of the theories in favour of the other.

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