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# Neuropsychological mechanisms of very long term memory loss: a cognitive neuropsychological case study approach

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## ABSTRACT

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# NEUROPSYCHOLOGICAL MECHANISMS OF VERY LONG TERM MEMORY LOSS: A COGNITIVE NEUROPSYCHOLOGICAL CASE STUDY APPROACH

by Jonathan J. Evans

Our understanding of the mechanisms underlying very long-term memory impairments remains rather limited. The aim of this thesis is to clarify the nature of various distinctive forms of very long-term memory disorder and to shed light on the mechanisms that give rise to these syndromes.

Chapter 1 provides a review of the relevant literature. Chapter 2 presents three sets of studies examining the nature and extent of retrograde amnesia following damage to temporal lobe and diencephalic structures. The extent to which medial temporal lobe structures are involved in the retrieval of autobiographical event memories across the lifetime is considered. The findings from these studies suggests that the hippocampal complex is critical to the ability to mentally re-experience or 'replay' events over a very extended period of time and probably as far back as childhood. These findings provide support for Multiple Trace Theory (Nadel and Moscovitch, 1997), and are less supportive of predictions derived from the Standard Consolidation Model of memory (Squire and Alvarez, 1995; Murre, 1996).

Chapter 3 is concerned with (i) the circumstances under which extensive retrograde amnesia may occur in the absence of anterograde memory deficits and (ii) the dissociation of episodic and semantic retrograde amnesia. Two cases are studied. The first case, a patient with cerebral vasculitis, presented with a severe impairment in autobiographical episodic memory, with normal anterograde memory. The second case presented with a progressive impairment in her ability to recognise familiar faces and a loss of knowledge of people in the presence of intact autobiographical memory. Although the findings from these cases highlight the dissociation of episodic and semantic memory, it is argued that in the undamaged human brain there is a complex and dynamic interaction between the experiential and factual components of long-term memory.

Chapter 4 presents two studies of very long-term anterograde memory. The first study compared and contrasted the acquisition of new episodic and semantic information in two patients – one patient with a focal hippocampal lesion and a second patient with more extensive medial temporal lobe damage. The study provides further evidence that semantic learning is possible in the context of focal hippocampal pathology, although such learning is not normal. The finding of a similar deficit in the ability to mentally replay anterograde events for the patient with pathology confined to the hippocampus, compared to the patient with more extensive medial temporal lobe pathology, provides further support for the critical role of the hippocampus in autobiographical event recollection. The second study investigated two patients who have a rare form of anterograde memory deficit involving a failure to retain information over extended time delays in the context of normal performance on standard anterograde memory tasks. Using a novel diary-based procedure, it appeared that epileptic seizures play a role in this condition, but that epileptic activity does not in itself provide a complete explanation for the pattern of impairment.

In the final chapter, the main theoretical, clinical and methodological implications of the findings from each of the studies are discussed. I conclude that Mesulam's (1998) formulation of Convergence Zone Theory provides the most comprehensive framework within which to account for the variety of very long-term memory disorders shown by the patients in these investigations.

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## Acknowledgements

This thesis is the result of work done during my period of registered postgraduate candidature, apart from the collection of data for the study presented in Chapter 2.2. Some of the work presented here is the result of collaboration, but the substantial part of it is my original work. Studies undertaken in collaboration with others have been published, as follows:

**Chapter 2**

Evans JJ., Wilson BA., Wraight EP., Hodges JR. (1993) Neuropsychological and SPECT scan findings during and after transient global amnesia: evidence for the differential impairment of remote episodic memory. *Journal of Neurology, Neurosurgery and Psychiatry;* **56**: 1227-1230.

**Chapter 3**

Evans, JJ., Breen, EK., Antoun, N., Hodges, JR. (1996) Focal retrograde amnesia for autobiographical events following cerebral vasculitis: A connectionist account. *Neurocase*; **2**: 1-11.

Evans, JJ., Heggs, AJ., Antoun, N., Hodges, JR. (1995) Progressive prosopagnosia associated with selective right temporal lobe atrophy: A new syndrome? *Brain*; **118**: 1-13.

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# Chapter 1 Introduction, literature review and aims of the thesis.

## 1.1 Introduction to the area of study

Memory impairment is one of the most common sequalae of brain injury or disease. The fact that many different patterns of impairment may arise from such damage reflects the now well established fact that 'memory' is not a unitary concept or process, at either a psychological or anatomical level of explanation. An important conceptual division within the broad concept of memory is that between short term or working memory and long term memory (Baddeley and Hitch, 1974). This thesis is concerned with long term memory. Within the domain of long term memory, conceptual divisions have been made at the level of - stimulus material (i.e. verbal vs. non-verbal); type of information (context-free factual or 'semantic' information vs. information relating to unique personal experience or 'episodic' information); and accessibility to conscious recollection (e.g. explicit vs. implicit memory). Squire (1992) proposed a taxonomy of memory systems to reflect these conceptual divisions, which has recently been updated (Squire, 1998). This is shown in Figure 1

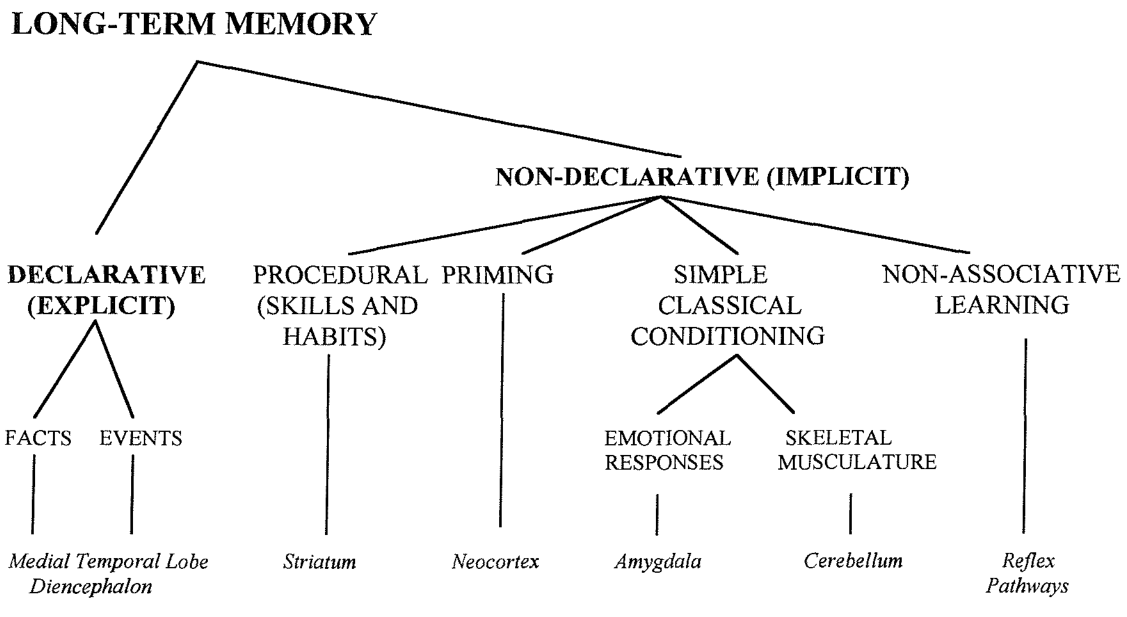


***Figure 1 Squire's (1998) taxonomy of long-term memory systems together with the brain structures considered to be critical for each system.***

The term amnesia means 'loss of memory.' However, in a neuropsychological context the term is typically used (Mayes and Downes, 1997) to refer to a syndrome or pattern of cognitive strengths and weaknesses which includes (1) intact working memory, (2) intact general intellectual functioning, (3) anterograde amnesia - impaired ability to learn (recall or recognise) new facts or personal episodes (4) a variable degree of retrograde amnesia - difficulty remembering information which had previously been available, prior to the onset of the memory impairment.

Mayes and Downes (1997, p. 3) note that there are wide variations in severity of anterograde and retrograde memory impairment in different amnesic patients. Because of this, Mayes, Daum, Markowitsch and Sauter (1997) note, "recent studies have suggested that this syndrome may dissociate into several more specific memory disorders. One of the dissociations suggested is between anterograde and retrograde amnesia" (p. 197). Establishing the pattern and nature of anterograde and retrograde memory impairments that may arise after brain injury or illness is important in developing our knowledge of the nature of the amnesic syndrome. Furthermore, the nature and pattern of anterograde and retrograde impairments that may occur also provides an important test of models of the cognitive and anatomical architecture of memory. A number of questions concerning the nature of anterograde and retrograde arising from brain lesions remain unanswered and these will be highlighted in this review of the literature. The main aims of this thesis are therefore (1) to clarify the nature of various distinctive forms of very long-term memory impairment and to shed light on the mechanisms that give rise to these syndromes, (2) to test predictions from contemporary models of memory and amnesia using data derived from patients selected for study on the basis of lesion location or pattern of anterograde and retrograde memory impairment.

The nature of the retrograde memory deficit within the amnesic syndrome is of particular interest since, as Mesulam (1998) noted, "one of the most important components of the amnestic state is retrograde memory loss" (p. 1027). Patterns of retrograde amnesia have been central to the development of fundamental concepts of human memory, such as the notion of consolidation, which suggests that memories initially exist in a fragile state and only become permanent over an extended period of time. However, in a recent review of a century of research on consolidation, McGaugh (2000) concluded that "despite theoretical conjectures little is as yet known about system and cellular processes mediating consolidation that continues for several hours or longer after learning to create our lifelong memories" (p. 250). Furthermore, the study of retrograde amnesia has been relatively neglected in comparison to the study of anterograde amnesia. As Gloor (1997) notes, "human studies on retrograde amnesia suffer from the fact that the nature of the items assessed lend themselves poorly to a rigorous quantitative treatment of the problem" (p. 561). This difficulty, discussed in more detail in the following section, accounts for some of the limitations of previous research on retrograde amnesia.

## 1.2 Amnesia: Terminological, measurement and methodological issues

### *1.2.1 Terminological issues*

Issues relating to terminology and measurement arise in a number of areas of human biology and have been highlighted in discussions of retrograde amnesia (Kapur, 1999). At the outset, it is therefore necessary to discuss the terminology used in this area of study and to clarify how this terminology is used in this thesis. Schacter (1996) notes that the terms anterograde and retrograde amnesia were coined in the late nineteenth century by the French physician Charles Azam, who described memory loss in a well-known case of multiple personality. Retrograde amnesia has traditionally been used to refer to loss of memory for information of various kinds that had been acquired prior to the occurrence of a brain insult. Anterograde amnesia has traditionally been used to refer to difficulties in retaining information acquired after the occurrence of a brain insult. In studies comparing anterograde and retrograde amnesia, anterograde amnesia is typically measured through the use of new learning tests such as story or design recall. The ability to retain information such as autobiographical experiences or more general factual knowledge from the post-insult period is frequently not included in the concept of anterograde amnesia, by virtue of not being assessed in most studies, for reasons discussed later. In this thesis, the terms anterograde amnesia and anterograde memory impairment are used to refer to an inability to retain memories of autobiographical experiences and/or factual knowledge over an extended time period.

Another area where issues of terminology arise relates to definitions of *severity* of impairment. In the case of anterograde memory, a severe impairment is typically defined by a performance on standardised tests of new learning that is significantly poorer than a comparative sample (e.g. below the 5th percentile). However, in the case of retrograde amnesia, the issue of defining severity is more complex. Severity is typically defined in terms of the length of time pre-insult for which memory is affected. However, a different dimension of retrograde amnesia is the density of the recall deficit. It is possible for one person to have a very dense period of retrograde amnesia which stretches back just a few years, whilst another may have a more patchy recall throughout a more extended period. It is not clear which of these should be considered to be the more 'severe'. This issue highlights the need for descriptions of retrograde amnesia to be precise in terms of the form of the impairments present and so in this thesis the term 'severe retrograde amnesia' will only be used with qualification.

A major distinction that arises in retrograde amnesia research is that between autobiographical event information, i.e. specific experiences which can be located in time and space, and information that would be described as 'semantic' or 'factual' i.e. knowledge that is context-independent and often acquired through multiple exposure to, or rehearsal of, the material. Kapur (1999) used the terms 'episodic retrograde amnesia' and 'semantic retrograde amnesia' to refer to deficits in these two forms of knowledge. He defined 'episodic retrograde amnesia' as a deficit in the ability to recollect personally experienced events. In this thesis, I use the terms episodic retrograde memory and autobiographical event memory synonymously. 'Semantic retrograde amnesia' was described as "reflecting well-established knowledge in any domain- for example, verbal, relating to people, relating to events, pictorial, spatial, motor etc." (p. 801), but Kapur also notes that, "in the case of semantic retrograde amnesia, memory for public events and memory for people have formed the primary corpus of research" (p. 801). Within the category of semantic retrograde knowledge, a further distinction is often drawn between personal semantic information, used to refer to knowledge of context-independent autobiographical information such as the names of friends, schools attended, employment history etc., and information that is in the public domain, such as famous personalities, news events. In this thesis, the terms personal semantic and public semantic memory will be used to refer to these two sets of knowledge.

Much of this thesis is concerned with the functioning of key structures in the medial temporal lobes. However, there remains considerable variation in the way in which these structures are delineated and labelled. For example, Galton, Gomez-Anson, Antoun, Patterson, Graves, Sahakian, Scheltens, and Hodges, (2001) draw a distinction between the hippocampus (which includes areas CA1-4, the dentate gyrus and the subiculum) and the parahippocampal region (which includes the entorhinal cortex and perirhinal cortex). Fujii, Moscovitch and Nadel (2000) contrast the hippocampus proper (CA1-4), the hippocampal formation (areas CA1-4, the dentate gyrus and the subiculum) and the hippocampal complex (hippocampus proper, entorhinal cortex, perirhinal cortex and parahippocampal gyrus). Nadel (2000) refers to the parahippocampal region as including entorhinal cortex, presubiculum, the parasubiculum and the perirhinal cortex. In this thesis, I will follow the scheme suggested by Galton et al. (2001), unless otherwise stated.

### *1.2.2 Measurement issues*

Retrograde memory forms a major focus of the studies presented in this thesis. However, measurement of retrograde memory is problematic for various reasons. A major difficulty is that one is seldom in a position to control exposure to material being tested. For example, it is not possible to be wholly confident that an individual did learn about a particular news event at the time of its occurrence or was exposed to a particular famous person or had specific life experiences. Furthermore, some events or people are in the news at a particular time, but then may re-occur as news items at later dates (as a result of anniversaries of events, or subsequent development in the story). Measurement difficulties of this kind have probably limited the development of knowledge relating to retrograde amnesia, and hence the development of comprehensive models of memory. Studies of retrograde memory have relied heavily on using tests of knowledge of famous events, TV programmes or famous people. Personal experiences have been relatively less well studied, though the development of the Autobiographical Memory Interview (AMI; Kopelman, Wilson and Baddeley, 1990) and the use of various forms of the Galton Crovitz technique (e.g. Hodges and Ward, 1989) have helped to redress this imbalance. Although news events are often associated with a specific time and place, coverage of the event can continue for a relatively long duration. The individual is thus exposed to multiple repetitions of the information (hence becoming more 'semantic' in nature). However, even with personal information, it is possible for information relating to personal events to become more 'semantic' in nature as a result of frequent telling of a particular personal anecdote. The implication of these difficulties is that it is necessary to use a wide range of test materials when examining retrograde memory, an approach that is adopted where possible in this thesis.

A further issue is that public event knowledge is often tested in a recognition format (e.g. Famous Events test in Hodges and Ward, 1989) or using other forms of retrieval cue. Marslen-Wilson and Teuber (1975) found that when they tested the amnesic patient HM and a group of other amnesic patients on a test of famous name knowledge, using a cueing procedure involving providing the first name and initial syllable of the surname, they found a major improvement in comparison to recall conditions. By contrast, autobiographical event knowledge has been more typically tested using tasks that have a significant retrieval demand. For example, the Crovitz technique requires the participant to recollect events on the basis of single words (typically concrete nouns). The Autobiographical Memory Interview (Kopelman et al., 1990) requests the recollection of events from particular time periods or associated with extended episodes such as a holiday. There are some reports in which recall of personal events have been strongly cued through the use of photographs or event descriptions (e.g. Hodges and McCarthy, 1993), but there are no reports of studies in which personal experiences have been tested using a forced-choice recognition format. This is a critical limitation of previous research on retrograde amnesia and has implications for understanding the nature of such deficits in terms of access or storage deficits. This issue will be addressed in Chapter 2, Section 2.3.

In studies of retrograde and anterograde memory, the long-term acquisition of anterograde autobiographical event or semantic knowledge is frequently not assessed. There are at least two major reasons for this state of affairs. Firstly, patients are sometimes tested relatively soon after the insult (within a matter of months or a small number of years), so that the number of memorable personal experiences or public events that have occurred are relatively limited. Secondly, tests of story or design recall provide a means of assessing new learning skills in a standardised manner, so avoiding many of the problems in measuring factual knowledge or personal experiences, which are acquired in an 'unstandardised' manner, so making comparisons with normative control subjects more difficult. Difficulties arise when comparisons are attempted between the ability to recall experiences or knowledge to which the individual was exposed *before* the insult and the ability to recall experiences or knowledge to which the individual has been exposed *since* the insult. Poliakoff and Meudell (2000) demonstrated in a study involving normal control participants that correlations existed between performance on new and remote memory tests only when tests tapped the same domain of memory. Mayes et al. (1997) made a similar point, noting that the relationship between anterograde and retrograde amnesia should be determined, "with a procedure that (a) identifies the precise date of onset of the condition, (b) ensures that the date of onset and the age of patients is such that pre and post-morbid memories can be assessed over many years and (c) matches the format and kind of information assessed by the pre- and post-morbid tests" (pp 215). Where possible, this general approach is adopted within this thesis.

### *1.2.3 Methodological issues*

The research methodology of choice in this thesis is the single-case study. It has been argued that single-case studies provide the most effective means of using data derived from the performance of people with brain lesions to understand normal cognitive functioning (Teuber, 1955; Caramazza and McClosky, 1988; McClosky, 1993). Although it has been argued that group studies may be superior to single-case studies (Robertson, Knight, Rafal, and Shimamura, 1993), group studies face the problem of lack of homogeneity within the patient group. While it is possible to study patient groups whose members are homogeneous at a gross level (e.g. lesions in the temporal lobe, or presence of memory impairment), this level of homogeneity may mask important individual variations. For example, two patients may both have temporal lobe lesions, but those lesions may be in completely different locations within the temporal lobes, be of different size and arise from different pathologies. Furthermore, some patterns of impairment or locations of lesion occur relatively rarely, making the assessment of groups of patients practically difficult. Nevertheless, rare patterns of impairment provide a useful test for models of cognitive function that may have been built around more typical patterns of impairment. If such models are adequate, they should be able to account for, and should in fact predict, atypical patterns of impairment that may only arise under certain unusual circumstances. Several of the cases in this thesis present with atypical patterns of impairment and are therefore used to test the explanatory breadth of several theories of memory.

The key theoretical tool within single-case studies is dissociation methodology. If a patient with a brain lesion is impaired on a particular task, which is hypothesised to make demands on a particular cognitive process, but normal (when compared to well matched control participants) on other tasks that are hypothesised to make demands on other cognitive processes, then this provides some evidence that the hypothesised cognitive process exists as a distinct cognitive module, within an integrated cognitive system. This pattern of performance is referred to as a single dissociation. A limitation of the single dissociation is that rather than being dependent upon a separate cognitive process, the impaired task could simply be more difficult than the unimpaired tasks and as such be more sensitive to any form of brain damage. A stronger form of evidence for modularity of cognitive processes is provided by the double dissociation. This occurs when one patient is impaired on task X, but unimpaired on task Y, while a second patient shows the opposite pattern. In this case, the argument that one task is more difficult than another cannot explain the differences in performance and hence the conclusion that tasks X and Y depend upon separable cognitive processes carries more weight. Furthermore, where the two patients have distinct and different lesions, conclusions concerning brain regions controlling the cognitive processes are easier to draw. Although double dissociations represent the 'gold standard' of evidence in cognitive neuropsychology, it is not always possible to demonstrate double dissociations. For example, if two cognitive processes form part of a sequence of interdependent processes then damage to one earlier in the processing sequence will inevitably lead to failure in the subsequent processing stages. Thus, it may be possible to demonstrate impaired performance on later stage processes and intact performance on earlier processes, but the reverse is not possible. Nevertheless as McCarthy and Warrington (1990) argue, "In-depth analysis of the characteristics of the patients' impairment may yield valuable (even critical) insights into the processing or procedures within the damaged system itself" (p. 20). A limitation of single-case research studies is that it may not be possible to establish a failure to replicate a dissociation between two tasks (McClosky, 1993, p.731). Thus, if the results from a single-case study had occurred by chance or because of a confound in the stimulus materials, this could not be demonstrated by showing that the study failed to replicate, since if a patient shows normal performance on both tasks this may simply indicate that neither mechanism is damaged and impairment on both tasks may reflect two separate deficits, one affecting each mechanism. McClosky (1993) notes the importance, therefore, of several measures that should be taken to ensure that the findings are very unlikely to have resulted from chance or from unrecognised characteristics of particular tasks or stimuli. These measures include, "testing extensively with a wide range of stimuli in each task, obtaining converging evidence from multiple tasks, examining data at a finer grain than that of overall performance on a task and carrying out appropriate statistical tests to assess whether observed effects are reliable" (p. 731). Such measures have been adopted in this thesis wherever possible. A further criticism of single-case studies is the possibility that a dissociation reflects an atypical pre-morbid characteristic of the patient (McClosky, 1993, p. 731). In any given cognitive domain, a small proportion of the normal population may conceivably have cognitive mechanisms that differ qualitatively from the rest of the population. To minimise the risk of this possibility, patients for study need to be selected with care, avoiding, for example, individuals with evidence of developmental cognitive deficit. Furthermore, what is required is multiple single-case replications of findings. Such an approach is adopted in this thesis wherever possible.

A further methodological issue in cognitive neuropsychological investigations is how impairment in performance on particular tests is determined, where a single test score is derived. In the present studies, the performance of patients under investigation was compared with either (1) published normative data from standardised test manuals, or (2) matched control groups. For the matched control groups, the scientific tradition is to use z-score data, with a cut-off for impairment being $z = -1.96$ for a two-tailed test or $z = -1.64$ when a directional hypothesis has been formed. Crawford and Howell (1998) note that in the case of small-N control samples, it is preferable to use a modified form of t-test as this treats parameters as sample statistics rather than population statistics, which the z-score does. Crawford and Howell (1998) therefore described the application of a modified t-test and this method was used with data presented in Chapters 2.1, 2.3, 4.1, and 4.2. The studies presented in Chapters 2.2, 3.1 and 3.2 were conducted and published in peer-reviewed journals prior to the development of this test and the data for those studies are presented here in their published form. However, a review of the results from these studies using Crawford and Howell's (1998) table of z score cut off values to attain significance (taking into account sample size) suggests that the z-scores are either sufficiently within or outside of a normal range, such that the conclusions drawn from the derived z-scores are likely to be reliable.

### 1.3 What do models of amnesia have to explain?

Models of the organisation of memory in the brain must be able to account for the range of memory disorders that may follow from damage to the brain. This section will discuss some of the major themes and patterns of memory impairment that have been described in the literature. I will note that several questions concerning these patterns of amnesia remain unanswered, and will address some of these in this thesis.

#### 1.3.1 The relationship between anterograde and retrograde amnesia

The central defining feature of the amnesic syndrome is a severe anterograde amnesia. In the case of retrograde amnesia, definitions of the amnesic syndrome frequently refer to a 'variable' degree of impairment in the ability to recollect pre-morbid events, suggesting that there is not a consistent relationship between anterograde and retrograde amnesia. Several group studies of people with amnesia have, however, found a correlation between anterograde and retrograde memory impairments. Kopelman, Wilson and Baddeley (1989) examined a group of 23 amnesic patients of mixed aetiology on the Autobiographical Memory Interview (AMI; Kopelman, Wilson and Baddeley, 1990) as well as on tests of anterograde memory (e.g. Logical Memory). They found that performance on both the Personal Semantic and Autobiographical Incidents components of the AMI correlated significantly with immediate recall on Logical Memory. Furthermore these correlations held up even when the analysis was confined to childhood and early adult facts/incidents, which are usually more definitely 'retrograde'. The Recent Events component of this test is typically anterograde for most patients tested. Kopelman et al. noted that in earlier work (e.g. Kopelman 1989) they found low correlations between anterograde and retrograde measures and suggested that the correlation in their study may have reflected a 'severity' factor in that some patients performed generally well and others performed generally badly. It is possible therefore that performance on the anterograde and retrograde tests was linked to a third factor such as IQ or executive functioning.

The relationship between anterograde and retrograde amnesia was also examined in a group study of 10 patients with 'typical global amnesia' by Mayes et al. (1997). The group consisted of six patients with Korsakoff's syndrome, two post-encephalitic patients, one patient with a closed head injury and one patient with a thalamic infarct. Each had preserved intellectual function and major anterograde amnesia. Patients were examined on various tests of anterograde and retrograde memory. The retrograde memory tests included the Autobiographical Memory Interview (Kopelman et al. 1990) as well as tests of famous events, faces and famous names. Mayes et al. (1997) demonstrated that the post-morbid section of the AMI (recent past/present life) correlated significantly with scores on tests of anterograde memory (passage recall and word recognition) and also with the early adulthood section of the AMI, but not with the childhood section of the AMI. There was a trend for the anterograde memory tests to correlate with the early adulthood section of the AMI, but it did not reach significance. The anterograde memory tests did not correlate with childhood memory recall, though the post-morbid section of the AMI did correlate with the childhood section. With tests of famous events, names and faces there was no correlation between these retrograde tests and the anterograde tests. Thus, this study produced some potentially conflicting results. On the one hand there was a correlation between anterograde and retrograde amnesia (when only the AMI was considered), which, as Mayes et al. (1997) note, "seems to suggest that one functional deficit underlies amnesia for the whole post-morbid period and not only the recent pre-morbid period, but also the remote pre-morbid period" (p. 214). On the other hand there was a correlation between the recent pre-morbid period performance and a number of different tests of anterograde memory, but no similar correlation for the remote pre-morbid period. This suggests that different systems are perhaps involved in retrieving recently acquired information as opposed to information acquired in the more distant past. This hypothesis, which forms the basis of a number of contemporary models of memory, is discussed in more detail later.

Mayes et al. (1997) note that one of the problems in this sort of study is that, "in many global amnesics, the damage that causes anterograde amnesia may be equivalent in extent to the damage that causes retrograde amnesia for remote memories" (p. 214). Thus, group correlation studies are not ideal or sufficient to identify whether or not clear dissociations can exist. This point highlights the importance of the detailed study of single cases, which allow the possibility that dissociations in deficits can be identified. Several studies have concluded that anterograde amnesia can exist without, or with only minimal, retrograde amnesia, and reflecting the double dissociation, that retrograde amnesia can exist without, or with minimal, anterograde amnesia. These studies are discussed in the following two sections.

### 1.3.2 Disproportionate anterograde amnesia

The most extensively investigated amnesic patient, HM, developed a severe anterogade amnesia in the context of bilateral medial temporal lobe lesions (Scoville and Milner 1957). Clinical assessment suggested at first that he had a retrograde amnesia of 2-3 years, and when assessed on tests of famous faces and famous events, a pattern of impairment only on the most recent items was obtained (Marslen-Wilson and Teuber, 1975). These findings suggested that it was possible for a very severe anterograde amnesia to occur, with a relatively short period of retrograde amnesia. However, when tested on a version of the Crovitz test, examining recall for incident information, his retrograde deficit was estimated at 11 years (Corkin, 1984).

In 1986, Zola-Morgan, Squire and Amaral described patient RB who experienced an ischaemic anoxic episode following coronary by-pass surgery in the context of severe and widespread atherosclerosis. Post-mortem histological examination revealed "a circumscribed bilateral lesion involving the entire CA1 field of the hippocampus" (p 2950). Zola Morgan et al. concluded that he had a significant anterograde memory deficit, with "little if any retrograde amnesia" (p 2950). Dusoir, Kapur, Byrnes, McKinstry, and Hoare (1990) reported the case B.J. who developed significant anterograde memory impairment following a penetrating brain injury caused by a snooker cue which entered his left nostril into the basal regions of the brain. MRI evidence indicated the main lesion to be in the mammillary bodies, though a later PET scan identified some loss of function in the left hippocampus. His retrograde amnesia was reported to be limited to a six-month period before the injury. Kapur, Thompson, Cook, Lang and Brice (1996) reported the case K.K. who developed an anterograde amnesia as a result of a tumour which affected the mammillary bodies, thalamus and brain stem. He was reported to show "significant anterograde memory impairment, with marked impairment on delayed story recall, but normal or only mildly impaired performance on retrograde memory tasks" (pp 1). Kopelman, Stanhope and Kingsley (1999) reported a study of anterograde and retrograde amnesia in patients with diencephalic, temporal lobe and frontal lesions. Amongst their group of diencephalic patients were two patients who had undergone surgical excision and irradiation of a pituitary adenoma, resulting in lesions of the anterior thalamus, the mammillary bodies, the mammillo-thalamic tract and the fornix. These two patients showed significant anterograde memory deficits, but on tests of retrograde memory, "showed no significant differences from controls, with only minimal impairment in recalling facts and incidents from their lives and actually performing better than controls in the recall of famous news events" (pp 947).

Kapur and Brooks (1999) reported two further cases, B.E. and L.C. both of whom "showed marked anterograde deficits, but mild, temporally-limited retrograde amnesia that covered a period of several years in both autobiographical and factual knowledge domains" (p. 247). Both patients had focal medial temporal lobe lesions, affecting the hippocampus only in the case of B.E., who suffered viral encephalitis, and the hippocampus and left uncus/entorhinal cortex in the case of L.C., who developed encephalitis as a complication of a bone marrow transplant for chronic myelocytic leukaemia.

The cases described above provide examples of patients with apparently minimal retrograde memory impairment in the context of marked anterograde impairment. From an anatomical point of view, the cases involved selective diencephalic or hippocampal lesions. It is worth noting that, in fact, in all patients there was evidence of at least some retrograde amnesia and in most cases, the immediately pre-morbid period (up to a couple of years) was not well covered by the tests of remote memory used. For example, Squire et al. (1986) noted that, "the possibility remains that he [R.B.] could have suffered some retrograde amnesia for a period of a few years prior to his coronary surgery in 1978. Although some of his test performance is consistent with this possibility (detailed recall of public events, television test), the tests are too coarsely grained and performance is too variable to reliably detect such a deficit in a single subject" (pp 2954). Dusoir et al.'s (1990) patient B.J. had a significant retrograde amnesia for a period of 6 months, but also had some difficulty recalling various other events going back several (at least 4) years. Kapur et al.'s (1996) patient

K.K. performed at 'borderline' levels on the autobiographical incidents sections of the AMI (Kopelman, et al. 1990) and also showed some impairment on indicating whether famous personalities were still alive on the 'Dead-or-Alive Test' (Kapur, Young, Bateman and Kennedy, 1989). In the case of Kopelman et al. (1999) pituitary adenoma patients, there was, as noted, minimal impairment on the autobiographical incidents section of the AMI, but no impairment on a News Event test, though it is of note that the News Event test used only had items up until 1990. Whilst the date of onset of problems for the patients is not provided, it is probable that they were tested at least a few years after 1990.

The cases described above demonstrate that, in the context of severe anterograde amnesia, some patients will not show an extensive retrograde amnesia. However, none of the patients can be confidently described as showing *no* retrograde amnesia. Most show a degree of retrograde amnesia for a period of time immediately pre-morbidly, though the limitations of tests of retrograde amnesia mean that it was difficult to determine the extent of any deficit. As noted earlier, Mayes et al. (1997) emphasised the importance of determining the relationship between retrograde and anterograde amnesia with procedures that identify the precise date of onset of the condition, and which ensure that the date of onset and age of the patients is such that pre- and post-morbid memories can be assessed over many years. They note that "future work...should by preference use patients for whom it is possible to determine the precise time of onset of the condition" (p. 216) adding that this is difficult to do with Korsakoff's patients. Chapter 2.1 of this thesis addresses this issue with a detailed study of five patients who presented as having either no retrograde amnesia or retrograde amnesia limited to a relatively short pre-morbid period.

According to Kopelman (2000), "...it is widely accepted that anterograde amnesia (AA) can occur with minimal or no RA" (p. 587). Although this statement might be accurate, this section has highlighted the possibility that this conclusion might be somewhat premature. However, one pattern of impairment that continues to be more controversial is 'focal retrograde amnesia' (Kapur 1993). This term has been used to describe retrograde amnesia that is present in the context of intact anterograde memory functioning and is discussed in the following section.

### 1.3.3 Disproportionate retrograde amnesia

Focal or disproportionate retrograde amnesia (FRA) has been reported following a number of different neurological conditions including;

1) *Mild head injury* e.g. Stracciari, Ghidoni, Guarino, Poletti and Pazzaglia (1994); Maravita, Spadoni, Massucchi and Parma (1995); De Renzi, Lucchelli, Muggia, and Spinnler (1995); Lucchelli, Muggia and Spinnler (1995); Della Sala, Freschi, Lucchelli, Muggia, and Spinnler (1996); Starkstein, Sabe and Dorrego (1997); De Renzi, Lucchelli, Muggia and Spinnler (1997).
2) *Severe head injury* e.g. Goldberg, Antin, Bilder, Gerstman, Hughes and Mattis (1981); Kapur, Ellison, Smith, McLellan and Burrows (1992); Markowitsch, Calabrese, Haupts, Durween, Leiss, and Gehlen (1993); Hunkin, Parkin, Bradley, Burrows, Aldrich, Jansari, and Burdon-Cooper (1995); Kapur, Scholey, Moore, Barker, Brice and Thompson (1996); Mattioli, Grassi, Perani, Cappa, Miozzo and Fazio (1996), Kroll, Markowitsch, Knight, and von Cramon (1997); Levine, Black, Cabeza, Sinden, Mcintosh, Toth, Tulving, and Stuss (1998).
3) *Epilepsy* e.g. Kapur et al. 1989.
4) *Encephalitis* e.g. Stuss and Guzman, (1988); O'Connor, Butters, Militosis, Eslinger and Cermak (1992); Yoneda, Yamadori, Mori and Yamahita (1992); Hokkanen, Launes, Vataya, Valanne, and Iivanainen (1995); Carlesimo, Sabbadini, Loasses, and Caltagone (1998); Fujii, Yamadori, Endo, Suzuki, and Fukatsu (1999).

There are few reports of FRA arising from vascular conditions, though the case described by Roman-Campos, Poser and Wood (1980) of a woman who had a persistent retrograde amnesia following transient global amnesia, may have had a vascular cause, though it was not possible to establish this for certain.

Despite the existence of the case studies listed above, the status of FRA remains controversial for several reasons (see Kopelman, 2000; Kapur, 2000). The first is that, as indicated above, many of the cases reported as examples of *focal* retrograde amnesia (FRA) are better described as *disproportionate* retrograde amnesia in that they do have a degree of anterograde amnesia. In a summary table of such cases presented by Kapur (1999), approximately 75% were reported to show some persisting anterograde memory deficits. Some cases have been cases of people with perceptual difficulties. For example, O'Connor et al. (1992) described a patient who had a mild verbal memory deficit (e.g. on Logical Memory), and showed a significant loss of autobiographical memory. However, this patient also showed significant visual agnosia and visual memory deficits. Similarly, Ogden (1993) described a head injured patient with bilateral medial occipital lobe damage and presumed damage to the efferent pathways to the temporal and parietal lobes. Once again this patient had a significant visual perceptual problem (e.g. prosopagnosia), along with a verbal memory deficit. Such patients are important in highlighting the importance of imagery in the recollection of autobiographical experiences and also in highlighting the importance of posterior brain regions for autobiographical recall (via their role in perception). However, in terms of patterns of anterograde and retrograde memory, they do not represent pure cases of focal or isolated retrograde amnesia.

Another concern is that several cases of purported FRA have occurred following mild brain injury, with no neurological evidence of structural brain injury. Thus, the possibility arises of an explanation of the deficits in terms of a psychogenic disorder. In this context it is noteworthy that the classic 'fugue' state (see Kopelman, Christensen, Puffett and Stanhope, 1994) involves a form of focal retrograde amnesia, usually with total inability to recall anything from an individual's past, including basic personal information, at least at the stage that an individual in this state presents him- or herself to an agency such as the police. Kapur (1999) describes a set of features of cases that may help in deciding whether there is a psychological basis for a focal retrograde amnesia. These include: (1) background e.g. history of pre-injury/pre-illness psychiatric symptoms, past history of minor head injury; (2) clinical presentation e.g. unconcerned or bemused attitude towards retrograde amnesia, delayed onset of severe retrograde amnesia some months after onset of brain pathology, severity of retrograde amnesia that is disproportionate to the severity of cerebral pathology, absence of diffuse cerebral pathology; (3) neuropsychological pattern e.g. loss of personal identity, loss of basic personal semantic information such as age, where lived as a child, evidence of malingering. Kopelman (2000) argues that there may be common pathophysiological mechanisms in organic and psychogenic amnesia, but further points out that the distinction remains important for clinical, neuropsychological and cognitive reasons. The case presented by Costello, Fletcher, Dolan, Frith and Shallice (1998) highlights the interaction between neural and psychological factors. They described the case of a man in his forties who suffered a left superior dorsolateral prefrontal haemorrhage and presented with a dense focal retrograde amnesia for 19 years preceding the stroke. It was noted that during this period of time the patient had suffered a series of very stressful life events. A PET functional imaging study examined activation levels in response to three conditions involving family photographs. In one condition, the patient looked at photographs of events where he had been present (referred to as the amnesic-present condition) and which were within his amnesic period; a second condition included photographs of events where he had been present and which were outside of his amnesic period; in a third condition, photographs of events where he had not been present were used. It was not stated from which period the events where he had not been present were drawn. The study showed that for the amnesic-present condition, activation was greater in the precuneus region, but lower for the right posterior ventrolateral frontal cortex and in a region close to the lesion. Costello et al. concluded that whilst malingering was not an adequate explanation for this patient's deficit, the period of immense stress in his life, which coincided with the period of retrograde amnesia was relevant. Costello et al.'s explanation for the imaging findings was that, whilst the initial elements of autobiographical memories were being activated (reflected in the precuneus activation), given the association of such memories with negative affect, the system responsible for subsequent processes of progressive deepening of the retrieval of a complete memory event would be, in effect, switched off. Costello et al. note that in this case, "it is most likely that the effects of the lesion and the predisposing psychological factors interact causally" (p. 444).

A further limitation of many of the previous case studies of FRA is that anterograde memory functioning is determined to be normal on the basis of performance on standardised tests of memory for stories or designs. Recall of autobiographical events or news event knowledge has rarely been tested over an extended post-morbid period. Thus the comparison of anterograde and retrograde memory functioning has not been tested on a 'like-for like' basis (Kopleman, 2000, p. 612).

All of the cases mentioned above presented with impairments in their recollection of autobiographical events and many were also shown to have *some* impairment in knowledge of their own general life history (personal semantics) or knowledge of famous faces, news events etc. In a recent review of FRA, Wheeler and McMillan (2001) identified five cases of patients with a deficit that appeared to be confined to autobiographical event knowledge. Four of these cases arose after closed head injury (Stracciari et al. 1994- 2 cases; Maravita et al. 1995; Klein, Loftus and Kihlstrom 1996), and in three of these cases the FRA was limited to a period of about a year prior to the trauma and resolved within a year following the accident. There is therefore a need to confirm in further cases the conditions under which selective retrograde *episodic* amnesia can occur. The fifth case identified by Wheeler and McMillan (2001) was in fact patient JM (Evans et al. 1996) who is described in Chapter 3.1 of this thesis.

In their review, Wheeler and McMillan also identified four cases of FRA with selective loss of *semantic* memory (DeRenzi, Liotti and Nichelli 1987; Grossi, Trojano and Grasso 1989; Yasuda, Watanabe and Ono 1997; Markowitsch, Calabrese, Neufeld, Gehlen and Durwen 1999). Each of these cases presented with deficits in knowledge of famous faces, names or events or in general knowledge, with better recall of autobiographical events. However, in each case there was some evidence of impairment in anterograde memory suggesting that the label 'disproportionate' semantic retrograde amnesia is a more appropriate term for such cases. The case described by DeRenzi et al. (1987) was a 44 year-old woman who developed an impairment in semantic knowledge after suffering from Herpes Simplex Encephalitis. The main areas of lesion were the anterior and inferior parts of the left temporal lobe, involving both medial and lateral structures. Her main complaint was a difficulty recognising familiar people, but she showed significant deficits on tests of object naming and meaning and on tests of public knowledge including famous events and famous people. DeRenzi et al. also commented on her difficulty with cooking, in which she had previously excelled. They noted that she failed to remember ingredients required and in cooking procedures or sequences. She was impaired on tests of verbal and non-verbal episodic anterograde memory. In contrast to all of these problems, she was able to provide detailed and accurate information on personally experienced events from both before and after the onset of her problems. She also had knowledge of linguistic and mathematical rules, procedures guiding over-learned skills, and spatial learning. She could also recall some public events, but only when she seemed to have some personal connection to them, leading DeRenzi et al. to emphasise the special status of autobiographical memory. They conclude that this patient suffered a "global semantic amnesia", characterised by: (1) impoverished knowledge of the meaning and attributes of words and their referents in concomitance with the intact command of grammatical syntactic rules and of preserved perceptual abilities; (2) amnesia for the stock of notions forming the cultural background of the members of the community, unless they are evoked as elements of a routine (e.g. mathematical skills); (3) intact recall of episodes having an autobiographic quality; (4) impairment on verbal and visual learning tests, when they involve the recall and recognition of semantically encoded stimuli; (5) proficient performance on intellectual tasks insofar as they do not imply semantic memory.

Most of the features of 'global semantic amnesia' as defined by DeRenzi et al. are also found in a condition referred to as semantic dementia, or progressive fluent aphasia (Mesulam, 1982, Snowden, Goulding and Neary 1989, Hodges et al. 1992). This condition has four main characteristics; (1) loss of verbal and non-verbal semantic knowledge about objects, facts, concepts, people and the meanings of words; (2) preservation of the phonological and syntactic aspects of language; (3) normal non-verbal problem solving; (4) good visual-spatial and perceptual abilities. The critical lesion in semantic dementia appears to be in the inferolateral gyri of one or both temporal lobes (more commonly the left), with relative sparing of the hippocampi, parahippocampal gyri and subiculum. Anterograde memory is often impaired on formal testing, but there is evidence of a degree of intact autobiographical episodic information particularly from more recent periods. This is the reverse of the usual temporal gradient associated with many amnesic conditions, in which more recent episodes are less well recalled than more distant ones (Ribot's Law).

Hypothesised sub-divisions of both semantic and episodic retrograde deficits require further evidence in terms of cases of selective impairments. Such deficits are also important to carefully document as they have methodological implications for the study of retrograde memory. Many studies of retrograde memory have used tests of famous face recognition or knowledge of information about famous personalities as the main tool for assessing retrograde memory. If knowledge of people dissociates from knowledge of events, other semantic information and autobiographical knowledge, then relying on famous people tests alone to assess retrograde amnesia may lead to inappropriate conclusions. In Chapter 3, the dissociation of autobiographical and semantic retrograde amnesia is examined with two cases. The first case, a patient with cerebral vasculitis, presented with a severe impairment in autobiographical episodic memory, with normal anterograde memory. The second case presented with a progressive impairment in her ability to recognise familiar faces and a loss of knowledge of people in the presence of intact autobiographical memory.

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### 1.3.4 Transient Global Amnesia

A major limitation for almost any study of retrograde memory is the lack of any specific control over what an individual had been exposed to prior to the onset of a memory impairment and a general ignorance as to how a patient would have performed on a range of memory tests prior to the lesion. Furthermore, even if information is available about events to which an individual had been exposed, it is not possible to be certain that the individual would have remembered the event if he or she had been questioned about it pre-morbidly. Comparing performance on the same type of task with well-matched control participants can provide some indication of the extent of a patient's impairment. The ideal situation would be to be able to compare an individual's performance prior to and then after the onset of the amnesic condition. Such an opportunity is rarely afforded. However, one condition that presents a unique opportunity to compare performance under 'normal' conditions and while the individual is amnesic is Transient Global Amnesia (TGA).

The syndrome Transient Global Amnesia, which was first described by Bender (1956) and named by Fisher and Adams (1964), is characterised by a sudden onset of severe amnesia. Cases of TGA are distinguished from other forms of acute memory dysfunction such as Transient Epileptic Amnesia (TEA; Hodges 1998; Zemen, Boniface and Hodges, 1998). Although many of the features are similar, Hodges (1998) notes that there are several distinct features; TEA rarely lasts more than an hour, where TGA usually lasts several hours; TEA attacks on waking are characteristic and there is often partial recall of the attack, these features being absent in TGA. According to strict diagnostic criteria (see Hodges 1991), the onset of a TGA attack should be witnessed (to exclude epilepsy or head injury as potential causes), and focal neurological features should be absent. By definition, the episode of amnesia is temporary and after a period of usually a few hours, the patient's ability to remember information recovers. It has been suggested that recovery of retrograde amnesia precedes recovery of anterograde amnesia, though this has only been systematically studied in one case (Kapur, Millar, Abbott and Carter 1998). The aetiology and pathophysiology of TGA remains uncertain, but converging evidence points to a disruption to the normal functioning of the medial temporal lobes (Simons and Hodges, 2000). Strupp, Bruning and Wu (1998) studied 10 patients (most within 48 hours of the attack) and showed using a diffusion-weighted MRI sequence, that 7 patients demonstrated signal changes in the left hippocampal region, with 3 of these having concomitant right-sided changes additionally. Strupp et al. argued that their study results were consistent with a spreading depression hypothesis of TGA (Olesen and Jorgensen, 1986). In this hypothesis, depression of hippocampal metabolism underlies TGA and the associated abnormalities on functional imaging. Spreading depression consists of the gradual spread of a wave of depolarisation, followed by neuronal depression, in response to a variety of insults including the infusion of excitatory neurotransmitter glutamate. Thus, the numerous possible triggers for TGA are believed to act via a common pathway, involving the release of glutamate. Schmidtke, Reinhardt and Krause (1998) carried out SPECT scans with six patients during TGA. Four patients showed hypoperfusion in the temporo-basal regions, with five of the six showing hypoperfusion in other cortical regions. Schmidtke et al. suggest that the origin of TGA-related changes lies at the level of sub-cortical structures that project widely to the cortex, though it seems likely that disruption to medial temporal lobe perfusion may underlie the development of amnesia.

The nature and severity of retrograde memory impairment in TGA appears to be very variable, or at least studies in which retrograde recall has been examined during an attack have reported varying types of retrograde deficit (Hodges 1998, p. 151). Clinical descriptions of patients studied during TGA typically describe a pattern of dense retrograde amnesia for a period of several months prior to the attack, with sparing of more remote memories. However, the problem with such descriptions is that it is not clear what type of information has been tested, with the possible confound that there may be a tendency to focus on recent episodes, in contrast to more general information (education, jobs history, marriage etc.) relating to more remote time periods. When remote memory has been tested more formally, several studies have used remote memory tests involving recall of public events, famous faces etc., rather than autobiographical information, although some have looked at autobiographical recall. Some of these studies have found no apparent deficit for public event knowledge (e.g. Wilson, Koller, and Kelly 1980 for famous events and Kritchevsky, Squire and Zouzounis 1988 for television programmes). Other studies have found a deficit in public event knowledge, with a temporal gradient being evident. Kritchevsky and Squire (1989) found that patients in TGA were impaired on retrograde memory tests when compared to their performance after TGA, apart from for the most remote decade (some thirty years previously). Hodges and Ward (1989) examined the performance of 5 cases of TGA on a test of famous faces (of people who were predominantly famous in specific decades from the 1930's to the 1980's), and on a test of famous event knowledge using a recognition format. There was considerable variation in performance across the 5 cases, with two performing normally, whilst the other three patients were impaired on all but the earliest decades. Kapur et al.'s (1998) study of the recovery of memory functioning as TGA resolves showed that their case SG was impaired on the most recent items from a public events test (Dead or Alive Test). On a news events test, administered in a recognition format, SG was impaired for 1980's events only in the very acute phase of the TGA, but then recovered. For the 1990's events, he was impaired for a longer period, only recovering to a normal performance after 24 hours.

Only a small number of studies have looked systematically at autobiographical *episodic* retrograde memory during TGA. Kritchevsky and Squire (1989) administered a personalised test of remote memory, though only 21% of the questions actually related to personal events. For these events, there was some indication of a temporal gradient in the ability to recall information, with more recent periods (i.e. the previous seven years) being poorer than more remote periods. Kritchevsky, Squire and Zouzounis (1988) found impairment on a test of recall of autobiographical memory using a modified version of the Crovitz test in which subjects are asked to recall incidents triggered by a list of 10 common nouns. Patients were impaired at retrieving detailed autobiographical information during TGA, though their performance was improved by detailed probing for information by the examiner. The same methodology was used by Hodges and Ward (1989) with three cases of TGA. They found that two of the three patients had difficulties producing detailed memories. Subjects were free to select memories from any period in their lives. For the control participants tested, 25% of recalled items were from the previous 5 years, with 16% being from the previous year. In contrast the patients produced only 4% from the previous 5 years and none were less than 1 year old. These patients also had difficulties dating such memories. A limitation of this methodology is that participants are free to retrieve information from any time period during their life. This means that whilst the method has produced an indication of a difficulty producing specific memories, the temporal extent of this difficulty is not clear. Kazui, Tanabe, Ikeda, Hashimoto, Yamada, Okuda and Wydell (1996) informally examined autobiographical retrograde events in two cases of TGA and concluded that there was evidence that retrograde amnesia was limited to a few years in both cases. However, only a very small number of events were examined and no attempt was made to systematically compare the amount of detail provided about the events during and after TGA. Kapur et al. (1998) examined autobiographical information with their patient SG using structured interviews about jobs he had held, schooling before starting work and houses in which he had lived. However, they did not assess for recall of specific incident memories. Nevertheless, they found that at first he appeared to have a retrograde amnesia stretching back 22 years (he was 39 at the time of the attack), and this gradually improved over the course of the recovery period. A similar result was found by Regard and Landis (1984), though with more informal testing of retrograde memory, in their study of two cases. Case 1 showed an improvement in retrograde amnesia from several months to just 2 days over a period of nine hours after onset whilst the anterograde deficit appeared largely unchanged. Case 2 showed a similar reduction in retrograde amnesia from several months to one month, whilst the anterograde deficit remained relatively unchanged.

It is possible that many of the accounts of TGA in which the retrograde deficit is described as 'patchy,' may reflect the fact that the patient can recall some information from more recent periods, where this information relates to generic events, whilst being unable to recall some specific information about incidents stretching back much further in time. This issue was highlighted earlier in discussion of the assessment of HM. Clinical assessment initially suggested a retrograde amnesia of 2-3 years, and when assessed on tests of famous faces and famous events, a pattern of impairment was found only for the most recent items (Marslen-Wilson and Teuber, 1975).

However, when tested on a version of the Crovitz test, examining recall for incident information, his retrograde deficit was estimated at 11 years (Corkin, 1984). This issue will be addressed with a case of TGA in this thesis (Patient BG; Chapter 2.2). Work with this patient will also address some predictions from contemporary models of memory relating to the pattern of deficits during TGA.

TGA therefore provides a unique opportunity to examine remote memory impairment in a situation where the subject effectively acts as his or her own control. One caveat to this point is that whilst memory functioning largely, and by definition, returns to normal after TGA, there may be *some* residual deficit. Hodges and Oxbury (1990) studied 41 patients 6 months following a TGA attack and found that there was evidence of a mild persisting impairment in verbal memory, identification of famous faces and events and in cued recall of autobiographical incidents. A critical limitation of most previous studies is that they have not involved a systematic assessment of the ability to recollect *detailed* autobiographical event knowledge from specified life-time periods nor compared performance on the same items during and after TGA. This approach was taken with the patient presented in Chapter 2.2.

### 1.3.5 Very long term accelerated anterograde forgetting

Huppert and Piercy (1978) demonstrated that when initial learning is equalised, patients with amnesia and control participants typically forget information at the same rate. However, it was noted earlier that a sub-set of cases cited as examples of 'focal retrograde amnesia' actually present with as distinctive pattern of impairment that includes significant retrograde amnesia, normal performance on standard tests of anterograde memory, but accelerated forgetting of newly acquired information over a period of days/weeks. Mayes and Downes (1997) note in relation to such cases, "the existence of this atypical kind of AA [anterograde amnesia] needs to be confirmed, as does its relationship with RA [retrograde amnesia], and the implications that this form of memory deficit have for our understanding of the amnesic syndrome need to be worked out" (p. 17). The small number of cases of this form of accelerated forgetting include those described by De Renzi and Lucchelli (1993), Kapur et al. (1996), O'Connor et al. (1997), and Lucchelli and Spinnler (1998).

DeRenzi and Lucchelli's (1993) case, PI, suffered an anoxic episode at the age of 24, when a tractor he was driving overturned on him. He complained of "a total loss of memory for past events, both personal and general, and the inability to recognise a familiar person" (p. 450). He appeared to be able to learn new information about, for example, people, and could retain it, but only for people he encountered regularly. He appeared to be able to hold on to information for up to a month, but after that appeared to forget unrehearsed information. A Flurodeoxyglucose (FDG) PET study showed bilateral reduction in activity in the posterior-superior temporal areas. No reference is made in the paper as to whether or not PI suffered from epilepsy following the injury. PI showed normal performance on several tests of anterograde learning when tested after the usual short delays. However on several tests that were administered after either 13 days or one month, he showed considerable impairment. Twelve different tests of pre-morbid knowledge or autobiographical memory were administered, and he performed poorly on all but three (all scholastic knowledge tests such as which region Italian cities were in, currency used in particular countries).

Kapur et al. (1996) described a case with this pattern of impairment. SP had previously worked as a marketing manager. She suffered a closed head injury in a road traffic accident. Magnetic resonance imaging revealed left temporal lobe atrophy and some involvement of the left hippocampus and right uncus/hippocampus. She experienced a single grand-mal seizure some two years post-injury, after which she commenced anticonvulsant medication. SP showed good performance on standard anterograde memory tests (e.g. delayed memory quotient 108). To assess long term retention, SP was assessed on sub-tests of the WMS-R at the usual 30 minute delay, and again at 6 weeks (with both recall and recognition conditions). In comparison to control subjects SP showed impaired recall and recognition on all sub-tests apart from recognition of verbal paired associates at six weeks. As far as retrograde memory is concerned, she was described as having a "marked loss of memory for events that occurred prior to her injury" (p. 427). Her personal semantic memory is reported as "minimally impaired compared to her memory for specific incidents, though she has been retold some of the information by her family" (p. 427). She did however, have difficulty recalling names of colleagues with whom she had worked over a seven years period. She also showed a marked impairment in her knowledge of pre-injury public events.

Case JT (Ahern, O'Connor, Dalmau, Coleman, Posner, Schomer, Herzog, Kolb and Mesulam, 1994; O'Connor et al., 1997) developed paraneoplastic limbic encephalitis secondary to testicular malignancy. The first sign of this was the onset of temporal lobe seizures and EEG studies were reported as being consistent with bitemporal epileptic foci, with a tendency for the right side to be more active. MR scans revealed pathological changes in the medial temporal regions bilaterally and in the anterior medial temporal lobe on the left. JT's performance on tests of memory was characterised by normal recall performance over the course of a day, but impaired recall after three days. He also presented with a poor recall of personal and public events (famous faces and events) prior to the onset of his problems. O'Connor et al.'s study of JT indicated that his retention decreased in conjunction with increased seizure activity. Furthermore, during a trial of paraldehyde, a decrease in seizure frequency was associated with enhanced memory functioning.

Lucchelli and Spinnler's (1998) case GB, presented with a two-year history of memory problems which included a difficulty recalling past personal events. He was subsequently diagnosed with temporal lobe epilepsy, though this apparently did not manifest itself until after he had presented with his memory impairment. No evidence of brain pathology was found with MR scanning. Testing showed that he was mildly impaired on some standard tests of anterograde learning, but showed a dramatic drop in his recall of a story between 1 day and 7 days, when compared to matched controls. His remote memory was tested, although in the absence of a precise date of onset of his illness, it is difficult for certain events to distinguish those that are retrograde and those that are anterograde. He was found to be impaired for autobiographical events and for public events. By contrast his personal semantic knowledge and knowledge of famous personalities (as well as broader general semantic knowledge) was good. In relation to the latter, he had some knowledge of famous people, but could not recount incidents in which they had been involved. Lucchelli and Spinnler also had the opportunity to examine the impact of seizure activity on recall. GB had learned a set of difficult paired associates just before the occurrence of a seizure. About 30 minutes after the seizure, he was able to recall items from the the test and three days later could still recall the 8 pairs he had learned pre-seizure. Lucchelli and Spinnler concluded that, "the clinically observed epileptic seizure did not affect recall of previously learned material even when checked after a long time" (p. 452).

In each of the above cases the problem of accelerated forgetting was accompanied by extensive and severe remote memory problems. By contrast Kapur et al. (1997) described another patient, P.A., who presented at the age of 62 with a difficulty in remembering holidays she had taken over the previous 18 months. Her autobiographical memory for pre-illness events was described as "normal or only mildly impaired". Three years after her initial presentation she developed absence seizures, and was diagnosed as suffering from epilepsy. EEG pointed to a focus in the left inferior-anterior temporal lobe structures. MRI scanning revealed a possible area of abnormality in the left anterior hippocampus, though the precise pathology was not determined. An FDG PET scan was normal. P.A. showed normal performance on standard anterograde memory tests (e.g. delayed memory quotient on the WMS-R, 116). However, similar to the cases described above, when tested on recall of information after 6 weeks P.A. showed an impaired performance compared to controls. On two tests of remote public event information (Dead or Alive test and Verbal News Events test) P.A. showed an impaired deficits for events from the 1990's (i.e. primarily since the onset of the long term retention symptoms), but normal performance for all decades from the 1950's to the 1980's. This case suggested therefore that as well as an impairment in personal event memory, there also seemed to be problems with the acquisition of public events knowledge and more general factual knowledge about famous people. However, this type of knowledge acquisition has not been studied in detail in many of the other previous cases and further studies are needed to more clearly identify the types of knowledge or information that fails to be consolidated in such cases.

The phenomenon of accelerated forgetting associated with epilepsy has been examined in group studies by Martin, Loring, Meador, Lee, Thrash and Arena (1991) and by Blake, Wroe, Breen and McCarthy (2000). Martin et al. (1991) showed that a group of 21 patients with temporal lobe epilepsy (including patients who had undergone surgery) were normal in their recall of a word list at 30-minute delay, but impaired after 24 hours. Blake et al. (2000) studied a group of 23 epileptic patients, comparing their performance on verbal memory tasks with a control group of 19 healthy subjects. None of the patient group had a history of head injury or any other neurological illness. Retention of the stories was tested after 30 minutes and approximately eight weeks. It was found that the two groups were not significantly different in their recall after 30 minutes, but were significantly different after eight weeks. Furthermore, there was evidence that the accelerated forgetting of verbal information was specifically associated with *left* temporal lobe epilepsy, since right temporal lobe patients performed normally.

The existence of the cases of accelerated forgetting described above has led to the conclusion that the process of consolidation of memories into a permanent record is one that takes place over an extended time period. The exact length of time is difficult to determine and probably depends on many different factors (e.g. emotional salience, level of rehearsal etc.), but is certainly longer than the 30 minute interval used to assess anterograde memory in routine clinical practice. These cases suggest that this consolidation process is susceptible to disruption for an extended period of time. In most of the reported cases, epileptic activity appeared to be relevant, or at least present. In most cases where it was documented, the epileptic focus was in the temporal lobes, though the Lucchelli and Spinnler's (1998) case suggested that epilepsy was not the key factor. However, the Blake et al. (2000) study, which included patients with epilepsy alone (i.e. no other pathology), seemed to support the role of seizure in disrupting long term memory consolidation. The possibility of patients incurring lesions as a result of repeated seizure activity obviously exists as does the possibility that a common structural pathology may be responsible for both the epilepsy and the accelerated forgetting. Conflicting evidence on the issue of the role of seizures in the long-term forgetting comes from two further studies. Bergin, Thompson, Fish and Shorvon (1995) gave 58 patients with refractory partial seizures a variety of memory tests shortly before they underwent video-EEG telemetry for a period of 48 hours. During this period 22 patients had seizures, but when compared on recall performance after this time period there was no significant difference in the scores of those who had had seizures and those who did not, leading to the conclusion that, "isolated seizures do not generally cause patients to forget material they have recently learned" (p. 236). By contrast, Bergin et al. (2000) found that patients with temporal lobe epilepsy were significantly worse than patients with extra-temporal lobe epilepsy, patients with primary generalised epilepsy or controls on a test of public event memory. Furthermore. Jokeit et al. (2001) carried out a study in which ten patients with refractory temporal lobe epilepsy performed a word-position association learning task every 24 hours during video EEG monitoring. On 55 occasions recall performance was tested 30 minutes and 24 hours after the initial learning phase. Patients with left- but not right-sided temporal lobe epilepsy exhibited impaired retention of word position if a seizure had occurred during the preceding 24-hour interval. The specific relationship between seizures and forgetting nevertheless remains uncertain.

In most cases of accelerated forgetting, there was a significant remote memory impairment. This did not appear to occur in Kapur et al.'s (1997) case, though no detailed assessment of retrograde autobiographical events was undertaken with this patient. Remote memory was not examined in the Blake et al. study, though in this study there was no temporally-specific pathology accounting for the epilepsy to act as a frame of reference for discriminating 'retrograde' from 'anterograde' autobiographical memory. In most of the cases where there was an extensive remote memory deficit there was, in addition to the presence of epilepsy, significant left or bilateral temporal lobe lesions. Retrograde memory was examined by Zeman, Boniface and Hodges (1998) in a series of patients diagnosed with Transient Epileptic Amnesia (TEA). TEA refers to a form of temporal lobe epilepsy in which transient amnesia may, for some attacks, be the only manifestation of seizure activity. Such attacks are characterised by an anterograde amnesia for the duration of the attack (often manifested by repetitive questioning) and a retrograde amnesia extending back in time for a variable period, which may be several years in some cases. Zeman et al. (1998) examined retrograde memory in a series of 10 patients with TEA. They noted that although the group performed normally overall on test of famous faces and the Autobiographical Memory Interview (Kopelman, Wilson and Baddeley, 1990), there was evidence that some patients had quite extensive retrograde memory deficits extending back well beyond the apparent onset of the TEA attacks. Zeman et al. discuss several possible explanations for the retrograde memory deficit. They reject a hypothesis that an encoding or initial registration impairment is present since patients perform normally (inter-ictally) on tests of anterograde memory. Instead they favour an explanation based on the idea that the seizures disrupt a memory consolidation process that occurs over a very extended time period, and point particularly to the possibility that sleep-related neurophysiological abnormalities may be a key factor. They note that it is "difficult to exclude the possibility that patients may have had subclinical seizures for some time before the onset of their TEA attacks" (p. 442). If this were the case, the interpretation of the impairment in remote memory would still be in terms of a consolidation failure, but it would become within an anterograde rather than retrograde time frame. Zeman et al. also note the possibility that undetected pathology in the temporal lobes (known to be associated with retrograde amnesia) might have been present and account for the remote memory deficits. It is possible therefore that the presence of the extensive remote memory deficit in most cases of accelerated forgetting and some cases of TEA is attributable to structural changes associated with left, or bilateral anterior temporal lobe lesions, whilst the accelerated forgetting is the consequence of temporal lobe epilepsy. To address this issue further, it would be useful to identify patients who have developed temporal lobe epilepsy at a clearly defined point in time in order to be able to identify what is anterograde and what is retrograde, but in whom there is an absence of major temporal lobe pathology. Such cases would be important in that they may shed more light on the time frame for which long-term consolidation processes are vulnerable.

In summary, several key issues remain to be addressed concerning long-term accelerated forgetting; (1) Is the forgetting of event information related to the occurrence of epileptic seizures? (2) What types of knowledge are affected by such long-term consolidation failure? (3) To what extent is retrograde memory affected in patients who show this pattern of impairment? These issues are explored in relation to Cases SG and TG, presented in Chapter 4 in this thesis.

### 1.3.6 New learning in the context of amnesia

The amnesic syndrome is defined as an inability to remember new facts or events. However, even the most severe amnesic patients appear to be able to demonstrate *some* new learning. Implicit memory is typically preserved in most forms of amnesia. An important question for clinicians and theoreticians alike is that of whether people with amnesia can also acquire new declarative information, even if not at a normal rate. Verfaellie (2000) highlighted the fact that for a period of time amnesia was represented as a selective deficit of episodic memory with sparing of semantic memory. But, as Verfaellie notes, this conclusion was not valid because of a confound between the way in which these two types of memory were evaluated- episodic memory was evaluated using standard tests of anterograde memory, while semantic memory was evaluated by using tests of retrograde knowledge. Hence the contrast was not between the acquisition of new episodic and new semantic knowledge, which would be necessary to be able to characterise amnesia as a selective deficit of episodic memory. Furthermore, when investigators began to address the question of new semantic learning in amnesia it was argued that amnesic patients are equally impaired at learning new semantic information as they are new episodic information. Gabrieli, Cohen and Corkin (1988) examined the status of new semantic learning in patient HM using stimuli such as famous faces and new vocabulary. They found that he performed very poorly, leading to a conclusion that semantic and episodic memory are equally affected. Nevertheless, they found that on non-declarative tests he performed above chance suggesting that *some* learning had occurred. However, patient SS (Verfaellie, Croce and Milburg, 1995) who became amnesic secondary to encephalitis, performed very poorly on tests of new vocabulary acquisition, including tests designed to minimise retrieval demands. In recent years there has been a great deal of interest in patients who developed amnesia at a very young age and hence have not had the opportunity to develop a great deal of semantic knowledge prior to the onset of their amnesia. Vargha-Khadem, Gadian, Watkins, Connelly, Van Paesschen and Mishkin (1997) described three patients who had developed amnesia in early childhood as a result of anoxic episodes that resulted in damage limited to their hippocampi. All three patients showed marked impairment on standard tests of anterograde memory, but all had attended mainstream schools and had been able to acquire a considerable amount of semantic information including vocabulary and other factual knowledge. The ability of these patients to acquire semantic information is attributed by Vargha-Khadem and colleagues to the fact that their lesions are restricted to the hippocampus, with the suggestion that the intact perirhinal, entorhinal and parahippocampal regions are able to support semantic learning. Two adult-onset amnesic patients have been described who also appear to show preserved semantic learning. Patient RS (Kitchener, Hodges and McCarthy, (1998) suffered a sub-arachnoid haemorrhage resulting in "multifocal limbic damage involving the left hippocampal complex (possibly sparing part of the perirhinal cortex) posterior thalamus and left medial frontal lobe and posterior right hippocampus" (p. 1315). Despite severe anterograde amnesia and an inability to recall personally experienced events from any period in his life, RS showed evidence that he had acquired information about public figures, events and new vocabulary. Van der Linden et al. (1996) showed that patient AC, who became amnesic following a subdural haematoma that resulted in occipital and presumed medial temporal lobe damage, was able to acquire personal and public semantic knowledge. Similarly, patient PS (Verfaellie, Koseff and Alexander, 2000) who became amnesic following an hypoxic episode that resulted in damage limited to the hippocampus, also showed an ability to identify famous faces and define new vocabulary to a level that was not normal, but nevertheless showed evidence of learning above chance levels.

The cases described above provide conflicting evidence with regard to the question of whether amnesic patients can acquire new declarative knowledge. One possible explanation for the discrepancy in the findings relates to the variations in the extent of the lesions involved, and in particular the extent to which regions outside of the hippocampus proper are involved. Verfaellie (2000) notes that " it is difficult to directly compare the ability for new semantic learning across patients because of potential differences in the severity of their amnesia". Studies are therefore needed that contrast patients with similar levels of anterograde amnesia (defined by matched performance on standard anterograde memory tests) with clearly defined lesions in terms of their learning of new information. Chapter 4 will present such a study.

### 1.4 The neuroanatomy of memory

The process of encoding, storing over time, and later retrieving information is dependent upon a number of different structures in the brain. Since Scoville and Milner's (1957) description of HM's severe amnesia following medial temporal lobe ablation, much of the focus of the search for the anatomical architecture of memory has focused on the limbic-diencephalic system. Current models of memory discussed later emphasise the importance of integrated systems within the brain working together. These models are not mass action models in the tradition of Lashley (Lashley, 1929), but rather suggest a modular contribution of specific brain regions. As noted, medial temporal lobe structures including the hippocampal formation have long been thought to be important for the normal acquisition of new information, including personally experienced episodes or events. The hippocampal formation includes the dentate gyrus, the cornu ammonis (including regions CA1 and CA3 in particular) and the subiculum. The subiculum projects to the anterior thalamus directly via the fornix and also indirectly via the mammillary bodies and mammillothalamic tract (Aggleton and Brown 1999, p.426). The anterior thalamus projects back to the subiculum via the fornix and cingulate cortex. Structures such as the amygdala (Markowitsch, 1994) and the septum (von Cramon, Markowitsch and Schuri, 1993) are probably important for the emotional salience of remembered events. The hippocampal formation is thought to be modulated by cholinergic input from structures that form the basal forebrain, such as the medial septum and the diagonal band of Broca. It has been argued that memory impairment may follow from lesions in the basal forebrain region, presumably because of the 'knock-on' effect of lesions in this area on medial temporal lobe structures. Adjacent temporal lobe regions, including entorhinal cortex, perirhinal cortex, parahippocampal cortex, and other areas of association cortex are generally viewed as necessary for the long-term storage of memories. Models of the relationship between the medial temporal lobe, diencephalic structures and lateral association cortex are discussed further in the following sections.

The frontal lobes are also viewed as important for memory, with evidence of modularity of function within the frontal lobes. At a general level, and in line with conceptions of the frontal lobes as being the primary site for executive functions, they have been attributed a role in the more strategic aspects of remembering. With regard to hemispheric specialisation, it is argued that the left frontal lobe makes an important contribution to the encoding of information, whilst the right frontal lobe makes a contribution to the retrieval of information, particularly in free recall situations where some form of strategic search for information is required (Tulving, Kapur, Craik, Moscovitch and Houle, 1994; Shallice, Fletcher, Frith, Grasby, Frackowiak and Dolan, 1994).

Aggleton and Brown (1999) have recently argued that the hippocampus, along with the anterior thalamic nuclei and the connections between them (fornix, mammillary bodies and cingulum), form a coherent functional system that is necessary for the efficient encoding and normal recall of new episodic information. This in fact is largely a restatement of the importance of what has previously been referred to as the Papez circuit (Markowitsch, 1999). This system is not considered vital for efficient recognition of stimuli, since recognition can be achieved through at least two independent processes (Mandler, 1980). One is through recollection of the stimulus ("remembering") and the other is through detecting stimulus familiarity ("knowing"). Aggleton and Brown (1999) argue that the former process is dependent on the hippocampal-anterior thalamic circuit, while the latter process is dependent on an entorhinal-medial dorsal thalamic circuit. However, this view has been challenged by Zola and Squire (1999) who argue that the evidence that hippocampal pathology impairs recognition memory is stronger than evidence that recognition memory is preserved with focal hippocampal lesions.

As far as retention of new information is concerned, according to Aggleton and Brown (1999) damage to any part of the hippocampal-anterior thalamic circuit will produce a similar pattern of impairment, involving a deficit in the ability to acquire new episodic memories. Thus, selective damage to anterior thalamic nuclei should produce a severe anterograde amnesia. This does indeed appear to be the case. Cases such as those described by Winocur, Oxbury, Roberts, Agnetti and Davis (1984), Stuss, Guberman, Nelson and Larochelle (1988), Graff-Radford, Tanel, van Hoesen and Brandt (1990), Hodges and McCarthy (1993), Parkin, Rees, Hunkin and Rose (1994) and Kapur et al. (1996) all present with discrete diencephalic (primarily thalamic) lesions and significant anterograde amnesia. Cases with selective mammillary body lesions are rare, though the two patients reported by Kapur, Crewes, Wise, Abbott, Carter, Millar and Lang (1998) presented with relatively mild anterograde memory impairment. This is consistent with the fact that although one of the hippocampal-thalamic routes is via the mammillary bodies, there is a separate direct link also available.

The impact of diencephalic lesions on retrograde memory has varied considerably between reported cases. Korsakoff's syndrome, which is associated with diencephalic lesions, typically leads to an extensive retrograde impairment, though interpretation of this finding has proved difficult because there are often other lesions present. In addition, distinguishing anterograde from retrograde memories in this condition is not always easy (Kopelman 1989). In several of the cases of selective thalamic damage mentioned above, retrograde memory was reported as being largely unimpaired, though closer examination of the data reveals a less clear picture. In Graff-Radford et al.'s (1990) study of four patients with bilateral medial thalamic infarctions, most performed normally on tests of famous face and event recognition, though one patient was described as having difficulty recollecting autobiographical information unless prompted. It seemed that she had problems using temporal context to retrieve appropriate autobiographical information. Kapur et al.'s (1996) patient suffered a muli-lobular lesion affecting hypothalamus, mammillary bodies and medial thalamus. He performed well on a test of famous event recognition and on the Dead-or-Alive test, in which he had to identify whether famous personalities were dead or alive and if they were dead, how they had died. On the Autobiographical Memory Interview (Kopelman et al., 1990) their patient showed evidence of difficulty with recollecting personal incidents, though it was reported that an interview with his wife failed to yield evidence that he was showing any retrograde autobiographical memory difficulties. Parkin et al.'s (1994) patient, who had a lesion affecting left dorso-medial, ventro-lateral and centro-median thalamic nuclei, showed no impairment on the Dead-or-Alive test, but was not tested on any autobiographical event memory tasks. Winocur et al.'s (1990) patient had a medial thalamic lesion and similarly showed no impairment on tests of famous person recognition, but autobiographical event memory was not tested. Stuss et al.'s (1988) patient had a dorso-medial lesion and was impaired on famous events and autobiographical enquiry. The patient described by Hodges and McCarthy (1993), PS, presented with severe anterograde and retrograde amnesia following symmetrical infarction of the dorsomedial nuclei, internal medullary lamina and mammillo-thalamic tract bilaterally. His retrograde amnesia was characterised by relative sparing of knowledge of famous people and public events, in the context of a severe impairment of personal event memory. The most striking finding with his personal memory was his persistent belief that he was on leave from the Navy as an account of why he was at home. He had been in the Navy for just five years some fifty years previously. Hodges and McCarthy interpreted PS's deficit in terms of an "inability to use the normal range of indexing procedures that are required for the retrieval of autobiographical memory" (p. 938). They attribute this inability to a failure of the link between anterior and posterior processing systems, normally operating via thalamo-frontal neural tracts.

In the following section, several contemporary models of memory are presented. Each one represents an attempt to described the cognitive architecture of memory as well as identifying the roles of the brain structures considered to be critical for human memory.

### 1.5 Contemporary models of memory and amnesia

There have been many attempts to account for the deficits which, following brain injury, cause amnesia. Mayes and Downes (1997) describe many of these approaches, though they conclude that "....very few detailed claims about the pattern of cognitive and memory deficit shown by patients or the lesions that cause their condition are universally accepted".

Some of the more recent global models of memory and amnesia have attempted to incorporate evidence from neuropsychological, neuroanatomical and computational modelling studies. In particular, these models have focused on characterising the relationship between a medial temporal lobe hippocampal system and neocortical regions. Marr (1971) is credited with emphasising separate roles for the hippocampus and neocortex in the form of his 'pattern associator' model which has formed the basis for subsequent models of hippocampus physiology and function. Table 1 provides a summary of the key features of the contemporary models of memory and amnesia described in more detail below. The table includes reference to the time-scale proposed by each model for the involvement of the hippocampal complex in the retrieval of autobiographical event memories.

What has come to be referred to as the Standard Consolidation Model was summarised by Squire and Alvarez (1995) and Alvarez and Squire (1995). In this model, sensory information registered in the neocortex is bound into a memory trace by the hippocampus and related medial temporal lobe/diencephalic structures. This process is thought to happen quickly (a matter of seconds or minutes). Initially, recall of the memory trace requires activation of the hippocampal-neocortical network. However, over time and through a process of rehearsal and re-experiencing the memory trace becomes established at the neocortical level so that eventually the trace is not dependent upon the hippocampus at all for retrieval. The time course of this process remains open to speculation, though it has been argued that in monkeys it takes about 4 weeks (Zola-Morgan and Squire, 1990). The process of establishing memory in the neocortex is referred to as 'consolidation'.

*Table 1 Key features of contemporary models of memory and amnesia. The table includes reference to the time-scale proposed by each model for the involvement of the hippocampal complex in the retrieval of autobiographical event memories.*

| **Model/Theory** | **Key Features** | **Involvement of hippocampal complex in autobiographical event recall** |
|---|---|---|
| Squire and Alvarez (1995) *Standard Consolidation Model* | Sensory information in the neocortex bound into a memory trace by the hippocampus and related structures. Over time, trace becomes established at the neocortical level so that eventually the trace is not dependent upon the hippocampus for retrieval. | Temporary |
| McLelland, McNaughton and O'Reilly (1995) | Hippocampus stores compressed representation of episode. Neocortically-based system gradually instantiates memory traces through reinstatement of neocortical patterns of neuronal activation by hippocampus. | Temporary |
| Murre (1996, 1997) *TraceLink Model* | Trace system (neocortex) is permanent store of event information. Link system (hippocampus) binds neocortical-based event elements, under influence of Modulatory system (basal forebrain). Over time, Link system not required for retrieval of event trace. | Temporary |
| Damasio (1989) *Convergence Zone Theory* | Distinctions drawn between: (1) neurone ensembles in primary and first order sensory association cortices that represent feature fragments; (2) 'local convergence zones' located downstream in single modality cortices that represent combinations of feature fragments or coherent entities; (3) 'non-local convergence zones' located in the hippocampal complex that represent co-occurrence of activity in the local convergence zones or episodes of experience. | Temporary |
| Sutherland and Rudy (1989)/ Gluck and Myers (1993) *Configural Association Theory* | Hippocampal system constructs a unique representation of the joint occurrence of the independent elements of a compound event. | Permanent |
| Rudy and Sutherland (1995) *Modified Configural Association Theory* | Critical neural system for configural associations is in cortical circuitry outside the hippocampus. Output from the hippocampal formation contributes to configural processing by selectively enhancing cortical units representing stimulus conjunctions, thereby making them more salient. | Hippocampus seen as modulatory system, rather than part of storage system. |
| Nadel and Moscovitch (1997) *Multiple Trace Theory* | Hippocampal complex acts as a pointer or index to the neocortical elements needed to provide the detailed content of the experience. Over time, autobiographical memories retrieved are re-coded so that multiple, related memory traces are formed in wider areas of the hippocampal complex. | Permanent |
| Mesulam (1998) *Modified Convergence Zone Theory* | A version of Convergence Zone Theory. Hierarchically organised regions code for feature fragments, coherent entities and events using five major sub-types of functional brain regions: primary sensory-motor; unimodal association; heteromodal association; paralimbic; and limbic. | Permanent |

McLelland, McNaughton and O'Reilly (1995) and Murre (1996, 1997) present models of memory and amnesia that are essentially versions of the Standard Consolidation Model. McLelland et al. (1995) provide an account of the organisation of learning that is also based around separate, but related, roles played by the hippocampus and the neocortex in the acquisition of semantic knowledge (information about categories and concepts), encyclopaedic information (specific factual information) and episodic information (information contained within a specific event in which the subject was an observer or participant). They argue that within their account, the same consolidation process applies to all three domains of knowledge/experience. Their account emphasises the role of a rapid learning mechanism based in the hippocampus and a neocortically based system that gradually changes through reinstatement of neocortical patterns of neuronal activation. The neocortical system is "optimised for the discovery of the shared structure of events and experiences" (p36). The hippocampal structures function to support this process of gradual discovery, thus avoiding catastrophic interference. McClelland et al. argue that the hippocampus stores a compressed representation of an episode, the compression occurring through neocortical - hippocampal complex pathways, with decompression occurring in reverse. This proposal of compressed representation storage, as opposed to the concept of the hippocampus as a means to bind anatomically diverse temporally contiguous neocortical representations, is similar to that of Teyler and Discenna (1986). Based on the common finding of a temporal gradient in retrograde memory deficits in organic amnesia, McClelland et al. (1995) concluded that the role of the hippocampus is time limited.

Murre (1996, 1997) presented the 'TraceLink' model of amnesia, which is also a variation on the Standard Consolidation Model. This consists of a trace system, which roughly equates to the neocortex, a link system, which includes the hippocampus and related medial temporal lobe/limbic structures and a modulatory system, which also involves the hippocampus, along with basal forebrain regions. The function of the neocortically based trace system is seen as the bulk storage of all memories. The trace system constitutes the basic features of all experiences and knowledge. The function of the link system is to form temporary links between the elements of episodic experiences. The functioning of the link system is seen as being influenced by a modulatory System, so inducing or preventing plasticity. This system, based in the basal forebrain, is sensitive to the 'usefulness' of potential episodic memories (responding particularly to novelty or to situations of high biological relevance) and thus facilitating the storage of key events. Over time, through conscious rehearsal, reinstatement of patterns during sleep (Wilson and McNaughton, 1994) or as a result of re-experiencing, links are developed between these elements of an episode at the level of the neocortex, such that in time the medial temporal lobe link system is no longer required to support recall of the particular episode or piece of information. Stage 1 involves the initial activation of neocortical traces, reflecting basic perceptual activity. In Stage 2, the elements in the trace system are linked, under the influence of the modulatory system. Stage 3 involves the gradual development of connections at the level of the trace system, through reinstatement of patterns of activation dependent upon the link system. Finally, Stage 4 reflects the establishment of a more permanent connective network representing the initial pattern of activation, which can now be reinstated (i.e. recalled) without recourse to the link system. As other similar models emphasise (see Gluck and Myers, 1997), the formation of connections into the Link system is seen as fast in contrast to the formation of connections within the trace system itself, which is seen a slow. The link system is seen as limited in capacity and subject to interference from subsequent learning. Interference refers to the likelihood that patterns overlap sufficiently such that retrieval of one will activate retrieval of part or all of additional patterns. Gluck and Myers (1997) note that one way to increase capacity and avoid catastrophic interference is to explicitly decrease the overlap between patterns. They note that it has been suggested that this is one effect of sparse connections between some regions within the hippocampus (dentate gyrus and CA3). However, they suggest that even with pattern separation, a pattern stored in the hippocampus will only remain intact for a limited period before it is overwritten by storage of newer memories, implying that memories stored in the hippocampus must be transferred elsewhere to survive for long periods of time.

Nadel and Moscovitch (1997; see also Moscovitch and Nadel, 1998, 1999; Moscovitch, 1992) presented a model that also involves the co-operation of medial temporal lobe and wider neocortical systems to represent autobiographical memories. However, their model differs from Standard Consolidation models including Murre's TraceLink model in relation to the time scale of the involvement of the hippocampal complex. Their Multiple Memory Trace model proposes that the hippocampal complex, "acts as a pointer or index to the neocortical elements needed to provide the detailed content of the experience" (Moscovitch and Nadel, 1999, p87). Over time as autobiographical memories are retrieved, they are re-coded so that multiple, related memory traces are formed and dispersed over wider areas of the hippocampal complex. They also argue that these medial temporal lobe units are needed to recover the memory as long as it lasts.

The models of Damasio (1989) and Mesulam (1998) also emphasise the relationship between the hippocampus and neocortical regions, but include greater detail relating to regional specialisation within the neorcortex. Damasio (1989) proposes a model of recall and recognition in which distinctions are drawn between: (1) neurone ensembles (located in multiple and separate regions of primary and first order sensory association cortices), which represent a code for the feature fragments which constitute the basis of perception; (2) 'local convergence zones' (neurone ensembles which code combinations of feature fragments and thus code for coherent entities) located "downstream" from the primary sensory areas in single modality cortices; (3) 'non-local convergence zones' which code the co-occurrence of activity in the local convergence zones (and thus code for episodes of experience), located throughout higher-order association cortices. Damasio argues that recall is achieved by "time locked retroactivation of fragmentary records in multiple cortical regions as a result of feedback activity from convergence zones" (p27). Furthermore, Damasio argues that there is "no localisable single store for the meaning of a given entity within a cortical region. Rather, meaning is reached by widespread multi-region activation of fragmentary records pertinent to a stimulus, wherever such records may be stored within a large array of sensory and motor structures, according to a combinatorial arrangement specific to the entity" (p28). In the same way, Damasio also argues that no single area of the brain is responsible for coding the combinations of co-occurring entities that constitute an event, since "...no single area in the human brain receives projections from all the regions involved in the processing of an event" (p38). However, in what appears to be a somewhat different argument within the same paper, he also emphasises the role of the area encompassing the hippocampal complex which "...is the only brain region in which signals triggered by neural activity in all sensory cortices and in centres for autonomic control can actually co-occur over the same neurone ensembles. As such, this is the appropriate substrate for a detector of temporal coincidences.." (p53). Thus, Damasio's theoretical framework requires multiple brain regions to be involved in recollection. The remembering of events is dependent upon activation of what might be described as the highest level of convergence zone, based in the hippocampus, which codes particularly for the temporal contiguity of event elements. Damasio argues that, on the basis of capacity limitations in the hippocampus and the evidence for very limited retrograde amnesia following focal hippocampal lesions (e.g. Zola-Morgan et al., 1986), the hippocampal convergence zone is only a temporary one and that "...the region acts via its powerful feedback system into neocortical and subcortical neural stations, to assist in the creations or modification of convergence zones located in the cortices that originally projected into the entorhinal cortex" (p54).

Mesulam's (1998, 2000) framework of hierarchically organised functional zones resembles Damasio's concept of convergence zones, but Mesulam's position with regard to the involvement of the hippocampal complex is more similar to the Multiple Trace model. Mesulam (1998) provides a description of the behavioural neuroanatomy of the cerebral cortex. He argues that there are five major sub-types of functional brain regions: primary sensory-motor; unimodal association; heteromodal association; paralimbic; and limbic. The primary sensory motor cortices undertake the first-line processing of sensory and motor activity and represent the most highly differentiated and specialised subdivisions of the cortex. Unimodal association areas receive projections from primary sensory areas and other unimodal associations areas in the same modality, and respond to stimulation in a particular modality.  Lesions in these areas lead to behavioural deficits confined to tasks under the control of a particular sensory modality. Unimodal visual association cortex includes peri-striate areas (Brodmann's areas 18-19) and fusiform, inferior temporal and middle temporal areas. The next stage of processing occurs in heteromodal areas which receive convergent inputs from unimodal areas in more than one modality. Lesions of heteromodal association cortex yield multimodal behavioural deficits. Heteromodal areas are thought to include the prefrontal cortex, posterior parietal cortex, parts of the lateral temporal cortex and portions of the parahippocampal gyrus. Paralimbic areas include, at least in the primate brain, the caudal orbitofrontal cortex, the insula, the temporal pole, the parahippocampal gyrus and the retrosplenial-cingulate-parolfactory complex. The last stage in the stream of sensory processing occurs within five core limbic regions; the hippocampal complex, the amygdaloid complex; the perpiriform olfactory cortex; the septal area and the substantia innominata.

Mesulam notes that, "one of the most important principles in the organisation of the primate cerebral cortex is the absence of interconnections linking unimodal areas that serve different sensory modalities" (1998, p1023). Thus, 'transmodal' areas are required for the process of binding distributed modality-specific fragments into coherent experiences, memories and thoughts. These include heteromodal, paralimbic and limbic areas. Mesulam argues that hippocampal-entorhinal cortex fulfils this role in relation to explicit autobiographical memory. The hippocampal-entorhinal complex also appears to promote the stable encoding of new associations in other parts of the neocortex, including unimodal sensory areas. This means that a limbic lesion will not only impair the retention of multimodal experiences, but also the acquisition of within-modality associations. However, given the connectivity within unimodal areas it may be that (and it seems to be the case) that new links can be formed over time (see Kitchener et al., 1998), but perhaps more slowly and through repeated exposure. Mesulam argues that the participation of the hippocampal-entorhinal complex is most critical for, "the most recently acquired memories, for those that have limited resonance with other mental contents, for those that have been registered casually rather than intentionally, for those with relatively weak emotional valence, for those that require extensive cross-modal integration, for those that have been recalled rarely and have therefore failed to establish associative elaboration and for those that require the reactivation of idiosyncratic contextual anchors related to temporal and spatial circumstances" (p1027). Thus, he further argues that the hippocampal-entorhinal complex may well participate in the retrieval of all autobiographical and episodic memories, recent and remote (since such memories would be classified as requiring extensive cross-modal integration) and even in the retrieval of semantic knowledge related to arbitrary facts about the world, but is not required for the recall of facts and events which have established a rich matrix of associations.

The models of memory described above all have as their theme a storage deficit as the key functional impairment underlying amnesia - amnesic patients fail to store the elements of an episode for later recall. Mayes (1992) has proposed a related hypothesis. He argues that amnesics have "a primary and severe deficit in aware memory for contextual information, and this causes a secondary and less severe deficit in aware memory for the facts and episodes that typically fall at the focus of attention during learning" (Mayes, 1992, p24). The role of the hippocampus in coding contextual information and configurations of multiple stimuli also forms the central concept in Sutherland and Rudy's (1989) configural association theory and Gluck and Myers' (1993) cortico-hippocampal model. Both of these models focus on these processes in the context of procedural, habit-based, associative conditioning tasks. Most of the work relating to tests of these theories has been carried out on non-human subjects. However, Myers, Warren, Brawn, McGlinchey-Berroth, Monti and Gluck (2000) have shown that amnesic patients are unimpaired in learning simple associative relationships, but are impaired when the conditioning paradigm involves more complex contextual, spatial, temporal or configural relationships. Rudy and Sutherland (1995) suggested a modification to their original configural association theory. In the original formulation of their theory, they argued that the hippocampal system constructs a unique representation of the joint occurrence of the independent elements of a compound. Whilst not explicitly articulated, the assumption was that this system was permanently required for retrieval of the compound representation. As such, the model was rather similar to that of Nadel and Moscovitch (1998). In the modified form, Rudy and Sutherland (1995) argued that the critical neural system for configural associations is in cortical circuitry outside the hippocampus and that output from the hippocampal formation contributes to configural processing by selectively enhancing, thereby making more salient, cortical units representing stimulus conjunctions. This enhancement has two effects: (1) it decreases the similarity between the configural units representing co-occurrence of cues and units representing the cues themselves and (2) it increases the rate at which the configural units can acquire associative strength. The reason for suggesting this modification was the finding that hippocampal-lesioned animals can acquire *some* non-linear configural associations i.e. associations that require more than simple linear associations for learning to occur, such as feature-neutral discriminations. This formulation of the theory would seem to be more similar to the model of Murre (1997), with the function of the hippocampal formation in Rudy and Sutherland's model being similar to the combined functions of the link system and the modulation system in Murre's model. What is not clear in the Rudy and Sutherland model is the time course for the involvement of their configural association system. It is harder therefore to identify what would be the impact on retrograde memory from a lesion of their postulated association system.

Are there then any differences between the various models? McClelland et al. (1995) note that whilst their model may at first glance seem different from several others, "many apparent differences may be matters of emphasis and perspective". This is indeed true. One issue is the question of how to conceptualise just what the hippocampus actually stores. McClelland et al.'s model refers to the hippocampus storing a compressed representation of an episode or event (or rather the neocortical pattern triggered by the event). This is contrasted with other models that emphasise that the hippocampus "does not store the memory itself, but rather stores only a list of addresses or pointers to the diverse locations in the neocortex where the memory is itself stored" (McClelland et al. 1995, p39). However, as McClelland et al. note, there is very little real difference between these two ideas. In fact, a compressed representation and an address are essentially the same thing, and certainly have the same functional characteristics.

A related issue is that McClelland et al. (1995) argue that other models predict a degree of fast learning in the neocortex, to the extent that patterns of activity in local circuits are stored via plastic changes that occur within these local circuits during the initial experiences and that the hippocampus only binds together these local patterns so that the patterns can be reactivated by patterns arising in other parts. They specifically refer to Teyler and Discenna (1986) in this discussion, but their point applies to other models too. In contrast, the McClelland model is presented as involving only slow learning at the neocortical level. McClelland et al. suggest that it is possible to reconcile their position with that of others by revising the placement of the anatomical boundary between the fast and slow learning systems. They argue that the superficial layers of the neocortex are part of the fast learning system and that the slow learning system is located in deeper cortex.

It could be argued that perhaps the only real area of difference between the models is the question of the time-frame for the involvement of the hippocampal complex and related medial temporal lobe structures in the storage of autobiographical event memories. The Standard Consolidation models of Murre (1986), Alvarez and Squire

(1995), McClelland et al. (1995) and Damasio (1989) all argue that the hippocampal formation/medial temporal lobe structures are only involved temporarily in storage of long term memories, though what constitutes 'temporary' is not yet clear. By contrast Moscovitch and Nadel's (1997) Multiple Trace Theory and Mesulam's (1998) version of Convergence Zone Theory involve the permanent involvement of the hippocampus in storage of episodic memories. Several of the studies in this thesis will address the question of whether data from selected cases supports the position that the hippocampal/medial temporal lobe structures have a temporary or permanent role in the recollection of autobiographical event memories. Recent debate (e.g. Graham 1999, Moscovitch and Nadel 1999) has contrasted the Standard Consolidation Model with Multiple Trace Theory to address this issue and therefore these two theoretical positions will be form the main focus of discussion in relation to the data presented in the thesis. However, as discussed later, the contrast could equally well be made between the differing versions of Convergence Zone Theory proposed by Damasio (1989) and Mesulam (1998).

## 1.6 Aims of this thesis

The models of memory described in the previous section have been built on the basis of findings from studies of anterograde and retrograde amnesia. However, this literature review has highlighted how some of the conclusions drawn from such studies may have been drawn prematurely. The aim of this thesis is therefore to clarify the nature of various distinctive forms of very long-term memory impairment and to shed light on the mechanisms that give rise to these syndromes. Predictions from contemporary models of memory and amnesia will be tested using data derived from patients selected for study on the basis of lesion location or pattern of anterograde and retrograde memory impairment.

Chapter 2 presents three sets of studies examining the pattern and extent of retrograde memory impairment following damage to temporal lobe and diencephalic structures. Section 2.1 examines the status of retrograde memory functioning in five patients with lesions limited to hippocampal or closely associated medial temporal lobe structures. Specific predictions from Multiple Trace Theory (Nadel and Moscovitch, 1997) and the Standard Consolidation Model of memory (Squire and Alvarez, 1995;

Murre, 1996) are tested. The central question addressed concerns whether or not the hippocampal complex is involved in the retrieval of memories of autobiographical events across the lifetime. Section 2.2 examines the nature of retrograde memory functioning in a patient during and after Transient Global Amnesia. This condition provides a unique opportunity to assess retrograde memory in individuals who can, upon return of normal functioning, act as their own controls with regard to pre-morbidly acquired knowledge. Predictions from Multiple Trace Theory and the Standard Consolidation Model of memory in relation to the nature of impairment of retrograde memory are tested. Section 2.3 examines memory for pre-morbid autobiographical events in six patients with lesions to temporal or diencephalic regions using both recall and forced-choice recognition formats.

Chapter 3 focuses on selective impairments of retrograde memory impairment and addresses two issues; (1) under what circumstances does extensive retrograde amnesia occur in the absence of significant anterograde amnesia and (2) is it valid to suggest that episodic retrograde memory dissociates from semantic retrograde memory amnesia? Section 3.1 describes the case of patient JM, who presented following recovery from cerebral vasculitis with a severe impairment in the ability to recollect pre-morbid autobiographical events in the context of normal anterograde memory functioning. Section 3.2 will describe investigations with patient VH, who presented with a progressive loss of knowledge of people. This began with prosopagnosia and developed into a more extensive loss of semantic information for people. The extent to which contemporary models of memory can account for the patterns of impairment demonstrated by these two cases is examined.

In contrast to Chapters 2 and 3, where the focus was on recall and recognition of *retrograde* episodic and semantic knowledge, in Chapter 4, recall and recognition of *anterograde* episodic and semantic knowledge was investigated. The chapter is concerned with two general questions - (1) what are the mechanisms by which new long term memories are laid down; (2) can disruption to long-term consolidation of information shed light on the normal process of acquiring new memories? These questions are addressed with several single case studies of patients with temporal lobe pathology. Section 4.1 presents studies of the acquisition of autobiographical and public event knowledge in two patients who varied in the extent of their medial temporal lobe pathology, but who were matched for performance on anterograde memory tests. Section 4.2 presents studies with two patients who have a rare form of anterograde memory deficit involving a failure to retain information over extended time delays in the context of normal performance on standard anterograde memory tasks.

Chapter 5 discusses the main findings and theoretical implications from the studies presented in the thesis. Clinical and methodological issues arising from the work are also highlighted.

# Chapter 2 The status of retrograde memory in selected cases of temporal lobe and diencephalic amnesia

**General Introduction**

This chapter presents three sets of studies with the general aim of achieving a better understanding of the nature of retrograde memory impairment following damage to temporal lobe and diencephalic structures. This is critical to developing and testing biologically plausible models of long-term memory consolidation. Section 2.1 examines the status of retrograde memory functioning in five patients with lesions limited to hippocampal or closely associated medial temporal lobe structures. Specific predictions from Multiple Trace Theory (Nadel and Moscovitch, 1997) and the Standard Consolidation Model (Squire and Alvarez, 1995; Murre, 1996) of memory are tested. Section 2.2 examines the nature of retrograde memory functioning in a patient during and after Transient Global Amnesia. Section 2.3 examines the role of memory retrieval processes for pre-morbid autobiographical events in six patients with lesions to temporal or diencephalic regions by assessing retention using both recall and recognition formats.

## 2.1 The status of retrograde memory in medial temporal lobe amnesia

### 2.1.1 Introduction

The critical difference between the two most influential contemporary models of long-term memory consolidation is whether damage to the medial temporal lobe, and in particular the hippocampus, produces lifelong impairment in the ability to recollect autobiographical episodes. Multiple Trace Theory (Nadel and Moscovitch, 1997) predicts that substantial damage should produce a lifelong impairment. The Standard Consolidation Model (Squire and Alvarez, 1995; Murre, 1996) predicts that a temporal gradient in autobiographical episode memory will follow from medial temporal lobe pathology. However, it has been difficult to draw conclusions regarding the form and extent of the retrograde amnesia that follows from medial temporal lobe lesions for several reasons. Firstly, case studies of patients with selective medial temporal lobe damage have revealed wide variation in retrograde amnesia ranging from no apparent retrograde amnesia (e.g. Zola-Morgan et al.., 1986, Reed and Squire, 1998) to a retrograde amnesia that covers an entire lifetime (e.g. Hirano and Noguchi, 1998; Cipolotti et al.., 2001). Secondly, the nature of tests used to assess retrograde memory has varied considerably between studies and many of these tools are limited in terms of the nature of the material used and the functions assessed. Fujii et al.. (2000) have argued that there is evidence that even when patients score quite well on several traditional tests of retrograde memory, if the level of detail is examined more carefully, patients with damage to hippocampal regions are found to be impaired. They note that, "amnesic patients retain the gist and major aspects of autobiographical episodes, but not a richness of detail that characterises these memories in normal people" (Fujii et al. 2000, p. 236).

One test that has frequently been used to examine autobiographical knowledge is the Crovitz test (Crovitz and Shiffman, 1974). This involves presenting the participant with a cue word and asking for the recollection of some personally experienced event associated with that word. The subject's recollection is then rated in terms of the richness, vividness or level of detail of the description. The standard format of the Crovitz task is such that the personal events sampled may be from any period in the patient's life. One of the limitations of this format is that the subject is free to choose all recollections from just one time period. It has been argued that this may happen as a result of the tendency for one recollection to cue another from the same time period (Rabbitt and Winthorpe, 1988). In the study of retrograde amnesia this can be a problem - an individual's pattern of test results may suggest the presence of a temporal gradient in a retrograde memory deficit, but this may not be because the individual cannot recall events from the more recent past, but because one or more recollections from a particular time period has triggered events from the same time period. Because of the limitation of the original Crovitz test, Kopelman, et al. (1990) developed a structured interview approach, the Autobiographical Memory Interview (AMI), which includes questions about personal (semantic) information and events from different periods of the life of the subject (childhood, early adult and recent). This tool is nevertheless still limited in that, depending on the age and experience of the subject, large sections of the subject's life may not be sampled. In one study with five amnesic patients, MacKinnon and Squire (1989) used the Crovitz technique in both a standard and modified form. They found that when the patients were unconstrained in terms of the period from which the memories were drawn, amnesic patients were impaired in relation to controls, even when they were given prompts to try to aid recollection. However, when the time period for recollection was constrained to the first 21 years of the lives of the subjects, the amnesic patients performed as well as controls, though only when provided with prompts. One potential problem with the second of MacKinnon and Squire's studies was that only 10 words were applied to the first 21 years of the person's lifetime. It seems likely that during this period there would be a considerable number of key life events that could be related to the cue words provided. It has been argued that some events, particularly those that are regularly rehearsed, become 'semanticised' (Cermak and O'Connor, 1983; Cermak, 1984). This is generally meant to indicate that the events lose some of the temporal and spatial contextual elements (i.e. some of the key episodic qualities of the memory) and become more like 'stories'. It is possible, therefore, that with a relatively small number of words and a relatively extended and important lifetime period, amnesic patients are able to produce events that are sufficiently detailed to be accorded a full score, but that these are essentially over-rehearsed 'stories'. Nadel, Samsonovich, Ryan and Moscovitch (2000, p. 359) also recently argued that the three point scoring system conventionally used with this test may be insensitive to differences in the richness or level of detail provided by amnesic patients in comparison to controls. In a study of autobiographical memory in semantic dementia, Graham and Hodges (1997) also used a modified form of the Crovitz technique in which subjects were asked to recollect events from four different specific time periods in response to 15 cue words. This technique proved useful in identifying different levels of performance for different time periods for their patient with semantic dementia in comparison to matched controls. The technique also involved a six-point scoring system designed to be sensitive to differences in richness or level of detail in memories.

The key question addressed in this section is - does medial temporal lobe pathology inevitably lead to impairment in the ability to recollect autobiographical events and if so, how far back in time does the deficit extend? This was tested using the Autobiographical

Memory Interview and in more detail using the modified Crovitz technique, with five patients who had lesions primarily confined to the medial temporal lobes. For some of these patients there was good imaging evidence that lesions were confined to the hippocampus.

Patients were also assessed on two tasks of public event memory. In published cases of patients with very limited retrograde amnesia, studies of public event knowledge have often not probed the years immediately preceding the onset of the amnesia in detail (e.g. Zola-Morgan et al., 1996). In the studies described in this chapter, the two tests of public event knowledge incorporated tests of both recognition and free recall of more detailed information. Each test also included items from the months/years immediately preceding the onset of amnesia.

A news events test was used in recognition and free recall formats that allowed a detailed examination of the period of the years immediately preceding the onset of amnesia. News events can range from being a highly emotional autobiographical event, such as the flashbulb-memory experience of hearing of the assassination of President Kennedy or the death of Princess Diana, through to an event that has no personal associations, but one that is repeated in the news several times over a period of days or weeks. Retrieving information about those events may therefore be akin to retrieving other general semantic facts for which the original learning context is not remembered, or it may be more akin to retrieving an autobiographical event. Although not explicitly discussed by proponents of Multiple Trace Theory, one prediction from that model is that the recollection of some news events would be facilitated by the multiple modality linking proposed to be the function of the hippocampus. For some events, this might even involve true autobiographical recollection (e.g. remembering the time, place and circumstances of learning about a news event). If this were the case, then it would follow from the Multiple Trace Theory that medial temporal lobe lesions would lead to poor (though not severely impaired) recollection of event details in comparison to control participants, with no temporal gradient to the performance. The Standard Consolidation Model would predict a temporal gradient in performance, with the gradient depending on the time period for consolidation. However, if consolidation of news events is considered to take place over a period of days or perhaps weeks (through repeated exposure in the media) then it would be predicted that no impairment would be apparent on tests of events that precede the onset of amnesia by at least a few months.

A version of Kapur's Dead-or-Alive Test (Kapur et al., 1989) was also used. This test has a 'semantic' element which probes knowledge relating to the identification of famous people. It also has what might be considered to be a more 'episodic' element which assesses knowledge relating to how and when individuals died. Recollection of the details of an individual's death may be enhanced by autobiographical event information that was encoded at the same time as the news event in question. Following the same arguments as for news events above, Multiple Trace Theory would predict that patients with limbic lesions would show preserved retrograde knowledge of the semantic information about people, but show poorer performance for retrograde knowledge of the details relating to the death of the same individuals. The Standard Model would predict that there would be no impairment in performance, with the caveat that this depends on an assumption that consolidation takes place over a period of days/weeks, at least for this type of information.

Five patients were selected for inclusion in the study. Cases were selected on the basis of having - (i) lesions primarily confined to medial temporal lobe structures; (ii) a severe impairment in the delayed recall of both verbal and visual information on standardised memory tests; (iii) well preserved general intellectual, perceptual, attention, executive and language skills.

### 2.1.2 Participants

The case histories of the five patients who took part in this investigation are presented below.

#### *2.1.2.1 BW*

BW was born in 1959. Pre-morbidly she worked as a shop supervisor in a pharmacy. She was estimated to have been of average intellectual ability premorbidly. She had no prior history of depression or other psychiatric illness, but in 1991, she became depressed and following an argument with her husband, she attempted suicide through carbon monoxide poisoning. She was discovered lying on the floor of her garage near the door. Her car engine was running and the door of the car was open. It is assumed by BW that she had changed her mind about killing herself and had attempted to leave the garage, but collapsed before escaping. She was admitted to hospital and was initially conscious, but lapsed into a coma and was ventilated for several days. On leaving hospital, she was described by her family as having a severe lack of initiative, with her mother describing her as being "like a Zombie". Her severe memory impairment was also apparent. Over time, her ability to initiate activities improved considerably, but there was little improvement in her memory. Early clinical records suggested that her "retrograde memory appears intact". After a period of three months separation from her husband, she went back to live with him. She was unable to return to work in her previous role, but did begin to go into work on a voluntary basis (and continues to do so) twice a week, carrying out a range of basic tasks, which she was able to perform through the extensive use of written notes to herself, and from pre- morbid knowledge of shop procedures. Her main difficulties relate to difficulties remembering what she has done and remembering to do things. She asks the same question of her husband, though her use of memory aids and strategies has helped her to function relatively independently.

MRI scans obtained two years and seven years post-onset were reported as showing small high signal intensities bilaterally in the globus pallidus and atrophy of the hippocampus bilaterally, which was more marked on the right. An independent neurologist rated the scans using a scale constructed by Galton et al. (2001). This scale relates to the temporal lobes as a whole and is an extension of a scale devised for the assessment of medial temporal lobe integrity (see Wahlund, Julin, Johansson and Scheltens, 2000). On this scale BW was rated as having significant atrophy of the right hippocampus (severity rating 3/4; maximum severity = 4/4) and left hippocampus (severity rating 2/4). All other parahippocampal and lateral temporal lobe regions were rated as within normal limits. Two images showing coronal sections through the hippocampus are shown in Figure 2.1.1.

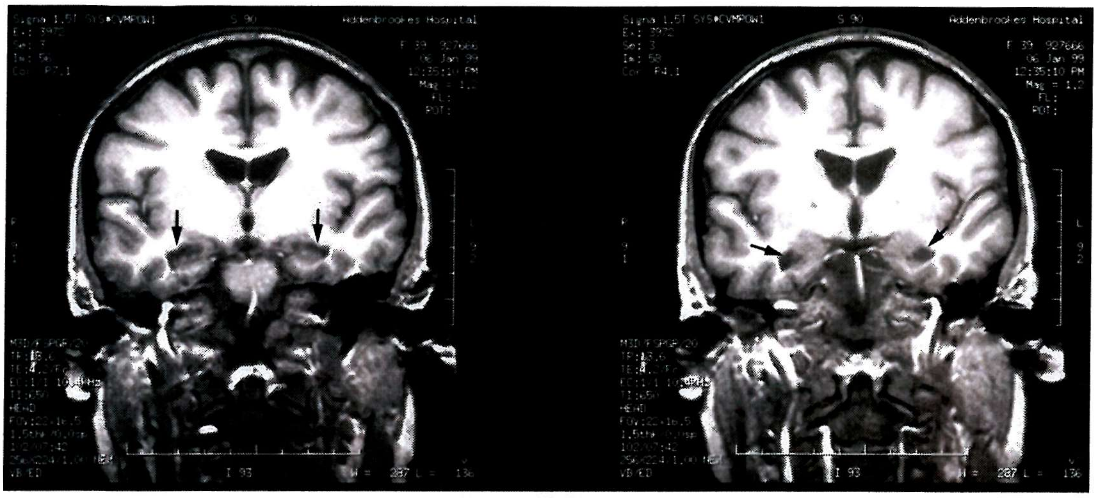


***Figure 2.1.1 Coronal MRI images of BW's brain showing hippocampal atrophy (arrowed).***

### *2.1.2.2 HW*

HW was born in 1958. She was born and brought up in Zimbabwe where she qualified as a physiotherapist, coming to live in the UK in 1982. Pre-morbidly she worked as a physiotherapist in private practice. She had no history of psychiatric illness. She had suffered from epilepsy since she was a child. This was relatively well controlled with medication (Phenytoin and Lamotrigine), though she did report that she had occasional seizures in her sleep and sometimes had a seizure if she experienced relief from any form of stress. Despite the presence of epilepsy, her husband indicated that there was no indication of pre-morbid memory problems, though there was no formal test of her memory prior to her illness. The fact that she was able to cope with the cognitive demands of a private practice setting suggest that she had no significant cognitive impairment before the onset of her amnesia. In 1992, six weeks before the birth of her second child she had a period of status epilepticus lasting several hours. Clinical records indicated that in the acute stages she had a severe anterograde amnesia with a retrograde amnesia which appeared to extend back about 18 months. She tried to return to her physiotherapy practice, seeing only patients she had seen pre-morbidly (so that she would be familiar with their conditions and treatment), but decided after a short while that her memory impairment was too severe to allow her to practice with confidence. She has cared for her children, making use of memory aids such as a kitchen whiteboard to help her manage daily tasks.

An MRI scan was reported as showing bilateral atrophy of the hippocampus. An independent neurologist rated the scans using the Galton et al. (2001) scale. On this scale, HW was rated as having moderate atrophy of the right (severity rating 2/4) and left (severity rating 2/4) hippocampi. All other parahippocampal and temporal lobe regions were rated as normal. Two images showing coronal sections through the hippocampus are shown in Figure 2.1.2.

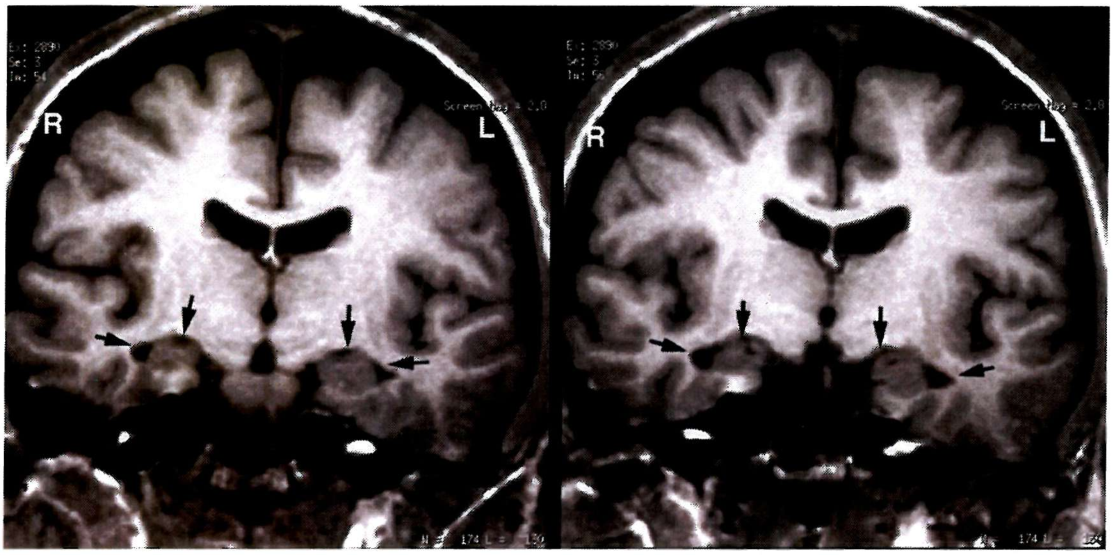



***Figure 2.1.2 Coronal MRI images of HW's brain showing hippocampal atrophy in more posterior (Left) and more anterior (Right) cuts.***

### *2.1.2.3 EA*

EA was born in 1950. She left school at the age of 15, undertook a secretarial course and also subsequently obtained 3 'O' levels. She worked as a typist in a local council office and then gave up secretarial work in order to care for her children. She is married with three children. She had no history of neurological or psychiatric illness. In 1984, following a few days of feeling unwell, she was admitted to hospital with an abrupt illness which led her to being on a ventilator in a deeply unconscious state. She was found to have spastic tetraplegia with bilaterally up-going toes and dilated pupils. Within two days of admission she regained consciousness, but it became apparent that she had severe memory difficulties. The cause of her illness remains uncertain. There was no clear evidence of a stroke or encephalitis. An MRI conducted in 1991 was reported as normal apart from some suggestion of an enlargement of the temporal horns. The most likely cause of her memory problems was considered to be an episode of anoxia with hippocampal damage, but without extensive tissue necrosis. Unfortunately, shortly after the MRI scan in 1991, EA suffered two epileptic seizures, which she attributed to the scanning procedure. She was therefore unwilling to undertake a further scan that was planned to examine the medial temporal lobe regions in more detail. While it was not possible to clarify the extent of any hippocampal atrophy, it was clear from her original scan that there was no major damage to more lateral temporal lobe structures or to other brain regions. EA returned home and through the extensive use of external memory aids, in particular a dairy, has been able to carry out most of the more straightforward routine roles associated with bringing up children and looking after the household. EA's husband commented that her retrograde memory functioning seemed to be intact, apart from a period of some 6 months prior to the illness onset. He did add, however, that she tended to be able to recall items from both the premorbid periods only if prompted.

#### *2.1.2.4 PR*

PR was born in 1971. He left school at the age of 18, but did not take his A-Level exams as a result of being depressed. He suffered with several short-lived, but severe bouts of depression that appeared to be triggered by stress (such as exams or the break up of a relationship). In between these periods, he maintained an active social life, was involved with church groups, and ran children's holiday clubs. He lived at home with his parents. He had a keen interest in pottery, having a workshop and kiln. He sold his work at local craft stalls and charity events. In 1995, PR attempted suicide by carbon monoxide poisoning following the break up of his relationship with a girlfriend. Following acute treatment, he was admitted to a psychiatric hospital for three to four weeks. He has not had any episodes of depression since his suicide attempt. The main problem reported was a severe anterograde memory problem that affected his memory for events, things to do, and routes. He had developed and continues to modify an external memory aid system that enables him to carry out basic day to day tasks relatively independently. He and his parents reported that his retrograde memory appeared to be "generally okay".

An MRI scan was reported as showing bilateral atrophy of the hippocampus, with no evidence of atrophy to other brain structures. All other parahippocampal and temporal lobe regions were reported to be normal. The scan was not available for rating on the Galton et al. (2001) scale or for presentation in this thesis as the film was reported as lost by the relevant scanning department.

***2.1.2.5 JC***

JC has previously been described by Wilson (1999). JC was born in 1965. After leaving school he went to university to study Law. At the age of 20, during a tutorial, JC had an epileptic seizure and collapsed. He was admitted to hospital where he had two further seizures. A CT scan at the time showed a large subarachnoid haemorrhage in the left occipital region. A subsequent angiogram showed a left posterior cerebral artery aneurysm, which was clipped three weeks later. JC initially had a right hemianopia with macular sparing and diplopia, though the latter resolved relatively quickly. His main residual deficit was severe anterograde amnesia. He was reported to have, an "almost complete lack of retrograde amnesia" (Wilson, 1999, pp 44), remembering events and details up to the time immediately preceding his haemorrhage. Since his haemorrhage, JC has not been able to return to his studies. Through the use of an extensive set of memory aids and strategies, he has been able to live independently and undertaken a furniture restoration course. He is self-employed as a French Polisher and maker of cane chairs.

An MRI scan showed an area of encephalomalacia in the left posterior parietal area involving primarily the medial and superior surfaces of the parietal lobe. This had resulted primarily from the surgical intervention to clip the aneurysm. Atrophy of the hippocampus bilaterally, more prominent on the left, was reported. Other temporal lobe structures were intact. The possibility was raised that JC also had a lesion of the retrosplenial cortex, but this could not be confirmed as a result of a signal void created by the surgical clip in the region of the retrosplenial cortex. Figure 2.1.3 shows two coronal images of JC's brain.

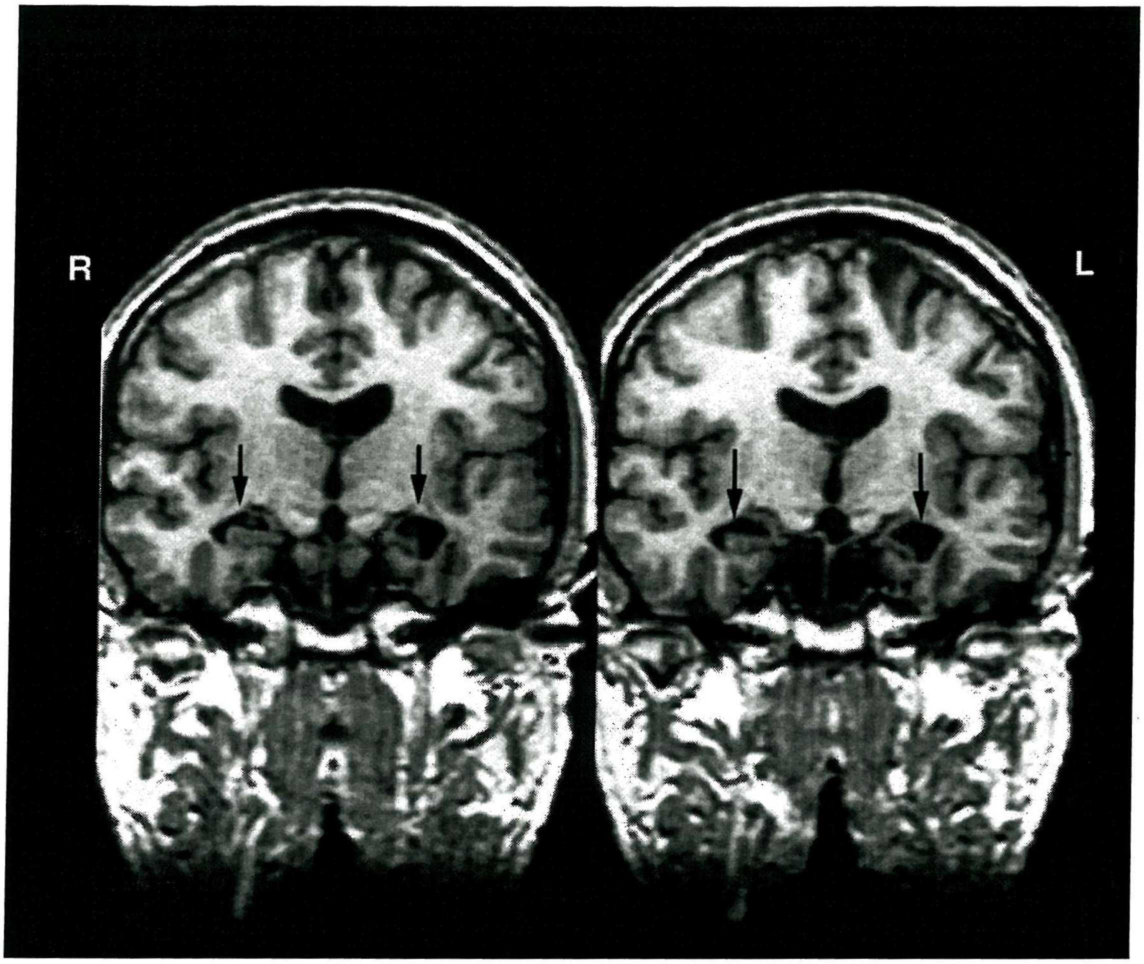



***Figure 2.1.3 Coronal MRI scan of JC's brain showing left and right hippocampal atrophy (arrowed).***

**2.1.3 General neuropsychological and anterograde memory test data**

Table 2.1.1 presents general neuropsychological data on each of the patients. Clinical considerations meant that not all patients had exactly the same battery of tests, but each of the main areas of cognitive functioning are represented by the tests given. All patients demonstrated well preserved general cognitive functioning in comparison to estimates of pre-morbid functioning. Table 2.1.2 presents results of tests of anterograde memory. All five patients presented with an amnesic syndrome.

*Table 2.1.1: Neuropsychological data for each of the study patients.*

| | BW | HW | EA | PR | JC |
|---|---|---|---|---|---|
| **NART Predicted pre-morbid IQ (Errors)** | 106 (20) | 113 (14) | 107 (19) | 121 (8) | 120 (9) |
| **WAIS-R:** | | | | (WAIS III) | |
| Verbal IQ | 99 | 118 | 97 | 119 | 124 |
| Performance IQ | 112 | 108 | 116 | 113 | 115 |
| Full Scale IQ | 103 | 115 | 104 | 118 | 121 |
| Information | 9 | 11 | 10 | 12 | 15 |
| Digit Span | 10 | 14 | 9 | 16 | 14 |
| Vocabulary | 9 | 13 | 10 | 14 | 16 |
| Arithmetic | 7 | 11 | 9 | 12 | 13 |
| Comprehension | 12 | 16 | 11 | 12 | 16 |
| Similarities | 13 | 12 | 11 | 13 | 13 |
| Picture Completion | 10 | 12 | 12 | 14 | 8 |
| Picture Arrangement | 16 | 11 | 15 | 11 | 8 |
| Block Design | 11 | 14 | 12 | 13 | 17 |
| Object Assembly | 12 | - | 10 | - | 17 |
| Digit Symbol | 8 | 9 | 10 | 7 | 13 |
| **Verbal Fluency** Letters FAS (60s, Total) | 38 | 38 | 43 | 37 | 50 |
| **Modified Wisconsin Card Sorting Test (Nelson version)** | | | | | |
| Categories | 5 | 6 | 6 | 6 | 6 |
| Total Errors | 17 | 1 | 5 | - | 0 |
| Total perseverative errors | 3 | 0 | 4 | - | 0 |
| **Cognitive Estimates** (error score) | 6 | 1 | 3 | - | 1 |
| **Behavioural Assessment of the Dysexecutive Syndrome** Age corrected Standardised Profile score (Normal=100) | 97 | 97 | 102 | 91 | 113 |
| **McKenna Graded Naming Test** (total/30) | 20 | 18 | 22 | 21 | 26 |

*Table 2.1.2 Anterograde memory test data for study patients*

| | BW | HW | EA | PR | JC |
|---|---|---|---|---|---|
| **WMS-R** | | | | | |
| Visual | 66 | 97 | 54 | - | 80 |
| Verbal | 66 | 99 | 57 | - | 75 |
| General Memory | 57 | 98 | <50 | - | 69 |
| Delayed | <50 | <50 | <50 | - | <50 |
| Attention and Concentration | 95 | 120 | 93 | - | 99 |
| Logical Memory Immediate (Percentile) | 3rd | 74th | 1st | - | 8/50 |
| Logical Memory Delayed (Percentile) | 1st | 1st | 0 | - | 0 |
| Visual Reproduction Immediate (Percentile) | 11th | 74th | 6th | - | - |
| Visual Reproduction Delayed (Percentile) | 1st | 1st | 0 | - | 1/36 (Rey Osterreith) |
| **WMS III (Age scaled scores)** | | | | | |
| Logical Memory I | - | - | - | 6 | - |
| Logical Memory II | - | - | - | 1 | - |
| Family Pictures I | - | - | - | 1 | - |
| Family Pictures II | - | - | - | 2 | - |
| Faces I | - | - | - | 7 | - |
| Faces II | - | - | - | 10 | - |
| Verbal Paired Associates I | - | - | - | 4 | - |
| Verbal Paired Associates II | - | - | - | 4 | - |
| **Rivermead Behavioural Memory Test** | | | | | |
| Standardised Profile Score (Max. = 24) | 7 | 13 | 6 | 0 | 5 |
| **Warrington Recognition Memory Test (Age scaled scores)** | | | | | |
| Words | <3 | 6 | 5 | 5 | <3 |
| Faces | 12 | 11 | 9 | 11 | <3 |
| **Doors and People (Age scaled scores)** | | | | | |
| Doors | 4 | 7 | 4 | 5 | - |
| Names | 5 | 6 | 1 | 6 | - |

### 2.1.4 Tests of retrograde memory

#### *2.1.4.1 Autobiographical Memory Interview (Kopelman, Wilson and Baddeley, 1990)*

This test is divided into three lifetime periods, Childhood, Early Adulthood and Recent Life. It is important to note that the Recent Life period relates to the anterograde (post-illness) period for all of the patients in this study. Within each lifetime period there are three topic areas, and each of these is divided into Personal Semantic and Autobiographical Incidents sections. The Personal Semantic sections incorporate questions relating to factual knowledge (e.g. the name of school attended, name of friends or teachers, qualifications). For some patients, certain questions from the Recent Life period were not relevant (e.g. name of present hospital or institution when the patient was seen at home) and so revised maximum scores are reported. In the Autobiographical Incidents section, the patient is asked to try to recollect specific events from the time period in question. Table 2.1.3 presents the results from the AMI.

***Table 2.1.3 Results from the Autobiographical Memory Interview***

| | BW | HW | EA | PR | JC |
|---|---|---|---|---|---|
| *Personal Semantic* | | | | | |
| Childhood | 21 | 21 | 19 | 21 | 19 |
| Early Adult Life | 20 | 16* | 21 | 21 | 20 |
| Recent Life | 21 | 12*** | 10*** | 21 | 14*** |
| *Autobiographical Incidents* | | | | | |
| Childhood | 9 | 6 | 0*** | 7 | 8 |
| Early Adult Life | 8 | 6* | 3*** | 6* | 9 |
| Recent | 2*** | 5*** | 0*** | 7 | 2*** |

Key
* = Borderline
** = Probably Abnormal
*** = Definitely Abnormal

#### *2.1.4.2 Time-Constrained Crovitz Test*

The version of the Crovitz technique used was based on the format described by Graham and Hodges (1997). Subjects were instructed to try to remember a specific event or episode from a particular lifetime period in response to each of 15 cue words. The number of lifetime periods selected was either three (for patients PR and JC) or four (for patients BW, HW and EA). The rationale for this related to the age at which the patients became amnesic. BW and HW became amnesic around the age of 30 years and EA was 34 years. It was decided to use three pre-morbid decades as separate time periods to be tested. The fourth time period was the post-onset time period. JC became amnesic at the age of 20 and I decided to use two pre-morbid time periods. Since there was a particular interest in examining the immediate pre-morbid period in some depth (as indicated earlier) I decided to use the periods 0-16 years and 17-Illness Onset. This was also considered appropriate because of the fact that late teenage/early adulthood years typically involve a series of key life events which can act as anchor points for facilitating retrieval of episodes (Mackavey, Malley and Stewart, 1991). PR became amnesic at the age of 23 and so the periods 0-16 years and 17 - illness onset were also used for him. For JC and PR, cued autobiographical recall was also sampled from a post-morbid time period. The test used the same 15 words for each time period. They were; Holiday, Accident, Game, Animal, Death, Birthday, Child, Meal, Hospital, Journey, Party, Friend, Book, Film, and Prize. The order of the task was that a cue word was given for a time period, then the next cue word was given for the next time period, and so on until all of the cue words had been given for all of the time periods. In order to encourage the production of as much detail as possible, there was no time limit for recall and participants were prompted (e.g. "Can you tell me more about that?"; "Can you give me a specific example?") if necessary. Responses were scored on a 6 point (0-5) scale according to the specificity of the memory (see Graham and Hodges, 1997 for details of the scoring system). Responses were scored by a trained independent rater who was blind to any experimental hypotheses.

For comparison purposes, the test was also administered to two groups of control participants. One group was selected to match subjects BW, HW and EA (BW 41 years, HW 42 years and EA 49 years at time of testing. Controls: N= 6 females; Mean age = 43.67, s.d. 4.41; Mean NART error score = 15.83, s.d. 8.75), while the other group were selected to match with subjects PR and JC (PR 30 years and JC 34 years at time of testing. Controls: N= 6 males; Mean age 31.33, s.d. 2.34; Mean NART error score = 8.5, s.d. 3.9).

*Results*

Patient EA was unable to do this task, which was abandoned. She reported that she was unable to retrieve any specific events, pre or post-morbidly without prompts and indicated that the cue words did not provide specific enough prompts for her to be able to retrieve memories of events. The performance of each of the other four patients is shown in Figures 2.1.4 (a) and (b). Performance is represented in terms of a z-score based on the difference between the patients and the relevant control group, as a proportion of the standard deviation of the control group scores. The two figures show that BW demonstrated normal performance on the task for all of the pre-morbid time periods, but was significantly impaired ($t^1 = -3.15$, $p = 0.03$) on the post-onset period. HW appeared to show evidence of a temporal gradient in her retrograde memory performance. Her score for the immediate pre-morbid period was considerably lower than that of the control participants ($z = -1.71$), though not statistically impaired ($t = -1.58$, $p = 0.174$), while her score for the earlier years was less discrepant from the controls. Her performance on the post-onset period was also somewhat below that of the controls ($z=-1.37$), but was not impaired ($t = -1.27$, $p = 0.26$), as can be seen from Figure 2.1.4 (a). PR and JC showed severe impairments for both pre-morbid periods and the post-morbid period with no evidence of any temporal gradient in performance.

[1] Crawford and Howell's (1998) modified t-test for comparing an individuals test score with norms derived from small samples.

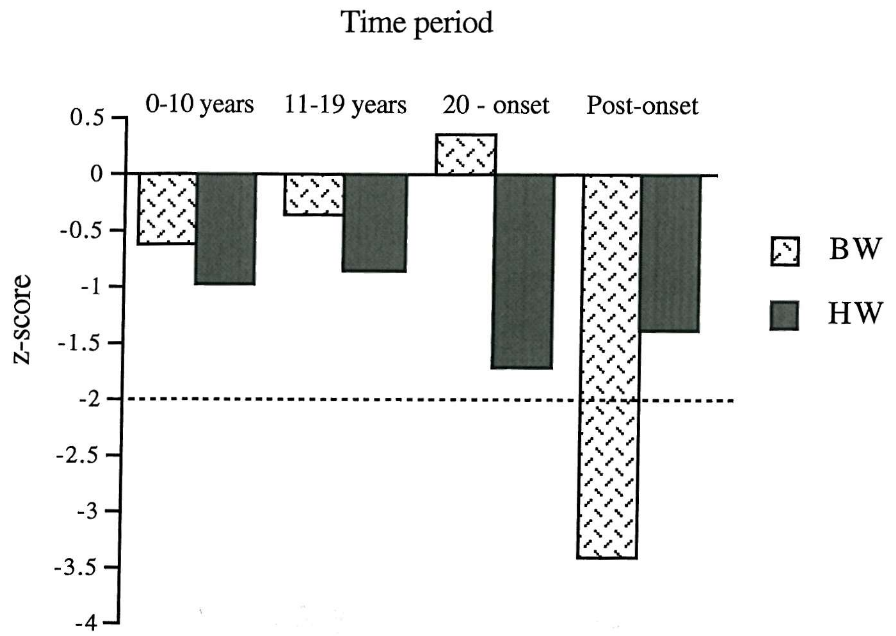



***Figure 2.1.4(a) Performance of BW and HW on the modified Crovitz task. Scores are z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviation of the control group scores. The dotted line indicates a two standard deviations below the mean.***

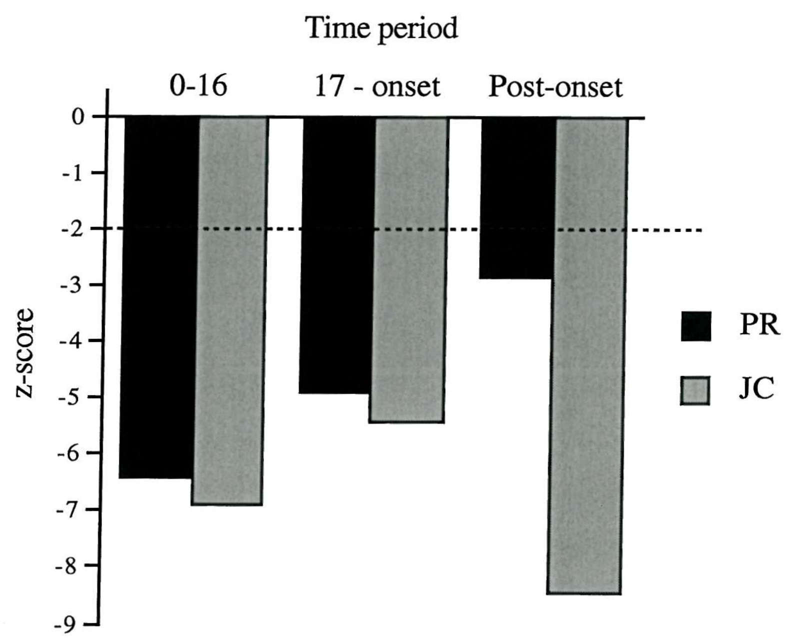



***Figure 2.1.4(b) Performance of PR and JC on the modified Crovitz task. Scores are z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviation of the control group scores. The dotted line indicates a two standard deviation level.***

#### *2.1.4.3 The Dead-or-Alive Test*

The Dead-or-Alive test used was adapted from the version described by Kapur et al. (1989). It consists of 50 names of famous personalities. Nine of the personalities in the test died during the 60's, nine during the 70's, nine during the 80's and nine during the 90's. A further 14 individuals were still alive. A list of the stimuli is provided in Appendix 1. All five amnesic patients were given the test, along with the two groups of control participants who performed the Crovitz task described above. As well as being matched on sex, age and NART, the control participants were matched with the patients in terms of their level of media exposure, by means of a Media Exposure Questionnaire (Kapur, Thompson, Kartsounis, and Abbott, 1999 p.30). This questionnaire asked participants how frequently they read newspapers, the type of newspaper, how frequently they watched the news on television or listened to the news on the radio and how often they read books or watched television programmes that contained information about recent historical events. A scoring system awards points according to the frequency of exposure, with a composite Media Exposure score being derived. The mean Media Exposure score for the six female control participants was 51.67 (s.d. 18.33). Scores for the female patients were: BW= 55; HW= 67; EA= 52. All of the female amnesic patients indicated that their media exposure was at about the same level pre-morbidly. The mean Media Exposure score for the six male control participants was 52.83 (s.d. 13.83). Scores for the male patients were: PR=44; JC=44. PR indicated that he read newspapers and watched documentaries much more often prior to the onset of his amnesia (giving a recalculated pre-morbid score of 63). JC indicated that he also read newspapers a little more and watched TV a little more. For the Dead-or-Alive test, participants were presented with each name in turn on a separate sheet of paper. They were asked if the name was familiar. If the name was recognised as familiar, participants were asked to provide information that would identify that individual. Participants were then asked if they believed the individual to be dead or alive. If the response was 'dead', they were asked to identify the cause of death from four options presented on a card. The options were; Murdered, Suicide, Accident or Natural Causes. They were then asked to identify the decade in which the individual died by selecting options presented on a card. The options were 1960's, 1970's, 1980's and 1990's. The scoring system allowed for three different elements of the test; (a) familiarity - a point was awarded for recognising the name as familiar; (b) information - two points were awarded for providing accurate detail regarding the individual (i.e. Tim Henman: Sportsman- Tennis player; John Wayne- Actor, in Westerns), with one point being awarded for only superordinate level information (e.g. Bill Clinton- Politician; Marilyn Monroe- Actress); (c) details - three points were awarded for correctly identifying that an individual had died, the cause of death and the decade of death. Scoring of the responses was carried out by an independent rater trained in the scoring method and blind to any experimental hypotheses.

*Results*

In this section, only data from the pre-morbid period will be presented. For BW and HW, this included those people who died in the 60's, 70's and 80's, though it should be noted that for the period of the 60's, BW and HW were both in early childhood. For EA, data are presented for 60's, along with combined data from 70's and early 80's, as EA's amnesia onset was 1984. For PR, data relating to those individuals who died in the 60's, 70's, 80's and the early 90's are included, with data for the 80's and early 90's being combined, since PR's amnesia onset was 1995. Although data for the 60's are included for completeness, it should be noted that this set of data relates to people who died before PR was born. Furthermore, the data for the 70's relate to people who died while PR was in early childhood. This is discussed later. For JC, data are presented for 1960's, along with combined data for 70's and early 80's as JC's amnesia onset was in 1986. For JC too, the 1960's relates to people who died in his early childhood.

Figure 2.1.5 (a) presents data for the Familiarity scores for each amnesic patient for each decade. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. For familiarity judgements, the only patient who showed any impairment was PR ($t=-4.16$, $p=0.009$), for the period covering the 1980's and early 1990's, prior to the onset of his amnesia.

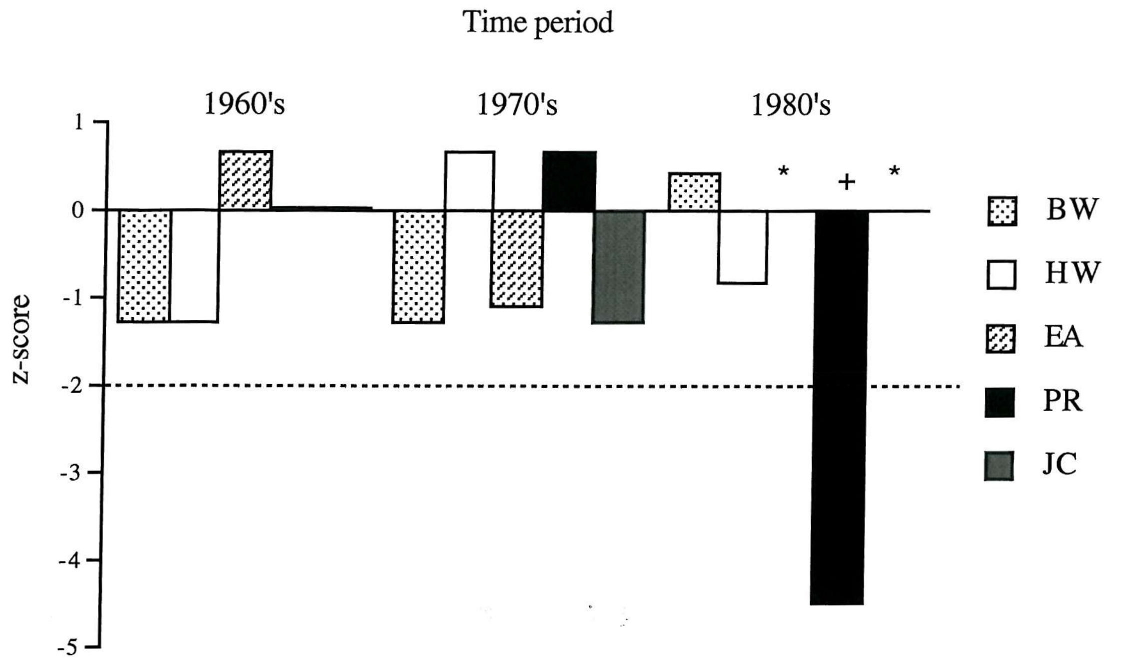



***Figure 2.1.5(a) Familiarity scores for each amnesic patient for each decade on the Dead-or-Alive test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. *Data for EA and JC for the early 1980's are included with their data for the 1970's. +Data for PR include the 1980's and the early 1990's. The dotted line indicates a two standard deviation level.***

Figure 2.1.5 (b) presents data for the Information scores for each amnesic patient for each decade. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. The graph shows that there was evidence of a temporal gradient in the performance of PR and HW. PR showed significant impairment for the decade immediately preceding the onset of his amnesia (t=-3.04, p=0.03), borderline impairment for the 1970's (t=-2.19, p=0.09) and unimpaired for the 1960's (t=-0.92, p=0.40). PR's impaired performance for the 1980/90's was primarily accounted for by lack of knowledge of just three personalities (WPC Yvonne Fletcher, Michael Ryan and Bobby Sands). One possible explanation for this is that PR was quite young at the time that these individuals died (PR was aged 13, 16 and 10 respectively). Although the control group were well matched in age with PR, some were a few years older and so at the critical time of these events, a small number of the controls were at an age where they may have been more aware of news events associated with the deaths of these three individuals.

HW's performance was borderline impaired (t=-2.09, p=0.09) for the decade immediately preceding the onset of her amnesia and unimpaired for the two previous decades. BW, EA and JC show no impairment for any decades.

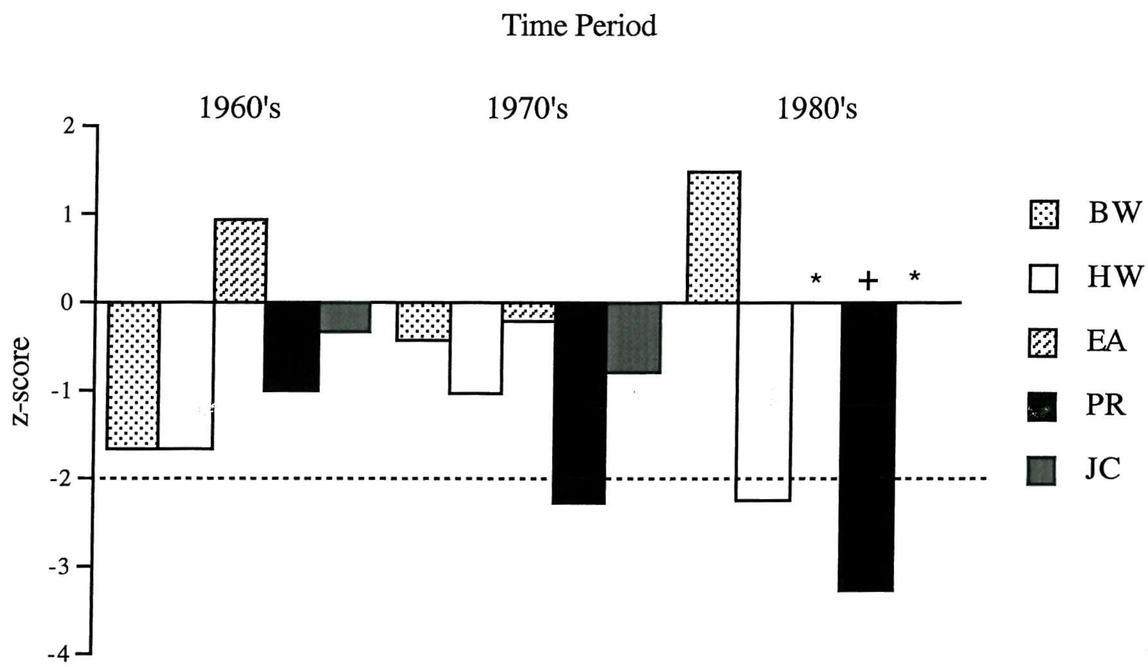



***Figure 2.1.5(b) Information scores for each amnesic patient for each decade on the Dead-or-Alive Test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. *Data for EA and JC for the early 1980's are included with their data for the 1970's. +Data for PR includes the 1980's and the early 1990's. The dotted line indicates a two standard deviation level.***

Figure 2.1.5 (c) presents data for the Details scores for each amnesic patient for each decade. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. The graph shows that none of the patients was significantly impaired for any decade, though there were some indications of a temporal gradient in the performance on HW.

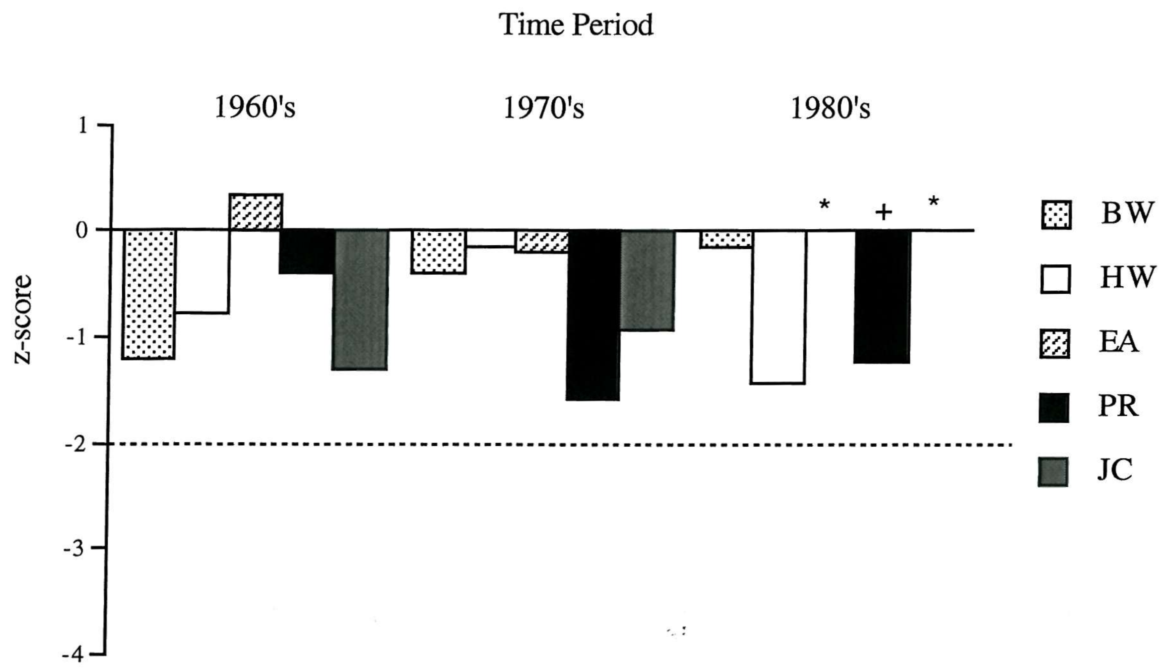



***Figure 2.1.5(c): Details scores for each amnesic patient for each decade on the Dead-or-Alive test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. *Data for EA and JC for early 1980's are included with their data for the 1970's. +Data for PR includes the 1980's and the early 1990's. The dotted line indicates a two standard deviation level.***

In summary, there was little evidence of significant impairment on the Dead-or-Alive test for all pre-morbid periods for almost all of the patients. PR showed some impairment. This might be accounted for by small differences in the ages of the control participants affecting three key personalities. However, it is worth noting that these three personalities were associated with particular events and therefore might be considered to have had a relatively discrete media coverage. HW showed a similar pattern to PR. There was no evidence that knowledge of details of how and when personalities died was more vulnerable than knowledge about the individuals. The fact that some of the younger patients were as effective with personalities who died before they were born suggests that this test might be considered to be dependent primarily on semantic knowledge. Episodic memory (e.g. remembering the circumstances of hearing about an individual's death) either had a minimal role in performance for both controls and patients or could be utilised to a similar degree by both.

A different way of exploring public event knowledge that might be considered more 'episodic' in quality is to use a test involving news events. Although some news events are referred to over extended periods of time, this is less likely to happen than for famous personalities (who apart from a few notable exceptions have become famous through very extended exposure). The next section describes the use of a news events test with the five amnesic patients. It was noted earlier that some of the previous studies of patients who present with minimal retrograde amnesia have failed to examine the period immediately preceding the onset of amnesia in detail (e.g. Zola-Morgan et al. 1986). It was therefore decided to use a news events test to examine a period of five to six years prior to the onset of amnesia in some detail, and to include tests of recognition and recall of event details.

#### *2.1.4.4 News Events Test*

A News Events Test was constructed similar to one described by Graham, Pratt and Hodges (1998). The test contained 76 news events that had occurred between 1979 and 1997. There were between three and five events per year. Events were selected on the basis of having had significant media coverage at the time of the event, primarily being selected from historical news sources such as the Chronicle of the 20th Century. For each event, three fictitious, but plausible events were generated (see Appendix 2 for a list of the events and distractor items). For the recognition component of the test, the four events were presented on a sheet of paper one above each other, with the position of the target event being equally likely to occur in any of the four positions. Participants were asked to identify the real event. Having selected an event, they were then asked to recall as many details of the event as possible.

The 'Recognition' component of the test was scored simply in terms of the total number of correctly identified items. For the event details 'Recall' component of the task, each response was scored according to a 4 point (0-3) scale: 0 = don't know or incorrect response; 1 = superordinate information only; 2 = a definition that described the event, but did not distinguish it from other similar events (i.e. did not uniquely identify the event); 3 = a definition that uniquely identified the event. An independent rater who was trained to use the rating system and who was blind to any experimental hypotheses undertook scoring.

The News Events Test was given to the two groups of control participants who had undertaken the Crovitz and the Dead-or-Alive tests. For the patients, sub-sets of events were given, events being selected for inclusion according to the year of onset of amnesia. This was done to focus the test on key time periods of relevance to the patient and in order to avoid as far as possible over-burdening patients with lengthy testing sessions. A limitation of this procedure is that controls were given more events overall than the patients and it is possible that exposure to one event might be more likely to cue information about other similar events that might have been contained in the test. However, after detailed consideration of test items, the likely impact of this was considered to be minimal. Patients were tested on events from a period of six years prior to the onset of amnesia. Data from the following specific pre-morbid periods for each patient will be presented: BW(1985-1990); HW (1986-1991); EA(1978-1983); PR(1989-1994); JC(1980-1985).

*Results*

Figure 2.1.6 (a) presents data for each patient for the recognition component of the News Events Test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. The figure shows that BW, HW and EA were all at or just below a two standard deviation point. Using Crawford and Howell's (1998) modified t-test for use with norms derived from small samples, BW's score was significantly impaired (t=-2.92, p=0.033) and EA's score approached significance (t=-2.23, p=0.076). It is noteworthy that BW and HW's relatively poor scores were the result of being only a small number of items below the control mean (BW scored 19/26, compared to the control mean of 23/26; HW scored 19/26, compared to the control mean of 22.17/26), in the context of very little variation in the controls for the periods 1985-1991. EA's performance for the period

1979-1983 was such that she only correctly recognised 5/15 events compared to the control mean of 11.17/15 (s.d.=2.56) events. Both PR and JC were clearly unimpaired on this component of the test.

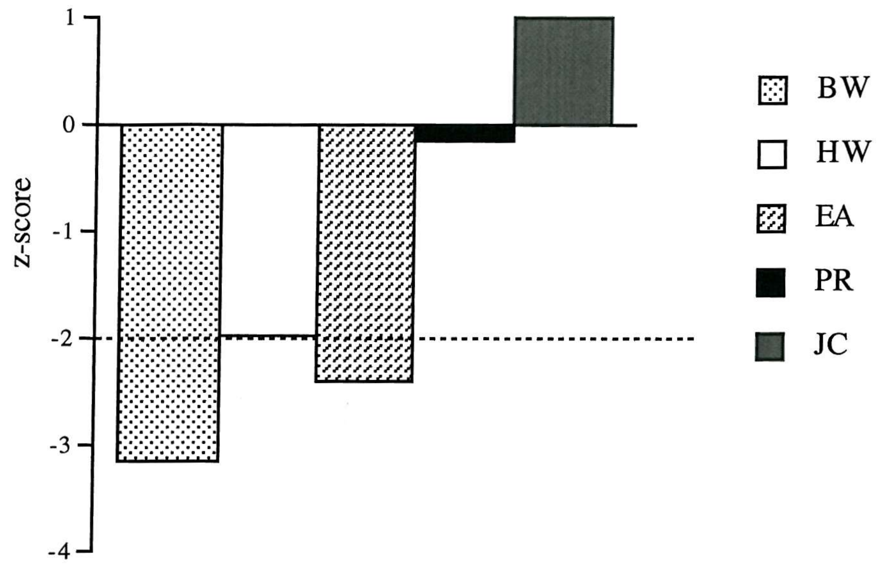



***Figure 2.1.6(a) Performance of each patient for the recognition component of the News Events Test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. The dotted line indicates a two standard deviation level***

Figure 2.1.6 (b) presents data for each patient for the event details recall component of the News Events test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. The data show that the only patient to fall below a two standard deviation point was EA, though her score did not achieve statistical significance ($t=-1.94$, $p=0.110$). BW, HW and PR all perform somewhat more poorly than the control participants, though again none of these scores were statistically significant.

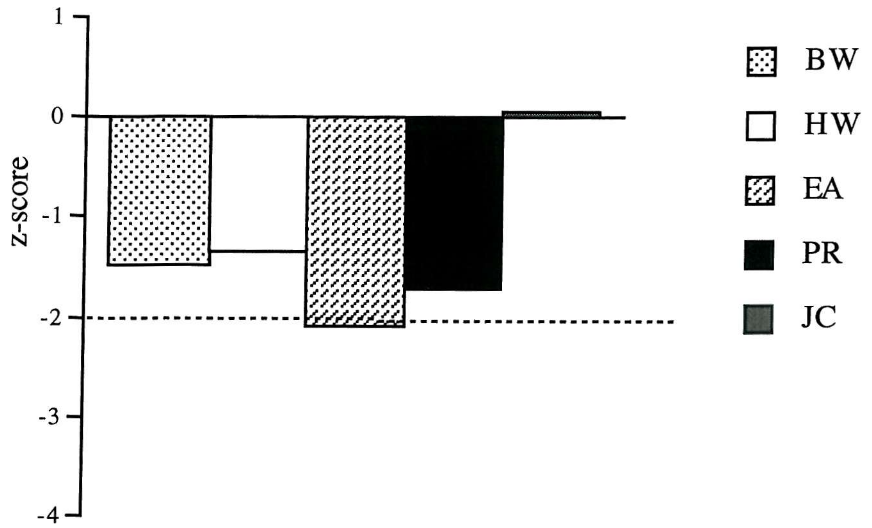



***Figure 2.1.6(b) Performance of each patient for the event details recall component of the News Events Test. Data are represented by z-scores derived from the difference between the patients and the relevant control group, as a proportion of the standard deviations of the control group scores. The dotted line indicates a two standard deviation level.***

Figure 2.1.7 shows the mean number of standard deviations the patients as a group were *below* the control mean, for each of the six pre-morbid years tested on the event details recall component of the News Events Test. Note that a higher score represents a greater impairment. The figure shows that there was no evidence of a temporal gradient in performance for the group (Friedman test Chi Squared = 6.46, df = 5, p = 0.264). None of the individual patients showed any evidence of a temporal gradient over this period.

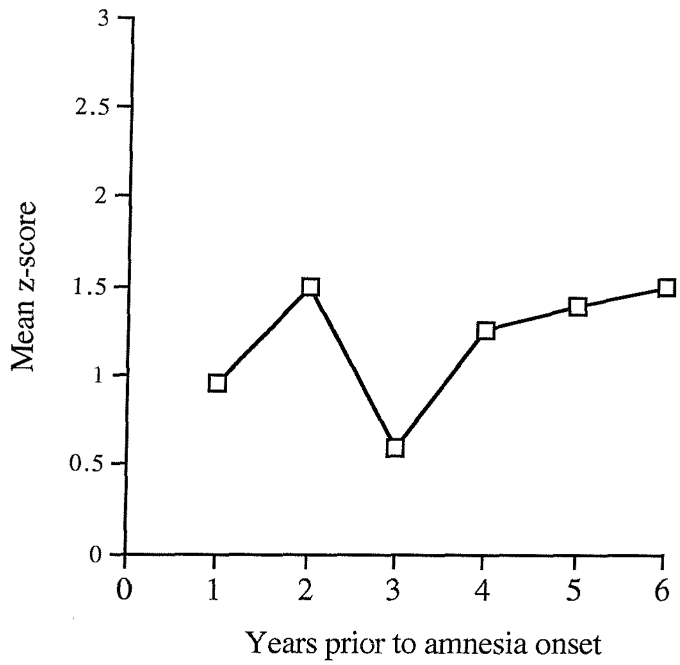



***Figure 2.1.7 Performance of the group of amnesic patients on the News Events details task for each of the six pre-morbid years tested. Scores indicate mean number of standard deviations below control mean. A higher score represents a greater impairment.***

In summary, on the News Events test that sampled the years immediately preceding the onset of amnesia for each of the five amnesic patients, one patient (EA) was poor (borderline impaired) on both recognition and recall components of the test. BW and HW were poor on the recognition component and somewhat below the control mean for the details component. However, as the controls participants performed close to ceiling levels, with very little variance, the patients only had to fail to recognise a small number of personalities in order to be classified as impaired. PR and JC were unimpaired on both test components, though PR's performance on the event details component of the task was somewhat poorer than the control participants.

### 2.1.5 Discussion

Four of the five cases studied here did show a deficit in autobiographical event recollection. For three cases, EA (presumed anoxic damage), JC (subarachnoid haemorrhage arising from a left posterior cerebral artery aneurysm) and PR (carbon monoxide poisoning), the deficit appeared to extend back to childhood memories using the modified Crovitz task. For HW, who was anoxic during a period of status epilepticus, there was evidence of a temporal gradient in her performance. However, for BW (who suffered carbon monoxide poisoning), there was no evidence of an impairment on autobiographical recall tasks such as the AMI and Modified Crovitz test.

The cognitive profiles of each of the five patients were similar. Each had preserved perceptual, language, and executive skills. Each presented with severe anterograde memory problems on standardised memory tests and in everyday life. Each also had damage to the medial temporal lobes. JC, who suffered a ruptured left posterior cerebral artery aneurysm, had some additional surgical damage to the left posterior parietal regions, but no impairments other than memory impairments have been detected in him. It was also suggested that JC may have a retrosplenial lesion and it has been argued that retrosplenial lesions may also damage the fornix (Valenstein et al., 1987). For EA (who was diagnosed as having suffered an episode of anoxia during an acute, possibly encephalitic, illness), the precise location of her pathology could not be determined, but it was presumed to be limited to medial temporal lobe regions. For the other three patients (PR, HW and BW), imaging evidence indicated that the pathology was primarily confined to the hippocampus, though the possibility of damage to extra-hippocampal regions not visible on MRI scans cannot be ruled out completely (Markowitsch, Weber-Luxemburger, Ewald, Kessler and Heiss, 1997).

The data were equivocal with regard to the predictions derived from the Standard Consolidation (Squire and Alvarez 1995) and Multiple Trace (Nadel and Moscovitch 1997) models. Evidence from EA, JC and PR supports Multiple Trace Theory, data from HW support the Standard Consolidation Model and the apparent complete lack of a retrograde amnesia evident with BW supports neither model, unless within the Standard Model it is assumed that the process of consolidation is fast. How might the differences be explained and in particular how should one account for the apparent lack of retrograde amnesia in the case of BW? One possibility is that BW is simply less severely impaired than HW who is in turn less impaired than the other patients. However there was little evidence for any marked differences in severity of anterograde amnesia. On the RBMT, BW scored 7/24 and was somewhat *more* impaired than HW who scored 13/24, whose MRI was rated as indicating less severe hippocampal damage. Nevertheless HW showed more impairment on the Modified Crovitz and AMI. It was however the case that BW had a higher score on the RBMT than EA, PR, and JC, who scored 6, 0 and 5 respectively, though the difference was only marginal when compared with EA and JC.

Nadel and Moscovitch (1997) used a 'severity difference' argument to account for the data from patients with no apparent retrograde amnesia such as patient RB (Zola-Morgan et al., 1996) and the patients described by Reed and Squire (1998). They argued that the formation of multiple memory traces in the hippocampus means that autobiographical memories are protected from insult so long as the damage to the hippocampus is limited. The problem with this argument, however, is that it results in the theory becoming untestable, unless very specific predictions about how much of the hippocampus or which specific regions of the hippocampus can be lesioned without having any measurable effect on autobiographical event memory. In a somewhat contrary position, Moscovitch and Nadel (1998) have, in fact, argued that there is accumulating evidence that sub-regions of the hippocampal complex have separate contributions to the storage and recovery of remote memories and, "because autobiographical episodic memories are multi-faceted and rich in detail it is likely that......the co-ordinated activity of all of [the sub-regions] would be necessary to retrieve a fully fleshed-out episode" (p. 297). If the latter argument is true, it follows that any lesion to the hippocampus should have *some* impact on autobiographical event recollection. One possibility is that the ability to truly re-experience an event or episode might be compromised, even though sufficient details are available to be able to give an account of the episode. This may result in being able to report facts about an event without the ability to 'replay' the event in mind. This distinction is somewhat similar to the remember-know distinction that has been examined in relation to anterograde recognition memory (Mandler, 1980; Gardiner and Richardson-Klavehn, 2000). The possibility that patients would report that they knew events to have occurred without the sense of being able to fully re-experience or replay them in mind was examined in a further study, described in section 2.3 below.

An issue that must be considered is the potential impact of mood on memory. None of the patients presented with significant disorders of mood. However, two patients (BW and PR) became amnesic as a result of suicide attempts with carbon monoxide poisoning. When considering tests of retrograde memory, the question must be raised as to whether pre-morbid depression might have an impact on performance, particularly on tests of autobiographical recall. Depressed patients have been shown to have impoverished autobiographical recall for event details (see Williams, Teasdale, Segal, and Soulsby, 2000). However, in the case of BW it would appear that her suicide attempt was an impulsive act in response to relationship difficulties and not the result of a long-standing depressive disorder. Pre-morbidly, she had never been diagnosed with depression, though of course this does not completely exclude the possibility that she had been depressed. However, BW's performance on the modified Crovitz task was normal, suggesting that she does not have an 'overgeneral' retrieval of autobiographical memories. In the case of PR, he had experienced more than one pre-morbid depressive episode, though these appeared to be triggered by highly stressful situations (such as exams or the break up of a relationship) and in between times he functioned well. Nevertheless, the possibility that his autobiographical memory might have been characterised pre-morbidly by an overgeneral response style cannot be ruled out completely.

The performance of the five patients on the tests of public knowledge did not provide consistent support for either model of memory. On the Dead-or-Alive test, HW showed some evidence of a temporal gradient in her performance, being worse for the 1980's and better for the 1970's and 1960's. PR also showed evidence of a temporal gradient, on the information section and to a lesser extent on the details of death section. What was striking about his performance was that it was best for the 1960's, but in fact PR was not born until 1971. This means that all the information he has acquired about the personalities, including whether or not they have died and if so how and when, must be based on historical information. It might be argued that PR and the control participants who were of a similar age, would gain less episodic support in relation to the acquisition of such information and this might account for why his performance is similar to control participants. It could also be argued that for the personalities who had died more recently, the control participants might have gained more support from episodic memory (i.e. remembering events associated with a particular individual), whereas this support might not be available for PR and this would account for his less effective performance on the more recent time periods. This argument of course only works if one assumes that learning about the recent death of a famous person would be likely to have somewhat more salience than learning about the death of someone who died many years ago, an assumption that is perhaps questionable. However, this did not seem to be relevant for JC or BW who showed no impairment for any time period. It was hypothesised that the test component most likely to be enhanced by episodic information would be the 'Details of Death' section. None of the patients showed impairment of the details of death component of the test, though there was a general tendency for the patients to be somewhat below the level of the control participants.

On the News Events test, three patients performed well below the control participants on the recognition component of the task, though just one was statistically impaired. It is necessary to be somewhat cautious in interpreting this latter result. The control participants performed very close to ceiling levels, with very little variance and so a very small reduction in performance by the patient led to a high negative z-score. On the event details recall section, four of the patients performed considerably below the control level, though only one score approached statistical significance. A study by Nadel et al. (2000) found that three amnesic patients performed less well than controls in terms of the number of details provided about news events, though no specific information was presented about either the patients or controls. They also found that the controls showed no temporal gradient in the recollection of details of news events. They suggested that this implies that "public events are somewhat semanticized from the beginning" (p. 361), since autobiographical episodic memory would be more likely to enhance memory for details of more recent events. Results from the present study concur with this to some extent, in that JC showed no impairment and three other patients did not show a severe impairment. However, the fact that four out of the five patients did perform some way below the controls does suggest that an autobiographical element may be exerting some effect on performance. Once again it is difficult to draw firm conclusions with regard to models of memory from these data, though the pattern of moderate impairment shown by three of the five is what would be predicted by Multiple Trace Theory. Although the period tested was relatively short, being six years in most cases, this does seem to be considerably longer than might be considered a reasonable period of consolidation within the Standard Consolidation Model, and hence the data would tend to be less consistent with the Standard Consolidation Model.

In summary, the weight of evidence from the use of the modified Crovitz task was marginally in favour of the Multiple Trace Theory and against the Standard Consolidation Model. Four of the five patients studied were shown to have deficits in recall of details of autobiographical events, which for three patients extended back to childhood. For one patient, there appeared to be a temporal gradient and another appeared to have no impairment at all. Even if one argues that limited lesions to the hippocampus will enable some details of autobiographical events to be recalled, Multiple Trace Theory predicts that there should nevertheless be some impairment in the ability to truly 're-experience' or replay events in mind. This hypothesis was tested as part of a further study, presented later in Section 2.3. Evidence from the two tests of memory for public events was somewhat equivocal in terms of support for either of the models of memory. A major problem with tests of public events is that it is possible that the amount of support for recall that might be provided by autobiographical episodic memory for the occasion of learning about an event is likely to be negligible, though this is something that would be useful to investigate in future studies. One type of retrograde public event that would be interesting to examine is the type of event that is considered to induce a 'flashbulb' memory (Brown and Kulik, 1977). Multiple Trace Theory would predict a lack of the flashbulb memory for patients with hippocampal lesions, while the Standard Model would predict preserved flashbulb memories, so long as the event occurred a significant period of time (perhaps at least a few months) prior to the onset of amnesia. This prediction remains to be tested.

A limitation of this study, and most other studies of retrograde amnesia, is that despite the use of matched controls, it is impossible to control effectively for prior exposure to autobiographical or public events (Kapur, 1999). However, one condition that offers a rare, but valuable opportunity to study retrograde memory in people for whom it is possible to establish pre-morbid levels of functioning with a reasonable degree of accuracy, is Transient Global Amnesia (TGA). As discussed earlier, the weight of evidence suggests that TGA involves a temporary disruption to the functioning of the medial temporal lobes. However, once the episode is finished there is a complete or almost complete recovery of functioning. Hence, if it is assumed that what can be recollected in the post-TGA phase represents accurately what could have been recollected pre-morbidly, then any discrepancy between what can be recollected during the TGA episode and what can be recollected post-morbidly may be considered to be a deficit. A study of the retrograde memory performance during and after TGA is presented in the following section.

## 2.2 Autobiographical event retrograde amnesia during transient global amnesia.

### 2.2.1 Introduction

It was noted earlier, in section 1.3.4, that a major methodological difficulty for the study of retrograde amnesia is the lack of experimental control over the study material. In almost all cases, it is impossible to know for certain what information or events an individual would have been able to recollect prior to the occurrence of a brain lesion and the onset of amnesia. However, one condition that presents an opportunity to compare performance under 'normal' conditions with performance while the individual is amnesic is Transient Global Amnesia (TGA). TGA is characterised by a transitory period of severe amnesia and confusion. According to strict diagnostic criteria, the onset of a TGA attack should be witnessed (to exclude epilepsy or head injury as potential causes), and focal neurological features should be absent (Hodges, 1991). The aetiology and pathophysiology TGA remain uncertain, but converging evidence points to a disruption to normal functioning of the medial temporal lobes (Simons and Hodges, 2000). The episode of amnesia is, by definition, temporary and after a period of usually around six hours, the patient's ability to remember information gradually recovers (Hodges 1991).

A limited number of previous studies of TGA have examined the nature and extent of retrograde memory impairment, but very few have included measures of autobiographical event recall (Kritchevsky, Squire and Zouzounis, 1988; Hodges and Ward, 1989). Even fewer studies have systematically examined autobiographical recall across specified lifetime periods. Several studies have used a form of the Crovitz technique in which there are no constraints on the time period from when memories should be recalled. This has led to the conclusion that patients tend not to spontaneously produce memories from the more recent time periods (Hodges and Ward, 1989), but the methodology does not allow the conclusion that patients *cannot* produce memories from the more recent time periods.

During the course of a temporary, but severe, disruption to medial temporal lobe systems, Multiple Trace Theory (Nadel and Moscovitch, 1997) would predict extensive autobiographical episodic retrograde amnesia, followed by complete recovery after resolution of the attack, apart from a period of amnesia for the period of temporary disruption. This is based upon the central premise that the hippocampus is always required for the retrieval of autobiographical memories. By contrast, the Standard Consolidation Model (Squire and Alvarez, 1995; Murre, 1996) would predict the presence of a temporally graded retrograde amnesia during the course of the TGA episode.

In the present study, autobiographical and semantic retrograde memory were examined in a patient during and after a TGA attack. In addition to being able to document anterograde and retrograde memory functioning, we were also in the relatively unique position of having evidence of brain integrity, as indicated by Single Photon Emission Computer Tomography. The Autobiographical Memory Interview was used to systematically sample lifetime periods. It was predicted on the basis of Multiple Trace theory that then an extensive autobiographical event memory deficit should be present. The Standard Consolidation Model, however, would predict a temporal gradient in retrograde memory performance.

### 2.2.2 Case History

The patient, BG, was a 55yr old right-handed woman with an uneventful past medical history. On the morning of the TGA episode, she made herself breakfast and afterwards drove to her son's house. On arriving, she was complaining of feeling muddled and was repeating the same questions. Her family contacted their general practitioner. He referred her to Addenbrookes Hospital around 4 hours after the onset of the attack and she underwent neuropsychological investigations. On admission, neurological examination was normal. She was oriented in person and place, but not in time. She had a severe anterograde amnesia and appeared, on informal questioning, unable to remember events from the previous month. She showed normal social interaction and was appropriately concerned about her condition. The episode lasted about 8-10 hours. A CT brain scan and an EEG performed on the day after the attack were both normal.

### 2.2.3 Brain Imaging

Single Photon Emission Computer Tomography (SPECT) was undertaken during the TGA attack. This was reported to demonstrate marked focal reduction in perfusion in the postero-medial temporal lobes bilaterally. When repeated at seven weeks post-attack, the appearances were reported to have returned to normal.

### 2.2.4. Neuropsychological Testing

During the attack, Orientation, Digit Span and Visual Memory Span sub-tests from the Wechsler Memory Scale-Revised (Wechsler, 1984) were used to assess memory for time, place, etc. and short-term memory. The National Adult Reading Test (NART; Nelson, 1991) was used to estimate pre-morbid IQ.

Anterograde memory was assessed by the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn and Baddeley, 1985). This battery of memory tests was chosen because it is relatively quick to complete, assesses a range of different forms of anterograde remembering and, most importantly for this study, parallel versions are available which makes repeat testing more valid.

Retrograde memory was investigated using the AMI (Kopelman et al.., 1990) which assesses both personal semantic knowledge (e.g. the names of friends or teachers or colleagues, addresses of places lived, knowledge of educational and work history), and autobiographical episodic memory (details of specific episodes) across lifetime periods. Modified versions of a Famous Faces Test and a Famous Events Test (Hodges and Ward, 1989) were also administered. The Famous Faces Test consists of 50 faces of people who have been famous in different decades between 1940 and 1990. Subjects are requested to name the person; if they are unable to provide the name spontaneously, semantic and first name cues are provided. In the Famous Events Test, the subject has to distinguish 50 famous events (across 5 decades) from 50 distractor events, and then to date the events judged to be real. A limitation of this test is that the events were from the period 1930's to 1970's, and therefore did not include more recent items.

Two days later the Orientation sub-test from the WMS-R, RBMT and AMI were repeated and 7 weeks later all the tests (apart from NART) were repeated. Different versions of the RBMT were used on each occasion in order to control for practice effects.

*Results*

*Orientation, working memory and anterograde memory*

Table 2.2.1 presents data relating to BG's performance on tests of orientation, working memory and anterograde memory.

BG was estimated to have an average IQ pre-morbidly. She was disorientated in time (month, date, time of day) during TGA, but well oriented when tested 2 days later. She showed unimpaired performance on tests of visual and verbal short-term memory. The initial RBMT score was indicative of a severe global anterograde amnesia, whereas the scores 2 days and 7 weeks later were in the normal range.

***Table 2.2.1 BG's performance on tests of orientation, working memory and anterograde memory.***

| | **During TGA** | **2 days post-TGA** | **7 weeks post-TGA** |
|---|---|---|---|
| **NART IQ** | 98 | N/A | N/A |
| **Digit span** | | | |
| Forwards | 7 | N/A | 8 |
| Backwards | 4 | | 3 |
| **Visual memory span** | | | |
| Forwards | 6 | N/A | 4 |
| Backwards | 4 | | 5 |
| **Orientation** | 11/14 | 14/14 | 14/14 |

| **Rivermead Behavioural Memory Test** | (Standardised Profile Score- Max = 2) | (Standardised Profile Score- Max = 2) | (Standardised Profile Score- Max = 2) |
|---|---|---|---|
| **Name learning** | 0 | 0 | 2 |
| **Belonging** | 0 | 2 | 2 |
| **Appointment** | 0 | 2 | 1 |
| **Picture recognition** | 0 | 2 | 2 |
| **Story (Immediate recall)** | 0 | 2 | 2 |
| **Story (delayed recall)** | 0 | 2 | 2 |
| **Face recognition** | 0 | 2 | 1 |
| **Route learning (Immediate recall)** | 1 | 2 | 2 |
| **Route learning (Delayed recall)** | 0 | 2 | 2 |
| **Message** | | | |
| **Orientation (not date)** | 0 | 2 | 1 |
| **Date** | 1 | 2 | 2 |
| | 0 | 2 | 2 |
| Standardised Profile Score Total | 2/24 (severely impaired) | 22/24 (normal) | 21/24 (normal) |

N/A = Not assessed

*Retrograde Memory*

(a) Autobiographical Memory Interview

In scoring the AMI, points are awarded for each item of semantic information and each autobiographical incident is rated on a 0-3 scale of descriptive richness and specificity in time and place. Data are classified as normal, probably abnormal or abnormal based on normative data provided in the test manual. Results of BG's performance on the AMI at each assessment stage are presented in Table 2.2.2.

*Table 2.2.2 Results of BG's performance on the Autobiographical Memory Interview at each assessment stage*

| | During TGA | | 2 days post-TGA | | 7 weeks post-TGA | |
|---|---|---|---|---|---|---|
| ***Personal Semantic*** | | | | | | |
| Childhood | 21/21 | (normal) | 21/21 | (normal) | 21/21 | (normal) |
| Early Adult Life | 20.5/21 | (normal) | 21/21 | (normal) | 21/21 | (normal) |
| Recent Life | 14/21 | (abnormal) | 21/21 | (normal) | 21/21 | (normal) |
| ***Autobiographical Incidents*** | | | | | | |
| Childhood | 3/9 | (abnormal) | 7/9 | (normal) | 7/9 | (normal) |
| Early Adult Life | 4/9 | (probably abnormal) | 8/9 | (normal) | 7/9 | (normal) |
| Recent Life | 2/9 | (abnormal) | 9/9 | (normal) | 9/9 | (normal) |

During the attack, scores on the personal semantic information were within the normal range, apart from the recent life section, some of which ask for information about the current hospitalisation and therefore reflect, in this case, impairment in anterograde rather than retrograde memory. In contrast to relatively normal personal semantic information, the patient's ability to describe detailed episodes in her life was significantly impaired. Two days later, however, she was able to provide detailed information. In addition, episodes that were produced only in very general terms during the attack, were elaborated in much more detail two days later. The same was true seven weeks later. Some examples will illustrate this:

*(1) Asked to describe an incident occurring while at primary school (age 5-11yrs)*

During TGA attack: " I can't think of anything, nothing exciting happened, I don't recall any trips. I remember one of our teachers went away for a year."

2 days later: " I remember being taken to a local canning factory, they showed us the vegetables being cleaned and the process involved. We had to do essays on it. We went on a bus, the head teacher took us and the boys rushed to the back."

7 weeks later: " We went to a local canning factory. We had to write essays about it. We went by coach. They took us all around and explained things. They were doing strawberries at the time. The whole class went and our head teacher took us."

*(2) Asked about a holiday taken within the last 5 years*

During TGA attack: " We all went in a chalet, but I can't remember where. I think it was last September, but I can't really remember. We just all enjoyed ourselves, my son went fishing, we just had fun."

Two days later: describing the same holiday: " We had a chalet near Weymouth last September. I remember one day getting up early and going out for a walk with my son to see what birds we could see. We were out before breakfast. We saw Blue Tits, Chaffinches, Long Tailed Tits and we also saw a Heron in a pond."

Seven weeks later: describing another holiday, " We went to the lakes last February. The scenery around was really pretty, there was snow on some of the mountains and the lakes were icy. We stayed in a friend's hotel and I remember we went over one night to play a board game and we were in teams of three."

(b) Famous Faces

Results of BG's performance on the Famous Faces Test during TGA and 7 weeks later is provided in Table 2.2.3.

***Table 2.2.3 BG's performance on the Famous Faces Test (Faces correctly named per decade)***

| ***Time of testing*** | **1940's** | **1950's** | **1960's** | **1970's** | **1980's** | **Total** |
|---|---|---|---|---|---|---|
| ***During TGA*** | 6/10 | 5/10 | 5/10 | 7/10 | 7/10 | 30/50 |
| ***7 weeks post-TGA*** | 6/10 | 6/10 | 5/10 | 9/10 | 9/10 | 35/50 |

BG was within normal limits (with reference to control data from Hodges and Ward 1989) during TGA for all decades. When reassessed seven weeks later, there was a mild (10%) improvement in naming with most improvement being for faces from the 1970s and 1980s, suggesting the presence of a modest temporal gradient to her performance.

(c) Famous Events

Results of BG's performance on the recognition and dating of Famous Events Test during TGA and seven weeks later is provided in Tables 2.2.4 and 2.2.5.

***Table 2.2.4 Recognition of famous events (number of correctly recognised famous events, non-famous events falsely identified as famous and non-famous events correctly rejected).***

| *Time of testing* | 1930's | 1940's | 1950's | 1960's | 1970's | False Positive | Correct rejection |
|---|---|---|---|---|---|---|---|
| ***During TGA*** | 7/10 | 5/10 | 9/10 | 8/10 | 7/10 | 11 | 39 |
| ***7 weeks post-TGA*** | 5/10 | 5/10 | 9/10 | 9/10 | 7/10 | 2 | 48 |

***Table 2.2.5 Dating of famous events (Number of items correctly dated for decade)***

| *Time of testing* | 1930's | 1940's | 1950's | 1960's | 1970's |
|---|---|---|---|---|---|
| ***During TGA*** | 1/10 | 3/10 | 7/10 | 4/10 | 1/10 |
| ***7 weeks post-TGA*** | 2/10 | 4/10 | 8/10 | 5/10 | 4/10 |

BG was within normal limits (within two standard deviations of control data from Hodges and Ward 1989) during TGA for all decades for recognition. For the dating task, compared to control data from Hodges and Ward 1989, she was impaired for the 1930's, 1940' and 1970's during TGA. Post-TGA her scores were normal for the 1970's, but were still impaired for the 1930's and 1940's.

In summary, BG's performance on identifying famous events was as good during TGA as afterwards, although the tendency to produce more false positive responses during TGA may obscure a mild impairment. Dating of events was poorer during TGA (21.3% overall increase in performance), with the greatest improvement being for the more recent events.

### 2.2.5 Discussion

The nature of TGA is such that it is very seldom possible to obtain neuropsychological and brain imaging data during the course of the episode. When TGA does become amenable to study it provides a valuable opportunity to test a memory impaired person who can, on recovery from the attack, act as their own control with regard to retrograde knowledge and anterograde memory functioning. This is a particular advantage given the difficulty of comparing across subjects with regard to pre-injury knowledge and experiences. This was noted in Chapter 1 to be one of the main measurement problems in the area of retrograde memory. It was noted in Chapter 1 that one caveat to the use of TGA patients as their own controls is the evidence that some patients are left with residual memory deficits (Hodges and Oxbury, 1990). However, BG presented with a characteristic severe global anterograde amnesia, which completely resolved over the course of a matter of hours, in that her performance on tests of anterograde memory and retrograde memory were normal when tested at both two days and seven weeks post-attack. It was not clear what had triggered her attack, though it did not appear to have been related to any particular stressful experience. The SPECT scan suggested that BG's attack was related to hypometabolism in the region of the medial temporal lobe, bilaterally.

The key issue addressed in this study was the nature and extent of the retrograde memory deficit during the TGA. On informal initial clinical questioning, BG appeared to have difficulty recollecting information for a period of approximately a month. Her performance on tests of personal and public semantic retrograde knowledge (AMI, Famous Faces, Famous Events) was generally satisfactory during and after the attack.

There was some evidence that improvements that were made post-attack were from the more recent periods, suggesting the possibility of a temporal gradient to her retrograde amnesia. A limitation of this testing was that neither the Famous Faces nor the Famous Events tests were designed to test the previous few years prior to the attack and so the data could have masked a poorer performance on the most recent retrograde knowledge. A particularly striking feature of BG's performance was her difficulty in recalling specific incidents from throughout her life. This contrasted markedly with her ability to produce rich details of events from the same time periods upon recovery from the attack. As noted above, informal clinical questioning had suggested a retrograde amnesia of about a month, and yet more detailed examination showed problems that covered most of her lifetime, at least in the domain of autobiographical event recall. One explanation for this finding was that, during the TGA attack, anxiety or poor attention could have limited the effort that was applied to recollecting specific memories. Although a possibility, this does not seem likely. Although she was clearly amnesic, she did not present as anxious or agitated. Furthermore, her performance on other tasks, including some of the personal semantic items in the AMI also might be considered to involve significant memory retrieval demands and on these she performed normally. This raises the possibility that some previous studies of retrograde memory in TGA may have failed to detect an impairment in autobiographical recall that extended across the lifetime period. Hodges and Ward (1989) found impairment in autobiographical recall, though as noted earlier, the particular form of the Crovitz task used meant that lifetime periods were not sampled. They also concluded that there was evidence of a temporal gradient in semantic retrograde memory (for famous events and faces). More recently, Guillery et al.. (2000) studied a TGA patient during and after the attack using a version of the AMI, modified to examine the more recent pre-morbid period in greater depth. They replicated the findings obtained in case BG in that their patient also showed an impairment in autobiographical recollection across all lifetime periods during TGA. However, in their study, there was also evidence of a temporal gradient in performance. While scores for the childhood and adolescence period were impaired, they were nevertheless better than scores for more recent pre-morbid years.

The pattern of results found with BG is consistent with the Multiple Trace Theory (Nadel and Moscovitch, 1997). The prediction derived from this model was that there would be a deficit in autobiographical event recall across the lifetime. In contrast, the prediction derived from the Standard Consolidation Model (Squire and Alvarez 1995; Murre, 1996) was that there would be a temporal gradient in the autobiographical event retrograde deficit, but this was only found for semantic retrograde memory.

Guillery et al..'s (2000) patient showed a mixed pattern of performance, with impairment across the lifetime periods, and with evidence of a temporal gradient. Other studies, including those that used a Crovitz technique (Kritchevsky et al.., 1988; Hodges and Ward, 1989), also found that performance in TGA is impaired. Those memories that can be recalled are from earlier time periods. The finding of a temporal gradient suggests support for the Standard Consolidation Model, although the temporal extent of the gradient, with only the very oldest events being recalled in any detail, indicates that a consolidation hypothesis is unlikely to be the most parsimonious explanation. One hypothesis which could account for this pattern is that under normal circumstances the hippocampal system can be involved in the recollection of autobiographical memories, but some autobiographical event memories, particularly memories from early life, become 'semanticised' through repeated rehearsal. For these memories, it should be possible to recollect considerable detail without the hippocampal system. For less well-rehearsed memories the hippocampal system is always required. Furthermore, if the hippocampus is not involved in recall, the level of detail and perhaps also the phenomenological experience of recollection are likely to be different. This possibility is examined further in the following section.

## 2.3 Recall and recognition of retrograde autobiographical events in amnesia arising from temporal lobe and diencephalic pathology.

### 2.3.1 Introduction

Studies of retrograde memory often include tests of famous person or event knowledge. Such tests are used in recognition formats (i.e. selecting the famous event or face from fictitious or non-famous alternatives) and sometimes in recall formats (i.e. recalling the famous person's name, or describing a news event). Tests such as these were described in Section 2.1. Tests of autobiographical event memory have been used less often, though the Crovitz cued recall test and the AMI (Kopelman et al.., 1990) have proved popular. However, these autobiographical event tests do not have a 'recognition' component. They rely on the individual producing a personal event memory in response to either a cue word or to a question relating to a particular lifetime period. Some studies (e.g. Kitchener et al.., 1998) have used the technique of questioning patients about specific autobiographical events where information about events has been gained from a relative. However, this approach is subject to the same problem that exists with any Yes-No recognition task, that of a response bias. There are no published studies of retrograde autobiographical event memory in people with amnesia that have used a forced-choice recognition format. In order to understand the nature of deficits in memory for autobiographical events that may accompany particular lesions or pathologies, it is important that recognition memory for autobiographical events or episodes is examined. If a person fails to recollect events in free recall format, but can recognise the event as having occurred when presented with a description of that event by selecting it from distractor items, this has important implications for our understanding of the nature of the memory deficits seen in retrograde amnesia. In particular it provides evidence for the role of key brain structures in *retrieval*, as opposed to storage, of information.

At the outset it is necessary to consider what is meant by a 'recognition' format in relation to autobiographical events. Recognition formats typically involve re-exposure to a previously encountered stimulus with a request to identify whether the stimulus has been present previously, or to select a previously encountered stimulus from distractor items.

However, with autobiographical events it is usually impractical or impossible to re-create actual events in order to test recognition. Instead a verbal or pictorial description of events can be presented that the individual tries to recognise. A verbal event description is clearly not the same as re-encountering the original event, and it is likely that a significant amount of effortful processing is still required to recollect an event on the basis of a verbal description or a photograph. This issue will be addressed further in the discussion.

What predictions would be made by Multiple Trace Theory (Nadel and Moscovitch, 1997) and the Standard Consolidation Model (Squire and Alvarez, 1995; Murre, 1996) with regard to performance on autobiographical event recognition tasks? Although both make different predictions about the extent of the autobiographical event memory deficit that should arise from lesions of the hippocampal complex, proponents of these models have not made specific predictions about the performance of patients tested in a recognition as opposed to a recall format. However, in the case of lesions limited to the hippocampus, Multiple Trace Theory would presumably predict that if a recognition cue in the form of an event description is presented, such information may be sufficient to activate some neocortically based event memory fragments leading to the event being 'recognised', but the cue would not be sufficient to activate all of the event fragments since this would require the involvement of the hippocampus. In this situation an event would be recognised as having occurred, but that event could not be 're-experienced' or 'replayed' in mind. This would apply to autobiographical episode memories throughout an individual's lifetime. Nadel et al.. (2000) argue that, "what is lost in amnesia is not the gist of a memory, but its details no matter how old the memory is" (p. 362). The Standard Consolidation Model would predict a similar pattern for more recent, unconsolidated memories, but older memories events should be recollected in full since these should be entirely neocortically based.

Both models should make similar predictions about cases where there is neocortical involvement in addition to hippocampal damage. As the extent of the pathology increases, so the likelihood of events being recognised should diminish, since the more fundamental event fragments are likely to be increasingly disrupted.

One type of lesion that might be expected to result in a significant advantage of recognition over recall is a lesion of diencephalic structures and in particular the thalamus. Hodges and McCarthy's (1993) case PS suffered bilateral thalamic lesions and was left with severe anterograde amnesia. His retrograde amnesia was characterised by relative sparing of knowledge of famous people and public events, in the context of a severe impairment of personal event memory. Hodges and McCarthy interpreted PS's deficit in terms of an "inability to use the normal range of indexing procedures that are required for the retrieval of autobiographical memory" (p. 938). They used a cued recall procedure to test PS's memory for autobiographical events, whereby they gave him a cue (based on event descriptions from his wife) and asked him to try to recall the event. He produced virtually no correct details. However, they did not test PS using a recognition format. If a major role of the thalamus is, perhaps on account of its frontal lobe connections, concerned with the strategic search of autobiographical memory, and assuming most tasks of autobiographical recall require a degree of strategic search (Conway et al.., 1999), then thalamic lesions should cause a deficit in autobiographical memory recall across the lifetime. The provision of event details in the context of a forced choice recognition task should result in substantial improvement in performance. Furthermore, if hippocampal-neocortical links are intact, once key elements of an event have been activated, then it seems likely that the event would be retrieved in full, resulting in the ability to correctly identify target items.

Aggleton and Brown (1999) argued that the anterior thalamic nuclei form a coherent episodic memory system in conjunction with the hippocampus, fornix and mammillary bodies and that, "damage to different parts of this system produces similar memory impairments" (p. 426). If, as Nadel and Moscovitch (1997) argue, the hippocampal system is required for the retrieval of autobiographical event memories across the lifetime, and if Aggleton and Brown (1999) are correct, it follows that anterior thalamic lesions should disrupt retrieval of autobiographical event memories too. It would further follow that as for focal hippocampal lesions, performance would be impaired in a recall format, enhanced by a recognition format, but once again there would be an inability to replay events in mind. This would not follow, however, if the thalamic nuclei are viewed as necessary for the initial formation of links between the unimodal neocortical regions, but not required for subsequent retrieval. If this were true, there should be no deficit in either recall or recognition formats. None of the previous studies of retrograde memory functioning following selective thalamic lesions have investigated autobiographical memory using a recognition format.

The present study investigated autobiographical event memory performance in six people with either thalamic, hippocampal or more extensive temporal lobe lesions using recall and recognition formats. Patients were selected for inclusion in this study on the basis of having a severe impairment in anterograde memory in the context of lesions which were primarily limited to either thalamus, hippocampus or temporal lobes. Five of the patients were included on the basis of having demonstrated evidence of retrograde memory impairments on clinical tests of retrograde memory or in previous studies for this thesis. One patient (BW) had a lesion limited to the hippocampus and no apparent retrograde amnesia (see Section 2.1). She was included to provide a rigorous test of the prediction from Multiple Trace Theory that even when events are recognised, there should be an impairment in the ability to replay events in mind. As noted earlier, the distinction between recognising an event as having occurred, but not being able to mentally replay it, is similar to the 'remember-know' distinction that has been applied to anterograde recognition memory (Mandler, 1980; Gardiner and Richardson-Klavehn, 2000). This distinction has not previously been applied to retrograde memory. In this study, 'remember-know' methodology was applied for the first time to the recognition of retrograde autobiographical events.

### 2.3.2 Case histories

Data showing the performance of the six patients on general neuropsychological tests and tests of anterograde memory are presented in Tables 2.3.1 and 2.3.2. Brief case histories are provided below.

#### *2.3.2.1 BW*

BW was described in detail in Section 2.1.2.1, which includes an MRI scan of her brain. In brief, she was born in 1959. She was 41 years of age at the time of this study. Premorbidly she worked as a supervisor in a pharmacy. In 1991, she attempted suicide with carbon monoxide poisoning. As a result, she developed an amnesic syndrome. She has bilateral lesions of the hippocampus, more marked on the right and has some additional pathology in the globus pallidus. She shows preserved language, perceptual and executive functions.

#### *2.3.2.2 EA*

EA was described in detail in Section 2.1.2.3. She was born in 1950. She was 50 years of age at the time of this study. Pre-morbidly she worked as a typist and then gave up paid work to bring up her children. In 1984, she developed an acute illness that led her to being on a ventilator in a deeply unconscious state for a period of two days. When she regained consciousness she had developed a severe amnesic syndrome, which is presumed to have resulted from an hypoxic episode. The location of her brain lesion has not been identified definitively though it is assumed to be restricted to the medial temporal lobes. EA shows preserved language, perceptual and executive functioning.

#### *2.3.2.3 PR*

PR was described in detail in Section 2.1.2.4. He was born in 1971. He was 30 years of age at the time of this study. In 1995, he attempted suicide by carbon monoxide poisoning following the break up of his relationship with his girlfriend. He was left with an amnesic syndrome, with selective bilateral hippocampal damage. PR shows preserved language, perceptual and executive functioning.

### 2.3.2.4 *MW*

MW was born in 1931. He was 70 years of age at the time of this study. He was a Consultant Opthalmologist, having retired prior to the onset of his memory impairment. He had no history of neurological or psychiatric problems prior to his present difficulties. He had undergone successful coronary artery by-pass grafting in 1983, continuing to work afterwards. In March 2000, he suffered a stroke, the first symptoms of which were comprehension problems when doing a crossword puzzle, calling his daughter by the wrong name and a mild level of confusion. MW subsequently developed an amnesic syndrome. MW lives at home with his wife, upon whom he depends to remind him about things he has to do. MW showed intact language and perceptual functioning. There was an indication of difficulties on some tests considered sensitive to executive dysfunction (e.g. Verbal Fluency and Hayling Test). Some of this poor performance could be accounted for by a more general slow speed of responses, though the possibility of verbal retrieval or strategy application difficulties cannot be ruled out.

An MRI scan (see Figure 2.3.1) showed a lesion that extended across both anterior and dorso-medial portions of the left thalamus and was considered to be haemorrhagic in origin. There were also smaller haemorrhagic lesions in the basal ganglia, and corpus callosum.

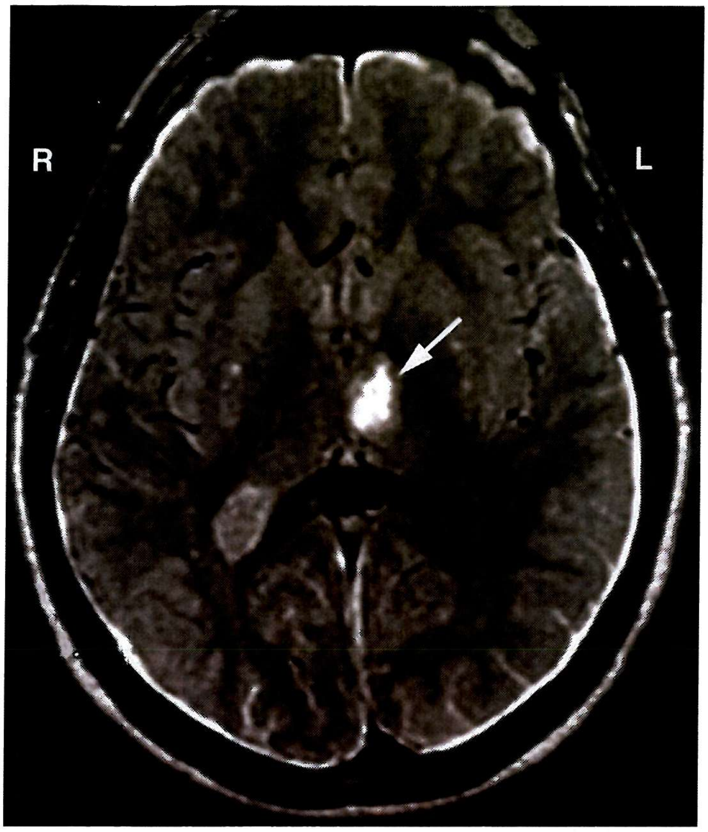



***Figure 2.3.1: Axial MRI scan of MW's brain showing the left thalamic lesion.***

*2.3.2.5 CW*

CW was described in detail by Wilson, Baddeley and Kapur (1995). He was born in 1939. He was 61 years of age at the time of this study. At the time of becoming ill in 1985, he was a gifted musical scholar and one of the world's leading authorities on Renaissance music. At the age of 46, he developed a flu-like illness. He was admitted to hospital and was in coma for 16 days. He had one grand mal seizure while in coma. He was diagnosed with viral encephalitis resulting from Herpes Simplex infection. The most striking problem for CW is his extremely severe anterograde amnesia. He lives in a permanent state of feeling he has just woken up, having not having seen, heard or tasted anything for a lengthy period. An MRI scan carried out in 1991 showed marked bilateral abnormality in hippocampus, amygdala, substantia innominata and mammillary bodies, the left fornix, both temporal poles, the left inferior temporal gyrus, the anterior portion of the left middle temporal gyrus, the anterior portion of the left superior temporal gyrus and the left insula. Mild abnormality was also reported in the posterior portion of the left middle temporal gyrus, the left medial frontal cortex, the left striatum, the right insula, the right fornix, and the anterior portion of the right inferior temporal gyrus. Apart from extremely severe anterograde amnesia, CW showed evidence of relatively intact basic perceptual processing, but significant deficits in both verbal and non-verbal semantics.

#### *2.3.2.6 JN*

JN was born in 1945. She was 55 years of age at the time of this study. She left school at the age of 16. She trained as a corsetière, working in a department store. She had also worked as a cleaner and a waitress. She is married with two children. In 1992, she suffered viral encephalitis as a result of herpes simplex infection. She developed a marked amnesic syndrome. She has been unable to work in paid employment since her illness, though helps at a local hospital serving teas. JN showed well preserved non-verbal abilities, but there was a weakness in verbal functioning compared to pre-morbid levels. There was evidence of word finding impairment on naming tests (on which she produced some semantic paraphasias). Although her performance on a verbal fluency task was low it was not significantly below the level predicted by Crawford, Moore and Cameron's (1992) NART based regression equations. However, it is likely that her score on the NART is somewhat impaired. An estimate of her pre-morbid IQ using Crawford et al..'s (1989) regression equation that uses age, socio-economic status and level of education produced a value of 25.3 errors, suggesting that her obtained score may be an underestimate of pre-morbid ability. She presented with normal spontaneous speech in general conversation.

An MRI scan (see Figure 2.3.2) showed pathology that included major abnormality to right hippocampus, and milder left hippocampal damage. In addition, she had bilateral lesions to the parahippocampal and entorhinal cortices, right temporal pole, inferior and middle temporal gyri, with milder damage to left temporal pole, and to inferior and middle temporal gyri. Superior temporal gyri on both sides were intact, along with diencephalic structures, frontal cortex, parietal cortex and occipital cortex.

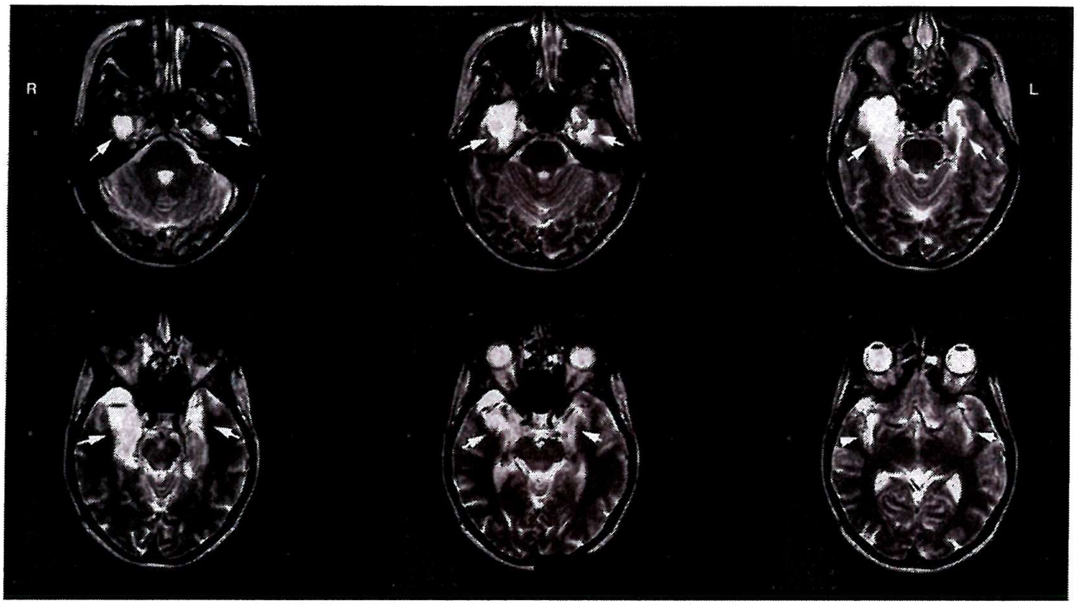



***Figure 2.3.2 MRI scan of JN's brain showing six horizontal slices through the temporal lobes showing lateral temporal lobe damage (see text for further details).***

*Table 2.3.1 Performance of the six patients on tests of general cognitive functioning*

| Test | BW | EA | PR | MW | CW | JN |
|---|---|---|---|---|---|---|
| **NART Predicted pre-morbid IQ (Errors)** | 106 (20) | 107 (19) | 121 (8)) | 126 (4) | 122 (7)) | 89 (34) |
| **WAIS-R:** | | | (WAIS III) | | | |
| Full Scale IQ | 103 | 104 | 118 | 119 | 97 | 86 |
| Verbal IQ | 99 | 97 | 119 | 122 | 92 | 82 |
| Performance IQ | 112 | 116 | 113 | 111 | 105 | 93 |
| Information | 9 | 10 | 12 | 15 | 8 | 4 |
| Digit Span | 10 | 9 | 16 | 14 | 8 | 7 |
| Vocabulary | 9 | 10 | 14 | - | 12 | 5 |
| Arithmetic | 7 | 9 | 12 | 13 | 6 | 8 |
| Comprehension | 12 | 11 | 12 | - | 9 | 8 |
| Similarities | 13 | 11 | 13 | 14 | 12 | 6 |
| Picture Completion | 10 | 12 | 14 | - | 11 | 8 |
| Picture Arrangement | 16 | 15 | 11 | 13 | 10 | 9 |
| Block Design | 11 | 12 | 13 | 15 | 15 | 8 |
| Object Assembly | 12 | 10 | - | - | 8 | 7 |
| Digit Symbol | 8 | 10 | 7 | 11 | 12 | 6 |
| **Verbal Fluency** | | | | | | |
| Letters FAS (60s, Total) | 38 | 43 | 37 | 22* | 27* | 24* |
| **Modified Wisconsin Card Sorting Test (Nelson version)** | | | | | | |
| Categories | 5 | 6 | 6 | 6 | 6 | 4 |
| Total Errors | 17 | 5 | - | - | 0 | 19 |
| Total perseverative errors | 3 | 4 | - | - | 0 | 3 |
| **Behavioural Assessment of the Dysexecutive Syndrome** | | | | | | |
| Age corrected Standardised Profile score | 97 | 102 | 91 | - | - | - |
| **Hayling Test** | | | | | | |
| Overall Scaled Score | - | - | - | 1* | - | - |
| **Brixton Spatial Anticipation Test** | | | | | | |
| Scaled score | - | - | - | 7 | - | - |
| **McKenna Graded Naming Test** (total/30) | 20 | 22 | 21 | 27 | 2* | 1* |

*Impaired

*Table 2.3.2 Performance of the six patients on standardised tests of anterograde memory*

| | BW | EA | PR | MW | CW | JN |
|---|---|---|---|---|---|---|
| **Rivermead Behavioural Memory Test** | | | | | | |
| Standardised Profile Score (Max. = 24) | 7 | 6 | 0 | - | 0 | 5 |
| **WMS-R** | | | | | | |
| Visual | 66 | 54 | - | | <50 | 68 |
| Verbal | 66 | 57 | - | | <50 | 78 |
| General Memory | 57 | <50 | - | | <50 | 64 |
| Delayed | <50 | <50 | - | | <50 | 50 |
| Attention and Concentration | 95 | 93 | - | | 105 | 78 |
| Logical Memory Immediate (Percentile) | 3rd | 1st | - | (AMIPB) <10th | <1st | 2nd |
| Logical Memory Delayed (Percentile) | 1st | 0 | - | (AMIPB) <5th | 0 | 2nd |
| Visual Reproduction Immediate (Percentile) | 11th | 6th | - | (AMIPB) <10th | 4th | 19th |
| Visual Reproduction Delayed (Percentile) | 1st | 0 | - | (AMIPB) <5th | 0 | 1st |
| **WMS III (Age scaled scores)** | | | | | | |
| Logical Memory I | - | - | 6 | - | - | - |
| Logical Memory II | - | - | 1 | - | - | - |
| Family Pictures I | - | - | 1 | - | - | - |
| Family Pictures II | - | - | 2 | - | - | - |
| Faces I | - | - | 7 | - | - | - |
| Faces II | - | - | 10 | - | - | - |
| Verbal Paired Associates I | - | - | 4 | - | - | - |
| Verbal Paired Associates II | - | - | 4 | - | - | - |
| **Warrington Recognition Memory Test (Age scaled scores)** | | | | | | |
| Words | <3 | 5 | 5 | <3 | 0 (no recognition | 4 |
| Faces | 12 | 9 | 11 | 5 | 0 (no recognition | <3 |
| **Doors and People (Age scaled scores)** | | | | | | |
| Doors | 4 | 4 | - | - | - | 3 |
| Names | 5 | 1 | - | - | - | 5 |

### 2.3.3 Standard retrograde memory tests

Five of the six cases described were shown to have significant impairments in retrograde memory on a range of standard tests. As can be seen from Table 2.3.3, there was significant variation between them as to the pattern of impairment, reflected by scores on the AMI (Kopelman et al., 1990). A brief summary of data relating to retrograde memory for each case is given below.

#### *2.3.3.1 BW (Carbon monoxide poisoning leading to bilateral hippocampal lesions)*

For BW there was little evidence of retrograde memory impairment on any of the standardised tests. She was included in this study in order to examine the extent to which she could recollect specific incidents produced by her husband as a further assessment of retrograde memory. Furthermore, the study also provided an opportunity to test her level of confidence in her recollections and the extent to which she can replay events in mind.

#### *2.3.3.2 EA (Presumed anoxic event leading to bilateral medial temporal lobe lesions)*

On the AMI, EA had good knowledge of premorbid personal semantic information, but was impaired in her ability to recollect autobiographical incidents. As discussed in Section 2.1.4.2, she was unable to do the Modified Crovitz task, reporting that she found it impossible to produce specific incidents in relation to word cues. She was also impaired in her ability to recognise and provide information about famous public events from the five years prior to the onset of her amnesia. On this type of task, EA always made the point that she finds it impossible to recollect memories of events unless a specific event is prompted. When this happens, she says she feels much more confident in her ability to recollect that an event happened.

#### *2.3.3.3 PR (Carbon monoxide poisoning leading to bilateral hippocampal lesions)*

On the AMI, PR showed a good performance for all periods for Personal Semantics items. On the Autobiographical Incidents section there were some examples of recollections being less detailed than might have been expected, and his score for the early adult period was 'borderline'. On the Modified Crovitz task described in Section

2.1.4.2, he had been able to produce some incidents from his life, but the overall level of detail he was able to provide was rated as significantly less than that provided by matched controls.

***2.3.3.4 MW** (Cerebro-vascular accident leading to left anterior and left dorsomedial thalamic lesions)*

As Table 2.3.3 shows, MW was severely impaired in his ability to recollect autobiographical incidents on the AMI. An attempt was made to carry out the modified Crovitz tasks but this was abandoned since, like EA, he reported that he was unable to recollect events in response to cue words. He was also assessed on the News Events Test as described in Section 2.1.4.4, including 85 events from 1979-1999. His performance was contrasted with data from 12 control participants (MW's age = 69 years; mean age of controls 69.3 years s.d. 10.25; MW's NART error score = 4; mean for controls = 5.8, s.d. 2.94). Using Crawford and Howell's (1998) modified t-test for small samples, MW was borderline impaired for recognition ($t=-1.92$, $df=11$, $p=0.081$) and impaired for recall of event details ($t=-3.22$, $df=11$, $p=0.008$).

***2.3.3.5 CW** (Herpes Simplex Encephalitis leading to extensive temporal lobe lesions)*

CW showed significant impairment on the AMI for both personal semantic and autobiographical incidents, as reported by Wilson et al. (1995). He was also reported by Wilson et al. to be impaired on a test involving estimating the current price of common objects and on a modified version of the Dead-or-Alive test. On this test he could provide information for only 1/20 famous personalities. The one personality about whom he could provide some information was Elvis Presley. He failed to recognise John Lennon, John F Kennedy, Lee Harvey Oswald and said that he had vaguely heard of Margaret Thatcher, Mohammed Ali and Cliff Richard, but could not say anything about them. CW was also shown photographs of Cambridge, where he had spent four years as a student. He identified only one photograph, that of Kings College Chapel, considered to be one of the most distinctive landmarks in Cambridge.

*Table 2.3.3 Results from the Autobiographical Memory Interview*

| | BW | EA | PR | MW | CW | JN |
|---|---|---|---|---|---|---|
| *Personal Semantic* | | | | | | |
| Childhood | 21 | 19 | 21 | 20.5 | 11*** | 12** |
| Early Adult Life | 20 | 21 | 21 | 18 | 6*** | 14*** |
| Recent Life | 21 | 10** | 21 | 7/18*** | 1*** | 17*** |
| *Autobiographical Incidents* | | | | | | |
| Childhood | 9 | 0*** | 7 | 2*** | 3*** | 0*** |
| Early Adult Life | 8 | 3*** | 6* | 3*** | 1*** | 0*** |
| Recent | 2** | 0*** | 7 | 0*** | 0*** | 1*** |

*Borderline **Probably Abnormal ***Definitely Abnormal

***2.3.3.6 JN** (Herpes Simplex Encephalitis leading to bilateral medial, and more lateral temporal lobe damage)*

JN showed significant impairment on both the personal semantic and autobiographical incidents components of the AMI. Like EA and MW, JN was unable to produce memories of events in response to cue words in the modified Crovitz test. JN was also given the News Events test, in the format described in Section 2.1.4.4, which included events from the premorbid period 1979-1991. Her performance was compared with five control subjects matched for age (JN's age at time of testing = 55 years, mean age of controls = 55.2 years, s.d. 1.8), years of education (JN= 11 years; mean for controls = 10.6 years, s.d. 0.55 ) and media exposure (JN's Media Exposure score = 63, mean media exposure for controls = 61.2, s.d. 12.24). JN was not matched on the NART with the controls (mean errors for controls 24.6, s.d 5.3) as there was some concern that her obtained NART score was probably an underestimate of her pre-morbid ability. She was however well matched with the controls on the estimated NART score (25.3 errors) derived from Crăwford et al.'s (1990) regression equation. Using a z-score transformation based on the difference between JN's score and the mean of the controls as a proportion of the standard deviation of the controls, JN's score for recognition was z=- 4.57 and for recall of details z=- 3.77. These scores both represent severe impairment for both recognition and recall of details. JN was also given a similar, updated version of the Dead-or-Alive test described earlier in Section 2.1.4.3. The test consists of 130 names of people, 79 of whom are famous, with 51 distractor names (see Appendix 1). Of the famous people, 9 died in the 60's, 11 died in the 70's, 11 died in the 80's, 15 died in the 90's and a further 33 are still alive. Data are presented here relating the personalities who died in the 60's, 70's and 80's. Data on those personalities who died in the post-illness period are presented later in Chapter 4, Section 4.1.5.4. JN's performance was compared to that of the same five control participants who were given the News Events Test. Participants were presented with each name on a card. They were asked to read the name (and were corrected if the name was read incorrectly). As with the test version described earlier, they were asked if the name was familiar and, if so, to identify the personality, whether the person is dead or alive and if dead, how and when they died. In this version of the test they were asked for some additional information (level of familiarity, whether the person had any particular personal significance, whether they were British or foreign and a brief description of the physical appearance of the individual). This additional data will not be presented here. The scoring system for measures of Familiarity, Information and Details of death were the same as for the version described above in Section 2.1.4.3. Table 2.3.4 presents a summary of the data. Scores are z-scores based on the difference between JN's score and the mean of the control participants as a proportion of the standard deviation of the control participants. The table shows that JN was severely impaired on this test for all decades. There was an indication of a mild temporal gradient in her performance, with her scores for the 60's being marginally better than the 70's or 80's.

***Table 2.3.4 JN's performance on the Dead-or-Alive test. Scores are z-scores based on the difference between JN's score and the mean of five matched control participants as a proportion of the standard deviation of the control participants.***

| | **1960's** | **1970's** | **1980's** |
|---|---|---|---|
| **Familiarity** | 7/9* | -10.67 | -4.91 |
| **Information** | -2.9 | -5.61 | -4.82 |
| **Details of death** | -1.86 | -3.60 | -3.33 |

* A z-score could not be computed as control participants achieved a ceiling score of 9/9, with a standard deviation of 0. JN's raw score was 7/9.

### 2.3.4 Autobiographical Events Test

An individually-tailored autobiographical events test was constructed for each participant. Autobiographical event information was obtained from relatives. In the cases of BW, EA and JN, the informant was the patient's husband. For PR, the informants were his parents. For MW, the informant was his wife. In the case of CW, the informants were his sister and his wife. Event information was collected that covered the whole period for which the informants had known the patient. Informants were given a set of cue words as a means of helping them to recollect events (Holiday, House, Car, Birth, Wedding, Death, Job, Accident, Hospital, Pets, Sport, Children). They were asked to try to recollect events that they would have expected the patient to recall (under normal circumstances), without necessarily only referring to highly rehearsed 'family stories'. For some of the patients, events were collected for both pre- and post-morbid periods, but for the purposes of this study, only data relating to the pre-morbid period are presented. Data relating to the post-morbid period for cases BW and JN are presented in a separate study in Chapter 4, Section 4.1.5.3. The majority of the events provided were distinctive 'one-off' events. A few referred to extended episodes, such as reference to events that happened several times on a holiday, or working in a particular place for a short time or living in a particular place for a short period. There was some variation in the number of events that informants were able to generate. BW was tested on 21 pre-morbid events, EA on 13 events, PR on 25 events, MW on 23 events, JN on 32 events and CW on 23 events. A recall task was constructed for each patient using cues that comprised partial information about the events provided. The patient was asked to recall as much about the event as possible. Recollections were scored using a three point scale (0 = no recollection; 1 = partial recollection, but lacking significant detail provided by the spouse; 2 = detailed recollection, including most of the detail provided by the spouse). The recall task was constructed in such a way that any information which was provided by a cue for an event would not be sufficient to prompt recognition on the recognition task. The recognition task involved a description of the target event together with two fictitious, but plausible events. For reasons of confidentiality, the tests are not reproduced in full in this thesis. However sample items that relate to each case are included in Appendix 3. The number of bits of information provided were not significantly different for target and distractor events. For each response on the recognition task, the patients were asked to say whether they were certain the event was true (CERTAIN), whether they thought the event was true, but were not completely sure (THINK), or whether they were guessing (GUESS). For events that they were certain were true or thought were true, they were also asked whether they 'remembered' the event (which was defined as the ability to replay the event in mind) or whether they simply 'knew' the event to be correct, without being able to replay the experience in mind. For each participant, the cued recall task was presented first. This was always followed by a short break, after which the recognition task was presented.

An assumption was made that the events produced by the informants should have been remembered by the patients, under normal circumstances. However, by way of a check on this assumption, Autobiographical Event Tests were also constructed for three control participants in the same way as for the patients. The three control participants were female and were aged, 39, 53 and 57. In each case the participant's husband was the informant. Once again information was collected across the whole period that the control participant had known their spouse. Since there is no formal anterograde/retrograde distinction for the control participants, data for the whole period are provided below so as to indicate the general performance of the controls, which turned out to be near to a ceiling level.

***Results***

Data for the recall and recognition tasks are shown in Figures 2.3.3 and 2.3.4. In the case of CW, the test was abandoned after 4 items as he indicated that he could not remember any of the items and refused to guess. The figures show that five of the six patients showed a better performance in the recognition task than the recall task. For the group of five this was statistically significant ($t = 3.539$; df 4; $p = 0.02$). CW's data were excluded from this analysis because in his case the recognition test was abandoned after four items (see below for details).

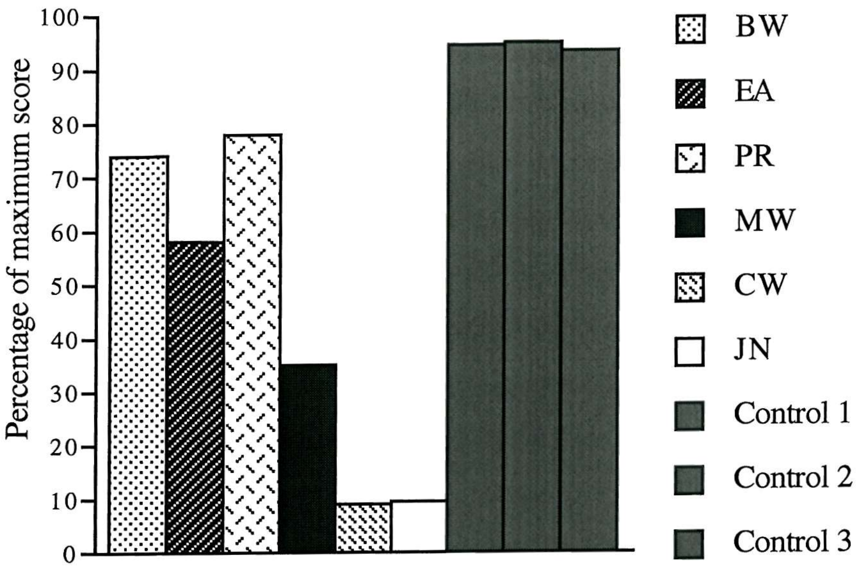



***Figure 2.3.3. Performance of the six amnesic patients and three control participants on the recall component of the Autobiographical Event Test***

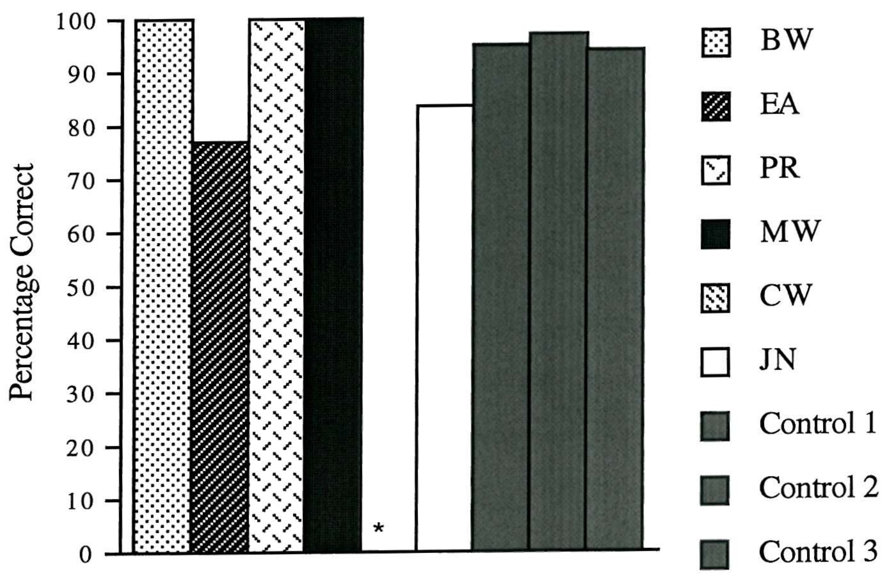



***Figure 2.3.4. Performance of the six amnesic patients and three control participants on the recognition component of the Autobiographical Events Test. *The test was abandoned after 4 items as CW indicated that he could not remember any of the items and refused to guess.***

Data on confidence and recollective awareness of responses are provided in Figures 2.3.5 and 2.3.6 respectively.

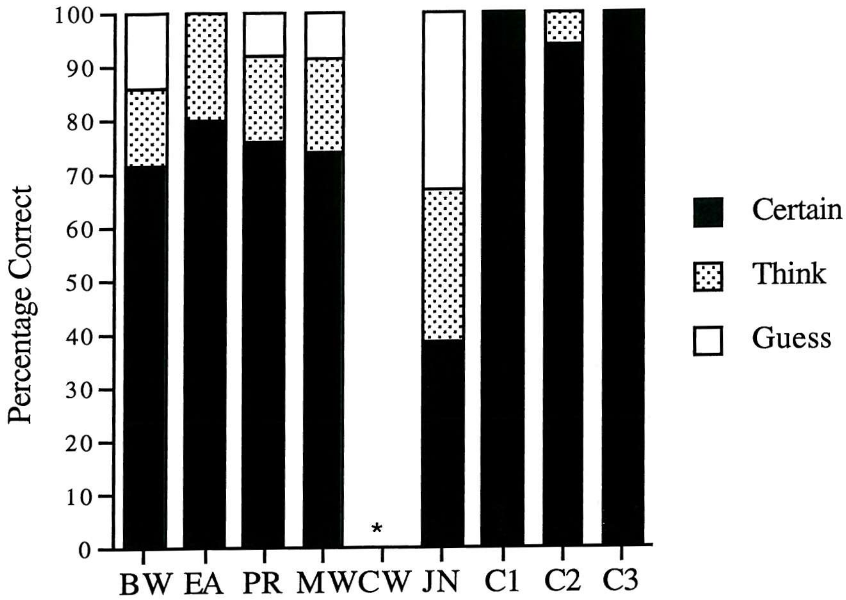



***Figure 2.3.5 Percentage of responses of each type (Guess/Think/Certain) for the items correctly identified as true events by the six patients and three control participants on the recognition component of the Autobiographical Events Test. *No data were available from CW.***

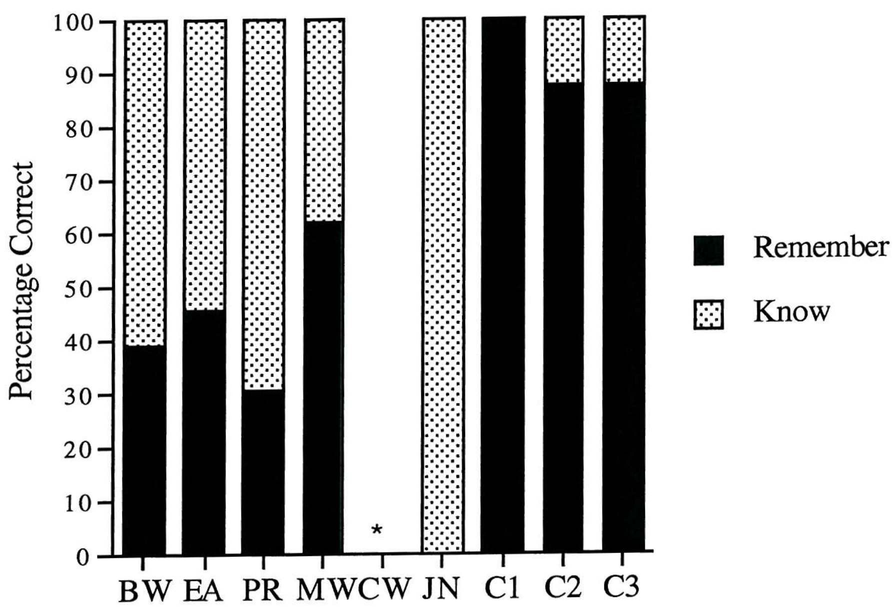



***Figure 2.3.6 Percentage of responses of each type (Remember/Know) for the items correctly identified as true events (excluding items to which the response was "Guess") by the six patients and the three control participants on the autobiographical recognition task. *No data were available from CW.***

A brief summary of the performance of each patient follows.

***BW (Carbon monoxide poisoning leading to bilateral hippocampal lesions)***

BW's performance on the recall task was somewhat below the near ceiling performance of the control participants, but was in line with all the previous tests of retrograde memory, in that her performance was clearly relatively good. Furthermore, on the recognition task her performance was perfect. However, as can be seen from Figures 2.3.5 and 2.3.6 she demonstrated a greater degree of lack of confidence in her recollections than controls. Rather strikingly, she reported that for a large percentage of the items she knew the event had happened, but found it difficult to replay the event in mind.

***EA (Presumed anoxic event leading to bilateral medial temporal lobe lesions)***

EA's performance for the cued recall format was poor in comparison to that of the controls. She was able to produce some information in response to cue questions about events, but there was a general trend of not being able to produce additional event details once prompted by a cue. It was as if the cue enabled her to either access some abstract knowledge that an event had happened or to access a discrete event element. However, she was not able to use an event-element cue to trigger other event elements. Like BW, she produced a large proportion of 'know' responses.

***PR (Carbon monoxide poisoning leading to bilateral hippocampal lesions)***

PR's performance was very similar to that of BW and EA. He performed relatively well on the recall task, though was a little below the performance of the controls. He performed perfectly on the recognition task. However, he also reported a greater lack of confidence in his memories than control participants and also made a high percentage of 'know', rather than 'remember' responses.

***MW (Cerebro-vascular accident leading to left anterior and left dorsomedial thalamic lesions)***

On the recall task, MW's performance was considerably below that of the control participants and that of the three patients with lesions primarily confined to the hippocampus. However he performed much better on recognition than on recall testing. He was also a little less confident than control participants in his responses, though still reporting that he was 'certain' for over 75% of events. With regard to the ability to replay events in mind, his performance was at a higher level than either BW, EA or PR, though still lower than that of control participants.

***CW (Herpes Simplex Encephalitis leading to extensive temporal lobe lesions)***

For CW, the recall test was administered, but the recognition test was abandoned after a limited number of items had been administered. CW responded that he did not recognise any of the events and refused to select an item, being unwilling to guess. On the recall task, he gave some partial information in response to two items and offered correct information in response to one item, but for the other 20 items he responded that he could not remember any information.

***JN (Herpes Simplex Encephalitis leading to bilateral medial, and more lateral temporal lobe damage)***

Figure 2.3.4 shows that, compared to her recall scores, JN's performance improved considerably when tested using the recognition format. However, it is worth noting that, for 13 of the 21 items which she correctly identified she reported that she had been told the information over the time period since she became amnesic. Figure 2.3.5 also shows that she reported that she was guessing for a third of the items she correctly identified. She was only certain of her answer for 38.1% of the items she correctly selected. She also reported that she did not 'remember' any of the events, but rather knew they had happened, primarily as a result of having been told the information.

Further data analysis was undertaken to investigate whether there was an effect of the age of the events on the probability of being given a rating of remember or know. For BW, EA, PR and MW, the events were split into early and late halves of the pre-morbid period. This resulted in approximately similar numbers of events in both early and late pre-morbid periods for each person. Table 2.3.5 shows the data and results of Chi Squared analysis. This indicates that there was no significant effect of time period on the probability of remember or know responses for any of the cases, though MW's data do show a trend towards a temporal gradient in the probability of remembering events, with more 'remember' responses for earlier events. JN was not included in this analysis since she only gave 'Know' responses.

***Table 2.3.5 Number of 'Remember' and 'Know' responses in the early and late pre-morbid period. Note that the early pre-morbid period refers to older events and late pre-morbid refers to events closer in time to the onset of amnesia.***

| | Remember | Know | |
|---|---|---|---|
| **BW** | | | |
| Early pre-morbid | 4 | 4 | Chi Squared = .748 |
| Late pre-morbid | 3 | 7 | p = .388 |
| **EA** | | | |
| Early pre-morbid | 3 | 4 | Chi Squared = .052 |
| Late pre-morbid | 2 | 2 | p = .819 |
| **PR** | | | |
| Early pre-morbid | 4 | 7 | Chi Squared = .350 |
| Late pre-morbid | 3 | 9 | p = .554 |
| **MW** | | | |
| Early pre-morbid | 8 | 2 | Chi Squared = 2.65 |
| Late pre-morbid | 2 | 6 | p = .104 |

### 2.3.5 Discussion

Five of the six amnesic patients completed both parts of the autobiographical events study in both recall and recognition formats. All five showed better performance when tested using a recognition rather than recall format. Control participants performed close to ceiling levels in both conditions. For the three participants with amnesia arising from hippocampal lesions (BW, EA and PR) and the participant whose amnesia arose from a thalamic lesion (MW), confidence ratings for event recall were relatively high, though below that of the three controls. For JN, who has more extensive temporal lobe lesions, her confidence ratings were low, such that she reported that she was guessing for around a third of the events she was able to correctly identify. The main reason for JN's uncertainty appeared to be that she was relying on remembering what she had been told about events since the onset of her illness rather than having any recollection of the events per se. This was reflected in her event-memory ratings on which she indicated that she could not 'remember' any of the events and only knew them to be true as she had been told about them. The three people with hippocampal lesions reported feelings of 'remembering' only 30-40% of events and MW, who has a thalamic lesion, reported 'remembering' about 60% of events.

The finding of better recognition than recall performance for five of the six patients suggests that the difficulty in recollecting autobiographical events could be conceptualised as a retrieval deficit. However, as Hodges and McCarthy (1993) noted, "simply categorising this retrograde disorder as a retrieval problem fails in capturing its characteristics at a cognitive/behavioural level" (p. 935). For example in the case of JN, in order to perform the task, she was relying on remembering what she had been told about events in her life since the onset of her illness. As such, the task became an anterograde memory test and the enhancement from recall to recognition testing could be considered to be in the anterograde rather than retrograde domain. In her case, the recognition items triggered very little event-specific information. Similarly CW, who has an even more extensive temporal lobe lesion, failed to recognise any of the limited number of items that were shown to him.

As noted in the introduction, BW was included in this study to provide a conservative test of the prediction from Multiple Trace Theory that even when events are recognised, there should be an impairment in the ability to replay events in mind. Previous investigations of BW's retrograde memory functioning using the modified Crovitz task described in Section 2.1 had failed to show any evidence of impairment. Her less than optimal performance on the recall task used in this study was the first indication that her retrograde memory was not completely intact. However, the most striking finding for BW was her rating that, whilst she knew the majority of events had occurred, she could not replay many of them in mind. Analysis indicated that this applied across the time span of events provided by her husband. It also applied to the other two patients with lesions presumed to be limited to the hippocampus, EA and PR. A common response amongst all three of these participants was that they could recognise as familiar key details provided in the target recognition items, but could not then recollect other event-specific information. This result could be said to be more compatible with Multiple Trace theory and is contrary to predictions derived from the Standard Consolidation Model. This novel application of the Remember/Know distinction was useful and did seem to capture a feature of the phenomenological experience of the patients not reflected in other tests. However a degree of caution is perhaps necessary in interpreting this finding. One potential caveat is that the experience of anterograde memory impairment, which involves not being able to remember event details, may have biased the patients towards a more cautious response style with regard to the experience of remembering pre-morbid events, so underestimating the number of 'remembered' events. On the other hand, it might be argued that the severe difficulty in remembering anterograde event details ought to make the ability to remember pre-morbid event details stand out and if anything bias a response towards 'remember' for these events.

Nevertheless, there does seem to be support for the assertion that amnesia arising from lesions to the hippocampus results in a failure to recall the details of events, but that more general information is retained. The possibility that even limited hippocampal lesions will have some impact on the ability to produce detailed autobiographical event memories raises the issue of how this ability should be assessed. It is a reasonable argument that some tests traditionally used to assess retrograde memory are likely to be insensitive to this subtle level of impairment. Many studies in the past have only included tests of famous face identification or event recognition which is clearly inadequate. Even tests such as the AMI (Kopleman et al., 1990) are likely be insensitive to this impairment, as was shown in the present studies, since the relatively small number of events solicited from each lifetime period may result in the production of event memories that do contain a lot of event detail, but which fall into the category of memories that have been over-rehearsed and are more like 'stories' than true recollections of events. However, there is an obvious danger in arguing that a failure to find an autobiographical memory deficit simply reflects the insensitivity of the assessment method. There is, therefore, a need to define the assessment methods, and specific tools, that should be sensitive to the type of deficit predicted to follow from selective hippocampal lesions. The use of scoring systems with more extensive gradations in scale, such as the one used with the modified Crovitz task here (Graham and Hodges, 1997), or the method of counting details provided (Nadel et al., 2000), are examples of possible methodologies, but this requires further research.

MW's pattern of performance was significantly different from the people with hippocampal complex lesions. He was much more impaired on the recall task, but showed a higher rate of 'remembered' memories than the three patients with lesions that involved the hippocampus. His performance was consistent with Hodges and McCarthy's (1993) view that the thalamus plays a role in the strategic retrieval of autobiographical event details. This role may be in the form of the link between frontal regions that initiate and direct strategic search mechanisms and medial temporal lobe systems that provide the access to event details. When the hippocampus, perihippocampal and neocortical regions are intact, as they appeared to be in MW, an event specific recognition cue will allow memories of that event to be accessed directly without need for strategic search mechanisms. MW recognised all of the events and the number of memories that he reported to 'remember' was higher than any of the amnesic patients with hippocampal lesions, although his performance was below that of the three controls. One possible explanation for this latter finding is that while some recognition cues are sufficient to trigger a complete set of event elements leading to the remembering of an event, some cues do not automatically trigger enough event features to cause an event to be remembered.

One conceptual framework that appears to be well placed to explain the findings from this study is the notion of a series of hierarchically organised convergence zones (Damasio, 1989; Mesulam, 1998), beginning with the lowest level in primary sensory cortex. According to this view the hippocampus acts as the highest level of convergence zone, linking all the elements that form an episode or event memory. Over time, event memories are 'consolidated' in extra-hippocampal medial temporal lobe regions and some of these memories retain links with the hippocampus. For those memories that retain hippocampal involvement, recollection leads to the phenomenological experience of being able to 'replay' the event in mind. For certain events, however, the hippocampal link is not maintained and while these events can be recollected in some detail, there is a loss of contextual detail (e.g. temporal or spatial information). Such events are those that are typically described as 'semanticised'. In the case of selective hippocampal lesions, there will be a loss of the ability to remember events in detail, but with more extensive medial temporal lobe damage (such as in the case of JN and CW) there will be greater impairment in the ability to recollect events. The application of this model as a unifying conceptual framework is discussed further in Chapter 5.

The three sets of studies presented in Chapter 2 have examined the nature of retrograde memory deficits that occur in the context of severe anterograde amnesia. In the following chapter, retrograde memory deficits occurring in the context of intact anterograde memory are investigated. Through the detailed investigation of two cases, the question of whether episodic and semantic retrograde amnesia can be dissociated is addressed. Data from the two cases is also used to provide a further test of the explanatory power of various contemporary models of memory.

# Chapter 3 Selective episodic and semantic retrograde amnesia.

**General Introduction**

As discussed in Chapter 1, this chapter focuses on selective impairments of retrograde memory impairment and addresses two issues; (1) under what circumstances does extensive retrograde amnesia occur in the absence of significant anterograde amnesia and (2) is it valid to suggest that episodic retrograde memory dissociates from semantic retrograde memory amnesia (Kapur, 1999; Wheeler and McMillan, 2001)? The phenomenon of focal retrograde amnesia remains controversial (Kopelman, 2000; and Kapur, 2000; see also Chapter 1, Section 1.3.3). Section 3.1 describes the case of patient JM, who presented following recovery from cerebral vasculitis with a marked impairment in the ability to recollect pre-morbid autobiographical events in the context of normal anterograde memory functioning. Section 3.2 will describe investigations with patient VH, who presented with a selective though progressive loss of knowledge of people, with relative preservation of autobiographical memories. The extent to which contemporary models of memory can account for the patterns of impairment demonstrated by these two cases is examined.

## 3.1 Selective episodic retrograde amnesia

### 3.1.1 Introduction

As has been noted by others (Kopelman 2000), many of the previously reported cases of focal retrograde amnesia (FRA) have presented with *some* anterograde amnesia in the context of retrograde amnesia. It still therefore needs to be established whether a severe retrograde amnesia can exist with no measurable anterograde amnesia being present. Furthermore, comparisons between anterograde and retrograde memory performance have typically used different testing formats and materials, typically contrasting retrograde memory for events (personal or public) with anterograde memory performance on standardised memory tests. There have been few attempts to compare 'like with like', contrasting memory for personal or public events in both retrograde and anterograde time periods, something that has been advocated by researchers in the field (Kopelman, 2000, Kapur, 2000).

Moscovitch and Nadel (1999, p89) noted that the existence of FRA is consistent with Multiple Trace Theory, at least for cases where there is neocortical damage resulting in loss of perceptual components of autobiographical recall (e.g. Ogden's, 1993 case). However, they also predicted that there will be anterograde deficits when trying to acquire material that is dependent upon the perceptual system that is damaged (e.g. visual memory impairment). The Standard Consolidation Model as formulated by Murre (1996), predicted that FRA will exist where there is an initial dense, but short-lived anterograde amnesia as a result of a temporary disruption to the medial temporal lobe system. The resulting retrograde amnesia will be time limited, producing a temporal gradient, except in the situation where there are very widespread diffuse lesions followed by a period of recovery. Robertson and Murre (1999) argued that recovery or repair after widespread damage will lead to the development of a great number of 'faulty connections' so that the system regains plasticity at the expense of its existing memories.

This section describes the case of patient JM, who presented with FRA following recovery from cerebral vasculitis. The Section is split into two sets of studies with JM. The first set of studies was undertaken in the relatively early period (1-2 years) following her illness and the second set of studies was undertaken somewhat later (6 years post-onset). The first study established the profile of her memory disorder. The second study established the longer-term status of her disorder. It also examined her ability to retain new autobiographical memories over an extended period of time as well as exploring in more detail her performance on tests of semantic retrograde amnesia (famous people and events).

### 3.1.2 Case history

JM is a right-handed woman, who was born in 1930. She is a retired university administrator with degrees in Law and English. She was admitted to Addenbrookes Hospital in Cambridge with an acute onset confusional state, accompanied by a change in personality and behaviour. Shortly after admission she was noted to have a seizure. All routine investigations including EEG, CT and CSF examination were normal. A combination of raised anti-neutrophil cytoplasmic antibody (ANCA) level, an abnormal uptake of labelled white blood cells into the brain and lungs, and a mildly abnormal cerebral angiogram, demonstrating 'beading' of small intracerebral arteries, led to a diagnosis of primary cerebral (granulomatous) vasculitis. Other markers of peripheral vasculitis/collagen vascular disease, including extensive autoantibody screening, were negative. It was decided not to perform a cerebral biopsy. She was treated with oral prednisilone and after about two weeks began to improve. Her ANCA level and labelled white cell count returned to normal. Clinical neuropsychological testing at this early stage revealed anterograde memory problems, impairments in speed of processing, alertness and executive/frontal lobe tasks such as verbal fluency. All of these improved over the first few weeks, but retrograde memory problems that were present did not improve. The period of anterograde memory deficit lasted around one month. She was discharged home three months post-onset, but was re-admitted again with a milder recurrence of her confusional state two months later. She was started on cyclophosphamide, which resulted in further improvement. She was discharged again one month later and remained well throughout the period of study. Although her anterograde memory functioning had improved within a month of her initial admission, following her second admission she remembered virtually nothing of the period between the two admissions. Anterograde memory functioning was normal following the second discharge. JM was examined by a consultant neuropsychiatrist who could find no evidence to suggest a psychogenic explanation for her retrograde amnesia. There was no past history of psychiatric problems, the illness was not preceded by any abnormal life stress, there was no loss of personal identity and there was no apparent secondary gain resulting from her memory difficulties.

### 3.1.3 Brain Imaging

*Magnetic Resonance Imaging*: Axial T2 weighted and 3D acquisition set with reconstruction of images in the coronal and horizontal planes were acquired two years post-illness (see Figure 3.1.1). There were marked bi-frontal and left parietal lobe atrophic changes with dilatation of the posterior part of the left lateral ventricle. The left Sylvian fissure was also slightly enlarged. The right temporal lobe appeared normal. On the left, a well circumscribed low signal intensity on T1 weighted, and high signal on the T2 weighted images, was demonstrated in the anterior part of the temporal lobe, suggestive of a mature infarct, with atrophy of the left temporal pole. The hippocampal complex was well visualised and appeared normal in size and configuration bilaterally.

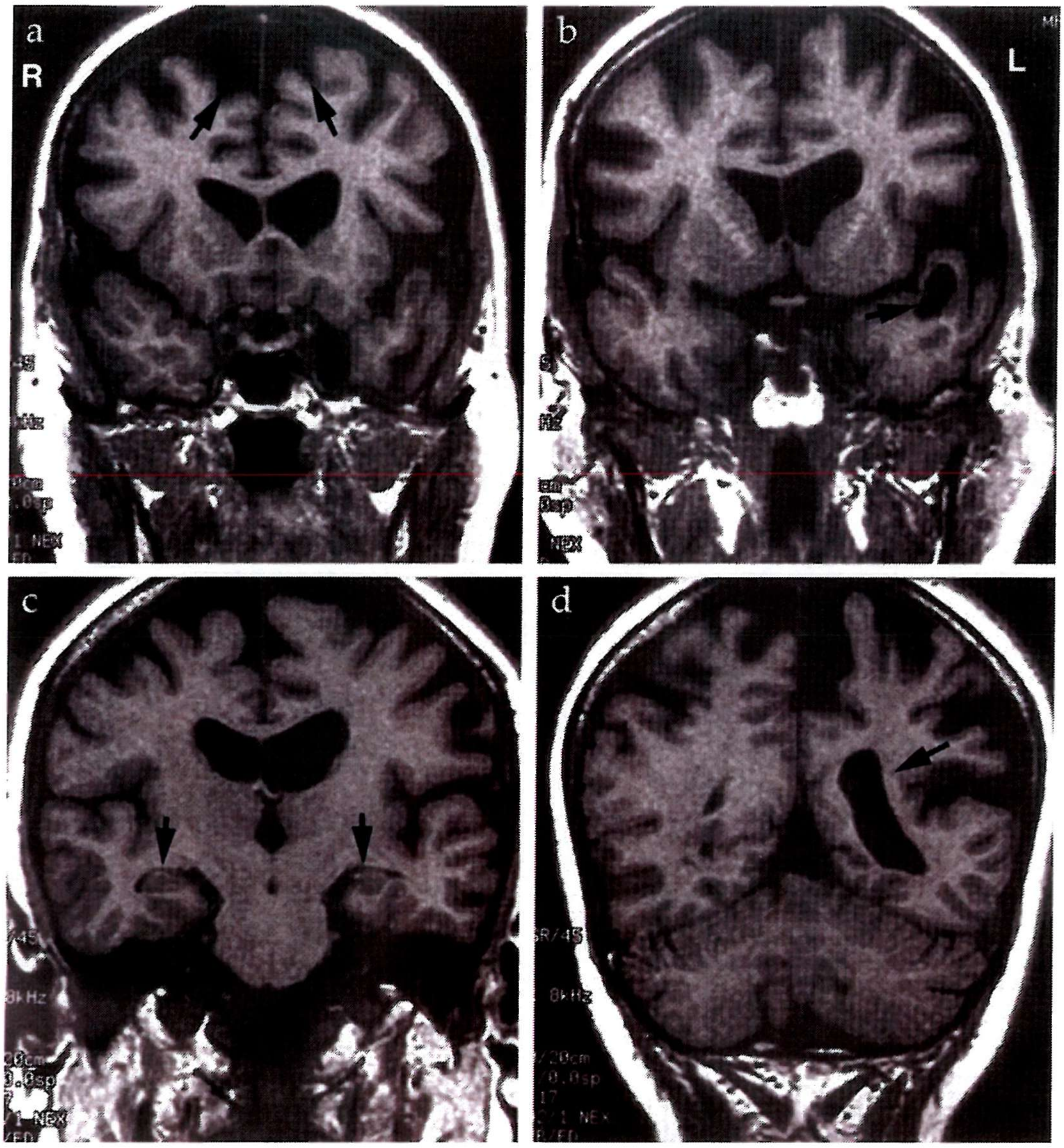



***Figure 3.1.1 MRI scans of patient JM: Axial T2 weighted 3D acquisition set with reconstruction of images in the coronal planes from front to back, (a) to (d). On the most anterior slice (a) atrophy of the left frontal pole and bilateral frontal lobes is apparent. On the next cut (b) there is a 1cm low density 'lacunar' lesion in the superior portion of the left temporal lobe. The two lower slices (c) and (d) through the body of the posterior part of the temporal lobe show preservation of the hippocampal complex (c) and atrophy of the left parietal lobe with compensatory ventricular enlargement (d).***

*Single Photon Emission Computed Tomography (SPECT)*: HMPAO perfusion scanning revealed generally patchy uptake of tracer in the frontal lobes with areas of more focal hypoperfusion in the left temporal and parietal regions.

### 3.1.4 General Cognitive Functioning

JM was first seen for neuropsychological assessment within two month of the onset of her acute illness when she performed significantly below her estimated pre-morbid level of functioning on verbal and non-verbal tests of general intelligence (see Table 3.1.1). At this time there was evidence of cognitive slowness and poor concentration. Behaviourally she showed mild disinhibition uncharacteristic of her pre-morbid personality.

Approximately one year after her acute illness, JM was given a repeat full neuropsychological assessment and the following test results are from that assessment or have been obtained since that time. When further clinical re-assessment was carried out on subsequent occasions, there was no indication of significant changes in cognitive functioning. Table 3.1.1 documents her performance on the WAIS-R along with tests of language, perception and executive functioning. In general, the results indicate that there was very little difference between her level of performance on general cognitive tasks one year post-illness and estimates of her pre-morbid functioning, except for some reduction in digit span (typically she achieved a consistent forward span of 5 and backward span of 4/5) . Language and perception were unimpaired. She performed normally on tests of object naming, naming to description and on the Pyramids and Palm Trees test of semantic access from pictures (Howard and Patterson, 1992). Executive functioning, as assessed by the Wisconsin card sorting test (Nelson 1976), Cognitive Estimates (Shallice and Evans, 1978) and verbal fluency, were also generally satisfactory, though in the early stages verbal fluency scores were below what might have been expected from someone with her background, and consistent with frontal lobe damage identified on MRI.

*Table 3.1.1 JM's general neuropsychological test performance*

| | **Acute phase (up to 2 months post-illness)** | **1 year post-illness (or later)** |
|---|---|---|
| **WAIS-R** | | |
| Verbal IQ | 101 | 117 |
| Performance IQ | 95 | 109 |
| Full Scale IQ | 97 | 115 |
| *Sub-tests (age scaled)* | | |
| Digit Span | 9 | 8 |
| Vocabulary | 14 | 15 |
| Arithmetic | 8 | 14 |
| Similarities | 13 | 15 |
| Picture Completion | 10 | 11 |
| Picture Arrangement | - | 12 |
| Block Design | 12 | 11 |
| Digit Symbol | 7 | - |
| **National Adult Reading Test** | | |
| (Nelson 1991) | | |
| Estimated pre-morbid IQ | 126 | - |
| **Graded Naming Test** | 18/30 | 25/30 |
| (McKenna and Warrington 1983) | | |
| **Semantic Battery (Hodges)** | | |
| Object Naming | | 47/48 |
| Naming to description | | 24/24 |
| **Pyramids and Palm Trees** | | 50/52 |
| (Howard and Patterson 1992) | | |
| **Visual Object and Space Perception Battery** | | |
| (Warrington and James 1991) | | |
| Incomplete Letters | | 18/20 Pass |
| Silhouettes | | 24/30 Pass |
| Object Decision | | 16/20 Pass |
| Dot Counting | | 10/10 Pass |
| Position Discrimination | | 19/20 Pass |
| Number Location | | 10/10 Pass |
| Cube Analysis | | 10/10 Pass |
| **Verbal Fluency (60')** | | |
| F | | 19 |
| A | | 19 |
| S | 7 | 16 |
| Animals | | 24 |
| **Cognitive Estimates** | | 4 error points |
| Unimpaired | | |
| (Shallice and Evans 1978) | | (Control mean = 3.6) |
| **Wisconsin Card Sorting Test** | Perseverative | 6 Categories |
| (Nelson 1976 modified version) | (Discontinued) | 0 Non-perseverative |
| errors | | 2 Perseverative errors |

### 3.1.5 Anterograde Memory

Table 3.1.2 summarises JM's scores on a number of standard anterograde memory tests of recognition and free recall. Test results demonstrate that she had entirely normal performance on tests of anterograde memory, both verbal and visual, and indeed was well above average for most tests. On the Rivermead Behavioural Memory Test (Wilson et al., 1985), she obtained a perfect profile score (24/24). On some additional measures of anterograde memory she also performed well above average; on a continuous word recognition memory test for items repeated several times (Warrington, unpublished), she scored 80/81 for high frequency and 79/81 for low frequency words and 70/81 for non-words. All of these scores represent above average performance. Similarly, clinical investigations of her memory for information presented in newspaper articles showed excellent immediate recall and she was able to reproduce a substantial amount of this information two months later.

***Table 3.1.2. JM's anterograde memory performance***

| | **Acute phase** | **1 year post-illness** |
|---|---|---|
| **Wechsler Memory Scale-Revised** (Wechsler, 1984) | | |
| Logical Memory | | |
| Immediate Recall | 25 (65th percentile) | 40 (99th percentile) |
| Delayed Recall | 3 (5th percentile) | 39 (99th percentile) |
| Visual Reproduction | | |
| Immediate Recall | 25 (25th percentile) | 33 (77th percentile) |
| Delayed Recall | 25 (42nd percentile) | 34 (94th percentile) |
| **Recognition Memory Test** (Warrington, 1984) | | |
| Words | 40/50 (Scaled score 8) | 49/50 (Scaled score 15) |
| Faces | 44/50 (Scaled score 12) | 44/50 (Scaled score 12) |
| **Rivermead Behavioural Memory Test** (Wilson, Baddeley and Cockburn, 1985) | | |
| Standardised Profile Score | | 24/24 Unimpaired |

### 3.1.6 Study Phase 1 (1-2 years post-illness)

A series of tests were administered to examine JM's retrograde memory. These included the AMI (Kopelman, Wilson and Baddeley, 1990), Crovitz Cued Personal Memory Test, Famous Faces Test (Hodges and Ward, 1989), and the Famous Events Recognition Test (Hodges and Ward, 1989). Prior to the administration of these tests, JM was asked for her recollection of events in the categories of life events used by Kapur et al. (1992).

#### *3.1.6.1 Autobiographical events*

JM was asked about her memory for autobiographical events in the categories used by Kapur et al. (1992) and some examples of her difficulties are given below. JM was not married and has few family members who would know the details of her life in detail. However, from her memory of general aspects of her life, as well as from diaries, letters and the comments of friends it was possible to identify particular events that had happened in her life, but which she had difficulty remembering.

*Holidays* Whilst she knew that she has been on many holidays (from photographs, diaries etc.), JM had virtually no memory of them. For example, a few years prior to her illness she went to Venice with a close friend and had no recollection of the trip, despite describing Venice as "my favourite city." On one occasion she noted that she was planning a trip to a number of places in South West England, believing she had not been there, but found (again from friends, diaries etc.) that she had visited many of the places previously.

*Occupational and Educational History* JM had good recall of her occupational history at a generic level. She knew where she worked and when, from her first job in 1952 until her retirement in 1989, though she initially missed out a two-year period from early in her career. She recalled a few prominent incidents, but found it very difficult to recall any detailed events. For example she worked as a senior administrator at a university, but could not recall having an interview for the post. She retired from her final post in 1989 and settled in Cambridge. She could not recall her reasons for moving to Cambridge, and did not remember moving. After moving to Cambridge, she knew (from diaries/friends) that she trained to work as a volunteer for the Citizen's Advice Bureau, but remembered virtually nothing of the 5 month training.

*Houses* JM described very accurately her present house, but could not recall moving there two years prior to the onset of her illness. She could not remember why she chose her house or how many others she might have looked at before deciding upon the present one. Her memory for the last house she lived in prior to her move to Cambridge was sketchy; "I think it was semi-detached.....it was the last but one in the road.....it had a shed or a garage...no I don't think it was a garage.....the main room was probably an all-through room.....I suspect there was a long corridor to the kitchen....I can't remember where the sink was in the kitchen, or if there was a door outside from the kitchen....upstairs I can't recall the layout at all..I'm pretty confident I slept at the front...." She had lived in this house for 2 years. This level of description is similar for most of the places she has lived as an adult, though her description of her childhood home was as detailed and as confident as her description of her present house. She had a cat in her present house, until its death, but did not remember how she came to acquire it. She thought that it may have 'adopted' her, though she could not really be sure. Whilst living in one of her previous houses she was burgled twice. She said that she remembered *that* she was burgled, but could not recall any details about the episodes.

*Hospital Admissions* JM's medical records show that she was admitted to hospital several months prior to the onset of her acute illness, complaining of deafness, and that she had undergone an operation, but she remembered nothing of this admission. This also applied to her more recent admissions, connected with the development of cerebral vasculitis, and the period between these two admissions. Her memory was, by contrast, good for the period following the second admission. For instance, she was able to recount accurate details of her visits to hospital out-patient clinics.

*Plays* JM had a great interest in literature and theatre. She had programmes from a large number of plays that she had been to see which she said "should have been memorable", but had no recall of them.

*Births/Christenings* JM was the god-mother to her niece, but remembered nothing of the christening which took place in 1968.

*Deaths/Funerals* She had been told that she was present when her father died, but does not remember this event. She also had no recall of the funeral of her mother.

*Weddings/Parties* She could not recall if she had been to many weddings. She knew that she went to her brother's wedding, but could not recall any details about it. Her diary indicated that in 1988 she attended a royal garden party at Buckingham Palace, but JM had no recall of this event.

#### *3.1.6.2 Autobiographical Memory Interview (AMI)*

As previously described, the AMI assesses memory for both 'personal semantic' information (factual knowledge such as the names of friends or teachers, addresses of places lived, educational/occupational history) and 'autobiographical incident' information (particular events or episodes experienced by the subject, across the whole life-span). It is worth noting that many of the items falling into the 'recent' time period are actually anterograde events, taking place since the onset of the memory impairment. Results for JM are presented in Table 3.1.3. On this test, based on normative data provided in the test manual, there was a clear demonstration of the discrepancy between personal semantic and autobiographical episode knowledge. JM demonstrated a marked impairment in her ability to recall details of specific episodes prior to the onset of the vasculitis, though her recall of events since that time was excellent.

***Table 3.1.3. JM's performance on the Autobiographical Memory Interview***

| | *Personal Semantic* | | *Autobiographical Incidents* | |
|---|---|---|---|---|
| Childhood | 18/21 | Normal | 3/9 | Abnormal |
| Early Adult Life | 16/21 | Borderline | 2/9 | Abnormal |
| Recent Life | 20/21 | Normal | 9/9 | Normal |
| Total | 54/63 | | 14/27 | |

#### *3.1.6.3 Modified Crovitz Test*

A modified version of the Crovitz test was used (Sagar, Cohen, Sullivan, Corkin, and Growden, 1988; Hodges and Ward, 1989; Hodges and Oxbury, 1990). In this test, the subject is asked to relate personally experienced life events from any time-period evoked by each of 10 high frequency nouns (bird, tree, car etc.) and then to estimate the date of the memory produced was used. A demonstration trial item was given before the test list. Participants were given up to four minutes to respond, including if necessary, two minutes with specific cues. During the first two minutes the examiner provided non-specific prompts (e.g. "Tell me more"). If after two minutes no episode was produced the examiner cues the subject by suggesting concrete possibilities involving the target word (e.g. "Have you ever been in a *boat*"). Responses were scored on a 0-3 scale according to the specificity in time and place of the memory recalled, and the richness of detail provided. JM was able to produce memories in response to nine of the cue-words. In total she scored 22/30 which reflects that fact that she could produce some specific memories, though a number were not specific enough to earn a score of 3, and the score was impaired compared to controls (n=41, age=65.5, s.d. 8.6, NART IQ =115, s.d.8.0; reported in Hodges and Ward, 1989) mean score of 28.3 (s.d. 1.9). Her score therefore placed her more than 3 standard deviations from the mean for the control participants.

The other striking feature of the memories that she was able to recall was that they were almost all from the early part of her life. Figure 3.1.2 shows the distribution of age of the memories that she was able to produce in comparison to controls (reported by Hodges and Oxbury, 1990). Control subjects tend to produce the greatest majority of memories from the previous decade, whereas JM produced none. However, it seemed clear that she had good recall of events since her episode of vasculitis. She was therefore given an additional word (the word *restaurant)* and asked if she could recall an incident associated with the word restaurant that had taken place since her illness and another event that had taken place prior to her illness. She was able to give a very detailed description of a trip to York, taken five months previously and therefore since her illness, which included a visit to a restaurant with some friends. She recalled who was present, what she ate, what was discussed and the general atmosphere of the event. In contrast, she was unable to come up with a detailed episode of visiting a restaurant prior to her illness, apart from a vague memory, again from childhood, of visiting a restaurant with her family.

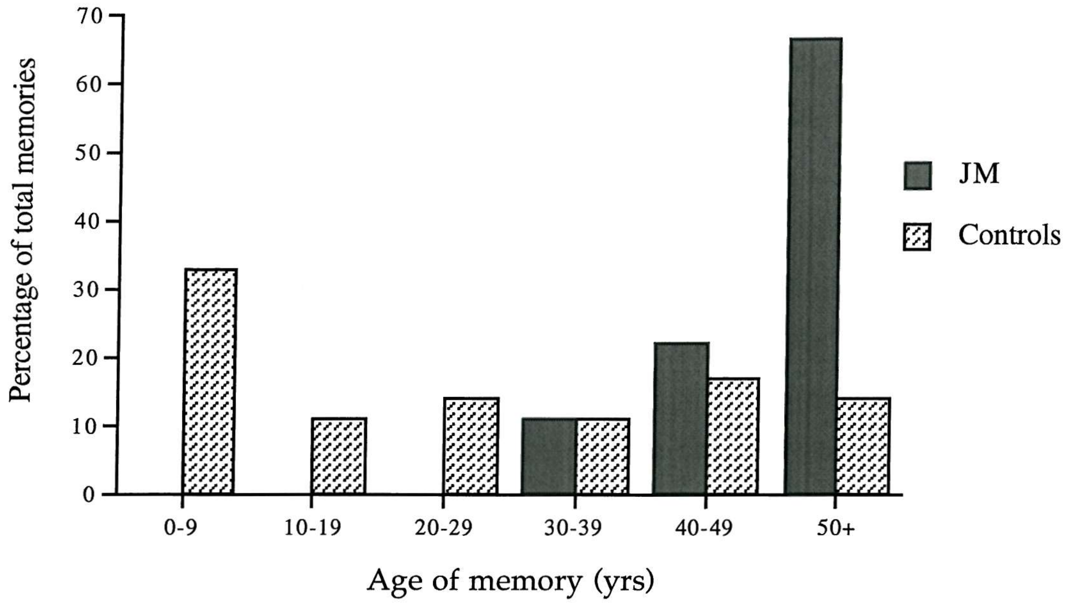



***Figure 3.1.2. Comparison of the age distribution of memories produced by JM and control participants on the Modified Crovitz Test.***

### *3.1.6.4 Famous Faces Test.*

This test has been described in detail by Hodges and Ward (1989) and involves presenting the subject with 50 faces of people who were famous primarily in one of the decades between the 1940's and 1980's and asking the subject to try to name the person. JM's performance, shown in Table 3.1.4, was above the average of a group of control subjects (reported by Hodges and Ward, 1989), presumably reflecting her high baseline intellectual level, with no indication of a temporal gradient in her performance.

***Table 3.1.4 Performance of JM and control participants on the Famous Faces Test (Hodges and Ward, 1989) showing the percentage of faces that were either named or for which specific identity information was provided.***

| | **1940's** | **1950's** | **1960's** | **1970's** | **1980's** |
|---|---|---|---|---|---|
| JM | 80 | 80 | 80 | 80 | 90 |
| Control participants Mean (standard deviation) | 65.6 (7.1) | 67.8 (6.5) | 63.5 (8.0) | 70.1 (7.0) | 72.3 (6.4) |

### *3.1.6.5 Famous Events Test.*

This test was also described in detail by Hodges and Ward (1989) and consists of a list of 50 famous events from the 1930's to the 1970's, randomly interspersed with 50 'made-up' event names. The task for the subject is to say whether each item is a real event or not. For those items reported as real the subject has to indicate the decade in which they think the event took place. Once again JM's performance, shown in Table 3.1.5, was normal in relation to a group of control subjects (n=41, age=65.5, s.d. 8.6, NART IQ =115, s.d.8.0). Although JM was good at recognising famous events as famous, she commented that for quite a lot of events she could not remember the details of the events, to the extent that she would have expected. For some events she had almost no knowledge (e.g. Space Shuttle Challenger Disaster- "Perhaps it went missing or got lost....was it an English thing?"), for other events she appeared to have partial knowledge (e.g. Camp David Agreement- "An agreement between Israelis and Arabs brokered by U.S., can't remember which people involved....wasn't Gadaffi was it?...or was it Egypt?) and for other events she was largely correct in details, but not at all confident (e.g. Chappaquidick- "It was the death of a mistress of one of the Kennedy's, not too sure if it was Robert....did she fall or was she pushed.....think it was a car accident....or did she drown.....could have done both").

***Table 3.1.5 Performance of JM and control participants on the Famous Events Test (Hodges and Ward, 1989)***

| | JM | Mean for Controls |
|---|---|---|
| Correct recognition of real events | 92% | 82% (s.d. 14.9%) |
| Hits minus false positives | 84% | 76.4% (s.d. 13.3%) |
| Correct dating (for decade) of events | 52% | 50.28% (s.d. 16.8%) |

### *3.1.6.6 Imagery*

It has been suggested that imagery deficits may give rise to deficits in autobiographical memory deficits (Ogden, 1993; O'Connor et al., 1992). However, despite some parietal hypoperfusion demonstrated by SPECT, JM appeared to have no imagery deficit. She passed all of the seven sub-tests administered from the Visual Object and Space Perception Battery. In addition, JM was informally asked to give a description of what a variety of animals and objects look like, which she was able to do with great clarity. Some examples are given here:

Camel: "There are two kinds, one has one hump and the other has two. Has a tail like an elephant. Kind of funny legs which end in rather large sploshy feet. It can kneel down. Head has got a projecting muzzle, rather small ears, can fold back its mouth to have a very sneering kind of an expression. Light yellowy brown colour. Normally has a lot of kit on it, like a saddle and reins. Has long legs, and a sagging undercarriage."

Rhino: "Quite long for its height, small tail, kind of loose skin, sort of sagging tops to its legs, which aren't long but are pretty thick, with spread out feet. Got very small ears, there are kinds with one or two horns on its nose. Pretty big mouth, called a pachyderm."

The Eiffel Tower: "It's got four legs which are wide at the bottom and then it gets narrower, into a smaller version of a square and then on top there is a smaller square that goes into a rounded top. Open charcoal grey metal work, looks solid, but kind of open."

A cheese grater: "There is a kind that is flat, which normally has one area for large slices and one area for small. Another sort has a flat side and a curved, semi-circular side. There is a bit to hold on to. The semi-circular one would be free standing. They are painful to touch."

#### *3.1.6.7 Study Phase 1 Discussion*

JM recovered from a period of generalised cognitive impairment, including both anterograde and retrograde amnesia, arising from a vasculitic illness and was left with a focal retrograde amnesia (FRA). Many of the previously reported cases of FRA document retrograde memory impairments which are disproportionately impaired in comparison to an anterograde impairment, but nevertheless there is some degree of anterograde impairment (see Kopelman 2000). Once she had recovered from the initial period of illness, JM had no detectable anterograde impairment, as evident from her performance on standard memory tests and her ability to recall in detail, events since her illness. In contrast, she did have a clear retrograde memory impairment. The retrograde amnesia was most severe for autobiographical episodes, whilst her personal semantic knowledge and knowledge of famous people and events were relatively intact.

At first glance, there appeared to be a temporal gradient in JM's deficit; her recall of autobiographical incidents was better for her childhood, though from relatively early adulthood onwards there was a flat impairment across the whole time period. If the pattern is examined from the perspective of the pre- and post-illness time periods, then there is a U-shaped curve; she is good at recalling episodes from the period since her illness and from her early life, but poor for the whole period in between. This pattern clearly distinguished JM from patients with Korsakoff's Syndrome and dementia of the Alzheimer's type who show a typical temporal gradient with poor memory for recent events, but better distant remote memory (Sagar and Sullivan, 1988; Kopelman, 1989; Greene, Hodges and Baddeley, 1995).

Autobiographical memory was examined using the modified version of the autobiographical recall task designed by Crovitz and described by Hodges and Ward (1989). One of the limitations of this free-recall version is that, because subjects are free to choose the time period from which to retrieve memories, there will be a bias towards retrieval of memories from the period where recall is easy. It is not therefore possible to conclude that the subject *cannot* recall, or even has more difficulty recalling, memories from particular time periods unless the subject is asked to constrain their recall to those time periods. Therefore in Study Phase 2, a version of the Crovitz task (the Time-Constrained Crovitz task) was used which involved the same basic task format, but required the subject to try to recall memories from specified lifetime periods (Graham and Hodges 1997).

What was most striking about JM in Study Phase 1 was the level of detail, accuracy, and confidence associated with her recall of post-illness or anterograde events. However, one possibility not formally explored in the Study 1 was that JM would show accelerated forgetting. As discussed in Chapter 1, several studies have described patients with apparent intact initial learning rate, and normal recall after a short delay (e.g. 30 minutes), but an abnormally fast forgetting rate over a period of days or weeks (De Renzi and Lucchelli 1993, Kapur et al. 1996, O'Connor et al. 1997, Lucchelli and Spinnler 1998). A number of these patients also demonstrated significant problems recalling events from the post-morbid period and have been described as cases of disproportionate retrograde amnesia (see Kopelman, 2000). It was therefore critical to establish whether JM showed any evidence of accelerated forgetting that might impact on her ability to retain information over longer periods. As well as examining her performance on a formal test of accelerated forgetting, it was also important to establish that she was able to recall autobiographical experiences from the post-illness period in a normal way, retaining that information over an extended period of time. Study Phase 2 was therefore carried out some six years post-illness in order to address this question.

Levine et al. (1998) describe the case of patient ML, who developed FRA following a head injury. Like JM, he showed impairment in pre-injury autobiographical recall (with preserved recall of general personal semantic knowledge), in the context of excellent performance on standardised tests of anterograde memory such as the Wechsler Memory Scale-Revised and word list learning tasks. ML's FRA was attributed to a lesion in his right ventral frontal cortex and underlying white matter including the uncinate fasiculus, with a resultant deficit in the strategic retrieval of autobiographical memories. Although ML's performance on tests of anterograde memory was normal, Levine et al. note that he, "reported a feeling of subjective distance from recall of events occurring after his recovery" (p1956). JM did not report such a feeling. Data collection for the previous study of JM, however, took place within the first one/two years post-injury. Although there was evidence that she was remembering post-illness events in a way that would be expected of someone who presents with normal performance on standardised anterograde memory tests, it was important to establish whether she was retaining information over several years, with a normal level of detail rather than perhaps being more superficially recalled. This is clearly critical for adjudicating between a general retrieval disorder, which would be expected to affect both pre- and post-morbid memories and alternative explanations for the genesis of FRA (see later for a fuller discussion).

Kapur (1999) argued that evidence from a number of single cases points to a double dissociation between retrograde amnesia for episodic material and retrograde amnesia for semantic knowledge. Within the category of semantic retrograde amnesia, knowledge of people and events also appear to dissociate (Ellis et al. 1989). In Study 1, JM's recall, or at least recognition, of famous people and events from over the same period was much better than her recall of personal events. A degree of lack of detail or uncertainty, however, was associated with her recall of famous events. Thus although she was broadly accurate in her recall, the level of error and uncertainty seemed greater than might have been expected from someone who took a very great interest in news and politics. In Study 2 this issue was explored in more detail, probing JM's knowledge of famous people and events, both pre and post-illness.

### 3.1.7 Study Phase 2 (Approximately six years post-illness)

Study Phase 2 was designed to answer the following questions:

Investigation 1: Would JM show ongoing impairment in recall of pre-illness autobiographical information?

Investigation 2: Would JM show any evidence of abnormally fast forgetting?

Investigation 3: Would JM have normal recall of post-illness autobiographical events?

Investigation 4: Would JM show impairments in her knowledge of famous people and famous events?

#### *3.1.7.1 Investigation 1: Would JM show ongoing impairment in recall of pre-illness autobiographical information?*

To address this question the Time-Constrained Crovitz task was used as described in Section 2.1.4.2. This involved the same basic task format as the Modified Crovitz task used in Study Phase 1, but required the subjects to try to recall memories from specified lifetime periods (Graham and Hodges, 1997). Subjects were instructed to try to remember a specific event or episode in response to each of 15 cue words, from the following lifetime periods: under 18; 20's and 30's; 40's and 50's; over 60. The test used the same 15 words for each time period. Time periods were sampled in a random order. In order to encourage the production of as much detail as possible, there was no time limit for recall and participants were prompted (e.g. "Can you tell me more about that?"; "Can you give me a specific example?") if necessary. Responses were scored on a 6 point (0-5) scale according to the specificity of the memory (for details of the scoring system, see Graham and Hodges, 1997). JM's ratings were scored by two raters independently. The ratings were generally similar and average ratings are presented.

The test was administered to JM and her performance compared with data from the three control subjects used in the Graham and Hodges (1997) study. The control subjects were well matched with JM, being aged 65 at the time of testing and all being university graduates.

*Results*

Figure 3.1.3 shows the results from the test. A Friedman analysis (reported in Graham and Hodges 1997 p.85) showed that there was no significant difference across the time periods for the control participants ($X^2 = 3.64$, $p = 0.30$). By contrast a Friedman analysis performed on JM's data (average ratings of two raters) showed a significant difference across time periods ($X^2 = 20.28$, $p < 0.0001$). Wilcoxon rank-sum tests showed that JM's memories were significantly less detailed than the controls for all time periods apart from the most recent (0-18: $z = -3.30$, $p = 0.001$; 19-39: $z = -2.27$, $p = 0.023$; 40-59: $z = -3.41$, $p < 0.001$; 60+: $z = -.489$, $p = 0.62$). It was noticeable that memories in the period of 20 years immediately prior to the onset of her illness appear to be particularly affected.

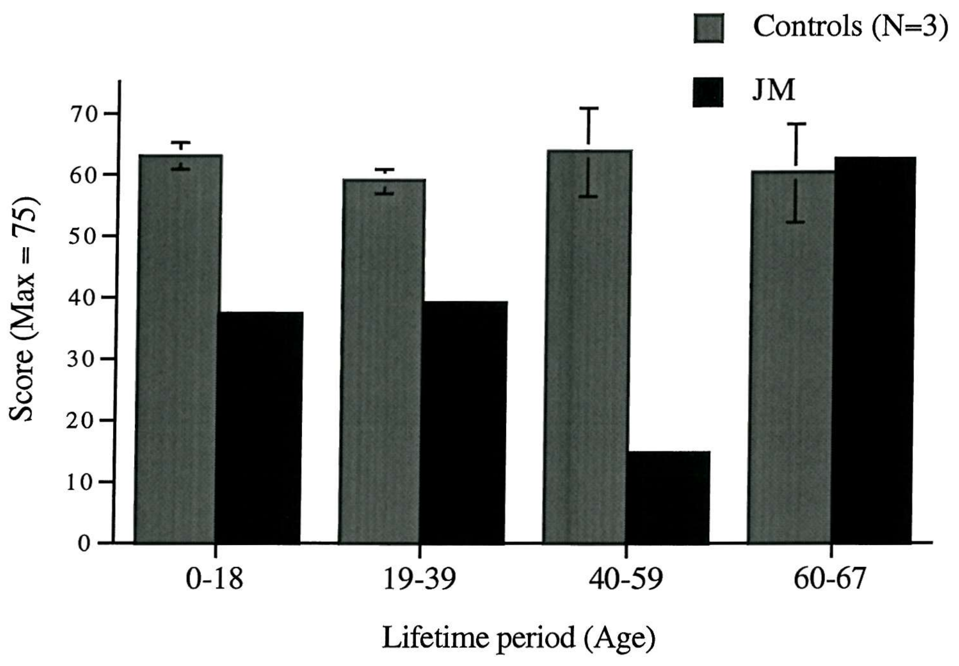



***Figure 3.1.3 Performance of JM and three matched controls (mean and two standard deviation marker bars) on the Time-Constrained Crovitz task***

JM's contrasting recall of memories in response to the cue word 'animal' provide an illustration of the marked difference in her ability to recall pre- and post-illness events. For the time period immediately prior to her illness, in response to the cue word 'animal' JM talked of how she had come to have a cat (which she had acquired some four years prior to her illness). The following is a transcript of JM's response, which is reproduced with her permission.

*Examiner*: The next word is animal. Have you got a particular memory of something to do with an animal from the time period between the ages of 40 and 59?
*JM*: Oh yes, well this was when I got this cat. But again, you see, I don't remember. Except in the vaguest terms. I think I've been told what the circumstances were. And of course that overlays, and you can't.....I knew that the cat had adopted me, that I could remember. I think she came...Well I thought that she had adopted me, but then I was told that it belonged...I have a whole memory of where the house is, but then it's probably a false memory, there was this young couple and they were concerned about the cat sitting on the baby. Well everyone says that's an old wives tale, but I do think it actually was. I mean she was capable of actually sitting on my face.
*Examiner*: So they were right...
*JM*: So they, no, I don't know whether...quite how it worked out, whether... One version of the story, and for that person it was only a story, was that I kind of had it while the baby was kind of stopping being a baby...and that I said, "will you have it back?"... and they said "No, you keep it". But I'm not sure.
*Examiner*: You can't remember?
*JM*: No, but I do think, I'm sure that they didn't come and say we're having a baby, or we've got a baby, will you look after this cat? I'm sure that she came and, errm, adopted me. Yes I'm sure that's right.
*Examiner*: OK. And can you remember when it was she adopted you?
*JM*: Well it wouldn't have been very...because I moved with her of course in 1989, so I tend to think I'd had her 2 years.

By way of comparison, the following transcript is of JM's response to the same cue word for the post-illness period.

*Examiner*: Can you tell me anything to do with 'animal' that's happened in the last seven years?
*JM*: Yes, yes yes. I had a cat and it died. That was a trauma as far as I was concerned.
*Examiner*: Can you tell me about how it died?

*JM*: Well, yes, it was awful because I kept being concerned that it wasn't well. My cousin had a vet and ....the part I remember was I went saying that I thought she had got cystitis. I think that was the first time I went. And,...I can't, but he said that it would be one of three things, ermm, but for one of them she'd have to have a blood test. I can't quite remember what the three things were, what he said they might be. But anyhow, he took the blood test and I rang up and he said that it wasn't whatever the blood test had been for. But she started to go off her food and so on, and I came back this particular day, because she wouldn't drink- that's right, and errm, this stuff that someone had suggested, this special kind of milk for cats which was easier for them to digest. Well, then I got home and she was in a very poor way.

*Examiner*: Oh dear

*JM*: So my neighbour kindly agreed to take me to this vet and I took her in and I put her on the table and he said to me, "She's dying on you". Well I think he expected that I was going to leave her behind. Well I took her home for the night because it was such a shock....my neighbour was very shocked by the vet's attitude. She actually died of kidney failure and I don't think that was one of the things he had suggested it might be. You know what I mean. I don't think anything could have been done about it if he had, because it's an irreversible thing, but if I'd had known...

*Examiner*: So did she die during the night that you had her?

*JM*: No, I took her in and fortunately for me he was away and it was another vet, a much nicer vet, who was acting as a locum. He's a man with his own practice, which is the practice I now go to with my new cat. And he was very nice.

*Examiner*: That's dreadful isn't it. So, when was this that she died?

*JM*: Well she died in '93.

These two transcripts illustrate the contrast in the level of detail and confidence in JM's recall of personally experienced events pre and post-illness. The results of the Crovitz test suggest that JM is laying down new memories post-illness and retaining those memories. The next investigation examined more formally the question of whether JM showed any evidence of accelerated forgetting.

### *3.1.7.2 Investigation 2: Would JM show any evidence of abnormally fast forgetting?*

To investigate forgetting over time, JM and four age and IQ matched controls were tested on story and complex figure recall immediately following presentation, and then three weeks and six weeks later. They were also tested on an object decision recognition memory test following delays of 30 minutes, three weeks and six weeks.

*Story recall*

The story used in this test was from Form 2 of the Coughlan and Hollows (1985) Adult Memory and Information Processing Battery. This story consists of 30 idea units. The story was read to the subjects, following which the subjects were asked to recall as much of the story as possible. Subjects were not told that they would be tested again. After three and six week delays subjects were re-tested on their recall of the story. The story was scored according to the scoring criteria described by Coughlan and Hollows. Data for each of the delay periods in terms of percentage of maximum points obtained for JM and the four controls are presented in Figure 3.1.4. It is noteworthy that JM's recall of the story was somewhat better than the four controls and showed a similar forgetting pattern.

*Complex Figure Recall*

The complex figure used in this test was from Form 2 of the Coughlan and Hollows (1985) Adult Memory and Information Processing Battery. Subjects were shown the figure and asked to copy it. Immediately afterwards subjects were asked to draw the figure from memory. Subjects were not told that they would be tested again. After three and six week delays subjects were re-tested on their recall of the figure. Drawings were scored according to the scoring criteria described by Coughlan and Hollows. Data for each of the delay periods in terms of percentage of maximum points obtained for JM and the four controls is presented in Figure 3.1.4. The figure shows that JM's recall of the figure did not differ from the control participants' level of recall and does not show evidence of accelerated forgetting in relation to controls.

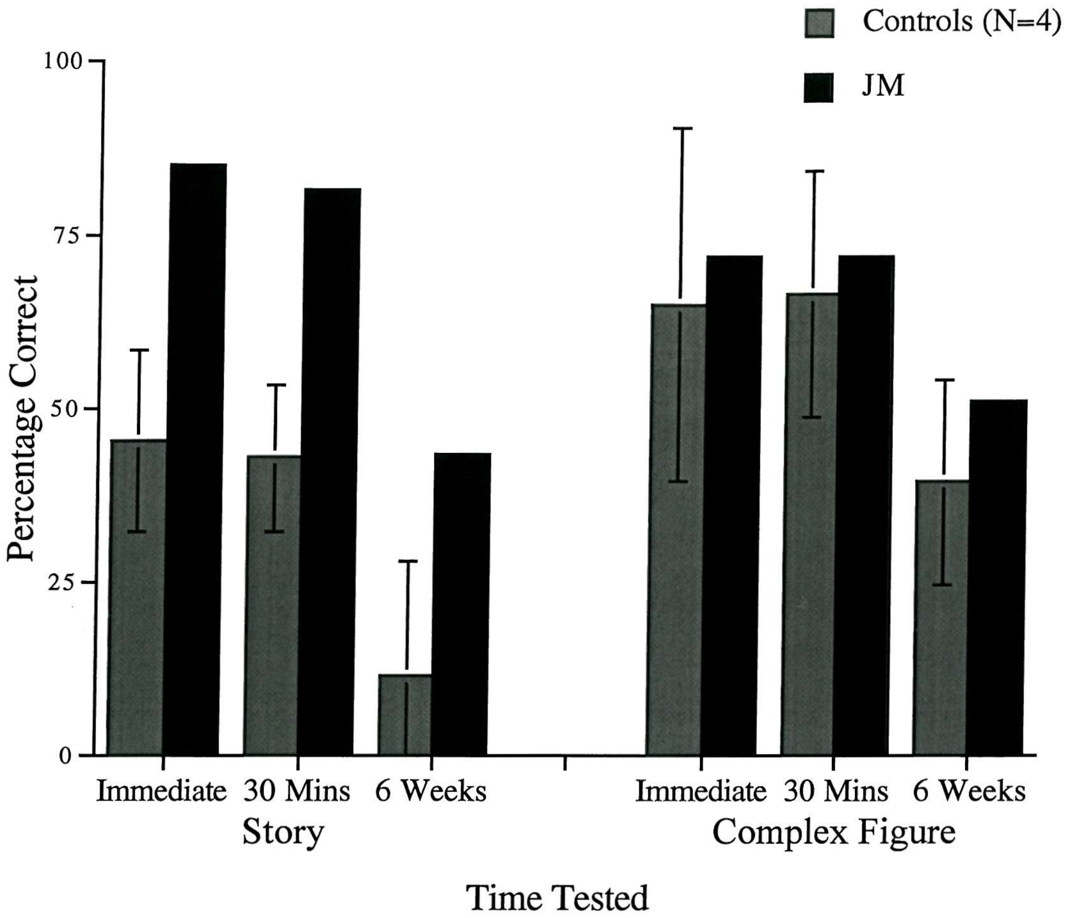



***Figure 3.1.4 Performance of JM and four controls (mean and two standard deviation marker bars) on the Story and Complex Figure tasks.***

*Object Decision Recognition Memory Test*

This test was derived from Graham's (1993) Test of Object and Animal Decision (TOAD). The test consists of line drawings of real and non-real man-made objects and animals. The non-real 'objects' are constructed of two halves of different real objects (e.g. light bulb and screwdriver) and the non-real 'animals' are composed of half one animal with half of another (e.g. Penguin-Owl). On the first part of the test, subjects were presented with items one at a time and asked to identify whether the item was real or not. 78 items were presented in total, half of which were real and half non-real.

After 30 minutes, a sub-sample of 26 items from the original list was presented along with 26 new items, not previously seen by the subject in a two-alternative forced choice procedure. At three weeks a further sub-sample of 26 pairs of items (half from the original sample and half new) was presented. The same procedure was repeated at six weeks. Studied items were always paired with a similar new drawing (e.g. real & real or non-real & non-real)

Figure 3.1.5 shows the performance of JM and the four controls at each of the three delays. The figure shows that JM's performance is unimpaired, suggesting that JM does not show any evidence of accelerated forgetting.

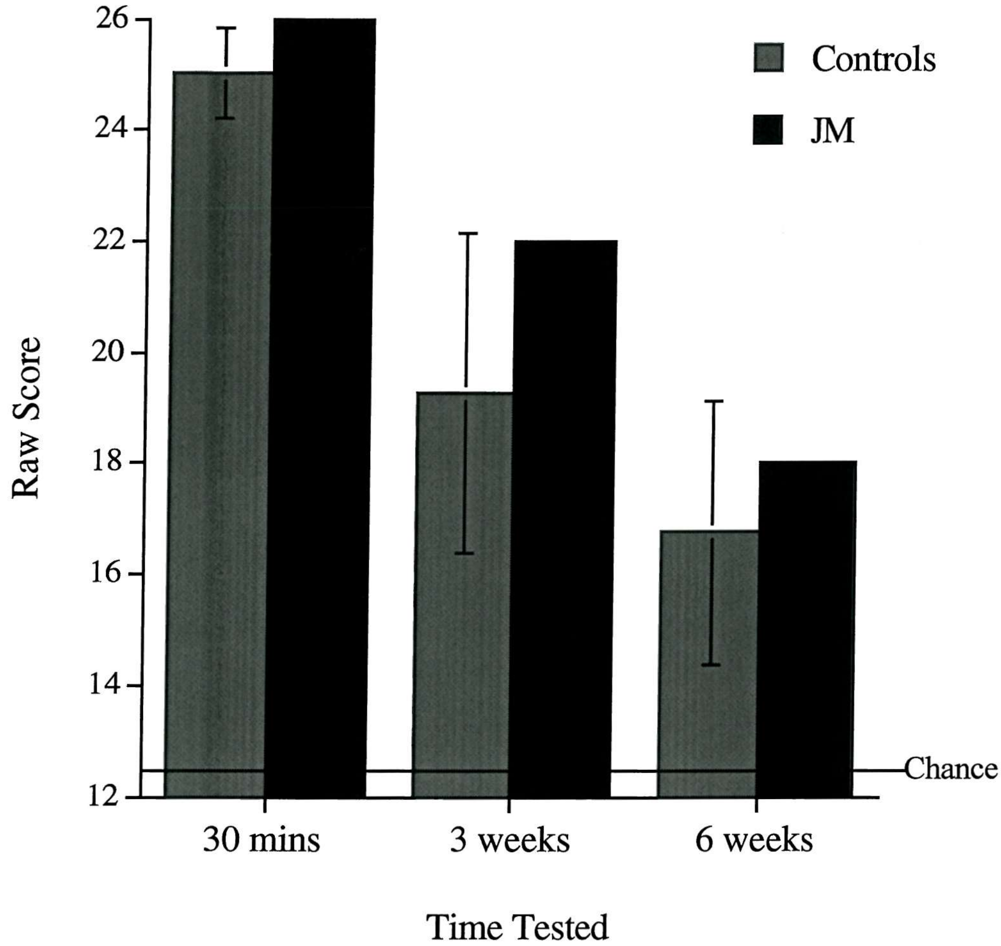



***Figure 3.1.5 Performance of JM and four controls (mean and two standard deviation bars) on the Test of Object and Animal Decision (TOAD).***

### *3.1.7.3 Investigation 3: Would JM have normal recall of post-illness autobiographical events?*

JM's Performance on the Crovitz task demonstrated that she was able to recall specific events from the post-illness period in a way that appeared normal. Data from the long-term forgetting tests demonstrated that she did not show evidence of very long-term accelerated forgetting of anterograde information. In order to informally identify whether she appeared to be retaining post-injury autobiographical memories, JM's memory for events in the post-illness period was explored in more detail in an interview focusing on recall of her medical history and a range of personal events that had occurred in the years post-illness and which had been raised during clinical interviews.

*Medical history*

Key events from JM's post-illness medical history were collated from her medical notes and through discussion with treating clinicians. There were no major medical problems during this time, but she had had a number of contacts with medical practitioners relating to follow up treatment and investigation of her condition. In an interview, JM was asked to describe her medical history since the onset of her illness. She was able to do this in some detail, spontaneously noting all of the major events (e.g. attending outpatient vasculitis and neurology clinics, undertaking a period of counselling, having brain scans, changing her General Practitioner). She was accurate in terms of the general order of events and broadly accurate in relation to dates over a six year post-illness period. Although no control data are available for this individually-tailored task, it was clear that JM did recall the relevant information accurately and furthermore that she had a degree of confidence in her memories which was lacking for pre-illness events.

*Personal events*

A list of personal episodes (including both 'one-off' events and activities that occurred over a more extended period) was compiled from clinical records of follow-up appointments which occurred regularly throughout the years after JM's illness up to the time of Study 2. These included events surrounding attendance at Russian language classes, acquiring a cat, having friends to visit, arranging for someone to clean her home, experiencing a burglary and attending a monthly Lunch Club. Once again control data were not available, so it is not possible to demonstrate conclusively that her recollections were entirely normal, but it was clear that she was able to recall the main details from each of these personal event areas. In the case of the Lunch Club, she had attended this club approximately monthly for over two years since its inception. The format for the club included lunch and there was a speaker who would give a presentation at each meeting. A list of all the topics (e.g. Landscape Design, Railways in Cambridge and Aerial Photography in Archaeology) was obtained and JM was asked to try to recall as many topic headings as possible. She was able to spontaneously recall just over half of all the topics covered (15/27). The topics she successfully recalled were spread over the whole period during which she had attended the club.

#### *3.1.7.4 Investigation 4: Would JM show impairments in her knowledge of famous people and famous events?*

In Study Phase 1, JM was tested on a famous face identification test and a famous event recognition test. As noted earlier, JM performed within the normal range on these tasks, but on the Famous Events test there were hints that JM could not access the level of detail that might have been expected of her. As the Famous Events test was scored only on the basis of recognition, there was no formal assessment of her ability to provide relevant event detail. In this investigation, a more detailed assessment of her knowledge of famous events and people with a series of tasks was therefore undertaken.

*(a) Famous People*

Famous People I

This test examined JM's knowledge of famous people from their names (Hodges and Graham 1998). The names of thirty people who were primarily famous in each of the following four time periods were included; 1950's, 1980's, early 1990's and current (i.e. famous at the time of testing or very recently famous). Recognition and identification of the famous names were tested. The 120 items were presented in a random order. Each famous name was presented with three other non-famous names, with the position of the target famous name varying randomly throughout the test. The subject was asked to point to the famous name (the recognition element) and then, if correct, to provide as much detail as possible about the person to uniquely identify that individual. If a subject incorrectly chose a non-famous foil, the correct name was provided and the subject asked to try to produce as much information about the person as possible.

The recognition component of the test was scored simply in terms of the total number of correctly identified items (Max. = 30 per time period). For the identification task, each response was again scored according to a 4 point (0-3) scale, according to the following criteria: 0 = don't know or incorrect response; 1 = superordinate information only (e.g. sportsman, politician); 2 = a definition that accurately described the person, but did not uniquely identify that individual; 3 = a definition that uniquely identified the person. There was a maximum possible score of 120 per time period.

The test was given to JM and her performance was compared with that of six control participants who took part in the Hodges and Graham (1998) study. The mean age of the controls was 63 years (just slightly below JM who was 67 at the time of testing).

*Results*

On the recognition component of the test, JM's performance was perfect (120/120), matching the performance of the controls.

Figure 3.1.6 shows the identification scores for each of the four time periods for JM and the six controls. A Friedman analysis showed that there was no significant difference across the time periods for the control participants ($X^2 = 2.83$, $p = 0.419$) or for JM ($X^2 = 0.690$, $p < 0.876$). Wilcoxon matched pairs signed ranks tests on each of the time periods comparing the performance of JM with the controls revealed no significant differences (50's, z=-.786, p=0.432; 80's, z=-1.28, p=0.196; Early 90's, z=-.813, p=0.416; Late 90's, z=-.148, p=0.882).

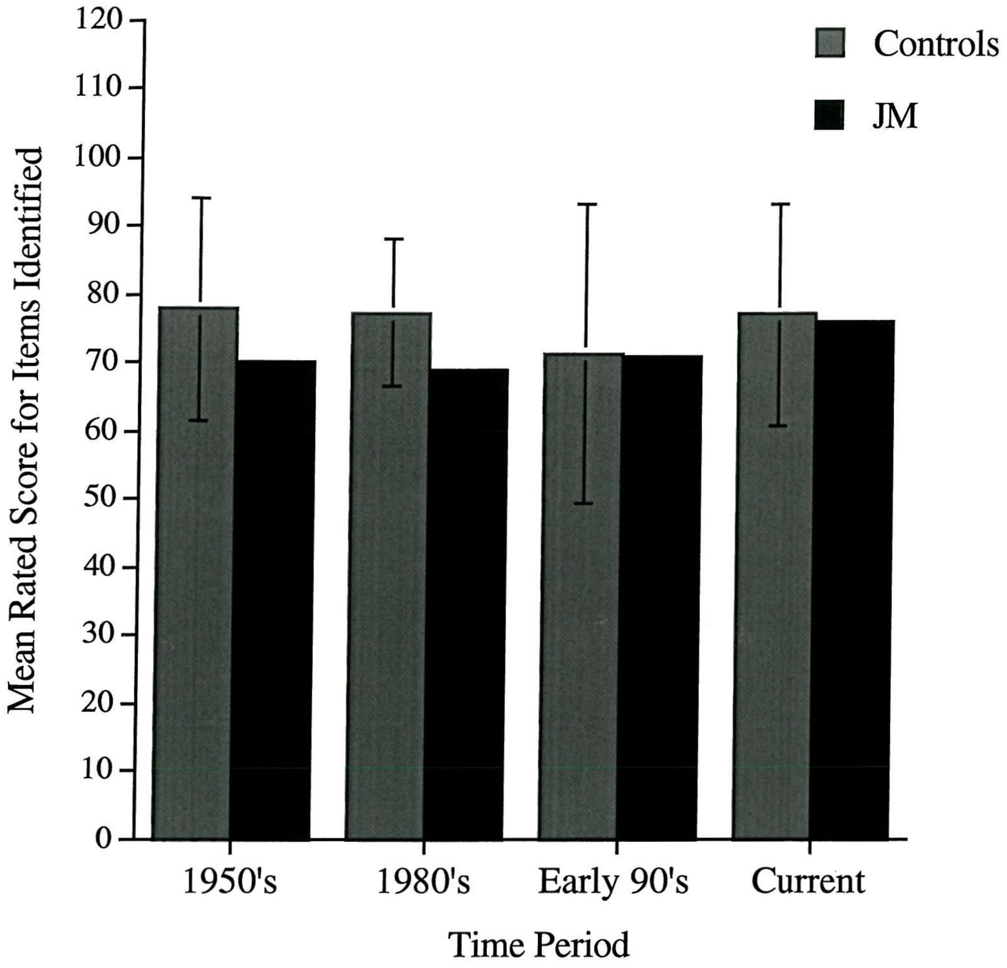



***Figure 3.1.6 Performance of JM and six control participants (mean and two standard deviation bars) on the Famous People I task.***

Famous People II

The previous famous people test included people who were famous across extended time periods rather than as a result of single events. Given JM's difficulty with pre-morbid episodic information, it was possible that she would have more difficulty with identifying people whose fame is primarily associated with a single event, or at least a limited set of events over a short time period. A test of knowledge of famous people primarily associated with particular events was constructed, with the same format as the famous events test described above. The names of eight people associated with events in each of five years pre-illness and five years post-illness was constructed making a total of 80 names. A further 240 'plausible', but non-famous, names were created. Recognition and identification of the famous names were tested by presenting each famous name with three non-famous names (e.g. David Koresh, Robert Purcell, Neil Reed, Adam Wall). The four names were arranged vertically on a piece of paper, with the position of the famous name (1, 2, 3, or 4) and the order of the names (with respect to year of event with which they were associated) arranged randomly. The subject was asked firstly to try to identify which of the four names was famous. If the subject correctly selected the real name, she was then asked to produce as much information as possible, with the aim of uniquely identifying the individual. If the subject made an error during the recognition phase, incorrectly identifying a non-famous name as a famous name, she was told which was the real name and asked to try to produce as much information as she could about that person.

The recognition component of the test was scored simply in terms of the total number of correctly identified items. For the identification task, each response was scored according to a 4 point (0-3) scale, according to the following criteria: 0 = don't know or incorrect response; 1 = superordinate information only (e.g. sportsman, politician); 2 = a definition that accurately described the person, but did not accurately identify the event with which s/he was associated; 3 = a definition that uniquely identified the person and event with which s/he was associated. A maximum total score of 120 was possible for each five-year time period.

The test was given to 6 control subjects who, like JM, had been educated to degree level. They were well matched with JM for age (JM: 67 years; Controls: 67.7 years, s.d = 1.86)

*Results*

Figures 3.1.7 shows the performance of JM and the control subjects on the recognition and identification components of this test. On the Identification task, for the pre-illness period JM was comparable to the controls (Wilcoxan matched pairs signed ranks test, $z = -1.219$, $p = 0.223$). For the post illness period JM's performance was significantly better than the controls (Wilcoxan matched pairs signed ranks test, $z = -2.02$, $p=0.043$). The controls did not show any significant difference between the two time periods (Mann Whitney $U = 8$, $p = 0.347$), whilst with JM there was a trend towards a difference, though this did not reach statistical significance (Mann Whitney

U = 4, p = 0.07). These data show that JM was good at identifying famous people from the pre- and post illness periods studied. However, there was some indication that her performance from the pre-illness period was perhaps somewhat weaker than the post-illness period.

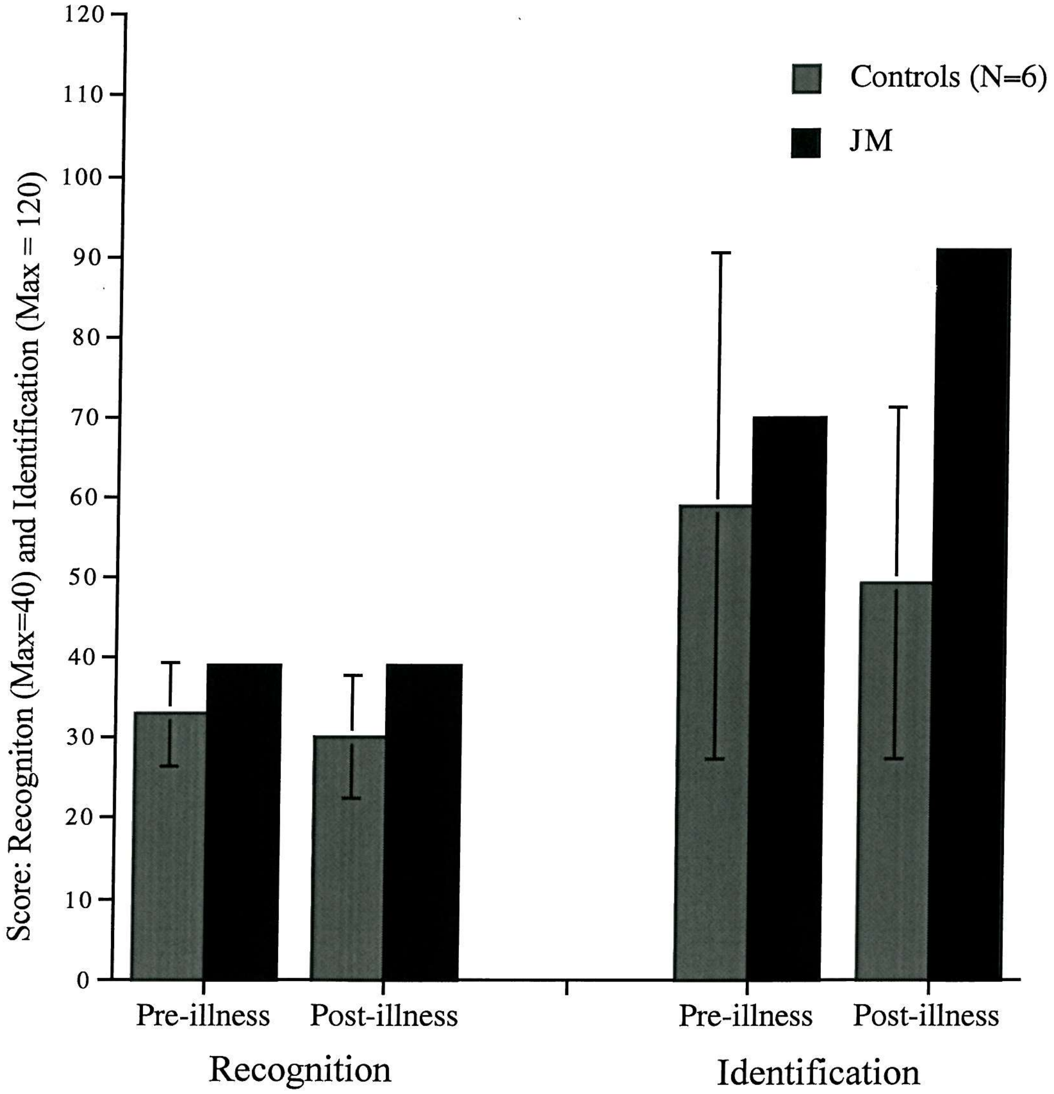



***Figure 3.1.7 Performance of JM and six control participants (mean and two standard deviation bars) on the recognition and identification tasks of the Famous People II test.***

*(b) Famous News Events*

The tests of JM's knowledge of famous people suggest she retained good knowledge of people, including those people who are primarily associated with single events, or at least events over a limited time period. JM's knowledge of famous news events was further examined in the following test. The news events in this test were selected as those that would be likely to be known by someone living in the UK. Eight events per year over two five year periods (5 years before she was ill and five years after she was ill) were selected for inclusion, making a total of 80 events. Each event was given a title designed to convey enough information about the event so that it could be recognised. A further 240 'plausible', but non-famous events were created using similar titles. The ability to (1) recognise the event as a famous news event and (2) to provide information about the event were assessed. Each famous event (e.g. The Tokyo Subway Gas Attack) was presented along with three non-famous events (e.g. The Jersey Killer Bee Invasion, The Napoleon Diaries Fraud, The Westwood Shooting). The four events were arranged vertically on a piece of paper, with the position of the famous event (1, 2, 3, or 4) and the order of the events (with respect to year) arranged randomly. The participant was asked first to identify which of the four events was real. If she correctly selected the real event she was then asked to produce as much information as possible with the aim of uniquely identifying the event.

The recognition component of the test was scored simply in terms of the total number of correctly identified items. For the information component of the task, each response was scored according to a 4 point (0-3) scale: 0 = don't know or incorrect response; 1 = superordinate information only; 2 = a definition that described the event, but did not distinguish it from other similar events (i.e. did not uniquely identify the event); 3 = a definition that uniquely identified the event. There was a maximum total score of 120 per five year time period.

The test was given to four control participants who, like JM, had been educated to degree level. They were well matched with JM for age (JM: 67 years, Controls: 68.3 years, SD=3.4).

*Results*

Figure 3.1.8 shows the performance of JM and the four controls on the Recognition and Information components of the Famous Events test.

On the Recognition task, it can be seen from Figure 3.8 that JM's performance was above the mean of the controls for both pre- and post-illness periods. On the Information task, for the pre-illness period JM was comparable to the controls (Wilcoxon matched pairs signed ranks test, $z = -.983$, $p = 0.326$). For the post illness period, JM's performance is in fact significantly better than the controls (Wilcoxon matched pairs signed ranks test, $z = -3.24$, $p=0.001$). The controls did not show any significant difference between the two time periods (Mann Whitney $U = 689.5$, $p = 0.287$), whilst JM's scores do show evidence of a difference (Mann Whitney $U = 607.5$, $p = 0.064$, tied $p = 0.036$). JM was clearly not grossly impaired for the pre-illness period, performing at a similar level to age and education matched controls. However, despite having well matched control participants, JM was considerably better in her performance in the post-illness period in comparison to the controls and also in comparison to her performance for the pre-illness period. By contrast the controls show no difference for the pre and post-illness period.

JM was clearly remembering details of many public events, both pre- and post-illness, and the most it seems possible to conclude is that for some of the pre-illness events there was a little less detail or confidence in recalled information. By way of example, for 'The Kuwait Invasion' (from 1990), she responded, "Iraq invaded Kuwait. Was that the origin of the Gulf War? Or did we get them out of there?", and for 'The Piper Alpha Incident' (from 1988), she responded, "An oil rig disaster- it went on fire or did it sink? Large numbers of people had to be rescued". This is entirely consistent with her pattern of performance on the Famous Events Recognition test described in Study 1.

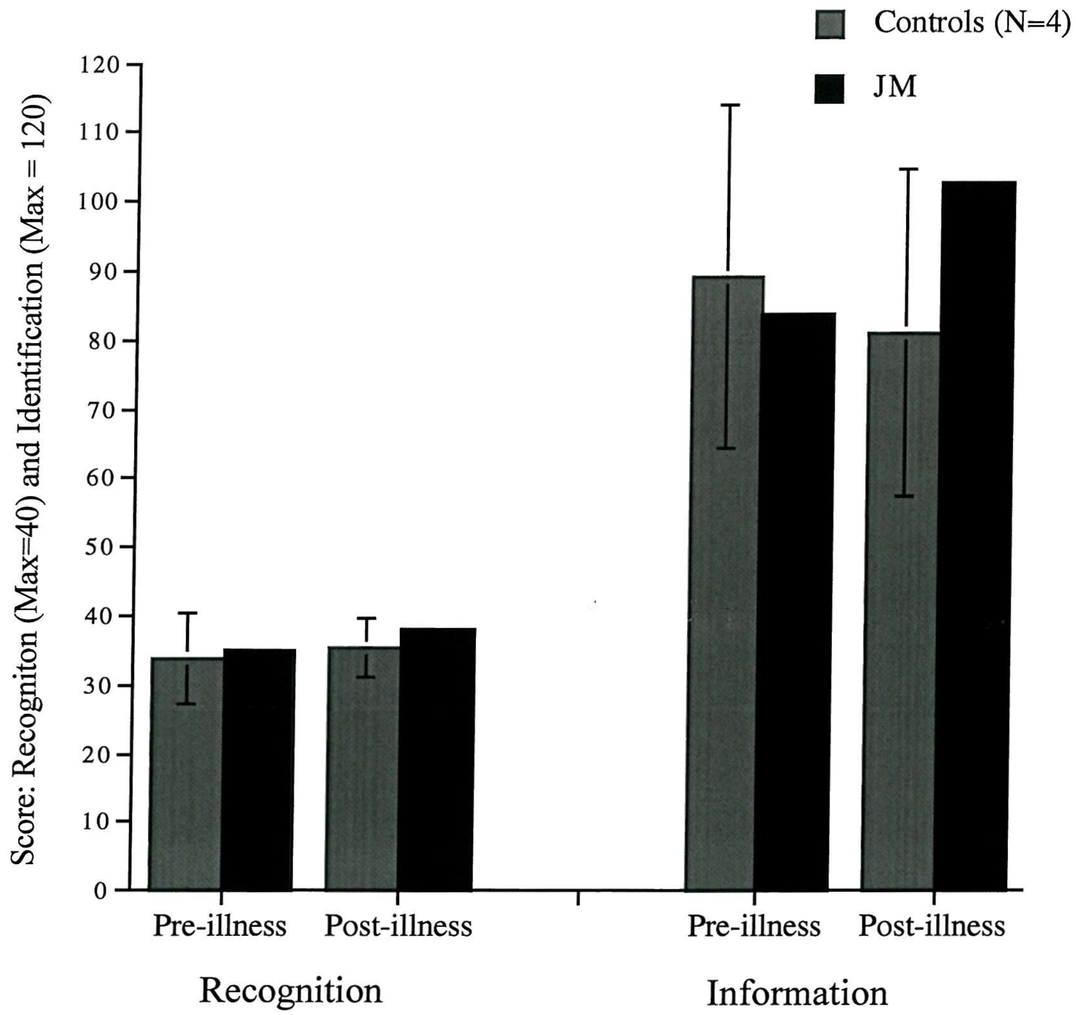



***Figure 3.1.8 Performance of JM and four control participants (mean and two standard deviation bars) on the Recognition and Information components of the Famous Events Test.***

### 3.1.8 Discussion

Study Phase 2 demonstrated that, some six years post-illness, JM continued to experience significant impairment in retrograde autobiographical memory in the context of intact anterograde learning. There was no evidence of accelerated forgetting and she appeared to have learned and retained a normal record of autobiographical information since recovering from her acute illness. Her knowledge of famous personalities from both before and after her illness was excellent. Her knowledge of famous events also appeared to be relatively good, though there were hints that her pre-illness knowledge was mildly impaired.

JM's results on the Crovitz task confirmed the finding from Study Phase 1 of a broadly U shaped pattern of recall, with good recall of recent events, moderate (but still impaired) recall of early life events and very poor recall of events over a period of some 20 years preceding the illness. The pattern is different from both the standard temporal gradient found in conditions such as Korsakoff's syndrome (who show impaired performance for post-morbid event recollection), or the reverse temporal gradient associated with semantic dementia (Snowden, Griffiths and Neary, 1996; Graham et al. 1998, Graham, 1999).

The anatomical data in this case did not provide a clear picture as far as identifying a single specific lesion responsible for the FRA. Both MRI and SPECT revealed evidence of parietal pathology, particularly on the left, but there was no indication of an imagery/perceptual deficit that might account for the autobiographical memory impairment. MR imaging demonstrated frontal lesions and in the early stages of her illness JM demonstrated executive impairments characteristic of frontal lobe lesions. Like other early impairments, her executive functioning improved. An hypothesis that the left anterior temporal lobe lesion caused the impairment would fit with many of the previous cases of FRA (see Kapur, 1993, Hodges, 1995). However, the *multifocal* nature of the neocortical damage might also be critical. Cerebral vasculitis is a rare disorder with many potential causes, includuding granulomatous angiitis (see Greenan, Grossman and Goldberg, 1992), the diagnosis reached in the case of JM. It can affect vessels of any size, but shows a predilection for small arteries and arterioles and causes necrosis of the vessel wall, with consequent infiltration by lymphocytes, plasma cells, large mononuclear cells and giant cells, resulting in turn in multiple foci of ischaemic or haemorrhagic infarction. It will be argued later that this multifocal damage may be critical to the relatively selective impairment of autobiographical memory which is perhaps uniquely dependent upon the integration of information from multiple brain regions.

To what extent are the results of the studies with JM consistent with predictions from contemporary models of memory described in Chapter 1? Before considering these models, it is necessary to address another hypothesis, namely that JM's FRA can be explained in terms of a general retrieval deficit. Levine et al. (1998) argued that their patient ML's FRA could be explained in terms of a retrieval deficit associated with lesions of the right ventral frontal cortex, with associated damage to the uncinate fasiculus leading to a fronto-temporal disconnection. They further argue that the preservation of anterograde memory functioning in ML can be accounted for by a degree of reorganisation of preserved pathways. In the case of ML, there was evidence on functional brain imaging of hyper-activation (in comparison with controls) in the left inferomedial temporal lobe system, which they claim, was responsible for normal performance on a cued-recall task. These 'preserved pathways' cannot, however, provide access to pre-injury information. One of the observations that Levine et al. made about ML was that he reports "a feeling of subjective distance from recall of events occurring after his recovery". Thus, his anterograde recall of autobiographical events is not entirely normal and perhaps the lack of feeling of personal connection with the events reflects a lack of the ability to recall autobiographical episodes in detail. Whilst ML has intact anterograde memory for unimodal memory settings (e.g. word lists, designs), he appears not to have normal recall of events that require integrated multi-modal or multi-sensory information (i.e. post-illness autobiographical episodes). By contrast, JM appears to have normal recall of such information. JM has MRI evidence of frontal lobe damage, but little in the way of behavioural evidence of executive deficit at the time of these studies. The fact that JM was able to encode and retrieve recent autobiographical events with a normal level of detail and phenomenological experience suggests that her difficulty cannot be ascribed to a general retrieval deficit, resulting from frontal lobe impairment.

As noted earlier, Moscovitch and Nadel (1999, p.89) noted that the existence of FRA is consistent with their Multiple-Trace model, at least for cases where there is neocortical damage that creates difficulty with basic perceptual processes that are important for autobiographical recall (e.g. Ogden's 1993 case). However, they also predict that anterograde memory deficits will occur for the acquisition of material where encoding is dependent upon the perceptual system that is damaged (e.g. visual memory impairment). In JM's case, there was no evidence of a perceptual deficit to account for a failure to retrieve particular elements of autobiographical memories.

According to the Moscovitch and Nadel model, the hippocampal complex continues to play a role over the lifetime of an autobiographical memory. Significant disruption to the system should therefore produce difficulty in recall over a longer time period.

As discussed earlier, they note that the temporal, 'Ribot' gradient often associated with retrograde amnesia can be accommodated within their theory by arguing that older memories are represented by more traces within the hippocampal formation than more recent episodes and are thus less vulnerable to damage that does not completely destroy the whole of the medial temporal lobe region. If this model is correct, a temporary, but severe disruption to this system would be expected to cause extensive retrograde amnesia in combination with the anterograde amnesia. A difficulty in recalling autobiographical memories should perhaps only last for as long as the system is disrupted and on return of functioning, recall should be normal once more. This pattern was demonstrated in Chapter 2.2, in the case of TGA. This was not the case with JM, who was left with a permanent retrograde amnesia following the return to normal functioning of anterograde recall and an apparently intact hippocampal complex. Another hypothesis is that the temporary disruption disturbed the multiple hippocampal traces to an extent that connectivity was lost, without there being significant loss of actual neuronal tissue (as evidenced by brain imaging). It was noted that JM had a seizure during the course of the acute phase of her illness. One possibility is that this seizure, with or without additional sub-clinical epileptic activity during the acute phase, disrupted hippocampal or hippocampal- neocortical links. It is uncertain how evidence could be gathered to confirm or refute this hypothesis.

The Standard Consolidation Model, as exemplified by Murre's (1996) theoretical framework, also predicts the presence of a FRA, in the context of a temporary disruption to the hippocampal-neocortical network. However, a temporally graded retrograde amnesia is predicted by the model. The time period of the impairment is dependent upon the time period associated with the length of the process of consolidation. However, in the case of JM, the time period of her autobiographical memory impairment was of the order of 20-30 years. It seems unlikely that the process of consolidation would last this long. It was noted earlier that, in his formulation of the Standard Consolidation Model, Murre (1996) added a caveat with regard to the development of FRA, which suggested that where there are widespread diffuse lesions, a process of self-repair will lead to the development of a great number of faulty connections so that the system regains plasticity at the expense of its existing memories (see Robertson and Murre 1999). A disorder such as cerebral vasculitis produces numerous, widely distributed, but discrete lesions. It is possible therefore that these lesions have disrupted distributed cortical networks so that memories relying on interconnectivity between multiple primary sensory and multi-modal areas will have a critical impact on autobiographical episodic memories, whilst sparing knowledge which is represented in more discrete localised regions.

As noted earlier in Chapter 1, a number of cases of focal or disproportionate retrograde amnesia have been described in which the impairment in retrograde recall is combined with intact initial learning, but impaired recall of anterograde information after a longer delay, usually of the order of a few weeks. The relationship between these two types of impairment is, however, not clear. The fact that FRA can occur without evidence of accelerated forgetting (as in the case of JM) suggest that the two phenomena are not automatically linked. But this does not mean that in the cases where both are present that there is not a common explanation. Several of the patients studied have had epilepsy and Blake et al. (2000) demonstrated accelerated forgetting in a group of patients with epilepsy. DeRenzi and Luchelli (1993) argued that both impairments could be conceptualised as consolidation deficits, but only if it is assumed that the FRA is caused by disruption to a consolidation process that must be happening over a period of decades. These issues are addressed further in relation to a study of retrograde memory in two cases of very long term accelerated forgetting described in Chapter 4.

For cases of FRA such as that of JM, who show intact anterograde learning, no accelerated forgetting, and significant impairment of autobiographical retrograde memory, it seems most likely that multi-focal damage to either lower level features of memories, or the pathways that are required to connect those mnemonic fragments into an event, is responsible for the pattern of impairment. It is perhaps helpful to draw upon the Convergence Zone theories of Damasio (1989) and Mesulam (1998) described earlier in Chapter 1, Section 1.5. Lesions to higher level convergence zones or connections between those zones would lead to disruption of consolidated, 'semanticised' autobiographical event memories and also mean that the hippocampal system would be unable to reinstate autobiographical event patterns. So long as sufficient tissue remained intact, then new links could be made (i) within convergence zones, (ii) between convergence zones and (iii) between convergence zones and the intact hippocampus. If this explanation is correct, then other cases of vasculitis or other conditions that result in multiple, discrete lesions, such as Systemic Lupus Erythematosus (SLE) or Polyarteritis Nodosa, should show a similar pattern. No other cases have been reported, but it is not clear as to whether this means that FRA never occurs in other conditions or whether appropriate assessment has not been undertaken.

JM showed a selective impairment in episodic retrograde memory. In the next Section, case VH is presented. In contrast to JM, she presented with a selective impairment in *semantic* retrograde memory.

## 3.2 Selective semantic retrograde amnesia

### 3.2.1 Introduction

The term 'semantic retrograde amnesia' has been used (Kapur, 1999) to refer to both personal semantic memories and public semantic memories. Personal semantic memories may include basic autobiographical facts (names of familiar people, schools attended, jobs etc.) along with non-verbal knowledge such as the ability to recognise familiar faces. Public semantic information includes knowledge of famous personalities, news events, etc. The distinction has been made between semantic retrograde knowledge and knowledge of objects, vocabulary and other encyclopaedic knowledge (Kapur, 1999, p 809), typically encompassed by the term semantic memory. The present study focused on the issue of impairment of semantic retrograde memory, though I will return to the issue of the utility of the distinction between semantic retrograde knowledge and semantic memory later. As discussed in Chapter 1, Section 1.3.3, Wheeler and McMillan (2001) identified four cases of a selective loss of semantic retrograde memory (DeRenzi, et al., 1987; Grossi, et al., 1989; Yasuda, et al., 1997; Markowitsch et al., 1999). Each of these cases presented with deficits in knowledge of famous faces, names or events or in general knowledge, with better recall of autobiographical events. Wheeler and McMillan noted that in each of these cases the level of semantic retrograde memory impairment was very significantly impaired in comparison to both autobiographical episodic retrograde amnesia and anterograde memory. Nevertheless, in each case there was some evidence of impairment in anterograde memory.

This chapter will describe investigations with case VH, who presented initially with a progressive prosopagnosia, which subsequently developed into a more general loss of person and public event knowledge in the context of relatively spared day to day and autobiographical retrograde memory. Although VH's everyday memory was satisfactory, it was hypothesised that a focal loss of knowledge of a class of objects (e.g. faces/people) might be expected to produce a loss of anterograde memory for this class of object in addition to the loss of retrograde information. This prediction was tested in the studies presented in this chapter.

From clinical and anatomical perspectives, the case presented in this chapter is significant in that the pattern of VH's impairments, lesion and disease process characterises a form of focal neurodegenerative process hitherto rarely described. Three major forms of fronto-temporal dementia have been described (Hodges, 2001; Neary, Snowden and Mann 2000; Mesulam 2001). These include (a) dementia of the frontal type characterised by changes in personality, behaviour and executive functioning (Neary, Snowden, Northern and Goulding, 1988; Gustafson 1987); (b) semantic dementia (progressive fluent aphasia) in which the basic impairment is in semantic knowledge. Patients typically have asymmetric anterolateral temporal atrophy, typically worse on the left, with relative sparing of the hippocampal formation (Chan, Fox, Scahill, Crum, Whitwell, Leschziner, Rosser, Stevens, Cipolotti, and Rossor, 2001); (c) progressive non-fluent aphasia, in which the phonological and syntactic components of language are affected in association with left perisylvian atrophy.

Furthermore, there are reported cases of progressive dementia in which the prominent deficits are visuo-perceptual and spatial impairments, with concomitant posterior parieto-occipital cerebral atrophy (Benson, Davis and Snyder, 1988; Mendez and Cherrier, 1998; Ross et al. 1996; Beversdorf and Heilman, 1998).

There have been only a few reports presenting both neuropsychological and brain imaging data on patients where the main focus of the atrophic process involves the right hemisphere. Tyrrell, Warrington, Frakowiak and Rossor (1990) reported neuropsychological and PET scan results in a patient with a twelve-year progressive history of prosopagnosia and naming difficulties. The patient was severely impaired at both identifying familiar faces and recognising whether or not they were familiar. He was weak on a series of visuo-perceptual tasks, though he scored in the normal range on a test of face perception. He was severely impaired on Warrington's Recognition Memory Test for faces, but was also weak on the verbal version. In addition, he had a severe naming deficit. The combination of visuo-perceptual problems, prosopagnosia, verbal and non-verbal memory weakness and a naming deficit indicated involvement of both right and left temporal lobes. PET scanning confirmed a reduction in oxygen metabolism in the superior temporal gyrus on both sides, the hypometabolism being more marked on the right. Structural brain imaging data were not presented.

DeRenzi (1986) described two patients with progressive impairment of visuo-perceptual abilities characteristic of apperceptive agnosia (and a further patient with progressive dyspraxia). Both patients were impaired at recognising objects and faces. They also demonstrated more basic perceptual problems with line length, angle size and figure-ground discrimination of overlapping figures. DeRenzi argued that although both patients showed more general cognitive deficits, these were much less marked than deficits on visual tasks. Their CT scans showed lateral ventricle enlargement, especially in the occipital horns, "compatible with an atrophic process mainly involving the posterior areas of the hemisphere" (p179).

All three patients reported above had slowly progressive prosopagnosia in the context of focal brain atrophy, but also had additional cognitive deficits, which complicated their assessment. In addition, none of these were the results of detailed structural brain imaging reported. Furthermore, detailed investigations of semantic and autobiographical memory were not undertaken.

A case of slowly progressive amusia and aprosody in association with orofacial and eyelid apraxias was reported by Confavreux et al. (1992). This patient was independent in activities of daily living. Insight, judgement and behaviour were reported as normal, as were language, visuo-spatial perception and memory. Brain imaging demonstrated focal degeneration of frontal and temporal regions, limited to the right hemisphere.

The patient investigated in this chapter presented with a pathological process that was primarily focused on the right temporal lobe. The key questions addressed were:

(i) Is there substantive evidence for a non-verbal right-temporal semantic dementia syndrome analogous to the well-documented classical verbal left-temporal semantic dementia syndrome?

(ii) Is autobiographical memory spared or impaired in such a condition?

(iii) What is the status of anterograde memory for information whose representation appears to have been degraded by the pathology in question?

### 3.2.2 Case history

VH, a 68 year-old right-handed woman who was a retired senior clerk, was referred with complaints of increasing difficulty in recognising people and some minor difficulty with day to day memory. She had no history of stroke, head injury, or any other prior neurological event, and she reported that her difficulties had become gradually worse over the previous 12 years, though only being noticeable to friends and relatives in the two years prior to referral. She noted that she had recently had experiences of being unable to recognise close friends and family members (including her daughter and her son), especially if they were out of context. She did not recognise familiar actors in films and had to rely on voice or other significant characteristics of people to aid recognition. It was striking that from one assessment session to the next, which were more than two weeks apart, she could recall in detail what she had done in the previous session, but was unable to recognise the person who had assessed her until she had devised a strategy, such as using hairstyle. She reported that she occasionally had problems losing her way, though in general she coped well in familiar environments. VH lived alone and managed day-to-day household affairs, including financial matters, without difficulty. Ophthalmologic assessment revealed normal visual acuity (6/6 bilaterally), pupillary responses and fundi. Her visual fields were full to confrontation without signs of visual inattention. Visually-guided reaching for single objects, colour matching and naming were normal. Contrast sensitivity examination revealed only a very mild weakness with middle and high spatial frequencies. The remaining parts of a neurological examination were also normal except for a severe unilateral deafness, which was known to be long-standing.

### 3.2.3 Brain imaging

#### *3.2.3.1 Single Photon Emission Computerised Tomography (SPECT)*

A HMPAO SPECT scan was obtained. This revealed marked reduction in perfusion in the antero-lateral part of the right temporal lobe.

#### *3.2.3.2 Magnetic Resonance Imaging*

The brain was imaged using a G.E. Sigma magnet. No focal areas of high signal intensity changes were seen on the T2 weighted images. There was however diffuse atrophic change involving the right temporal lobe with relative sparing of the hippocampal region. This was best seen on the T1 weighted coronal and reformatted axial images, shown in Figures 3.2.1 and 3.2.2.

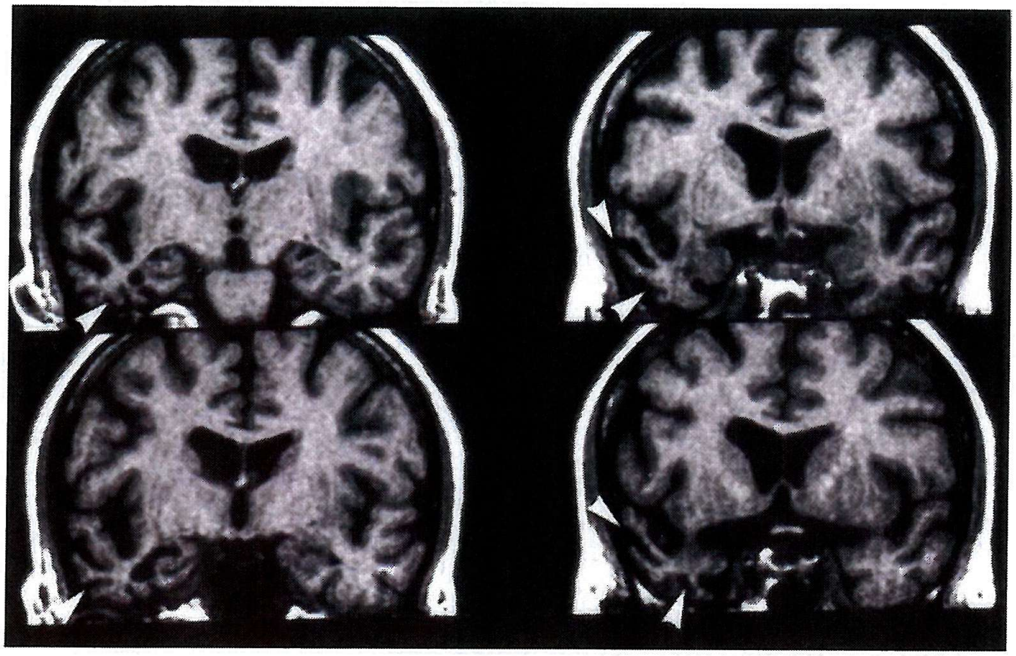


***Figure 3.2.1 Coronal MRI of patient VH's brain demonstrating selective atrophy of the right temporal lobe (arrowed).***

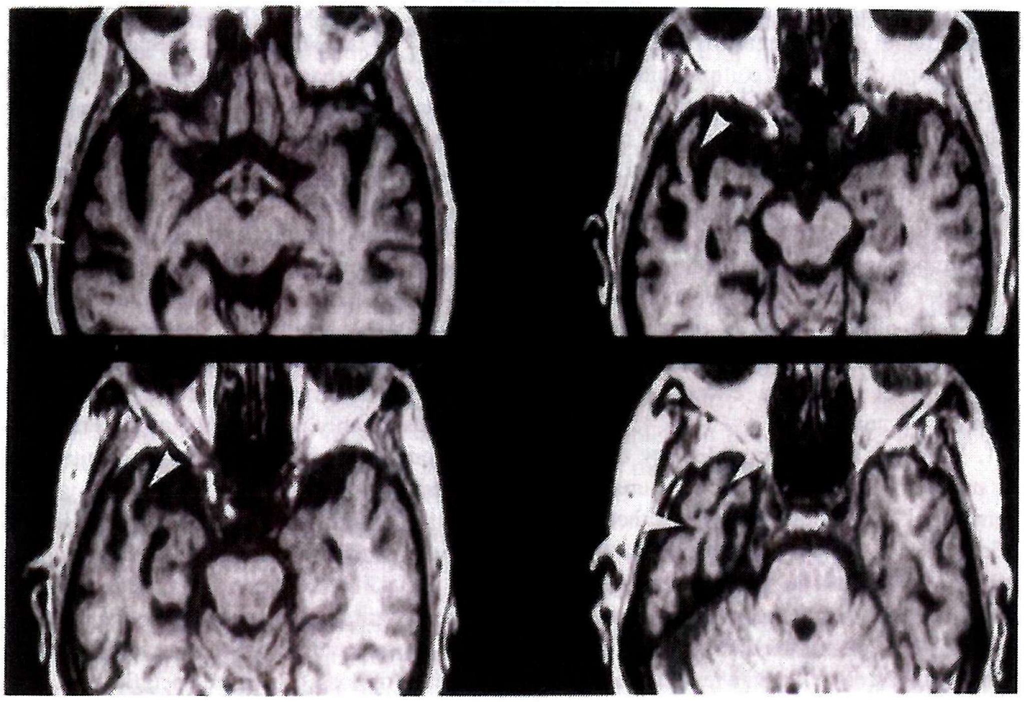


***Figure 3.2.2 Axial reformatted images of patient VH's brain showing striking atrophy of the right temporal lobe(arrowed).***

### 3.2.4 General cognitive and anterograde memory functioning

VH underwent detailed neuropsychological assessment on two occasions, the second assessment being carried out six to nine months following the first. For a small number of tests, a third assessment was undertaken some 11 months later. Results of standard clinical neuropsychological tests are shown in Table 3.2.1.

#### *3.2.4.1 Assessment 1*

On the first assessment VH was fully oriented and on the Mini-Mental State Examination (Folstein, Folstein and McHugh, 1975) obtained a perfect score of 30/30. The level of measured IQ, in the high average range, was commensurate with her estimated pre-morbid IQ, as judged by the National Adult Reading Test (Nelson, 1991). Spontaneous language was well articulated and fluent, without word finding difficulties or paraphasic errors. Her performance on the Graded Naming Test (McKenna and Warrington, 1983) was well within normal limits, though below what one might have expected on the basis of her WAIS-R vocabulary score. She was normal on a shortened version of the Token Test and on a more specific syntactic comprehension task, the Test for the Reception of Grammar (TROG; Bishop, 1982). She also performed normally on a range of tasks taken from the Semantic Memory Test Battery (Hodges et al., 1992) including category fluency, naming of line drawings, naming to description, and on category sorting tasks in which 48 items are sorted firstly according to the superordinate categories of living/man-made, and then into various subordinate categories.

On the visuo-perceptual tests from the Visual Object and Space Perception Battery (Warrington and James, 1990), she was entirely normal, apart from the Silhouettes task in which the subject has to identify an animal or object from a foreshortened view in silhouette. On the Benton Line Orientation Test (Benton, Varney and Hamsher, 1978), she achieved a perfect score.

Anterograde memory tests indicated that she had excellent working memory (forward and backwards digit span), and only marginal impairment on delayed recall of passages and designs, when compared with what might have been expected pre-morbidly. On the Rivermead Behavioural Memory Test (Wilson et al., 1985), she scored at the top end of the moderately impaired range; she was poor on the story recall (though her performance might have been somewhat affected by hearing difficulties), but was satisfactory on most of the other tasks.

***Table 3.2.1 VH's general cognitive test scores***

| | Assessment 1 | Assessment 2 |
|---|---|---|
| WAIS- R sub-tests (age scaled scores) | | |
| Information | 9 | 10 |
| Digit Span | 17 | 19 |
| Vocabulary | 14 | 12 |
| Arithmetic | 13 | 13 |
| Comprehension | 16 | 14 |
| Similarities | 10 | 9 |
| Picture Completion | 14 | 15 |
| Picture Arrangement | 10 | 14 |
| Block Design | 11 | 11 |
| Object Assembly | 11 | 10 |
| Digit Symbol | 10 | 10 |
| Verbal IQ | 118 | 120 |
| Performance IQ | 111 | 114 |
| Full Scale | 117 | 119 |
| Estimated pre-morbid IQ (NART) | 115 | - |
| Mini-mental State Examination | 30/30 | 28/30 |
| Visual perception | | |
| Visual Object and Space Perception Battery | | |
| Incomplete Letters | 20/20 | 20/20 |
| Silhouettes | 8/30 (Impaired) | 8/30 (Impaired) |
| Object Decision | 17/20 | 13/20 (Impaired) |
| Dot Counting | 10/10 | 10/10 |
| Position Discrimination | 20/20 | 20/20 |
| Number Location | 10/10 | 10/10 |
| Cube Analysis | 10/10 | 10/10 |
| Benton Line Orientation | 30/30 | 23/30 |
| Language | | |
| Spontaneous speech | Normal | Normal |
| Graded Naming Test | 17/30 | 14/30 |
| Token Test | 33.5/36 | 35/36 |
| TROG | 80/80 | - |
| Anterograde Memory | | |
| Forward Digit Span | 8 | 9 |
| Backward Digit Span | 8 | 8 |
| WMS-R Logical Memory (Immediate) | 21.5 (52nd percentile) | 21.5 (52nd percentile) |
| WMS-R Logical Memory (Delayed) | 12 (32nd percentile) | 15 (45th percentile) |
| WMS-R Visual Reproduction (Immediate) | 39 (99th percentile) | 37 (99th percentile) |
| WMS-R Visual Reproduction (Delayed) | 21 (45th percentile) | 38 (99th percentile) |
| Rivermead Behavioural Memory Test | 16/24 (moderate impairment) | 15/24 (moderate impairment) |

| | | | |
|---|---|---|---|
| Rey Complex Figure: | Copy | 33/36 | 32/36 |
| | Delayed Recall | 11.5/36 | 12/36 |

She scored within the normal range on the delayed recall of the Rey-Osterreith complex figure. In summary, there was no evidence of any significant decline in her general intellectual, language or visuo-perceptual abilities with only a very mild deficit in anterograde memory functioning.

#### *3.2.4.2 Assessment 2*

There was very little change between the two assessments. VH's IQ remained at the top end of the high average range. Her Mini-Mental score although two points below the previous assessment was still well above the proposed impairment cut-off score of 23. Her score on the Graded Naming Test was also lower by three points, though again it remains well within the normal range. Performances on the Rivermead Behavioural Memory Test, Wechsler Memory Scale (Logical Memory and Visual Reproduction) and the Rey-Osterreith Complex Figure were virtually unchanged. On the Visual Object and Space Perception Battery, she was again impaired on the Silhouettes. On this occasion, she was also impaired on the Object Decision task (in which the subject has to identify which of four silhouettes is a 'real' object), though her score of 13/20 is well above chance level. Her score on the Line Orientation test was poorer than in Assessment 1, though it is still well within the normal range.

### 3.2.5 Investigations of face processing and knowledge of famous people from faces.

A series of investigations of different aspects of face processing and knowledge of famous people were carried out to determine the nature of VH's difficulties. Once again, most of these tests were administered on two occasions, separated by a six to nine month interval, though for some specified tests a third assessment was also carried out a further 11 months later.

#### ***3.2.5.1. Unfamiliar face matching and face perception***

*Materials and methods*

*Face matching.* On Benton and van Allen's (1968) Facial Recognition Test, the subject is presented with a photograph of a face, lit so as to reveal only the central region of the face, excluding the hair, and is required to match this face with other views of the same face photographed from different angles. These are presented amongst similarly lit views of different faces.

*Age perception.* On this task (provided by Prof. Andy Young) VH was presented with 40 black and white full face photographs and for each one was asked to judge the face as either 'old' (above 50 years) or 'young' (below 50 years).

*Gender perception.* Two tasks were administered (provided by Prof. A. Young). In the first task (Gender Perception A), the same 40 full face photographs used in the age perception task were shown and VH was asked to judge whether the face was male or female. In the second task (Gender Perception B) a further set of 40 black and white face photographs were shown, but for this set only the central part of the face (excluding most of the hair) was shown and once again a gender judgement was made.

*Eye gaze sensitivity.* To examine sensitivity to direction of eye gaze VH was presented with 18 pairs of full face colour photographs of a man. In one of each pair of photographs the eyes are looking directly into the camera (though head angle varies) and in the other the eyes are looking away with a deviation of either 5, 10 or 20 degrees. Across the 18 pairs, there are six examples of each deviation. The subject's task is to choose the face in each pair in which the eyes are looking directly into the camera.

For the age, gender perception and eye gaze sensitivity tasks performance was contrasted with that of nine age and IQ matched controls (mean age 70.1 years, s.d. 2.35, mean NART IQ 117.8, s.d. 4.9).

*Results*

Results are provided in Table 3.2.2

*Assessment 1.* In this assessment only the Benton and van Allen face perception test was administered and VH scored well within the normal range (with an age and education corrected score of 47/54).

***Table 3.2.2. Unfamiliar face matching, face perception and facial expression analysis.***

| | **Assessment 1** | **Assessment 2** | **Control Data** |
|---|---|---|---|
| Benton and van Allen Facial Recognition Test | 47/54 | 45/54 | Normal range 40-54 |
| Gender Perception A | - | 39/40 | n=9, mean=38.8, s.d.=0.67 |
| Gender Perception B | - | 35/40 | n=9, mean=36.7, s.d.=1.87 |
| Age judgement | - | 39/40 | n=9, mean=37.56, s.d.=1.88 |
| Eye gaze sensitivity | | 18/18 | n=9, mean=16.86, s.d.=0.63 |

*Assessment 2.* On the Benton and van Allen test VH's performance was again well within the normal range and was only two points below her previous performance (age and education corrected score of 45/54). She demonstrated good perception of age and gender, and achieved a perfect score on the eye gaze sensitivity task.

### *3.2.5.2. Facial expression analysis*

VH was given an expression identification task and an expression matching task (both described in Young et al., 1993). In the recognition task, VH was shown photographs from the Ekman and Friesan (1976) series, displaying one of six possible emotional expressions (happiness, anger, sadness, surprise, fear and disgust). The names of the six emotions were printed below the photograph in vertical alignment, with the order of the names randomised across trials. VH was asked to choose the name which best described the facial emotion shown in the photograph. Six practice trials were followed by 24 experimental trials, four for each of the six emotions.

In the expression matching task, a photograph of a face displaying one of the six possible emotions had to be matched against four simultaneously presented alternatives, including another example of the same target emotion and three distractors selected from the remaining possibilities. All five photographs were of five different people of the same sex, again taken from the Ekman and Friesan set. Materials for both tasks were kindly loaned by Prof. A. Young.

*Results*

Results of these tests, which were only given in Assessment 2, are given in Table 3.2.3. VH's performance was entirely normal on both tasks.

***Table 3.2.3: Results from the assessment of expression matching and identification.***

| | | |
|---|---|---|
| Expression matching | 17/18 | n=32, mean=16.23, s.d.=1.91 |
| Expression identification | 20/24 | n=32, mean=20.93, s.d.=1.70 |

***3.2.5.3. Famous face recognition***

Two different face familiarity tasks were administered.

*Yes/No familiarity task.* VH was shown 50 famous faces adapted from the famous faces test of Hodges and Ward (1989) to include 10 famous personalities from each of the decades 1940's -1980's randomly mixed with 50 photographs of non-famous people from the same period as the famous faces. She was asked to make a yes/no judgement as to whether she thought the face was famous or not.

*Forced choice triplets task.* VH was given 15 sets of face triplets consisting of one famous face and two non-famous distractors and asked to try to identify the famous face.

*Results*

*Assessment 1*

*Yes/No familiarity:* Results are presented in Table 3.2.4. A d' analysis indicated VH was able to distinguish famous from non-famous faces to a significant degree. She was, however, significantly poorer than a group of age and IQ matched controls; nine subjects (mean age, 61.3 years, s.d. 8.4, mean NART IQ, 112.9, s.d. 9.9), correctly classified an average of 90.6/100 faces (s.d. 9.4) as either famous or not famous, which contrasts with VH's total score of 69/100 correct classifications (giving a z score of -2.28). VH was confident at rejecting the non-famous faces, but tended to also reject the famous faces unless she was very confident that the person was famous.

*Forced choice triplets task:* She was accurate on 14/15 triplets. On a subsequent identification task (described below) it was noted that, of the 14 she had correctly chosen as famous, she was able to correctly identify five; of the other nine, she reported she 'guessed' that they were famous, though knew neither their names nor anything about them.

***Table 3.2.4 VH's performance on the face familiarity task***

Assessment 1

| | | Correct response: Famous | Correct response: Unknown |
|---|---|---|---|
| VH's response | Famous | 23 | 4 |
| | Not-famous | 27 | 46 |

d' = 1.377, s.e.= 0.331

Assessment 2

| | | Correct response: Famous | Correct response: Unknown |
|---|---|---|---|
| VH's response | Famous | 36 | 22 |
| | Not-famous | 14 | 28 |

d'= 0.738, s.e.=.261

*Assessment 2*

*Yes/No familiarity:* Results of d' analysis confirm that VH was again able to distinguish famous from non-famous faces. Once again, however, her performance was significantly poorer than the control participants (her score of 64/100 represents a z score of -2.83). On this assessment the pattern of performance was different such that VH was much more likely to incorrectly identify non-famous faces as famous (i.e. make false positive responses).

*Forced choice triplets:* She was accurate on 11/15 triplets. On the subsequent identification task (see below) it was noted that, of the 11 she had correctly chosen as famous, she was able to correctly identify only two; of the other nine, she once again reported that she 'guessed' that they were famous, though knew neither their names nor anything about them.

### *3.2.5.4. Famous face identification.*

VH was asked to identify the 50 famous faces used in the familiarity task. If unable to name the person, she was asked to provide as much identifying information as she could, the main score of interest here being the number of faces she could name or provide sufficient information to uniquely identify the person. Normative data was collected using 14 control subjects, matched with VH for age (mean age, 66.1 years, s.d. 6.42) and IQ (mean IQ, 113, s.d. 9.7). Each of the people whose faces were used in the test was primarily famous during one of the five decades from the 40's to the 80's. VH's pattern of performance was examined to discern whether there was any evidence of a temporal gradient in the accuracy of her identification of the famous faces. If VH was unable to provide a name or identifying information, she was given first a semantic cue (i.e. some identifying information about the person) and if she was still unable to produce the name she was given a phonemic cue (i.e. the first name of the person) and asked if she could complete the name.

*Results*

Results are provided in Table 3.2.5

*Table 3.2.5. VH's performance on famous faces identification test.*

| | Assessment 1 | Assessment 2 | Control Data (N=14) |
|---|---|---|---|
| Reported to be familiar | 35/50 | 20/50 | |
| Named | 9 | 4 | |
| Identified, but not named | 2 | 3 | |
| Overall identification score (Named/identified) | 11/50 | 7/50 | mean = 44.5 (s.d. = 4.99) |
| Named when provided with semantic cue. | 14 | 10 | |
| Named when provided with phonemic (first name) cue. | 16 | 12 | |

*Assessment 1.* VH was able to identify only 11/50 faces ($z=-6.61$, $p<0.0001$), naming nine (including Ronald Reagan, George Formby, Ian Botham and Terry Wogan) and providing specific identifying information for a further two faces. For a small number of the other faces she was able to give very general information about occupation (e.g. actor, politician), but was unable to provide any more specific identifying information. For a few faces she responded that she was sure that she should know the person (i.e. they seemed familiar), but she was unable to provide any identifying information whatsoever. When given a semantic or phonemic cue she was better at producing the name of the individual, leaving a total of 11 that she was unable to name under any condition. There was no evidence of a temporal gradient in her recall, as can be seen from Table 3.2.6.

*Assessment 2.* VH was able to identify only 7/50 faces, ($z= -7.41$, $p<0.0001$) naming four and providing identifying information for a further three. Of the seven identified, four were also identified in Assessment 1. Of the three others identified in this assessment, she had provided general information about one (Harold Wilson) in Assessment 1 and in this assessment said she had guessed the identity because of the pipe in the photograph (for which she knew Harold Wilson was famous), but she had not provided any information about the other two (Anthony Eden and Mikhail Gorbachev) in Assessment 1. In Assessment 2 she said she identified Gorbachev by his birthmark. For most of the rest she responded that she had no idea about identity or occupation. Once again there was no evidence of a temporal gradient in her performance. Semantic or phonemic cueing again produced a further improvement in naming performance, though this improvement was less than at Assessment 1.

***Table 3.2.6. The pattern of VH's performance on tests of famous face identification in terms of decades in which individuals were primarily famous, for familiarity judgement and naming/identification***

| | **Assessment 1** | | **Assessment 2** | |
|---|---|---|---|---|
| Decade | Familiarity (max=10) | Naming or identification (max=10) | Familiarity (max=10) | Naming or identification (max=10) |
| 40's | 8 | 2 | 4 | 2 |
| 50's | 5 | 0 | 4 | 1 |
| 60's | 7 | 1 | 1 | 1 |
| 70's | 6 | 4 | 5 | 1 |
| 80's | 9 | 4 | 6 | 2 |

*Assessment 3.* A third assessment was carried out some 11 months later, at which point VH rated just 3/50 items as familiar, and provided some identifying information for each of these (one from each of the 40's, 70's and 80's), but named none. She was unable to name any when provided with either a semantic or phonemic cue.

**3.2.6 General semantic knowledge of famous people.**

VH's general semantic knowledge of people was assessed by giving her the names of each of the 50 famous people who featured in the photographs and asking her to provide as much information about them as possible. A response was scored as correct if it included detail that was more detailed than a superordinate level (e.g. 'leader of the labour party' rather than just 'politician', or 'played ukulele and sang' rather than just 'entertainer') Her performance was contrasted with a group of 30 control subjects (mean age 68 years, s.d. 8.7).

***Results***

*Assessment 1.* VH was able to provide detailed information about 39 (78%) of the 50 famous people (e.g. Sarah Ferguson, "The Duchess of York, a very natural person who is doing what is natural to her generation. Her life made unhappy by the media, as she was photographed going swimming with another man"; Mikhail Gorbachev, "Russian, was trying to get rid of Soviet way of life and change it to a more democratic way. Got himself into trouble for it." ). However, this performance was mildly impaired when compared to the controls ($z=-2.42$, $p=0.0156$).

*Assessment 2.* VH was able to provide detailed information about 23 (46%) of the 50 famous people ($z=-6.68$, $p<0.0001$). In assessment 1, she had been able to provide specific information for all 23 of these famous names, but she had also provided specific information for a further 16 names. For many of this group of 16, VH would say that she was sure she knew who they were, but she simply couldn't "access" the information. There was some evidence for the validity of VH's assertions that she had some knowledge about various people - if she was cued with some information about a person she could then produce further information spontaneously. For example, she was unable to provide information about Richard Dimbleby, but when cued she accurately responded that he had been a broadcaster and said, "Oh yes, and his two sons do it now."

*Assessment 3.* Once again a third assessment was carried out some 11 months after the second. On this occasion VH provided detailed information for just 11 (22%) of the 50 famous people.

**3.2.7 Investigations of other category exemplars: Famous places and flowers.**

Individual faces represent unique exemplars of the general category faces/people. The possibility arose, therefore, that although VH did not have a problem identifying objects, she could have had a problem identifying unique exemplars of particular categories of objects. To explore this possibility VH was assessed on two further tasks. The first was a famous places task (described by McCarthy, Evans and Hodges, 1996) in which she was asked to identify a set of 25 famous landmarks/buildings (such as Eiffel Tower, Leaning Tower of Pisa, Statue of Liberty, White House, Big

Ben). As with the famous face task, VH was first asked to identify the famous places from photographs and later, in order to assess her semantic knowledge of the places, she was asked to provide as much detail as possible about the place when provided with the name of the famous place. Her performance on the photograph task was compared with that of 29 control subjects (mean age 56.8 years, s.d. 16.1, mean NART IQ 112.1, s.d. 11.2) and performance on the knowledge from name task was compared with 14 control subjects (mean age 43.8 years, s.d. 17.8, mean NART IQ 111.9, s.d. 8.2).

In the second task (only administered in the second assessment), VH was shown black and white photographs of 20 flowers and asked to name them. Although types of flower are not *unique* exemplars of a category in the same way that faces or buildings are, they clearly represent a sub-category within a specific object category. Previously reported prosopagnosic patients (e.g. patient PH., DeHaan Young and Newcombe, 1991) have been shown to be impaired on recognising particular flower types, whilst maintaining the ability to identify them as flowers. VH's performance was contrasted with nine age and IQ matched controls subjects (mean age 70.1 years, s.d. 2.35, mean NART IQ 117.8, s.d. 4.9).

***Results***

Results for the famous places task are summarised in Table 3.2.7

***Table 3.2.7 VH's performance on the famous places task***

| | **Assessment 1** | **Assessment 2** | **Controls** |
|---|---|---|---|
| Identification from photographs | 18/25 | 15/25 | n=29 mean=19.8/25, s.d.=4.26 |
| Information from names | 23/25 | 20/25 | n=14, mean =18.7/25, s.d.=3.56 |

*Assessment 1*: On the famous places test she correctly identified 18/25 places from photographs, which is well within the normal range for a group of control subjects . When providing information from the name of the place she scored 23/25, which is above the mean of a group of control subjects.

*Assessment 2*: She correctly identified 15/25 famous places from photographs which is clearly a deterioration, though still within the normal range. All of the places she identified on this occasion she had also previously identified in Assessment 1. However, on this Assessment she was unable to identify the Golden Gate Bridge, Arc de Triomphe and St Peter's, Rome. She correctly identified 20/23 places when given the names. As with the photographs, all of the places she identified on this occasion she had also identified on the previous assessment, but this time she could not provide information for Brandenberg Gate (Assessment 1: "It's in Germany, part of Berlin Wall, entrance between East/West; Assessment 2: "I should know, but I can't remember"), Arc de Triomphe (Assessment 1: "It's in Paris, France and it is a beautiful archway; Assessment 2: "In London, marble, built for a reason, but I can't remember what) and Red Square (Assessment 1: "Moscow, parliament of Russian State based there"; Assessment 2: "Nothing, not registered anything."). Once again., however, her performance was above the control group mean.

On the flowers task, she correctly identified 10/20 flowers. This score was weak when compared to controls (control mean = 17.78, s.d.= 1.2). However, it appeared that her mild anomia (rather than a failure of recognition) contributed significantly in many of her failures to identify particular flowers, since she was able to describe distinct features about many unnamed items. Therefore, in a subsequent task, all 20 photographs were laid out in front of VH and she was asked to locate each flower in turn when provided with the name. On this word-picture matching task, she correctly identified 19/20 flowers.

### 3.2.8 Famous events

VH was assessed on a test of famous event recognition described by Hodges and Ward (1989). The test includes 50 true events from the 30's to the 70's and 50 distractor, fictitious event items. Each item was read to VH, after which she was asked to identify whether the item was a famous event or a fictitious event. If she identified an event as famous she was asked to try to date the event for the decade in which it occurred. The results from this test were that VH correctly identified 34/50 events, and incorrectly identified 14 fictitious events as real. When her hits-minus-false-positives score (20) was compared with data (Hodges and Ward, 1989) from 41 control subjects (mean age 65.5 years, s.d. 8.6 years, mean hits-minus-false-positives score 38.2, s.d. 6.6), her performance is impaired. On this test, VH found it impossible to date events even for decade, and gave a response of "not sure" for all but one item (the Berlin Airlift), which she did correctly date as occurring in the 40's. Further assessment of this aspect of her performance by Kitchener and Hodges (1999) confirmed her deficit with identifying famous events.

### 3.2.9 Autobiographical memory

In a clinical interview, VH was able to give an accurate account of her life including details of family structure and history, her work, and information about current and past friends. She was able to remember the content of sessions (though not recognising who she saw), give a good account of recent relevant personal events and was able to give detailed episodic information relating to events in her life such as her wedding, holidays she had been on and events at work. The conclusion that VH showed intact autobiographical memory for personal semantics and autobiographical incidents was subsequently confirmed in testing carried out with VH, described in Kitchener and Hodges (1999). VH was shown to demonstrate intact performance on the AMI, and on tests of autobiographical name recognition, the Crovitz test, and a cued recall test of autobiographical events, using information about events obtained from VH's daughter.

### 3.2.10. Anterograde memory for faces, words and buildings

As part of routine clinical neuropsychological testing the Recognition Memory Test (RMT; Warrington, 1984) was administered in assessments 1 and 2. In addition, in Assessment 2, VH was also given a 'buildings' analogue of the RMT kindly loaned by Prof A Young. In each of the three tasks, VH was shown 50 target stimuli (words, black and white photographs of faces or buildings) one by one seeing each target for 3 seconds. Following presentation of all 50 targets, she was shown stimuli pairs and asked to chose the target she had seen previously. Her performance on the buildings task was compared with nine age and IQ matched subjects (mean age 70.1 years, s.d. 2.35, mean NART IQ 117.8, s.d. 4.9).

***Results***

The results, shown in Table 3.2.8, were striking in that her performance on both words and buildings was well within normal limits, whilst performance on the faces task was at chance levels.

***Table 3.2.8 Anterograde recognition memory for faces, words and buildings***

| | **Assessment 1** | **Assessment 2** |
|---|---|---|
| Faces | 29/50 (<5th percentile) | 24/50 (<5th percentile) |
| Words | 47/50 (75th percentile) | 46/50 (75th percentile) |
| Buildings | - | 41/50 (Control mean 42.11, s.d.3.26) |

### 3.2.11 Discussion

VH presented with a severe impairment in her ability to recognise familiar faces, including family members and famous public figures. Over a period of several months, her ability to recognise famous personalities from their names also deteriorated, and the severity of her prosopagnosia progressed to the point that she was almost completely unable to recognise any faces. VH was also impaired in her ability to identify famous public events. In striking contrast, VH's recall of autobiographical information including both personal semantic and autobiographical events was intact. She also showed intact anterograde memory for names and buildings, but impaired anterograde memory for unfamiliar faces.

The results of the investigations of VH's pattern of impairments are significant in several respects. The localisation of atrophy to the right temporal lobe, and the neuropsychological profile characterised by severe and relatively selective deficits of face recognition, famous people and famous event knowledge represent a highly atypical degenerative process. As with almost all presentations of progressive cognitive dysfunction it is impossible to be certain of the pathology responsible until post-mortem. The repeat assessment schedule confirmed the progressive nature of the disorder. Other evidence for the progressive nature of her disorder include the reports of VH and her relatives that she had gradually become more impaired at recognising faces over the course of a number of years, the absence of any indications of a discrete neurological event, and the MRI evidence of selective atrophy of the right temporal lobe. Although deficits of face recognition undoubtedly occur in patients with dementia of the Alzheimer's type (DAT), it seems unlikely that VH was suffering from classical DAT, though it is possible that the pathology (i.e. plaques and tangles) may turn out to be the same. In DAT, the earliest and most prominent cognitive deficit is almost invariably one of episodic memory. Patients show marked impairment in learning new verbal and non-verbal information with rapid forgetting (Corkin, 1982; Sagar and Sullivan, 1988). There is also a progressive breakdown in semantic memory which manifests itself as reduced category fluency, impaired naming and a general loss of knowledge about the attributes of living and man-made items (Cherkow and Bub, 1990; Hodges, Salmon and Butters, 1990). These features were largely absent in VH. The impairment in recognition and naming of famous faces found in patients with DAT has been found to mainly reflect a disorder of semantic memory for famous people (Hodges, Salmon and Butters, 1993). A group of patients with mild to moderate dementia in the latter study, who showed considerably more general cognitive impairment than VH, were much better at recognising and identifying famous faces than VH.

Visuo-spatial deficits are also prominent in patients early in the course of DAT. Indeed, it has been recognised for some time that a subgroup of DAT patients may present with prominent visuo-perceptual and spatial impairment. Confirmatory evidence of Alzheimer's pathology in such cases has been largely unavailable, but a number of patients presenting with relatively isolated visual processing deficits have reached post-mortem and been shown to have characteristic neurofibrillary tangles and plaques (see Hof and Bouras, 1991; Kiyosawa, Bosley, Chawluck, Jamieson, Schatz, Savino et al., 1989; Levine, Lee and Fisher, 1993; Ross et al., 1996). However, in comparison with VH, these patients all exhibited more basic perceptual deficits such as restriction in visual fields or impairment in colour perception, stereopsis, spatial location and figure-ground discrimination. Severe disruption of visually-guided hand movements and of visuo-spatial ability (such as copying the Rey Complex figure) has also been a consistent feature. In keeping with this profile of cognitive deficits, neuroradiological and neuropathological examination has shown striking involvement of the occipital and posterior parietal lobes. Likewise, Benson et al. (1988) reported a series of five patients with progressive dementia heralded by a variety of disorders of complex visual function, although in these cases pathology was not obtained and none had the pattern of deficits observed in VH. In VH, the pattern of SPECT and MRI changes were those of a focal lobar atrophy involving anterior temporal lobe structures; these changes mirror those seen in patients with the left-hemisphere syndrome of semantic dementia (Hodges et al.. 1992). The neuropathological basis of semantic dementia is not clearly established, but the evidence to date suggests that it rarely results from Alzheimer's disease. Some cases have shown typical Pick's inclusions, whilst others have shown non-specific neuronal loss with spongiform changes (Graff-Radford, Bolling, Earnest, Shuster, Caselli, Nd Brazis, 1993, Snowden et al., 1992). The pattern of impairment with which VH presented might represent an early localised form of semantic dementia (Snowden et al., 1996). Gentileschi, Sperber and Spinnler (1999) have also recently described a case of progressive impairment in recognition of familiar people associated with predominantly right-sided temporal lobe atrophy. In their patient, an impairment of face recognition was accompanied by some impairment in basic (apperceptive) visual skills and some difficulty in recognition and naming of a small number of common objects, which Gentileschi et al. attribute to less pronounced left-temporal lobe atrophy. Gentileschi et al. concluded that their case was one of fronto-temporal dementia.

Bruce and Young's (1986) model of face processing has been useful in accounting for the deficits present in prosopagnosic cases. The model proposes a series of independent stages leading to the identification of familiar faces. The first stage, 'structural encoding', provides the basic facial percept which will activate 'face recognition units' (FRU's) or stored descriptions of known faces. Structural encoding also precedes the independent and parallel processes of expression analysis, facial speech analysis and directed visual processing. Activation of face recognition units enables access to 'person identity nodes', which represent semantic information or knowledge about known people. The final stage in the process is name generation, separated in the model to account for the common 'tip of the tongue' state in which we can identify a face as familiar, but cannot recall the individual's name. An important aspect of the model is that the person identity nodes are part of the general semantic system and are thus accessible from face, voice, name or any other associative trigger.

It would appear that VH had no problem at the level of structural encoding of face information, nor facial expression analysis.

At the first assessment, VH was able to provide very detailed information about many of the people she was unable to identify from their face. This suggests that at that stage her person semantics (person identity nodes) were largely intact. The question arises, therefore, whether the functional lesion was at the level of the face recognition unit or was subsequent to this processing stage (i.e. a disconnection between face recognition units and person identity nodes). At first glance, the data from the forced-choice recognition task suggest that the FRUs were functioning adequately in that she was able to select most of the famous faces from the triplet arrays. However, on the yes/no familiarity task her performance was impaired (although substantially better than chance). One hypothesis which might account for this apparent discrepancy is that the forced choice procedure may tap some form of covert recognition process, a point made by Tranel and Damasio (1987) and discussed further by De Haan et al. (1992). In the forced choice task, VH reported that for the majority of faces she correctly chose as familiar she was simply guessing and had no real feeling of familiarity. De Haan et al. (1992) argue that it is not necessary to invoke independent *covert* processes in this situation, and that it may be more parsimonious to suggest that *overt* recognition processes are simply so weak as to be below a threshold of overt recognition, but sufficient to positively influence performance in a forced choice situation. On the second administration of the recognition tasks (Assessment 2), her performance was different - she was a little poorer on the triplet arrays, though still well above chance, and on the yes/no recognition task she made many more yes or 'famous' responses (both correct and false positive responses). It is not clear what accounts for this change. One hypothesis is a simple criterion shift in her responding from a cautious style to a more relaxed criterion for judging a face to be famous. A second hypothesis relates to the 'false fame' effect demonstrated in both younger and older healthy adults and amnesic patients (see Dywan and Jacoby, 1990, Squire and McKee, 1992). Prior exposure to non-famous names can result in false attribution of fame in a subsequent fame-judgement task especially in people who have deficient recognition memory for the names. Although such tasks have primarily used names (rather than photographs) and tend to have short intervals between pre-exposure and fame judgement, it seems plausible that the increase in VH's 'famous' responses (to both famous and non-famous faces) could have been affected by prior exposure to the stimuli, albeit many months previously.

In summary, at Assessment 1 it seems likely that VH did have at least a partial deficit at the level of the face recognition units. The discrepancy between her levels of performance on tests of recognition and identification suggests that the major deficit was one of accessing person identity semantic information. When the second assessment was undertaken, the situation with regard to face/person identification had changed in that VH's ability to identify people from faces had deteriorated further (11/50 to 7/50), and her ability to provide information when given the name was considerably poorer (39/50 to 23/50). There were indications from her weak performance at Assessment 1 that this latter process was already compromised, but at that stage the deficit was mild. It is hypothesised that the primary deficit was originally one of accessing semantic information from faces (i.e. between the face recognition units and the person identity node, according to the model outlined above). With progression of the disease, however, there was evidence of loss of person-specific knowledge independent of modality of access or at least a loss of the ability to access person-semantic information from both verbal (i.e. name) and visual (i.e. face) modalities. Thus, at the stage of the second assessment, VH had changed from being relatively selectively prosopagnosic and appeared to resemble more closely the patients described by Ellis, Young and Critchley (1989), and Hanley, Young and Pearson (1989) both of whom had a cross-modality deficit in knowledge of people, attributed to a failure at the level of person identity nodes. In anatomical terms, this pattern suggests that the major locus of damage was initially more posteriorally placed, since evidence from neuropsychological and PET studies (see Sergent, Ohta and Macdonald, 1992) implicates the fusiform gyrus of the right temporal lobe in face recognition processes, but this progressed to involve the temporal pole which appears to be critical for person-based semantic knowledge. Ellis et al.'s (1989) and Hanley et al.'s (1989) patients had sustained right temporal lobe damage. In the former case, this was as a result of right temporal lobectomy for intractable epilepsy, and in the latter case as a consequence of Herpes Simplex Encephalitis which appeared to selectively involve anterior right temporal structures.

Prosopagnosia frequently occurs in the context of other recognition deficits which might be at the level of between-category identifications (e.g. cars vs. dogs vs. houses) or at the level of within-category identifications (e.g. types of car or even individual cars, breeds of dog or individual dogs, particular houses etc.). However, double dissociations between the ability to recognise faces and other objects have been reported. For instance, Bruyer et al.'s (1983) patient, a farmer, could not recognise the faces of his family, but could recognise his livestock; McNeil and Warrington's (1993) case learned to recognise his sheep, but was poor at recognising people, with the double dissociation provided by Assal, Favre and Anderes' (1984) patient, another farmer, who could recognise people but not his livestock. Such findings suggest that faces are 'special' in the sense that they are processed separately from other objects. Further evidence in support of this position comes from the present studies with VH, who could identify other objects normally and whose performance on the famous buildings test and the flowers test suggested that she could make within-category identifications for objects other than faces. Although her naming performance on the flowers task was somewhat weak, it was clear from the subsequent location task that she could identify different exemplars of a visually similar class. The dissociation between faces and buildings contrasts with the opposite dissociation demonstrated by patient SE described by McCarthy, Evans and Hodges (1996) who showed a relatively selective deficit in the recognition of familiar buildings and landmarks.

VH's initial prosopagnosia cannot be explained by a loss of person semantic knowledge, since this was not severely compromised at first. The progression in severity of the prosopagnosia could plausibly be explained by this deficit, but there also seemed to be a progression in the severity of the impairment at the level of face recognition units. It is hypothesised that the deterioration in function of these two modules was the result of the same disease process, but nevertheless there was evidence for the functional separation of the two processes. One question that arises from this work relates to how best to conceptualise a loss of the ability to recognise people from their faces. An issue that is relevant to this question is that of the nature of the impairment that causes prosopagnosia. For example, prosopagnosia might be caused by an impairment of structural encoding of faces. If this occurs, the deficit is primarily viewed as a problem of perception. However, if the deficit is at the level of

Face Recognition Units or Person Identity Nodes (as in the case of VH), should the deficit be classified as a problem of semantic memory (since this is defined as stored knowledge of the world) or of semantic retrograde memory, as defined by Kapur (1999). Classifications of deficits in terms of class of object (faces, objects, buildings etc.) or information modality (visual or auditory) seem more likely to prove to be more helpful than other distinctions.

The data presented here suggest that knowledge of famous people and famous events dissociates from autobiographical knowledge. As noted earlier, case JM described in Chapter 3, presented with the opposite pattern - impaired autobiographical information in the context of spared knowledge of famous faces and events. These two cases therefore provide strong evidence for the conceptual distinction between autobiographical and semantic retrograde amnesia. One possible explanation for the preservation of autobiographical knowledge and apparent impairment of famous people/event knowledge is that VH was never very interested in public figures or news events. This is not a satisfactory explanation, however, since the evidence from the progressive nature of her disease demonstrated that at first her loss of knowledge of famous people was mild (though famous events were not tested until the disease had progressed somewhat). However, a modified form of this hypothesis is still plausible. In the same way that frequency and age of acquisition appear to be important factors in the loss of general semantic information (Hirsh and Funnell, 1995), it might be argued that much of a person's autobiographical information is likely to be more frequently encountered either directly (i.e. meeting friends and family, going to work, engaging in hobbies, etc.) or indirectly (i.e. thinking about friends/family/work/hobbies/etc.) than information relating to famous people or events, which are usually fairly transitory. Autobiographical information is also built upon a greater number of personal experiences in which the individual is an active participant. This contrasts with knowledge of famous people/events, which is perhaps more likely to be acquired in a more passive form, through media sources. Thus, autobiographical knowledge is likely to be represented by more widely distributed networks, in contrast to knowledge of famous people/events which may be more restricted in connectivity terms. One possible implication of this view is that autobiographical knowledge is likely to be more resilient to brain disease. If this is the case, then we should not expect to find preserved knowledge of famous people/events in the context of impaired autobiographical knowledge and yet this was the pattern with JM. However, in actual fact, JM's deficit was only for autobiographical *event* knowledge and not personal semantics. Thus it can be argued that autobiographical event knowledge is likely to be quite vulnerable to brain disease, though may only appear as a selective deficit in the context of (1) discrete multi-focal lesions or (2) selective medial temporal lobe lesions. In the former case, there may not be accompanying impairment of anterograde memory (as in the case of JM), but in the latter case, there will be an accompanying anterograde amnesia. By contrast, if knowledge of famous people and public events is dependent upon a less widespread network, and the brain region supporting this network is damaged, then a selective deficit is possible.

A further question that arises is whether or not VH's deficits can be explained in terms of a lack of access to semantic knowledge or represent an actual loss of stored information (Shallice, 1988). The consistency of performance across test sessions observed in VH is more in keeping with a storage deficit for person-specific knowledge, although there was some evidence that knowledge was not always completely lost, such that when cued, VH could sometimes produce *some* other relevant information. One possibility is that both deficits were occurring in that the process of cell loss was causing a difficulty accessing some knowledge and at the same time effectively destroying other knowledge.

The selective nature of VH's deficit was also strikingly demonstrated by her performance on the recognition memory tests for words, faces and buildings. Her good performance on words and buildings and chance level performance on faces provides further convincing evidence that faces are processed in a highly specialised cognitive system. It also supports the initial hypothesis that a focal loss of knowledge of a class of objects (e.g. faces/people) might be expected to produce an impairment in anterograde memory for this class of object in addition to the loss of retrograde information. The finding of a selective anterograde memory deficit for faces raises the possibility that VH's prosopagnosia was a consequence of a potentially long-standing inability to learn new faces. However, if this were the case one would expect to find a temporal gradient in her ability to identify people's faces (i.e. be able to identify people who were famous a long time ago or where people are still famous and only be able to identify 'young' photographs of those people). No temporal gradient was found in VH's performance on the Famous Faces Test (which contains many faces of people who were famous up to fifty years ago, and were identified by age matched controls). Material-specific anterograde memory deficits have been reported previously, but these have primarily been at the level of verbal vs. non-verbal, or visual vs. spatial (see McCarthy and Warrington, 1990). Indeed 'selective' impairments on memory for faces have been reported (e.g. Warrington, 1984), though such studies have typically contrasted memory for faces with verbal material, rather than with another class of visual stimuli. In a detailed study of a patient with visual memory loss, following a ruptured right middle artery aneurysm (Hanley, Pearson and Young, 1990), the patient demonstrated impaired new learning for faces, objects, and voices, but normal performance on new learning involving words and non-words.

In summary, several key observations emerge from the experimental investigations carried out with VH. Firstly, the combination of neuropsychological and imaging data represent convincing evidence for a primary degenerative process that initially emanates from the right temporal lobe and provides a complement to the classic cases of semantic dementia associated with left temporal pathology. Secondly, VH's pattern of impairments also highlights the double dissociation between knowledge for famous faces/people/events and autobiographical information. Thirdly, evidence from anterograde memory testing indicated that focal loss of knowledge of a class of objects is associated with a selective deficit in anterograde memory for that class of objects.

Chapters 2 and 3 have focused on investigations of recall and recognition of *retrograde* episodic and semantic knowledge. In Chapter 4, two studies of recall and recognition of *anterograde* episodic and semantic knowledge are presented. As with the previous chapters, the aims of the studies were two-fold - firstly to clarify the nature of various distinctive forms of very long-term memory impairment and to shed light on the mechanisms that give rise to these syndromes; secondly, to examine the extent to which the patterns of impairment identified provide support for particular models of memory.

# Chapter 4 The status of long term anterograde memory functioning in cases of selective temporal lobe pathology.

**General introduction**

This chapter is concerned with two general questions - (1) What are the mechanisms by which new long term memories are laid down? (2) Can selective disruption to long-term consolidation of new information shed light on the normal process of acquiring memories? These questions are addressed by several single case studies of patients with temporal lobe pathology. Section 4.1 presents studies of the long-term acquisition of autobiographical and public event knowledge in two patients with a varying degree of medial temporal lobe pathology, but who were matched for performance on anterograde memory tests. Section 4.2 presents studies with two patients who have a rare form of anterograde memory deficit involving a failure to retain information over extended time delays in the context of normal performance on standard anterograde memory tasks.

## 4.1 A comparison of long-term memory consolidation in two cases of focal medial temporal lobe pathology.

### 4.1.1 Introduction

As discussed earlier (Section 1.3.6), even those patients with the most severe amnesia show evidence of some new learning. To understand both amnesia and normal human memory better it is important to understand what can be learned and under what circumstances. Recent years have seen an upsurge of interest in issues relating to whether or not people with amnesia can learn new factual or semantic information. However, studies to date have produced equivocal results. Patients HM (Gabrieli et al., 1988) and SS (Verfaille et al., 1995) showed very little new semantic learning. By contrast, patient RS (Kitchener et al., 1998) and PS (Verfaille et al., 2000) were shown to have acquired new (post-illness) knowledge of public figures, events and new vocabulary. Similarly, the patients described by Vargha-Khadem et al. (1997) whose amnesia onset was in childhood, were shown to have acquired extensive semantic knowledge throughout their developing years. One of the potential explanations for the conflicting findings is the difference in the extent of the lesions involved (Verfaille et al., 2000). Although all patients have been described as having primarily medial temporal lobe damage, some have had discrete hippocampal pathology, while others have had much more extensive damage involving entorhinal, parahippocampal, perirhinal, temporal pole, and more lateral temporal lobe neocortical areas. Verfaille (2000) argued that, "the possibility that semantic learning is relatively preserved in patients with lesions limited to the hippocampus proper requires further scrutiny" (p. 352). There is therefore a need for studies that compare performance of patients who have clearly defined lesions and in particular to contrast patients who have pathology limited to the hippocampus with patients who have damage to the hippocampus and additional medial temporal lobe structures. It is also critical for such patients to be matched in terms of their performance on standardised anterograde memory tests. If such patients are not matched, then it is possible to argue that any difference in new learning might simply be attributable to the severity of anterograde memory deficit.

The main aim of the studies reported in this section was to compare two patients in terms of their post-morbid acquisition of information about autobiographical events, public knowledge (famous personalities and news events) and new vocabulary. The two patients performed at a similar level on standardised anterograde memory tests and were well matched in terms of media exposure and time since illness onset. One had a lesion that was largely confined to the hippocampus, whilst the other had more extensive medial temporal lobe damage. Based on the studies described earlier, it was predicted that the patient with discrete hippocampal pathology would show impaired ability to acquire new personal event memories, but have preserved ability to acquire new factual or semantic information, though the level of knowledge acquisition would not be as high as control participants. By contrast, it was predicted that the patient with more extensive medial temporal lobe involvement would show an impairment in both personal event *and* factual or semantic knowledge acquisition.

The study presented in Section 2.3 demonstrated that patients with a discrete hippocampal lesion and those with more extensive temporal lobe damage, appeared to have a significant impairment in the ability to mentally replay pre-illness autobiographical events. This was demonstrated though the application of a 'remember-know' judgement paradigm. In the present study, this paradigm was used to test memory for anterograde (post-illness) memories.

### 4.1.2 Case histories

The two patients in this study were BW and JN. BW was described in detail in Section 2.1.2.1 and JN was described in detail in Section 2.3.2.6. Brief clinical details, highlighting key comparisons will be described here. BW developed an amnesic syndrome in 1991 as a result of an anoxic episode arising from carbon monoxide poisoning. An MRI scan revealed bilateral lesions of the hippocampus, more marked on the right and has some additional pathology in the globus pallidus. JN suffered viral encephalitis in 1992 as a result of herpes simplex infection. She developed a severe amnesic syndrome. An MRI scan showed pathology that included major abnormality to right hippocampus, and milder left hippocampal damage. In addition, she had bilateral lesions to the parahippocampal and entorhinal cortices, right temporal pole, right inferior and middle temporal gyri, with milder damage to left temporal pole, and to inferior and middle temporal gyri. Superior temporal gyri on both sides were intact, along with diencephalic structures, frontal cortex, parietal cortex and occipital cortex.

Both have similar socio-economic backgrounds. Both patients left school at the age of 16 and both worked as shop assistants. Neither patient had been able to return to paid employment since the onset of amnesia, though both had undertaken voluntary work. Both had been married for more than 20 years. Both described a similar level of interest and exposure to news media. Each patient read a tabloid newspaper every day and watched the television news several times a day. BW's score on the Media Exposure Questionnaire (Kapur et al. 1999) was 55 and JN's score was 63.

### 4.1.3 General neuropsychological test results

General neuropsychological test results were presented in Chapter 2, but are reproduced here in Table 4.1.1. The test results indicate that BW showed well-preserved verbal and non-verbal cognitive functioning in relation to an estimate of her pre-morbid level of functioning. She showed spared perceptual, executive and language skills. JN showed well preserved non-verbal abilities, but there was a weakness in verbal functioning compared to pre-morbid levels.

***Table 4.1.1 General neuropsychological test results for patients BW and JN***

| **Test** | **BW** | **JN** |
|---|---|---|
| **NART Errors (Predicted pre-morbid IQ)** | 20 (106) | 34 (89) |
| **WAIS-R:** | | |
| Full Scale IQ | 103 | 86 |
| Verbal IQ | 99 | 82 |
| Performance IQ | 112 | 93 |
| Information | 9 | 4 |
| Digit Span | 10 | 7 |
| Vocabulary | 9 | 5 |
| Arithmetic | 7 | 8 |
| Comprehension | 12 | 8 |
| Similarities | 13 | 6 |
| Picture Completion | 10 | 8 |
| Picture Arrangement | 16 | 9 |
| Block Design | 11 | 8 |
| Object Assembly | 12 | 7 |
| Digit Symbol | 8 | 6 |
| **Verbal Fluency** | | |
| Letters FAS (60s, Total) | 38 | 24 |
| **Modified Wisconsin Card Sorting Test (Nelson version)** | | |
| Categories | 5 | 4 |
| Total Errors | 17 | 19 |
| Total perseverative errors | 3 | 3 |
| **McKenna Graded Naming Test** (total/30) | 20 | 1 |
| **Boston Naming Test** | - | 26/60 (43.3%) |

For JN, there was evidence of significant word finding impairment on naming tests (on which she produced some semantic paraphasias), in spite of fluent and clinically normal conversational speech. Although her performance on the FAS verbal fluency task was weaker than BW's performance it is not significantly below the level predicted using Crawford et al.'s (1992) NART- based regression equations. However, as discussed earlier, in Section 2.3.2.6, it is possible that her score on the NART is somewhat impaired. An estimate of her pre-morbid IQ using Crawford et al.'s (1989) regression equation that uses age, socio-economic status and level of education produced a value of 25.3 errors, suggesting that her obtained score may be an underestimate of pre-morbid ability.

In Section 2.3, JN was shown to have a very significant retrograde memory deficit, affecting both semantic and episodic retrograde memory. By contrast BW was shown to have no significant impairment in semantic retrograde memory, with relatively good recall of autobiographical events. She was, however, shown to be impaired in her ability to mentally replay autobiographical events.

**4.1.4 Standard anterograde memory test performance**

Table 4.1.2 reproduces the data on the performance of BW and JN on a range of standardised anterograde memory tests, illustrating that they present with a similar level of anterograde memory functioning. Both were impaired on immediate recall of verbal and visual material, with a particularly marked impairment following a delay. Although there are a few differences between the memory performance of the two patients (e.g. JN has poorer face recognition scores than BW), composite indices of severity of amnesia, such as the RBMT profile score or WMS-R indices are very similar.

*Table 4.1.2 Results of the performance of patients BW and JN on a range of standardised anterograde memory tests*

| | BW | JN |
|---|---|---|
| **Rivermead Behavioural Memory Test** | | |
| Screening Score (Max. = 12 ) | 2 | 2 |
| Standardised Profile score (Max= 24) | 7 | 5 |
| **WMS-R** | | |
| Visual | 66 | 68 |
| Verbal | 66 | 78 |
| General Memory | 57 | 64 |
| Delayed | <50 | 50 |
| Attention and Concentration | 95 | 78 |
| Logical Memory Immediate- Raw Score (Percentile) | 12 (3rd) | 11 (2nd) |
| Logical Memory Delayed- Raw Score (Percentile) | 2 (1st) | 2 (2nd) |
| Visual Reproduction Immediate- Raw Score (Percentile) | 25 (11th) | 25 (19th) |
| Visual Reproduction Delayed - Raw score (Percentile) | 3 (1st) | 3 (1st) |
| **Warrington Recognition Memory Test (Age scaled scores)** | | |
| Words | <3 | 4 |
| Faces | 12 | <3 |
| **Doors and People (Age scaled scores)** | | |
| Doors | 4 | 3 |
| Names | 5 | 5 |

### 4.1.5 Post-morbid autobiographical and factual knowledge

BW and JN's post-morbid autobiographical and factual knowledge was assessed using a range of tasks.

#### *4.1.5.1 Autobiographical Memory Interview (Kopelman et al., 1990)*

The Recent Life section of the AMI referred to the post-morbid period for both JN and BW. Results are presented in Table 4.1.3. This shows that both patients were impaired on the autobiographical episodes section, consistent with their amnesic syndrome. On the Personal Semantic section, BW was normal. JN's score of 17/21 indicates that she was accurate on a considerable number of items, but in relation to the near ceiling performance of the normative sample on this test, her score is impaired.

*Table 4.1.3 Performance of BW and JN on the Recent Life Section of the AMI*

| | BW | JN |
|---|---|---|
| **Personal Semantic** | 21/21<br>(Normal) | 17/21<br>(Definitely abnormal) |
| **Autobiographical Episodes** | 2/9<br>(Definitely abnormal) | 1/9<br>(Definitely abnormal) |

### *4.1.5.2 Time-constrained Crovitz task*

This test was described in Section 2.1.4.2. It involved participants being asked to generate examples of autobiographical events in response to 15 cue words for each of four lifetime periods. Data from the post-morbid time period are presented here for patient BW. This test was not administered in full with JN as she indicated that she felt she could not produce any detailed autobiographical events from any time during the post-morbid period. Further evidence for this severe difficulty was seen with her performance on the AMI (see above) and on the cued recall section of the Autobiographical Event Recall Task (see section 4.1.5.3 below). BW's performance is shown in Figure 4.1.1 and is contrasted with six, age, sex and education matched controls (BW's age at time of testing = 41 years; mean age of controls = 43.67, s.d. 4.41; mean years of education 12.5 years, s.d. 2.74). BW was significantly impaired in comparison to the controls ($t=-2.545$, $df=5$, $p=0.05$). Nevertheless BW was able to produce detailed memories for a number of the cue words.

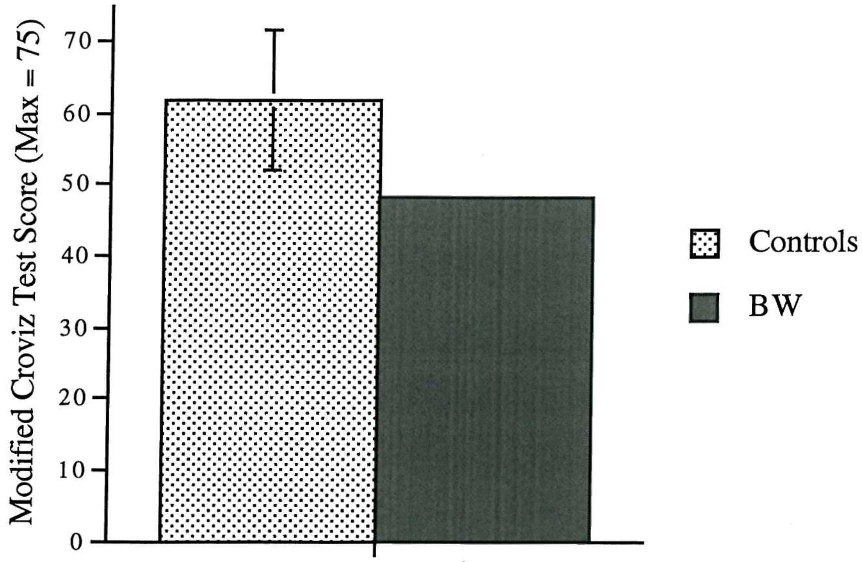



***Figure 4.1.1 Performance of BW and six control participants on the post-morbid section of the Modified Crovitz Task, with two standard deviation marker bar.***

#### *4.1.5.3 Autobiographical Events Test.*

This test was described in Section 2.3.4. In brief, autobiographical event information was obtained from the husband of each patient. Event information was collected that covered the whole period for which the spouse had known the patient. For the purposes of this study, only the events relating to the post-morbid period are presented. For this period 12 events were obtained from JN's husband and 24 events from BW's husband. The majority of the events provided were distinctive 'one-off' events, though a small number referred to relatively brief extended episodes (e.g. reference to meeting someone on holiday without reference to a specific event). A cued recall task was constructed for each patient using partial information about the events provided. The patient was asked to recall as much about the event as possible. Recollections were scored using a three point scale (0=no recollection; 1=partial recollection, but lacking significant detail provided by the spouse; 2=detailed recollection, including most of the detail provided by the spouse). A recognition task was also constructed for each event, with the target event description being presented along with two false, distractor events. For each response on the recognition task, the patients were asked to say whether they were certain the event was true (CERTAIN), they thought the event was true, but were not completely sure (THINK), or whether they were guessing (GUESS). For events that they were certain were true or thought to be true, they were also asked to say whether they remembered the event or whether they simply knew the event to be correct. Participants were instructed to give a 'remember' response if they were able to replay the event in mind and a 'know' response if they knew the event had occurred, but were unable to replay the event in their mind. As noted in Section 2.3.4 recall and recognition tests for autobiographical events were constructed for three controls participants in the same way. Once again information was collected across the whole period that the control subject has known their spouse. Since there is no formal anterograde/retrograde distinction for the controls, data for the whole period will be reproduced here to indicate the general performance of the controls.

*Results*

Data for the cued recall and recognition tasks are shown in Figures 4.1.2. and 4.1.3. Degree of certainty responses and remember/know judgements shown by the patients are provided in Figures 4.1.4 and 4.1.5 respectively.

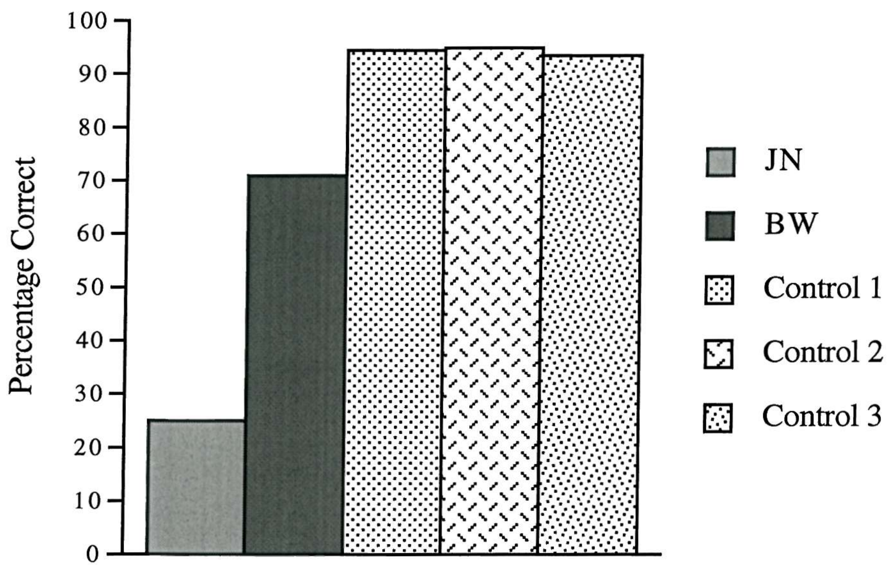



***Figure 4.1.2 Performance of BW, JN and three control participants on the cued recall component of the Autobiographical Events Test.***

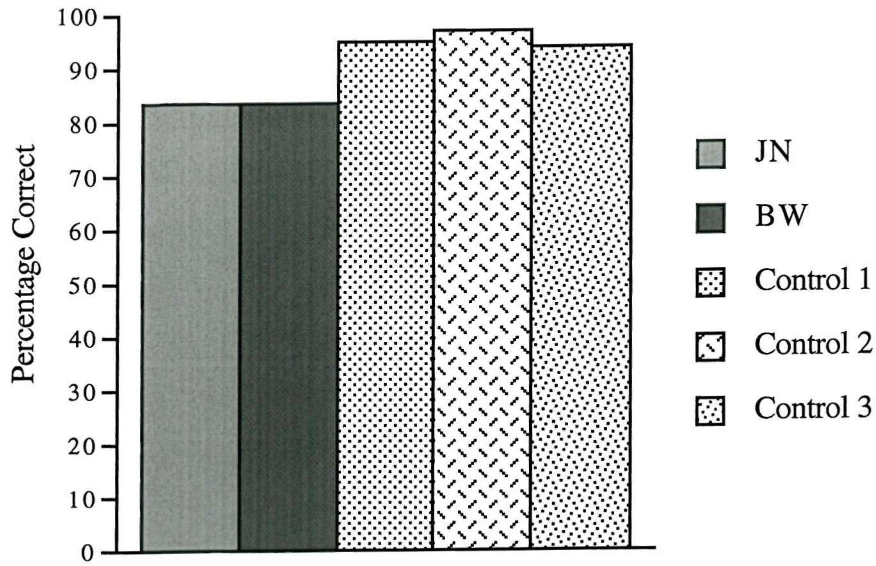



***Figure 4.1.3 Performance of BW and JN and three control participants on the recognition component of the Autobiographical Events Test.***

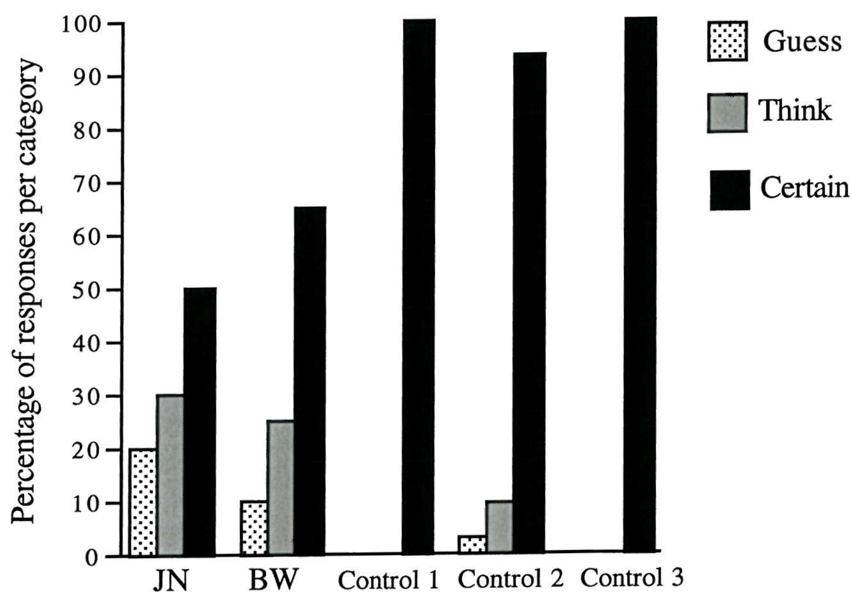



***Figure 4.1.4 Percentage of responses of each type (Guess/Think/Certain) for the items correctly identified as true events by JN, BW and the three control participants on the Autobiographical Events Test.***

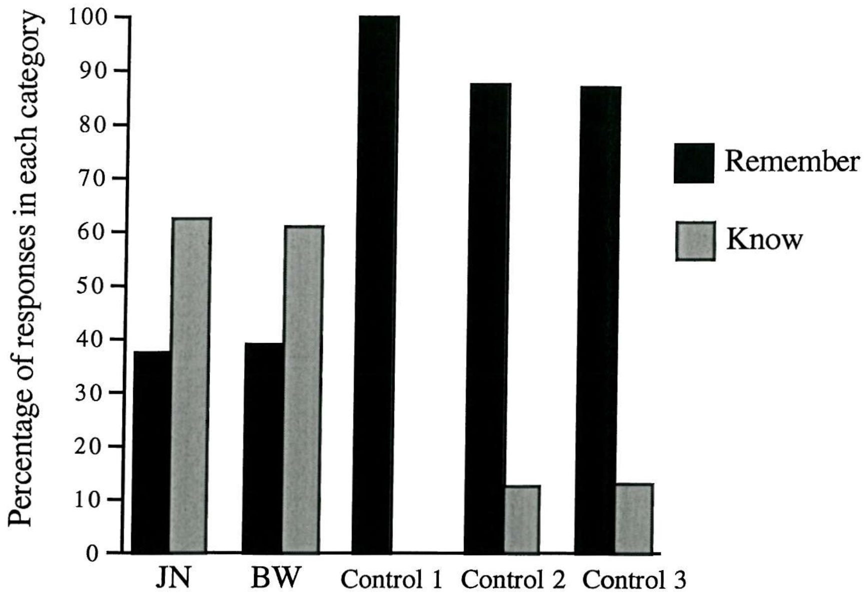



***Figure 4.1.5 Percentage of responses of each type (Remember/Know) for the items correctly identified as true events (excluding items to which the response was "Guess") by JN, BW and the three control participants on the Autobiographical Events Test.***

#### *4.1.5.4 Dead-or-Alive Test*

BW and JN were given separate versions of the Dead-or-Alive test (adapted from the version described by Kapur, et al. 1989) that differed in minor ways as they were administered at different times, an updated version of the test being available at the time that JN was tested. However, most of the content of the two versions was similar.

*Version 1: Administered to BW*

The test consists of 50 names of famous personalities and was described in Section 2.1 (see Appendix 1 for list of the stimuli). Nine personalities died during the 60's, nine during the 70's, nine during the 80's and nine during the 90's. A further 14 personalities were still alive. Data from the anterograde period (died in the 90's) will be presented here, along with data from six female control participants matched for age (BW's age at time of testing = 41 years, mean age of controls = 43.76, s.d. 4.41) education (mean length of education for controls = 12.5 years. s.d. 2.74), and media exposure (BW's media exposure score = 55, mean media exposure for controls = 54.83, s.d. 16.41).

*Version II Administered with JN*

This test, described earlier in Section 2.3.3, differed from Version 1 in that there were a larger number of test items. Furthermore in this version, target items *and* distractor items were presented, with the first task being for the participant to recognise the target personalities. The test consisted of 130 names of people, 79 of whom were famous, with 51 distractor names (See Appendix 1 for a list of the stimuli). Of the famous people, 9 died in the 60's, 11 died in the 70's, 11 died in the 80's, 15 died in the 90's and a further 33 were still alive. Data presented here relate only to those 12 individuals who died in the anterograde or post-morbid period for JN. Her performance was compared with five control participants matched for age (JN's age at time of testing = 55 years, mean age of controls = 55.2 years, s.d. 1.8 ), years of education (JN= 11 years; mean of controls = 10.6 years, s.d. 0.55 ) and media exposure (JN's Media Exposure score = 63, mean media exposure for controls = 61.2, s.d. 12.24). JN was not matched on the NART with the controls (mean errors for controls 24.6, s.d 5.3) as there was some concern that her NART score was probably an underestimate of her pre-morbid ability.

*Results*

The data for the two patients on the Dead-or-Alive test are presented in Figure 4.1.6. This figure shows the performance of BW and JN using a z-score based on the distance of the patient's score from the mean of their respective control samples, as a proportion of the standard deviation of the control participants. Data are presented for the Familiarity, Information and Details of Death Sections. The figure shows that BW was unimpaired for information and details. For the familiarity task, BW failed to recognise only one personality, but because the control participants were at ceiling, a z-score could not be calculated. In contrast to BW, JN's performance was impaired on all tasks (Familiarity, $t=-2.65$, $p=0.056$; Information, $t=-3.45$, $p=0.03$; Details, $t=-3.91$, $p=0.017$)

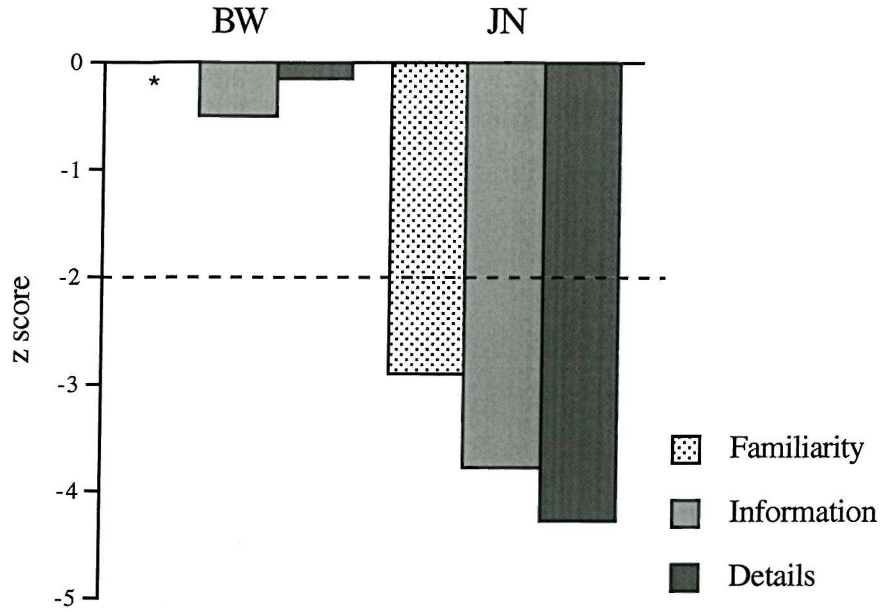



***Figure 4.1.6 Performance of BW and JN on the Dead or Alive test for people who died post-morbidly. The graph represents performance in terms of the number of standard deviations that the patients' performance was below the means of their respective control groups (z-score). The dotted line illustrates a 2 standard deviation level. *A z-score could not be computed for BW's performance on the familiarity task as all of the controls produced a perfect score (i.e. s.d. = 0) and BW failed to recognise as familiar one famous name.***

### *4.1.5.5 News Events Test*

BW and JN's knowledge of public news events that had occurred since the time of the onset of their memory impairments was also assessed using a test similar to one described by Graham et al. (1998). The testing and scoring method was the same as that described for this test in Section 2.1.4.4. In brief, each news event was presented on a sheet of paper with three other fictitious but plausible news events. Participants were asked to select the famous event. If they chose the correct event, they were then asked to provide as much detail as they could about the event. One point was scored for each item correctly identified. The information about the event provided by participants was scored using the four point (0-3 scale) described by Graham et al. (1998). Scoring was undertaken by an independent rater who was trained to use the rating system and who was blind to any experimental hypothesis. BW was assessed on a version of the test that included 27 events that occurred between 1992 and 1997. Her performance was contrasted with the same set of six control participants who performed the Dead or Alive test above. JN was assessed on a version of the test that included 34 events that occurred between 1993 and 2000. Her performance was contrasted with the same set of five controls who performed the Dead or Alive test above.

The results from the News Events test are shown in Figure 4.1.7. The score for each patient presented is a z-score based on the distance of the patient's score from the mean of their respective control samples, expressed as a proportion of the standard deviation of the controls. The figure shows that both BW and JN were considerably below the means of the control participants, though BW's scores for both familiarity and information were not significantly different from the control mean (Familiarity, $t= -1.59$, $df=5$, $p=0.17$; Information, $t= -1.53$, $df=5$, $p=0.185$). By contrast, JN was very severely impaired on both familiarity and information components (Familiarity, $t= -5.96$, $df=4$, $p=0.004$; Information, $t= -3.15$, $df=4$, $p=0.017$).

Like personal events, some news events are referred to in the media many times after the event, while others receive very little further attention, following initial news coverage. Potential differences in the level of post-event coverage on the likelihood of an event being recalled by the patients was explored in a further study. It was predicted that BW would show relatively good performance on events that had received frequent reference in the media, but would be impaired for events that had received little in the way of subsequent coverage. This prediction was based on the assumption that frequent reference to an event in the media would enable a semantic representation of the event to be acquired. In contrast, it was predicted that JN would show poor performance on all events, whether or not they had been referred to frequently. Eight control participants ranging in age from 32 to 59 years (mean = 39.3 years, s.d. 9.12), all of whom were university educated, were asked to rate each of the news events in the News Events Test according to the extent of initial coverage received and the extent to which the event had been referred to in the media since the time of the event.

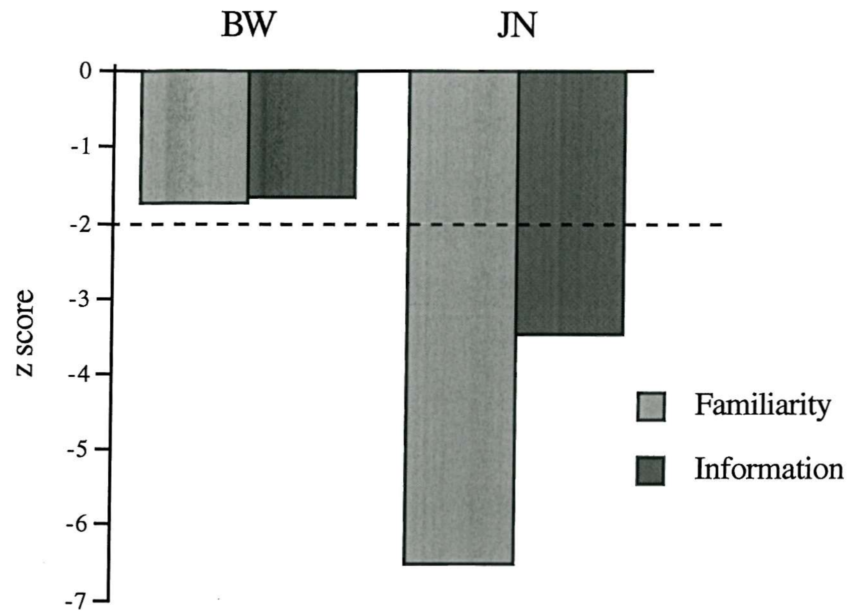



***Figure 4.1.7. Performance of BW and JN on the News Events test for post-morbid events. The graph represents impairment in terms of the number of standard deviations the patient's performance was below the mean of their respective control group (z-score). The dotted line illustrates a 2 standard deviation performance level.***

The rating system involved the following scale: 0 = Not familiar with the event; 1= Some (but not major) media coverage at the time of the event, and little subsequent reference to the event in the media; 2 = Major coverage at the time of the event, but little subsequent reference to the event in the media; 3 = Some (but not major) media coverage a the time of the event, and regular subsequent reference to the event in the media; 4 = Major coverage at the time of the event, with regular subsequent reference to the event in the media. Based on the responses provided by the participants, a set of events that had received little media coverage after the initial coverage at the time of the event (Infrequent Reference) and a set of events that had been frequently covered in the media since the time of the initial event itself (Frequent Reference) were constructed. The Infrequent Reference events were selected using a criteria that at least 7/8 of the control participants were familiar with the event and all seven indicated that there had been little reference to the event in the media after the initial coverage. Eleven events were selected using these criteria. The Frequent Reference events were selected using a criteria that at least 7/8 participants were familiar with the event and the average score for the event was over 3.125. This meant that the majority of the participants rated the event as having been referred to frequently in the media since the initial coverage. 6 events were selected using these criteria. A mean score per event for the recognition task and the recall tasks for the two event sets was calculated using the combined groups of control participants (N = 11) matched to BW and JN described earlier in relation to the News Events Test. A z-score for each patient for recognition and recall tasks for each set of events was calculated based on the mean and standard deviation scores for the control group and these data are shown in Figures 4.1.8 and 4.1.9.

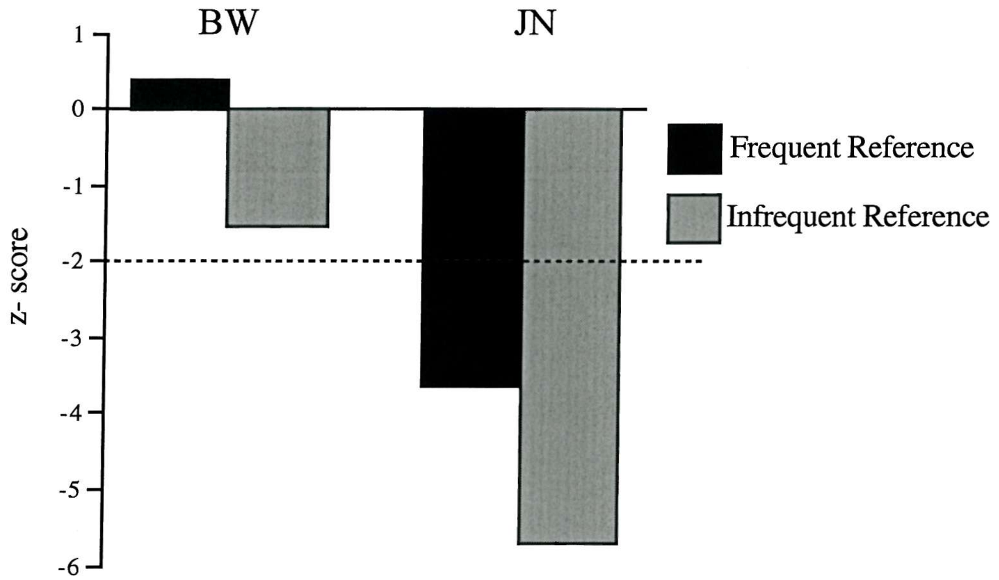



***Figure 4.1.8 Performance of BW and JN on the recognition component of the News Events Test for events rated as being frequently covered in the media since the initial coverage (Frequent Reference) and for events rated as infrequently referred to in the media since the initial coverage (Infrequent Reference). Data are presented in terms of z-scores based on the patient's mean score per event in relation to the mean (and standard deviation) of the control group (N=11). The dotted line indicates a two standard deviation performance level.***

The graphs show that, as predicted, BW demonstrated better performance for the 'frequent reference' events to the extent that she was just above the control group average in both recognition and recall formats. By contrast, her performance for the 'infrequent' events was poorer, though not statistically impaired in either recognition or recall formats

(Recognition, Infrequent; t= -1.46, df=10, p=0.175; Recall, Infrequent t= -1.59, df=10, p=0.142). JN also showed better performance for the 'frequent reference' events. Her performance was severely impaired for both 'frequent' and 'infrequent reference' events in the recognition format (Frequent t= -3.47, df=10, p=0.006; Infrequent t= -5.45, df=10, p=0.0002). For the recall format, her score was not significantly impaired for 'frequent' items (t= -1.641, df=10, p=0.13), but was just on the borderline of significance for the 'infrequent' items (t= -2.16, df=10, p=0.056).

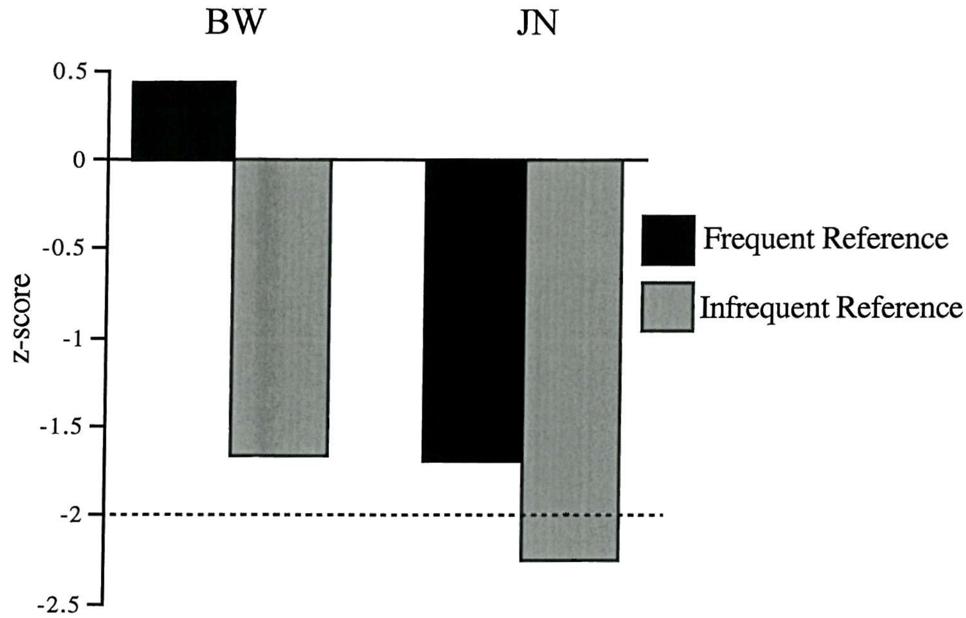



***Figure 4.1.9 Graph showing the performance of BW and JN on the recall component of the News Event Test, for events rated as being frequently covered in the media since the initial coverage (Frequent Reference) and for events rated as infrequently referred to in the media since the initial coverage (Infrequent Reference). Data are presented in terms of z-scores based on the patient's mean score per event in relation to the mean (and standard deviation) of the control group (N=11). The dotted line indicates a two standard deviation performance level.***

### *4.1.5.6 New Vocabulary Test*

A test of new vocabulary (Kapur, unpublished) was administered to BW and JN and a set of 7 control participants (Mean age of controls = 52.7 years, s.d 6.4 years, range 40- 57 years; All participants 11 years of education or less). Participants were asked to define 10 words/acronyms that have come into prominent usage during the course of the 1990's. The words were: Airbag; DVD; Eurostar; ISA; Internet; Camelot; London Eye; The

Dome; Pokemon; GM Food. Subject's answers were scored on a 0-2 scale (0= No answer or incorrect answer; 1= vague or partially correct answer; 2 = correct answer). Responses were scored by an independent rater who was blind to any experimental hypothesis.

Figure 4.1.10 shows the mean scores for the 10 words for the controls, BW and JN. The figure shows that the controls are performing almost at ceiling level. BW is significantly below the level of the controls, as is JN (BW, t= -2.57, df=6, p=0.04,; JN, t=-4.26, df=6, p= 0.005).

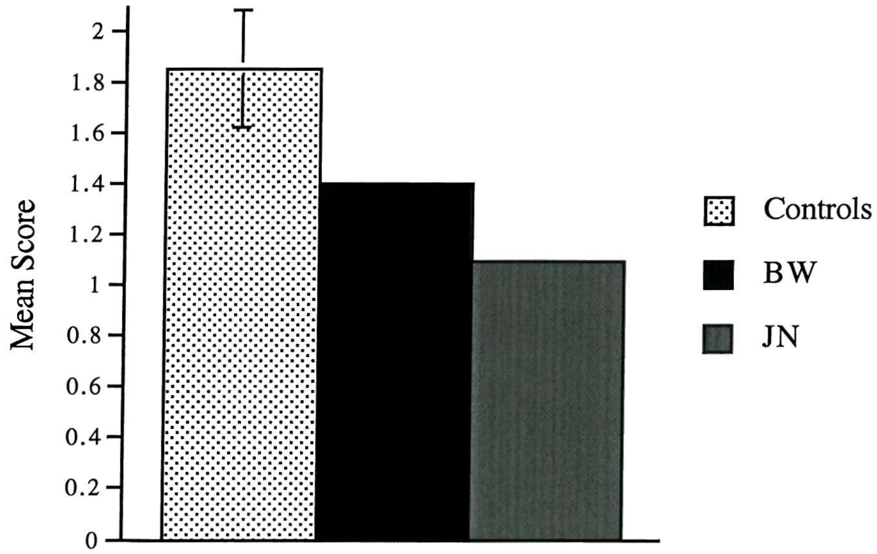



***Figure 4.1.10: Mean scores on the New Vocabulary test for seven controls, BW and JN, with two standard deviation bars for the controls.***

**4.1.6 Discussion**

The key findings from studies in this section were – (1) medial temporal lobe structures appear to play an important role in *retrieval* of post-illness autobiographical event memories; (2) medial temporal lobe structures, and in particular the hippocampus, are critical to the ability to 'mentally replay' post-illness autobiogaphical events; (3) hippocampal pathology does not prevent new semantic learning taking place, though information is not acquired at a normal level; (4) extensive medial and lateral temporal lobe damage impairs the acquisition of new semantic information; (5) information about news events can be acquired despite hippocampal pathology, as long as there is frequent repetition of the information.

BW and JN have similar socio-economic, educational and occupational backgrounds. Both patients have been amnesic for a similar length of time. Both were severely impaired on standard anterograde memory tests, with the level of impairment being comparable on all tests apart from a test of face recognition. JN was, however, more impaired than BW in terms of her performance on general cognitive tasks, particularly in the verbal domain. JN showed some evidence of loss of semantic knowledge, as indicated by her performance on the Information, Vocabulary and Similarities sub-tests of the WAIS-R. BW and JN differ significantly in terms of the extent of their lesions. BW's lesion is confined to the hippocampus with some additional discrete lesions in the globus pallidus. JN's lesion includes a much greater part of the temporal lobe, extending to the temporal pole, with evidence of some involvement of the lateral temporal lobes. The involvement of more lateral, extra-hippocampal, temporal lobe structures is likely to account for JN's naming and mild semantic difficulties (as evidenced by her performance on Vocabulary and Similarities). When compared to the anatomical profiles drawn up in a recent paper by Stefanacci et al. (2000), JN's lesion and cognitive profile is in fact very similar to that of patients HM (Corkin, Amaral, Gonzalez, Johnson, and Hyman, 1997) and EP (Stefanacci et al., 2000). HM, and more recently EP, have been cited as cases that characterise the function of the medial temporal lobe, with a particular emphasis on the involvement of hippocampal structures. However, it is clear that, like JN, both HM and EP have lesions that extend well beyond hippocampal and even parahippocampal structures and this may explain the pattern and severity of memory impairment that they display.

In the present studies, the acquisition of new information was examined in several different ways. There was evidence that both patients were impaired in their ability to recall personal events, as shown by performance on the AMI and the Time-Constrained Crovitz task. However, there was clear evidence that BW was able to retain *some* knowledge of autobiographical events and was able to produce detailed information in some instances, in contrast to JN who indicated that she could not recall *any* personal events in detail. On the Autobiographical Events Test, although impaired in relation to controls, BW's performance was better than JN's for the recall task, while both showed enhanced performance in the recognition version. JN's performance showed a considerable increase from cued recall to recognition tasks. Both patients reported a relatively high level of either guessing or lack of certainty of their responses, in contrast to control participants who were certain of their responses for almost all of the events presented. JN reported that she was either guessing or was not certain for over 50% of the events. Furthermore, when both patients were asked to make judgements as to whether or not they could clearly remember the events, both reported that for over 60% of events, they knew the events had occurred, but could not clearly recollect them. This was, again, in contrast to the control participants who reported that they clearly remembered almost all of the events presented. The superior performance under recognition conditions, particularly for JN, suggests that the recollection impairment could be interpreted in terms of a retrieval deficit. However, when recollection was triggered by a recognition cue, the cue did not trigger a detailed 'episodic' memory of an event. Instead, sufficient information was activated to either give a sense of familiarity, or to implicitly prompt the correct choice of event. It seemed that the phenomenological experience of remembering was different for both patients in comparison to the controls.

With regard to memory for public events, such as that tested by the Dead or Alive Test and the News Events Test, BW showed evidence of acquisition of such information, while JN showed a severe impairment. On the test of new vocabulary, both patients were impaired compared to controls, who performed close to a ceiling, though BW had acquired a little more knowledge than JN. These results are consistent with previous studies in which patients with more extensive temporal lobe lesions, such as HM (Gabrieli et al., 1988) and SS (Verfaille et al., 1995) show evidence of a severe impairment on tests such as knowledge of famous face or new vocabulary acquisition, while patients who have lesions more restricted to limbic structures show better, though not necessarily normal, performance (Kitchener et al., 1998; Verfaille et al., 2000). The Dead-or-Alive test and the News Events tests both have 'episodic' elements in that the

Dead-or-Alive test seeks information relating to circumstances of the death of a person and the News Events obviously refers to particular events. It was noteworthy however that BW's performance on the Dead or Alive Test was somewhat better than that on the News Events Test, perhaps reflecting the greater 'episodic' quality to the News Events Test. This issue was further explored through the comparison of news events to which there has been frequent reference in the media since the time of the event, with those to which there has been little reference since the initial media coverage. BW showed normal performance for recognition and recall of details of the frequent events, but a much poorer performance for the infrequent events. JN also showed better performance for the frequent events, though her score was still very impaired. These data provide further evidence that patients with focal hippocampal lesions are capable of learning about 'events', but only through a high degree of exposure to information about the events. By contrast it appears that the more extensive lesions present in JN mean that this type of learning is very limited. Baddeley, Vargha-Khadem and Mishkin (in press) demonstrated that the developmental amnesic patient Jon, who has focal hippocampal pathology, could acquire new information from video-tapes of newsreels when he had the opportunity to look at the newsreels four times. However, Jon's performance was still below that of two control participants, but above that of his performance on the same task when he had only one opportunity to view the newsreel.

One interpretation of the results of the comparison of BW and JN is simply that BW is less memory-impaired than JN. Zola and Squire (2000) noted that, "If there were some independent function for the hippocampal region that is not also shared by adjacent cortex, then a patient with damage limited to the hippocampal region...should exhibit some deficit that is as severe as that observed in patient HM, who has damage to the hippocampal region as well as to most of the medial temporal lobe. Yet however memory is measured, patients with damage limited to the hippocampal region appear to have a milder version of the deficit observed in patient HM. Perhaps a deficit will eventually be found in these patients that is as severe as in patient HM" (p. 496). If the key role of the hippocampus is to represent autobiographical events by acting as a link between multiple modality event-elements, then it would be predicted that a patient with a lesion limited to the hippocampus would have the same level of impairment as a patient with a more extensive medial temporal lobe lesion in the ability to re-experience or replay events in mind. This is exactly what occurred with BW and JN, as evidenced by the data relating to relatively high and similar level of reporting of 'knowing' that events took place without the ability to clearly 'remember' them. Mandler (1980) proposed that recognition is composed of at least two independent processes. One is through recollection of the stimulus ("remembering") and the other is through detecting stimulus familiarity ("knowing'). Tulving (1985) proposed that requiring participants to judge whether they truly "remember" a word, or simply "know" that it was previously presented, may prove to be a productive way of investigating episodic memory. This has indeed proved to be the case with studies of recognition memory (see Gardiner and Java, 1993 for a review). The present studies indicated that even when recollection performance as measured by performance on an autobiographical event recognition task was close to normal, the phenomenological experience of recollection was far from normal. Sufficient event elements were activated to enable both patients to 'recognise' events, but there was insufficient activation of enough event elements (particularly visual, spatial and temporal elements) to provide a phenomenological sense of 'remembering' an event. Tulving (2001) has used the term 'autonoesis' (or 'autonoetic consciousness') to characterise the ability to mentally replay events, or mentally 'time travel'. Maguire, Vargha-Khadem and Mishkin (2001) reported that the developmental amnesic patient Jon, referred to earlier, also made the distinction between autobiographical and public events he remembered and others he knew had happened, but did not truly remember. Furthermore in an fMRI study, Maguire et al. (2001) demonstrated that Jon's hippocampi and medial frontal cortex were significantly more active "during retrieval of events for which he had clear autonoetic conscious recollection compared with those he knew just as much about, including the context, but could not remember experiencing" (p.1166).

Aggleton and Brown (1999) suggested that the process of recognition (of new items) is dependent upon a non-hippocampal circuit that includes the entorhinal cortex and the medial dorsal thalamus. While this explanation would work for BW, it does not work so well for JN who has bilateral entorhinal pathology. In JN's case it is more likely that neocortical areas outside of the medial temporal lobes were sufficient to support recognition of elements of autobiographical memories. Following on from this, studies with non-human primates contrasting focal hippocampal lesions with focal rhinal (entorhinal plus perirhinal) or parahippocampal lesions suggest that hippocampal lesions have minimal effects on recognition memory, and on some associative memory (stimulus-stimulus) tasks (see Nadel, 2000, p. 135). This finding has lead to the speculation that in primates the rhinal cortex has a function that is analogous to semantic memory in humans. Findings from the comparison between BW and JN support a role for the rhinal cortex in semantic memory, though with the caveat that JN's lesion extends beyond the parahippocampal region. BW showed evidence of learning factual information about famous people, news events and new vocabulary, even though her performance was not necessarily at the level of control participants. This finding of semantic knowledge acquisition, even if not at normal levels, suggests that the extra-hippocampal regions can support learning of new factual information, but also suggests that under normal circumstances, the hippocampal-based episodic system contributes significantly to semantic knowledge acquisition. JN was severely impaired in her ability to acquire new semantic information in comparison to control participants. One important consideration in her case is that there was some loss of pre-morbid semantic knowledge (as well as episodic knowledge), though she does not present with the severe loss of semantic memory associated with more extensive inferolateral temporal lobe damage in conditions such as semantic dementia (Snowden et al., 1989, Hodges et al., 1992). Nevertheless, it is possible that the loss of pre-morbid knowledge would make the acquisition of new information more difficult. Although Craik and Lockhart's (1972) levels of processing theory was viewed as having several limitations (Baddeley, 1997 p. 115), it has long been recognised that the opportunity to relate new information to old knowledge will lead to better retention of new information. William James made this point in 1890, arguing that of two men with equivalent mental capacity, "the one who thinks over his experiences most, and weaves them into systematic relations with each other will be the one with the best memory...All improvement of the memory lies in the line of elaborating the associates" (see Baddeley 1997, p. 119). In a patient like JN, there is a loss of associated knowledge into which she can weave new information. JN has however managed to acquire *some* new semantic information. For example, she knows the general facts about her current situation, she knows facts about her husband's health, her children and grandchildren, and she has re-learned some facts about her pre-morbid life that she had forgotten. She carries out a voluntary job in a hospital tea-room and has learned the procedures involved in that job. She knows some of the medical professionals involved in her care. How is JN acquiring this knowledge? Although she was described as having less marked damage to the left hippocampus than the right, she has major pathology in parahippocampal and entorhinal cortices bilaterally suggesting that all main routes into the hippocampus are compromised. It seems unlikely therefore that the hippocampus is playing any significant role in knowledge acquisition. Damage to the left temporal pole, along with left inferior and middle temporal gyri, was milder than that on the right. It is possible that that these structures, along with the unaffected superior temporal gyrus in both hemispheres, are able to support the acquisition of a certain amount of new knowledge without input from the more medial limbic structures. For JN, her family life essentially provides a continuous experience with frequent repetition of facts, which is almost certainly critical in acquiring such information. Snowden et al. (1996) showed that in semantic dementia it is possible to acquire both episodic and semantic information, but only for items which the individual encounters on a regular basis. People with semantic dementia have relative sparing of the hippocampal region that almost certainly supports episodic as well as factual knowledge acquisition. Cases such as JN, however, indicate that some factual knowledge can be acquired without the support of either the hippocampus or the parahippocampal region. Nevertheless, the amount of knowledge that can be acquired this way is very limited. In order to clarify the precise role that the parahippocampal region does play in the acquisition of semantic knowledge it would be useful to conduct similar studies on patients with either focal parahippocampal region lesions or combined hippocampal/ parahippocampal lesions, though of course such patients are likely to be extremely rare.

It appears from the findings of this chapter, that amnesia may be characterised by relative sparing or loss of the ability to acquire new knowledge, depending upon the extent of medial temporal lobe pathology and the degree of additional cognitive impairment. The particular learning demands of a new task will also interact with this additional cognitive impairment to determine the extent of knowledge acquisition. The two cases presented in this section had many of the features of a classical amnesic syndrome, but with contrasting ability to acquire new memories. In the next section, I will describe two cases where there was *no* evidence of amnesia on standard anterograde memory tests, but where there appeared to be impaired consolidation of new information.

## 4.2 Long term accelerated forgetting: two cases of consolidation failure.

### 4.2.1 Introduction

A small number of patients described in the literature have shown a pattern of abnormally fast rate of forgetting that occurs not during the first few minutes or hours after exposure to a particular stimulus or event, but after a period of days or weeks. Although forgetting is a normal and adaptive feature of human memory functioning, such patients seem to show a significant failure of very long-term consolidation, despite apparently encoding, storing and retrieving such information in a normal fashion over the typical time periods used in standard anterograde memory assessment. Mayes and Downes (1997) note in relation to such cases, "the existence of this atypical kind of AA [Anterograde Amnesia] needs to be confirmed, as does its relationship with RA [Retrograde Amnesia], and the implications that this form of memory deficit have for our understanding of the amnesic syndrome need to be worked out" (p. 17). This chapter presents detailed studies of anterograde and retrograde memory functioning in two patients who presented with this pattern of memory disorder.

Most of the reported cases of very long term accelerated forgetting suffered from epilepsy. Blake et al. (2000) and Martin et al. (1991) have demonstrated the phenomenon in people for whom temporal lobe epilepsy was the primary diagnosis, though it is assumed that nevertheless the epilepsy is caused by some form of structural lesion. This points to the involvement of epileptic seizures in the impairment. However, a question that remains unanswered is that of the nature of the relationship between epileptic seizures and the phenomenon of long term consolidation failure. Is it epileptic seizure activity that disrupts consolidation or, alternatively, is an underlying structural abnormality responsible for the long-term memory impairment? Lucchelli and Spinnler (1998) "cautiously rejected" epilepsy as the cause of the problem when they showed that there was no apparent impact of a seizure on their patient's ability to recollect a set of paired associates, learned just prior to the occurrence of seizure activity. Furthermore, Bergin et al.'s (1995) study of 58 patients with refractory partial seizures demonstrated that when compared on recall of memory after a 48 hour delay there was no difference in the performance of those who had had seizures during the intervening period and those who did not, leading to the conclusion that, "isolated seizures do not generally cause patients to forget material they have recently learned" (p. 236). By contrast, while Bergin et al. (2000) found that patients with temporal lobe epilepsy were significantly worse than patients with extra-temporal lobe epilepsy, patients with primary generalised epilepsy or controls on a test of public event memory. The specific relationship between seizures and forgetting therefore remains uncertain. One of the aims of the studies presented in this chapter was to investigate this issue further.

It was noted in Chapter 1 that there were indications that the failure to consolidate information affects both personal event and public event/factual knowledge, something that was evident in Kapur et al.'s (1997) case PA. However, this type of knowledge acquisition has not been studied in detail in many of the other cases and so it is not clear how consistent this finding might be. This type of knowledge acquisition was assessed in detail with the two cases presented here.

As discussed earlier in Section 1.3.4, in most cases of very long term accelerated forgetting, the anterograde memory deficit was accompanied by a significant remote memory impairment, with the exception of Kapur et al.'s (1997) case. Remote memory was not examined in the Blake et al. (2000) study, though this aspect of memory would in fact not have been relevant since there was no temporally specific pathology accounting for the epilepsy to act as a temporal frame of reference demarcating anterograde memory from retrograde memory. In most of the accelerated forgetting cases, where there was an extensive remote memory deficit, in addition to the presence of epilepsy, there were significant left or bilateral temporal lobe lesions, apart from Lucchelli and Spinnler's (1998) case. In Kapur et al.'s (1997) case PA, who did not show the extensive remote memory deficit, there was EEG evidence of temporal lobe pathology mostly in the left hemisphere, but also in the right. It has been speculated that the presence of an extensive remote memory deficit might be attributable to left, or bilateral anterior temporal lobe lesions, whilst the accelerated forgetting is the consequence of temporal lobe epilepsy. To clarify this issue, it is therefore critical to identify patients for whom the onset of epilepsy can be dated (in order to distinguish anterograde and retrograde memories), but in whom there is no evidence of widespread temporal lobe pathology. The two patients presented in this chapter are examples of such cases.

The proponents of Multiple Trace Theory (Nadel and Moscovitch 1997) and the Standard Consolidation Model (Squire and Alvarez, 1995, Murre, 1996) have not made specific predictions in relation to this type of memory disorder. However, it seems likely that both models would predict the same pattern of impairment of retrograde memory in cases of this sort. The prediction is that there should be a temporally graded retrograde amnesia present in such cases. In the case of the Standard Consolidation model this would be a result of the fact these memories which were not fully consolidated (i.e. wholly neocortically based) might be vulnerable to disruption by temporal lobe seizures. In the case of the Multiple Memory Trace model, it is assumed that seizure activity might disrupt the process of forming multiple traces within the hippocampus and hence also, in effect, disrupt a consolidation process. Therefore, whilst the cases presented in this chapter will not help to differentiate between the two models, they provide a further test of a prediction that is common to both models. Furthermore, if the assumption is made that epileptic seizures will only cause problems for memories that are not fully consolidated (either entirely in neocortex or in hippocampal-neocortical networks) then such cases may also go some way to addressing the question of how long the consolidation process may take. The length of the period of retrograde amnesia might be considered to reflect the period of time for which the consolidation process is vulnerable to disruption. This issue will be discussed further in the context of the nature of the retrograde amnesia in the two cases.

In summary, therefore, there remains a need to identify and characterise further cases of this atypical memory disorder. This chapter will present two patients who presented with this condition. Several important questions concerning very long term accelerated forgetting remain unanswered and these will be addressed in this chapter - (1) What is the mechanism responsible for very long term accelerated forgetting? The specific hypothesis that epileptic seizures are the main causal factor will be tested. (2) Is the acquisition of new knowledge (of famous personalities, news events, new vocabulary) impaired in very long term accelerated forgetting? (3) What is the relationship between anterograde and retrograde memory impairment in this disorder?

Patients were selected for inclusion in this study according to the following criteria: (1) Presenting complaints of difficulty remembering events such as holidays, trips, or social events over the preceding weeks, months or years; (2) normal performance on standard tests of anterograde memory; (3) clinical or imaging evidence to suggest the presence of cerebral pathology.

### 4.2.2 Case 1 SG

#### *4.2.2.1 Case history*

SG was born in 1919. She obtained a degree in Modern History and worked for the Home Office during the 2nd World War. She also worked as a researcher for the BBC. She is married. Prior to 1997, she had no history of neurological problems. However, during 1997, at the age of 79, she reported memory problems and in particular difficulty remembering events such as holidays and theatre visits. These difficulties were confirmed by her husband. He reported that he did not think that her "everyday short-term memory" was affected. He said that he had first noticed that there were difficulties some two and a half years previously when she forgot a holiday they had been on. Over the ensuing year she continued to show memory loss for holidays and places they visited. At that time, he did not report obvious epileptic seizures, but he did mention nocturnal 'funny turns' whereby she would sit up in bed in the middle of the night, mumble something incomprehensible, ask where she was and what day it was and then go back to sleep. He reported that there had been about 10 of these episodes over the previous 4-5 years, but nothing of that nature prior to the early 90's. About a year after first presenting with the problems, SG experienced a grand mal seizure in the middle of the night. Since that time she was commenced on Carbamazepine and she has had no further seizures or episodes of her nocturnal 'funny turns'.

SG did not present with any significant mood disorder. She described herself as "frustrated [with her difficulties], but not depressed". There was no pre-morbid history of psychiatric illness. At the time of testing, she continued to lead an independent, active life, including foreign travel several times a year. A particular advantage of the opportunity to study this patient was that she had taken many holidays/trips over a very long period of time prior to the onset of her seizures, and furthermore had diary records that could be used to examine retrograde memory performance.

#### *4.2.2.2 Brain Imaging*

An MRI scan performed in 1998 was reported to be essentially normal for someone of her age. One neuro-radiologist was asked to specifically focus on the temporal lobes to identify whether there was any evidence of lesion or atrophy, but none was detected. A second neuroradiologist reported that there was minor ischaemic vascular change with a degree of atrophy in the anterior hippocampus bilaterally. EEG recording did not reveal major abnormality from surface electrode recording.

#### *4.2.2.3 General Neuropsychological Assessment*

Table 4.2.1 presents summary data of SG's performance on a range of standard cognitive tests, including a number of standard tests of anterograde memory.

The general neuropsychological assessment data indicated normal performance on all standard tests of anterograde memory, with the exception of impaired performance on the Warrington Faces Recognition Memory Test. She performed normally on the immediate and 30 minute delayed recall of the WMS-R Visual Reproduction task. The testing also indicated problems with verbal fluency and with the Brixton Spatial Anticipation Test, suggesting some frontal lobe involvement, though she performed more normally on the Weigl task and there was no indication of executive dysfunction in her clinical presentation.

***Table 4.2.1 SG's performance on a range of standardised neuropsychological tests.***

| | |
|---|---|
| **National Adult Reading Test** (Predicted pre-morbid IQ) | 127 |
| **Mini Mental State Examination** | 29/30 |
| **Wechsler Adult Intelligence Scale-Revised:** | |
| Full Scale IQ (Prorated) | 122 |
| Verbal IQ (Prorated) | 121 |
| Performance IQ (Prorated) | 112 |
| | (Age Scaled Scores) |
| Information | 12 |
| Comprehension | 13 |
| Similarities | 15 |
| Block Design | 13 |
| Object Assembly | 12 |
| Digit Symbol | 11 |
| **Rivermead Behavioural Memory Test** | |
| Standardised Profile Score (1997) | 18/24 (~50th percentile for age and IQ). |
| Standardised Profile Score (2001) | 17/24 (~50th percentile for age and IQ). |
| **Auditory Verbal Learning Test** | |
| T1 | 6 (Control mean = 4, s.d. 2.0) |
| T2 | 6 (Control mean = 7.2; s.d. 2.9) |
| T3 | 10 (Control mean = 8.5; s.d. 2.5) |
| T4 | 8 (Control mean = 10; s.d. 3.3) |
| T5 | 10 (Control mean = 10.9; s.d. 2.9) |
| **Wechsler Memory Scale- Revised** | |
| Visual Reproduction I | 30/41 (Control mean 24.2, s.d. 7.3) |
| Visual Reproduction II | 25/41 (Control mean 16.5, s.d. 8.3) |
| **Warrington Recognition Memory Test** | |
| Words | 47 (>75th percentile) |
| Faces | 35 (5th percentile) |
| **Verbal Fluency (FAS)** | 36 words (predicted = 52, $P<0.05$) |
| **Brixton Spatial Anticipation Test** | 2 (Abnormal) |

### *4.2.2.4 Assessment of very long-term anterograde memory*

*Procedure*

SG's ability to retain information over an extended period of time was examined using tests of story recall, visual design memory and the Camden Picture Recognition test. Her performance was contrasted with a group of six participants matched for age (SG's age at time of testing = 81; control mean age = 79 years, s.d. 2.3 years; range 77-82 years) and education (all participants educated to university or professional training level). SG and the controls were assessed on the AMIPB Story (Form 2) and Visual Reproduction tasks of the Wechsler Memory Scale- Revised for immediate, 30-minute recall and four-week recall. No warning was given to SG that she would be tested after four weeks, but when she was assessed she reported having anticipated that she would be tested and indicated that she had, in fact, made some attempt to rehearse the information. Control participants (who were assessed after SG had completed her 4 week delayed test) were therefore warned that they would be tested again, but asked not to actively rehearse the story if they were reminded of it in the intervening weeks. Recognition tests for the Story and Designs tasks were also administered. For the Story task, 25 items were included consisting of a question (e.g. What was the woman's surname?) and four possible answers (e.g. Hawkins, Harper, Hutchings, Howard). For the Designs task, each design was presented along with three distractor items and participants were asked to select the target design. The Camden Picture Recognition task (Warrington, 1996) was also administered, in a modified form. SG and control participants were asked to look at each of the 30 pictures for 5 seconds and say whether the picture was of a British or foreign place. They were then shown the pictures for a second time, again for five seconds each and this time asked to say whether they thought the picture had been taken by a professional or an amateur. They were not given an immediate retention test, but four weeks later were given a retention test that involves the subject being shown 30 pages one at a time. Each page has a target item along with two previously unseen distractors. The subject is asked to pick out the target item.

*Results*

The results for the three separate tasks are shown in Figures 4.2.1 (a) - (d). The results show that for the story recall, SG's performance was somewhat below, but not statistically significant from the level of the controls for immediate ($t=-1.07$, $df=5$, $p=0.166$) and 30 minute delay ($t=-0.76$, $df=5$, $p=0.240$), as well as at four-week delay ($t=-0.72$, $df=5$, $p=0.253$). It was noted above that SG reported having rehearsed the story over the 4 week period and so her score at 4 weeks may represent an overestimate of her true performance. A further factor was that one of the control participants appeared to be something of an 'outlier' in relation to the performance of the others. At the four-week delay this control participant reported remembering nothing of the story on free recall or on cued recall. However, there did not appear to be any obvious medical or motivational problem that might account for this performance and so her scores were retained in the control group. For the design recall, there was somewhat better evidence of an accelerated forgetting process, though even here it was not striking. On immediate recall, SG's performance was significantly below that of the controls ($t=-2.06$, $df=5$, $p=0.05$), but by the 30 minute delay test her performance was well within the control range ($t=-0.53$, $df=5$, $p=0.31$). By the four week delay her performance had dropped to be considerably below that of the controls, with her score showing a trend towards being significantly different ($t=-1.56$, $df=5$, $p=0.08$). On the four-week recognition tests, there was a similar finding of no significant difference for the story ($t=-0.15$, $df=5$, $p=0.44$), but significantly poorer performance by SG for the designs ($t=-2.53$, $df=5$, $p=0.03$). On the Camden Picture Recognition test, SG's performance was above chance (which would be 33.3%), but was considerably below that of the controls, though the difference did not reach statistical significance ($t=-1.67$, $df=5$, $p=0.08$).

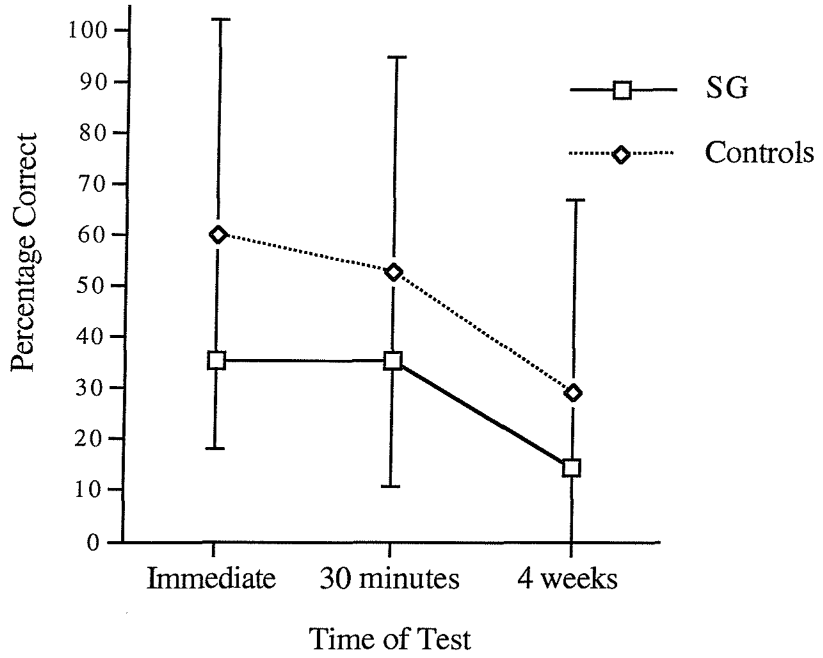



***Figure 4.2.1(a) Performance of SG and six controls on the WMS-R Story recall task, at immediate, 30 minute and 4 week delay periods. Bars indicate two standard deviations from the control mean.***

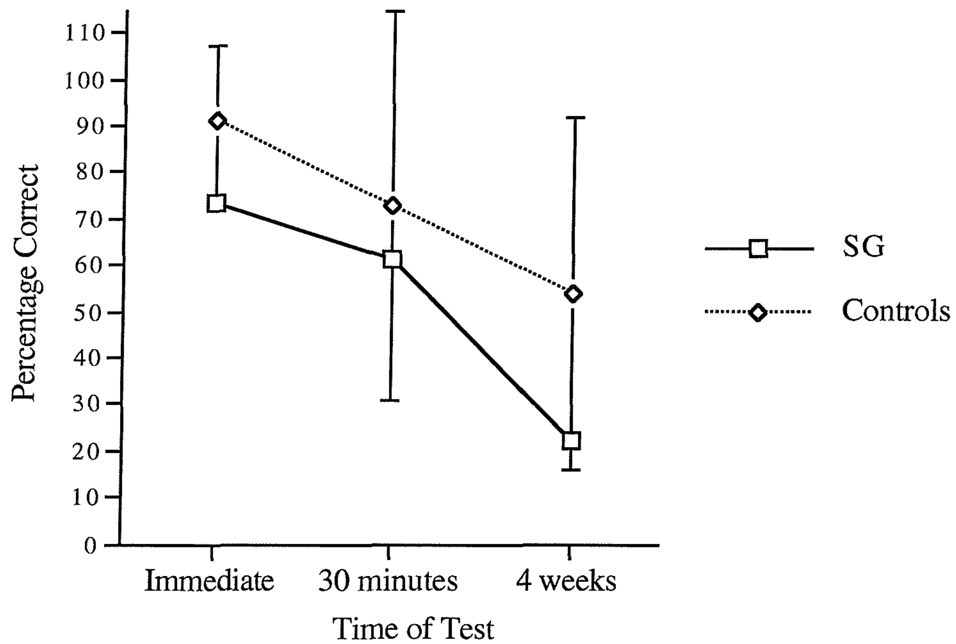



***Figure 4.2.1(b) Performance of SG and six controls on the WMS-R Designs recall task, at immediate, 30 minute and 4 week delay periods. Bars indicate two standard deviations from the control mean.***

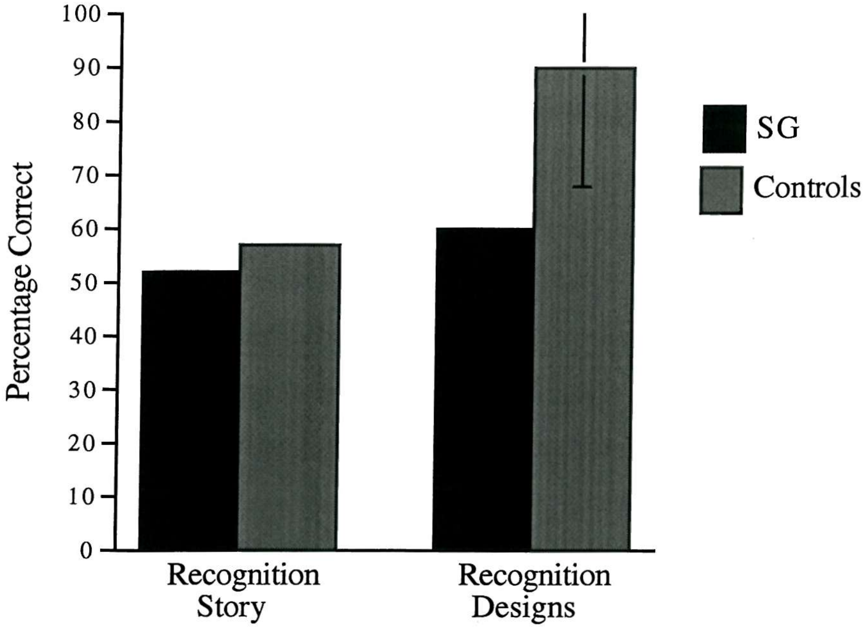



***Figure 4.2.1(c) Performance of SG and six controls on the recognition tasks of the story and designs tests at the four week delay. The bar represents two standard deviations from the control mean. No standard deviation marker bar is provided for the Story Recall tasks as the standard deviation was very large (31), reflecting a wide range of performance amongst the control participants.***


***Figure 4.2.1(d) Performance of SG and six controls on the Camden Picture Recognition Test at the four week delay. The bar represents two standard deviations from the control mean.***

#### 4.2.2.5 Studies of very long-term autobiographical and public event knowledge.

A range of different tests were used to assess SG's memory for personal semantics, autobiographical episodic events and public events relating to the period since the onset of her illness. The opportunity was also taken to examine her retrograde memory for the same knowledge domains. In SG's case (unlike TG presented below) the date of onset of her condition could not be precisely determined. However, her clinical history indicated that the epileptic activity had been present from about 1992.

*4.2.2.5.1 The Autobiographical Memory Interview (Kopelman et al., 1990)*

SG was assessed on the AMI. Results are shown in Table 4.2.2. SG showed normal personal semantic memory performance for all time periods sampled. Her score for recollection of autobiographical incidents was normal for her early adult life, while scores for childhood and recent life were poorer.

***Table 4.2.2 SG's performance on the AMI***

| ***Table 4.5 SG's performance on the AMI*** | **Personal Semantic** | **Autobiographical Incidents** |
|---|---|---|
| Childhood | 20 (Normal) | 4 (Probably abnormal) |
| Early Adult Life | 20.5 (Normal) | 7 (Normal) |
| Recent Life | 19 (Normal) | 6 (Borderline) |

*4.2.2.5.2 Memory for holidays*

Since 1970, SG had kept diary records of every holiday she and her husband had taken. They have taken quite a number of holidays, most involving travel abroad. To test her memory for these holidays, the name of each holiday destination was given and SG was asked to recall any information she could about the holiday. She was encouraged to try to recollect specific events if possible. A four-point scoring system was used as follows; 0= no recall, 1= very limited general semantic information such as type of place stayed, 2 = more detailed general semantic such as multiple events or greater detail about the place visited, 3= evidence of recollection of at least one specific event.

*Table 4.2.3 Ratings of SG's recollection of holidays she has taken since 1970*

| **Year/Holiday** | **Score** |
|---|---|
| 1970 | 1 |
| 1972 | 0 |
| 1973* | 1 |
| 1974* | 1 |
| 1975* | 1 |
| 1976 | 1 |
| 1977 | 1 |
| 1978 | 0 |
| 1979 | 0 |
| 1980 | 0 |
| 1982 | 0 |
| 1983 | 0 |
| 1984 | 0 |
| 1985 | 2 |
| 1987 | 0 |
| 1988 | 0 |
| 1989 | 0 |
| 1990 | 1 |
| 1991* | 1 |
| 1993* | 1 |
| 1994* | 1 |
| 1995 | 0 |
| 1996 | 0 |
| 1997 | 0 |
| 1998 | 0 |
| 1999a | 0 |
| 1999b | 2 |
| 2000a | 2 |
| 2000b (3 months prior to testing) | 3 |

*The holidays taken in 1973, 1974 and 1975, were in the same destination. as were holidays in 1991, 1993 and 1994.

SG showed a marked impairment in her ability to recollect details about holidays, with this memory loss stretching back for 30 years. The only trip for which SG was able to produce some event information was the most recent, involving a trip taken some three months prior to testing. For this trip she was able to describe the places visited and the journey details.

SG was also asked to read an entry in her diary that related to each holiday and asked to identify whether the events referred to in her diary felt familiar. She reported that she could not remember any of the specific events happening, though sometimes knew things to be true. For example on the holiday that she took in 1985, SG fell and broke her leg on an escalator. She said that she knew this had happened, but could not picture it in her mind.

*4.2.2.5.3 Dead-or-Alive Test*

SG was given the modified version of the Dead-or-Alive described in detail in Section 2.3.3. 130 names were presented one at a time on individual cards. 79 were the names of famous people. The other 51 were plausible names, but were not the names of famous people. Of the 79 famous people, 9 died in the 60's, 11 died in the 70's, 11 died in the 80's and 15 died in the 90's. A further 33 people are still alive. SG's ability to recognise famous names, provide identifying information and details of death for those who have died was contrasted with six controls matched for sex, age (SG's age at time of testing = 81; control mean age = 79 years, s.d. 2.3 years; range 77-82 years) and education (all participants educated to university or professional training level) and media exposure (SG's media exposure score = 71; Controls mean media exposure score = 69.5, s.d. 3.94; range 64-75). Scoring of the responses was carried out by an independent rater, trained in the scoring method, who was blind to any experimental hypotheses.

The results from the Dead or Alive test are shown in Figures 4.2.2 (a) - (c). On the familiarity task, SG's performance was only significantly different from the controls for the Alive category ($t=-2.01$, $df=5$, $p=0.05$). For the Information task, SG's performance was only significantly different from the controls for the 70's ($t=-2.21$, $df=5$, $p=0.04$) and for the Alive category ($t=-2.17$, $df=5$, $p=0.04$). For the Details of Death task, SG's performance was significantly different from that of the controls for the 60's ($t=-3.60$, $df=5$, $p=0.008$), 70's ($t=-4.36$, $df=5$, $p=0.004$), and 90's ($t=-2.94$, $df=5$, $p=0.02$) and showed a trend towards significance for the 80's ($t=-1.76$, $df=5$, $p=0.07$).

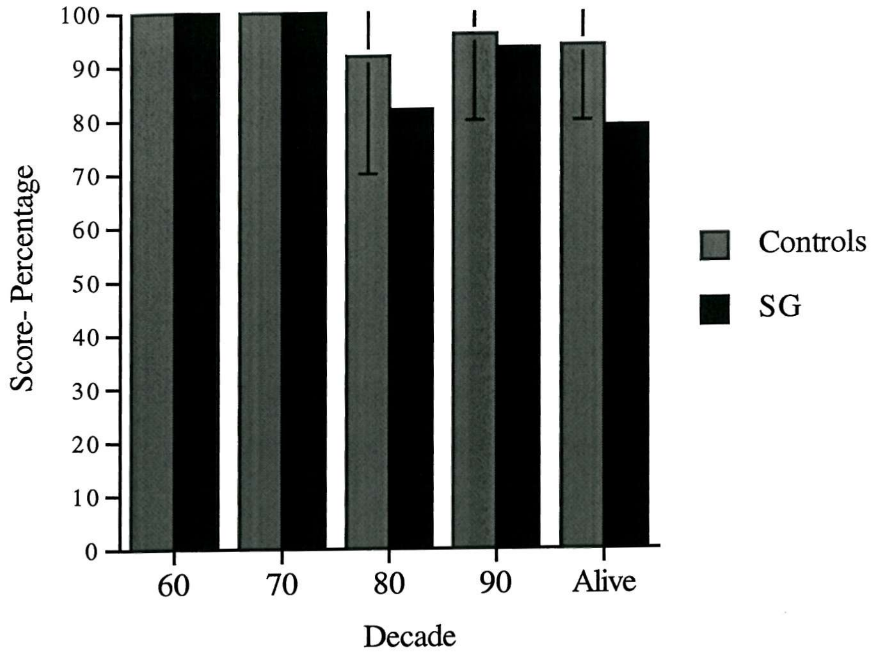



***Figure 4.2.2(a) Performance of SG and six matched controls on the Dead-or-Alive Familiarity Task, with two standard deviation bars.***

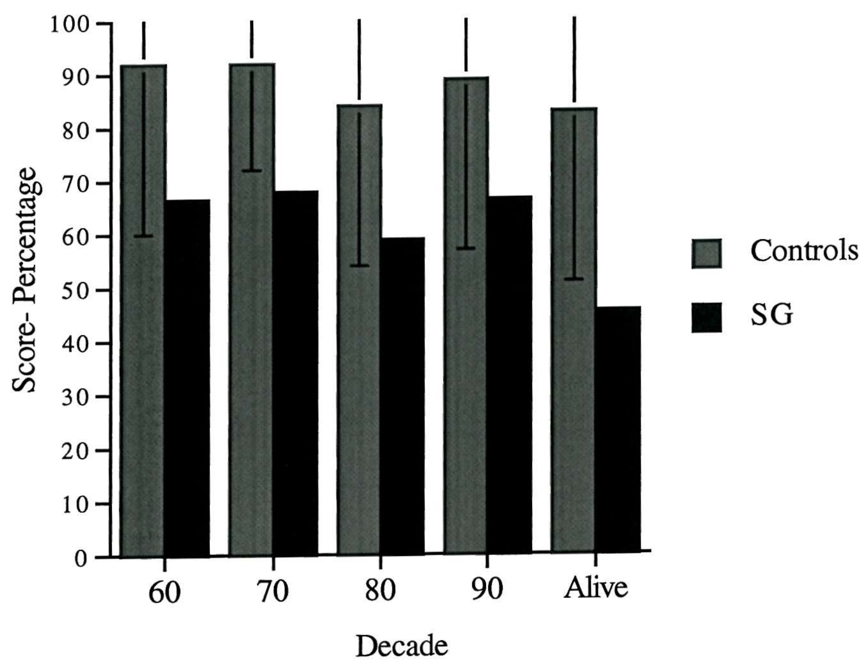



***Figure 4.2.2(b) Performance of SG and six matched controls on the Dead-or-Alive Information Task, with two standard deviation bars.***

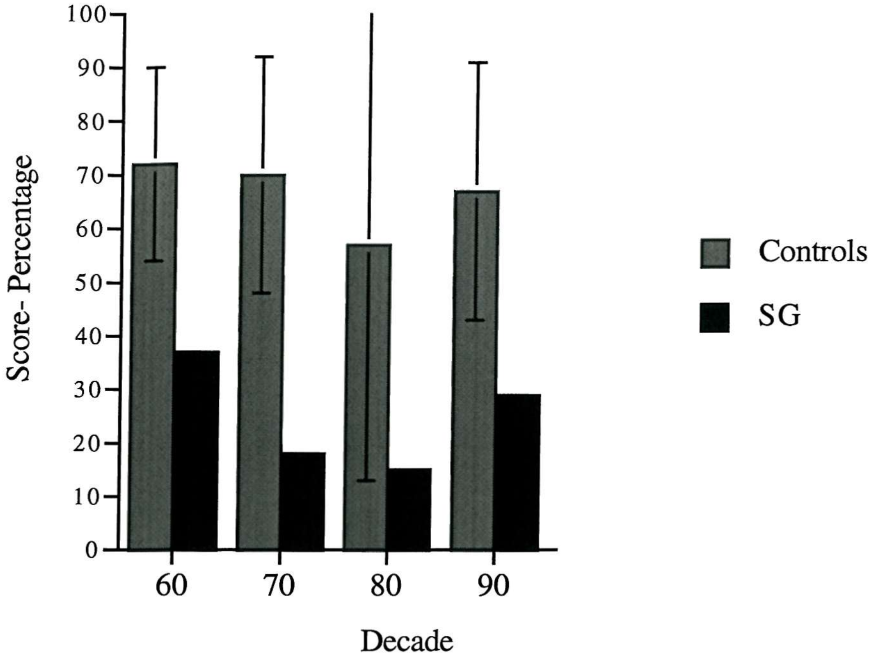



***Figure 4.2.2(c) Performance of SG and six matched controls on the Dead-or-Alive Details Task, with two standard deviation bars.***

*4.2.2.5.4 News Events tests*

SG's knowledge of public news events was assessed using two different tests.

*News Events Test 1*

This test consisted of 28 items (See Appendix 4 for a list of the items). Each item included descriptions of three news events, one of which was a real event, the other two being plausible, but untrue distractors. For each item the subject was asked to identify which event actually happened. There were seven events from each of four decades (60's, 70's, 80's and 90's). An example is provided below, with the correct item in italics:

Which one of these events actually happened?

(a) An American nanny, working in Britain, is found guilty of the manslaughter of a child in her care.

(b) A French au pair, working in America, is found guilty of the manslaughter of her employer.

*(c) A British nanny, working in America, is found guilty of the manslaughter of a child in her care.*

SG's performance was contrasted with the same six controls as for the Dead or Alive test above, matched for sex, age, level of education and media exposure.

The results from the verbal news events test are shown in Figure 4.2.3. The graph shows that SG demonstrated a marked temporal gradient in her performance. She was not significantly different from the control participants for 60's ($t=-0.015$, $df=5$, $p=0.49$) or 70's ($t=-0.32$, $df=5$, $p=0.38$), but was significantly different for the 80's ($t=-6.89$, $df=5$, $p=0.0005$) and 90's ($t=-3.59$, $df=5$, $p=0.008$).

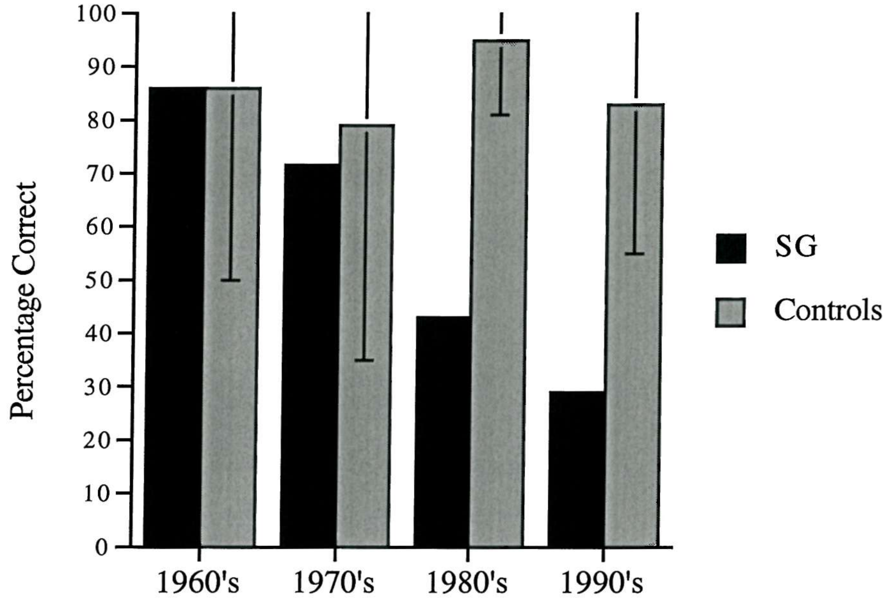



***Figure 4.2.3 Performance of SG and the six control participants on News Events Test 1, with two standard deviations bars.***

*News Events Test 2*

This test was based on the format described by Graham et al. (1998). Forty-nine famous news events from a period covering 13 years pre-illness (79-91) and 38 events from a period covering nine years post-illness (92-00) were included. The testing and scoring method was the same as that described for this test in Section 2.1.4.4. For the recognition component of the test, four events (target and three distractors) were presented on a sheet of paper one above each other, with the position of the target event being equally likely to occur in any of the four positions. Participants were asked to identify the real event. Having selected an event, they were then asked to recall as many details of the event as possible. The recognition component of the test was scored simply in terms of the total number of correctly identified items. For the event details recall component of the task, each response was scored according to a 4 point (0-3) scale: 0 = don't know or incorrect response; 1 = superordinate information only; 2 = a definition that described the event, but did not distinguish it from other similar events (i.e. did not uniquely identify the event); 3 = a definition that uniquely identified the event. Scoring was undertaken by an independent rater who was trained to use the rating system and who was blind to any experimental hypotheses. SG's performance was contrasted with the same six controls as for the Dead or Alive test above, matched for sex, age, level of education and media exposure.

The results shown in Figures 4.2.4 (a) and (b) indicate that SG was significantly impaired in her familiarity with both pre-morbid events ($t=-2.11$, $df=5$, $p=0.04$) and post-morbid events ($t=-2.84$, $df=5$, $p=0.02$) and more detailed knowledge of pre-morbid events ($t=-2.98$, $df=5$, $p=0.02$) and post-morbid events ($t=-3.43$, $df=5$, $p=0.01$). She was extremely impoverished in her ability to recall any details about events that she was able to recognise. There was no indication of a lack of retrieval effort on her part.

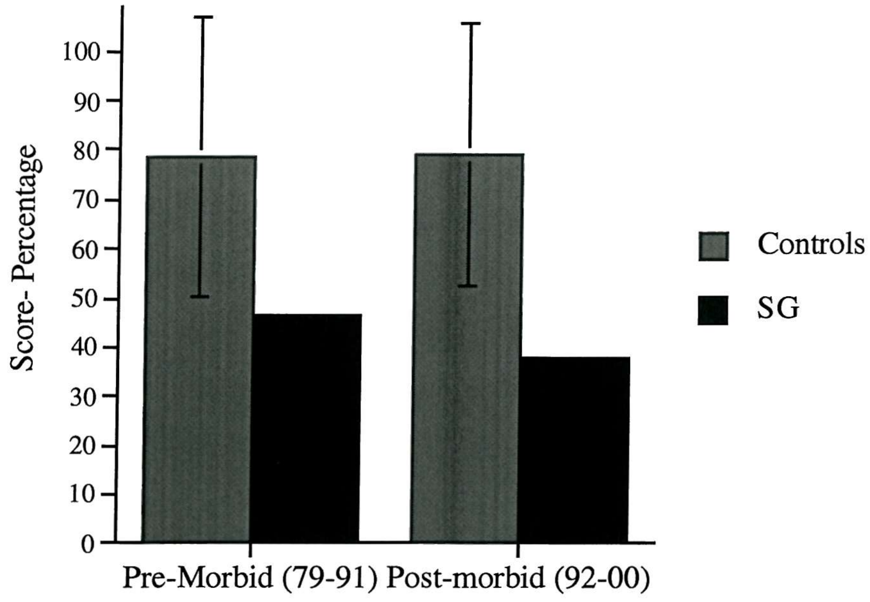



***Figure 4.2.4(a) Performance of SG and six controls on the recognition component of the News Events Test for the pre-morbid period (79-91) and the post-morbid period (92-00), with two standard deviation bars.***

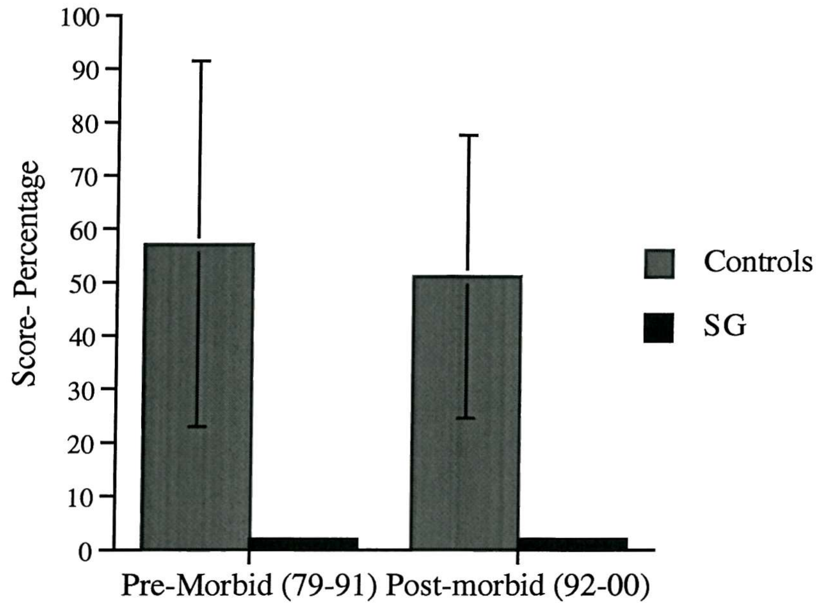



***Figure 4.2.4(b) Performance of SG and six controls on the event details recall component of the News Events Test for the pre-morbid period (79-91) and the post-morbid period (92-00), with two standard deviations bars.***

#### *4.2.2.6 Summary of findings in case SG*

On standard anterograde memory tests such as the Rivermead Behavioural Memory Test (RBMT) and Wechsler Memory Scale- Revised, using age appropriate (and in the case of the RBMT, NART IQ-appropriate) norms, SG's performance was normal. When she was compared with six age and education matched controls for the purpose of examining her long-term retention of verbal and visual information there were indications of some weakness in verbal recall at immediate and 30-minute delays as well as after four weeks. For recall of designs, there was some indication of weakness in comparison to the controls for immediate delay, though after 30 minutes she was within normal limits. After four weeks, there was some evidence of greater forgetting for SG than the controls. On the story recognition task her performance after four weeks was not different from the controls, but her performance on recognition of the designs was significantly different. On the Camden pictorial recognition task, she was considerably poorer than the controls at four weeks, though her score just failed to reach statistical significance. These tests provided confirmation of her complaint of accelerated forgetting in everyday tasks, though with some suggestion of a mild degree of impairment existing after much shorter delays too. Nevertheless her anterograde memory performance on standardised tests cannot in any way be said to be similar to that of patients with a classical amnesic syndrome. SG was unable to recall events or even much general information about holidays she has taken over the previous thirty years, other than for the most recent trip taken three months prior to testing. On tests of memory for famous personalities and news events, SG was impaired for post-morbid periods. For pre-morbid periods, she was impaired for a period of about 20 years, with some evidence of better performance on more remote events. Before discussing the implications of the pattern of SG's memory disorder, a second patient will be described. In the case of SG, the date of onset of her difficulties could not be determined precisely. However, this was accurately demarcated in the second patient, TG. Furthermore, with TG it was possible to study the extent of his acquisition and retention of autobiographical event memories using a novel prospective diary based procedure.

### 4.2.3 Case 2 TG

#### *4.2.3.1 Case history*

TG was born in 1970. In 1990, at the age of 19, while studying Landscape Design at university, TG collapsed following a seizure, having been generally unwell for the previous two days. On admission to hospital, he was unconscious and was ventilated for three days. He was diagnosed as suffering from viral encephalitis. Following removal of ventilation he recovered rapidly, but on discharge two weeks later he was still confused and had no memory of his illness. At the time of his illness, he was in the second term of his second year at university. After spending some time at home recuperating, he tried to return to university for the final term of the second year. However, this was not successful in that he could not keep up with the work. Following a summer vacation at home, he returned to university, but after two terms he was awarded a pass degree and left the course, as he was again not coping with his studies. He returned to live with his parents. He undertook a few garden design jobs for friends or local contacts, but did not pursue landscape design work in the long term. Around two years after the illness, TG obtained a job in a D.I.Y superstore as a general assistant, primarily working in the garden centre section of the store.

The onset of TG's illness was marked by an epileptic seizure and he continued to experience seizures after recovery from the acute illness. EEG recordings carried out two years post-illness showed frequent bilateral discharges, though primarily arising from the left temporal lobe. TG's seizures usually involve a combination of a metallic taste, a feeling of nausea and a sense of fear/anxiety. The frequency of seizures has varied over the years since their onset, ranging from 1 or 2 per month to up to 10 per month, often occurring in "a batch" over a period of a few days. He has been prescribed a wide range of anti-convulsants, but none have been able to eliminate the seizures completely. He continues to take Epilim at present. A formal neurological examination found no other abnormality.

After recovering from the acute phase of his illness, TG's main complaint was that although he could remember events that had happened in the previous day or two, he could not remember things that had happened a week or several weeks before. He indicated that if he was reminded that he had done something, he could sometimes recall that he had done it, but still found it difficult to recall events in detail.

A psychiatric assessment undertaken as part of his referral to a memory clinic found no evidence for formal psychiatric illness pre-or post-morbidly. TG was frustrated by his memory problem, but maintained a positive outlook and managed to keep up social activities. He was involved in a local youth group as a leader and also took on the role of Clerk to the Parish Council. In relation to the latter, he said that he managed to do this job by keeping extensive minutes of meetings and by immediately carrying out necessary actions. He began to use an electronic organiser to support his prospective memory. He has also kept a personal diary intermittently, though reported that when he goes back to look at things that he has done, often he does not recollect the events in question.

#### *4.2.3.2 Brain imaging*

An MRI scan was performed in 1998 (see Figure 4.2.5). This was reported as being normal. A visual rating assessment was carried out by an experienced rater using the method described by Galton et al. (2001). The rater was blind to TG's diagnosis or any experimental hypothesis. The ratings for TG's scan were 1 (minimal atrophy, within normal limits) for left and right hippocampi, and 0 (no atrophy) for all other temporal lobe structures.

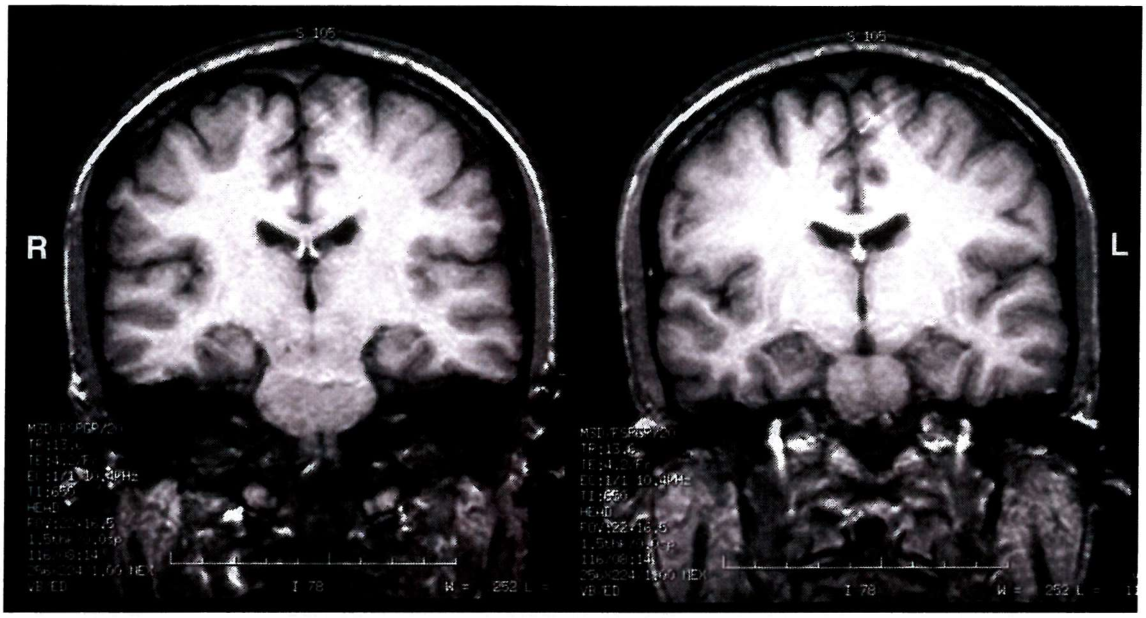



***Figure 4.2.5: TG's MRI brain scans showing two coronal cuts through the temporal lobes showing no significant abnormality***

### *4.2.3.3 General Neuropsychological Assessment*

Table 4.7 presents summary data of TG's performance on a range of standard cognitive tests, including a range of tests of anterograde memory. There were some indications of a mild weakness in verbal short term memory (Digit Span). By contrast, TG shows a considerable strength for visuo-spatial tasks (e.g. Block Design and Object Assembly). Given his pre-morbid educational choices (i.e. studying landscape design), this discrepancy might reflect a pre-morbid characteristic. There was no evidence of significant general intellectual, perceptual, language or executive function decline. The most significant finding from these assessments was that TG's performance on the different anterograde memory tests was within normal limits for all tests that were given.

*Table 4.2.4 Summary data of TG's performance on a range of standard cognitive tests.*

| | | |
|---|---|---|
| **National Adult Reading Test** (Predicted pre-morbid IQ) | 114 | |
| **Wechsler Adult Intelligence Scale-Revised:** | | |
| Full Scale IQ | 108 | |
| Verbal IQ | 100 | |
| Performance IQ | 119 | |
| Information | 9 | (Age Scaled Scores) |
| Digit Span | 7 | |
| Vocabulary | 11 | |
| Arithmetic | 10 | |
| Comprehension | 11 | |
| Similarities | 12 | |
| Picture Completion | 11 | |
| Picture Arrangement | 12 | |
| Block Design | 17 | |
| Object Assembly | 13 | |
| Digit Symbol | 9 | |
| **Rivermead Behavioural Memory Test** | | |
| Standardised Profile Score | 24/24 | |
| **Wechsler Memory Scale- Revised** | | |
| Verbal Index | 90 | |
| Visual Index | 109 | |
| General Memory | 94 | |
| Delayed Index | 96 | |
| Logical Memory I | 25 (47th percentile) | |
| Logical Memory II | 20 (41st percentile) | |
| Visual Reproduction I | 40 (97th percentile) | |
| Visual Reproduction II | 37 (89th percentile) | |
| **Warrington Recognition Memory Test** | | |
| Words | 46 (~50th percentile) | |
| Faces | 43 (~50th percentile) | |
| **California Verbal Learning Test** | | |
| List A Trials 1-5 | T=57 | |
| List B | z = -1 | |
| List A short recall | z = 1 | |
| List A long delay | z = 0 | |
| Recognition | 14/16 | |
| **Modified Wisconsin Card Sorting Test (Nelson version)** | | |
| Categories | 6 | |
| Total Errors | 8 | |
| Total perseverative errors | 1 | |

| | |
|---|---|
| **Cognitive Estimates** (error score) | 2 |
| **Behavioural Assessment of the Dysexecutive Syndrome** | |
| Age corrected Standardised Profile score | 102 |
| **Paced Auditory Serial Addition Test (PASAT)** | |
| **2.4 sec/digit** | 49/60 (Control mean = 46, s.d. 6) |
| **2.0 sec/digit** | 38/60 (Control mean = 40, s.d. 7) |
| **1.6 sec/digit** | 33/60 (Control mean = 32, s.d.8) |
| **1.2 sec/digit** | 18/60 (Control mean = 22, s.d. 5) |
| **Visual Object and Space Perception Battery** | |
| Incomplete Letters | 19/20 |
| Position Discrimination | 20/20 |
| Cube Analysis | 10/10 |
| **McKenna Graded Naming Test** (total/30) | 19 |

#### *4.2.3.4 Assessment of very long-term anterograde memory*

##### *4.2.3.4.1 Story and complex figure recall*

TG's ability to retain information over an extended period of time was examined using a story recall test and a complex figure memory test. His performance was contrasted with a group of five sex, age and education matched participants (TG was 21 years at the time of testing, mean age of controls 22.2 years, s.d. 2.17; all participants educated to university level). The story used was taken from the Rivermead Behavioural Memory Test (Version D) which has 54 words, with 21 'story units'. The complex figure used was Form 2 from the Adult Memory and Information Processing Battery (AMIPB; Coughlan and Hollows, 1985). All participants were unfamiliar with both the story and the figure prior to testing.

*Procedure*

Each participant was told that he would hear a short story and immediately afterwards should try to recall as much of the story as he could remember. The story was read aloud and immediately afterwards the participant was asked to recall the story. The participant was then told he would be asked to recall the story again later. Next, the participant was asked to copy the complex figure. Upon completion, he was asked to draw the figure from memory. The participant was told that he would be asked to recall the figure again later. One hour later, the participant was asked to recall the story and the figure once more (participants carried out other unrelated tasks in the intervening period). The participant was then given a set of three sheets of paper labelled '1 day'; '1 week' and '4 weeks'; a set of three smaller envelopes; and one large stamped addressed envelope. The participant was told that on pre-arranged days, he would be telephoned and asked to try to recall the story once again and then asked to draw the complex figure on one of the labelled sheets, after which he should place the sheet in the corresponding envelope. The participant was asked not to actively rehearse the story or design during the inter-trial periods. He was told that if the story came to mind he should simply try to move on to thinking about something else. The participant was telephoned according to the pre-arranged schedule of testing and asked to recall the story and then to complete the complex figure recall task, sealing the completed figure in the appropriate envelope. After the fifth test trial, the participant was asked to post back the completed figures.

The schedule of testing was as follows, with testing occasions labelled T1-T5 and the intervals between each test occasion ranging from 1 hour to 4 weeks. The total time between T1 and T5 was 36 days (i.e. five weeks and 1 day).

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **T1** | 1 hour | **T2** | 24 hours | **T3** | 1 week | **T4** | 4 weeks | **T5** |

*Results*

The performance of TG and the mean performance of the controls (with one standard deviation bars) for both story recall and complex figure recall are shown in Figures 4.2.6. and 4.2.7. Figure 4.2.6 shows that TG's performance was similar to that of the control participants up to 24 hours delay. After a one week delay his performance was considerably below that of the control participants ($t=-1.87$, $df=4$, $p=0.07$), and after a four week delay it was significantly impaired ($t=-3.33$, $df=4$, $p=0.01$). Figure 4.2.7 shows a similar pattern. TG's initial performance was somewhat below that of the control participants ($t=-1.85$, $df=4$, $p=0.07$), though his performances after one hour ($t=-1.15$, $df=4$, $p=0.16$) and 24 hours ($t=-0.58$, $df=4$, $p=0.30$) were normal. However, after one week (t=-3.37, df=4, p=0.01) and four weeks (t=-10.70, df=4, p=0.0002) his performance was impaired. TG noted that he had suffered several seizures in the period between 24-hour testing and four-week testing. He did not record exactly how many and when they had occurred, but noted that he had had at least five in the week immediately preceding the four week test.

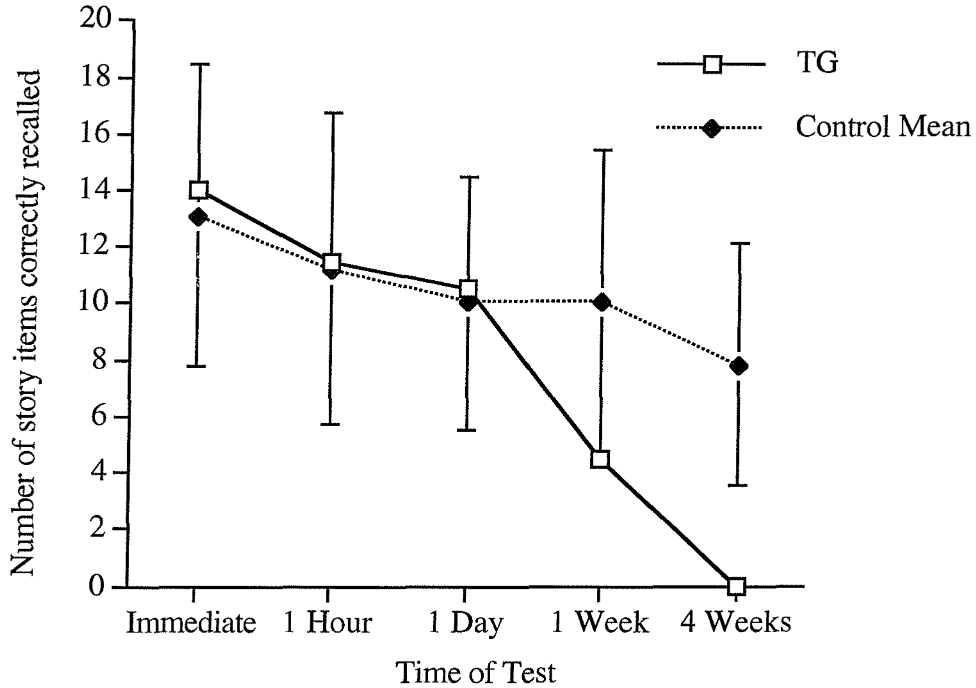



***Figure 4.2.6 Recall of Story by TG and control participants, with two standard deviation bars.***

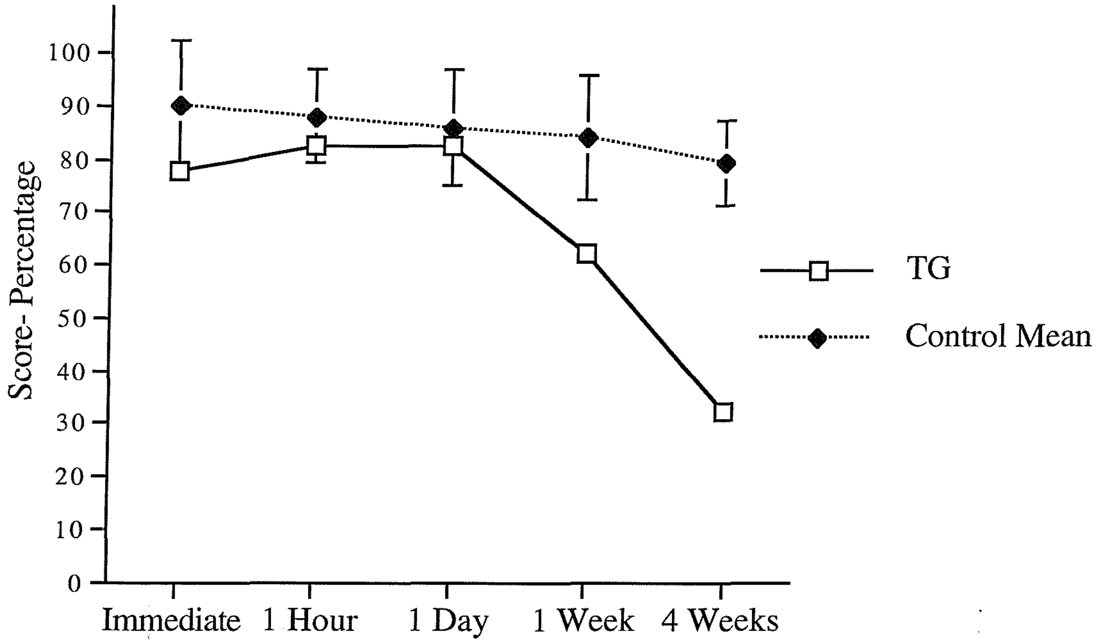



***Figure 4.2.7 Recall of Complex Figure by TG and control participants, with two standard deviation bars.***

*4.2.3.4.2 Autobiographical event diary studies*

TG's memory for personal events was examined through the use of two diary studies. The studies were also used to examine the relationship between forgetting of events, the effect of personal significance of events and the occurrence of epileptic seizures. It was hypothesised that if seizure activity disrupts long-term consolidation processes, then the more closely an event was followed by a seizure, the more likely it would be for that event to be forgotten.

*Diary Study 1*

TG was asked to keep a diary in which he recorded one personal event that happened to him each day. He was also asked to rate each event according to the personal significance of the event to him using a three point scale (Very Significant/Somewhat Significant/Not at all Significant). The diary was kept for a total of 34 days. TG also recorded all seizures during this period. TG's memory for the events recorded in his diary was examined in two ways, firstly using a cued recall test and then an event recognition memory test.

For practical reasons it is very difficult to recruit control participants who will agree to keep diaries for an extended period of time and carry out subsequent memory tests. However, for this study a control subject (FG) was recruited. He was a similar age to TG (control aged 31, TG aged 29 at the time of the study), educated to university level and with no history of neurological disease. He was assessed using the same format as for TG. FG kept a diary for 41 days and also rated items using the three-point personal significance scale. FG's memory for the events was also examined in two ways, using a cued recall test and a recognition test.

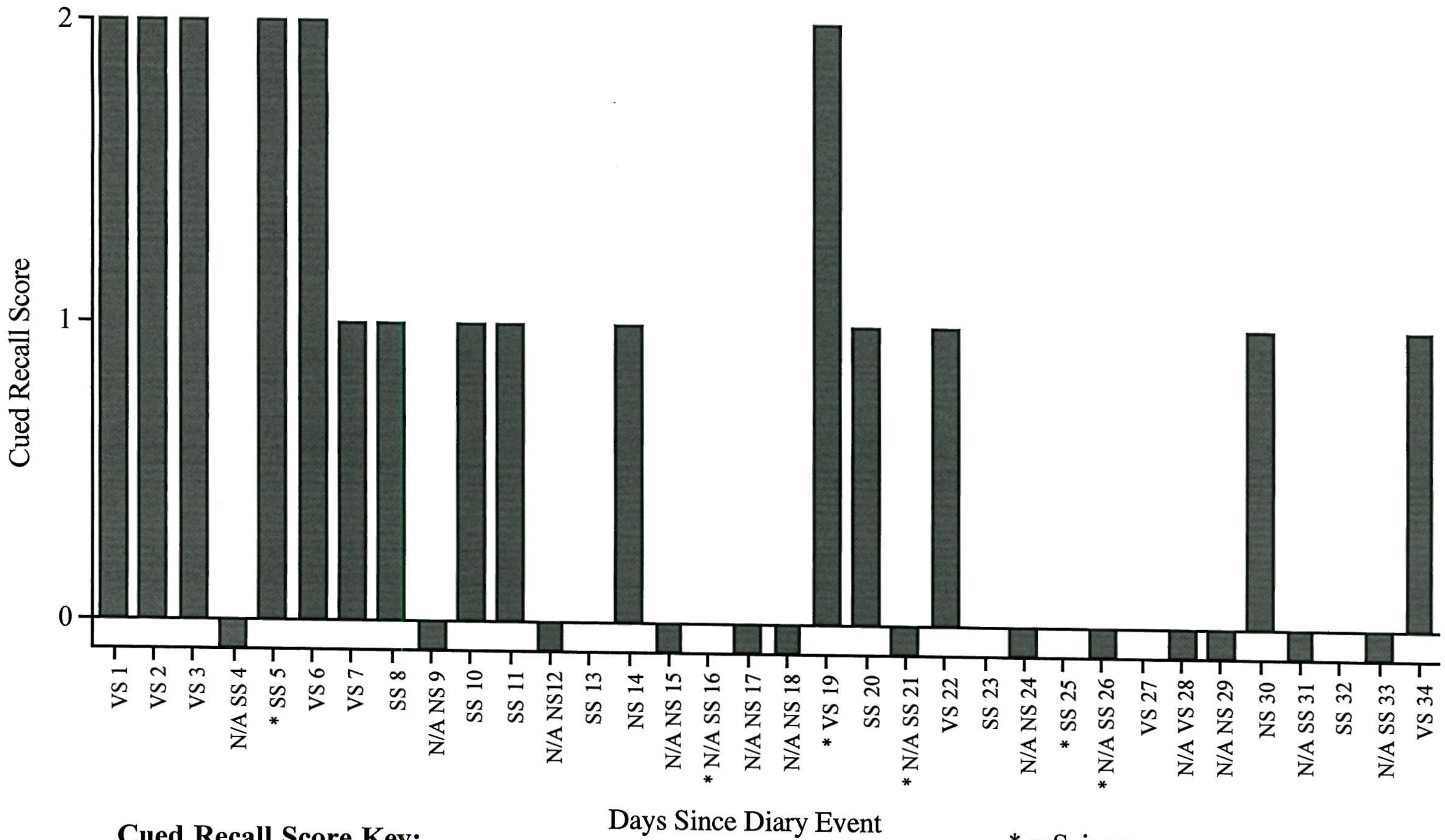
Results from TG

*(i) Cued recall test*

On the day following the last diary entry, TG was given a cued recall test for 21 items spread throughout the diary period. These 21 items were selected on the basis that the events described were relatively distinctive and it was possible to construct a partial cue. For reasons of confidentiality, the diary entries are not given in full in this thesis. However, one example of a diary entry was, "I had an appraisal at work today- all staff are being given them, I'd lost my appraisal form and so had to redo that for 3/4 hour before we could have the meeting. N. took it and said basically I'm doing really well- I got 50 points- a very good score." For this item TG was given the cue "Can you tell me about an appraisal you have had at work". Another diary entry was, "One lovely event today was, on getting onto a crowded bus I had to go right to the back for a seat, where I sat next to a 50-60 year old lady reading a book. For the next 30-40 minutes we chatted away about out lives, where we'd lived, what we'd done, the weather, politics, everything! It was lovely- just sad that I never got her name". For this item, TG was given the cue "Can you tell me about meeting someone new on a bus". If TG was unable to produce any information when given a cue, the next item was administered. If he produced partial information, he was asked for more details, but if he was unable to produce more details the next item was administered. TG's answers were tape-recorded. Some diary entries were non-specific in that they related to routine events at work or home and these were therefore not tested.

TG's responses to the cued-recall task were scored using a 0-2 scale, where 0 = No recollection or inaccurate recollection; 1 = Partial recollection, but lacking in details provided in the diary; 2 = Full account of event including details provided in the diary entry.

The results from this test are shown in Figure 4.2.8. This figure also shows the occasions that TG had an epileptic seizure. He recorded 6 seizures over the 34 day period. For 6/21 (28.6%) events, TG was unable to recall any information relating to the event. For a further 9/21 (42.8%) events, he was able to provide some information, but this lacked detail. For 6/21 (28.6%) items he was able to provide more full answers. TG's overall score was 21/42 (50.0%). Several observations can be made from the figure. Firstly, TG recollects much more detail for events up to about a week old than for events older than a week. There was a significant negative correlation between the time since the event occurred and the cued recall score (Spearman's Rho {corrected for ties} = -0.676, p= 0.003). Beyond 6 days prior to testing, only one event was recollected in detail (19 days before test day), this event being rated by TG as being 'very personally significant'. A Mann Whitney analysis of the difference in scores for items rated as 'Very Significant' compared with those rated as 'Somewhat Significant' revealed a significant difference (U=19; p = 0.02). However, it can be seen from the figure that the events from 7, 22, 27 and 34 days prior to the day of testing were either recollected only partially or not at all despite being rated as very significant. Furthermore, four of the six most recent events were rated as being very personally significant to TG, suggesting that the apparent association between recollection and significance rating could represent a coincidental relationship based on a chance occurrence that the more recent items were also of significant personal relevance.




**Cued Recall Score Key:**
<0= Not assessed
0 = Incorrect or no recall
1 = Partial recal, lacking detail
2 = Detailed recollection

* = Seizure
N/A = Event not tested
VS = Very personally significant
SS = Somewhat personally significant
NS = Not at all personally significant

*Figure 4.2.8 Graph showing TG's performance on the Diary Study 1 autobiographical event cued recall task.*

There was no evidence of epileptic activity consistently preventing recollection of events that occurred immediately prior to a seizure. For example, an accurate recollection was made of an event one day prior to the seizure that occurred five days before testing. Prior to that, the picture was mixed with regard to the impact of seizures. On the one hand, an event from 19 days before testing was recollected in detail, despite two seizures occurring since that time, while other events from up to 34 days before testing, including events rated as very significant, were poorly recalled despite an absence of seizures for up to 8 days.

*(ii) Recognition test*

A recognition test was created using the events from TG's diary. This test was administered two weeks after the end of the 34-day dairy period. Twenty-three events were considered suitable to use (i.e. were considered distinctive enough and did not repeat information relating to other events). Each event was combined with two distractor events, designed to represent plausible alternatives. The correct answer was equally likely to be in position (a), (b) or (c). There was no significant difference between the number of bits of information contained in the target and distractor items across the test. One of the items (item 10) is provided below to illustrate the task (with the correct answer underlined)

10 (a) I had a very nice conversation with an older couple who I had not met before on a crowded bus coming home from work.

(b) <u>I had a very nice conversation with an older lady whom I had not met before on a crowded bus coming home from work.</u>

(c) I had a very nice conversation with an older gentleman whom I had not met before on a crowded bus coming home from work.

TG was asked to read each of the three options for each item and to choose which was the true item. He was asked to make a rating (Certain/Think/Guess) according to how confident he was in his selection. For those items that he accorded a "Think' or 'Certain' response, he was also asked to say whether he could remember the event (i.e. be able to visualise it happening) or whether he just knew that it had happened.

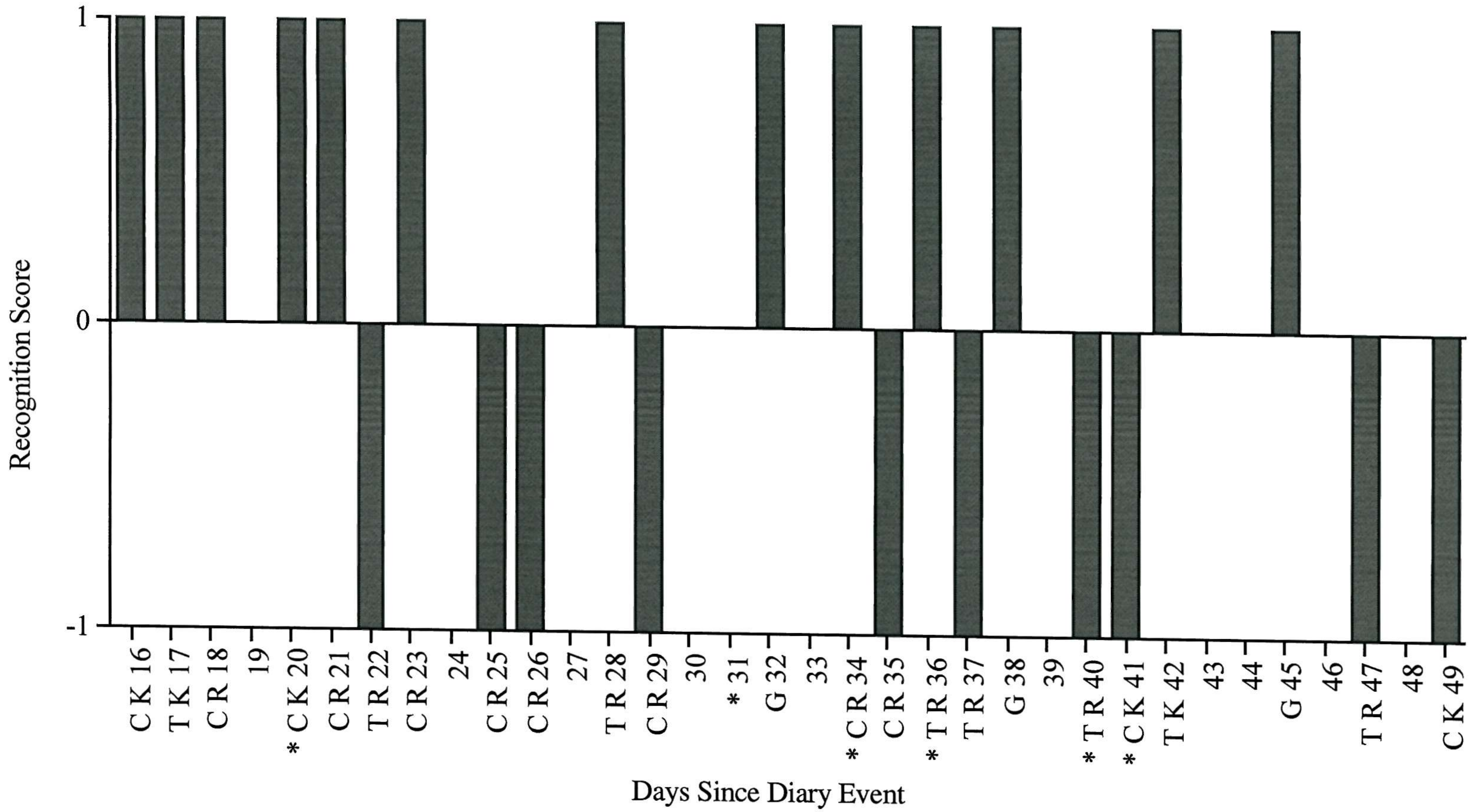
The results from this test are shown in Figure 4.2.9. Thirteen items (56.5%) were correctly identified. Of these 13 items, TG said that he was guessing for 3 items (23.1%), he thought (but was not certain) that 4 of the items (30.8%) were true and he was certain that 6 of the items (46.2%) were true. For 6 of the 14 items (46.2%) correctly identified as true, TG reported that he had some memory of the event, while for 4 (30.8%) he said that he knew them to be true, though could not actually remember the event itself. For just 4/21 (19.1%) events, TG responded that he was certain which was the target event *and* that he could remember the event happening. Of note is the fact that TG gave a rating of "certain" for 6 of the 10 items that he incorrectly identified as true.

Table 4.2.5 shows the number of target events identified or not identified according to TG's significance rating for the event. Chi squared analysis indicated that there was no effect of the personal significance of an event on the probability of that event being correctly identified by TG (Chi Squared = 1.05, p=0.59).

*Table 4.2.5 Number of target events identified or not identified according to TG's significance rating for the event.*

| Significance rating category | Target events correctly identified | Target events not identified |
|---|---|---|
| Very significant | 6 | 3 |
| Somewhat significant | 5 | 6 |
| Not at all significant | 2 | 1 |

Table 4.2.6 shows TG's recognition memory performance in relation to whether or not an event was followed within 24 hours by a seizure. A Chi Squared analysis revealed no significant effect (Chi Squared = 0.069, p = 0.793) relating to perceived importance of the event.




**Recognition Score Key:**

| | | | |
|---|---|---|---|
| 1 = Correct | C = Certain | R = Remember | * = Seizure |
| 0 = Not Tested | T = Think | K = Know | |
| -1 = Incorrect | G = Guess | | |

*Figure 4.2.9 Graph showing TG's performance on the Diary Study 1 autobiographical event recognition task.*

***Table 4.2.6 TG's recognition performance in relation to the occurrence of seizure activity within 24 hours of the event.***

| **Type of event** | **Recognised** | **Not Recognised** |
|---|---|---|
| **Event followed by a seizure within 24 hours** | 3 | 3 |
| **Event not followed by a seizure within 24 hours** | 9 | 7 |

<u>Results from FG (Control Subject)</u>

*(i) Cued Recall Test*

A cued recall task was created based on 39 of the 41 diary entries made by the control subject, FG. Two entries were excluded as they duplicated other events. The test took place one day after the final diary entry. As for TG, a set of cue sentences were created, being constructed to provide part information without key details. FG's overall score was 73/78 (93.6%). For one item he was unable to recall the event in response to the cue and for a further 3 items some detail was missing in his answer.

*(ii) Recognition Test*

A recognition test was constructed in the same way as for TG, with 2 plausible, but untrue distractor events being generated. Target events were equally spread across positions (a), (b) and (c) and there was no difference in the number of items of information contained in target and non-target items. FG correctly identified 38/39 (97.4%) of the target events. FG indicated that he was 'certain' about all of his responses and said that he 'remembered' all of the events.

*Comparison between TG and Control Participant FG.*

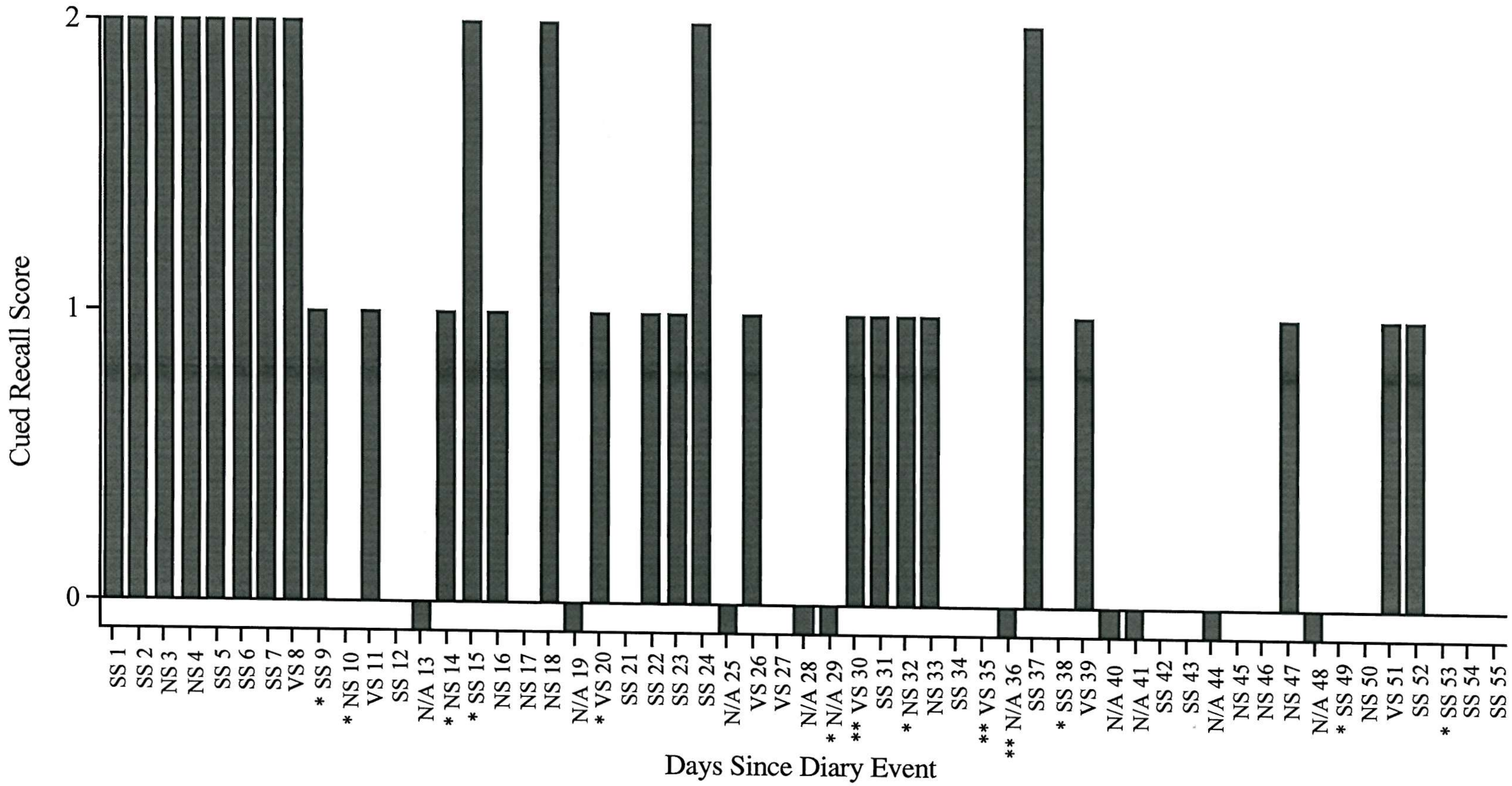
The control participant FG performed close to perfect for recall when tested in both cued recall and recognition formats. TG's performance clearly represents a considerably poorer performance, with evidence of better recollection of more recent items. TG showed that some items not recalled in detail or at all in a cued recall format were correctly identified when tested in a recognition format. This suggests that TG's difficulty might, in part, be explained in terms of a retrieval deficit. However, although TG's performance was better in the recognition format, it was not perfect and there was a significant number of items, including several recorded by him as very personally significant, that TG failed to remember. This pattern would favour an explanation in terms of a failure of long term consolidation affecting at least some of the events. With regard to causal mechanisms, it had been hypothesised that if seizure activity is the primary cause of the forgetting, then events closely followed by a seizure (for which there would have been less time for consolidation) would be most severely affected by the occurrence of a seizure. This did not appear to be the case. It was also hypothesised that if seizures were the most likely cause of TG's forgetting, then they would affect to an equal degree events rated by TG as 'very significant', 'somewhat significant' or 'not significant'. By contrast, it was predicted that, if the difficulty with long-term recollection of events results from the lesion that causes the seizures rather than the seizure activity itself, then there would be an effect of personal significance on the likelihood of remembering, since it would be the case that only more relevant events would be the focus of recollection and remembering on the part of TG. However, there were several limitations with this study. Since TG had a relatively small number of seizures during the diary period, the opportunity to examine the relationship between seizures and forgetting was limited in scope. Furthermore the issue of whether personally significant events are more likely to be consolidated was problematic as a result of the confounding factor of several recent items having been of particular personal significance for TG. A second diary study was therefore conducted with TG over a more extended time period.

*Diary Study 2*

TG was again asked to record one event each day, to rate the event on the personal significance rating scale (Very Significant, Somewhat Significant or Not at all Significant), and to record any seizures he experienced. TG kept the diary for 55 days. Cued recall was tested for 45 events beginning with events from the day preceding the test. The cued recall method was similar to that for Diary Study 1. TG's responses were again tape-recorded and scored using the 0-2 scale. A recognition task was constructed for 36 events beginning with the event that occurred 9 days before the test day. The difference in the number of days tested in each condition was a result of the time required to construct the recognition task and the availability of TG for testing. The recognition memory test was constructed using the same method as for Diary Study 1.

*Results*

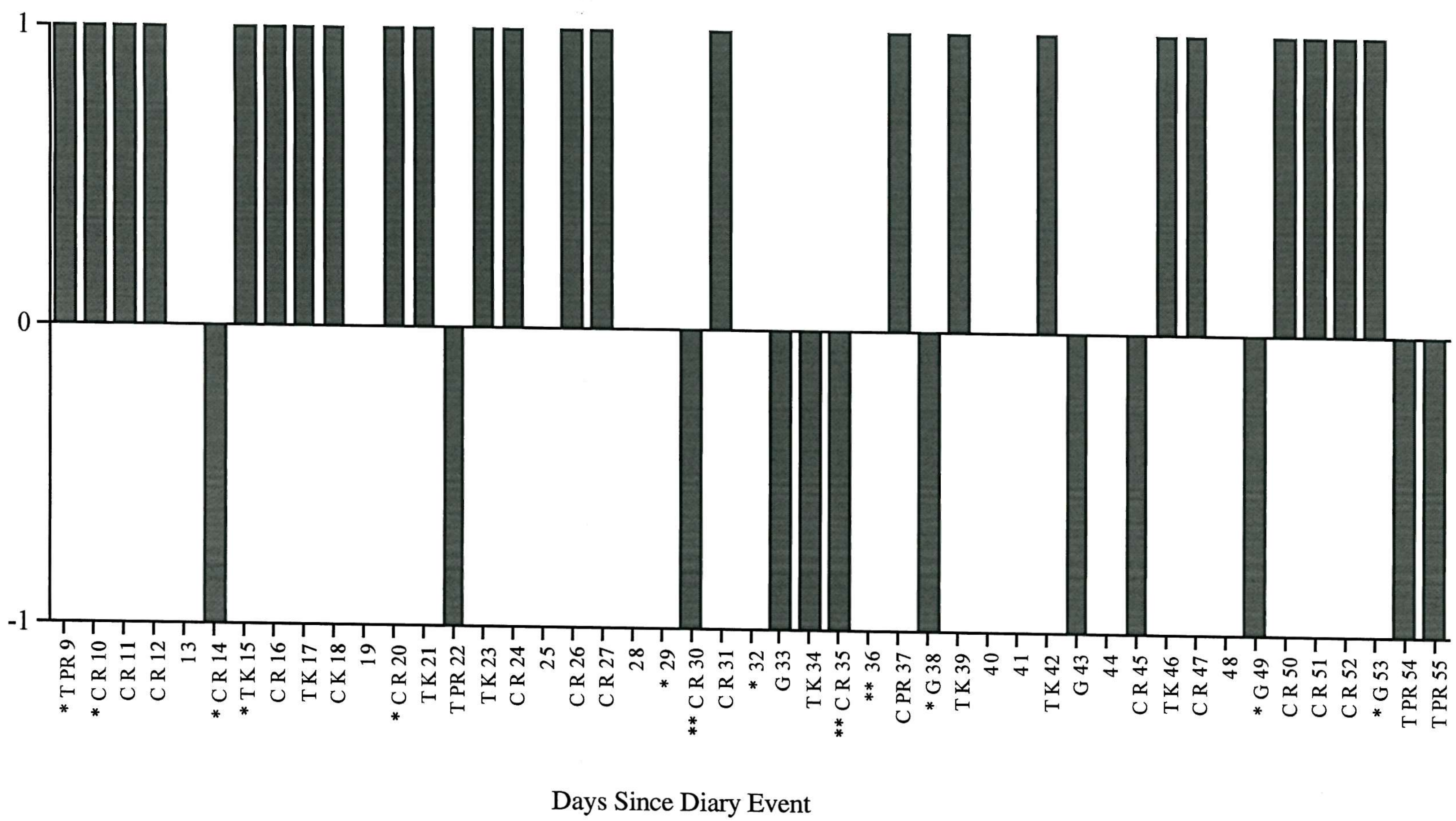
The results from the cued recall test are shown in Figure 4.2.10. This figure also includes details of TG's ratings of the personal significance of the diary events. The pattern is very similar to that from Diary Study 1. TG recollected in detail events that had occurred over the course of approximately the previous week, but beyond that time his recall was more variable. TG produced detailed information for 12/45 (26.7%) events, partial or vague information for 16/45 (35.6%) and no information for 17/45 (37.8%). His overall score was 40/90 (44.4%). These scores are quite similar to those for Diary Study 1 and once again are a long way below the performance of the control subject FG. It is noteworthy that TG had no seizures in the week prior to testing, something that is discussed further below. The results from the recognition test are shown in Figure 4.21. This figure also includes details of TG's rating of the certainty of his responses and his remember/know ratings. TG correctly identified 24/36 (66.7%) events. Again this is similar to his performance for Diary Study 1. Of the 24 events TG correctly recognised, he said he was certain for 15 (62.5%), he was not certain, but thought to be true 8 (33.3%) and was guessing for 1 (4.2%). When asked about whether he remembered events or just knew they had happened, TG responded for several events that he could remember *some* elements of an event, but said that he found it hard to remember all the details he felt to be significant. For this reason a category, Partial Remember, was used in relation to these events. For 13/24 (54.2%) events, he said that he remembered the event. For 2/24 (8.33%) he said he had a partial memory of the event. For 8/24 (33.3%) he said he knew them to be correct, but could not remember the event happening. Overall, for 13/36 events (36%) TG said that he was certain an event to be true *and* he remembered the event.




**Cued Recall Score Key:**
<0 = Not Tested
0 = Incorrect or no recall
1 = Partial recall, lacking detail
2 = Detailed recollection

* = Seizure
N/A = Event not tested
VS = Very personally significant
SS = Somewhat personally significant
NS = Not at all personally significant

*Figure 4.2.10 Graph showing TG's performance on Diary Study 2 autobiographical event cued recall test.*




**Recognition Score Key:**

-1 = Incorrect
0 = Not Tested
1 = Correct

C = Certain
T = Think
G = Guess

R = Remember
PR = Partial Remember
K = Know

* = Seizure

*Figure 4.2.11 Graph showing TG's performance on Diary Study 2 autobiographical event recognition test.*

The relationship between TG's recollection of events and time was examined by averaging his score for each week of the diary study for the cued recall task and the average proportion correct each week for the recognition task. These data are shown in Figures 4.2.12 (a) and (b). In these graphs, the most recent week was week 8. There was a significant correlation between study week and cued recall score (Spearman's Rho = 0.874, $p = 0.02$). For the recognition task data, the correlation showed a non-significant positive trend (Spearman's Rho = 0.685, $p = 0.09$). There was no correlation between the number of seizures each week and either the cued recall score (Spearman's Rho = -0.327, $p = 0.34$) or the proportion of events recognised (Spearman's Rho = 0.257, $p = 0.62$). However, figures 4.2.12 (a) and (b) demonstrate a marked dip in TG's performance for week 4, which was most striking for the recognition task and it is noteworthy that this was the week that TG suffered the most seizures (six in total).

The potential relationship between seizures and performance was examined in a further analysis. It was hypothesised that the events which TG was better at recalling would be those that had the greatest opportunity to be consolidated and thus would be further away from a seizure than those that TG was unable to recollect. To test this, the number of days by which each event preceded a seizure was calculated. Then the mean number of days preceding a seizure for those events for which TG scored 0 and the mean number of days preceding a seizure for those events for which TG scored 1 or 2 on the cued recall task were calculated (as there were only 4 events for which TG scored 2, events with scores of 1 or 2 were combined). This only included events that occurred before the most recent seizure. A Mann Whitney test revealed no significant difference between these two means (mean number days preceding a seizure for events on which TG scored zero = 3.53 days, s.d. 3.11; mean for events on which TG score more than zero = 2.35, s.d. 2.25; $U=133.5$, $p = 0.26$). A similar analysis was conducted for TG's performance on the recognition task, contrasting the mean number of days an event preceded a seizure for events he recognised with those that he failed to recognise. Again, a Mann Whitney analysis indicated no significant difference (mean number of days preceding a seizure for events recognised = 3.00 days {s.d. 2.49}; mean for events not recognised = 2.75 days {s.d. 3.31}; $U=120.5$, $p = 0.42$).

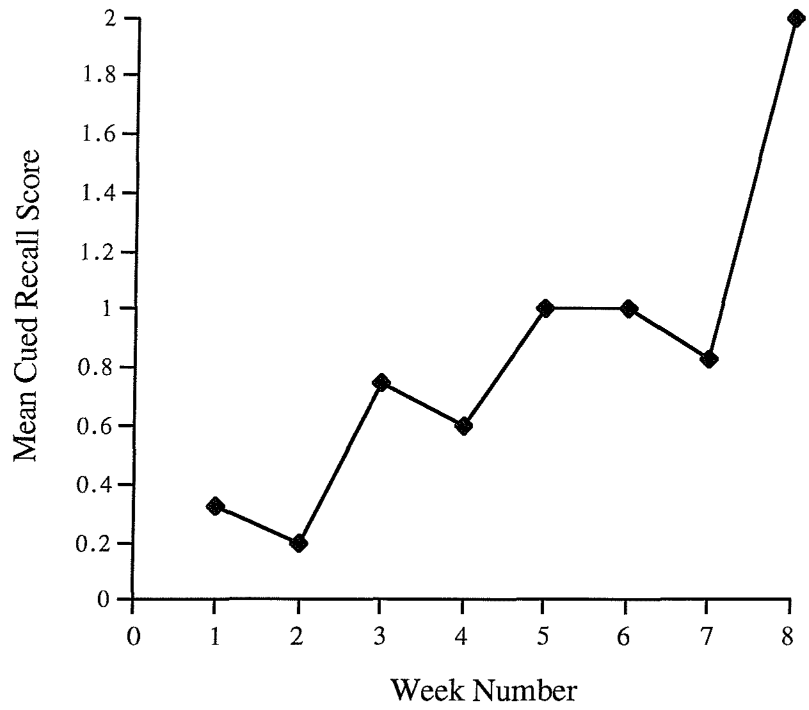



***Figure 4.2.12(a) TG's mean performance over successive weeks on the autobiographical event cued recall test.***

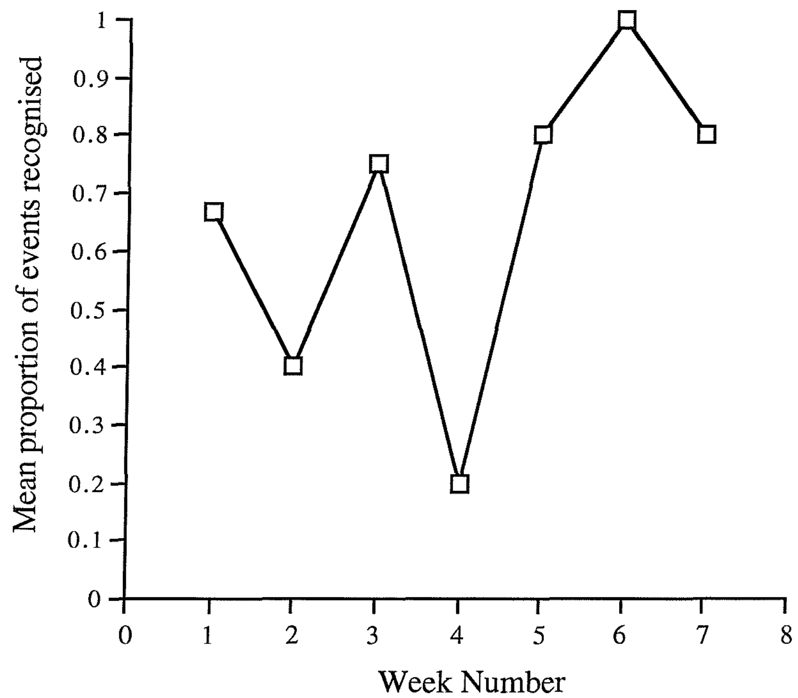



***Figure 4.2.12(b) TG's mean performance over successive weeks on the autobiographical event recognition memory test.***

In the case of the significance ratings, there was no effect of significance on TG's recollection of events. The average cued recall scores for the various ratings were; Very Significant 0.889 (n=8); Somewhat Significant 0.913 (n=23); Not at all Significant - 0.846 (n=13). A Kruskal-Wallis test showed there to be no significant difference between these rating categories in terms of cued recall score (H= 0.047, p= 0.979). Table 4.2.7 shows the number of target events recognised or not identified according to TG's significance rating for the event. Chi squared analysis indicated that there was no effect of the personal significance of an event on the probability of that event being correctly identified by TG (Chi Squared = 0.355, p=0.837).

***Table 4.2.7 Number of target events identified or not identified according to TG's significance rating for the event.***

| Significance rating category | **Target events correctly identified** | **Target events not identified** |
|---|---|---|
| Very significant | 6 | 2 |
| Somewhat significant | 12 | 7 |
| Not at all significant | 6 | 3 |

*Post-seizure recollection*

It was noted above that a feature of both the diary studies was that TG had not suffered seizures in the days immediately preceding the testing and so his better recall of these events may have been the result of not having had a seizure, rather than simply a 'recency' effect. To examine, informally, the impact of a seizure on recollection, TG was asked to telephone as soon as possible after a seizure. He did this a few hours following a seizure he had early one morning. He was asked to try to recall the previous day and he was able to do this in reasonable detail, describing what he had done at work, an incident that had occurred on his journey home from work and what he had watched on TV the previous evening. He was asked about the previous few days. He recollected that two days before he and his family had gone to visit his sister. His memory for this day appeared to be patchy in that he reported finding it hard to think what they did while at his sister's. He was prompted with a cue word (train) by his father (they had been on a train journey), and although TG was able to mention some aspects of the journey, there was considerable detail missing (which his parents were able to recall). He reported that for much of it he was aware that he could not really picture in his mind what had happened.

***4.2.3.5 Studies of long-term autobiographical and public event/factual knowledge.***

A range of different tests was used to assess TG's memory for personal semantics, autobiographical episodic events and public events relating to the period since the onset of his illness. The opportunity was also taken to examine his retrograde memory for the same knowledge domains. The majority of this testing took place some 6-9 years post-illness.

*4.2.3.5.1 The autobiographical memory interview (Kopelman, Wilson and Baddeley 1990)*

TG was assessed on the AMI. This was administered six years post-illness. Results are shown in Table 4.2.8

***Table 4.2.8 TG's performance on the AMI***

| | **Personal Semantic** | **Autobiographical Incidents** |
|---|---|---|
| Childhood | 19.5/21 (normal) | 9/9 (normal) |
| Early Adult Life | 16/16* | 3/9 (abnormal) |
| Recent Life | 20/21 (normal) | 4/9 (abnormal) |

*The section relating to children was not administered as TG has no children and did not have any close family or friends who had had children that it would be reasonable to expect him to recall details.

Because of TG's age, much of the time span covered by the sections on Early Adult Life and Recent Life relate to the post-illness period. In the Early Adult Life period, he produced one incident (which was scored as 3/3) relating to a field trip he had made whilst in his second year of university, relatively close in time to the onset of his illness.

*4.2.3.5.2 Time-constrained Crovitz task*

The Time-Constrained Crovitz task (Graham and Hodges, 1997; described in Section 2.1.4.2) was used. TG's performance was contrasted with that of six control participants matched for age, sex, and educational level (TG's age at time of testing was 29; controls mean age 31.33, s.d. 2.34 range 28-35; all participants educated to university level). The task required participants to try to recall memories from specified lifetime periods. Participants were instructed to try to remember a specific event or episode in response to each of the 15 cue words, from a particular lifetime period. Because of TG's relatively young age at the time of the onset of his illness, three time periods were used; 0-16 years; 16-illness and post-illness. The rationale for the varying time periods was that the period of time between 16 and the onset of illness involved a series of key life stages (completion of GCSE's, attending sixth form education for A levels and commencing university) that were expected to be rich in autobiographical episodic memories. Furthermore, it was considered important to be able to contrast the immediately pre-illness period with the more remote lifetime period. Controls were asked to recall items from periods 0-16; 16-20, 21-present, matching the age range for TG, but without the illness-related time cues. The test used the same 15 words (see Section 2.1.4.2) for each time period. Time periods were sampled in a random order. In order to encourage the production of as much detail as possible, there was no time limit for recall and participants were prompted (e.g. "Can you tell me more about that?"; "Can you give me a specific example?") if necessary. Responses were scored on a 6 point (0-5) scale according to the specificity of the memory (see Graham and Hodges (1997) for details of the scoring system). Ratings were scored by an independent rater who was trained to use the rating system and who was blind to any experimental hypotheses.

The results from the Time-Constrained Crovitz test are shown in Figure 4.23. TG's performance was impaired for all three time periods (0-16 $t=-2.54$, $df=5$, $p=0.05$; 16-20 $t=-5.76$, $pdf=5$, $p=0.002$; 20-present $t=-3.29$, $df=5$, $p=0.02$) . It is apparent that the control participants were performing almost at ceiling on this test. While TG's performance was impaired, it is clear that he was nevertheless able to produce some detailed memories in all three time periods. TG's data appears to show a trend towards a temporal gradient in his retrograde recall (i.e. better performance for the earlier period compared to the immediately pre-illness period). A Friedman analysis was carried out on the raw scores per cue-word for TG across the three time periods, to examine whether there were statistically significant differences across the time periods for TG. However, this analysis indicated that there was no statistically significant difference across the three periods ($X^2 = 2.08$, $p = 0.35$).

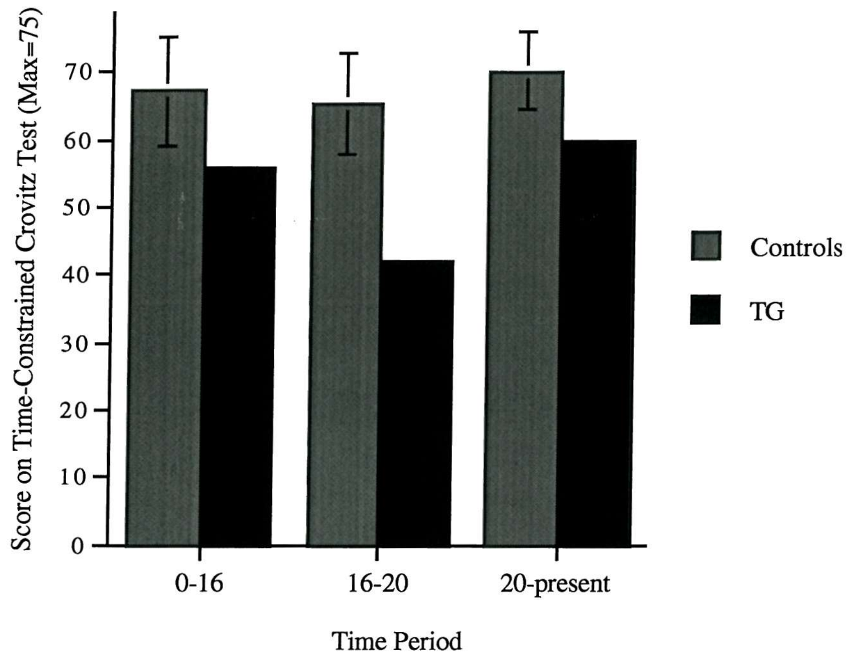



***Figure 4.2.13 Performance of TG and six matched controls on the Time Constrained Crovitz task, with two standard deviation bars.***

TG's performance for the post-illness period at first glance appears surprising for someone who reports difficulty recalling events since the onset of his illness. Although his overall performance was impaired, he was nevertheless able to produce sufficiently detailed recollections to score 60 out of a possible maximum of 75. However, analysis of TG's responses revealed that 66% of the recollections related to events that had in fact taken place in the previous week.

*4.2.3.5.3 Dead or Alive Test*

The version used was the same as that described in Chapter 2, Section 2.1.4.3. The test consists of 50 names of famous personalities. Nine individuals died during the 60's, nine during the 70's, nine during the 80's and nine during the 90's. A further 14 individuals were still alive. Given TG's relatively young age the decades of main interest were the 80's (retrograde for TG) and the 90's (anterograde for TG) and so data are presented here just for those periods. TG's performance was contrasted with six control participants matched for sex, age (TG's age at time of testing was 29; controls mean age 31.33, s.d. 2.34 range 28-35) and education (all participants educated to university level). TG and the controls were also given a Media Exposure Questionnaire (Kapur et al., 1999). The aim of this was to ensure that TG was compared with control participants who had comparable exposure to news media. TG's score on this questionnaire was within the range of the controls (TG score = 47; mean for controls 55.33, s.d. 16.85, range 29-77).

The graphs show that for the familiarity judgement (Figure 4.2.14a), TG had no problems with the personalities who have died in the 90's, though there was a ceiling effect for both TG and the controls in these categories. TG was, however, impaired compared to the controls for the 80's ($t= -6.44$, $df=5$, $p=0.001$). For the Information task (Figure 4.2.14b) TG was borderline impaired for the 80's ($t= -2.48$, $df=5$, $p=0.056$) and impaired for the 90's ($t=-2.98$, $df=5$, $p=0.03$) and Alive ($t=-6.62$, $df=5$, $p=0.001$) categories. On the Details of Death task (Figure 4.24c) TG was impaired for both the 80's ($t= -2.77$, $df=5$, $p=0.04$) and 90's ($t=-4.52$, $df=5$, $p=0.006$).

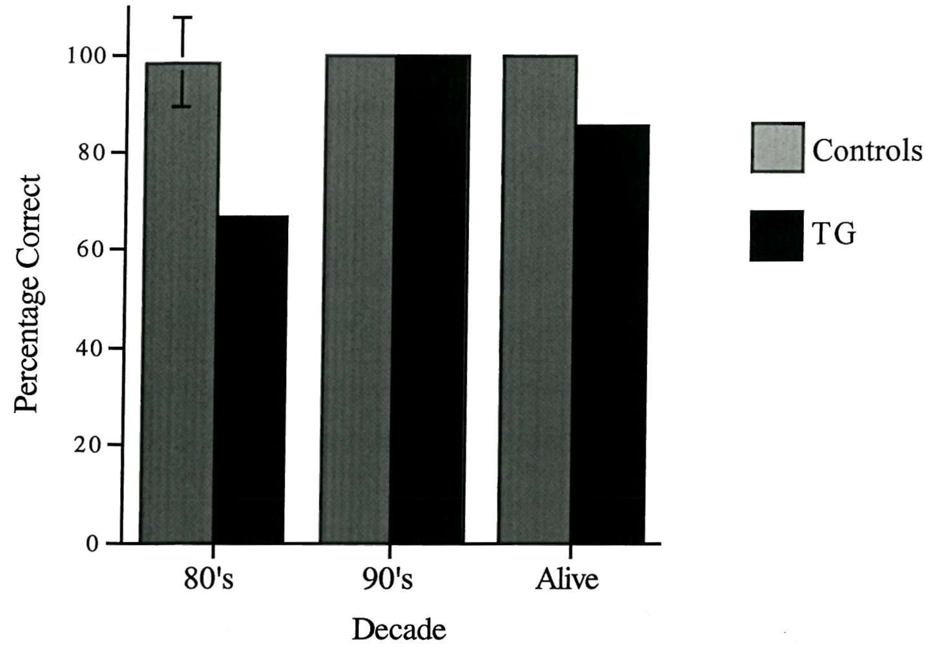



***Figure 4.2.14(a) Performance of TG and six controls (mean and two standard deviation bars) on the Familiarity component of the Dead-or-Alive Test. There was a ceiling effect for controls on for the 90's and Alive items, and therefore no variance in scores.***

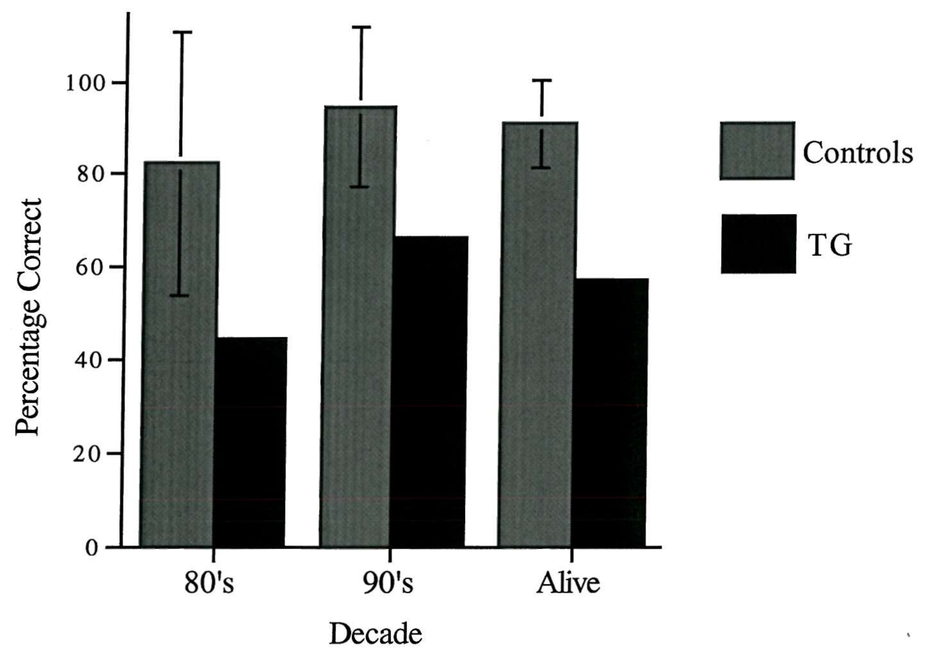



***Figure 4.2.14(b) Performance of TG and six controls (mean and two standard deviation bars) on the Information component of the Dead-or-Alive Test***

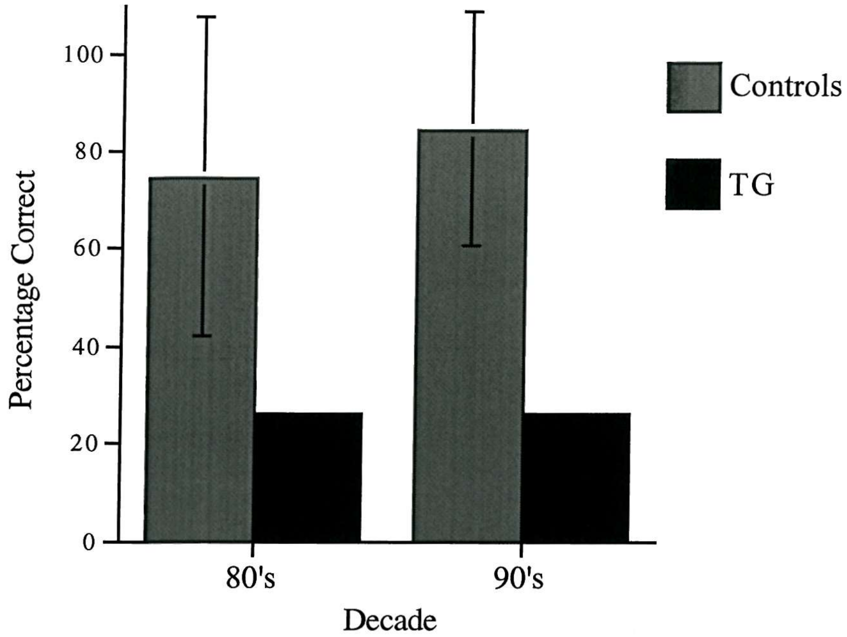



***Figure 4.2.14(c) Performance of TG and six controls (mean and two standard deviation bars) on the episodic details component of the Dead-or-Alive Test.***

*4.2.3.5.4 News Events Test*

The testing and scoring method was the same as that described for this test in Section 2.1.4.4. Twenty-nine famous news events from a period covering seven years pre-illness (83-89) and 32 events from a period covering seven years post-illness (91-97) were included. For the recognition component of the test, four events (target and three distractors) were presented. Participants were asked to identify the real event. Having selected an event, they were then asked to recall as many details of the event as possible. TG's performance was contrasted with the same six controls as for the Dead or Alive test, matched for sex, age, level of education and media exposure.

The results from the News Events Test for the Recognition and Event Details Recall tasks are shown in Figures 4.2.15 (a) and (b). The score presented is the proportion of the total possible score obtained by the participants for the pre-morbid and post-illness time periods.

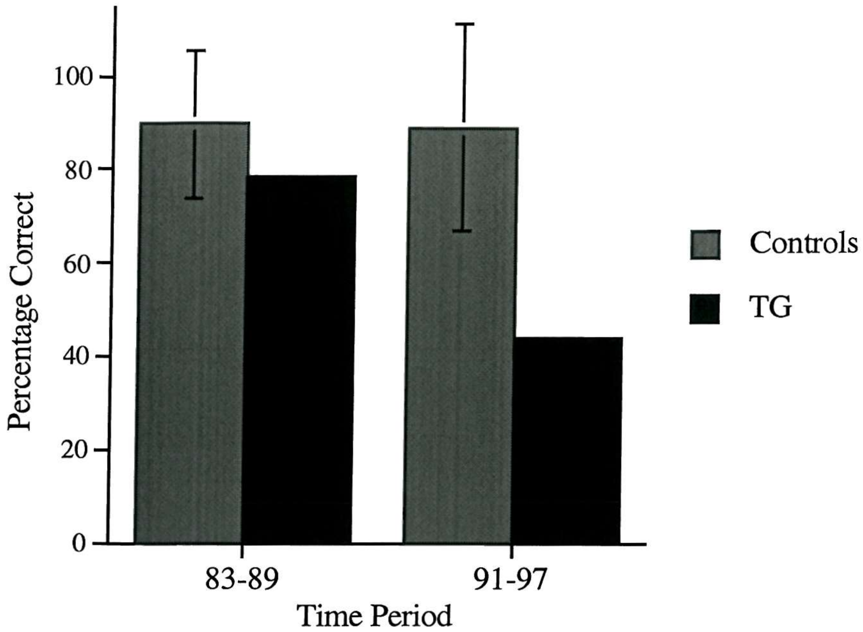



***Figure 4.2.15(a) Performance of TG and six matched controls (mean and two standard deviation bars) on the Recognition component of the News Events Test.***

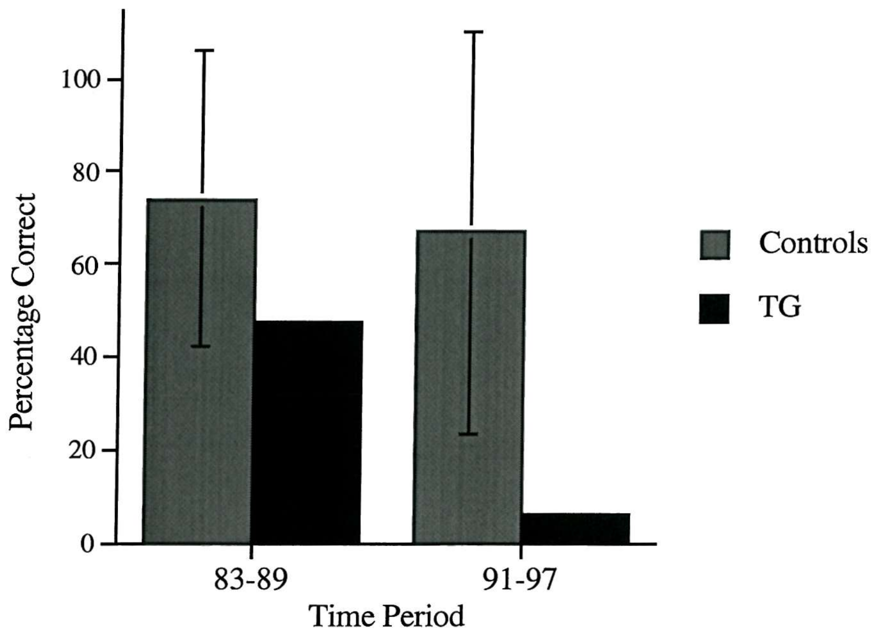



***Figure 4.2.15(b) Performance of TG and six matched controls (mean and two standard deviation bars) on the Event Details component of the News Events Test.***

TG was significantly impaired for the post-illness period for both familiarity ($t=-3.83$, $df=5$, $p=0.012$) and event details tasks ($t=-2.59$, $df=5$, $p=0.048$), but not impaired for the pre-morbid period for either familiarity (t=-1.32, df=5, p=0.245) or event details. (t=-1.53, df=5, p=0.186). A Mann Whitney comparison between the pre-illness (83-89) and post-illness (91-97) shows a highly significant difference for TG, (U=3, p=0.006), but not for the controls (U=16, p=0.276). The question of whether there was evidence of a temporal gradient in TG's performance on the pre-morbid items was examined by contrasting TG's score for each year on the information task with that of the controls. This is illustrated in Figure 4.2.16 which shows the number of standard deviations TG's score was below the mean for each year (note that a high score represents a poor performance), but was only significantly impaired for the year immediately preceding his illness (t=-3.05, df=5, p=0.028).

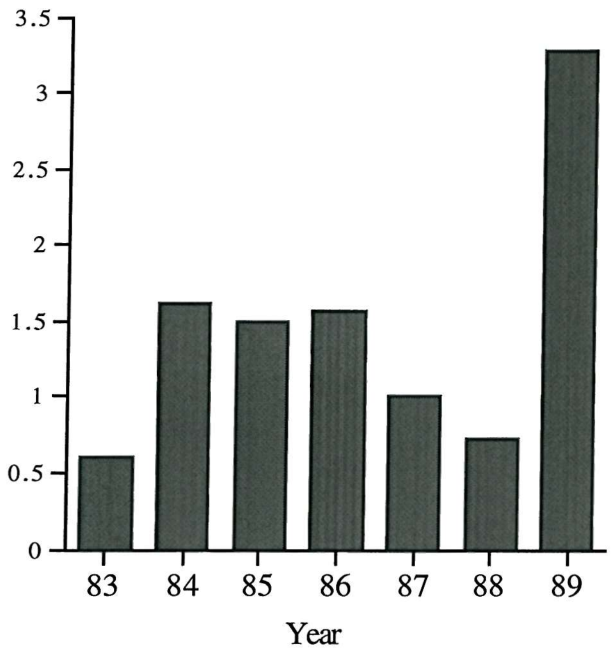



***Figure 4.2.16 Performance of TG on the Famous Events test for individual pre-morbid years in terms of the number of standard deviations his score was below the mean for the controls.***

*4.2.3.5.5 New Vocabulary Acquisition*

TG was given a task designed to assess whether he had acquired knowledge of words that had primarily come into common usage shortly before or after the onset of his illness.

This New Vocabulary Test included the following 17 items, which are listed with the approximate year of entry into common usage (Mir [1986], Acid House Party [1988], Satellite Dish [1988], BSE [1989], Paparazzi [1990], Mondeo [1990], Modem [1990], Camcorder [1990], CJD [1990], Airbag [1992], Internet [1993], Eurostar [1994], Camelot [1995], DVD [1998], ISA [1998], London Eye [1999], The Dome [1999]. TG was asked to define the words. His responses were rated on a 0-2 point scale (0= No answer or incorrect answer; 1= vague or partially correct answer; 2 = correct answer). TG's performance was contrasted with that of four control participants matched for age and media exposure (TG's age at time of testing = 29 years; mean age of controls = 29.5, s.d. 1.29; TG's media exposure score = 47, mean media exposure score for controls = 49.0, s.d. 15.73, range 33-63). Responses were scored by an independent rater who was blind to any experimental hypotheses.

*Results*

TG's overall score on the test was 22, which was well below that of control participants, who performed close to the ceiling on this test (mean score = 33.0, s.d. 0.816). TG's responses are given below in Table 4.2.9 in approximate year of entry order.

TG's performance on this task suggests that although he has acquired new vocabulary since the onset of his illness, this is not at a normal level. There is some indication that the more recent items were less well learned. This may reflect the possibility that, whilst TG can acquire this type of new information, it takes him considerably longer than normal for such knowledge to be learned to the degree that it is retained over time, and perhaps before it can withstand seizure-related disruption to consolidation processes.

***Table 4.2.9 TG's responses on the New Vocabulary Test***

| Item | Year of Entry | TG's response |
|---|---|---|
| Mir | 1986 | Space station - Russian. |
| Acid House Party | 1988 | A rave, where the drug Acid is used. |
| Satellite dish | 1988 | TV aerial, put it on the roof, for satellite TV. |
| BSE | 1989 | An illness you get from cow meat. |
| Mondeo | 1990 | Car- Ford. |
| Paparazzi | 1990 | The press, out for a scandal. |
| CJD | 1990 | Disease of some sort. |
| Modem | 1990 | Part of a computer, for communication to the telephone. |
| Camcorder | 1990 | Video-recorder, a camera. |
| Airbag | 1992 | A bag in the middle of the steering wheel to protect driver from a crash. |
| Internet | 1993 | Use of a computer via the telephone system to get in touch with anyone and anything quickly. |
| Eurostar | 1994 | Don't know. |
| Camelot | 1995 | Don't know |
| DVD | 1998 | Don't know. |
| ISA | 1998 | Don't know; is it to do with education? |
| London Eye | 1999 | Don't know. |
| Dome | 1999 | Millennium Dome in London |

### 4.2.4 Discussion

Patients SG and TG provide two further examples of a rare memory disorder characterised by relatively normal ability to remember information over several hours or even days, but impaired retention over more extended time periods. Studies with these two patients have shown that the ability to acquire new episodic *and* semantic information is compromised. In addition to accelerated long-term forgetting of anterograde information, both patients demonstrated extensive retrograde memory impairment. The ability to recollect autobiographical event details was particularly severely affected. There was evidence that seizure activity plays a role in the memory impairment, but the relationship between seizure activity and forgetting is not a one-to-one correspondence. It is likely that structural pathology and sub-clinical pathology may also be critical factors in accounting for this memory disorder.

A novel diary-based procedure was used to substantiate the clinical reports of patients relating to forgetting day to day events over a period of weeks. The diary studies with TG also highlighted the importance of retrieval factors in accounting for his memory impairment, since his performance on the event recognition tasks was better than the cued recall task. Nevertheless, TG's performance on the recognition task also showed considerable impairment, suggesting that retrieval factors alone are not sufficient to account for the forgetting. However, as was discussed in relation to the autobiographical event recognition task in Section 2.3.1, the format used was not a 'true' recognition task in that such a task would need to recreate the exact event circumstances for it to be truly a recognition task. This would be impossible to achieve. Although one could perhaps recreate the place and objects associated with an event, it would not be possible to recreate a range of other contextual features. It would, however, perhaps be useful for future studies with such patients to try to 'stage' events that could then be recreated as closely as possible to the original in order to examine the impact of recognition cues on event retrieval. Nevertheless, as the diary study of the control subject FG showed, over the time course of at least a month, events are normally well remembered when cued by a written statement describing the event. Yet TG was unable to recollect several events under these circumstances, including some rated by him as being highly personally significant.

In SG's case, there was some evidence of 'frontal' dysfunction on two tests, though little in the way of clinical evidence of a dysexecutive syndrome. If there was frontal lobe involvement in her case, then the possibility of a retrieval deficit is more likely since frontal regions are frequently cited as being critical to memory retrieval (Hodges and McCarthy, 1993, Conway, Turk, Miller, Logan, Nebes, Meltzer and Becker, 1999). However, an executive retrieval deficit is not a satisfactory explanation for several reasons. Firstly it would be expected that such a deficit would be evident on the more immediate or short delay recall tasks too, but there was no evidence that this was present.

Secondly it would be expected that SG would show an improvement in recollection if presented with event information directly. However, SG was unable to gain any feeling of familiarity when reading extracts from her diary in relation to holidays she has taken (both pre and post-morbidly).

The specific question of the relationship between forgetting and the occurrence of seizures is discussed later, but the question arises as to whether the patients described here warrant a diagnosis of transient epileptic amnesia. In fact, neither case meets the diagnostic criteria for TEA (Zeman et al., 1998) primarily because neither has specific episodes of amnesia associated with seizures. In the case of SG, her nocturnal episodes that were assumed to be seizure-related did appear to include some confusion about where she was or what day it was, but they were very short lived and so the extent to which anterograde or retrograde memory was affected during these episodes was not clear. In the case of TG, his seizures are not associated with amnesic episodes in that he does not apparently show the repetitive questioning that typically characterises TEA attacks (Zeman et al., 1998, p.436).

Almost all of the previously described cases of this form of accelerated forgetting have been people with acquired epilepsy. Furthermore, there is evidence that some people with congenital or very long-standing epilepsy show a similar pattern of consolidation failure (Martin et al. 1991; Blake et al., 2000, Bergin et al., 2000). This suggests that epileptic seizures have a causal role in the pattern of impairment. However, the possibility exists that it is not the seizures per se that are the critical causal factor, but rather some underlying structural pathology that is responsible for the generation of the seizures and also responsible for the failure to consolidate memories. The present studies show that there is not a simple relationship between seizures and loss of information (i.e. seizures do not simply wipe out all recent memory traces), but nevertheless there is evidence for a contribution of the seizures to the forgetting. In the case of SG, she has not had any seizures since she commenced anti-convulsant medication and yet continues to experience the accelerated forgetting problem. However, it is possible that sub-clinical activity could still be occurring and perhaps account for the problem. Aarts, Binnie, Smit and Wilkins (1984) and Kasteleijn-Nolst Trenite (1995) have demonstrated the presence of detectable cognitive dysfunction accompanying sub-clinical epileptiform discharges.

In the diary studies with TG, the strongest relationship was simply between time and forgetting. However, when TG's recollection performance was averaged over the 8 weeks of Dairy Study 2, there did seem to be evidence of an impact of seizures in the week where he had an above average frequency of seizures. If structural pathology was responsible for the accelerated forgetting, then one might predict there to be some effect of personal significance ratings on recollection. This is based on the assumption that personally significant events would, in effect, compete more effectively for limited mnemonic resources available. In contrast, if seizures were responsible, then it might be predicted that there would be a random effect, so that there would be no relationship between significance and probability of recall. The data showed that there was in fact no relationship between significance and probability of recall, thus providing some support for the latter hypothesis.

It was noted that the strong relationship between time and forgetting might have been confounded by the fact that in both diary studies TG had not suffered a seizure in the days immediately preceding the day of testing. The informal evaluation that was undertaken of TG's recollection of events of the previous few days following a seizure indicated that he had a detailed recollection of events from the previous day, but there was evidence of impoverished recollection of events that had occurred two days previously. This contrasts with his detailed recollection of events up to six days prior to the assessment day in Diary Study 1 and nine days previously in Diary Study 2. During both of these time periods there had been no seizures. It is possible that temporally distal events may be more vulnerable to the effects of seizures than events that occurred close to the time of the seizure.

Although the data from studies with TG seem to favour an explanation of his accelerated forgetting in terms of seizure activity, it is clear that there is not a simple relationship between seizures and forgetting. It is difficult to rule out the possibility that some critical underlying structural pathology is responsible for both the epilepsy and the forgetting, or that the seizures have caused some structural pathology that is responsible. In SG's case, given that she does not have observable seizures, one must speculate that either sub-clinical epileptiform activity is occurring that is responsible or again raise the possibility that an underlying pathology (which either caused the epilepsy or was caused by the epilepsy) is responsible for her impairment. Studies of patients with selective perirhinal/parahippocampal region lesions without any history of epilepsy might shed some light on this issue. Mayes, van Eijk, Gooding, Isaac and Holdstock (1999) note that to date there have never been any such cases reported. They refer to a patient they have studied who has such damage, though the pathology does extend to the association cortex at the temporal pole. MR imaging findings point to an intact hippocampus. They report that this patient shows preserved recognition and recall at delays of 30 minutes, but forgets rapidly over delays of a few weeks. It was not reported whether or not this patient also suffered with epilepsy. If not, she does provide some evidence that selective perirhinal region lesions are sufficient to disrupt long-term memory consolidation.

Which types of information are particularly vulnerable to long-term accelerated forgetting? In addition to autobiographical events, the Dead or Alive and News Events tests both demonstrate that SG and TG have difficulty remembering public events that have occurred since the onset of their conditions. On the Dead or Alive test, both patients were impaired on the 'Details' section, which might be considered to be more episodic in quality since it relates to the specific circumstances surrounding the death of an individual. They were also impaired on the Information section of this test, which is more 'semantic' in that it relates to general information about individuals who have had considerable media exposure over extended time periods. The News Events test dramatically highlighted the impairments of TG and SG, whose scores for events since the onset of their difficulties were severely impaired. This deficit seemed to be equally significant, at least as far as the recall of details was concerned, for events that had received repeated exposure in the media, compared to those that might have been major events at the time, but had had less exposure since. One striking example of this was the death of Princess Diana and Dodi Fayed. TG was able to report that he knew they had died, but he had no recollection of where, when and how they died. SG performed a little better in that she was able to report that they had died in a car crash, but she reported that the crash had happened in London. These observations suggest that both SG and TG have difficulty in acquiring new semantic information as well as episodic information. However, with regard to their personal semantics, they have both clearly been able to acquire a significant amount of semantic information. For example, SG is able to keep up with major developments in her immediate family, though this is more problematic for the more extended family with whom she has less frequent contact. She is able to describe the key medical staff with whom she has contact in connection with her neurological problems.

Similarly, TG is able to hold down a full time job, knows the details of procedures associated with his role and appears to keep up to date with major personal and family developments. However, both at work and at home, the knowledge that he does acquire is almost certainly the result of daily contact or exposure to the relevant information. Even so, it would appear that such information is not easily acquired; at one time the DIY store in which he works had a re-fit and most of the locations of products changed. After several weeks of working within the new environment, he had been unable to learn many of the new locations for products outside of the section in which he worked. This was affecting his work performance as he was frequently asked by customers the location of items. However, with support, using a store plan and daily rehearsal of product locations, taking each section in turn and gradually building up the number of sections with which he was familiar, TG was able to increase the number of items for which he could identify the exact location from 19% to 57%. The idea that TG can acquire information, but only after extensive exposure is further supported by his performance on the New Vocabulary Test. On this test, he was able to perform well on items that have been in common usage for several years, but for some of the more recent items he still seemed to have difficulty.

What do the findings from these studies tell us about the process of memory consolidation? If we make the assumption that seizures play an important contribution to the long-term accelerated forgetting and also that seizures are more likely to affect 'unconsolidated' or less well consolidated memories, then we can examine the question of how long memories are vulnerable to disruption. This can be considered in relation to both anterograde and retrograde memory test results. The data from the anterograde period are, however, less useful in this respect since, at least for TG, the gap between events and seizures is usually relatively short, only ever being a maximum of a few weeks. One interpretation of the diary study data is that a period of one or two weeks appears to be insufficient to fully consolidate events, even those considered to be very personally significant. But the short event-to-seizure time scale makes it difficult to draw conclusions.

Turning to retrograde memory, although there was some evidence of a temporal gradient in both patients, they also both presented with very considerable deficits in some aspects of retrograde knowledge. For patient SG, it was not possible to establish precisely the date of onset of either her seizures or her memory difficulties. However, her clinical history indicates that prior to about 1992 there was no indication of seizure activity. Neither she nor her husband had noticed any memory difficulty before this time. Certainly a conservative estimate of what constituted a retrograde period for SG would include all of the 1980's and before. In this context, SG presents with extensive retrograde memory impairment for autobiographical events, news events, and information about famous people. With regard to autobiographical events, the study of SG's holiday diaries that date back to 1970 would suggest a retrograde amnesia of at least 30 years. Similarly she showed an impairment on the news events test for the whole of the 20 year period covered by the test which spanned the period through to 1979, though there was evidence of a temporal gradient in her performance on the test that covered the period through to the 1960's. She showed an impairment on the Dead or Alive Test, which also extended back to the 1960's. This was particularly striking in view of her educational and occupational background. There was some indication that she could remember events from the earlier part of her life, though there was also an indication that she had difficulty recalling detailed event information. For example in the case of her wedding (when she was 21 years old), she said that she knew the general information about where and when she married. On the Autobiographical Memory Interview, she could offer a fragment of information about the wedding cake, but reported not being able to picture the wedding itself in her mind.

In the case of TG, what constitutes the retrograde period can be determined precisely. Furthermore, he also does not have any structural damage to the temporal lobes, or at least none that is evident on MRI. On the Dead-or-Alive test there was evidence of difficulties for the period of the 1980's, though on the News Events test there was no overall difficulty other than for the year immediately preceding his illness. On the Time-Constrained Crovitz task he showed an impairment in comparison to control participants for both retrograde periods that were sampled. There were hints of a temporal gradient, but this was not statistically significant. However, based on information provided by TG's parents, there was further support for the idea that there was a temporal gradient. Overall, there was greater evidence for a temporal gradient to his retrograde memory difficulties, than there was for SG, though with some indication of difficulty recollecting events in the same level of detail as control participants, for the whole of his lifetime period. This latter finding is rather similar to the picture with the focal hippocampal patients described in Chapter 2. The finding of particular difficulty with retrograde autobiographical events is similar to several of the previously reported cases of long-term accelerated forgetting, including those of Kapur et al. (1996) and Lucchelli and Spinnler (1998). Although some cases of long-term accelerated forgetting have been reported to have little in the way of retrograde impairment (e.g. Kapur et al. 1997), there has been less detailed assessment of memory for autobiographical events undertaken with these patients. Furthermore, it was noted earlier that a problem with many of the previous cases of this memory disorder, is that the precise date of onset of the condition could not be determined. This raises the possibility that any retrograde memory deficits may in fact have been the result of sub-clinical epileptic activity. While this could also partly account for SG's difficulties, it cannot account for TG's impairment, suggesting that the retrograde deficit is a genuine feature of this memory disorder.

Does the finding of very extensive retrograde amnesia provide evidence that consolidation takes many years? The problem with such a conclusion, however, is that by suggesting that events which are not remembered have not been 'consolidated' is essentially defining 'consolidation' in terms of ability to withstand the effects of a pathological process such as epilepsy. The argument thus becomes circular - events that are not remembered are those that are not consolidated, but 'consolidation' is considered to take place over an extended time period because events are not remembered after longer time delays. It may be more parsimonious to suggest that under normal circumstances there is a wide range of factors that will influence whether or not an event is remembered. There is also likely to be a wide range of factors that affect whether or not memories are vulnerable to disruption from seizures. If 'consolidation' is equated with a process of 'semanticisation' of memories, then it is likely that 'unconsolidated' event memories will be more vulnerable to disruption, particularly if the focus of epileptic seizures is the medial temporal lobes. There is perhaps a need for the concept of consolidation to be redefined, or at least more specifically defined.

In the following chapter, the findings from this study are reviewed along with the results of the other studies that have been presented. General implications for models of memory and amnesia are considered.

# Chapter 5 General Discussion

This main findings and conclusions from the studies presented in this thesis are:

(1) Medial temporal lobe structures, and in particular the hippocampal complex, are important for the recollection of autobiographical events across the lifetime. The hippocampal complex is necessary to be able to mentally travel back in time and 're-experience' or replay autobiographical events in mind, no matter how distant they are in time.

(2) When memory for retrograde autobiographical events is tested in patients with medial temporal lobe pathology, the provision of recognition items leads to improved performance in comparison to recall tasks. This supports the notion that these structures have a specific role in the retrieval of information located elsewhere in the neocortex. However, the provision of target items as part of a recognition memory test does not lead to a re-experiencing of the memory for the events in question, providing further evidence of the critical role of the medial temporal lobe structures for the process described by Tulving as 'autonoetic consciousness' (see Wheeler, Stuss and Tulving, 1997; Tulving, 2001).

(3) The distinction that has been made between episodic and semantic retrograde memory is supported. However, to draw the conclusion that these represent functionally and anatomically independent systems would be inappropriate. I propose that the data best fits the view that in the undamaged human brain, there is a complex and dynamic interplay between cognitive sub-systems that enables the individual to learn about the more stable elements of the world, to modify that knowledge as and when necessary, as well as facilitating recollection of particular events in which the individual has been an active participant.

(4) Patients with lesions of the medial temporal lobe can acquire semantic knowledge, but such knowledge is not acquired in a normal manner. The more extensive the lesion in

medial temporal lobe and related structures, the more difficult it will be to acquire information. Some knowledge of post-illness autobiographical events can be recollected, particularly if tested in a recognition format, but recognition of events does not lead to re-experiencing of those events in mind. The finding of an equally severe deficit in the ability to replay events in mind for a patient with pathology confined to the hippocampal complex compared to a patient with more extensive medial temporal lobe pathology provides further support for the role of the hippocampal complex in autobiographical event recollection.

(5) In cases of accelerated long-term forgetting, seizure activity appears to play a role in the forgetting of event information. However, the relationship between seizures and long-term forgetting is not one-to-one and other factors, such as structural damage, may play a critical role in such memory loss.

(6) There is considerable need to develop better techniques for examining anterograde and retrograde memory for autobiographical events and personal semantics. In particular, measures that can capture potentially subtle deficits in the ability to recollect autobiographical event details are required. Approaches used in the investigations presented in this thesis that appear to hold promise include the extended scoring system used with the Time Constrained Crovitz task developed by Graham and Hodges (1997); forced-choice recognition tests for autobiographical events; diary-based techniques for autobiographical events; and the remember-know judgement task for autobiographical events.

The following sections discuss the key issues arising from the studies presented in this thesis. They include (1) the nature of retrograde amnesia, (2) the nature of long-term knowledge acquisition in the context of temporal lobe pathology, (3) implications of the work for models of memory and amnesia. Clinical and methodological lessons are highlighted in the final section.

**The nature of retrograde amnesia**

The results of the investigations presented in this thesis address several key questions concerning the nature retrograde amnesia.

*Is retrograde amnesia distinct from anterograde amnesia?*

The five patients with amnesia arising from lesions thought to be confined to the hippocampus or closely related structures reported in Section 2.1 presented clinically with largely intact retrograde memory and severe anterograde amnesia. Patients JM and VH, described in Chapter 3, presented with severe retrograde amnesia and little or no anterograde amnesia. Anterograde amnesia therefore appears to dissociate from retrograde amnesia. However, with more sensitive testing, all of the patients with lesions limited to the hippocampus presented with some form of retrograde memory impairment. Even BW, who performed normally on almost all of the retrograde memory tests was shown to be impaired in her ability to mentally replay autobiographical events. Similarly, VH, who performed well on several standardised tests of anterograde memory, was shown to have an anterograde memory deficit for faces. These findings highlight the importance of testing anterograde and retrograde memory on a 'like-for-like' basis, before conclusions concerning dissociations are drawn (Mayes et al., 1997).

The case that provided the most convincing evidence for a dissociation between retrograde and anterograde memory was JM. Following recovery from cerebral vasculitis, JM presented with a selective impairment in her ability to recollect autobiographical event memories from at least 30-40 years prior to becoming ill. She performed normally on standardised tests of anterograde memory. The concept of 'focal retrograde amnesia' (FRA) continues to be controversial. Kopelman (2000) concluded his "exceptionally critical" review of FRA, by arguing that, while FRA may exist, many of the cited cases of FRA do not provide convincing evidence for the existence of the disorder. A critical limitation of many previous studies of selective retrograde memory has been the failure to use similar tests of anterograde and retrograde memory. In the studies carried out with JM, tests of autobiographical event memory (e.g. the Modified Crovitz task) and public semantic knowledge (e.g. Famous Events) covering extended pre- *and* post-morbid periods were used. These showed that she had a selective deficit for *retrograde* autobiographical events, with intact retrograde (and anterograde) semantic knowledge including personal semantics, knowledge of famous people and events. Critically, she also had intact memory for anterograde autobiographical events. Recently Manes, Hodges, Graham and Zeman (2001) demonstrated a similar pattern of impairment in a patient with transient epileptic amnesia.

Even with these cases, however, a dissociation in performance on tests of anterograde and retrograde memory cannot be taken as evidence for distinct cognitive or anatomical systems for acquiring new information and recollecting old information. While anterograde *amnesia* might dissociate from retrograde *amnesia*, this does not mean that anterograde memory *functioning* dissociates from retrograde memory *functioning* since this distinction is based on a temporal relationship with a brain insult, not on hypothesised cognitive processes. In the case of JM, and also VH, the extent of lesions to key structures is relevant. Partial lesions may lead to loss of some old knowledge, while the remaining undamaged tissue is sufficient to support acquisition of new information. The dissociation between anterograde and retrograde amnesia results, therefore, from a partial lesion to a complex, multi-element cognitive system.

*Are there different forms of retrograde amnesia?*

Patients JM and VH, who were investigated in Chapter 3, provide some support for making the distinction between episodic and semantic retrograde memory (Kapur, 1999). JM could not produce detailed recollections of autobiographical events, but had good knowledge of people. VH had lost knowledge of people, but could produce detailed autobiographical events.

However, once again it seems prudent to be cautious about the extent to which this distinction is taken to suggest that there are two cognitive systems operating independently. One specific reason for caution is the fact that in the studies presented here, VH was not tested for autobiographical event recall in relation to people about whom she had lost knowledge. Kitchener and Hodges (1998) did provide evidence that VH had preserved knowledge of public events in which she had been to some extent an active participant (e.g. VE day), highlighting the importance of key autobiographical events in semantic knowledge. However, they did not systematically test her knowledge for autobiographical events involving people about whom she had lost knowledge. At the time of testing however, she had much better preservation of knowledge of personally relevant people. This provides support for the view that current autobiographical experience may enhance retention of semantic knowledge within an otherwise impaired system. This idea was first explored by Snowden et al. (1996) who demonstrated that patients with semantic dementia were better at recognising contemporary celebrities rather than past or historical figures. In the case of VH there was no evidence of a temporal gradient in her performance on the famous faces test, but this may have been because even the most recent of the faces were primarily famous several years previously. VH was not assessed on her recognition or knowledge of current personalities whom she might have encountered in the news or on television, though this would have been useful.

The studies by Snowden et al. (1996) and Graham and Hodges (1997) have highlighted the importance of current or recent experience in maintaining semantic knowledge in people with semantic dementia. Further exploration of the extent to which people with semantic impairments can recollect events that involved people or objects, for which there is impaired factual knowledge would be informative. The 'reverse' temporal gradient in autobiographical incidents performance on the Autobiographical Memory Interview (Snowden et al., 1996), whereby recent events are recalled much easier than older events, suggests that loss of semantic knowledge leads to an associated loss of autobiographical information. However, one of the challenges in such studies is the likelihood that the semantic impairment will make any descriptions of events severely impoverished and it may be difficult to both cue event recall and also to determine the extent to which a vivid autobiographical experience is being recollected (see Graham, 1999 and Moscovitch and Nadel, 1999 for a discussion of this issue and its implications for models of memory). Tulving and Markovitsch (1998) suggested that episodic memory is dependent on semantic memory, but not vice versa. One way of thinking about the dependency of episodic and semantic memory is that in the absence of semantic information, the capacity for episodic recall is present, but the content will be degraded. The question arises as to whether there may be some preservation of purely perceptual information relevant to an autobiographical event. This is something that requires further empirical exploration.

The pattern of deficits shown by patient BW appears to constitute a distinct form of retrograde amnesia. She had a focal hippocampal lesion as a consequence of carbon monoxide poisoning. She showed a specific deficit in the ability to mentally re-play or re-experience retrograde autobiographical events despite the ability to recollect some event details, particularly when presented in a recognition format. The results from the studies using the remember-know judgement methodology suggest that this technique is one that may be useful in further explorations of the nature of both retrograde and anterograde memory for autobiographical events.

*Is retrograde amnesia a storage or retrieval deficit?*

Mayes and Downes (1997, p. 29) and Kopelman (1997, p. 109) discuss several lines of evidence that retrograde amnesia may be the result of a retrieval deficit, rather than a storage deficit. Section 2.3 in this thesis presented a study of retrograde autobiographical event memory, contrasting performance on a recall task with performance on a forced choice recognition format. Six people with lesions of either (a) hippocampus only, (b) hippocampus plus parahippocampal region and some lateral temporal involvement, or (c) thalamus, were studied. The hippocampal lesioned patients all showed substantial improvement in performance when tested using a recognition format, though this was not accompanied by the ability to mentally re-experience or replay events. The patient with the most extensive medial/lateral temporal lobe damage (CW) did not benefit from recognition testing. One patient with bilateral medial temporal lobe damage (JN) showed enhanced recognition compared to recall, but reported that this primarily related to post-morbidly acquired knowledge of pre-morbid events. A patient with a thalamic lesion provided further support for the idea that this diencephalic structure also has an important role in memory retrieval. He showed a dramatic improvement in performance from recall to recognition conditions and also showed a somewhat higher, if still impaired, level of reporting of the ability to replay events than the medial temporal lobe patients. This supports the idea that the thalamus plays a critical role in retrieval, or strategic search, processes (Hodges and McCarthy, 1993).

Consistent with the view that there are different forms of retrograde amnesia, these studies suggest that some forms of retrograde amnesia result from storage deficits and some from retrieval deficits. When there is extensive neocortical damage, retrograde knowledge is lost. When the lesions are confined to the medial temporal lobes, and in particular the hippocampus, there is evidence that the deficit is primarily one of retrieval. One caveat to this conclusion, however, is that the provision of retrieval cues did not lead to a full or normal recollection experience in the case of the hippocampal lesioned patients, since these patients were unable to fully remember or re-experience the target events. While the hippocampus could therefore be considered to be part of a retrieval system, it can also be considered to be one element in a hippocampal – neocortical memory network that stores or represents event memories.

**The nature of long-term knowledge acquisition in the context of temporal lobe pathology**

Verfaille (2000) highlighted the importance of determining whether or not patients with lesions of the medial temporal lobes can acquire new semantic information. This has important theoretical and clinical implications. Section 4.1 of this thesis addressed this issue by comparing the acquisition of anterograde autobiographical and semantic information in two patients who differed in the extent of their medial temporal lobe damage. BW had damage limited to the hippocampus. JN had medial temporal lobe damage that extended beyond the hippocampus to include parahippocampal, temporal pole and more lateral temporal lobe regions. Both patients were severely impaired on standardised tests of anterograde memory. Both were compromised in their ability to acquire autobiographical event information, though there was evidence that BW was able to acquire some event information. BW also showed evidence of acquiring more information about famous personalities, news events and new vocabulary than JN. With news events, both showed sensitivity to frequency of repetition within the news media. The results demonstrate that *some* semantic information can be acquired when the medial temporal lobes are lesioned, as has also been documented in cases of adult-onset amnesia (Verfaille et al. 2000) and developmental amnesia (Vargha-Khadem et al., 1997), but the nature of the acquired information is not normal. In patients with medial temporal lobe pathology, the acquisition of semantic information probably necessitates much more extensive repetition (Baddeley et al., in press).

Although BW and JN were well matched in terms of their demographic characteristics and their performance on standard tests of anterograde memory, on all of the tests of autobiographical or semantic knowledge acquisition, BW performed better than JN. Zola and Squire (2000) suggested that such a finding may lead to a conclusion that the hippocampus does not have a unique contribution to memory. They suggested that one way to demonstrate a unique contribution would be to identify a measure of memory that was equally compromised in patients with lesions limited to the hippocampus and those with additional extra-hippocampal lesions. The finding from the present study that both BW and JN were severely compromised in terms of their ability to replay or re-experience post-morbid events they 'knew' had occurred may provide evidence for the unique role of the hippocampus. As discussed above, this applied both to the recollection of pre-morbid events as well as post-morbid events.

Section 4.2 presented studies of two patients (TG and SG) with a highly atypical pattern of memory impairment arising from temporal lobe pathology, hitherto reported in only a small number of cases. Each presented with a complaint that although they could remember events that had occurred over a period of hours or days, they could not remember things that occurred weeks or months previously. Formal memory testing showed normal or near normal performance when tested with a delay of up to a day, but when tested after a week or four weeks, performance was severely impaired. Detailed diary based studies with one patient (TG) suggested that epileptic seizure activity may be one factor in his failure to consolidate information, but that the relationship between overt seizures and the memory impairment was not a simple one. Diary-based studies of event memory proved to be a useful methodology in this case and further use of this technique with patients who present with similar complaints would be valuable. Although clinical and sub-clinical seizures seemed the most likely cause, it was difficult to rule out the possibility that structural damage, perhaps in the parahippocampal region, was responsible for his accelerated forgetting. It would be useful to identify patients without epilepsy, but with damage confined to this region, to examine this possibility, acknowledging the fact that such patients are very rare.

Both patients showed evidence of significant retrograde memory impairment. Both showed some indication of a temporal gradient in memory performance on some tasks, though not all. TG showed significant autobiographical event deficits on the Modified Crovitz task, though this was more severe for the period of about a year prior to his illness. Although SG showed evidence of a temporal gradient on a news events test, she demonstrated a deficit that stretched back several decades. It was suggested earlier, in relation to patient JM, who had focal retrograde amnesia following cerebral vasculitis, that a focal retrograde amnesia for autobiographical events of several decades was not consistent with an account of the deficit in terms of a disruption of consolidation processes as this would require consolidation to take place over an unrealistically long period of time. However, this conclusion is based on a simple dichotomy within consolidation processes, whereby a memory is either in some form of temporary store or a permanent store. However, it may be more appropriate to view the 'permanent' store as open to considerable change and modification as a result of further experience, mental rehearsal or reflection, or in the case of SG and TG, epileptic seizures. Although temporary system dysfunction (such as in the case of TGA) does not lead to a permanent change to the memory representations, it may be that repeated insults from seizure activity do disrupt memory networks. One possibility is that this disruption would affect 'weak' memories (defined as those from the relatively recent, but not immediately preceding, period that have not been extensively rehearsed). Over time, such disruption would also affect well-established memories. One implication of this hypothesis is that patients with such a disorder might show a progressive deterioration in retrograde memory performance. There was some evidence of this in a patient reported by O'Connor et al. (1997) who declined over several years in his performance on tests of famous faces. This aspect of very long-term memory loss would be useful to evaluate in further single-case studies.

**Models of memory and amnesia**

Several of the studies presented in this thesis tested predictions derived from Multiple Trace Theory (Nadel and Moscovitch, 1997) and the Standard Consolidation Model (Alvarez and Squire, 1995; Murre, 1996) concerning the nature of retrograde amnesia that arises from lesions of temporal lobe and diencephalic structures. Multiple Trace Theory predicts that the hippocampal complex has a lifelong role in the recollection of autobiographical events. In contrast, Standard Consolidation Theory states that over time autobiographical event memories become consolidated in neocortical regions and that the hippocampus is no longer needed for retrieval of older autobiographical memories. The weight of evidence from the data presented in Chapter 2 was in favour of Multiple Trace Theory. A central function of the hippocampal complex appears to be to provide a detailed recollection of an event, producing the phenomenological experience of 'replaying' an event in mind. Further evidence for the lifelong involvement of the hippocampus in autobiographical event recollection comes from a study by Maguire, Henson, Mummary and Frith (2001). In an fMRI study, Maguire et al. found that activity levels in the frontal lobes varied with the age of memories being recalled, but there was no similar variation in hippocampal activation. One of the limitations of human lesion studies is that it is rare for lesions to be very discrete and limited to a single structure such as the hippocampus. This is easier to achieve in work with experimental animals, though Jarrard (2001) noted that many of the conclusions about the role of the hippocampus in animals have been drawn from studies in which the location of the lesion has not been determined and described precisely. In particular, Jarrard noted that insufficient attention has been paid to possible damage to parahippocampal regions. This has arisen from an assumption that structures within the medial temporal lobe function as a single unit, though this assumption is questioned. A further limitation of animal studies is that animals cannot report on their phenomenological experience of events! Nevertheless, some recent studies have found a qualitative difference in the performance of rats with and without hippocampal lesions on a spatial learning task where there was a long learning-surgery interval. Nadel and Bohbot (2001) interpreted the findings of Kubie, Sutherland and Muller (1999) as showing that when the hippocampus is lesioned, performance of previously learned spatial tasks takes a different form than that seen in intact animals. Instead of using an integrated, map-like representation of the spatial environment, "rats without a hippocampus fall back upon a 'vector based' system that can support considerable spatial behaviour, but which lacks the flexibility and integral nature of a hippocampal-dependent spatial map" (Nadel and Bohbot, 2001, p. 57).

Although there was evidence that amnesic patients with hippocampal complex lesions were impaired in their ability to produce richly detailed autobiographical events or at least were unable to fully re-experience events in mind, they were nevertheless able to produce certain types of information about events, some of which were relatively detailed. This suggests that each of these individuals had a significant amount of event information represented by extra-hippocampal regions, though the possibility remains that incomplete hippocampal lesions left intact portions of hippocampus that supported these event memories. One of the limitations of the Multiple Trace and Standard Consolidation Theories is that proponents of both theories have not addressed in detail the issue of representation of memories in the neocortical system, concentrating instead on the relationship between the neocortical and hippocampal systems. I propose that the conceptual framework that best accounts for the data from the studies of retrograde amnesia reported in Chapter 2 is one that involves the concept of a hierarchically organised set of mnemonic convergence zones (Damasio, 1989; Mesulam, 1998), referred to here as Convergence Zone Theory. Damasio (1989) distinguishes three stages of information storage, involving the processing of (1) basic perceptual elements (2) coherent entities and (3) co-occurence of coherent entities. Derived principally from cytoarchitectronic evidence, Mesulam (1998) identifies five critical regions undertaking information processing. These include (1) primary sensory areas, (2) unimodal association areas, (3) heteromodal association areas, (4) paralimbic zone and (5) limbic zone. Mesulam's region (1) processes information corresponding to Damasio's first processing stage. Mesulam's regions (2-4) might be considered to be important for Damasio's second processing stage and Mesulam's region (5) corresponds to Damasio's third processing stage. Reflecting the difference between Multiple Trace Theory and the Standard Consolidation Model, Damasio and Mesulam differ in the period of time for which they view the final processing stage being involved in the retrieval of event memories. Damasio's position is similar to Standard Consolidation Theory and Mesulam's position is closer to Multiple Trace Theory. As noted above, the weight of evidence from the studies presented in Chapter 2 is in favour of the view that the hippocampus may be involved in autobiographical event retrieval across the lifetime.

Following Mesulam's (1998) conceptual framework, it might be speculated that some event information is represented in regions lower down the processing hierarchy than the top-level hippocampal region. One possibility is that the paralimbic region could play a role in the retrieval of such information. According to Mesulam (1998), this region incorporates the parahippocampal and posterior cingulate regions, which he notes, "constitute the hippocampocentric subdivision of the paralimbic zone because they provide a transition between the hippocampal formation.....and the homotypical cortex" (p. 1016). If regions much below this in the hierarchy are lesioned one might expect that there would be accompanying impairments in more fundamental semantic knowledge such as knowledge of objects, people, faces and words. JN, who was described in Chapters 2.3 and 4.1, provides some support for the notion of the importance of parahippocampal regions in event recollection. She had bilateral lesions to the parahippocampal and entorhinal cortices in addition to bilateral lesions of the hippocampus. She presented with a major loss of autobiographical event information. Although her performance improved using a recognition format, there was evidence that this improvement was based on post-illness information she had been told. While JN did not present with the severe semantic information loss associated with disorders such as semantic dementia (Mesulam, 1982; Snowden et al., 1989; Hodges et al., 1992) she did show some impairment in naming and was poor on tests of general knowledge. This might be accounted for by the fact that she had additional bilateral lesions to the temporal poles, and the inferior and middle temporal gyri. Patients HM and EP (Steffanacci et al., 2000) both had lesions that are remarkably similar to that of JN. These are illustrated in Figure 5.1, which shows the axial MRI scans of the three patients.

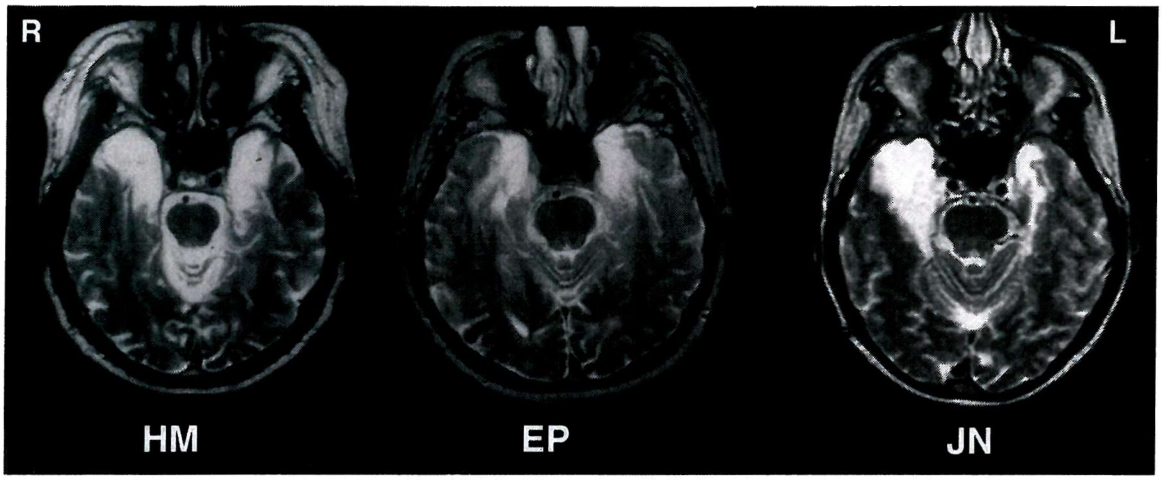



***Figure 5.1 Axial MRI scans through the level of the temporal lobes of patients HM, EP and JN showing similar profiles of medial temporal lobe damage.***

EP was described as having "severe and extensive retrograde amnesia for facts and events" (p. 7028), though he is also described as being able to retrieve some memories from his early life. HM was described as having 11 years of retrograde amnesia, which extended back to age 16. Although JN described difficulties recollecting events throughout her childhood, this period was not tested using the recognition format as her husband, who was the informant in this case, had only known her from the age of 16. Mayes and Downes (1997) noted that "one of the most puzzling features of RA [retrograde amnesia] is its often reported temporal gradient. This varies markedly across patients and it has to be admitted that its anatomical and functional determinants are still not well understood" (p. 31). The relatively common finding in amnesic conditions of some preservation of childhood or early adulthood memories may, however, have led to an over-emphasis on time as the critical factor in determining the probability of recall. One possibility is that childhood and early adulthood are richer in terms of salient, emotionally important, life events. This was discussed in relation to JM in Chapter 3. Mackavey et al. (1991) studied the autobiographies of 49 eminent psychologists and analysed them to identify 'autobiographically consequential experiences', concluding that such memories were concentrated during the college and early adult years. While eminent psychologists are not necessarily a representative sample of the general population, these data lend support to the proposition that perhaps the first 20 years or so of life contain a larger number of events that are subject to repeated recollection/rehearsal as a result of their personal significance. The possibility arises, therefore, that these memories become more extensively represented in extra-hippocampal regions, including perhaps the parahippocampal region or other higher level regions within Mesulam's hierarchy. Although this is broadly what Standard Consolidation Theory suggests, one prediction that deviates from Standard Consolidation Theory is that recollection of such events may normally involve both neocortex *and* hippocampus, with the hippocampus remaining important for enabling a detailed re-experiencing of the event. In the absence of any hippocampal contribution, the recollection of such memories is possible, though if the hippocampus does provide a distinctive, qualitatively different function, then there should always be some detectable difference between recollection of such events with and without a hippocampus.

A further point to note in relation to patients HM, EP and JN is that they all have temporal pole lesions. Maguire, Mummery and Buchel (2000) recently highlighted the importance of this region in relation to memory for both autobiographical and public events. They conducted a functional-MRI study of levels of activation in key temporal lobe regions in relation to four types of memory task (autobiographical events, autobiographical facts, public events and general knowledge). They demonstrated that connectivity between the temporal pole and the parahippocampal gyrus was increased during autobiographical event recall. By contrast, connectivity with the lateral temporal cortex was increased during recall of general facts and public events. It would be useful, though difficult, to identify individuals with pathology confined to the parahippocampal region exclusively in order to help clarify the role of this structure. It would also be useful for future testing of such patients to extend testing through to early childhood to examine the extent to which this period is also affected.

Proponents of Multiple Trace Theory (Nadel and Moscovitch, 1997) and the Standard Consolidation Model (Alvarez and Squire, 1995; Murre, 1996) have identified the type of pathologies that would be expected to produce selective retrograde amnesia. None of these fit the data derived from patient JM, presented in Chapter 3.1. One possibility that is consistent with Multiple Trace Theory is that the initial disruption to medial temporal lobe structures (evidenced by the period of anterograde amnesia present during the acute phase of the illness) was sufficient to disrupt existing hippocampal-neocortex links, without destroying tissue. However, if this were the case one might expect a condition such as TGA to produce a similar pattern of focal retrograde amnesia, since this also appears to involve a period of severe disruption to medial temporal lobe functioning. However, as was shown in Chapter 2.2, this does not follow from TGA. It was therefore suggested that the discrete, multi-focal nature of the pathology associated with cerebral vasculitis might be the key to understanding the deficits. It is again helpful to draw upon the Convergence Zone theories of Damasio (1989) and Mesulam (1998). Lesions to higher level convergence zones or connections between those zones would lead to disruption of consolidated, 'semanticised' autobiographical event memories and also result in the hippocampal system being unable to reinstate autobiogaphical event patterns. So long as sufficient tissue remained intact, then new links could be made (i) within convergence zones, (ii) between convergence zones and (iii) between convergence zones and the intact hippocampus. If this explanation is correct, then other cases of vasculitis or other conditions that result in multiple, discrete lesions, such as Systemic Lupus Erythematosus (SLE) or Polyarteritis Nodosa, should show a similar pattern. No other cases have been reported, but it is not clear if this is because focal retrograde amnesia does not occur in such diseases or whether there has not been appropriate assessment undertaken in people with these conditions.

**Clinical and methodological issues**

Findings from the studies presented here raise methodological issues concerning how retrograde memory and long-term anterograde memory should be assessed. For example, several tests traditionally used to assess retrograde memory are likely to be insensitive to the subtle level of impairment that may be associated with selective hippocampal lesions.

Famous face identification or public event recognition are clearly inadequate as measures of retrograde memory on their own since they do not make demands on the ability to recollect autobiographical events. Even tests such as the Autobiographical Memory Interview (Kopleman et al., 1990) may be insensitive to this impairment, as was shown in the present studies. In the case of this test, the relatively small number of events solicited from each lifetime period may result in the production of event memories that do contain some event detail, but which fall into the category of memories that have been over-rehearsed and are more like 'stories' than true recollections of events. However, there is an obvious danger in arguing that a failure to find an autobiographical memory deficit simply reflects the insensitivity of the assessment method (Nadel et al., 2000). There is therefore a need to define the assessment methods, and specific tools, that should be sensitive to the type of deficit predicted to follow from selective hippocampal lesions. The use of scoring systems with more extensive gradations in scale such as the one used with the Time-Constrained Crovitz task here (Graham and Hodges, 1997) or the method of counting details (Nadel et al., 2000) are examples of possible methodologies, but these require further research.

A further issue concerning the ability to recollect autobiographical event memories is the degree of prompting or retrieval support provided within the test format. A major problem for tests that ask a participant to describe an event is that the level of event detail expected, needs to be made clear to the participant. Prompting for detail is typically necessary in order to be sure that as much detail as possible has been provided, but the type and level of prompting needs to be specified. The present studies also highlighted the value of using a forced-choice recognition test format in relation to autobiographical events. The use of a recognition format is important in addressing the question of the role of key structures in retrieval as opposed to storage of memories. Furthermore, the use of the 'remember-know' distinction proved theoretically productive in helping to characterise the nature of the difference between apparently similar levels of performance in patients with selective hippocampal lesions and control participants.

The finding of accelerated forgetting that takes place over the course of a period of days or weeks rather than seconds or minutes highlights the need for tools to assess memory over this time span (Tombaugh and Hubley 2001). A test that was standardised for these durations would be helpful in making the identification of such cases more straightforward, though there are inevitable difficulties associated with variations in the extent to which participants (patients or controls) rehearse relevant material, which may produce less reliable tests.

In conclusion, the results of the investigations reported in this thesis highlight the contribution that studies of very long-term memory loss may make to our understanding of issues such as the nature of retrograde amnesia and long-term memory consolidation. Retrieval processes appear to play a critical role in the dense retrograde amnesia that accompanies some form of cerebral pathology. Retrograde amnesia is not a single entity – fractionation can occur along several lines, with the episodic/semantic distinction being one of the key forms of dissociation that may occur. While the study of very long-term retention holds many challenges for clinical neuroscientists, novel methodologies, such as those that explore online recording of autobiographical events, offer considerable promise for elucidating the processes involved in the laying down of new event memories.

## Appendix 1: Dead or Alive Test Stimuli (Whether alive or year of death)

**Version 1 (See Section 2.1)**

| | |
|---|---|
| Louise Woodward | A |
| **John F Kennedy** | **63** |
| **Mother Teresa** | **97** |
| Michael Owen | A |
| **Charles deGaulle** | **70** |
| **Dodi Fayed** | **97** |
| **Peter Sellers** | **80** |
| Tony Blair | A |
| **Marilyn Monroe** | **62** |
| **Roy Castle** | **94** |
| **Yvonne Fletcher** | **84** |
| **Martin Luther King** | **68** |
| **Yitzak Rabin** | **95** |
| **Louis Armstrong** | **71** |
| **Tony Hancock** | **68** |
| **Eamon Andrews** | **87** |
| Gerry Adams | A |
| **Elvis Presley** | **77** |
| **Winston Churchill** | **65** |
| **Linda McCartney** | **98** |
| François Mitterand | 96 |
| OJ Simpson | A |
| Monica Lewinsky | A |
| **Michael Ryan** | **87** |
| **Clement Atlee** | **67** |
| **Airey Neave** | **79** |
| **Princess Diana** | **97** |
| **Yuri Gagarin** | **68** |
| **Roy Kinnear** | **88** |
| Margaret Thatcher | A |
| **John Wayne** | **79** |
| Peter Sutcliffe | A |
| **Francis Chichester** | **72** |
| **Lee Harvey Oswald** | **63** |
| Bill Clinton | A |
| **Robert Maxwell** | **91** |
| **John Lennon** | **80** |
| **Harry Truman** | **72** |
| **Richard Nixon** | **94** |
| William Hague | A |
| Sophie Rhys-Jones | A |
| **Russell Harty** | **88** |
| **Noel Coward** | **73** |
| John Major | A |
| Tim Henman | A |
| **Bobby Sands** | **81** |
| **Lyndon Johnson** | **73** |
| **Hugh Gaitskill** | **63** |
| **Eric Morecombe** | **84** |
| Martin McGuiness | |

**Version 2 (See Section 2.3/4.1/4.2)**
X = Fictitious names

| | | | |
|---|---|---|---|
| Louise Woodward | A | Gerry Adams | A |
| **John F Kennedy** | **63** | **Elvis Presley** | **77** |
| ***Adam Beach*** | ***x*** | *Alfie Randall* | *x* |
| **Mother Teresa** | **97** | *Tom Ashley Smith* | *x* |
| *Alan Saxon* | *x* | **Winston Churchill** | **65** |
| Mikhail Gorbachev | A | Menachim Begin | A |
| Michael Owen | A | **Linda McCartney** | **98** |
| *Brendon Purkis* | *x* | *Mohad Badat* | *x* |
| **Charles deGaulle** | **70** | **François Mitterand** | **96** |
| **Dodi Fayed** | **97** | *Marion Witcher* | *x* |
| *Kathleen Wright* | *x* | O J Simpson | A |
| Benazir Bhutto | A | **Basil Hume** | **99** |
| **Peter Sellers** | **80** | *Alistair Baynes* | *x* |
| *Albert deVere* | *x* | Yassir Arafat | A |
| *Philip McCormick* | *x* | Monica Lewinsky | A |
| Tony Blair | A | *Douglas Caroll* | *x* |
| *Colin Lambert* | *x* | *Frank Reistman* | *x* |
| **Jill Dando** | **99** | **Michael Ryan** | **87** |
| *Lenny Hiscock* | *x* | *Amos Calder* | *x* |
| General Pinochet | A | **Clement Atlee** | **67** |
| **Marilyn Monroe** | **62** | Brigette Bardot | A |
| **Roy Castle** | **94** | **Airey Neave** | **79** |
| *Albert Driscoll* | *x* | **Princess Diana** | **97** |
| **Yvonne Fletcher** | **84** | *Ashwin Mohamed* | *x* |
| *Walter Jennings* | *x* | Idi Amin | A |
| *Sue Latham* | *x* | *Danny Spear* | *x* |
| Tim Henman | A | **Yuri Gagarin** | **68** |
| *Robert Neaton* | *x* | *Laura Hayward* | *x* |
| Nicolae Ceausescu | 89 | **Roy Kinnear** | **88** |
| **Martin Luther King** | **68** | *Malcolm Taylor Brown* | *x* |
| *Alex Everett* | *x* | *Ray Shergold* | *x* |
| **Yitzak Rabin** | **95** | Margaret Thatcher | A |
| *Billy Tubbs* | | Greg Rusedski | A |
| **Louis Armstrong** | **71** | **John Wayne** | **79** |
| Lech Walesa | A | *Richard Webber* | *x* |
| **Tony Hancock** | **68** | Peter Sutcliffe | A |
| *Henry Morgan* | *x* | *Sally Cooke Hurle* | *x* |
| **King Hussein** | **99** | *Matthew Dixon* | *x* |
| *Jacques Cartine* | *x* | **Francis Chichester** | **72** |
| *Martin Baron* | *x* | *Sandra McKinley* | *x* |
| **Eamon Andrews** | **87** | **Lee Harvey Oswald** | **63** |
| *Linda Salisbury* | *x* | *Simon Edwards* | ***x*** |
| Pelé | A | Gary Linekar | A |

| | |
|---|---|
| Bill Clinton | A |
| *P K Milsom* | *x* |
| **Robert Maxwell** | **91** |
| *Nigel Mount* | *x* |
| **John Lennon** | **80** |
| Jacques Chirac | A |
| *Dennis Locksley* | *x* |
| **Harry Truman** | **72** |
| *Andrei Odberg* | *x* |
| Celine Dion | A |
| **Richard Nixon** | **94** |
| William Hague | A |
| *Stanley Isaacs* | *x* |
| Sophie Rhys-Jones | A |
| **Russell Harty** | **88** |
| *James L Kircaddy* | *x* |
| **Nikita Khrushchev** | **71** |
| *Arthur Chiverton* | *x* |
| **Noel Coward** | **73** |
| John Major | A |
| *Grant Wilton* | *x* |
| Kenneth Kaunda | A |
| **Bobby Sands** | **81** |
| *Stephen Colewood* | *x* |
| *Margaret Ogden* | *x* |
| **Lyndon Johnson** | **73** |
| Gordon Buckingham | x |
| Muhammad Mubarak | A |
| Harold Shipman | A |
| *Gilbert Ayling* | *x* |
| *Geoff Foreman* | *x* |
| **Hugh Gaitskill** | **63** |
| Robert Mugabe | A |
| **Eric Morecombe** | **84** |
| *Neil Tindall* | *x* |
| **Enoch Powell** | **98** |
| Martin McGuiness | A |
| **Deng Xiaoping** | **92** |
| Martina Navratilova | A |
| *George Sargent* | *x* |
| **Alexander Dubceck** | **92** |
| Slobodan Milosevic | A |
| **Louis Mountbatten** | **79** |
| **Ayatollah Khomeini** | **89** |

# Appendix 2: News Events Test Stimuli

## (1979-1997)

The Crow Tanker Disaster
The Pearson Scogan Case
The Hamburg Riots
**The Enniskillen Bombing**

**The Irish Drought**
The Festival of Wales
The Irish Sea Storms
The Tiananmen Square Massacre

**Dunblane**
The Nottingham Forest Fire
The Shetland Isles Invasion
The Starburst Collision

The Blackfriars Bridge Collapse
**The Challenger Space Shuttle**
The Howard Scandal
The Martian Asteroid

The Smith Space Telescope
**Desert Storm**
The Moonlight Mission
The Fuel Tax Riots

**The Camp David Agreement**
The Fowler Trial
The Balmoral Castle Robbery
The Jaguar Car Plant Explosion

The Rowntrees Poisoning Incident
The Harpur Incident
**The Grand Hotel Brighton Bomb**
The Floyd Report

The Sinking of the Spirit of Lisbon
The Forest of Dean Fire
The Scottish Avalanche Tragedy
**The Eruption of Mount St. Helen's**

The Amsterdam City Bombing
The Meadowside Scandal
The Fleet Street Crash
**The West Murders**

The Downing Street Break-In
The Sellafield Leak
**The Windsor Castle Fire**
The Eiffel Tower Fire

**The Lockerbie Disaster**
The Boston Bombing
The Empire Plan
The Ayr Football Stadium Tragedy

The Apollo Space Meeting
The Barclays Bank Affair
The Prudential Fraud
**Whitewater**

The Lloyds Bank Fraud
The Gresham Report
**Live Aid**
The Battersea Power Station Explosion

The Downing Street Robbery
The Invasion of Mexico
**The Death of Princess Grace of Monaco**
The Wimbledon Fire

The Sinking of the Celestial Prince
The Nottingham Queens Hospital Evacuation
The Esbjerg Treaty
**The Death of Bobby Sands**

**The Kings Cross Fire**
The Newcastle Coach Trip Tragedy
The Beach Murders
The Galloway Murders

The Mexican Airplane Shooting
**The Death of Dodi and Diana**
The B27 Incident
The Hoch Crisis

The Shell Montez Disaster
The MacLuen Plan
The Severn Bridge Tragedy
**The Brent Spar Affair**

The Gregory Report
The Amazon Forest Fires
**The Birmingham Six Freed**
The Jamaica Shootout

**The Sinclair C5**
The Venus Mission
The Brazilian Rainforest Fire
The Boeing Affair

**The Salman Rushdie Incident**
The Lagos Massacre
The Plymouth Rail Crash
The Southampton Bomb

The Canadian Embassy Fire
**The Death of John Lennon**
The Bombay Power Station Explosion
The Harper Kidnapping

**The Death of Lord Mountbatten**
The Jane Smithson Allegations
The Eiffel Tower Bomb Explosion
The Marwell Fraud Case

The Matthew Taylor Abduction
The Dover Cliffs Collapse
The Swansea Power Station Explosion
**The Bhopal Disaster**

The Black Knight Resignation
The Bucharest Summer
The Vauxhall Safety Scare
**The Closure of Checkpoint Charlie**

The St Mark's Square Massacre
**The Ratner Jewellery Scandal**
The Oxford Affair
The Green Beetle Crisis

The Madrid Football Riot
Vasnik 1
The Tracey Hunt Affair
**The Saudi Nurses Trial**

**The Rwandan War**
The Vienna Air Lift
The Plymouth March
The Michael Jones Resignation

The Humber Bridge Explosion
**The Warrington Bombing**
The Dentists' Strike
The Ross Hunt Convictions

**The Kremlin Coup**
The Tendo War
Golden Sands
The Cook Murders

The Filbert Street Stadium Disaster
The Arrest of Cliff Richard
**The Hitler Diaries Fraud**
The Grounding of the Royal Yacht Britannia

The Branson Glider Crash
**The Intruder in the Queen's Bedroom**
The Dartford Tunnel Flooding
The Sorenson Inquiry

The IBM Takeover
The Knightsbridge Riot
**The Heycel Stadium Disaster**
The Santa Fe Gold Find

**The Iron Lady Resignation**
The Carpathian Massacre
The Bristol Bomb
The London Gridlock

**The Piper Alpha Incident**
The Russell Suicides
The Samuels Scandal
The Dusseldorf Rail Disaster

The R.J. Downing Report
The Southampton Hilton Hotel Fire
**The Bombing of Tripoli**
The Princess Margaret Tax Case

The Jersey Killer Bee Invasion
**The Tokyo Subway Gas Attack**
The Napoleon Diaries Fraud
The Westwood Shooting

The Carpond Lane Murders
**The Pope John Paul II Assassination Attempt**
The Bank of England Robbery
The Disappearance of the Oil Tanker Pride of Shell

The Elephant and Castle Gas Explosion
The Canadian Parliament Coup
**The Iranian Embassy Siege**
The Carlsberg Trial

The European Banning of British Sugar
The Lotte-Kepler Gang
The Norwegian Astronaut Tragedy
**The London City Bombing**

The Maine Strangler
The Labour Conference Bombing
**The Southall Train Crash**
The FA Cup Final Gas Attack

The Baker Abductions
**The Docklands Bombing**
The Neville Trial
The Surgeons' Strike

The Fenwick Fraud
**The Herald of Free Enterprise Sinking**
The A-Level Exam Scandal
The RDS Disaster

The Andrews Murders
The Pontypridd Disaster
The Drayton Murders
**The Maxwell Incident**

The Westminster Abbey Fire
The Shooting of Constable Bradley Williamson
The Asfordby Coach Crash
**The Three Mile Island Atomic Leak**

The Thomson-Clarke Affair
The Cancellation of the Cannes Film Festival
**The WPC Yvonne Fletcher Shooting**
The Tyne Bridge Rail Disaster

The Tate Gallery Fire
**The Reagan Star Wars Plan**
The Release of the Coventry Three
The Armitage Report

The Gilroy Trial
The Sinking of the QE2
**The Philip Lawrence Murder**
The Miss World Shooting

The A167 Accident
**The Camilla-Gate Scandal**
The Irish Sea Discovery
The Molteno Riots

The Mexico Shootout
The Ankara Agreement
The Crystal Palace Gas Attack
**The TWA Disaster**

The Barbara Cartland Scandal
The Fulham Blues Boats
The Wimbledon Hostage Incident
**The Royal Ski Party Avalanche Tragedy**

The Pearson Murders
The Manchester Doctor Trial
**The Indonesian Smog Disaster**
The Welsh Nationalists' Scandal

**The Hubble Space Telescope**
The Isle of Man Social Services Scandal
The Badminton Fire
Ringwood

The Compton Investigations
The Cambridge University Fraud Scandal
The M25 Murder Case
**The Falklands War**

**The Ronald Reagan Assassination Attempt**
The Parkes Trial
The London Zoo Escape
The Hammersmith Tunnel Plan

**The Red Square Aeroplane Incident**
The Election of Quayle
Felton
The Jackson Trial

The Vatican Massacre
The Glasgow School Hostages
**The Los Angeles Riots**
The LMO Cease-Fire

**The Waco Siege**
The Darlington Disaster
The Ferrybridge Explosion
The Empire State Building Bombing

The Alaskan Invasion
The Edinburgh Castle Fire
**The Channel Tunnel Fire**
The Belgium Crisis

The Derby Doping Scandal
**The Bradford Stadium Fire**
Barton Street Riots
The Launch of the Vauxhall P20

The Bruno Scandal
The New Zealand Invasion
Red Friday
**The Hong Kong Handover**

The Reagan Arrest
The Watts Kidnapping
**The Grand National Declared Void**
The Monroe Cult Slaughter

The Finsbury Park Fire
The Colonel Aid Programme
**The Exxon Valdez Disaster**
The London Marathon Declared Void

The Paper Disaster
**The Johnson Olympics Affair**
The Library Murders
The Hopkins Kidnapping

The Red Sea Flooding
The Royal Yacht Tragedy
The Amine Virus Scare
**The BCCI Scandal**

The Shropshire Strangler
The Tunisian Crisis
**The Estonia Sinking**
The Summerville Scandal

**The Chernobyl Diaster**
The Fulham Nine
The Trent Bridge Gas Explosion
The 003 Concorde Crash

The Vancouver Bombings
The Grand Prix Bomb Attack
**The Barings Bank Scandal**
The Ontario Quake

The Caribbean Bubble
**The Poll Tax Riots**
The Aeroflot Hijacking
The Goldberg Affair

The Selfridges Bombing
**The Oliver North Conviction**
The Norfolk Flooding
The Newby Hangings

The National Hospital Porters Strike
The Davidson Crime Report
The Empire State Building Blackout
**The Sinking of the Rainbow Warrior**

The Branson Trial
**The Windsor Gems Auction**
The Atkinson Arrest
The Detroit Siege

**The Clapham Rail Disaster**
The Statue of Liberty Incident
The Conviction of the Ealing Terrorists
The Sinking of the Isle of Wight Ferry

The Kray Brothers Proved Innocent
**The Paula Jones Allegations**
The Inkblot Mission
The Azores Fire

The Trent Disaster
The Bordeaux Raid
The Potato Health Scare
**The Maastricht Treaty**

**Additonal items for patients tested with test including period from 1998-2000**

The Hyde Park Inquiry
**Linda McCartney Dies**
The Alfred Winston Charges
Euro Disney Closure

The McArthur Investigation
**The Cornwall Total Solar Eclipse**
Great White Shark Attacks Swimmer at Brighton Beach
The British Museum Sold to Japanese

Japan/New Zealand Compromise
**Monica Lewinsky Scandal**
The Charles Fisher Report
The Dutch Market Collapse

**The French Concorde Disaster**
Buckingham Palace Salmonella Outbreak
Martin Jones Wins 5 Olympic Gold Medals
Trawsfynned Nuclear Power Station Disaster

The Livingstone Mugging
Meenly Farm Incident
**Ron Davies Clapham Common Scandal**
The STTP Toxic Release

First Manned Space Mission to Mars Abandoned at Half Way Point
**Oil Refinery Blockades Lead to Fuel Crisis in Britain**
PC David Brentnall Saves Princess Margaret's Life
Epsom Derby Cancelled Because of Lack of Runners

The Green Belt Tremor
The ADH Explosion
**Hurricane Mitch In Honduras**
Norfolk Aeroplane Catastrophe

Italian Olive Oil Contamination
**France Beat Brazil in World Cup**
Welsh Assembly Attacked by Rioters
Irish Sea Fishing Charter

Archbishop of Westminster Resigns Over Scandal
James Hartley Commits Suicide
**Nato Bombs Kosovo/Serbia**
English Green Peas Sanction

Caduggen Report Published
John Cleese Charged With Assault
**The Turkish Earthquake Disaster**
Spider Monkeys Escape From London Zoo

Dutch Queen Abdicates
Carlton Enquiry Into Foreign Office Blunders Opens
**Terrorist Bomb Explodes in Omagh Shopping Centre**
Shrimp War Develops Between Local Cornish Fishermen

## Appendix 3: Sample items for each of the six patients and three control participants for the Autobiographical Events Test.

**Patient BW**

*Cued recall question*

What happened while you were working as a waitress Woolworth's?

*Recognition task*

(a) After leaving school I worked as a waitress in Woolworth's and once accidentally pulled the chair out from a customer who was about to sit down.

**(b) After leaving school I worked as a waitress in Woolworth's and once accidentally dropped a tray on a customer.**

(c) After leaving school I worked as a waitress in Woolworth's and once accidentally knocked off and broke a customer's glasses.

*Cued recall question*

What happened when you were unwell on holiday in Majorca?

*Recognition task*

(a) On holiday in Majorca I had food poisoning and had to go to hospital in Palma.

**(b) On holiday in Majorca I fainted while in Palma and was taken into a shop.**

(c) On holiday in Majorca I developed a heat rash and had to see a Doctor in Palma.

**Patient EA**

*Cued recall question*

What happened when your car broke down on a trip to York?

*Recognition task*

(a) On a trip to York our car broke down on the way, but my husband managed to fix the problem before the AA arrived.

(b) On a trip to York our car broke down on the way and because we couldn't get it fixed that day we stayed overnight in a hotel and travelled up to York the next day.

**(c) On a trip to York our car broke down on the way. It took us all day to get it fixed and we ended up driving around in an AA lorry.**

*Cued recall question*
What did you do one night while building the extension when there was too much dust and rubble around?

*Recognition task*
(a) Whilst building the extension, one night there was so much dust and rubble around that we all had to go and stay with my parents to escape the mess.
**(b) Whilst building the extension, one night there was so much dust and rubble around that we ended up sleeping in the lounge on a mattress with a pile of rubble as a bed-head.**
(c) Whilst building the extension, one night there was so much dust and rubble around that we treated ourselves and the children to a night in a hotel to escape the mess.

**Patient PR**
*Cued recall question*
What happened while on a holiday in France for which you had to go to the doctor?

*Recognition task*
(a) On a holiday in France I was stung by a jellyfish washed up on a beach and had to go to the doctor.
**(b) On a holiday in France I was bitten by a dog while we were on a beach and had to go to the doctor.**
(c) On a holiday in France I was stung by a hornet while we were on a beach and had to go to the doctor.

*Cued recall question*
What happened when you had an accident in which a car drove into you?

*Recognition task*
(a) A car once drove into the back of my car and dented the boot. I was able to drive the car, but it needed a big repair.
(b) A car once reversed out of a parking space in a car park into the front of my car. I was able to drive the car, but it needed a big repair.
**(c) A car once drove out of a side road into the right hand front wing of my car. I was able to drive the car, but it needed a big repair.**

**Patient MW**

*Cued recall question*

What happened to the coach you went on while on your honeymoon?

*Recognition task*

(a) During our honeymoon, we went on a coach trip, but the coach broke down on a motorway.

**(b) During our honeymoon, we went on a coach trip, but the coach landed up in a dyke by the road.**

(c) During our honeymoon, we went on a coach trip, but the coach was involved in a head-on crash with another coach.

*Cued recall question*

What happened once on a canal holiday when your son went off to look for mushrooms?

*Recognition task*

(a) On a canal holiday with the family our son went off to look for mushrooms and we saw him being followed by a flock of sheep.

(b) On a canal holiday with the family our son went off to look for mushrooms and we saw him being followed by several horses.

**(c) On a canal holiday with the family, our son went off to look for mushrooms and we saw him being followed by a herd of cows.**

**Patient JN**

*Cued recall question*

What happened when something pulled out in front of you while driving on your honeymoon?

*Recognition task*

(a) On our honeymoon we were driving down a road when suddenly a milk float pulled out in front of us and we skidded and nearly ended up in a ditch.

(b) On our honeymoon we were driving down a road when suddenly a tractor pulled out in front of us and we skidded and nearly ended up in a ditch.

**(c) On our honeymoon we were driving down a road when suddenly a removals van pulled out in front of us and we skidded and nearly ended up in a ditch.**

*Cued recall question*
What happened when you went to see your husband running in the London marathon?

*Recognition task*
**(a) We once went to watch my husband running in the London Marathon. We managed to see him going past us despite the huge number of people running.**
(b) We once went to watch my husband running in the London Marathon. We never managed to see him because of the huge number of people running.
(c) We once went to watch my husband running in the London Marathon. We thought we saw the back of him, but when we checked the number it turned out to be someone else.

**Patient CW**
*Cued recall question*
What part did you play when you appeared in The Mikado?

*Recognition task*
a) While at school, my brother and I once appeared in the Mikado. We played two of the three little maids.
**(b) While at school, my brother and I once appeared in the Mikado. I played Katisha and my brother was one of the three little maids.**
(c) While at school, my brother and I once appeared in the Mikado. My brother played Katisha and I was one of the three little maids.

*Cued recall question*
What important event happened on the beach on the last day of a holiday in Spain, in Malgrat de Mar?

*Recognition task*
**(a) Once, on the last day of a holiday in Spain, in Malgrat de Mar, my wife and I were on the beach. A strange man pushed his wife under the sea. She screamed. My wife and I ran into the sea and saved her.**
(b) Once, on the last day of a holiday in Spain, in Malgrat de Mar, my wife and I were on the beach. A strange man assaulted me while I was lying on the sand. My wife was in the sea, but came running out and fended off the man.
(c) Once, on the last day of a holiday in Spain, in Malgrat de Mar, my wife and I were on the beach. A strange man pushed my wife under the sea. She screamed and I ran into the water and saved her.

**Control Participant 1**

*Cued recall question*

How did Christy find out that his pet rabbit had died?

*Recognition Task*

(a) I had to tell Christy when he came home from school one day that I had found his pet rabbit Jenny dead in the hutch. He look horrified and wept.

(b) Out neighbour who had been looking after Christy's pet rabbit Jenny had to tell him she had died while we were away on holiday. He looked horrified and wept.

**(c) John and I watched as Christy found his pet rabbit Jenny dead in the hutch. He looked horrified and wept.**

*Cued recall question*

What happened when Christy caught his leg in the rear wheel of the bike?

*Recognition task*

(a) On a cycling trip Christy once managed to catch his leg in the rear wheel of the bike, but I managed to bandage it up for him and take him to the GP.

**(b) On a cycling trip Christy once managed to catch his leg in the rear wheel of the bike and had to be taken to hospital.**

(c) On a cycling trip Christy once managed to catch his leg in the rear wheel of the bike and buckled the wheel, but somehow wasn't injured.

**Control Participant 2**

*Cued recall question*

What problem did you find when you woke up on the first day of your honeymoon?

*Recognition task*

**(a) On the first day of our honeymoon we woke up to find that the caravan gas bottle had frozen up.**

(b) On the first day of our honeymoon we woke up to find that a caravan tyre had completely deflated.

(c) On the first day of our honeymoon we woke up to find that the electricity supply had been cut off.

*Cued recall question*
For the birth of your first child, how did you get into hospital?

*Recognition task*
(a) When I went to hospital to have our first baby, I went in by ambulance. My husband followed as he had to stop for cigarettes on the way.
**(b) When I went to hospital to have our first baby, my husband drove me in the works van and had to stop for cigarettes on the way.**
(c) When I went to hospital to have our first baby, a neighbour drove us as our car was in the garage for service and he had to stop for cigarettes on the way.

**Control Participant 3.**
*Cued recall question*
What came into the tent on a camping holiday in Wales while you were playing scrabble?

*Recognition task*
(a) On a camping holiday in North Wales, we were playing scrabble one evening when a cat came into the tent and ran out again.
(b) On a camping holiday in North Wales, we were playing scrabble one evening when a rat came into the tent and ran out again.
**(c) On a camping holiday in North Wales, we were playing scrabble one evening when a squirrel came into the tent and ran out again.**

*Cued recall question*
How did you write off the Polo?

*Recognition task*
(a) I wrote off the red Polo when I drove into a lorry that was stopped at some traffic lights.
**(b) I wrote off the red Polo by running into the back of a van at a roundabout.**
(c) I wrote off the red Polo by driving into a lamppost after swerving to avoid a cat in the road.

**Appendix 4 Stimuli for the News Events Test I used in Section 4.2.2.5.4**

1. Which one of these events actually happened?
**(a) Kuwait is invaded by Iraq**
(b) Kuwait is invaded by Saudia Arabia
(c) Iraq is invaded by Kuwait

2. Which one of these events actually happened?
(a) In Belfast twelve people are killed and thirty people are injured in an IRA bomb attack on Orangeman's Day.
(b) Eleven people are killed and twenty more injured by an IRA bomb attack in Dublin on St Patrick's Day
**(c) Eleven people are killed and sixty more are injured by an IRA bomb attack in Enniskillen on Remembrance Day**

3. Which one of these events actually happened?
(a) Terrorists take over a sports village in Berlin during the European Games, killing a number of athletes.
**(b) Terrorists take over a sports village in Munich during the European Games, killing a number of athletes.**
(c) A number of athletes are killed when terrorists take over a sports stadium in Innsbruck during the Winter Olympics.

4. Which one of these events actually happened?
(a) An American nanny, working in Britain, is found guilty of the manslaughter of a child in her care.
(b) A French au pair, working in America, is found guilty of the manslaughter of her employer.
**(c) A British nanny, working in America, is found guilty of the manslaughter of a child in her care.**

5. Which one of these events actually happened?
(a) A yacht with French passengers on board capsizes and sinks in the Italian port of Naples.
**(b) A ferry with British passengers on board rolls over and sinks in the Belgian port of Zeebrugge.**
(c) A cruiseliner with German passengers on board keels over and sinks in the Dutch port of Rotterdam.

6. Which one of these events actually happened?
**(a) An American spacecraft with two astronauts on board lands on the moon.**
(b) A Russian spacecraft with two cosmonauts on board lands on the moon.
(c) An American spacecraft with two astronauts on board lands on Mars.

7. Which one of these events actually happened?
(a) In Belfast, thirteen civilians are shot dead by British soldiers after mass protests against the British occupation in Northern Ireland.
(b) In Londonderry, thirteen soldiers are injured by rioting civilians.
**(c) Thirteen civilians are shot dead by British paratroopers in Londonderry after a civil rights march turns into a riot.**

8. Which one of these events actually happened?
**(a) England wins the Football World Cup by beating West Germany.**
(b) England wins 20 gold medals in the Tokyo Olympic games.
(c) England wins the Rugby World Cup by beating New Zealand.

9. Which one of these events actually happened?
(a) A section of the Channel Tunnel has to be closed after two trains collide.
**(b) A section of the Channel Tunnel is devastated by fire.**
(c) Flooding leads to the closure of the Channel Tunnel.

10. Which one of these events actually happened?
(a) Three IRA terrorists are shot by security forces in Cyprus.
**(b) Three IRA terrorists are shot by security forces in Gibraltar.**
(c) Security forces in Germany shoot three IRA terrorists.

11. Which one of these events actually happened?
**(a) The Beatles receive a major honour from the Queen for their services to music.**
(b) The Beatles honour the Queen in a special birthday concert.
(c) The Beatles receive an award from the US President for their services to music.

12. Which one of these events actually happened?
(a) A Brighton train rams into wall killing 44 passengers.
(b) A Glasgow tube train runs off the rails killing 34 passengers.
**(c) A London tube train rams into the end of a dead-end tunnel killing 34 passengers.**

13. Which one of these events actually happened?
**(a) A car bomb attack on a Federal Government building in the United States of America kills nearly one hundred people and injured many more.**
(b) Nearly two hundred people are killed and many more are injured following a gas explosion in a Federal Government building in the United States of America.
(c) More than one hundred people are killed and many others are injured after lightning strikes a Federal Government building in the United States of America.

14. Which one of these events actually happened?
(a) A gravel mountain slips onto a school in Southern Ireland killing many children.
**(b) A slag heap at coal tip collapses on a school in South Wales killing many children.**
(c) Quarry debris collapses on a school in the South of England killing many children.

15. Which one of these events actually happened?
(a) Troops storm the British Embassy in Rome to free hostages.
(b) Civil Guards storm the American Embassy in Madrid to free hostages.
**(c) The SAS storms the Iranian embassy in London to free hostages.**

16. Which one of these events actually happened?
(a) Fourteen people are killed when an explosion rips through a textile plant in England.
**(b) Twenty eight people are killed when an explosion rips through a chemical plant in England.**
(c) Thirty people are killed when an explosion rips through a gas works in England.

17. Which one of these events actually happened?
**(a) John F Kennedy is assassinated during a Presidential visit to Dallas, Texas.**
(b) Lyndon B Johnson is injured in an assassination attempt during a presidential visit to Dallas, Texas.
(c) John F Kennedy is injured in an assassination attempt during a Presidential visit to Chicago, Illinois.

18. Which one of these events actually happened?
(a) The Premier of France is forced to resign following the Westgate scandal.
(b) After the accusations of the Westpoint affair, the Prime Minister of Canada is forced to resign.
**(c) As a result of the Watergate scandal, the US president is forced to resign.**

19. Which one of these events actually happened?
(a) British stockbroker based in Hong Kong carries out dealings that result in the collapse of a major bank.
**(b) British stockbroker based in Singapore carries out dealings that result in the collapse of a major bank.**
(c) British stockbroker based in Bombay carries out dealings that result in the collapse of a major bank.

20. Which one of these events actually happened?
(a) A train carrying radiation waste crashes into a French school killing many children.
(b) An atomic weapon establishment in England catches fire resulting in many deaths.
**(c) A radiation leak at a power station kills many in the Soviet Union.**

21. Which one of these events actually happened?
**(a) The Russians shoot down an American spy plane and capture the pilot.**
(b) The Russians shoot down a German spy plane and capture the pilot.
(c) A Chinese spy plane is intercepted and shot down by the Russians.

22. Which one of these events actually happened?
(a) A lone knifeman kills fourteen children and their teacher on a school picnic.
**(b) In a school gym, sixteen children and their teacher are killed by a lone gunman.**
(c) Sixteen children and their teacher are killed in an explosion in a village school.

23. Which one of these events actually happened?
(a) £2.5 million worth of jewellery is stolen from an aeroplane at Heathrow airport.
(b) £2.5 million is stolen from the QE2 in Southampton.
**(c) £2.5 million is stolen from a Royal Mail train in Cheddington, Buckinghamshire.**

24. Which one of these events actually happened?
(a) Two IRA gunmen are surrounded by police in a siege in Haze Street, Brighton.
**(b) Four IRA gunmen are surrounded by police in a siege in Balcombe Street, London.**
(c) A siege in Regent's Street, London ends when police arrest four IRA gunmen.

25. Which one of these events actually happened?
**(a) A bomb brings down a jumbo jet over Lockerbie, killing all on board and some on the ground.**
(b) All of the passengers on board a jumbo jet are killed when it crashes down onto the town of Kilmarnock.
(c) A bomb brings down a jumbo jet over Edinburgh, killing all of the passengers and crew.

26. Which one of these events actually happened?
(a) A cut-price air service between London and Sydney is launched by Rupert Murdoch.
**(b) A cut-price air service, run by Freddie Laker, starts operating between London and New York.**
(c) Clive Sinclair launches a new cut-price air service between London and Paris.

27. Which one of these events actually happened?
**(a) A passenger jet belonging to TWA explodes and crashes into the sea shortly after take-off from New York.**
(b) A Lufthansa passenger jet explodes and crashes into the sea shortly after take-off from Paris.
(c) A British Airways passenger jet catches fire and crashes shortly after taking off from New York.

28. Which one of these events actually happened?
(a) At Twickenham, nearly one hundred rugby supporters are crushed to death.
(b) Nearly one hundred spectators at a cricket match at Old Trafford are crushed to death.
**(c) Nearly one hundred football fans are crushed to death at a football stadium in Sheffield.**

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