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INVITED REVIEW

Semantic dementia: relevance to connectionist models of long-term memory

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Summary

Semantic dementia is a recently documented syndrome associated with non-Alzheimer degenerative pathology of the polar and inferolateral temporal neocortex, with relative sparing (at least in the early stages) of the hippocampal complex. Patients typically show a progressive deterioration in their semantic knowledge about people, objects, facts and the meanings of words. Yet, at least clinically, they seem to possess relatively preserved day-to-day (episodic) memory. Neuropsychological investigations of semantic dementia provide, therefore, a unique opportunity to investigate the organization of human long-term memory and, more specifically, to determine the relationship between semantic memory and other cognitive systems, such as episodic memory. In this review, we summarize recent empirical findings from patients with semantic dementia and discuss whether the neuropsychological phenomena of the disease are consistent with current cognitive and computational models of human long-term memory and amnesia. Six specific issues are addressed: (i) the relative preservation of category-level (superordinate) compared with fine-graded (subordinate) semantic knowledge as the disease progresses; (ii) the better recall of recent autobiographical and semantic memories compared with those in the distant past; (iii) the preservation of new learning, as measured by recognition memory, early in the disease; (iv) the interaction between autobiographical experience and semantic knowledge in the current, but not the distant, time-period; (v) increased long-term forgetting of newly learned material; and (vi) impaired implicit memory. It is concluded that recent findings from semantic dementia offer strong support for the view that memory consolidation in humans is dependent upon interactions between the hippocampal complex and neocortex. Furthermore, these investigations have provided computational modellers of human memory with a novel set of neuropsychological data to be simulated and tested.

Keywords: connectionist models; hippocampus; long-term memory; memory consolidation; retrograde amnesia; semantic dementia

Abbreviations: BA = Brodmann area; rCBF = regional cerebral blood flow

1. Introduction

In 1957, Scoville and Milner described eight patients who showed an extensive and persistent loss of memory after bilateral lesions of the medial temporal lobe. Three of these patients (H.M., D.C. and M.B.) were severely amnesic: they were unable to remember events from moment to moment (anterograde amnesia) and appeared to have a mild loss of old memories extending back in time for 2–3 years only (retrograde amnesia). Since Scoville and Milner's paper, there have been over 50 reported cases of patients with amnesia associated with hippocampal damage (see Anon., 1996).

Early studies of amnesic patients, like H.M., initially suggested that human long-term memory could be fractionated into at least two types: episodic and semantic (Tulving, 1972). The term episodic memory refers to our store of personally based memories, the retrieval of which involves conscious recollection of the specific temporal–spatial setting of a previous experience, so called 'mental

time travel' (see Tulving, 1972, 1983, 1995; Tulving and Markowitsch, 1998). In contrast, the term semantic memory applies to our 'knowledge of the world', including the meaning of vocabulary, concepts and facts: information which is retrieved without recalling when and where it was first learnt (Patterson and Hodges, 2000). Tulving (1972, 1983) proposed that these two types of memory were psychologically and neurologically distinct and that amnesia was the result of damage to the episodic memory system. Moreover, Scoville and Milner's data suggested a critical role of the medial temporal lobe, in particular the hippocampus, in this type of memory (Scoville and Milner, 1957).

Over the 25 years since Tulving's highly influential precis of human long-term memory (Tulving, 1983), it has become clear that a simple fractionation between episodic and semantic memory cannot explain all the data from patients with amnesia. For example, Tulving's view predicts that patients with amnesia should not show impairments to the acquisition or retrieval of semantic memory. In fact, H.M. himself shows poor post-morbid semantic learning, as measured by his knowledge of vocabulary that has entered the English language after 1955 (Gabrieli *et al*., 1988; see also the patient described by Verfaellie *et al*., 1995). For a fuller discussion of semantic learning in amnesia, see section 4.4.

In the domain of remote memory, amnesic patients have equal difficulty in retrieving recent episodic and semantic memories, but older events and knowledge can sometimes be retrieved (Ribot, 1882; Reed and Squire, 1998). The fact that episodic memories can be affected by time (with better preservation of distant events compared with more recent memories) is not predicted by a model in which amnesia is caused by a selective impairment to episodic memory. These neuropsychological findings strongly suggest that Tulving's original hypothesis (Tulving, 1972, 1983) regarding the organization of human long-term memory, in which episodic and semantic memory are neurologically and psychologically distinct, is clearly incorrect.

In order to accommodate these conflicting and complex findings from amnesia, some researchers have proposed a neuroanatomically based theory in which medial temporal lobe structures (i.e. the hippocampus, subiculum and entorhinal cortex) play a temporary, time-limited role in the acquisition of human long-term memories (Rempel-Clower *et al*., 1996; Graham and Hodges, 1997; Reed and Squire, 1998; although see Nadel and Moscovitch, 1997). More specifically, the hippocampal complex is necessary for the retrieval of recently experienced events, but is not involved in the retrieval of older episodic and semantic memories. In contrast, regions of the neocortex are thought to be the 'permanent repository of memory' (Squire and Alvarez, 1995, p. 172). This theory provides a reasonable explanation for why patients with damage to the hippocampal complex show a temporally graded loss of memory, with recent memories affected more severely than older memories. In this article, we discuss this model of long-term memory consolidation in more detail, concentrating on data from the syndrome of semantic dementia and on current neuroanatomically informed computational models of human memory. These connectionist models allow us to test predictions from different cognitive theories of human long-term memory: computer simulation is used as a technique to determine the effects of different types of lesions on memory recall. For example, a number of researchers have shown that lesioning of the hippocampus in a connectionist model results in a similar temporal gradient in memory retrieval to that seen in amnesic patients with hippocampal damage (Alvarez and Squire, 1994; McClelland *et al*., 1995; Murre, 1996). Other experimental data related to retrograde amnesia, derived from studies with amnesic patients, have also been tested and modelled (Murre, 1996, 1997). This 'two-pronged' approach to the study of human long-term memory allows neuropsychological theories to be tested in detail and results in the generation of new hypotheses, which can be investigated in brain-damaged subjects.

Patients with semantic dementia have a disorder that appears to be, both cognitively and neuroanatomically, the mirror image of that seen in amnesia (Snowden *et al*., 1989; Hodges *et al*., 1992, 1995; Hodges and Patterson, 1996; Graham *et al*., 1999*b*). This syndrome offers a challenge, therefore, to computational models of human memory; such models can only be regarded as valid models of long-term memory if they are able to simulate the neuropsychological phenomena observed in semantic dementia, as well as amnesia. The aims of this paper are, therefore (i) to introduce the neuropsychological profile of semantic dementia by describing data collected in a patient (A.M.) with the disease, (ii) to briefly discuss three neuroanatomically based computational models of long-term memory (Alvarez and Squire, 1994; McClelland *et al*., 1995; Murre, 1996, 1997), (iii) to suggest a number of predictions about semantic dementia that can be made from one of these models, TraceLink (Murre, 1996, 1997), (iv) to determine the validity of an interdisciplinary approach to semantic dementia by comparing Murre's predictions with empirical data from recent experimental studies of remote memory and new learning in patients with the disease, (v) to provide a theoretically and computationally driven explanation for the neuropsychological findings from semantic dementia, and (vi) to bridge the gap between neuropsychology and computational modelling by providing cognitive neuroscientists interested in long-term memory with a better understanding of how these two disciplines can inform each other and provide new directions for research.

2. Disorders of long-term memory: semantic dementia

2.1 *Background*

In 1982, Mesulam described six patients who showed a progressive, yet selective, impairment to language, a

phenomenon he referred to as 'a slowly progressing aphasic disorder without the additional intellectual and behavioural disturbances of dementia' (Mesulam, 1982, p. 592). While these were not the first reported cases with progressive aphasia (Pick, 1892; Warrington, 1975; Schwartz *et al*., 1979), Mesulam's paper highlighted the fact that patients with neurodegenerative disease could present with relatively focal cognitive deficits. Following this seminal report, more than 100 patients with progressive aphasia have been reported and it has become apparent that this broad term has been used to describe two very different syndromes: progressive non-fluent aphasia and progressive fluent aphasia (for a review of these two disorders see Hodges and Patterson, 1996).

While patients with non-fluent aphasia present with breakdown in the phonological and syntactic aspects of language (Croot *et al*., 1998), those with progressive fluent aphasia retain normal speech structure, but are unable to produce the names of previously familiar places, people and objects. Such patients also show deficits in word comprehension and fail to understand questions and follow conversation, television programmes, etc. Although anomia and impaired word comprehension are the most striking neuropsychological features, more detailed testing reveals a breakdown in both verbal and non-verbal semantic knowledge about people, objects, facts and words. Deficits are seen, therefore, on a number of different verbally based semantic tasks (Hodges *et al*., 1992; Hodges and Patterson, 1995), such as picture naming, word–picture matching (pointing to a picture from eight other semantically related foils), category fluency [producing as many exemplars from a semantic category (e.g. animals) in 1 min], naming an item when given a description (e.g. 'an electrical kitchen appliance that is used for browning bread'), picture sorting (i.e. grouping black-and-white line drawings depending on various pre-specified criteria, such as living versus non-living; electrical versus non-electrical and so on) and generating verbal descriptions from a spoken label. On non-verbal testing of semantic memory, patients show deficits when asked to select the appropriate colour for a black-and-white line drawing of a familiar object (e.g. yellow for banana), to draw animals and objects from memory, to use previously familiar objects (e.g. a box of matches, kitchen utensils, etc.) and to match common object and animal sounds to the appropriate picture (Bozeat *et al*., 2000; Hodges *et al*., 2000; S. Bozeat, M. A. Lambon Ralph, K. S. Graham, K. Patterson, H. Wilkin, J. Rowland *et al*., unpublished results). In contrast to the impairments seen on tests of semantic knowledge, the patients perform well on tests of visuo-perceptual and spatial ability, non-verbal problem solving and working memory, even at the relatively late stages of the disease (Breedin *et al*., 1994; Hodges *et al*., 1994, 1995; Graham *et al*., 1997*b*; Waltz *et al*., 1999).

The relatively selective loss of semantic memory shown in this disease has led many researchers to adopt the term 'semantic dementia' as opposed to the designation 'progressive fluent aphasia' (see Snowden *et al*., 1989; Breedin *et al*., 1994; Hodges *et al*., 1994; Snowden *et al*., 1994). Readers should also be aware that patients with semantic dementia may be described clinically as having the temporal variant of frontotemporal dementia (Miller *et al*., 1993; Edwards-Lee *et al*., 1997). Criteria for the diagnosis of semantic dementia, very similar to those employed in Cambridge, have been proposed by the consensus study group on frontotemporal lobar degeneration (Neary *et al*., 1998). The two major subtypes of frontotemporal dementia—reflecting the major locus of pathology, predominantly frontal versus temporal—have distinct cognitive profiles, including the status of semantic and episodic memory (Hodges *et al*., 1999; Rahman *et al*., 1999; Perry and Hodges, 2000). In this paper, the neuropsychological data we will review pertains only to the temporal variant of frontotemporal dementia (i.e. semantic dementia).

2.2 *Neuroradiology and neuropathology*

In all cases of semantic dementia, including more than 30 studied in Cambridge, there is focal atrophy of the inferolateral aspect of the temporal lobe, which is typically most marked on the left, but may be bilateral (Breedin *et al*., 1994; Hodges *et al*., 1995, 1998). A recent voxel-based morphometry analysis of the MRI scans of six patients with semantic dementia demonstrated that the most significant and consistent locus of atrophy was the left polar and inferior temporal lobe [Brodmann area (BA) 38/20] (Mummery *et al*., 2000) and a neuropathological study by Harasty *et al*. (1996) found significant bilateral atrophy to the inferior and middle temporal gyri. The status of structures in the medial temporal lobe is more controversial: it has been widely thought that the hippocampi are relatively spared in semantic dementia, at least in the early stages of the disease (Graham and Hodges, 1997; Graham *et al*., 1999*b*, 2000). In support of this view, Mummery and colleagues' voxel-based morphometry study found no evidence of hippocampal atrophy in their group of patients with semantic dementia (Mummery *et al*., 2000).

Evidence concerning the pathological basis of semantic dementia is still scant, although earlier speculation that this was unlikely to reflect a variant of Alzheimer's disease is currently upheld: two cases that have been subject to post-mortem in Cambridge have shown changes consistent with Pick's disease and a meta-analysis of 13 cases from the literature revealed that all had either Pick bodies or non-specific histological changes without either Alzheimer's or Pick's pathology (Hodges *et al*., 1998). In terms of the integrity of neuroanatomical structures at post-mortem, while on the one hand there is consensus about the involvement of the anterior temporal regions, temporal pole and inferomedial temporal cortices (Snowden *et al*., 1996*b*; Hodges *et al*., 1998), there is variability in the degree of reported hippocampal pathology. Graff-Radford and colleagues noted severe involvement of the hippocampus, but Harasty and co-workers and Scheltens and colleagues found absolute and

relative sparing of this structure, respectively (Graff-Radford *et al*., 1990; Scheltens *et al*., 1990; Harasty *et al*., 1996).

This brief overview of the literature on neuroradiological and neuropathological studies of semantic dementia illustrates that further investigations of the status of temporal lobe structures are needed in semantic dementia, in particular those that compare methods of hippocampal measurement *in vivo* and that correlate neuropsychological performance and neuroanatomical damage. Three recent studies have attempted to address this issue and provide more informative data about the neuropathological basis of the disease. Galton and co-workers used a visual rating scale (validated against volumetric measures) to assess the extent of atrophy in the hippocampus, parahippocampal gyrus, anterior and lateral temporal lobe in 30 patients with probable Alzheimer's disease, 30 patients who fulfilled consensus criteria for frontotemporal dementia (17 with semantic dementia and 13 with the frontal variant of frontotemporal dementia) and 18 control subjects (Galton *et al*., 2001). The major findings from this study were: (i) 50% of the patients with Alzheimer's disease had moderate to severe bilateral hippocampal atrophy compared with the control subjects, but little involvement of other temporal lobe structures; (ii) patients with semantic dementia also had some hippocampal atrophy, particularly evident on the left, in conjunction with significant atrophy bilaterally of parahippocampal regions, lateral temporal lobe and temporal pole; and (iii) the frontal variant frontotemporal dementia group had atrophy in the temporal poles, hippocampi and right parahippocampal gyrus (a pattern that was largely indistinguishable from that seen in Alzheimer's disease). 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 Alzheimer's disease and semantic dementia. Taken together these studies confirm that atrophy of the polar and infero-lateral temporal regions differentiates patients with Alzheimer's disease and semantic dementia, but that atrophy to hippocampal and parahippocampal regions can be present in both diseases, with bilateral involvement in Alzheimer's disease and predominantly left-sided atrophy in semantic dementia.

To date, only one empirical study has compared episodic memory performance and degree of temporal lobe atrophy in semantic dementia (Simons *et al*., 2000). Simons and colleagues used the validated visual rating scale described above (developed by Galton *et al*., 2001) to assess the degree of involvement of temporal lobe regions in the disease, and on the basis of results from this scale, characterized the laterality of a patient's atrophy as either predominantly left ($n = 4$), predominantly right ($n = 4$) or bilateral ($n = 5$). Subsequently, the authors analysed which of these groups showed a significant episodic memory deficit on the faces component of the Warrington recognition memory test (Warrington, 1984). It was found that so long as atrophy was restricted to the left temporal lobe, patients showed preserved recognition memory. In contrast, patients with right temporal lobe damage, in particular with involvement of the hippocampus and parahippocampal gyrus, were significantly impaired on the test. This study is important for two reasons: (i) it confirms that episodic memory, at least as measured by the faces version of the Warrington recognition memory test, can be preserved in some patients with semantic dementia; and (ii) it reveals that performance on episodic memory tests in the disease is affected by both the extent of atrophy and the laterality of the pathology.

In summary, recent studies that have used rating scales and volumetric measures of temporal lobe regions support the view that anterior and inferior areas of the temporal lobe are affected early in the disease and that this profile is different from that seen in Alzheimer's disease. With respect to medial temporal lobe regions, Chan and colleagues' and Galton and co-workers' investigations clearly demonstrate that the hippocampi and parahippocampal gyri are involved at some point in the progression of the pathology of the disease, although it is unclear how neuropathological involvement correlates with neuropsychological profile (Chan *et al*., 2001; Galton *et al*, 2001). Simons and colleagues' experiment reveals that the status of episodic memory, as measured by recognition memory, correlates negatively with atrophy in medial temporal lobe structures and that asymmetrical patterns of pathology may play a critical role in explaining the pattern of performance exhibited by a patient on tests of episodic and semantic memory (Simons *et al*., 2000). To date, however, a number of important issues relating to the neuropathology in semantic dementia remain unclear and must be considered along with the issues discussed in detail later in this review. For example, at what stage in the disease are medial temporal lobe regions implicated and does the progression of pathology from more lateral to medial areas in the temporal lobe correspond to increasing difficulty on tests of episodic memory? Furthermore, it is important to note that measures of atrophy, such as the rating scales and volumetrics used by Galton, Chan, Simons and colleagues, are not measures of functionality and that we must be careful in extrapolating directly between these structural measures and our cognitive models of memory function.

The only functional imaging study in patients with semantic dementia illustrates how we need to be cautious about interpreting structural MRI data (Mummery *et al*., 1999). The authors measured regional cerebral blood flow (rCBF) using PET in a semantic decision task in four patients compared with six control subjects. Surprisingly, the patients showed a significant reduction in activity in the left posterior inferior temporal gyrus (BA 37). Voxel-based morphometry, however, revealed significant anterolateral temporal lobe damage (especially on the left side) but no significant structural damage to BA 37. Mummery and colleagues propose that the reduced rCBF seen in BA 37, which is thought to be involved in lexical retrieval (Moore and Price, 1999), is consistent with a loss of activation from more anterior, structurally damaged, temporal regions. The study

also shows that lack of structural damage in neurodegenerative patients (as measured using volumetrics or rating scales) does not necessarily conform to normal functionality in that neuroanatomical region.

2.3 *Case history*

The following case-history, from a patient who was studied longitudinally over 3 years (1994–97), illustrates the pattern of cognitive deficits commonly seen in semantic dementia (see also Hodges and Patterson, 1996; Graham and Hodges, 1997; Knott *et al*., 1997).

A.M. (d.o.b. 1930), an ex-works manager, presented in April 1994 with an informant-confirmed history of progressive word-finding and comprehension difficulties. The following transcription illustrates this point: while A.M.'s speech was fluent and contained few phonological or syntactic errors, it was strikingly devoid of content.

E.: Can you tell me about a time you were in hospital?
A.M.: Well one of the best places was in April last year here (ha ha) and then April, May, June, July, August, September and then October, and then April today.
E.: Can you remember April last year?
A.M.: 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 bar of the brain (indicates left), not the, the other one was okay, but that was lousy, so they did that and then doing everything like that, like this and probably a bit better than I am just now (indicates scanning by moving his hands over his head).

A.M. was a well-educated man with a wide-range of sporting and academic interests. After leaving school at the age of 16 years, he went to night school and then on to university to complete an undergraduate degree in engineering and a master's degree in science. For the rest of his working life, he was employed by the same internationally renowned company, where he eventually became a manager with responsibility for over 450 employees. During his career he travelled extensively, including a 2-year period in the southern hemisphere. The number of awards received by A.M. during his career is testimony to the success he had in his chosen profession.

Formal neuropsychological testing in April 1994 revealed that A.M. was severely impaired on tests of picture naming. He was able to name only three out of 48 black-and-white line drawings of highly familiar objects and animals. On a word-picture matching test based on the same 48 items, A.M. scored 36 out of 48 (25 age-matched controls score, on average, 47.4 $\pm$ 1.1; see Hodges and Patterson, 1995). On the picture version of the Pyramid and Palm Trees Test, a test 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 and Patterson, 1992), A.M. scored 39 out of 52. Control subjects typically score close to ceiling on this test. On non-semantic tasks, e.g. copying the Rey Complex Figure (Osterrieth, 1944), however, A.M.'s performance was faultless. When asked to reproduce the Rey Complex Figure after a 45 min delay, A.M. scored 12.5 (control mean = 15.2 $\pm$ 7.4). On non-verbal tests of problem solving, such as Raven's Coloured Matrices (Raven, 1963), a multiple-choice test of visual pattern matching which requires the subject to conceptualize spatial relationships, A.M.'s performance was also remarkably unimpaired.

A.M. was tested approximately every 6 months for the next 3 years. Figure 1A shows his longitudinal performance on the 48-item picture naming and word–picture matching test mentioned previously. A.M. was profoundly anomic when he first presented. This pattern remained remarkably consistent over the six testing sessions (for a more detailed discussion pertaining to A.M.'s anomia see Knott *et al*., 1997). With respect to word–picture matching A.M. showed a dramatic loss of semantic knowledge over time, which resulted in him performing close to chance by 1996 (5 out of 48; controls = 47.4 $\pm$ 1.1). Figure 1B reveals a similar pattern on the pictorial version of the Pyramid and Palm Trees Test: in May 1996, A.M. scored 25 out of 52 (controls = 51.2 $\pm$ 1.4).

Despite this rapid loss of semantic knowledge, A.M. showed no significant decline on tests of non-verbal problem solving, such as the Raven's Coloured Matrices (Raven, 1963), scoring 36 out of 36 in November 1996. As noted previously, his copying of the Rey Complex Figure (Osterrieth, 1944) was similarly preserved and stable over time (Fig. 1C): in November 1996 he scored 33 out of 36 (controls = 34.0 $\pm$ 2.9). Figure 1C also shows A.M.'s longitudinal performance on delayed recall of the Rey Figure. While it is clear that A.M.'s performance on this non-verbal memory test has declined over time, even in November 1996 he was still able to reproduce some of the figure (scoring 5 out of 36; controls = 15.2 $\pm$ 7.4). Auditory-verbal short-term memory, as measured using forwards and backwards digit span, was initially normal, but has since declined: A.M.'s forwards digit span dropped from 7 to 4 (controls 6.8 $\pm$ 1.0), while his backwards span fell from 6 to 0 (controls 4.8 $\pm$ 1.2) over the six testing sessions.

A.M.'s loss of 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 rain storm), selected an inappropriate item (e.g. bringing his wife, who was cleaning the upstairs bathroom, a lawn mower instead of a ladder), and mistaken various food items (e.g. at different times, 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 have acquired a new and frightening quality to him: on a plane trip early in 1996 he became clearly distressed at his suitcase being X-rayed and refused to wear a seat-belt in the plane.

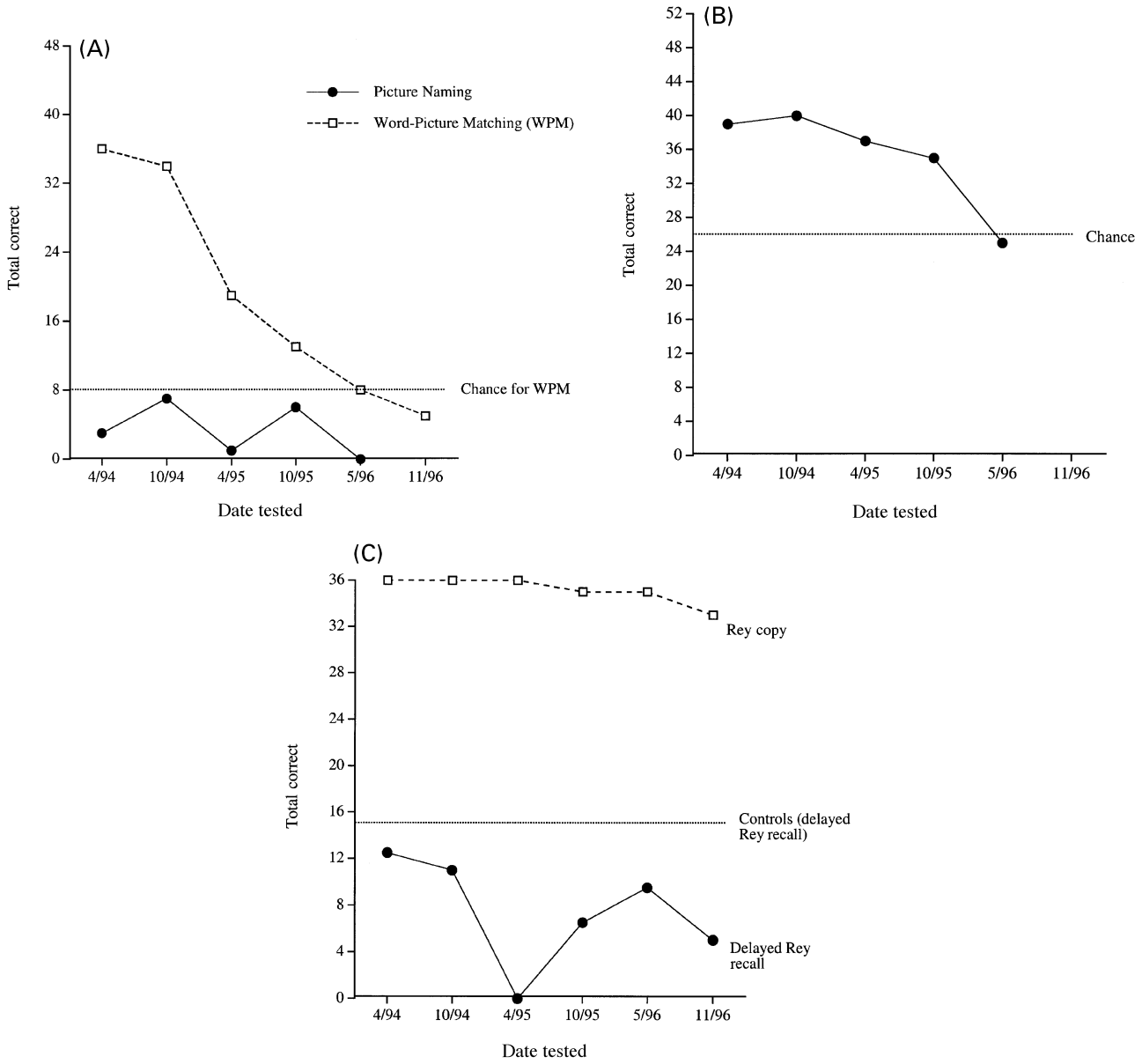

Fig. 1 A.M.'s performance on a number of standard neuropsychological tests over six testing sessions (from April 1994 to November 1996). (**A**) A 48-item picture naming and word–picture matching test from Hodges' semantic battery (Hodges *et al.*, 1992; Hodges and Patterson, 1995). (**B**) A three-picture version of the 52-item Pyramid and Palm Trees Test (Howard and Patterson, 1992). (**C**) Copying and delayed recall (45 min) of the Rey Complex Figure (Osterrieth, 1944).

Since 1997, A.M. has deteriorated generally, becoming increasingly withdrawn, time-obsessed and disinhibited. Like another patient (J.L.) described by Hodges and colleagues, A.M. showed a fascinating mixture of 'preserved and disturbed cognition' (Hodges *et al.*, 1995, p. 467). J.L. would set the house clocks and his watch forward in his impatience to get to a favourite restaurant, not fully comprehending the nature of the relationship between the clock and world time. In A.M.'s case, 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 rather obsessive about his 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 that his wife had taken the keys from his key-ring. Despite his semantic problems, A.M. continued to play sport (particularly golf) regularly each week, remembering correctly when he was to be collected by his friends. In late 1997, however, A.M. lost his sense of time and took to sitting up at night waiting for his golfing partners. His wife reported, however, that despite these profound comprehension difficulties he still possessed problem-solving skills: for example, in 1997, he successfully took up dominoes.

Figure 2 shows two coronally orientated, T_1-weighted MRI images of A.M.'s brain, obtained in November 1995. The

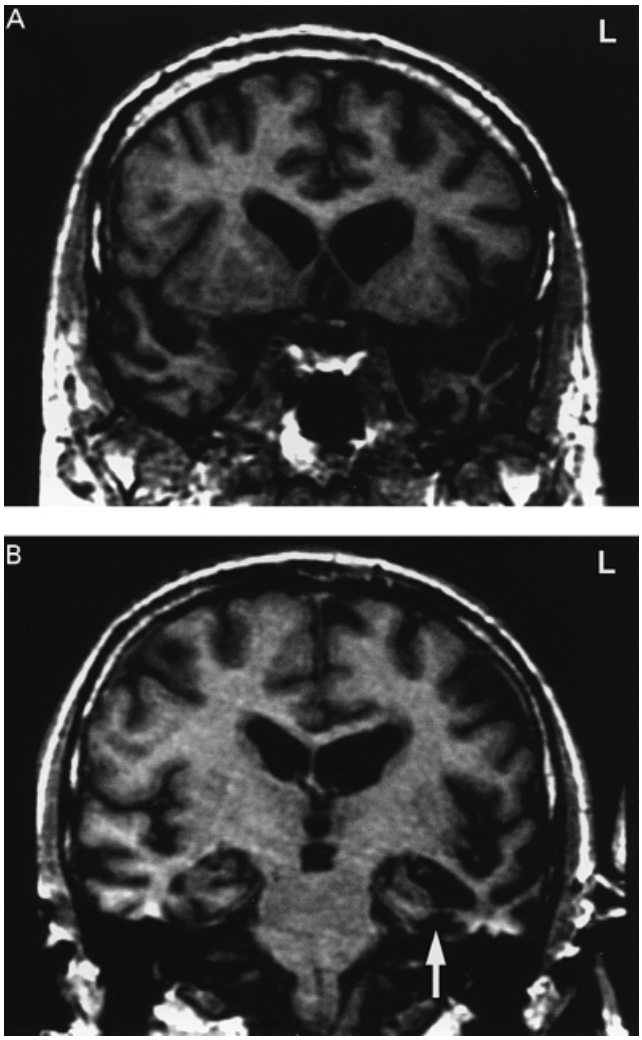

Fig. 2 Two coronal MRIs, T_1-weighted, taken from A.M. in November 1995. (**A**) Severe left temporal pole atrophy with a lesser degree of shrinkage to the right temporal pole. (**B**) This scan reveals that the left-sided temporal lobe atrophy involves the infero-lateral region and, possibly, the superior temporal gyrus. Both hippocampi look relatively preserved, although there is evidence of some shrinkage to the entorhinal and perirhinal cortices on the left. Rating of A.M.'s brain from an MRI scan (February 1995) using measures developed by Galton *et al*. (2001) confirmed these observations, although there was also evidence of significant atrophy to the hippocampus and parahippocampal gyrus bilaterally [see Simons *et al*. (2000), Fig. 1].

upper panel (A) illustrates severe left temporal pole atrophy with a lesser degree of shrinkage to the right temporal pole (note that the frontal lobes appear normal). The lower panel (B) shows that the left-sided temporal lobe atrophy involves the inferolateral region and to a lesser degree the superior temporal gyrus. The left hippocampal complex is relatively preserved, but the entorhinal cortex and perirhinal cortex are almost certainly affected, as evidenced by the gross enlargement of the collateral sulcus (indicated with an arrow). The right medial temporal lobe appears normal. The rating of A.M.'s brain from an MRI scan (February 1995), using measures developed by Scheltens and colleagues and Galton and co-workers, confirmed, to some extent, these observations (Scheltens *et al*., 1992; Galton *et al*., 2001). Notably, however, there was evidence of significant atrophy to all regions (including the hippocampus and parahippocampal gyrus) bilaterally (see Fig. 1 from Simons *et al*., 2000).

In summary, A.M.'s case history illustrates a number of characteristics (see Hodges *et al*., 1992) associated with 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) relative sparing of syntactic and phonological aspects of language; (iii) normal perceptual skills and non-verbal problem-solving abilities; and (iv) relatively preserved recent autobiographical and day-to-day (episodic) memory.

In some senses, the neuropsychological profile observed in patients with semantic dementia (i.e. poor semantic knowledge with relatively preserved episodic memory) seems to provide support for a fractionation between episodic and semantic memory, at least at the psychological level. Patients with semantic dementia provide us, therefore, with a unique opportunity to investigate the organization of human memory and to test the validity of current models of memory consolidation. Before summarizing some of the recent work in semantic dementia, which has addressed this issue, we will briefly review current computational models of amnesia and discuss how these networks can inform us about neurological disorders of long-term memory.

3. Models of long-term memory

3.1 *Neuroanatomy and global architectures of connectionist models*

At present, only one connectionist model of long-term memory, TraceLink, makes specific reference to semantic dementia (Murre, 1996, 1997). As we will discuss, however, several other computational models can easily be extended to incorporate the neuropsychological data from this disorder. In this section, we will concentrate on the model by Murre and on two other connectionist models that are felt to be particularly promising in explaining the cognitive phenomena arising from semantic dementia, namely those described by Alvarez and Squire (1994) and McClelland *et al*. (1995). A more extensive and general review of computational models of amnesia, the hippocampus, and long-term memory can be found in the papers by McClelland *et al*. (1995) and Gluck and Myers (1995). Recent special issues of *Hippocampus* (Gluck, 1996) and *Memory* (Mayes and Downes, 1997) also provide a good overview of the current state of computational modelling in this area.

Recent developments in neuroanatomy suggest that the neocortex is densely and bidirectionally connected with the hippocampus and related areas. Although the connectionist models (and non-connectionist theories) of long-term memory

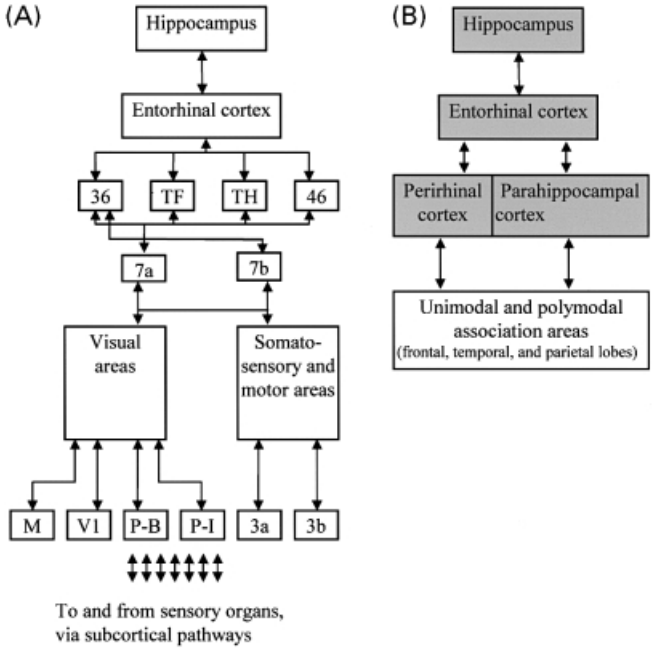

Fig. 3 (**A**) A highly simplified scheme of the visual, somatosensory and motor areas in the neuroanatomical hierarchy, derived from work by Felleman and Van Essen (1991, Figs 4 and 7; see also Squire and Zola-Morgan, 1991, Figs 1 and 6). The top of the hierarchy is formed by the hippocampus and entorhinal cortex. Below this is the perirhinal area 36 (a higher associative area), temporal areas TF and TH, and frontal area 46. While parietal area 7a is mainly visual and 7b is mainly somatosensory, both have cross-modal connections. The box labelled 'Visual areas' covers ~26 other areas, and the box labelled 'Somatosensory and motor areas' covers an additional 10. The lower visual areas are magnocellular (M), visual area 1 (V1), parvo blob stream (P-B) and the parvo-interblob stream (P-I). The lower somatosensory and motor areas are 3a and 3b. (**B**) Schematic drawing of the medial temporal lobe memory system (including the shaded boxes), derived from work by (Squire and Zola-Morgan (1991, Fig. 1) (see also Squire, 1992, Fig. 2).

stress the importance of the hippocampus, there is little doubt that other medial temporal lobe structures (e.g. entorhinal and perirhinal cortices, parahippocampal gyrus, etc.) are crucially involved in long-term memory consolidation. As will be discussed in more detail later in this article, it is possible that the hippocampus is critical for episodic retrieval, but that other regions of the medial temporal lobe can support learning and consolidation of semantic facts. Felleman and Van Essen position the hippocampus at the top of the neuroanatomical hierarchy of interconnected brain areas, with the sensory and motor organs at the bottom (see Fig. 3A, and Felleman and Van Essen, 1991). Figure 3B illustrates a similar hierarchy described by Squire and Zola-Morgan, in which the entorhinal area is bidirectionally connected to the perirhinal (BA 36) and the parahippocampal cortices (Squire and Zola-Morgan, 1991; Squire, 1992). The lower part of the hierarchy is less specified and represented by a single box called 'unimodal and polymodal association areas' (frontal, temporal and parietal lobes).

The three computational models described in this paper assume this basic neuroanatomical framework and subscribe to the view that the neocortex and hippocampus play distinct, but complementary, roles in long-term memory storage (i.e. memories are acquired and stored in the brain via the process of memory consolidation). Although different with respect to some details (see later), the general principles underlying these three models are very similar. Whereas 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. The nature of the consolidation process is largely unknown, but some recent evidence suggests that it may take place during sleep: Wilson and McNaughton (1994) proposed that, during slow-wave sleep, hippocampal representations may be re-activated and used to reinstate the entire cortical activation pattern that was present during the initial learning experience.

At this point, it is important to consider the reasons why we may have evolved a complementary learning system. Murre and Sturdy (1995) argued that this process was necessary because there is compelling neuroanatomical evidence that the neocortex does not have sufficient connectivity to rapidly link activated areas in the short time that an individual experiences an event. This cortical connectivity problem has two important effects: (i) it is highly unlikely that neural connections will be in place when two brain sites must be associated in order to form (part of) a new memory representation; and (ii) the formation of synaptic connections in the neocortex will be slow and accumulative. The neuroanatomical and modular hierarchy of the cortex (as illustrated in Fig. 3A and B) solves this connectivity problem because the hippocampus functions as an intermediate site, which can (i) link distant neocortical regions (see also neuroanatomical models by O'Reilly and McClelland, 1994; Treves and Rolls, 1994; McClelland and Goddard, 1996) and (ii) reinstate patterns of cortical activation (compare Abeles, 1991; Murre, 1996, 1997). Murre and Sturdy suggest, therefore, that memory consolidation is an essential biological process which allows us to circumvent the problems of sparse connectivity and create the long-range neocortical connections necessary for storing permanent memory representations.

McClelland and colleagues have proposed an alternative, although not necessarily mutually exclusive, hypothesis: memory consolidation helps prevent catastrophic interference in sequential learning (McClelland *et al*., 1995). Using computer-based simulations of semantic memory, they demonstrated that integrating new semantic facts into our existing neocortical database of semantic knowledge can have a negative impact on the integrity of that database. For example, they describe an experiment in which they compared presenting the concept of 'penguin' (a bird that swims but does not fly) directly to semantic memory (focused learning) as opposed to indirectly, via a training set (interleaved

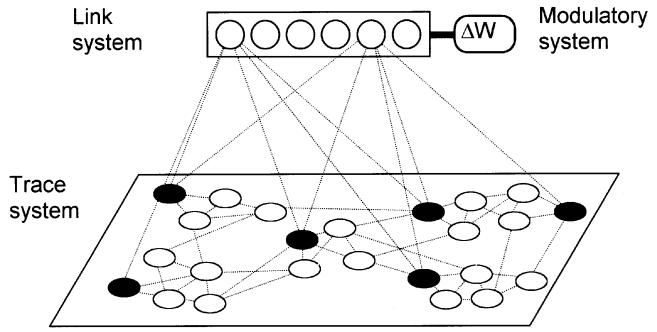

Fig. 4 TraceLink model by Murre (1996, 1997). Connectivity in the trace system (neocortex) is sparser than within the link system (hippocampus). The modulatory system (basal forebrain) regulates plasticity in the hippocampus and it also receives important control signals from there.

learning). In the focused learning condition, the network learnt about 'penguin' rapidly, but this acquisition of information had a detrimental effect on other bird concepts (e.g. 'robin'). Interleaved learning, while slower, did not result in such catastrophic interference.

Although initially counterintuitive, therefore, it might actually be desirable, both neuroanatomically and functionally, for the human brain to have evolved a complementary learning system in which the hippocampus and neocortex interact in the formation of long-term memories. Furthermore, as will become clear, there is strong evidence from studies of amnesia and semantic dementia that the retrieval of memories is influenced by time, a direct prediction from models in which memories are consolidated in the human brain.

3.2 *TraceLink model*

A schematic drawing of the TraceLink model is shown in Fig. 4. Its three main components are (i) a trace system, (ii) a link system, and (iii) a modulatory system. We will briefly summarize some of the details of the model's implementation, in particular specifics relating to the interaction between the three systems and the formation and maintenance of episodic (and semantic) memories.

Trace system

This system represents the neocortical basis for memories. The input to the trace system originates in the sensory areas, although these regions are not represented in the model. Similarly, output or motor areas are not included but are assumed. In the model, we abstract from the complex hierarchical structure of the cortex, reducing it to a system with many modules. Each of these modules contains a number of interconnected 'nodes', which are highly abstracted neurones. An episodic memory representation in the trace system is simply a number of activated (firing) nodes (for more details about the implementation of the nodes see Murre, 1996). It is presumed that a relatively small percentage of the nodes participate in a given representation and that nodes in the trace system are sparsely connected in a random fashion. Each node also has connections to and from a random subset of the nodes in the link system. A central assumption in the TraceLink model is that the formation of new long-range associations (i.e. associations between faraway neurones that are not directly connected) is a slow process compared with the formation of associations between the trace and link system.

Link system

The link system's function in the model is to interconnect remote trace nodes (i.e. those without direct cortico-cortical connections). The anatomy of the link system includes the hippocampus and certain other structures, such as the anterior medial temporal lobe structures of the brain. In the model, the link system has a much smaller number of link nodes than the trace system (i.e. it is of limited capacity) and each link node is connected to a random subset of trace nodes. These features are in accordance with our knowledge of the neuroanatomy, as described earlier in the review (Felleman and Van Essen, 1991). Link nodes are also interconnected within the link system (i.e. there are link–link connections). If the modulatory system is functioning well (see below), link–trace and link–link connections are formed more rapidly than trace–trace connections. Other models of amnesia also make a similar assumption of rapid hippocampal learning and slow cortical learning (e.g. Alvarez and Squire, 1994; McClelland *et al*., 1995).

Modulatory system

The modulatory system includes certain basal forebrain nuclei, especially the nucleus basalis with its cholinergic inputs to the hippocampus via the fornix (see Hasselmo, 1995, 1999) and several areas that have a more indirect, controlling function. The role of the system is to trigger increased plasticity in the link system and hence the ability of the link system to record rapidly a new episodic representation. The modulatory system may be activated directly through central states such as arousal and attention, and through stimulus-specific factors such as novelty and biological relevance (i.e. emotional stimuli involving danger, food, sex, shelter, etc.; these aspects are thought to be processed through the amygdala).

In the following section, we will discuss briefly the processes of normal episodic learning and retrieval, and comment on how TraceLink accounts for some of the data on retrograde amnesia.

Normal learning and recall

Under normal circumstances, a memory representation passes through roughly four stages (see Fig. 5).

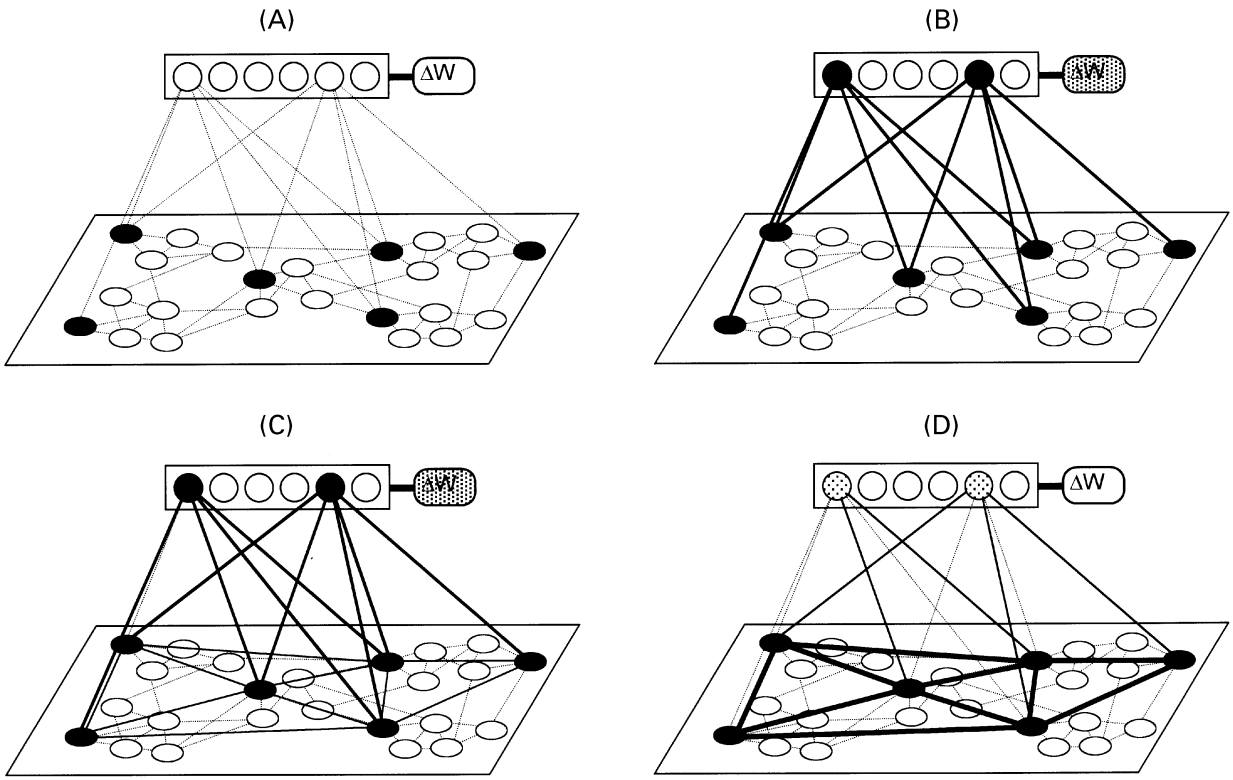

Fig. 5 Four consolidation stages in the TraceLink model. See text for an explanation.

Stage 1 (Fig. 5A). Sensory and motor information, comprising an episode-to-be-remembered, activates a set of trace nodes (filled circles).

Stage 2 (Fig. 5B). The trace elements activate a set of link nodes within seconds. The modulatory system is sufficiently active (e.g. a new or interesting pattern is present), allowing an increase in plasticity in the link system and a subsequent strengthening of connections between activated link nodes and trace nodes (shown by the thickening of the connections). In both the link and trace system, the activation of new memory ensembles will gradually result in the overwriting of older representations (i.e. forgetting). This interference process is more evident in the link system compared with the trace system, however, because the hippocampal system has lower capacity and higher plasticity.

Stage 3 (Fig. 5C). This stage represents the initial consolidation process. Repeated activation—via rehearsal, reminiscence and perhaps sleep—of the link–trace ensemble leads to the gradual formation of trace–trace connections. These are initially weak, but grow in strength with each consolidation episode.

In TraceLink, the repeated re-activation of learned representations that drives the consolidation process is simulated as follows. The link system is given a burst of random activation, which initiates a random search for the nearest representation. During the search, both the trace system and the link system are active. After a stable representation has been found, the representation remains active until the next burst of random activation in the link system. The search time for a representation is much shorter than the post-search time during which the actual consolidation takes place. Consolidation occurs through the formation and strengthening of connections within the trace system at a fixed base rate (i.e. the trace system's plasticity is not modulated and is the same at all stages). Unlike the trace system, the link system is not plastic during the consolidation process (i.e. there is no change to the link–link or the link–trace connections): if the link system was plastic this would result in runaway consolidation where one particular memory would become overly strong (see later discussion). We refer to Murre for more details on the implementation of the consolidation process (Murre, 1996).

Stage 4 (Fig. 5D). In the final stage of consolidation, trace–trace connections have become very strong. Link–trace connections may have decayed or been reassigned to other memory traces and retrieval of the initial memory is now independent of the link system.

Initially, a memory representation is dependent upon the link system, but towards completion of the consolidation process it becomes predominantly reliant on the trace system. This 'transfer' of memory representations is the basis for explaining retrograde amnesia. By making the link nodes inactive (i.e. modelling a hippocampal lesion) all memory representations at stage 2 are lost. Stage 3 representations may be preserved if they have received sufficient consolidation,

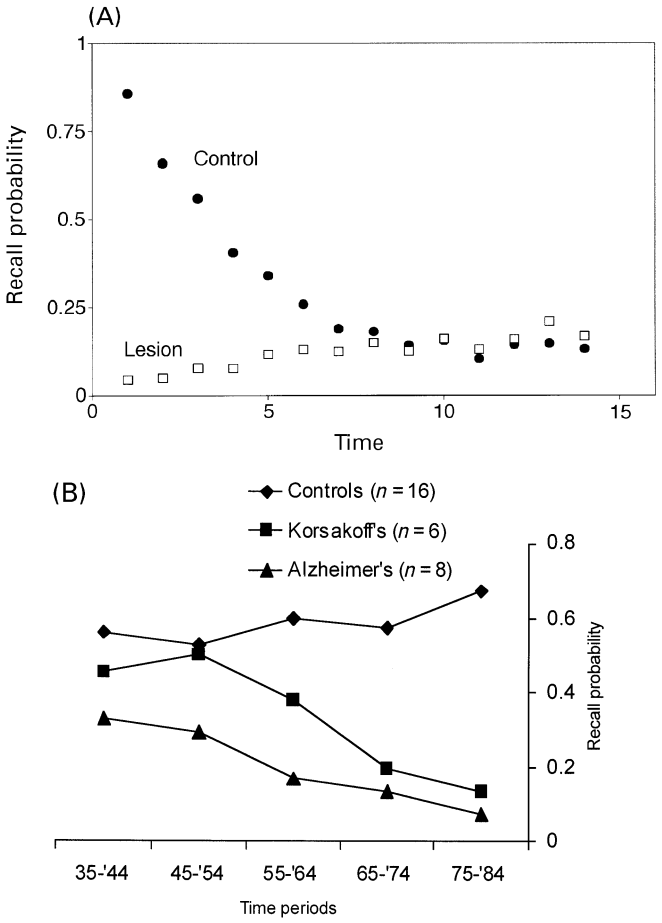

Fig. 6 (**A**) Simulation described in J. M. J. Murre and M. Meter, unpublished results. The normal forgetting gradient (Control) is contrasted with a Ribot gradient (Lesion), where the link system is lesioned. Although the effect is not very prominent, recent representations were significantly better preserved. Since 1996, this simulation has been replicated and similar, as well as steeper, Ribot gradients have been obtained. The TraceLink model was implemented with a link system of 42 neurones and a trace system of 200 neurones. The learning rate in the link system was chosen to be twice as high as that in the cortex. Probabilistic 'spiking' neurones were used, with high inputs increasing the probability of firing (Ackley *et al.*, 1985). A threshold was automatically adjusted in each system, so that, on average, a pre-chosen number of neurones was firing. Learning followed a modified Hebbian learning rule [after Hebb (1949) and Singer (1990)]. (**B**) The simulation may be compared with data from Kopelman (1989) on a public events test in Alzheimer and Korsakoff patients (reproduced here). Note that these tests are typically constructed such that normal subjects (Controls) show very little forgetting for remote time periods. This causes the Ribot gradients in the patient groups to appear more prominent.

whereas stage 4 representations will always be intact. If we assume that the majority of autobiographical memories are consolidated at about the same rate, taking into account the fact that emotional and environmental factors will result in some memories being reinstated more or less often, recent memories will be lost because these will be mainly at stages 2 and 3. Lesioning of the link system, therefore, results in a characteristic Ribot gradient (see Fig. 6A), which fits a power

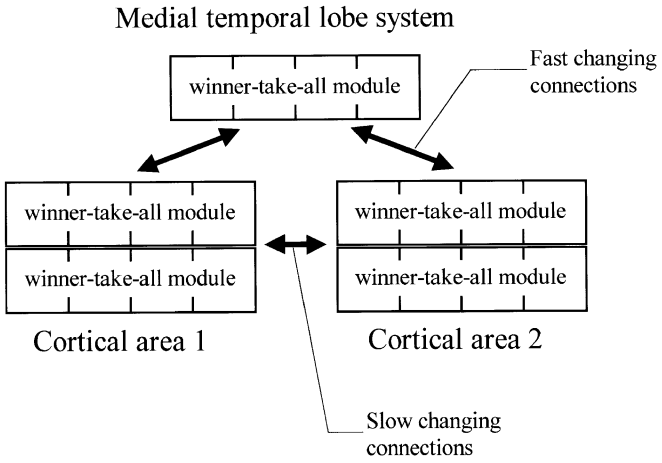

Fig. 7 Model by Alvarez and Squire (1994). The neurones in each module are in a 'winner-take-all' competition, such that only the 'winner' is activated, whereas the other three neurones are set to 0. 'Winner' is the neurone that receives the highest net input. Activations can take any value between 0.0 and 1.0. The thick arrows indicate bidirectional connections between all neurones in the connected areas. The connections shown are all excitatory and modifiable (initially they are very low). They are changed by a normalized Hebbian learning rule that keeps the weight values between 0.0 and 1.0.

function [control (forgetting): $P(t) = 1.1031t^{-0.8384}$, $r^2 = 0.9324$; Ribot: $P(t) = 0.041t^{0.5682}$, $r^2 = 0.922$] and can be compared with remote memory data in patients with Alzheimer's disease and Korsakoff's syndrome (Fig. 6B) (Kopelman, 1989). The exponent of the Ribot curve of 0.5682 indicates that there is a clear increase of recall probability with memory age. More details on the explanations of amnesia by the TraceLink model can be found in other papers (Murre, 1996, 1997), where we describe anterograde amnesia, preserved implicit memory, shrinkage of retrograde amnesia and details of the consolidation process.

3.3 *Other connectionist models of amnesia*

Two other models of amnesia have been published, one by McClelland and colleagues and one by Alvarez and Squire (Alvarez and Squire, 1994; McClelland *et al.*, 1995). Alvarez and Squire (see also Squire and Alvarez, 1995) present a connectionist implementation based on earlier, non-computational, models of long-term memory by Squire and co-workers (e.g. Squire *et al.*, 1984; Squire and Zola-Morgan, 1991; Squire, 1992). In this model, the entire medial temporal lobe system (see Fig. 3B), rather than just the hippocampus, functions as a site that binds together remote cortical areas (in a similar manner to that suggested by Murre, 1996). Each of these specialized cortical areas contributes to a complete memory representation. A consolidation process is assumed during which cortico-cortical connections emerge between the disparate cortical sites.

The model is implemented in a small connectionist network, where the medial temporal lobe system is represented by four neurones (see Fig. 7). Similar modules

of four neurones make up two 'cortical areas'. In each of these 'winner-take-all' modules, only one out of the four neurones can remain activated. An assumption in this model is that links to and from the medial temporal lobe system have a higher learning rate than the cortico-cortical connections (50 times higher).

Simulations with the model showed an initial steep forgetting curve due to fast decay of the medial temporal lobe connections. The system continuously received intermittent consolidation trials, so that additional forgetting was lessened after the initial stage because the cortico-cortical connections, which have a slower decay rate, became more important for recall. Forgetting is simulated by weight decay in the medial temporal lobe initially and then in the cortico-cortical areas. Recall was tested by presenting half of a pattern and assessing how well the other half was recalled.

When the medial temporal lobe system was lesioned immediately after training, performance was near chance because the system had not yet received any consolidation trials and was thus still fully dependent on the (lesioned) medial temporal lobe connections. After sufficient consolidation, lesioning showed no effect on performance because pattern recall had become fully independent of the medial temporal lobe system. The simulations thus showed a clear Ribot gradient in that recent memories had a higher chance of being lost when the medial temporal lobe system was lesioned.

While Alvarez and Squire's (1994) and Murre's (1996) models stress that the hippocampus (medial temporal lobe) links geographically separate cortical regions, McClelland *et al*. (1995) view the role of the hippocampus slightly differently. These authors have suggested that recent memories are initially stored through fast-changing synapses in the hippocampal system. More specifically, during initial learning a copy of the cortical representation resides in the hippocampus. This 'summary sketch' of the memory must be sufficient to retrieve the whole of the neocortical trace. Repeated reinstatement of the hippocampally based memory results in the accumulation of subtle neocortical changes, allowing the new memory to be integrated gradually into existing neocortical networks. McClelland and colleagues propose, therefore, that the hippocampus functions as a 'trainer', teaching the hippocampal representations to the cortex, thereby achieving the necessary integration of new and old semantic knowledge and avoiding catastrophic interference. Without such gradual integration of new semantic information, via interleaved learning of new and old patterns by the hippocampus, the cortex part of the model would suffer from very strong interference, whereby new patterns would overwrite old patterns very rapidly. The reason for catastrophic interference in McClelland and colleagues' model is that learning is implemented with the back-propagation algorithm (Rumelhart *et al*., 1986). Other models of amnesia, such as TraceLink, do not use a backpropagation method and, therefore, do not show such catastrophic interference.

McClelland *et al.* (1995) report simulations with recall curves before and after lesioning (i.e. disabling) of the hippocampal system and show that while hippocampal lesioning results in a Ribot effect, whereby recent memories are harder to retrieve than older memories, the unlesioned model shows normal forgetting over time. The simulations are in excellent agreement with the experimental data by Zola-Morgan and Squire who obtained evidence for memory consolidation in monkeys over a period of ~10 weeks (Zola-Morgan and Squire, 1990).

In contrast to the TraceLink model, the 'hippocampus' in the connectionist model by McClelland *et al.* (1995) is not implemented as a neural network, but simply as a set of stored patterns. As pointed out by McClelland and colleagues, this simulation should be viewed as a computational implementation of a more biologically and anatomically plausible model that has been analysed in some detail by McClelland and co-workers (O'Reilly and McClelland, 1994), although no amnesia simulations have yet been undertaken with this more biologically plausible model. The approach whereby the function of biological structure is simulated by a non-biologically plausible model is used with success in computational cognitive neuroscience. For example, a similar approach was taken by Gluck and Myers, who simulated a large number of experiments on learning in healthy and hippocampally lesioned animals using backpropagation to approximate the role of the hippocampus in mediating the compression of redundant representations in the brain (Gluck and Myers, 1993). Unfortunately, the non-connectionist implementation of the hippocampus in McClelland's model makes it less straightforward to predict certain characteristics of the neuropsychology of amnesia. It should be noted that the model by McClelland *et al.* (1995) is still being developed further. For example, O'Reilly and colleagues reported an up-dated form of the model, which includes recollection (implemented by the hippocampus) and familiarity (implemented by cortical regions) components (O'Reilly *et al.*, 1998).

3.4 *Modelling of other aspects of the amnesic syndrome: anterograde amnesia*

Whereas all three of the models discussed above can simulate the temporally graded retrograde amnesia seen in patients with bilateral damage to the medial temporal lobe, anterograde memory deficits are more difficult to implement. Most theoretical views accept that retrograde amnesia can occur in isolation, predominantly due to damage to temporal neocortical areas and/or frontal regions (Levine *et al*., 1998; Kapur, 1999), but it is controversial whether such a phenomenon as truly isolated or pure anterograde memory exists. In the models by McClelland *et al.* (1995) and Alvarez and Squire (1994), anterograde amnesia is explained exclusively in terms of loss of the hippocampal component (see Table 1), a view which predicts that retrograde and

Table 1 *Summary of the three connectionist models discussed in this paper*

	McClelland, McNaughton and O'Reilly model	Alvarez and Squire model	Murre TraceLink model
Learning in hippocampus (or MTL or link system)	Immediately stored in hippocampal store (no weight changes involved)	Fast, normalized Hebbian learning	Fast Hebb–Singer learning
Learning in neocortex	Gradual training of neocortex via error backpropagation	Slow, normalized Hebbian learning	Slow Hebb–Singer learning
Forgetting in hippocampus	Loss of hippocampal patterns via a stochastic (rule-based) process	Fast, spontaneous decay of weights	Gradual overwriting of old representations by new ones
Forgetting in neocortex	(Catastrophic) overwriting of old representations by new ones	Slow, spontaneous decay of weights	Gradual, slow overwriting of old representations by new ones
Activations	Continuous between 0 and 1	Continuous between 0 and 1	Stochastic 'spikes' of either 0 or 1
Consolidation of a single representation	A pattern p is selected from hippocampal store with probability D_p; the neocortex is trained with this pattern p; D_p declines over time	A neurone is selected randomly in the MTL, activation is allowed to spread to neocortex; Hebbian learning is applied to cortico-cortical connections	Random activations are allowed to settle into a stationary pattern in the link and trace system; Hebbian learning is applied to cortico-cortical connections
Cause of RA	Lesion of hippocampus	Lesion of medial temporal lobe	Lesion of link system
Cause of AA	*Lesion of hippocampus*	*Lesion of medial temporal lobe*	Lesion of modulatory system and/or lesion of link system
Correlation RA and AA	*High*	*High*	RA predicts a minimal level of AA, but AA does not strongly predict RA

Entries in italics indicate information that is deduced from the source papers, rather than stated by the authors of the model.
RA = retrogade amnesia; AA = anterograde amnesia.

anterograde memory should be strongly intercorrelated. From the neuropsychological literature, however, the degree of anterograde amnesia is not always a clear predictor of retrograde amnesia. For example, some studies note that retrograde amnesia and anterograde amnesia are correlated only weakly (ranging from 0.3–0.6) in populations with Alzheimer's and Korsakoff's disease (Shimamura and Squire, 1986; Kopelman, 1989, 1991; Schmidtke and Vollmer, 1997). More importantly, retrograde amnesia can occur in isolation (Kapur, 1993; Evans *et al*., 1996; Markowitsch, 1996). There are also reports of patients with varying aetiologies, such as fornix damage and transient global amnesia, who show moderate anterograde memory deficits with virtually absent retrograde amnesia (e.g. Hodges and Carpenter, 1991; Kazui *et al*., 1995). These results seem to suggest that a partial independence of anterograde and retrograde amnesia is possible (Kopelman, 1989; Meudell, 1992). Squire and Alvarez (1995) argue, however, that the findings of a relatively positive relationship between retrograde and anterograde amnesia in some patients is strongly indicative of a common lesion underlying both forms of amnesia. Whatever one's stance on this controversial topic, the experimental literature presents at least one very strong example of complete independence of anterograde and retrograde amnesia. Kopelman (1986) reported that cholinergic blockade results in a severe anterograde amnesia with virtually no accompanying retrograde amnesia. This study provides strong evidence in favour of a separate system that can trigger and modulate learning and that can be disrupted independently of other systems.

The TraceLink model does not show the same limitations, at least with respect to modelling anterograde memory, as the other two networks. This is because there are two main causes of anterograde amnesia in the model: (i) lesions of the non-hippocampal component of the modulatory system (e.g. through damage to certain basal forebrain lesions); and (ii) lesions of the link system. The latter lesion results in a correlated degree of anterograde and retrograde amnesia, but when the modulatory system is lesioned, this causes anterograde amnesia with little or no retrograde amnesia (for a more detailed discussion see Murre, 1996, 1997).

It is clear from the discussion above that all existing simulations of amnesia have severe limitations with respect to scale, generality and application (see Table 1 for a point-by-point summary of the three connectionist models described above). They do, nevertheless, allow us to investigate some of the assumptions present in existing, non-computational theories of amnesia. The example of consolidation strategy is especially illustrative here. It is extremely difficult to predict in advance how different factors, such as rate of decay from the hippocampus and rate of incorporation into the neocortex (McClelland *et al*., 1995), novelty (Murre *et al*., 1992), frequency of event re-occurence (see Anderson and Schooler, 1991) or biological relevance (LeDoux, 1996), would influence the length and outcome of memory consolidation. Fortunately, simulations exploring these topics

enable the generation of more precise constraints on what we mean by the term 'relevance' (see discussion in Murre, 1997) and also enable us to devise models in which the 'relevance' of a memory representation (in some form) is a guiding factor in consolidation (rather than random selection).

Questions about the implementation of consolidation strategies may also benefit from computational investigations. For example, TraceLink simulations showed that it was important to keep link connections (i.e. within, to and from the hippocampal area) fixed during consolidation and allow only within-trace (i.e. cortico-cortical) connections to be strengthened (see also Hasselmo, 1995, 1999). If this strategy was not followed, randomly selected patterns would become stronger in the link system, making it more likely that they would be selected again for further consolidation. This self-reinforcing strengthening would typically degenerate to a state whereby a single pattern would become extremely strong in the model, overwriting all others. McClelland *et al*. (1995) did not encounter this problem because their hippocampus was not implemented as a neural network model. Alvarez and Squire (1994) used only two patterns, making the system much less sensitive to such runaway consolidation.

3.5 *Multiple trace theory of memory consolidation*

Before turning to the question of whether these computational models can usefully explain the neuropsychological patterns seen in amnesia and semantic dementia, it is worth considering another theoretical view of memory consolidation that is relevant to semantic dementia. Nadel and Moscovitch pointed out that very few documented amnesic cases actually show a short duration temporally limited retrograde amnesia after bilateral hippocampal atrophy (as would be predicted by the interactive hippocampal–neocortical view described above: Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1999). Instead, many patients actually show retrograde memory deficits extending back as far as 25–40 years (Victor and Agamanolis, 1990; Kartsounis *et al*., 1995; Rempel-Clower *et al*., 1996). The authors proposed, therefore, 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.

Considering Nadel and Moscovitch's (1997) view in more detail, the initial stages of memory encoding are similar to that of the standard model: the 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 [as is true of Murre's (1996) TraceLink model]. Unlike the standard model, 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 recoded 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.

The implications of the formation of multiple traces within the hippocampal complex in Nadel and Moscovitch's (1997) model is that older memories have more traces and are more widely dispersed over the hippocampal complex, thereby reducing the vulnerability of these memories to selective hippocampal damage. In terms of retrograde amnesia, therefore, the extent of the lesion (selective hippocampal versus hippocampal and other medial temporal lobe regions) will be positively correlated with the extent of retrograde amnesia. Moscovitch and Nadel (1999) argue that this view is consistent with results from amnesic patients, such as those reported by Reed and Squire (1998), showing that patients with selective hippocampal lesions had only limited retrograde amnesia, while those with temporal neocortical damage had extensive, non-temporally graded impairments to autobiographical memory.

A noteworthy feature of the multiple trace model is that, unlike episodic memories, new semantic knowledge is consolidated in the cortex and thus becomes hippocampally independent. Consolidation of semantic information is useful because it helps prevent catastrophic interference in sequential learning [as demonstrated by McClelland and colleagues (1995) and discussed earlier in this paper]. The implication of this view is that a patient with a bilateral hippocampal lesion may show a flat gradient for the retrieval of autobiographical memories from the past, but a clear temporal gradient for remote semantic memory, e.g. knowledge of famous personalities. This pattern has not yet been demonstrated. At present, it is unclear how the multiple trace model 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 acquisition and storage of semantic knowledge.

Further evidence in favour of this compelling theoretical view was reviewed in a recent article (Nadel *et al*., 2000), including the results of analytical and connectionist simulations of the multiple trace model. The paper also describes a study of remote memory in patients with unilateral temporal lobe epilepsy either prior to surgery or following unilateral excision of the anterior temporal lobe (Viskontas *et al*., 2000) and a functional MRI study of retrieval of recent versus remote autobiographical memories (Ryan *et al*., 2001). The neuropsychological study found that participants who had undergone a unilateral temporal lobectomy showed an extensive retrograde amnesia, extending back in time to childhood. The side of lesion (left versus right) made no

difference to the extent of retrograde memory deficit. The neuroimaging study also found support for the multiple trace model: there was no significant difference in the magnitude of activation in the hippocampus when the recollection of recent memories was compared with the retrieval of remote memories. Activity in the hippocampus for both these episodic conditions, however, was significantly greater than for two control conditions (relaxing and sentence completion). This finding is clearly challenging to the standard model of memory consolidation as this theory would predict that the hippocampus is selectively involved in the retrieval of recent, but not older, autobiographical memories.

A further interesting aspect of the recent paper by Nadel *et al.* (2000) is the inclusion of two computational instantiations of their multiple trace theory: an analytical and a connectionist model. To implement the analytical solution appropriately, the process of trace multiplication in the hippocampus needed to be constrained in some manner, either by recent memories with a high probability of forming additional traces ('recency' case) or older memories, with more traces, having a lower replication rate ('saturation' case). Without such constraints on memory formation, some episodes end up with an exceedingly high number of traces at the expense of the majority of the other episodes. This process is reminiscent of the 'runaway' consolidation described earlier for TraceLink and would eventually result in the survival of a single event.

Having determined that the model required constraints on trace multiplication, Nadel and colleagues derived analytical results describing how an event accrues traces over time and the expected probability of recall of a memory with different ages and lesion sizes. These curves (Nadel *et al*., 2000, Fig. 2), however, cannot immediately be compared with data in patients with retrograde amnesia because the model does not take into account a reasonable amount of trace forgetting. More specifically, Nadel and colleagues only show the results for items that are successfully replicated and do not take into account the fact that a proportion of the events will not replicate and will subsequently be lost. It is likely that including a significant measure of forgetting will alter the curves described in the paper. At present, therefore, it is difficult to judge whether simulations from the model are/will be in agreement with reported data in amnesic patients.

The relative absence of forgetting in the analytical model is remedied in the connectionist model, which bears some similarities to TraceLink (Murre, 1996). The major difference, however, is that while trace replication takes place only in the hippocampus in Nadel and colleagues' model (Nadel *et al*., 2000), in TraceLink a similar process (i.e. consolidation) takes place only in the neocortex (trace system). To model trace replication, Nadel and colleagues created 15 learning episodes, each of which was followed by seven 'replay' events. During 'replay', a randomly selected partial cue is provided and one of the patterns that had been learnt already in the neocortex is retrieved by a pattern completion process. Pattern completion in the neocortex also causes retrieval of the hippocampal representation. A new 'neurone' is then activated in the hippocampal representation and the hippocampal trace undergoes learning. This process causes the hippocampal representation of a repeated event to become bigger and less vulnerable to damage.

Nadel *et al*. (2000) demonstrated that their model can account for data from amnesia by lesioning the 'hippocampus' after the entire learning process for all memories had been completed. The 'hippocampus' in the model was lesioned between 0 and 100%, resulting in a forgetting (control) curve for the 0% lesion, and in a variety of Ribot gradients in which the remote memory deficit became progressively more extensive in time the greater the damage to the hippocampus. In the control condition (0% lesion), the forgetting curve dropped from perfect recall at t_0 to 0.7 at t_{15}, an effect probably due to overlapping patterns overwriting already learned representations. The 100% lesion looks very different from the 90% lesion curve, the latter following a gradual slope upward from a recall probability of 0 (for the recent pattern) to ~0.5 (for the most remote pattern). The 100% lesion curve, however, is almost flat, at ~0.4. This paradoxical result, where the greater lesion results in less memory impairment, has not been fully explained by Nadel and colleagues.

Both the analytical and the connectionist model show that the multiple trace theory can indeed exhibit plausible forgetting curves and Ribot gradients. A more systematic comparison with the empirical neuropsychological data will be interesting, particularly in the analytical model. Given the increasing influence of the multiple trace model and the compelling results described in Nadel *et al.* (2000), it is important to consider data from studies of semantic dementia in terms of this view. As will become clearer in the following sections, the data from semantic dementia may be challenging to a theory in which the hippocampus is critical for the retrieval of all autobiographical experiences. For this reason, we will consider this alternative view of memory consolidation with respect to semantic dementia in more detail later.

4. Can computational models of human long-term memory and amnesia explain semantic dementia?

According to the models discussed above, semantic dementia is explained by assuming that the connectivity of the cortex (or trace system) becomes progressively reduced during the course of the disease, while there is initially little or no damage to structures in the medial temporal lobe (or link system). Over time, the pathology progresses from more lateral areas to the medial temporal lobe region and involves the hippocampal complex and adjacent cortices (Chan *et al*., 2001; Galton *et al*., 2001).

There are two main effects of reduced connectivity within the trace system: (i) loss of memory representations (both

semantic and episodic) stored in the neocortex; and (ii) an inability to consolidate newly experienced events. The first point is consistent with the main characteristic of semantic dementia: a profound and progressive loss of semantic knowledge. With respect to the second point, we have already discussed how, in a fully functioning memory system, a consolidation process takes place that increases the connectivity of neocortical representations so that they become less dependent on the link system over time. If consolidation cannot take place, as is probable with reduced connectivity within the trace system, any new experiences will remain critically dependent upon the hippocampus (link system). In principle, these new memories may survive for a limited period of time (in the order of weeks or months). Eventually, however, new learning will overwrite more remote memory representations because of the limited capacity of the link system, unless such memories are refreshed by rehearsal during new experiences.

The view that semantic dementia is caused by reduced connectivity in the trace system leads to six testable predictions about the disorder.

(i) As lesions in the trace system are diffuse in semantic dementia, we predict that subordinate semantic knowledge is likely to be affected earlier than superordinate semantic knowledge. The reason for this is that superordinate categories have a better developed network of neural connections, which causes them to be more resistant to lesioning.

(ii) TraceLink, and the other models, predict an inverse Ribot gradient in semantic dementia [e.g. better preservation of recent memories (autobiographical and semantic) compared with more distant memories]. The reason for this is that recall of all memories in the trace system is diminished, whereas the formation and recall of memories in the link system is still relatively intact. Since the latter are recent memories, we would expect a step-like pattern of performance, whereby very recent memories are recalled better than more remote memories.

(iii) New learning, being predominantly dependent upon the undamaged link system, will not be impaired initially. For as long as the link system still functions and the trace system is sufficiently dense to store a representation, initial storage of a memory can take place. Further consolidation, whereby the memory becomes increasingly independent of the link system, will be impaired.

(iv) One consequence of the deterioration of the semantic system represented in the neocortex will be an increasing reliance upon recent autobiographical experiences that are dependent upon the link system. More specifically, patients with semantic dementia will be able to provide semantic information (of an impoverished nature) if they have had recent experiences that comprise that semantic knowledge.

(v) As hippocampally dependent memories will no longer have the benefit of cortical consolidation, we predict that patients with semantic dementia will show increased long-term forgetting of recent experiences (i.e. as measured over weeks or months).

(vi) The TraceLink model predicts shorter and weaker priming effects than normal, reflecting the inability to achieve normal activation of representations (which are degrading) in the trace system.

In the following six sections, we will compare these predictions with data from recent experimental studies that have investigated long-term memory in semantic dementia. It should be noted that at present, there are no published simulations of the aforementioned predictions. Several such simulations have been undertaken with the TraceLink model and a more complete computational model of semantic dementia is currently being developed, but will not be discussed in this article.

4.1 *Breakdown of semantic memory*

Much of the research in patients with semantic dementia has concentrated on the nature of the semantic memory loss. For example, Hodges and co-workers investigated the integrity of patient J.L.'s semantic knowledge serially between March 1991 and September 1992 (Hodges *et al.*, 1995). J.L.'s performance on the semantic test battery (Hodges *et al.*, 1992; Hodges and Patterson, 1995) provided a number of interesting insights: (i) when J.L. was able to name an item correctly, he almost never made an error on that item on other semantic tests based on the same set of items (e.g. word–picture matching); and (ii) when he was unable to name a picture on one occasion, he was unlikely to name the same picture on all other subsequent testing sessions. Longitudinal analyses of J.L.'s sequence of naming errors on the four occasions he was given the 260 pictures from the Snodgrass and Vanderwart (1980) corpus revealed a progression from closely related semantic to prototypic and stereotyped responses, and finally generic or superordinate labels (e.g. for giraffe $\rightarrow$ tall African animal, horse $\rightarrow$ animal, etc.).

J.L.'s performance on other tests from the semantic battery also suggested that he was losing specific semantic information with relative preservation of superordinate knowledge. This pattern could be seen within a test: for example, when asked to sort pictures of animals and objects into 'living' and 'non-living' categories, J.L. initially showed relatively preserved performance. In contrast, he was much poorer at sorting the same pictures into more specific categories (e.g. 'electrical' versus 'non-electrical', 'foreign' versus 'native'). Over time, his sorting at the superordinate level stayed relatively stable but there was a decline in his ability to sort at category and subordinate levels. Hodges and colleagues argued that, while it was not possible to distinguish between a hierarchically organized or a network-based semantic memory system, J.L.'s use of prototypical names fits more clearly with a semantic memory system that is organized as a distributed network (Hodges *et al.*, 1995).

We showed in a separate study how the TraceLink model produces a similar breakdown of categories to that seen in J.L. The effect is robust and can easily be produced by the

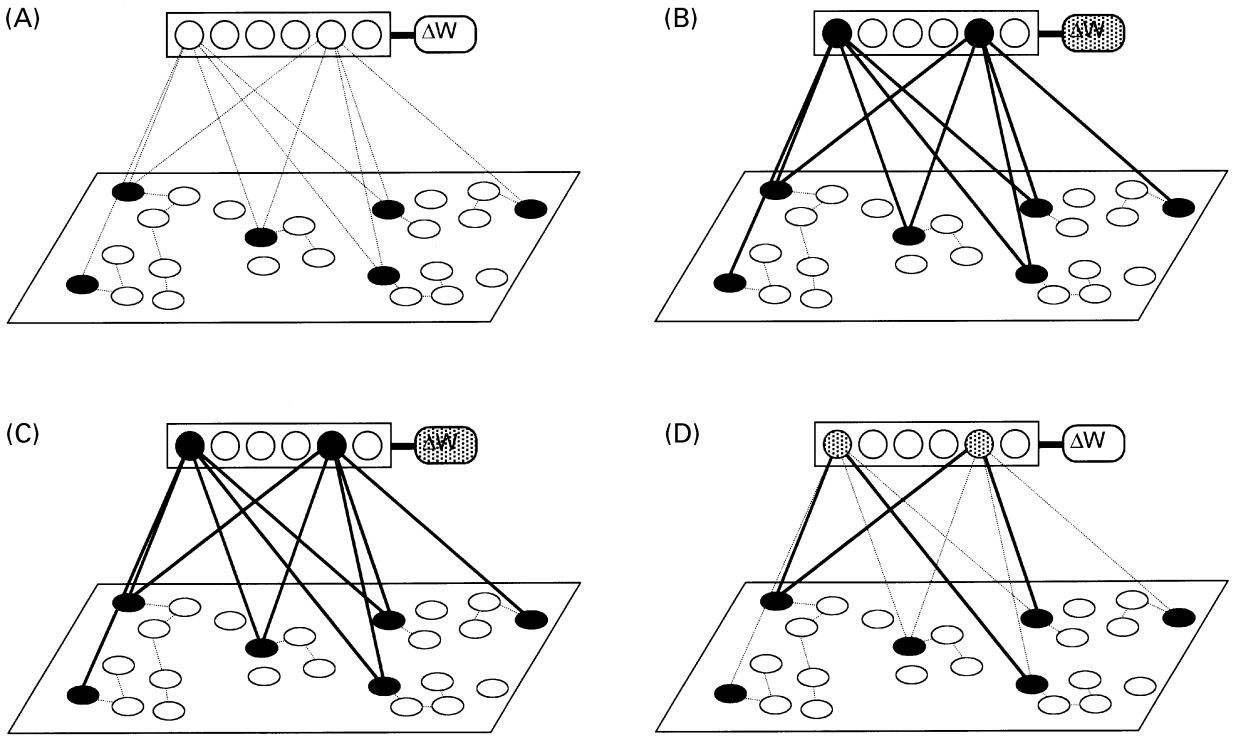

Fig. 8 Different stages of memory acquisition in the TraceLink model in semantic dementia. See text for an explanation.

model if the progression of semantic dementia is simulated by administering diffuse lesions [i.e. removing a small percentage of all (remaining) connections in the model] in subsequent steps. Prior to lesioning, superordinate and subordinate category information were functioning equally well. Superordinate categories were implemented as two patterns (e.g. a 'living' pattern and a 'non-living' pattern) and subordinate categories as four patterns. In addition, there were eight 'exemplar' patterns. Four of the example patterns were connected to the 'living' pattern and four others were connected to the 'non-living' pattern. Similar connections existed between the 'exemplars' and the four subordinate patterns. When the lesioning progresses and, hence, the connectivity becomes more sparse, both types of category information suffer, but the subordinate categories are much more sensitive to the diffuse lesions than the superordinate categories. This corresponds directly to the observations seen in semantic dementia mentioned above (see also discussion in Garrard *et al*., 1997).

The representations of categories and prototypes in neural networks is well established (e.g. Knapp and Anderson, 1984; McClelland and Rumelhart, 1986; Kruschke, 1992). The simulation described above carried out in TraceLink could probably be repeated in the models by McClelland *et al.* (1995) and by Alvarez and Squire (1994) because producing the effect seen in semantic dementia relies on emergent properties that are common to many types of neural networks. In fact, a detailed and systematic study of hierarchy effects in semantic dementia, based on a combination of neuropsychological data and computer simulations, has been carried out by McClelland and co-workers (McClelland and Rogers, 1997; Patterson *et al*., 1997; Lambon Ralph *et al*., 2001).

4.2 *Remote autobiographical and semantic memory*

Murre noted that patients with semantic dementia should show better preservation of recent memories compared with memories from the more distant past [a reversal of the Ribot effect (Ribot, 1882)] (Murre, 1996). In computational terms, such a pattern can be explained by preservation of the link system and strongly diminished cortico-cortical connectivity in the trace system. This situation would result in a loss of old memories represented at a purely cortical level and inefficient consolidation of new memories because the trace connectivity is no longer dense enough to allow cortico-cortical connections to be formed. Figure 8 illustrates how a new memory can pass through stages 1 and 2 as in the normal case (compare Fig. 5), but how it cannot reach stage 3 because the reduced connectivity is not able to support many cortico-cortical connections. The effect of this will be a loss of distant memories with relative preservation of more recently experienced memories. The same prediction could, in principle, be derived from the models by Alvarez and Squire (1994) and McClelland *et al*. (1995) as the hypothesis relates to the global architecture and consolidation processes that are common to all the models discussed in this paper.

The first study to suggest that time might be an important factor in semantic dementia was that of Snowden and

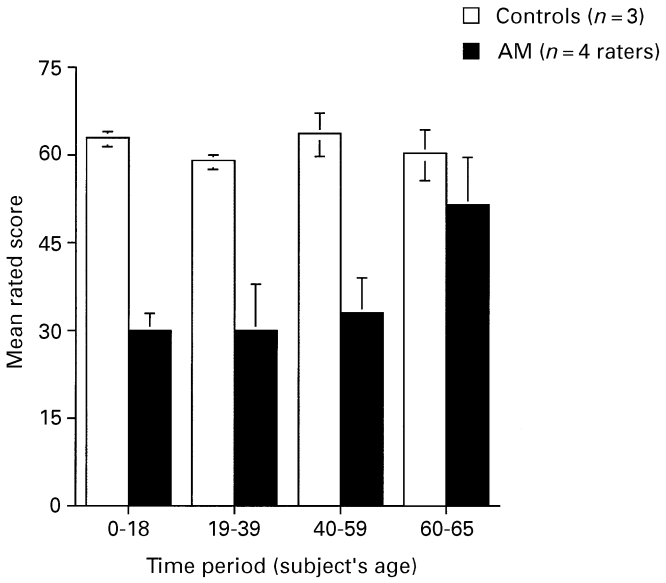

Fig. 9 The performance of A.M. (the patient described in detail in this article) on a modified version of the Galton–Crovitz test (Crovitz and Schiffman, 1974). A.M. was asked to produce 15 autobiographical memories from each of four different time periods spanning the whole of his life (including the period not tested by the Autobiographical Memory Interview). A.M.'s ability to produce autobiographical memories was strongly affected by time: virtually all his specific episodes were recalled in the last 2 years (see Graham and Hodges, 1997, for more details).

colleagues (Snowden *et al*., 1994). Although they did not test the integrity of autobiographical memory directly, they demonstrated that patients with semantic dementia were better at selecting proper names as familiar if they were currently relevant, compared with names from the more distant past (see also Graham *et al*., 1997*b*).

More recently, Snowden *et al.* (1996*a*) tested autobiographical memory using the Autobiographical Memory Interview (Kopelman *et al*., 1990) and found that 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 and Hodges 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 recent memories were more impaired than those from further in the past (Graham and Hodges, 1997).

Graham and 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 earlier in this paper), to retrieve event-based memories across the whole of his lifetime. A.M. was much better at retrieving autobiographical memories from the last 5 years of his life compared with the 60 years that encompassed the rest of his life (see Fig. 9). In contrast, a group of age- and education-matched control subjects showed no significant difference between their performance on any of the time-periods tested. Graham and Hodges (1997) proposed that patients with semantic dementia showed better retrieval of current autobiographical memories compared with those from the distant past because the hippocampal complex was relatively spared early in the disorder (see Harasty *et al*., 1996; Mummery *et al*., 2000). The dissociation in performance between the patients with amnesia and the group of patients with semantic dementia on the Autobiographical Memory Interview (Kopelman *et al*., 1990) provides strong evidence for the view that there is a temporally based interaction between the hippocampal complex and the neocortex in long-term memory storage (Graham and Hodges, 1997).

A further study investigated the integrity of knowledge of famous people across different time periods in semantic dementia: Hodges and Graham argued that if autobiographical memory was affected by time, then it was reasonable to suspect that semantic knowledge might also be better in the current time-period compared with the distant past (Hodges and Graham, 1998). In support of this hypothesis, Hodges and Graham found that their patient's knowledge of famous people was strongly affected by the time-period in which the celebrity had been famous. D.M., a 60-year-old patient with mild semantic memory loss, was significantly better at producing information about currently famous people compared with people who had been famous in other time periods, such as the 1950s, 1980s and early 1990s. This pattern of knowledge loss is in contrast to that seen in Alzheimer's disease. Greene and Hodges tested a number of patients with presumed Alzheimer's disease and demonstrated a mild temporal gradient on both a Famous Names and Famous Faces Test (Greene and Hodges, 1996). The patients were worse at providing information about people from the 1970s–1990s compared with people who had been famous in the 1940s–1950s. Further confirmation of the reverse temporal 'gradient' for semantic knowledge in semantic dementia was demonstrated in D.M.: Graham and colleagues found that D.M. was significantly better at producing information about public events from the last three years (1995–1997) than from two other, more distant, time-periods (1989–1991 and 1992–1994) (Graham *et al.*, 1998).

The use of the term 'gradient' is slightly confusing when considered in connection with semantic dementia. In all the studies that we have discussed here, the patients were found to show preservation of autobiographical or semantic knowledge for only a short period of time (2–3 years in most cases): more of a 'step' effect rather than a gradient. While this very short-term preservation of memories is consistent with a model in which the hippocampus and neocortex interact, it should be noted that it is contradictory to Nadel and Moscovitch's multiple trace theory in which the hippocampus is necessary for the retrieval of all autobiographical memories (Nadel and Moscovitch, 1997; Graham, 1999).

To explain this step function found in semantic dementia, Nadel and Moscovitch proposed a number of alternative explanations: (i) that there was only one patient (A.M., reported in Graham and 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 patient's remote memory deficit (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1999). Elsewhere, we have shown that the pattern seen in semantic dementia on tests of autobiographical memory is unlikely to be due to any one or a combination of these factors (P. J. Nestor, K. S. Graham, J. S. Simons and J. R. Hodges, unpublished results). For example, other patients with semantic dementia show the same effect of time on the detailed Crovitz test as A.M.; patients with the frontal variant of frontotemporal dementia do not show effects of time similiar to those seen in semantic dementia in their autobiographical retrieval (see Della Sala *et al*., 1993 for similar data in patients with non-degenerative fronted lesions) and the use of family photographs as cues in an autobiographical memory test did not improve A.M.'s performance in the remote time period [P. J. Nestor, K. S. Graham, J. S. Simons and J. R. Hodges, unpublished results, although see also Westmacott *et al*. (2001) who reported a significant improvement in autobiographical retrieval from family photographs in a case of semantic dementia].

Nonetheless, it may be possible to reconcile the multiple trace model with the data from semantic dementia (see also Moscovitch and Nadel, 1999). A recent paper by Rubin and Greenberg proposed that the loss of a critical component of memory recollection, the ability to evoke visual memories, could result in an inability to activate other aspects of the memory experience, thereby causing an extensive and non-temporally graded deficit in episodic memory retrieval (Rubin and Greenberg, 1998). In support of their view, Rubin and Greenberg report that five of their 11 cases with bilateral damage to occipital regions had a severe retrograde amnesia (most without a temporal gradient), with only mild to moderate anterograde deficits. Moscovitch and Nadel extend this view by suggesting that semantic memory, like visual imagery, is a critical component of autobiographical memories, and that loss of this memory component might, therefore, result in a similar pattern of autobiographical memory loss to that seen in Rubin and Greenberg's (1998) patients (Moscovitch and Nadel, 1999). It is clearly still necessary to explain the preservation of recent memories on the basis of selective sparing of medial temporal regions, in particular the hippocampus, which allow the binding of new memory traces in neocortical regions not affected by the pathology, such as parietal and occipital areas.

To explain the remote memory data in terms of the standard model of memory consolidation it is necessary to argue that reduced connectivity in the temporal lobe will disrupt intracortical connections, leading to an inability to activate autobiographical memories. As in the multiple trace account, the better preservation of recent events is probably related to the ability of patients to bind new experiences using undamaged areas within the neocortex (e.g. perceptual and auditory regions; Graham *et al*., 2000). The data from semantic dementia can therefore be accommodated within both the standard and multiple trace models and further studies of remote memory in semantic dementia and amnesia will be necessary to determine which view is more accurate.

Returning to the computational models discussed earlier, it is hoped that simulations will be able to replicate the intriguing pattern of autobiographical and semantic memory deficit seen in semantic dementia. Furthermore, it may be possible to compare different types of memory consolidation, e.g. the standard view versus Nadel and Moscovitch's multiple trace model (Nadel and Moscovitch, 1997). While all three computational models have attempted to simulate the classic Ribot gradient seen in patients with amnesia, to date there have been no studies that have replicated the pattern of memory loss seen in semantic dementia. As the remote memory data from semantic dementia remain controversial, such investigations could prove highly enlightening.

4.3 *Recognition memory and re-learning of vocabulary*

Until recently, there had been few formal investigations into the integrity of anterograde episodic memory in semantic dementia. The predictions of connectionist models are that new learning should be relatively intact in the disorder, as long as the link system still functions and the trace system is sufficiently dense to hold a representation. Anecdotal evidence supports the view that patients show preservation of new learning, 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 had 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: with respect to delayed recall of the Rey Complex Figure, A.M.'s score was markedly better than the performance of a group of amnesic patients with early Alzheimer's disease (see Fig. 1C here and Table 1 in Graham and Hodges, 1997). 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. In contrast, recognition memory for paintings was preserved.

Recently, more experimentally driven studies of new learning in patients with semantic dementia have begun to confirm the anecdotal reports. Graham and colleagues 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*a*) (see Fig. 10). In contrast, the patients were significantly impaired, compared with both control subjects and patients in the early stages of Alzheimer's disease, in their performance in the study task in which they had to say whether the animals were real or not real.

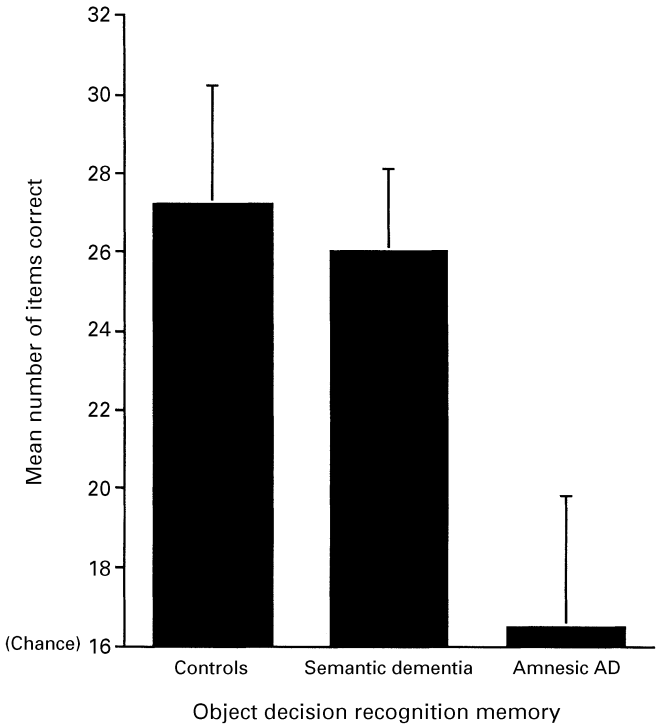

Fig. 10 Mean number of items correct on a two alternative recognition memory test for real and non-real animals for 10 normal control subjects, five patients with semantic dementia and four patients in the early amnesic stage of presumed Alzheimer's disease (AD) (data from Graham *et al*., 1997*a*). Standard deviations are represented as bars and the horizontal axis starts at chance (number correct = 16). The patients with semantic dementia showed no significant impairment on this test compared with control participants, despite poor performance on the study test in which they had to decide whether the stimuli were real or not. In contrast, the patients with early Alzheimer's disease performed at chance on the test of episodic memory but showed equivalent performance to the controls on the semantic study task (see Graham *et al*., 1997*a*, for more details).

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, 1983, 1995). The patients in Graham and co-workers' study clearly remembered items in the recognition memory test that they labelled incorrectly (real or non-real) in the semantic task (Graham *et al.*, 1997*a*).

Two further experiments have provided further insights into our understanding of the processes involved in new learning in semantic dementia. Graham and colleagues 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 (Graham *et al.*, 2000). In 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 supported further 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.

Another study by Simons and co-workers found further evidence for the involvement of perceptual processes in new learning (Simons *et al.*, 2000). They investigated face recognition memory 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 (Warrington, 1984); and (ii) 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 that were no longer familiar to the patients. This replication of Graham and colleagues' study (Graham *et al.*, 2000) 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 link system receives multiple sensory inputs from many disparate areas of the brain, only some of which are damaged in semantic dementia. While TraceLink and the other models predict that new learning should be intact in semantic dementia, further work on the models is required before it will be possible to undertake simulations of the neuropsychological patterns described by Graham *et al.* (2000) and Simons *et al*. (2000).

It should be noted that performance on recognition memory tests, while remarkably preserved early in the disease, declines as the patients deteriorate over time (for more details see Graham *et al*., 1997*a*, 2000). There are two possible explanations for this pattern: (i) the loss of neocortical representations declines to a precipitous extent, resulting in the inability to activate neurones (or groups of neurones) within the trace system; and/or (ii) the disease spreads from the lateral temporal lobe structures to those in the medial temporal lobe, resulting in anterograde amnesia. Given that the patients described in Graham *et al*. (2000) showed good perceptual processing and that we now know that recognition memory in semantic dementia is heavily dependent upon perceptual information, it seems most plausible that the poorer recognition memory, seen in the latter stages of semantic dementia, reflects the spread of pathology into medial temporal lobe structures (especially entorhinal and perirhinal cortices). The neuropathological studies seem

consistent with this view: at presentation, structural abnormality is often restricted to one of the temporal lobes (Simons *et al*., 2000), while in the later stages, atrophy is usually bilateral and involves medial temporal lobe structures (Graff-Radford *et al*., 1990; Hodges *et al*., 1998; Garrard and Hodges, 2000; Chan *et al*., 2001).

One further facet of the new learning experiments deserves comment. In their Experiment 1, Simons *et al*. (2000) found that laterality strongly affected performance on the recognition memory test (i.e. patients with atrophy to the right hippocampal and parahippocampal gyrus were most impaired on the faces recognition memory test, while those with predominantly left temporal lobe atrophy showed normal performance). The issue of asymmetrical patterns of medial temporal lobe atrophy in semantic dementia may well turn out to be fundamentally important to understanding why patients with this disease have such good episodic memory, yet patients with Alzheimer's disease, who typically have bilateral medial temporal lobe atrophy, do not. Another important consideration is the role of pathology outside the temporal lobe in Alzheimer's disease, particularly the basal forebrain cholinergic system, which has been rather neglected in current models of amnesia. Furthermore, modellers of human long-term memory may have to develop methods to take into account hemispheric function when attempting to simulate the neuropsychological data from semantic dementia.

While hemispheric asymmetry makes the simulations more time-consuming and difficult to perform, important insights about the organization of memory can be made using modelling. For example, Lambon Ralph *et al*. (2001) implemented a computational model of naming to explain the neuropsychological pattern of performance seen on tests of naming and comprehension in semantic dementia. They noted that patients with greater right than left temporal lobe atrophy typically showed a parallel decline in naming and comprehension, while those with predominantly left-sided atrophy showed disproportionately greater anomia compared with their level of comprehension deficit. The computational model simulated this neuropsychological pattern by implementing a single distributed semantic system, which was bilaterally represented across left and right temporal regions. The semantic units on the left were more strongly linked to the left-lateralized phonological representations. This study clearly illustrates two points: (i) the theoretical benefit of combining neuropsychological and computational methods to understand memory organization; and (ii) that it is possible to successfully simulate asymmetrical patterns of pathology that require differentiation between left and right hemispheres.

4.4 *The relationship between autobiographical and semantic memory*

New data from semantic dementia suggests a crucial interplay between autobiographical and semantic memory in the recent time period (i.e. a period of time 2–5 years prior to the brain injury). In this section, we review these recent results and discuss how they correspond with predictions from the computational models. Snowden *et al.* (1994) investigated the ability of their patients to match first names to surnames (a familiarity judgement task): the patients were much better at matching the names of current personally relevant friends and famous celebrity names compared with personally relevant names and celebrity names from the distant past. Graham *et al.* (1997*a*) also investigated the ability of patients with semantic dementia to make familiarity judgements. Their two patients were significantly better at matching the names of current personal golfing/bowling colleagues compared with the names of famous golfers/bowlers (current and past). These initial experiments demonstrate that personally relevant autobiographical experience can have an impact on the ability of patients with semantic dementia to make familiarity judgements. There is some evidence to suggest that repeated media exposure can also have an impact on familiarity judgement: Hodges and Graham (1998) found that four patients with semantic dementia were better on familiarity judgements for current famous names compared with names from other time periods.

Hodges and Graham (1998) suggested that the greater exposure to the name (and presumably the face) of a current famous person (compared with someone famous in the past) helps boost the integrity of multi-modal cognitive modules called person identity nodes (PINs). These pre-semantic person-specific nodes are thought to subserve familiarity judgements within a model of face and name processing (see Burton *et al*., 1990; Valentine *et al*., 1996). It seems reasonable to assume, therefore, that the greater recognition of names in the current time period in Snowden *et al.*'s and Graham *et al.*'s patients may reflect an effect of repeated exposure at this level.

A further aspect of Graham *et al.*'s (1997*b*) experimental investigation was to determine whether Snowden *et al.* (1994) had been correct to presume that autobiographical experience also has a beneficial impact on the integrity of semantic knowledge. Although recent semantic knowledge is helped by autobiographical memory (see Hodges and Graham, 1998), the impact of autobiographical experience on previously learned (presumably neocortically represented) semantic knowledge was unknown. Graham *et al.* studied the ability of their two patients to perform semantic memory tasks testing knowledge of golf, bowls, tennis and football. If Snowden *et al.* (1994, 1995) were correct to assume that autobiographical experience was important for maintaining semantic knowledge, regardless of the time period, A.M. and M.S. should have been able to perform better on tests tapping knowledge of their current sports (golf and bowls). Graham *et al.* showed that A.M.'s and M.S.'s knowledge of golf and bowls, respectively, was exceedingly poor. This suggests that repeated autobiographical experience does not help support previously acquired semantic knowledge, which is represented within the temporal neocortex (see also the lack

of semantic knowledge acquisition shown by the patient described in Graham *et al.,* 1999*c*). However, as proposed by Snowden *et al.* (1994, 1995), there is an important interaction between autobiographical and semantic memory in the current time period. Graham *et al.* (1997*b*, 1999*a*) suggest that the preservation of the hippocampal complex in patients with semantic dementia allows them to encode (and maintain for a short period of time) new episodic memories, a part of which will be fragments of factual (semantic-type) information, for instance, recalling semantic knowledge about a swan ('people feed it bread', 'it is found in rivers') based on recalling an event when driving a spouse to the train station.

There is some evidence to support this view. Snowden *et al.* (1994) demonstrated that one of their patients with semantic dementia was better at recognizing her own objects (e.g. her telephone) compared with alternative examples of the same objects. The patient also showed a strong effect of 'topographical context' (Snowden *et al*., 1994, p. 280). She was much better at recognizing the items when they were placed in their usual location. For instance, she had no problem recognizing a clothes peg when it was taken out of a peg bag, but had no idea what the peg was when it was shown in an unusual context, such as in the bathroom among the toothbrushes. In semantic dementia, semantic facts about an object could be determined by the context (including location) in which the object is found and by the ability to recall recent autobiographical experiences with that object. It is interesting to note that the ability to infer 'semantic knowledge' from autobiography will be reduced as the capacity to acquire recent experiences declines [as disease progresses, see prediction (ii) at the start of this section]. From this point of view, it is no surprise that spouses report increasing misuse of objects at later stages in the disease, despite the patient having repeated autobiographical-type experiences with the objects, e.g. A.M. placing a closed umbrella horizontally over his head during a rain storm, despite the fact that he frequently uses and sees people using umbrellas when he is playing golf (four or five times a week).

These studies provide support for the suggestion that under normal circumstances semantic knowledge and autobiographical memory (in the recent time period) share a common mechanism of acquisition and are, therefore, highly interdependent (as is also suggested by McClelland *et al*., 1995). It can be argued that the permanent storage of a semantic fact versus an autobiographical incident depends upon whether time information is encoded along with the contents of the experienced event. If time information is not reinstated in the neocortex, we will end up with a piece of information that is not autobiographically constrained (i.e. a semantic fact). It is important in this context to note that we are not suggesting that semantic dementia patients differ from normal human beings in this respect. The acquisition of new semantic facts (e.g. information about Tony Blair and the meaning of the new words that have come into the English language, such as 'council tax' and 'millennium bug') may occur through our autobiographical experiences (although see discussion in the next paragraph). In semantic dementia, the semantization process (i.e. the consolidation of information into the neocortex) is arrested because of the strongly reduced density of wiring in the neocortex. Thus, over time, the ability of patients with semantic dementia to produce semantic facts will become more and more dependent upon current autobiographical experience (see Graham *et al*., 1999*a*; Snowden *et al*., 1999)

It should be noted that the mechanism by which we acquire new semantic information is controversial. It is, for example, possible that knowledge (such as new vocabulary) could be acquired in the absence of a functional hippocampal (link) system by repeated stereotyped exposures, although such information is less likely to be integrated and generalizable. This explanation was favoured by Kitchener *et al.* (1998) to account for the finding of, at least some, knowledge acquisition in their profoundly amnesic patient R.S., which had occurred in the 13-year period since he become amnesic. This mechanism is also discussed in Murre (1997). Other patients, however, such as H.M. (Gabrieli *et al*., 1988; see also the patient described by Verfaellie *et al.*, 1995) show little or no evidence of semantic learning, although this may reflect additional damage to neocortical structures (Corkin *et al*., 1997). Another hypothesis is that the perirhinal and entorhinal cortices are necessary for semantic learning, whereas the hippocampus is crucial for the acquisition of multi-modal episodic experiences (Vargha-Khadem *et al*., 1997). Vargha-Khadem and colleagues described three patients with poor episodic memory after bilateral hippocampal damage sustained early in life. Contrary to expectations, these patients showed relatively normal levels of academic achievement during their school years, suggesting that there may be different learning systems for episodic and semantic memory within the medial temporal lobe.

As will be discussed in more detail in the next section, there is little evidence that patients with semantic dementia can re-learn lost semantic knowledge (Graham *et al.*, 1999*c*). One possible explanation for this is that patients with semantic dementia may have significant damage to the perirhinal cortex, which Vargha-Khadem *et al.* believe to be critical for context-independent (semantic) learning. The exact location of perirhinal cortex in man is somewhat controversial: it is currently thought that the rostral portion occupies the banks of the collateral sulcus and that the caudal part extends onto the medial aspect of the temporal pole (Corkin *et al*., 1997; Van Hoesen, 1997). There is some evidence that this area is damaged in semantic dementia (Simons *et al*., 2000), although one is left with the paradox that visual recognition memory, also presumed dependent upon perirhinal cortex by some authors (Vargha-Khadem *et al*., 1997; Aggleton and Brown, 1999; Murray and Bussey, 1999), is preserved in semantic dementia.

4.5 *Increased long-term forgetting*

Murre (1996, 1997) has suggested that in semantic dementia there may be increased rates of long-term forgetting because

the hippocampal system is of limited capacity and, therefore, is sensitive to interference from new events. As there is little or no consolidation into the trace system in semantic dementia, patients will be heavily reliant on hippocampally dependent memories. The limitations on the hippocampus (i.e. size and capacity) will eventually lead to new experiences overwriting existing memories. In healthy subjects, the gradual 'over-writing' of memories in the hippocampus is partially counteracted by the cortical consolidation process, in which the increasingly strong cortical base of a memory compensates for the gradual loss of hippocampal support. In semantic dementia, however, the gradual overwriting of memories without the benefit of cortical consolidation will be reflected in an increased forgetting rate for newly learned events.

So far, there have been very few formal investigations of forgetting in semantic dementia. A recent study by Graham *et al.* (1999*c*) suggests that patients may show the predicted fast forgetting rates, although this study did not contain matched control data. One patient, D.M., was asked to re-learn 160 words from eight separate semantic categories (breakfast cereals, herbs and spices, TV shows, stones and gems, etc.) in two experiments, each lasting 2 weeks. The authors selected categories on which D.M. showed profoundly impaired performance when asked to produce the names of exemplars belonging to that category (e.g. for stones and gems, topaz, diamond, garnet, ruby, etc.). The experiment revealed three fascinating results: (i) D.M. was able, via repeated practice (30 min a day for 2 weeks), to boost dramatically his ability to produce the names of exemplars on a category fluency test to normal levels; (ii) this learning did not extend to the acquistion of semantic facts about the words; and (iii) D.M. showed a rapid rate of forgetting when he stopped practising the recently acquired words. It was clear from the results that D.M. was only able to boost his production of these category exemplars by practising every day. If he stopped practising, even for 2 weeks, his performance declined dramatically. Overall, D.M. lost almost 60% of the category exemplars he had newly obtained within 6–8 weeks of stopping practising. Inferences about the rate at which D.M. lost his newly acquired words must, however, be considered with caution, as the experiment used semantic categories that were likely to be familiar to normal subjects (e.g. breakfast cereals, television shows, etc.), it was not possible to compare directly D.M.'s forgetting with that of control subjects.

A longitudinal study of D.M., in which he was asked to produce exemplars from eight standard semantic categories (category fluency from the semantic battery; Hodges and Patterson, 1995), revealed further support for the view that D.M. was able to acquire vocabulary rapidly with practice but not appropriate semantic knowledge about the words (Graham *et al*., 2001). In the final testing session, D.M. produced a number of non-category responses (e.g. 'cement' as a household item, 'beak' as a bird, 'canvas' as a vehicle, and 'garlic' as an animal) for the first time. Furthermore, when he was asked to produce semantic information about items he had correctly produced in category fluency, he was profoundly impaired (e.g. D.M. did not know what 'punt' or 'barge' meant, despite producing these as items for the category 'types of boat'). These two aspects of D.M.'s performance illustrate that D.M. was using rote memory to support his learning (i.e. he was learning in a mechanical manner without proper reflection or understanding of the materials in question). This rote learning, while beneficial for vocabulary acquisition, had little or no impact on his deteriorating semantic system (even though he was using pictures and descriptions of the names of concepts as his learning materials).

Kapur *et al*. (1996) have reported recently experiments on long-term forgetting in two patients, both suffering from non-progressive lesions in the temporal lobes (left greater than right). In both patients, the hippocampi were relatively spared compared with more lateral temporal lobe structures. It was found that one of the patients, S.P., showed normal learning and retention (e.g. story retention, visual design retention and verbal paired-associate learning) over a 30-min interval when compared with controls. When S.P. was tested 6 weeks later, however, her performance was much worse than the control subjects. Similar findings have been reported by Ahern *et al*. (1994) and De Renzi and Lucchelli (1993). These studies, along with the data from D.M., suggest that Murre (1996, 1997) may be correct in predicting increased rates of forgetting in patients with temporal lobe damage. It should be noted that increased forgetting is not typically observed in Alzheimer-type dementia or Korsakoff's syndrome (Kopelman, 1985; Greene *et al*., 1996), and that semantic dementia would thus be an exception in this respect.

Not all cases of accelerated forgetting can be explained by overwriting of hippocampally based memories. Kapur *et al*. (1997) reported a patient who suffered from temporal lobe epilepsy and who showed increased forgetting with little retrograde amnesia. There was evidence of damage to the left temporal lobe with a possible epileptogenic focus in the left anterior hippocampus. One possible explanation for the accelerated forgetting rates in this patient is that there is a reduced density of connectivity in the neocortex (temporal lobes). The reason for the accelerated forgetting would then be the same as that suggested for semantic dementia and patient S.P. (Kapur *et al*., 1996). In the case of a severely weakened cortical base, however, we would also expect a significant degree of loss of semantic memories because of damage to the trace system. As this was not present to a significant degree in Kapur *et al.*'s patient (Kapur *et al.*, 1997), a weakened trace system seems an unlikely explanation. An alternative possibility is that the frequent epileptic seizures, including during sleep, interfered with the consolidation process, thus preventing the development of a neocortical basis for new memories. This hypothesis was proposed by Zeman *et al.* (1998) to account for the retrograde amnesia reported by patients with transient epileptic amnesia, who typically have abnormal sleep but normal daytime EEG.

It is clear from this brief overview of the literature on forgetting in semantic dementia that further empirical studies are required before we can attempt to test Murre's (1996, 1997) hypothesis in more detail. Furthermore, long-term forgetting in semantic dementia is likely to be a more complex issue than we have discussed here. For example, we hypothesize that both learning and subsequent forgetting of vocabulary in semantic dementia may be strongly influenced by the integrity (i.e. known versus unknown) of the patient's conceptual knowledge about the items tested. Furthermore, the method of testing (recall versus recognition) and the provision of additional cues, such as perceptual information about the target items in a non-verbal memory task, is likely to affect forgetting over time.

4.6 *Implicit memory*

One prediction from Murre's TraceLink model that remains to be explored in any detail is that patients with semantic dementia will have impaired 'conceptual' implicit memory. Virtually all recent studies of episodic memory in semantic dementia have used explicit assessments of memory that require conscious retrieval on recall or recognition memory tests. Implicit memory tasks, in particular those that measure priming (i.e. the facilitation in performance on a non-memory task that results from previous exposure to the same stimuli) can provide another view on the integrity of components of long-term memory. For example, an implicit memory task such as category verification, in which a subject responds more quickly to a category decision (e.g. 'furniture'–'table', if the word 'table' was seen in a previous semantic study task in which they had reponded to 'manmade' with 'table'), may be useful in determining the integrity of semantic representations.

If we assume that implicit memory operates by strengthening semantic cortical traces and that there are fewer, and generally weaker, cortical traces in semantic dementia, we would predict that the effects of various types of priming will be shorter and less enduring (for a more extensive discussion of priming see Murre, 1997). In particular, we predict an ordering of priming effects for items (words/pictures) as follows. (i) If an item is no longer known by a patient, it will have (very) low priming effects. (ii) If the subject still has partial knowledge about an item (e.g. the subject knows that 'giraffe' is an animal but not much more), it will have intermediate priming effects. (iii) If the item is known to a high degree, we predict that it will be primed well, although even for these items we may still see a smaller priming effect than in normal controls, because the cortical base for 'known' items may well be partially eroded. This prediction applies to all cases in which there may be significantly reduced neocortical connectivity (trace–trace connectivity), including Alzheimer's disease. For the latter disorder, a recent meta-analysis supports this prediction, showing that a group of patients with Alzheimer's disease were significantly impaired on implicit memory tests (Meiran and Jelicic, 1995).

One of the first studies of priming in semantic dementia used a word monitoring experiment, in which the subject presses a reaction time button as soon as they hear a word pre-specified by the experimenter, to investigate category coordinate priming (e.g. spade–rake) and functional priming (e.g. broom–floor) in a single case of semantic dementia in P.P. (Moss *et al*., 1995). While control participants showed priming for both conditions, P.P. showed a normal priming effect for the functional relation, but not for category coordinates. Like Moss *et al*. (1995), Nakamura *et al*. (2000) found no evidence of semantic priming for words from the same category, as measured using a lexical decision task, in three patients with semantic dementia, despite finding priming effects on the same paradigm in four patients with Alzheimer's disease and a matched control group.

Tyler and Moss (1998) reported results from a longitudinal study of semantic memory, using explicit and implicit tests in A.M., the patient with semantic dementia described previously. In the first testing session, he showed priming for perceptual (e.g. fox–red) and functional (e.g. fox–sly) properties, but not for category coordinates (e.g. fox–dog) or category labels (e.g. fox–animal). Eleven months later, only functional properties showed a robust priming effect and at the final testing session, there were no effects of priming in any of the conditions. Tyler and Moss proposed that the relative preservation of priming for perceptual and functional properties, in conjunction with no priming for category coordinates and labels, argues against the view that semantic memory is organized hierarchically. An earlier study of another patient with semantic dementia, P.P. (Moss *et al*., 1995), had also shown relative preservation for functional information. Tyler and Moss explain this effect by suggesting that functional knowledge is learnt early in life and may, therefore, be more resistant to brain damage. The authors also clearly demonstrated that in semantic dementia, 'the structure of semantic knowledge itself, even when assessed by the most sensitive priming paradigms, can be severely degraded' (Tyler and Moss, 1998, p. 1322).

Another priming study further illustrates how tests of implicit memory can provide an important perspective on semantic dementia (Srinivas *et al*., 1997). The authors used a test of perceptual priming to determine whether a patient with semantic dementia, D.M. (note that this patient is a different patient from the D.M. reported in Graham *et al*., 1999*c*), had good access to representations within stored structural descriptions. The normal level of priming exhibited by D.M. provided some evidence that he possessed an intact system for object representation. The authors proposed that the anterior inferior temporal cortex, which was damaged in D.M., is not critical to the computation, storage and retrieval of structural descriptions about objects (at least in humans), but that this area of the brain may be critical for linking stored structural descriptions with conceptual knowledge about objects. The normal perceptual priming showed by

D.M. is consistent with Graham *et al.*'s (1999*b*, 2000) proposal that the high level of recognition memory for objects seen in semantic dementia is probably based largely on the products of good pre-semantic perceptual information. From Srinivas *et al.*'s study (1997), it is clear that implicit memory techniques have many other potential applications with respect to our understanding of the relationship between semantic memory and other, linked, cognitive domains.

6. Conclusion

One of the aims of this paper is to demonstrate that experimental studies in patients with semantic dementia have produced a large number of new insights into the neural and cognitive organization of long-term memory. We have shown that a theoretical approach that combines neuropsychology, neuroanatomy and computational modelling, provides many specific predictions that can be tested in patients and in connectionist simulations. For example, computational models predict that neocortical damage, with sparing of the medial temporal lobe, will result in better recall of very recent memories compared with older autobiographical experiences. This prediction has been convincingly supported by studies of autobiographical memory in semantic dementia (Snowden *et al*., 1996*a*; Graham and Hodges, 1997). In turn, specific findings from patients with semantic dementia can be used to refine the computational models: for instance Graham *et al*. (2000) and Simons *et al*. (2000) found that new learning in semantic dementia was perceptually based, yet no model of long-term memory has attempted to fractionate the 'neocortex' into separate areas (e.g. semantic and perceptual).

This paper draws attention to the fact that the pathology and the functional impairments seen in semantic dementia are complementary to those found in the amnesic syndrome and that the disease offers an excellent test case for current computational models of long-term memory. Whereas the precise nature and mode of human long-term memory largely remains a mystery, we believe that significant progress has been made in our understanding of the organization of memory by studying semantic dementia. This review also highlights, however, that many aspects of long-term memory in semantic dementia remain underexplored. Hopefully, combined studies of long-term memory, which incorporate new neuroanatomical, neuropsychological and computational data from patients with amnesia and semantic dementia, will provide answers to some of these as yet unanswered questions.

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