Episodic memory: insights from semantic dementia

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Semantic dementia, also known as the temporal lobe variant of fronto-temporal dementia, results in a progressive yet relatively pure loss of semantic knowledge about words, objects and people, and is associated with asymmetric, focal atrophy of the antero-lateral temporal lobes. Semantic dementia provides a unique opportunity to study the organization of long-term memory particularly since initial observations suggested sparing of episodic memory. Recent studies reveal, however, a more complex but theoretically revealing pattern. On tests of autobiographical memory, patients with semantic dementia show a 'reverse step function' with sparing of recall of events from the most recent 2 to 5 years but impairment on more distant life periods. Anterograde recognition memory for visual materials is extremely well preserved, except in the most deteriorated cases, although performance is heavily reliant upon perceptual information about the studied stimuli, particularly for items that are no longer known by the subjects. On tests of verbal anterograde memory such as word learning, performance is typically poor even for words which are 'known' to the patients. A source discrimination experiment, designed to evaluate familiarity and recollection-based anterograde memory processes, found that patients with semantic dementia showed good item detection, although recollection of source was sometimes impaired. Semantic knowledge about studied items and measures of item detection and source discrimination were largely independent. The implications of these findings for models of long-term memory are discussed. The results support the concept that episodic memory, or at least the recall of temporally specific autobiographical experiences, draws upon a number of separable memory processes, some of which can function independently of semantic knowledge.

Keywords: semantic memory; episodic memory; frontotemporal dementia; hippocampus; Alzheimer's disease

1. INTRODUCTION

Memory, in its broadest sense, refers to the storage and retrieval of any form of information but, when considered as an aspect of human cognition, it clearly does not describe a unitary function. Memorizing a new telephone number, recalling the details of a past holiday, acquiring the facts necessary to practise medicine, learning a new language or knowing how to drive a car are all tasks that depend on memory, but proficiency in one does not guarantee competence in the other. More importantly, these abilities may break down differentially in patients with brain disease.

There is, as yet, no universally accepted classification of subcomponents of memory, but virtually all contemporary cognitive models distinguish between working (immediate) and longer-term memory—and within the latter recognize both explicit and implicit types. Within explicit long-term memory an influential distinction is that between episodic and semantic memory. The former refers to our personal store of temporally-specific experiences (or episodes), the retrieval of which has been

likened to 'mental time travel' in which the person doing the remembering experiences the conscious sensation of travelling back in time to relive the original event (Tulving 1985, 1999). In contrast, semantic memory refers to our database of knowledge about things in the world and their inter-relationships, which includes words, objects, places and people (Garrard *et al.* 1997; Patterson & Hodges 2000). Semantic memory is, therefore, the most central of all cognitive processes and is fundamental to language production and comprehension, reading and writing, object and face perception.

Despite the central role of semantic memory, its study is relatively recent and in the modern era begins in 1975 with the description by Elizabeth Warrington of three patients with selective loss of semantic memory (Warrington 1975). Such patients had been described in the neurological literature for over 100 years, under the rubric of Pick's disease and, in the neuropsychological literature, as cases of associative agnosia or amnesic aphasia (Hodges 2000). Warrington, drawing on the work of Tulving, recognized the cross-modal nature of their cognitive deficit and the fundamental loss of the conceptual knowledge that underlay the patients' various symptoms. The term 'semantic dementia' was coined for this syndrome by Snowden *et al.* (1989) and has now been

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widely accepted in the cognitive literature. Readers should also be aware that patients with semantic dementia may be described clinically as having the temporal variant of fronto-temporal dementia (FTD) (Edwards Lee *et al.* 1997; Hodges & Miller 2001*a*,*b*). Criteria for the diagnosis of semantic dementia have been proposed by an international consensus study group (Neary *et al.* 1998).

Semantic memory breakdown also occurs in a number of other conditions, most notably after herpes simplex encephalitis (for a review, see Garrard *et al.* 1997) and Alzheimer's disease (Hodges & Patterson 1995). In these conditions, the semantic deficit is almost always accompanied by other major cognitive deficits. For this reason, the study of patients with semantic dementia, who have progressive, yet selective and often profound, breakdown of semantic memory, provides unparalleled insights into the organization of semantic memory and the impact of semantic disintegration on other cognitive processes. Following the description of a typical case, the rest of this review deals with our work on episodic memory in semantic dementia and attempts to answer four key questions:

 (i) what is the impact of semantic memory loss on episodic memory? and, more specifically,
 (ii) is autobiographical memory spared in semantic dementia?
(iii) does loss of semantic knowledge result in impaired new learning?, and finally,
(iv) what does this tell us about the nature of episodic memory?

2. CASE REPORT

The following case-history, of a patient who was studied longitudinally over 5 years, illustrates the pattern of cognitive deficits commonly seen in the disorder (see also Graham & Hodges 1997; Hodges & Patterson 1996; Knott *et al.* 1997).

A.M. (b. 1930) presented in April 1994 with a history of 'loss of memory for words', which had progressed slowly over the previous two years. His wife has also noted a decline in his comprehension ability initially affecting less common words. Despite these problems he still played golf (to a high standard) and tennis. He was still driving and able to find his way to various golf clubs alone and without difficulty. Day-to-day memory was also good and when seen in the clinic he was able to relate—albeit with prominent word finding difficulties—the details of their recent holiday in Australia and his latest golfing achievements. There had been only a slight change in personality at that time with mild disinhibition and a tendency to stick to fixed routines.

The following transcription illustrates that A.M.'s speech was fluent and without phonological or syntactic errors but strikingly devoid of content. It also shows his recall of undergoing a brain scan some six months previously.

E: Can you tell me about a last time you were in hospital?

AM: That was January, February, March, April, yes April last year, that was the first time, and eh, on the Monday, for example, they were checking all my whatsit, and that was the first time when my brain was, eh, shown, you know, you know that bit of the brain (indicates left), not that one, the other one was okay, but that was lousy, so they did that, and then like this (indicates scanning by moving his hands over his head) and probably I was a bit better than I am just now.

Formal neuropsychological testing in April 1994 revealed that A.M. was severely impaired on tests of picture naming. On the category fluency test, in which subjects are asked to generate exemplars from a range of semantic categories, within a set time, he was able to generate a few high-frequency animal names (cat, dog, horse) but no exemplars from more restricted categories such as birds or breeds of dog. He was only able to name three out of 48 black and white line drawings of highly familiar objects and animals from the Hodges and Patterson semantic battery (Hodges & Patterson 1995). Most responses were vague circumlocutions such as 'thing you use' but he also produced some category coordinate errors, such as horse for elephant. On a word–picture matching test, based on the same 48 items, in which A.M. had to point out a picture from eight other exemplars (e.g. zebra from eight other foreign animals), he scored 36 out of 48 (25 age-matched controls scored on average 47.4 ± 1.1). When asked to provide descriptions of the 48 items in the battery from their names, he produced very few details, most were vague or generic responses containing the superordinate category only ('a musical instrument', 'in the sea' etc.). On the picture version of the Pyramid and Palm Trees Test, a measure of associative semantic knowledge in which the subject has to decide which of two pictures (a fir tree or a palm tree) goes best with a target picture (pyramid) (Howard & Patterson 1992), A.M. scored 39 out of 52 when he first presented. Control subjects typically score close to ceiling on this test.

On tests of reading A.M. showed the typical pattern of surface dyslexia (Patterson & Hodges 1992): normal ability to read aloud words with regular spelling to sound correspondence, but errors when reading aloud irregular words (pint, island, leopard, etc.).

By contrast, on non-semantic tasks (such as copying the Rey Complex Figure) A.M.'s performance was faultless. When asked to reproduce the Rey Complex Figure after a 45-minute delay, A.M. scored well within the normal range. On non-verbal tests of problem-solving, such as Raven's Coloured Matrices, a multiple-choice test of visual pattern matching that requires the subject to conceptualize spatial relationships, A.M. was also remarkably unimpaired. Auditory–verbal short-term memory was spared as judged by a digit span of six forwards and four backwards.

A.M. was tested approximately every 6 months over the next 3 years. A.M. was so profoundly anomic when he first presented that there was little room for further decline. On tests of comprehension, by contrast, there was a relentless drop; for instance, on the word–picture matching test, A.M.'s score fell from 36 to 5 out of 48 in November 1996 (controls = 47.4 ± 1.1). Likewise on the pictorial version of the Pyramid and Palm Trees Test his score fell progressively from 39 out of 52 to chance.

Despite this rapid loss of semantic knowledge, A.M. showed no significant decline on tests of non-verbal problem-solving or visuo-spatial ability over the same time period. For instance, on Raven's Coloured Matrices he still scored perfectly in November 1996.

A.M.'s impairment in semantic knowledge had a considerable impact on his everyday activities. On various occasions he misused objects (e.g. he placed a closed umbrella horizontally over his head during a rainstorm), selected an inappropriate item (e.g. bringing his wife, who was cleaning in the upstairs bathroom, the lawnmower instead of a ladder) and mistook various food items (e.g. on different occasions, A.M. put sugar into a glass of wine, orange juice into his lasagne and ate a raw defrosting salmon steak with yoghurt). Activities that used to be commonplace acquired a new and frightening quality to him: on an aeroplane trip early in 1996 he became clearly distressed at his suitcase being X-rayed and refused to wear a seat belt in the aeroplane.

After 1996, behavioural changes became more prominent with increasing social withdrawal, apathy and disinhibition. Like another patient described by Hodges *et al.* (1995), A.M. showed a fascinating mixture of 'preserved and disturbed cognition'. Hodges *et al.*'s patient, J.L., would set the house clocks and his watch forward in his impatience to get to a favourite restaurant, not realizing the relationship between clock and world time. A.M. made similar apparently 'insightful' attempts to get his own way. For example, his wife reported an incident in which she secretly removed his car keys from his key-ring to stop him taking the car for a drive. At this point, A.M. was obsessed with driving and very quickly noticed the missing keys. He solved the problem by taking his wife's car keys off her key-ring without her knowledge and going to the locksmiths, successfully, to get a new set cut. At no point did A.M. realize his wife had taken the keys from his key-ring. Despite virtually no language output and profound comprehension difficulties he still retained some skills, e.g. he continued to play sport (particularly golf) regularly each week, remembering correctly when he was to be picked up by his friends, until 1998 when he entered permanent nursing care.

Serial brain imaging using magnetic resonance imaging (MRI) images showed the pattern typical of semantic dementia, namely striking asymmetrical atrophy of the anterior temporal lobes involving the temporal pole, fusiform gyrus and infero-lateral region, but with relative sparing of the hippocampus. Figure 1 shows an illustrative coronal T1 weighted MRI image from another more recently studied patient with semantic dementia and a comparative normal brain from a control subject of the same age.

In summary, A.M.'s case-history illustrates a number of the characteristic neuropsychological features of semantic dementia: (i) selective impairment of semantic memory causing severe anomia, impaired single-word comprehension, reduced generation of exemplars on category fluency tests, and an impoverished fund of general knowledge; (ii) surface dyslexia; (iii) relative sparing of syntactic and phonological aspects of language; (iv) normal perceptual skills and non-verbal problem-solving abilities; and (v) relatively preserved recent autobiographical and day-to-day (episodic) memory.
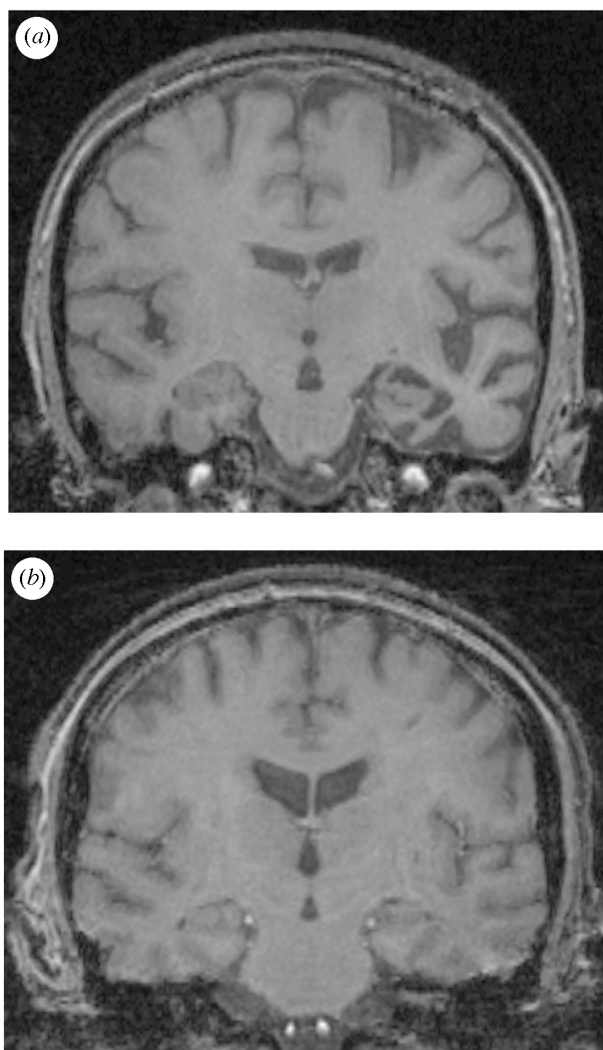
Figure 1. An illustrative coronal T1 weighted magnetic resonance imaging (MRI) image from a patient in the early stages of semantic dementia (*a*) and a comparative normal brain from a control subject of the same age (*b*). The scan from the patient with semantic dementia reveals moderate to severe atrophy of the left temporal lobe, including the para-hippocampal gyrus, fusiform and inferior temporal gyrus. The left hippocampus is mildly atrophied.

3. AUTOBIOGRAPHICAL MEMORY IN SEMANTIC DEMENTIA

Initial clinical descriptions of patients with semantic dementia suggested that this syndrome provided compelling evidence for a dissociation between preserved autobiographical and impaired semantic memory. Patients are typically well orientated and can relate the details and incidents—albeit anomically—about their life. They also retain broad facts about their own life, such as past occupation, whether they are married, numbers of children and grandchildren, etc. (Hodges *et al.* 1992). Clinically, therefore, the neuropsychological profile of semantic dementia is quite unlike that seen in patients with classic amnesia.

More detailed empirical investigation of episodic memory (in particular, autobiographical memory) has revealed, however, a more complex, and theoretically

interesting pattern with a major confound of memory age. While patients with the amnesic syndrome, as a result of hippocampal damage (following anoxic brain damage or in the early stages of Alzheimer's disease), typically show preservation of autobiographical memory for their early life compared with the more recent past (Greene & Hodges 1996; for a review, see Hodges 1995), patients with semantic dementia show the opposite pattern, i.e. a reversal of the usual temporal gradient effect, with memory for remote events most vulnerable (Graham & Hodges 1997; Hodges & Graham 1998; Snowden *et al.* 1996).

The first clear evidence of this unusual pattern came from Snowden *et al.* (1996) who tested autobiographical memory using the Autobiographical Memory Interview (AMI) (Kopelman *et al.* 1990): patients with semantic dementia were significantly better at retrieving both personal semantic and autobiographical memories from the recent time period compared with two earlier life periods (childhood and early adulthood). A similar study by Graham & Hodges (1997) replicated this pattern in six patients with semantic dementia, as well as demonstrating that a group of severely amnesic patients, with presumed early Alzheimer's disease, showed the more typical pattern where current memories were more impaired than memories from the past.

Graham & Hodges (1997) also reported a more detailed single case-study in which they investigated the ability of a patient with semantic dementia, A.M. (described in § 2 above), to retrieve event-based memories from cue words (e.g. party, animal, etc.) across the whole of his lifetime. A.M. was much better at retrieving autobiographical episodes from the last five years of his life compared with the 60 years which encompassed the rest of his life (see figure 2). By contrast, a group of age- and education-matched control subjects showed no significant difference between their performance on any of the time-periods tested. Other patients with semantic dementia, such as patient J.H., have been shown to demonstrate a similar pattern (figure 2).

The use of the term 'gradient' is slightly confusing when considered in connection with semantic dementia. On the AMI (Kopelman *et al.* 1990) patients seem to show a reverse temporal gradient because the test taps only three time-periods: childhood, early adulthood and recent life. When more detailed autobiographical memory tasks are used, however, patients were found to show preservation of autobiographical memories for only a short period of time (in most cases, two to three years prior to testing)—more of a 'step' effect rather than a gradient (Nestor *et al.* 2001). It appears then that autobiographical memory, at least for more remote time-periods, is deficient in semantic dementia.

(a) *Theoretical explanations for the reverse step function of autobiographical memory found in semantic dementia*

There is a number of possible explanations for the pattern seen in semantic dementia. One view is that semantic and autobiographical memory may represent independent 'stores' within the brain, and that both of these memory repositories are damaged in semantic dementia. Within long-term memory there is now over-
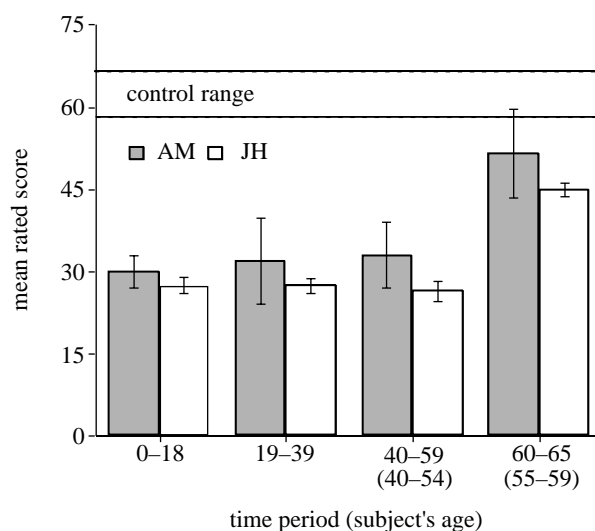

Figure 2. The performance of two patients with semantic dementia (A.M. and J.H.) and three age- and education-matched control subjects on a modified version of the Galton–Crovitz autobiographical memory test (Crovitz 1986). The subjects were asked to produce 15 autobiographical memories from each of four different time-periods spanning the whole of their life (A.M.: 0–18, 19–39, 40–59 and J.H.: 0–18, 19–39, 40–54 and 55–59). These memories were scored from 0–5 for detail and episodic specificity (for details, see Graham & Hodges 1997). A.M.'s and J.H.'s ability to produce detailed memories from the past was strongly affected by time: virtually all their specific events were recalled in the most recent five years.

whelming evidence for the separation of knowledge according to a number of dimensions, including: natural kinds versus artefacts, and nouns versus verbs or actions (Caramazza 1998). It is possible, therefore, that autobiographical memory is also neurally segregated from our semantic knowledge about the world, to the extent that knowledge about objects and animals, such as a dog, is stored separately from any personal experiences related to dogs. This multiple stores hypothesis cannot be entirely dismissed but seems implausible given that there is little in the way of neuropsychological evidence to support such a model (see Kitchener & Hodges 1999). In particular, although there are now numerous case reports of patients with isolated autobiographical amnesia (Kopelman & Kapur 2001) there are practically no descriptions in the literature of patients with loss of semantic memory in the context of spared autobiographical memory (for an exception, see De Renzi *et al.* 1987). This finding suggests that autobiographical memory may actually be dependent, to some extent, on the normal functioning of semantic memory. By contrast, loss of autobiographical episodes does not necessarily have a direct impact on access and retrieval of previously learned semantic facts.

The reason for this may be as follows. Autobiographical memories tend to be composed of different pieces of information typically involving different modalities (e.g. vision, sound). For example, remembering a particular episode that occurred during a visit to the zoo may necessitate the retrieval of visual and sound information, plus spatial knowledge about the location of participants and how they interacted (see Conway 2001). At least two

different types of pathological process could lead, therefore, to extensive autobiographical memory loss in the context of preserved semantic memory: (i) diffuse but patchy neocortical damage, which is insufficient to cause loss of semantic memory but impairs cortico–cortical interconnectivity (Evans *et al.* 1996); and (ii) severe damage to a vital component of autobiographical memory, such as visual imagery (Rubin & Greenberg 1998) or semantic knowledge (Kitchener & Hodges 1999). Rubin & Greenberg (1998) observed that loss of visual imagery is almost invariably associated with severe impairment of autobiographical memory. They argued that loss of a critical component of memory recollection, such as the capability to evoke visual memories, could result in an inability to activate other aspects of the memory experience thereby producing an extensive and non-temporally graded deficit in episodic memory retrieval. Moscovitch & Nadel (1999) have extended this view by suggesting that semantic memory, like visual imagery, is a critical component of autobiographical memories, and that loss of this type of information might result in a similar pattern of autobiographical memory loss to that seen in Rubin and Greenberg's patients. In support of this proposal, it is notable that the pattern seen in semantic dementia seems to correspond closely to that seen in Rubin and Greenberg's patients.

In addition to the effects of cortical damage and loss of memory representations or their interconnections, a number of authors have emphasized the role of frontal lobe based processes in strategic search, verification and cross-checking, and have pointed out that autobiographical recall typically involves these processes to a greater degree than does retrieval of semantic knowledge (Burgess & Shallice 1996; Moscovitch 1994; Hodges & McCarthy 1993). At present, it seems unlikely that poor strategic retrieval is the cause of the long-term memory deficit seen in semantic dementia, although further studies are required to address this issue (Nestor *et al.* 2001).

(b) *Preservation of recent memories in semantic dementia and the role of the hippocampal complex*

Having discussed the possible reasons for the loss of old autobiographical memory in semantic dementia, it is still necessary to explain the preservation of recent memories. Our initial explanation for this effect was in terms of what has become known as the standard model of long-term memory consolidation (Graham & Hodges 1997). According to this view, the neocortex and hippocampus play distinct, but complementary, roles in long-term memory storage. While initially the retrieval of a recently experienced event is reliant upon the hippocampal system, repeated reinstatement of the hippocampal–neocortical ensemble over time results in the formation of a more permanent, hippocampally independent, memory representation in the neocortex (for a review, see Murre *et al.* 2001; Mayes & Roberts 2001). We suggested, therefore, that the better recall of recent memories in semantic dementia might be due to relative preservation of the hippocampal complex, thereby allowing the encoding of new experiences. Loss of more distant personal events could be attributed neuroanatomically to the significant atrophy seen in the temporal neocortex and to the

progressive loss of semantic memory caused by this type of pathology.

Our view that the hippocampus is spared in semantic dementia was based on a number of lines of evidence. Clinical scanning experience in semantic dementia, including more than 30 patients studied in Cambridge, suggested that the most consistent finding in the disease is marked focal atrophy of the polar and infero-lateral aspect of the temporal lobe, which is typically most marked on the left but may be bilateral (Garrard & Hodges 2000). Our first quantitative analysis using the technique of voxel-based morphometry of the MRI scans of six patients with semantic dementia confirmed that the most significant and consistent locus of atrophy was the left polar and inferior temporal lobe (Brodmann area 38/20) but suggested that the hippocampus was spared (Mummery *et al.* 2000). A detailed quantitative neuropathological study by Harasty *et al.* (1996) also found significant bilateral atrophy to the inferior and middle temporal gyri but sparing of the hippocampal formation. Given these studies, it seems plausible that the better recall of recent episodic memories is attributable to the relative preservation of the hippocampus.

Two more recent MRI based studies have, however, cast doubt on these earlier findings. In Cambridge, we have now measured the volume of the hippocampus, parahippocampal region and multiple temporal lobe regions in a much larger series of semantic dementia cases ($n = 18$), as well as in a similar-sized set of patients with Alzheimer's disease (AD) matched for disease severity and a group of normal controls (Galton *et al.* 2001*a*,*b*). The major findings from this study were: (i) patients with AD typically had moderate to severe bilateral and symmetrical hippocampal atrophy compared with the control subjects, but little involvement of other temporal lobe structures; (ii) patients with semantic dementia had severe but asymmetric atrophy of the temporal pole, fusiform and inferolateral gyri and parahippocampal regions, but in addition the degree of involvement of the left hippocampus was largely indistinguishable from that seen in AD. The majority of cases had preservation of the right hippocampus and, as a group, the volume of the right hippocampus was not significantly different from controls (see figure 3). In summary, there was little difference in hippocampal volumes, at least on the left side, between the two patient groups, although it should be noted that there was considerable variability in the semantic dementia population. In terms of other medial temporal lobe structures, the entorhinal cortex, which constitutes a major component of the parahippocampal gyrus, is also severely affected in semantic dementia. The rostral part of the perirhinal cortex, which has a complex anatomy in man, occupying the banks of the collateral sulcus and medial aspect of the temporal lobe, is almost certainly affected, although the caudate part might be partially spared (Simons *et al.* 1999).

Almost identical findings emerged from a recent study by the London Dementia Research Group (Chan *et al.* 2001), which obtained volumetric measures of temporal atrophy in patients with AD and semantic dementia. Taken together, these studies confirm that atrophy of the polar and infero-lateral temporal regions differentiates patients with AD and semantic dementia, but that
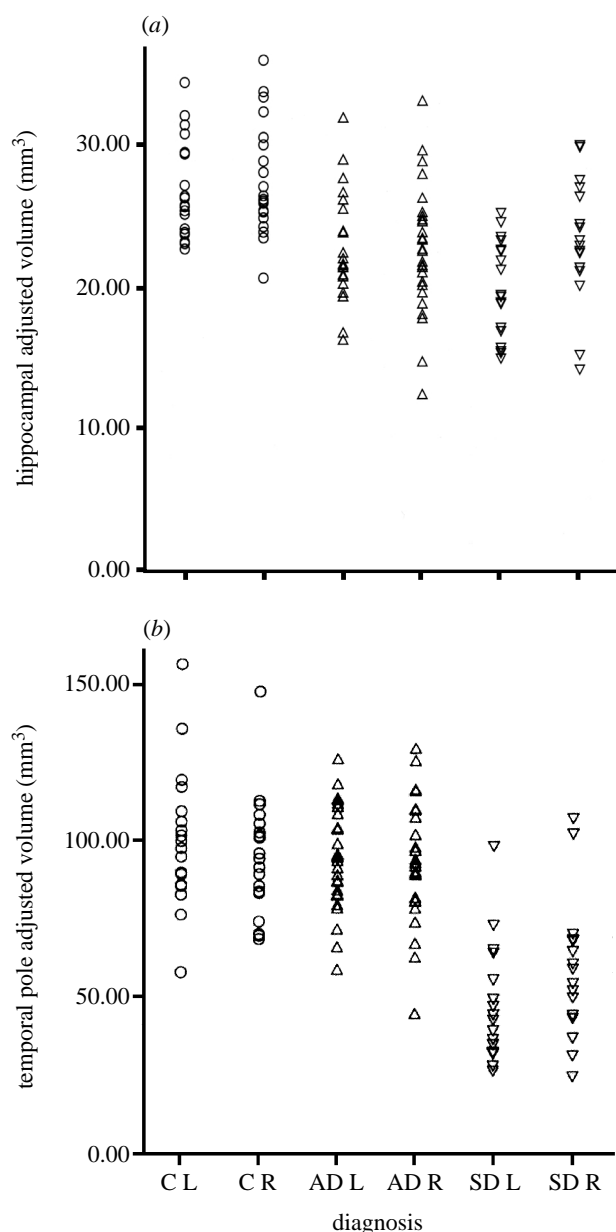
(a)

(b)

Figure 3. Scatterplots of adjusted hippocampal (a) and temporal pole volumes (b) in mm² by group (CL, control left; CR, control right; ADL and ADR, Alzheimer's disease left and right; SDL and SDR, semantic dementia left and right). Volumetric analysis was conducted by tracing round the components of the temporal lobes and correcting for head size (Galton *et al.* 2001b). There was little difference in hippocampal volume, except on the right, across the AD and SD groups. The temporal pole volumes were, by contrast, normal in the AD group and significantly reduced bilaterally in the SD group.

atrophy to hippocampal and parahippocampal regions can be present in both diseases, with bilateral involvement in AD and predominantly left-sided atrophy in semantic dementia.

Comparisons of the degree of atrophy of temporal regions in the AD patients with that in the group with semantic dementia provide some explanation for our initial assumptions about the relative preservation of the hippocampus and other medial temporal lobe structures. In the patients with semantic dementia, there was

profound atrophy of surrounding structures compared with the hippocampus: the average volume loss of the temporal pole, fusiform and infero-lateral gyri was 50% and in some cases up to 80% compared with an average of 20% loss of hippocampal volume. This dramatic difference in extent of atrophy may result in one incorrectly assuming that the hippocampus is 'relatively' preserved. In contrast, the 20% loss of hippocampus in AD stands out against the normal polar and infero-lateral structures (Galton *et al.* 2001b).

These findings clearly cast some doubt on an explanation of the autobiographical memory data, in particular the relatively better recall of recent events, simply in terms of hippocampal preservation. Future work may well reveal that the asymmetric nature of the pathology in semantic dementia is critical to understanding the pattern of autobiographical memory loss, and the variability seen across patients needs to be taken into account. Moreover, equivalent volume loss in patients with AD and semantic dementia should not be taken as evidence of equivalent pathology. It is quite likely that the pathological processes that cause the two dementias affect different cell populations within the hippocampus.

(c) *Multiple-trace theory of memory consolidation*

Another important recent development that needs to be considered with respect to the findings in semantic dementia is the recent development of the multiple-trace model of long-term memory by Nadel & Moscovitch (Nadel & Moscovitch 1997; Moscovitch & Nadel 1999). Contrary to the accepted model discussed above, these authors have argued that the neuropsychological literature is more in keeping with the view that the hippocampus is necessary for the retrieval of all episodic memories regardless of the age of the memory. Nadel & Moscovitch (1997) hypothesize that, just as in the standard model, geographically separate neural components of a recently experienced memory are bound together by the hippocampal complex, creating a medial temporal–neocortical ensemble. The hippocampal constituent acts as an indexer pinpointing the different neocortical areas that need to be activated to produce the full content of the event. Unlike the standard model, however, whereby repeated reinstatement of memories results in the formation of a permanent, hippocampally-independent, neocortical representation of the episodic memory, repeated retrieval of personal experiences in the multiple trace model creates re-coded traces of the experience within the hippocampal complex. These traces are distributed throughout the medial temporal lobe and the number of traces is positively correlated with how often an event has been retrieved.

To explain the reverse step function found in semantic dementia, Nadel and Moscovitch (Moscovitch & Nadel 1999; Nadel & Moscovitch 1997) proposed a number of alternative explanations: (i) that there was only one patient (A.M., reported in Graham & Hodges 1997) who showed preservation of very recently experienced memories (1–2 years prior to testing); (ii) the pattern may be due to strategic retrieval deficits caused by concomitant frontal pathology; and (iii) verbally-based testing of autobiographical memory may have exacerbated the
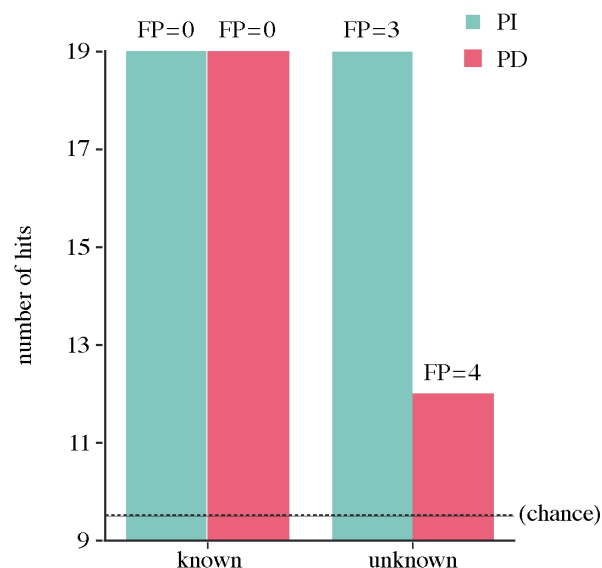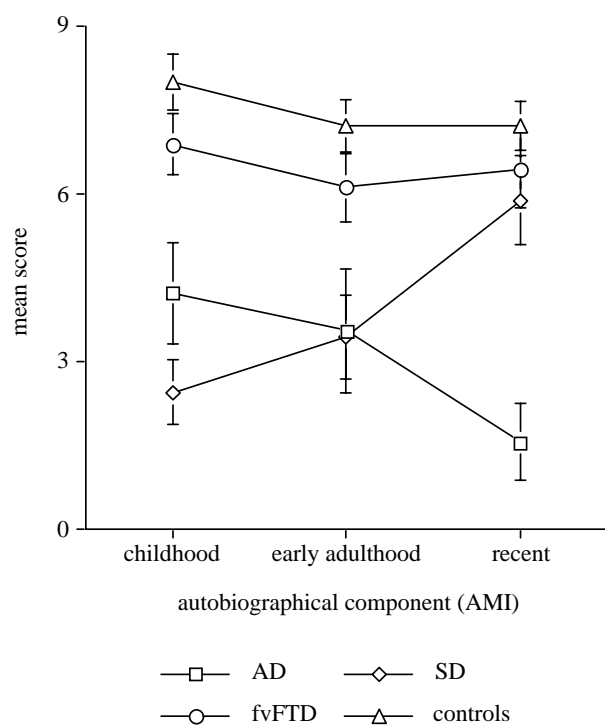
Figure 4. Performance of control subjects, patients with semantic dementia (SD), frontal variant fronto-temporal dementia (fvFTD) and early Alzheimer's disease (AD) on the incidents component of the Autobiographical Memory Interview (AMI) (Kopelman *et al.* 1990). Subjects are asked to relate three specific life events from each of three life periods: childhood, early adulthood and the most recent five years. Each memory is then scored for richness of detail and specificity on a 0–3 scale.

patient's remote memory deficit. We have now shown that the pattern seen in semantic dementia on tests of auto-biographical memory is unlikely to be due to any one or a combination of these factors (see Nestor *et al.* 2001). As shown in figure 2, other patients with semantic dementia show the same effect of time on the detailed autobiographical tests as A.M. In a recent study, we compared the performance of groups of patients with early AD, semantic dementia and the frontal variant of fronto-temporal dementia (fvFTD) on the AMI (Nestor *et al.* 2001). Patients with fvFTD have profound behavioural changes with frontal executive dysfunction and evidence of frontal lobe atrophy in the absence of significant semantic memory impairment. Only those patients with semantic dementia demonstrated the reverse step function. Patients with AD had a classic temporally graded impairment, while the group with fvFTD performed within the normal range (see figure 4). In addition, the use of family photographs to prompt recall of episodes appeared not to benefit one of our patients (for contrary results, see Westmacott *et al.* 2001).

4. NEW LEARNING IN SEMANTIC DEMENTIA

Until very recently, there had been few formal investigations of the integrity of anterograde episodic memory in semantic dementia. Anecdotal evidence supports the view that patients show preservation of new learning,
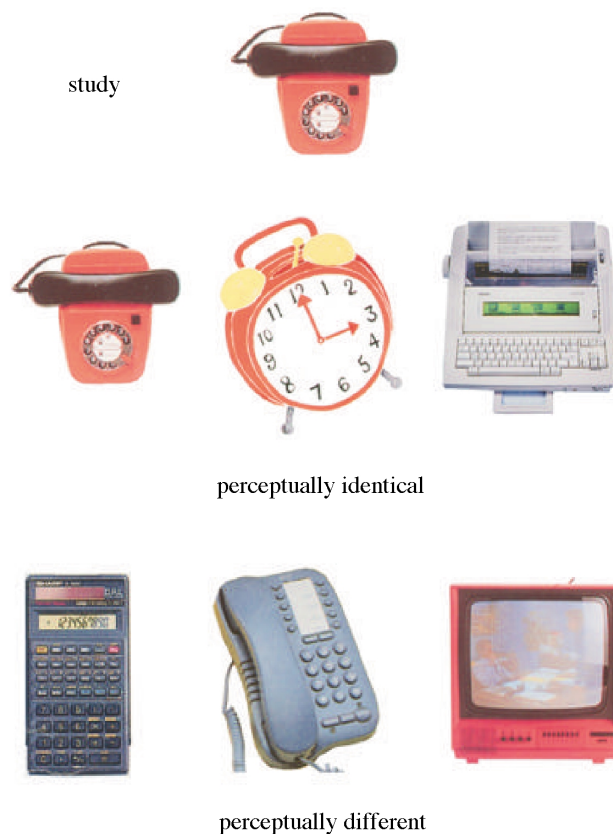

Figure 5. Examples of the stimuli used in the semantic naming task (top), the perceptually identical condition (middle) and the perceptually different (bottom) conditions of a forced choice episodic recognition memory test (see experiment 1, Graham *et al.* 2000). The graph shows the performance of a patient with semantic dementia (J.H.) on the perceptually identical (PI) and perceptually different (PD) conditions of the recognition memory test for 'known' and 'unknown' but previously familiar objects (see experiment 2, Graham *et al.* 2000). The only significant impairment shown by J.H. was on the perceptually different condition for 'unknown' items.

despite their loss of semantic knowledge. For example, in November 1996, when A.M. was scoring at chance on tests of semantic memory, he was still able to tell his wife that someone had rung while she was out. He showed no problems finding his way around his town and remembered golfing appointments, etc. A.M.'s performance on non-verbal tests of new learning at that time also pointed to some preservation of episodic memory (e.g. delayed recall of the Rey Complex Figure). Warrington (1975), however, noted that her three cases showed poor episodic memory as measured by story recall, reproduction of visual designs and recognition memory for words and faces; by contrast, recognition memory for paintings was preserved.

(a) *Recognition memory for non-verbal stimuli*

Recently, more experimentally driven studies of new learning in patients with semantic dementia have begun to confirm the anecdotal reports but, as with the findings on autobiographical memory discussed above, a more complex picture is emerging. In our first study, we found evidence of completely normal recognition memory for real and non-real animals in a group of patients with semantic dementia (Graham *et al.* 1997). Compared with both control subjects and patients in the early stages of AD, by contrast, the patients were significantly impaired on the study task in which they had to say whether the animals were real or not real. These data provided compelling evidence for the separation of semantic knowledge and new learning (at least as judged by tests of recognition memory).

Two further experiments have provided additional insights into our understanding of the processes involved in new learning in semantic dementia. Graham *et al.* (2000) found that a group of eight patients with semantic dementia showed normal recognition memory when the target item in the recognition memory task was identical to the item that had been seen at study. By contrast, when the target item was changed between study and test (e.g. a round dial telephone was replaced with a push button telephone), the patients were significantly impaired (compared with control subjects) on items that they were unable to name from a picture. This result suggests that loss of semantic knowledge only affects recognition memory when the target item is perceptually different from the studied item. Graham and colleagues suggested that the striking difference between the perceptually identical and perceptually different conditions reflected the differential involvement of higher-order perceptual areas and semantic knowledge in new learning. This hypothesis was further supported by a case study in which recognition memory for 'known' and previously familiar 'unknown' items was investigated. The only circumstances under which the patient showed poor recognition memory was for perceptually different items that were no longer known. Recognition memory for all perceptually identical items and for 'known' perceptually different items was not significantly impaired (see figure 5).

We have since extended this technique to studying face recognition memory. Simons *et al.* (2001) investigated face recognition in a series of patients with semantic dementia and showed that: (i) patients with selective left temporal lobe atrophy were not significantly impaired on the faces component of the Warrington Recognition Memory Test; (ii) a group of patients with predominantly right temporal lobe atrophy performed poorly on the test; (iii) within this group, the status of the parahippocampal gyrus (which includes the perirhinal cortex) was most important; and (iv) that, like the object data described above, face recognition memory was affected by a change of picture (e.g. the Queen without a head-scarf and the Queen with a head-scarf), but only for items which were no longer familiar to the patients.

These results are illuminating with regard to current cognitive models of long-term memory as they suggest that the ability to form an episodic memory is not critically dependent upon the integrity of semantic knowledge (as proposed by Tulving 1985, 1995). The replication by Simons *et al.* (2001) of the Graham *et al.* (2000) study using different stimuli (faces compared with objects) provides strong support for the view that new learning in semantic dementia is based largely on good perceptual processing as input to the episodic memory system. A wider implication is that the medial temporal-based episodic system receives multiple sensory inputs from many disparate areas of the brain only some of which are damaged in semantic dementia.

(b) *Verbal learning in semantic dementia*

In contrast to their good performance on different forms of non-verbal anterograde memory tests, semantic dementia patients typically perform very poorly on classic clinical tests of verbal memory such as story recall and word list learning. Even their performance on more simple recognition memory tests is often impaired. The experiments discussed above help to understand this finding. If new learning in semantic dementia relies heavily upon intact perceptual processes, than one would expect performance on word-based tests to be particularly poor since words, unlike pictures and faces, are perceptually impoverished. The ability to recall words is, therefore, almost entirely dependent on semantic encoding. Furthermore, unlike pictures, there is an arbitrary relationship between phonological (and orthographic) forms and semantic representations. In other words, there is nothing about the word 'horse' which gives any clue to its meaning, and in fact the phonological form is ambiguous out of context. Another fact to take into consideration is that the pathology in semantic dementia almost always involves the left temporal lobe to a greater degree than the right. We predict, therefore, that experiments based on the learning of known and unknown words would produce the same advantage for known items as in the experiments described above but, unlike pictures, we also expect patients to be impaired on the apparently 'known' items since it is very likely that the underlying semantic representations for these items are not totally intact.

Very recently we have gone some way to testing these predictions using a word list learning paradigm with delayed recall and recognition, based on the shortened version of the Rey Auditory Verbal Learning Test described by Greene *et al.* (1996). A group of semantic dementia patients were pretested on the entire Snodgrass & Vanderwart (1980) corpus of 260 pictures to determine sets of known and unknown words (based on naming and word–picture matching) matched for word frequency and

length. Compared with controls, semantic dementia patients showed very poor recall of both known and unknown words but with an advantage for known stimuli. Delayed recall for both categories was very poor. Even in the recognition format, there was a significant impairment of item recognition when analysed using signal detection methods, particularly for items that were no longer known to the patients. Analysis of the performance of individual cases showed a very marked effect of disease severity: those with mild semantic breakdown showed good item detection for all items, those with moderate semantic loss for known items only, and more demented cases showed marked impairment in both conditions (Graham *et al.* 2001). We have also shown that a patient with semantic dementia can relearn 'forgotten' vocabulary through frequent practice but the benefit of this rote learning is quickly lost once practice ceases (Graham *et al.* 1999). These two studies suggest that verbal learning can occur with practice in semantic dementia but that recall, and to a lesser extent recognition memory, is strongly affected by semantic knowledge and the delay between study and test.

(c) *Source memory in semantic dementia: recollection and familiarity*

It has recently been proposed that two functionally and neurally separate processes contribute to recognition memory: 'recollection', subserved by the hippocampal memory system—the hippocampus, fornix, mammillary bodies and anterior thalamic nuclei—and 'familiarity', supported by the perirhinal cortex–dorsomedial thalamic nuclei system (Aggleton & Brown 1999; Aggleton 2001). According to this view, the hippocampal system supports the recollection of stored memories with their associated temporal, spatial and semantic context (remembering) as measured by tests of recall, associative memory, memory for spatial location and temporal source memory. By contrast, the perirhinal system underlies familiarity-based recognition of prior occurrence ('knowing'), as indexed primarily by recognition memory. There is fairly good evidence to support the separation of recollection- and familiarity-based memory systems from lesion studies in animals, including rats and non-human primates (for a review, see Aggleton & Brown 1999; Murray & Bussey 1999). The evidence from human studies is more controversial but is strongest in the case of patients with fornix lesions and development amnesia secondary to hypoxic hippocampal damage early in life (Vargha-Khadem *et al.* 1997; Vargha-Khadem 2001).

The experiments described so far have demonstrated consistently that recognition memory for pictorial stimuli (pictures of objects, animals and faces) is preserved in many patients with semantic dementia although patients are heavily dependent on perceptual features. Given the proposed dichotomy between recollection- and familiarity-based memory systems it is important to establish whether there is evidence for the preservation of recollective memory in semantic dementia or alternatively whether patients are performing well on recognition memory tests purely on the basis of familiarity judgments. We have already shown that autobiographical memory, at least for recent life events, is fairly well preserved in semantic dementia which would lead to

the prediction that patients should show good performance on recollective tests which might be dependent upon the hippocampus.

To examine this hypothesis we recently used a standard source monitoring paradigm (Mitchell & Johnson 2000) in 10 patients with semantic dementia, ranging in severity of semantic impairment from mild to severe, and 12 matched controls. All subjects were given two sets of 30 line drawings at study, in which they were asked to name the pictures. After a short delay, memory for the pictures and in which set they had been presented was examined using a three-choice alternative forced-choice test. The results were analysed using a multinomial model to produce separable estimates of familiarity- and recollection-based memory. Volumetric analysis of the hippocampus and parahippocampal gyrus was also available (Galton *et al.* 2001*b*). Item detection (akin to familiarity) was normal in seven out of the 10 semantic dementia patients. This finding is in keeping with prior studies and confirms that even in a difficult test, on which normal subjects perform below ceiling, most patients with semantic dementia showed normal ability to detect items that have been seen previously from those which had not. The three patients who showed deficits were the three most semantically impaired cases. A more complicated picture emerged from the analysis of the source discrimination parameter. Seven out of the 10 patients performed no differently from the control group. The three patients showing impairment of source discrimination were not, however, the most semantically impaired; indeed, two were among the five mildest cases. An analysis of the correspondence between naming and both item detection and source discrimination on an item-by-item basis in four of the patients revealed no relationship between semantic status and test performance.

If source discrimination is hippocampally dependent then perhaps the variability seen in semantic dementia reflects differences in the status of the hippocampal formation, which we now know is involved in at least some cases with semantic dementia (see above). Analyses in our group, however, failed to confirm this hypothesis: there was no significant relationship between performance on the source monitoring tests and volumetric measures of the hippocampus and parahippocampal gyrus. Instead, a further experiment in seven patients found that the variability in source discrimination was significantly related to performance on a battery of frontal executive tasks (Simons 2000).

5. IMPLICATIONS FOR MODELS OF LONG-TERM MEMORY

The results of studies of different aspects of long-term memory in patients with semantic dementia reveal a complex picture but two principal conclusions can be drawn. First, although semantic breakdown has an impact on some aspects of episodic memory (notably remote autobiographical memory and anterograde verbal recall), other aspects (recognition of pictures of objects, animals and faces, and even source discrimination) can function independently of semantic memory. Particularly critical were the recognition memory test analyses that

consistently showed no evidence, at least on an item-by-item level, that degraded knowledge about a particular stimulus necessarily leads to failure of recognition of that item in a memory test. These findings are clearly contrary to the view that the acquisition of 'episodic memory depends upon an intact semantic system' as proposed by Tulving in his serial processing model of long-term memory (Tulving 1995). The explanation we prefer is that successful recognition memory in semantic dementia is supported by information from perceptual processing systems. Rather than recognition memory proceeding in a strictly serial fashion, with perceptual information about a stimulus feeding only into the semantic system, which subsequently transmits information about the meaning of the stimulus to the episodic memory system, we have proposed an alternative multiple input hypothesis. According to this view, information from the perceptual system can feed directly into episodic memory: in healthy individuals, therefore, recognition memory typically draws upon multiple inputs from perceptual and semantic systems (Graham *et al.* 2000; Simons *et al.* 2001).

The second conclusion concerns the nature of episodic memory. This term has been applied to a broad range of memory processes, including anterograde and remote autobiographical memory, recall of stories and non-verbal materials, recognition memory for a range of different stimuli and source discrimination. Yet, as shown above, these processes disassociate and it is increasingly apparent that they do not have a single neural substrate. It is meaningless, therefore, to argue about which type of memory is truly 'episodic'. Although the term 'episodic memory' is an extremely useful heuristic, particularly in clinical practice, the work in semantic dementia, and in patients with classic amnesia, suggests that it describes a family of processes rather than a single definable entity. In recent formulations, Tulving and colleagues (Tulving & Markowitsch 1998; Tulving 1995) have stressed the uniquely human aspects of episodic memory, which involves the ability to engage in 'mental time travel' when retrieving the temporal and spatial elements of a prior experience. In terms of the neuropsychological literature, this equates most closely to autobiographical memory. Yet, compared with the vast literature on other aspects of memory we really know very little about autobiographical memory in brain injured patients and particularly the relationship between performance on tests of autobiographical memory and other types of new learning (Conway 2001). Our studies of semantic dementia patients suggest that autobiographical memory depends in turn on a range of different memory processes some of which can function in the absence of semantic knowledge. The ability to store and retrieve personally-based memories from the distant and very recent past requires the interaction of a number of different cognitive processes which must be subserved by different neural substrates.

Finally, the investigations of long-term memory in semantic dementia described here have also provided a new challenge to memory researchers. This task is to understand how patients with equivalent, albeit asymmetric, medial temporal lobe damage, as seen in semantic dementia and AD, can show such disparate patterns of performance on tests of human long-term memory.

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