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Episodic memory and the self in a case of isolated retrograde amnesia

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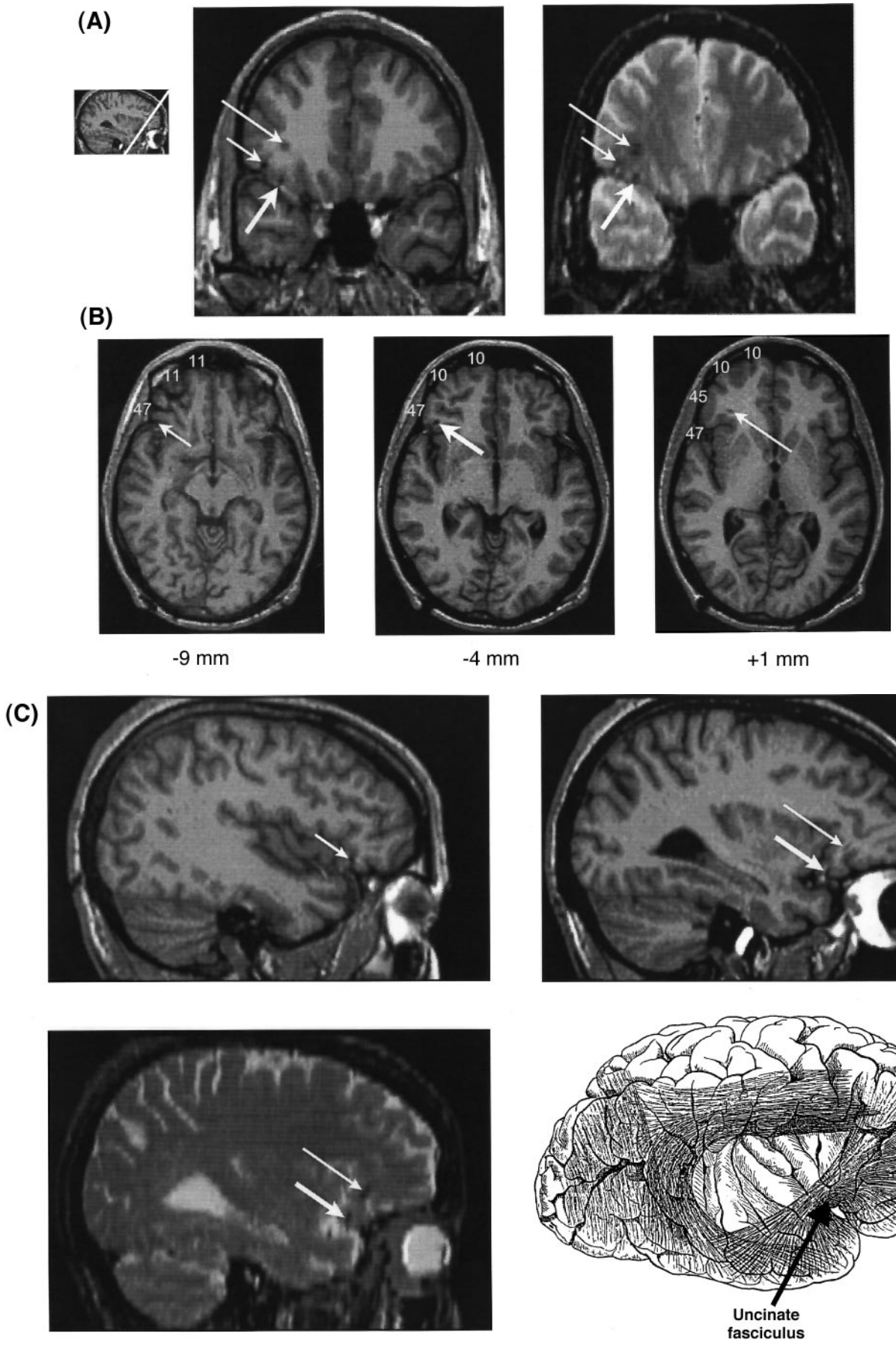
Summary

Isolated retrograde amnesia is defined as impaired recollection of experiences pre-dating brain injury with relatively preserved anterograde learning and memory. We present findings from a patient (M.L.) with isolated retrograde amnesia following severe traumatic brain injury (TBI) that address hypotheses of the inter-relationships of focal neuropathology, episodic memory and the self. M.L. is densely amnesic for experiences predating his injury, but shows normal anterograde memory performance on a variety of standard tests of recall and recognition. The cognitive processes underlying this performance were examined with the remember/know technique, which permits separation of episodic from non-episodic contributions to memory tests by quantifying subjects' reports of re-experiencing aspects of the encoding episode. The results demonstrated that M.L. does not episodically re-experience post-injury events to the same extent as control subjects, although he can use familiarity or other non-episodic processes to distinguish events he has experienced from those he has not experienced. M.L.'s MRI showed damage to the right ventral frontal cortex and underlying white matter, including the uncinate fasciculus, a frontotemporal band of fibres previously hypothesized to mediate retrieval of specific events from one's personal past. Recent functional neuroimaging evidence of an association between right frontal lobe functioning and episodic retrieval demands suggest that M.L.'s memory deficits are related to this focal injury. This hypothesis was supported by right frontal polar hypoactivation in M.L. in response to episodic retrieval demands when he was examined with a cognitive activation $H_2{}^{15}O$ PET paradigm that reliably activated this frontal region in both healthy controls and patients with TBI carefully matched to M.L. (but without isolated retrograde amnesia). He also showed increased left inferomedial temporal activation relative to control subjects, suggesting that his spared anterograde memory is mediated through increased reliance on medial temporal lobe structures. Re-experiencing events as part of one's past is based on autonoetic awareness, i.e. awareness of oneself as a continuous entity across time. This form of awareness also supports the formulation of future goals and the implementation of a behavioural guidance system to achieve them. The findings from this study converge to suggest that M.L. has impaired autonoetic awareness attributable to right ventral frontal lobe injury, including right frontal–temporal disconnection. Reorganized brain systems mediate certain preserved cognitive operations in M.L., but without the normal complement of information concerning the self with respect to both past and future events.

Keywords: MRI; PET; functional reorganization; amnesia; autonoetic awareness

Abbreviations: ERP = event related potential; FDG = fluorodeoxyglucose; HERA = hemispheric encoding–retrieval asymmetry; PTA = post-traumatic amnesia; rCBF = regional cerebral blood flow; R/K = remember/know; SPM = statistical parametric mapping; TBI = traumatic brain injury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Introduction

Amnesia following brain damage is typically characterized by a deficit in the acquisition and retention of new information (anterograde amnesia). Impaired recall of information acquired prior to the onset of the damage (retrograde amnesia) has traditionally been observed in the context of anterograde amnesia attributable to medial temporal or diencephalic damage (Squire and Alvarez, 1995), and is nearly always less severe than anterograde amnesia. In the past two decades, the opposite pattern, referred to as focal or isolated retrograde amnesia, has been reported in patients without medial temporal/diencephalic pathology (N. Kapur, 1993).

The semantic–episodic distinction (Tulving, 1972, 1983) provides a useful framework for conceptualizing differences in patterns of retrograde amnesia (Cermak, 1985). Semantic impairment (i.e. deficient factual knowledge about the world or oneself) is usually assessed with materials that received wide exposure in the patient's culture prior to the injury, such as famous faces or events. Many isolated retrograde amnesia patients show deficits for such information (e.g. N. Kapur *et al*., 1986, 1989, 1992; O'Connor *et al*., 1992; Calabrese *et al*., 1996; Mattioli *et al*., 1996). However, these patients' semantic knowledge, especially factual knowledge pertaining to their own past, can be improved through re-exposure to the information (O'Connor *et al*., 1992; De Renzi and Lucchelli, 1993; Brown and Chobor, 1995; Hokkanen *et al*., 1995; N. Kapur *et al*., 1996; Kroll *et al*., 1997). Episodic impairment (i.e. inability to recollect past episodes from a specific place and time prior to the injury), although harder to quantify, is more prominently impaired in isolated retrograde amnesia patients, and is more resistant to improvement. Even when patients learn and retain information about personal past events, they consistently report an inability to re-experience these events as part of their own subjective past; the events may just as well have happened to someone else (Goldberg *et al*., 1981; N. Kapur *et al*., 1992, 1996; De Renzi and Lucchelli, 1993; De Renzi *et al*., 1995; Hunkin *et al*., 1995; Mattioli *et al*., 1996; Kroll *et al*., 1997). Similar qualitative reports are noted for amnesic patients with combined anterograde and retrograde deficits (Cermak and O'Connor, 1983; Tulving *et al*., 1988; Hodges and McCarthy, 1993).

Given the relatively selective nature of episodic memory impairment in isolated retrograde amnesia, these cases provide a unique opportunity to investigate the neuroanatomical correlates of episodic memory dysfunction. In this paper, we report findings from structural neuroimaging, functional neuroimaging and cognitive psychological testing in a case of isolated retrograde amnesia with a unique and potentially illuminating lesion localization. We investigated two issues: (i) the neuropathology of isolated retrograde amnesia and (ii) the processes supporting preserved anterograde mnemonic function in isolated retrograde amnesia.

Neuropathology of isolated retrograde amnesia

No single lesion has accounted for the spectrum of isolated retrograde amnesia syndromes. Medial temporal and diencephalic structures, while associated with retrograde amnesia (Butters and Stuss, 1989; Hodges and McCarthy, 1993; Squire and Alvarez, 1995; Nadel and Moscovitch, 1997), are more strongly associated with anterograde amnesia; cases of isolated retrograde amnesia are not characterized by damage in these regions. Most cases of isolated retrograde amnesia are precipitated by either traumatic brain injury (TBI) or herpes simplex encephalitis, suggesting that multifocal lesions are necessary (Damasio, 1989; Markowitsch, 1995; N. Kapur, 1997). Critical locations for the focal lesions have included the anterior temporal lobes, frontal lobes and posterior regions.

The anterior temporal region, which receives input from every sensory association area as well as from limbic nuclei, is considered 'integration' cortex involved in the cataloguing of multimodal memory traces (Damasio *et al*., 1985; Markowitsch *et al*., 1985) and a convergence zone important in triggering cortical representations (Penfield, 1975; O'Connor *et al*., 1992; Markowitsch *et al*., 1993*a*; N. Kapur, 1997). While isolated retrograde amnesia is more likely to result from bilateral anterior temporal lesions (N. Kapur *et al*., 1996), there is evidence in favour of hemispheric specificity of anterior temporal functional representation of remote memory (Kopelman, 1993). Patients with left anterior temporal lesions have impaired knowledge of historical events, famous faces and other semantic information (De Renzi *et al*., 1987; Barr *et al*., 1990; Tranel, 1991; Leplow *et al*., 1997), whereas many patients with retrograde amnesia for episodic autobiographical information have anterior temporal damage that is right-lateralized, or bilateral with more damage on the right (N. Kapur *et al*., 1992; O'Connor

Fig. 1 M.L.'s right inferior frontal lesions appear as three hypointensities on T_1- and T_2-weighted MRI. Each lesion is depicted in three planes, each lesion marked with a different sized arrow. (**A**) Oblique coronal slices through the lesioned area. The T_1-weighted image is on the left, and the T_2-weighted image (reconstructed from axial slices) is on the right. The angle of the slices (35° from the coronal plane perpendicular to the AC–PC line) is shown in the small schematic diagram. (**B**) Axial T_1-weighted images. The right side of the brain is depicted on the left side of the image. Numbers indicate Brodmann areas. The measurements below each image give the distance in millimetres from the AC–PC line. (**C**) Sagittal views through the lesioned area. The upper two figures are T_1-weighted images, and the lower left figure is a T_2-weighted image (reconstructed from axial slices and through the same plane as the upper right figure). In the lower right is a depiction of white matter pathways, including the uncinate fasciculus, illustrated on the lateral cortical surface, from Déjérine (1895), Vol. 1, p. 757. The figure has been reversed from the original to correspond to the right hemisphere.

et al., 1992; Markowitsch *et al*., 1993*b*; Calabrese *et al*., 1996; Kroll *et al*., 1997).

The presence of frontal damage in cases of isolated retrograde amnesia (O'Connor *et al*., 1992; Markowitsch *et al*., 1993*a*; Brown and Chobor, 1995; Calabrese *et al*., 1996; Kroll *et al*., 1997) is consistent with the involvement of the frontal lobes in the performance on memory tasks that stress strategic processing of contextual information (Schacter, 1987; Petrides, 1989; Stuss *et al*., 1994*b*), including tasks of remote memory (Kopelman, 1991; Della Sala *et al*., 1993; Mangels *et al*., 1996*a*). Furthermore, the right frontal involvement in these cases would be predicted by functional neuroimaging evidence of preferential involvement of the right prefrontal cortex in episodic retrieval (for reviews, see Nyberg *et al*., 1996*a*; Fletcher *et al*., 1997). The presence of anterior temporal pathology in most of these cases, however, suggests that frontal pathology is not sufficient to cause isolated retrograde amnesia. It is more likely that disrupted frontal–temporal interaction is involved, a hypothesis supported by a $H_2{}^{15}O$ PET study in which recollection of episodes from healthy subjects' personal past was specifically associated with right anterior temporal, insular and ventral frontal activation (Fink *et al*., 1996; see also Tulving, 1989; Andreasen *et al*., 1995). The uncinate fasciculus (Ebeling and von Cramon, 1992) (see Fig. 1), providing a direct, reciprocal anterior-temporal–inferior-frontal connection, is considered critical to this process (Markowitsch, 1995).

Several researchers have suggested an association between retrograde amnesia and damage to posterior regions, including inferior temporal, parietal and occipital regions (O'Connor *et al*., 1992; Ogden, 1993; Hunkin *et al*., 1995; Eslinger *et al*., 1996). These findings have been interpreted within a framework of interaction between primary, first-order and higher-order association cortices advanced by Damasio (1989). This theory states that recollection requires a pattern of firing similar to that which occurred when an event was originally perceived. Damage to posterior regions could disrupt unimodal input (e.g. a visual image) to convergence zones (association areas), interrupting networks of activation normally involved in recollection (Ogden, 1993).

Preserved anterograde mnemonic functioning in isolated retrograde amnesia

A second major issue in isolated retrograde amnesia is the apparent paradox that processes operating successfully on retrieval of newly learned information cannot be used to retrieve information pre-dating the injury. It is unlikely that nature would evolve separate systems for long-term retrieval that are differentially affected by neurological disease: one that operates on post-injury information and another on pre-injury information. Rather, recovery from brain injury most probably involves functional reorganization in which spared cerebral mechanisms participate in recovery from, or compensation for, cognitive deficits (Heiss *et al*., 1993; Engelien *et al*., 1995; Weiller *et al*., 1995; Buckner *et al*., 1996). In cases of isolated retrograde amnesia following brain injury, anterograde mnemonic processes may be supported through a re-organized system, but recollection of remote events formerly mediated through lesioned pathways remains disrupted (Hodges and McCarthy, 1993; Markowitsch, 1995; N. Kapur *et al*., 1996).

Some evidence in favour of this hypothesis comes from an early ^{133}Xe study of regional cerebral blood flow (rCBF) responses during retrieval activation in a patient with left medial temporal pathology who had recovered from anterograde amnesia but had persistent temporally graded isolated retrograde amnesia (Wood *et al*., 1980*a*). In response to an anterograde recognition memory task, healthy subjects showed bilateral occipital rCBF suppression that was hypothesized to be inversely related to hippocampal flow (Wood *et al*., 1980*b*). In contrast, the patient, whose performance was normal, showed occipital suppression only on the right side. It appeared that her recovered anterograde memory performance was mediated by the intact (right) hippocampus without any contribution from the left hippocampus.

Functionally reorganized mediation of test performance following brain damage should affect the underlying cognitive processes, even if it is not reflected in the test performance itself. In addition to the above rCBF study, behavioural evidence of altered anterograde mnemonic functioning comes from case studies of isolated retrograde amnesia in which standard memory tests were supplemented with tests at delay intervals of up to 6 weeks (O'Connor *et al*., 1992; De Renzi and Lucchelli, 1993; Maravita *et al*., 1995; N. Kapur *et al*., 1996). In each case, there was disproportionate impairment at the longer delay intervals relative to performance at the standard delay intervals, suggesting a process of accelerated forgetting that was not detected by the standard tests.

If anterograde mnemonic processes are impaired in isolated retrograde amnesia, then how do isolated retrograde amnesia patients perform standardized 'episodic' memory tests? The explanation may lie in the multifactorial nature of these tests. In healthy adults, both episodic and non-episodic mnemonic systems contribute to test performance. Chief among the non-episodic systems is semantic memory, although other non-conscious systems can be involved (e.g. perceptual priming and procedural memory). In patients with isolated retrograde amnesia and impaired episodic memory, performance can still be achieved through semantic or other non-episodic processes. While these different processes cannot be directly assessed through behaviour, their contribution to test performance can be estimated with the remember/know (R/K) technique (Tulving, 1985; Gardiner, 1988). This technique can be applied to any memory test. Each time an item from a previously studied list is recalled or recognized, subjects classify the item as 'R' or 'K' according to their subjective mnemonic experience associated with the item. 'R' responses are assigned to items that are associated with episodic recollection of an aspect of the

encoding episode (e.g. something they thought about, saw or heard when the item was presented). Items recalled or recognized without recollection of something specific from the encoding episode are classified as 'K'. As 'R' responses correspond to re-experiencing aspects of the encoding episode, they provide a more specific measure of episodic memory than do simple recall or recognition.

Consistent with the hypothesized relationship between the frontal lobes and episodic memory (Tulving, 1985; Stuss, 1991*b*; Wheeler *et al*., 1997; Stuss *et al*., 1998), R responses are specifically associated with frontal lobe functioning (Parkin and Walter, 1992; Düzel *et al*., 1997). In individuals with frontal pathology and impoverished episodic memory, normal test performance may be attained on the basis of intact semantic memory or other non-episodic processes, without the phenomenal experience of remembering (Tulving, 1985; see also Parkin and Walter, 1992; Huron *et al*., 1995). This reliance on non-episodic processes could account for the relatively preserved anterograde learning in patients with isolated retrograde amnesia and would predict that these patients experience a lack of subjective connection to the products of their anterograde learning.

Episodic memory entails autonoetic ('self-knowing') awareness, i.e. the awareness of oneself as a continuous entity across time (Tulving, 1985). With regard to past experiences, autonoetic awareness facilitates the knowledge that 'the self doing the experiencing now is the same self that did so at an earlier time' (Wheeler *et al*., 1997: p. 349); it allows one to mentally travel back in time to an earlier experienced event. As will be elaborated later, episodic memory is but one manifestation of autonoetic awareness, which also affects one's management of future events (i.e. personally-relevant plans, goals and expectations). Semantic memory, on the other hand, entails noetic awareness, a more general capacity for awareness of knowledge derived from familiarity or other implicit information that can occur in the absence of mentally re-experiencing the encoding episode (Tulving, 1985; Wheeler *et al*., 1997). We suggest that the episodic impairment in patients with isolated retrograde amnesia and right frontal dysfunction arises from a deficit in autonoetic awareness.

Summary

The neuropathological substrate of isolated retrograde amnesia has not been precisely delineated. Cases with documented lesions have frontal, anterior temporal or posterior (inferior temporal, parietal or occipital) damage in the context of multifocal injury. Clearly, there is heterogeneity in both lesion configuration and behavioural deficits in patients with retrograde amnesia (N. Kapur, 1997). In this paper, we focus on retrograde amnesia specific to episodic memory for autobiographical events pre-dating the injury that has been linked to right anterior temporal/ventral frontal damage.

By definition, isolated retrograde amnesia patients have relatively preserved anterograde memory test performance, but several reports indicate abnormalities in their anterograde mnemonic processes as evidenced by altered retrieval-related rCBF or accelerated forgetting. We propose that the episodic memory deficit in patients with isolated retrograde amnesia following right frontal/temporal damage is attributable to a deficit in autonoetic awareness. As such, it is not limited to events pre-dating the injury, but is also present for events encountered after recovery has taken place. We further propose that patients' intact anterograde memory test performance is accomplished through reliance on non-injured neurocognitive systems served by noetic awareness. The effects of reliance on these systems in the absence of episodic recall should be observable through patients' subjective reports, quantified with the R/K technique.

Patient M.L.

We present a case of severe TBI with isolated retrograde amnesia (patient M.L.) in which neuropathology and mechanisms of new learning were analysed with structural and functional neuroimaging as well as the R/K technique. There are several features that make this case unique. Because M.L. was enrolled in a separate study on the acute effects of TBI (Schwartz *et al*., 1998), he was followed by us from the date of injury and his injury severity and acute recovery characteristics were meticulously documented. Although M.L. had a very severe brain injury, he made a good neuropsychological recovery, including good performance on anterograde learning tests in spite of his significant isolated retrograde amnesia. To examine the neuroanatomical correlates of M.L.'s behaviour, an MRI was done with gradient echo, spin echo and 3D T_1-weighted sequences. The main site of damage was in the right ventral frontal cortex and white matter, including the uncinate fasciculus, making him a good candidate to test the frontal–temporal disconnection hypothesis in isolated retrograde amnesia.

Considering previous research on the role of the right frontal lobe in episodic retrieval (Milner *et al*., 1985; Tulving *et al*., 1994; Fink *et al*., 1996; Nyberg *et al*., 1996*a*; Schacter *et al*., 1996*b*) and the location of M.L.'s lesion, we predicted that he would show right frontal dysfunction relative to control subjects in response to anterograde episodic retrieval tasks. We tested this hypothesis using $H_2{}^{15}O$ PET paradigms that were previously shown to elicit a specific pattern of left and right frontal rCBF activations during episodic encoding and retrieval, respectively (S. Kapur *et al*., 1996; Cabeza *et al*., 1997), a pattern known as HERA (Hemispheric Encoding/Retrieval Asymmetry; Tulving *et al*., 1994).

If M.L.'s right frontal contribution to anterograde learning tasks is impoverished, task performance must be mediated through a preserved neural system involved in memory. A likely candidate would be the medial temporal lobe memory system (Squire and Zola-Morgan, 1991) which is activated in association with successful retrieval of recently learned verbal information (Grasby *et al*., 1993; Nyberg *et al*., 1996*b*;

Schacter *et al*., 1996*a*; Rugg *et al*., 1997). Left lateralization of this effect would be predicted on the basis of the verbal materials in our PET task, on the lateralization of the previous medial temporal PET findings and on the right frontal–temporal disconnection in M.L.

Finally, we attempted to dissociate the impaired and spared aspects of M.L.'s anterograde memory processes with the R/K technique, where we predicted low R responses in comparison with control subjects (reflecting impaired episodic memory and autonoetic awareness), without a deficit in K responses (reflecting spared semantic and other non-episodic processes corresponding to noetic awareness).

Case report

Background information

M.L. completed high school and 3 years of technical training in electronics. Developmental history was normal and there was no history of learning problems; he was an average to high-average student. He worked in various sales and service positions. At the time of his injury, he had been selling high-technology factory automation equipment for 2 years and was the top-rated salesperson in his company. M.L. was an active hobbyist and athlete, competing at the regional level in wine-tasting, running and bicycling.

Apart from a left shoulder injury from a bicycling accident in 1992, he was previously healthy. There was no reported history of psychiatric disorders or substance abuse in M.L. or his family. He was married in 1987. At the time of his accident in 1993, he had a 2-year-old daughter and his wife was pregnant with his son. He is right-handed with no history of left-handedness in his immediate family.

Injury characteristics

In June 1993, M.L. sustained a severe TBI when he was struck by a car while cycling. His Glasgow Coma Scale score (Teasdale and Jennett, 1974) at the scene of the injury was 10 (of 15), and it deteriorated to 3 upon hospital admission, and was 7.5 at 6 h (pro-rated due to intubation). Additional injuries included a small left pneumothorax, left shoulder lacerations and possible spine subluxation. Serial CTs were classified according to criteria specified by Marshall *et al*. (1992). The initial head CT carried out upon hospital admission was normal. On the sixth day post-injury, CT showed a small subdural haematoma along the falx and right tentorium, small left inferior posterior temporal contusions, small right frontal lobe contusions, mild diffuse oedema and small bifrontal subdural hygromas. He remained unconscious (Glasgow Coma Scale score <8) for 6 days; this coma was followed by 1 week of delirium and agitation. After 33 days, he was discharged to a rehabilitation hospital.

During hospitalization, post-traumatic amnesia (PTA) was being assessed daily with the Galveston Orientation and Amnesia Test (Levin *et al*., 1979). M.L.'s score was 69 on day 32 and 95 on day 33 (maximum score = 100). Therefore, by the criterion of two consecutive Galveston Orientation and Amnesia Test scores of $\geqslant 75$ (Levin *et al*., 1979), M.L. was still in PTA at the time of discharge. Thus, we conservatively place M.L.'s PTA duration at 34 days.

Recovery

In the rehabilitation hospital, M.L. received in-patient speech, occupational, psychological and physical therapies for 10 weeks. In the early phases of this rehabilitation, confabulation was observed. For example, the day after walking to the hospital's patio for the first time, M.L. claimed he had just walked to Lake Ontario, several kilometres away.

M.L.'s retrograde amnesia was apparent immediately upon his recovery of consciousness, when he did not recognize family members or friends. During the post-acute phase, he incorrectly reported aspects of his personal past. Initially, this retrograde amnesia was observed in the context of a generalized retrieval deficit including impairment in semantic knowledge. For example, he did not appreciate the significance of his wife's physical appearance of advanced pregnancy. Object naming was impaired (Boston Naming Test score = 40) and he made gross grammatical and spelling errors in writing. Through rehabilitation and aggressive efforts of his own (e.g. recording unfamiliar words in a notebook and looking up their definitions), M.L.'s semantic deficits recovered and he re-learned significant facts of his own past, but his ability to re-experience events pre-dating the injury showed little change. To date (4 years and 8 months post-injury), his recall of events from his personal past has been limited to a handful of fragmented images, not specific in time or place, with no temporal gradient.

Upon his return home, M.L.'s judgement errors necessitated supervision. He has had considerable difficulty understanding and executing his responsibilities as a parent (e.g. allowing his children to play in dangerous situations). Over time, he has taken on increased parenting responsibilities by applying structured routines with the help of his wife. At the time of this writing, he was acting as 'house-husband.' Although he was unable to resume his former sales position, his employer gave him a part-time trial with reduced responsibilities. This trial failed due to fatigue and difficulty managing the long commuting distance. He has pursued volunteer positions, but has not secured paid employment.

Apart from retrograde amnesia, persistent symptoms have included impaired sensory functioning in his right knee, sleep maintenance difficulties, absence of hunger/thirst sensations and fatigue. Socially, he reported difficulty knowing how to behave around family members and friends, and had to be taught socially acceptable behaviour. His wife noted that he has retained little of his former outgoing personality. Furthermore, in spite of his normal performance on standard memory tests, M.L. reported a feeling of subjective distance from recall of events occurring after his recovery.

M.L.'s pre-morbid personality, injury characteristics and

recovery pattern are inconsistent with 'functional' or 'psychogenic' retrograde amnesia (Schacter *et al*., 1982; Kopelman, 1995; Markowitsch, 1996). Nevertheless, a psychogenic contribution to M.L.'s behaviour was probed with a sodium amytal interview. While this procedure had no permanent effect on his memory disorder, during the interview M.L. described some events that were previously lost to him. In response to very general prompts or prompts about life periods, he recalled two events from high school as well as a visit by some friends that occurred during PTA. He was also prompted with five highly emotional events from his life that had not been discussed with him since the injury. Of these, two were recognized and elaborated upon by M.L. He had no recognition of the other three.

The pre-injury events recalled during the sodium amytal interview, like the other scattered pre-injury events that he has spontaneously recalled, were lacking in temporal, spatial and emotional contextual information. In particular, he was unable to describe what his emotional reactions were at the time of these events, even though they were of a highly emotional nature (e.g. a friend's death). Therefore, the evidence of a positive sodium amytal abreaction was at best partial in that few events were retrieved, and several highly significant events were not recognized. Furthermore, it highlighted M.L.'s inability to re-experience the events that he does recall.

Neurological examination

Apart from impaired position sense and numbness in his right leg and generally brisk reflexes, neurological examination was normal. Due to visual complaints, a neuro-opthamological consultation was sought (in August 1995). The Humphrey automated visual field showed a subtle upper right quadratic defect, greater for the right eye than for the left eye. The examination was otherwise normal.

Clinical scans

An early 1994 ^{99m}Tc-HMPAO (hexamethylpropyleneamine oxime)-SPECT (single-photon emission computed tomography) scan showed left superior medial parietal hypoperfusion, but this resolved in a repeat SPECT scan conducted 1 year later. A late 1994 [^{18}F]fluorodeoxyglucose (FDG)-PET study of resting glucose metabolism was normal. Brain MRI with gradient echo, spin echo and 3D T_1-weighted sequences showed several foci consistent with post-acute severe TBI. The largest area of damage was in the right ventral frontal cortex and white matter, although there were other smaller foci. These findings are described in detail below.

Neuropsychological assessment

In our August 1994 assessment, basic neuropsychological functions had recovered, including anterograde memory; intellectual testing indicated abilities in the average to high-average range (see Table 1). There was evidence of a relative deficit on tests of visuoperceptual and visuomotor processes, a finding also noted on previous clinical neuropsychological evaluations. While his performance on several tests was most probably influenced by prior assessments, we also administered tests developed in our laboratory to which M.L. had not been previously exposed. Most notably, his performance on all measures from a word list learning task sensitive to frontal dysfunction (Stuss *et al*., 1994*a*) was normal, as were performances on tests of conditional associative learning (Levine *et al*., 1997) and conceptual processing (Levine *et al*., 1995), both experimental tests of executive functioning associated with the frontal lobes. The only test in our battery on which M.L. was significantly impaired was a strategy application measure modelled on Shallice and Burgess's Six-Element Task (Shallice and Burgess, 1991; Levine *et al*., 1998). This test consists of a large number of simple 'paper and pencil' tasks (e.g. naming common objects), some of which have a high payoff and others which do not. Subjects learn the basic constraints of the test and are told values of the items, but they must decide how to budget their time to maximize points. Although M.L. learned the rules and could do the items, he approached the whole test in a sequential manner, doing items indiscriminately without respect to their value. Whereas the mean ($\pm$ SEM) proportion of high payoff items completed by 20 TBI control subjects (friends and family members of TBI subjects) was 0.81 ± 0.042 (Levine *et al*., 1998), M.L.'s proportion was only 0.21.

On the Autobiographical Memory Interview (Kopelman, 1994), M.L. achieved near maximum scores for personal semantic information, but recall of autobiographical events (episodes) was impaired for childhood and early adult periods. Recent autobiographical event recall was normal, but limited to post-injury events. Similarly, nearly all events recalled in response to cue words (Crovitz and Schiffman, 1974) had occurred <1 month prior to testing.

A vocational assessment conducted in August 1995 was notable for scores on mechanical comprehension, electronics and arithmetic knowledge which were uncharacteristically low for someone with M.L.'s technical background. He could not, for example, complete algebraic equations.

Summary

M.L. sustained a severe TBI. Following an extended post-traumatic amnesia, he had a generalized retrieval deficit for semantic knowledge (both personal and non-personal) and autobiographical episodes. Over time, his retrograde amnesia was isolated to episodes from his personal past, although there was evidence of residual retrieval deficits for some semantic information (i.e. complex arithmetic or mechanical knowledge). Neuropsychological deficits were limited to subtle visuomotor and visuoperceptual problems and a low score on a novel test of strategy application. Neurological

Table 1 *Neuropsychological testing in M.L. at 14 months post-injury**

Subtest/response measure	Score
WAIS-R	
Information	11
Digit Span	10
Vocabulary	12
Picture Completion	8
Block Design	9
Digit Symbol	11
NAART-R	
Estimated IQ	108
WMS-R	
Mental Control	6 (of 6)
Logical Memory—Immediate	41 (of 50)
Logical Memory—Delayed	37 (of 50)
Verbal Paired Associates—Immediate	19 (of 24)
Verbal Paired Associates—Delayed	8 (of 8)
Verbal Memory Index	128
Visual Reproduction—Immediate	40 (of 41)
Visual Reproduction—Delayed	40 (of 41)
Word List Learning	
Uncategorized	38 (of 64)
Unblocked categorized	47 (of 64)
Blocked categorized	61 (of 64)
Recognition—Immediate	21 (of 24)
Recognition—Delayed	24 (of 24)
Autobiographical Memory Interview	
Personal semantic—childhood	18 (of 21)
Personal semantic—early adult life	19 (of 21)
Personal semantic—recent life	21 (of 21)
Autobiographical incidents—childhood	3 (of 9)
Autobiographical incidents—early adult life	2 (of 9)
Autobiographical incidents—recent life	8 (of 9)
Crovitz Cue-Word Test	
Unprompted	24 (of 36)
Prompted	33 (of 36)
Boston Naming Test	
Number correct	56 (of 60)
Verbal Fluency	
Letter (F, A and S, 60 s each)	47
Grocery list (60 s)	24
Trail Making	
Part A	33 s, 0 errors
Part B	54 s, 0 errors
Stroop Interference Procedure	
Word reading	50 s, 0 errors
Color naming	60 s, 0 errors
Interference	96 s, 3 errors
Wisconsin Card Sorting Test (WCST)	
Categories	9
Perseverative errors	14
Set loss	0
Conditional Associative Learning	
Correct first responses	30 (of 32)
Concept Generation	
Correctly named groupings	5 (of 6)
Repetitions	0
Strategy Application	
Efficiency Score	0.21

Note. All tests administered in standard format as described by Spreen and Straus (1991) with the following exceptions: Word list learning (Stuss *et al*., 1994*a*), Autobiographical Memory Interview (Kopelman, 1994), Crovitz cue-word test (Moscovitch and Melo, 1997; autobiographical events only), WCST (Milner, 1964; all 128 cards administered), Stroop Interference Procedure (Stuss, 1991*a*), Conditional Associative Learning (Levine *et al*., 1997), Concept Generation (Levine *et al*., 1995), Strategy Application (Levine *et al*., 1998). See text for test score interpretations. *The Autobiographical Memory Interview and Crovitz cue word test were administered at 3 years post-injury.

examination indicated altered sensory functioning in the right leg and a subtle right upper quadrantanopsia. There was neuroimaging evidence of cortical and subcortical lesions consistent with TBI sequelea, most prominently in the right ventral frontal lobe.

Methods

Subjects

Two groups of subjects served as controls for the PET and behavioural studies. M.L.'s activation PET data were compared with data from 12 subjects in previous studies of the functional neuroanatomy of verbal encoding (S. Kapur *et al*., 1996) and retrieval (Cabeza *et al*., 1997) (see Table 2). To control for the effects of TBI, we also applied the PET paradigm to four TBI subjects (with no significant retrograde amnesia), matched as closely as possible to M.L. for age, education, TBI severity, recovery as measured by standard neuropsychological tests and time since injury (Subjects 1–4 in Table 2). A fifth TBI control subject was used for the R/K testing, but not the PET study (Subject 5 in Table 2). TBI control Subject 1 did not participate in the R/K testing.

MRI

In order to achieve precise lesion localization information in M.L. and to localize PET activations in M.L. and the TBI control subjects, these subjects were scanned with a 1.5-T MR system (Signa version 4.7, General Electric). A sagittal T_1-weighted 3D volume technique produced 124 1.3-mm slices [repetition and echo times (TR and TE) were 35 and 5 ms, respectively, flip angle was 35°, number of excitations (NEX) was 1.0 and a field of view of 22 cm)]. Proton density and T_2-weighted images with a slice thickness of 3 mm were obtained using an interleaved sequence (TR/TE of 3000/30, 80 ms, 0.5 NEX and a field of view of 22 cm). Gradient echo T_2 sequences with a slice thickness of 6 mm were obtained to emphasize haemosiderin deposits (TR/TE of 750/35 ms, flip angle of 20°, 2.0 NEX and a field of view of 22 cm). For M.L., the MRI was conducted 2.4 years post-injury. TBI subjects' MRI scans occurred within 1 month of their PET scans (see Table 2).

Lesion localization on M.L.'s images was accomplished

Table 2 *Subject characteristics*

	Age (years)	Education estimated	IQ*	WAIS-R† Vocabulary	WMS-R verbal memory index	6 h GCS	PTA‡ (days)	Coma§ (h)	TSI¶	Lesions on T_2-weighted MRI
TBI control subjects#										
1	41	10	109	13	123	7.5	21	24	4.4	Small hyperintensity in R inferior frontal lobe white matter
2	24	13	93	11	99	12	2	3	4.1	Small hyperintensities in R frontal lobe white matter, R parietal lobe, L frontal lobe, and L cerebellum
3	29	17	104	11	111	3	23	48	3.9	Small hypo-intensities in R and L superior frontal lobe
4	23	12	105	12	107	11	23	32	3.9	L temporal lobe polar encephalomalacia. Small hypointensities in bilat inferior frontal lobe, superior parietal lobe, and splenium
5	28	16	108	12	95	6	28	72	4.3	Large L frontal lobe encephalomalacia
Mean	29	13.6	104	11.8	107	7.9	19	36	4.1	
SD	7	2.9	6	0.8	11	3.7	10	26	0.2	
M.L.	36	14.0	108	12.0	128	7.5	34	128	3.2	See Fig. 1 and text
Healthy control subjects (n = 12)										
Mean	26	17.8	NA	NA	NA	NA	NA	NA	NA	NA
SD	4	2.5	NA	NA	NA	NA	NA	NA	NA	NA

GCS = Glasgow Coma Scale score; GOAT = Galveston Orientation and Amnesia Test; L = left; R = right; NA = not applicable. *As determined by the North American Adult Reading Test–Revised (Spreen and Strauss, 1991). †WAIS–R standard scores. ‡As determined by 2 consecutive days of GOAT scores ⩾75 (Levin *et al*., 1979). §Number of hours with GCS <8. ¶Years from the date of injury to the date of testing. #Subject 1 participated in the PET but not the R/K study. Subject 5 participated in the R/K but not the PET study.

by reformatting the images parallel to the AC–PC (anterior–posterior commmissural) line based on sagittal and axial views of the brain and matching them to the templates of the Talairach atlas (Talairach and Tournoux, 1988) using the Analyze software system (Biodynamic Research Unit, Mayo Foundation, Rochester, Minn., USA).

PET

The activation PET studies were done on a GEMS-Scanditronix PC2048–15B head scanner. M.L. and the TBI control subjects were scanned from 3.3 to 4.4 years post-injury (see Table 2). Eight 60 s scans were performed, separated by an 11 min inter-scan interval and preceded by an injection of 40 mCi of $H_2{}^{15}O$. Stimuli for this study consisted of eight lists of 24 semantically related word pairs (e.g. penguin–tuxedo) presented on a computer screen at a fixed rate of 4 s per pair with a 1 s inter-stimulus interval. During the encoding scans, subjects were instructed to make a mental note of any meaningful relation between the words in each pair and to say the second word aloud. Cued recall was tested during the retrieval scans by presenting the first word of each pair, followed by 'WORD?'. Subjects said the second word of the pair, or said 'Pass' if they could not remember the word.

The study lists for the retrieval scans were presented during the inter-scan interval 1–2 min prior to the retrieval tasks. The instructions for these tasks were identical to those used during the encoding scans. Retrieval of the stimuli presented during the encoding scans was tested at the end of the scanning session.

The TBI subjects and M.L. alternately performed the encoding and retrieval tasks during eight scans, beginning with retrieval. The healthy control subjects performed the encoding and retrieval tasks during four scans (two encoding and two retrieval), counterbalanced with additional reading and recognition conditions that were analysed for other studies (S. Kapur *et al*., 1996; Cabeza *et al*., 1997). In order to increase the number of scans available for encoding and retrieval (thereby increasing the stability of the signal for the small group studies), reading and recognition were not administered to the TBI control subjects and M.L. Therefore, for all subjects, encoding and retrieval served as comparisons for one another.

To correct for inter-scan head movement, subjects' scans were realigned to their first scan using the AIR software (Woods *et al*., 1992). The Statistical Parametric Mapping (SPM) software (Wellcome Department of Cognitive Neurology, London, UK) was used to transform the realigned scans into a standard space (Talairach and Tournoux, 1988) and to smooth them using an isotropic Gaussian kernel of full width at half maximum of 10 mm. The differential effects of encoding and retrieval on rCBF across groups were estimated using ANCOVA (analysis of covariance), with the changes in global counts as covariates (Friston *et al*., 1995). Data were analysed using two-way ANCOVA in SPM as

two studies (healthy control subjects or TBI control subjects versus M.L.), with two conditions (encoding versus retrieval). The threshold for significance in within-study comparisons and interactions was $P < 0.001$ (uncorrected, one-tailed). Localization of activations was accomplished with the assistance of the Talairach and Tournoux atlas (1988) and the Talairach Daemon database server on the World Wide Web (http://ric.uthscsa.edu/projects/talairachdaemon.html).

Region of interest analyses

Several of the PET findings concerned hippocampal activations. Because of the importance of these findings to our predictions, and because of potential problems inherent in localization of small structures on transformed images of patients with brain damage, we confirmed these findings in the TBI control subjects and in M.L. with region-of-interest analyses.

Hippocampal regions of interest were defined anatomically in the coronal plane of the MRIs, resliced with Analyze into 57 slices orientated perpendicular to the long axis of the hippocampus (for details of our methods for defining hippocampal volumes, see Kidron *et al*., 1997; Köhler *et al*., 1998). The regions of interest were transferred to the axial PET images, which had been co-registered to the MRIs (resliced into 57 slices parallel to the long axis of the hippocampus) and averaged for encoding and retrieval. PET counts were taken from the five slices in each subject on which anterior, middle and posterior portions of the hippocampal regions of interest were represented. The data were normalized by dividing by the mean global blood flow for all brain slices. Two analyses of variance (one for the left hippocampus and one for the right hippocampus) were conducted, each with group (M.L. versus TBI control subjects), condition (encoding versus retrieval), subject and slice as factors; condition and slice were treated as repeated measures. The critical effect in these analyses was the interaction between group and condition, indicating different patterns of encoding–retrieval activations in M.L. versus TBI control subjects.

Remember/know judgements

M.L.'s anterograde mnemonic processes were probed with a cued recall and recognition test supplemented by remember/know (R/K) judgements (Tulving, 1985). To assess changes in forgetting rates, recall and recognition testing were conducted in four test sessions spanning 2 weeks from the encoding session. A pool of 264 amusing definitions of single-meaning words (e.g. 'A talkative featherbrain–parakeet'; Tulving and Watkins, 1977; Donnelly, 1988) provided stimuli with high associative value that could be retained over the 2 week interval. Half (132) of these served as targets, and half as distracters. In the encoding session, the target definitions were read aloud twice by the examiner. To promote deep encoding, subjects indicated whether or not each definition made sense to them.

Targets and distracters were randomly assigned to one of four test sessions such that each session employed a list of 66 randomized targets and distracters (33 each). Although these tests were rather lengthy, the extra items increased reliability for the small group study. Test sessions were conducted over the phone at 24 h, 72 h, and 1 week and 2 weeks post-encoding. For each definition, the first part (e.g. 'A talkative featherbrain') was read aloud by the examiner. If the subject completed the definition correctly, credit was assigned for cued recall. If the subject did not correctly complete the definition, the examiner read the second part, and recognition was assessed through subjects' judgements of definitions as old (a target definition from the encoding session) or new (a distracter). Target definitions that were completed by the subject in cued recall were automatically designated as correctly recognized. (It was nearly impossible for subjects to guess the answer to distracter definitions without having heard them before. False recognition of a distracter, however, was quite common among TBI control subjects. These responses were tallied for the purposes of computing recognition accuracy.)

Prior to testing, the R/K distinction was introduced to subjects. The instructions stressed two types of memory. The first type, corresponding to 'remember' judgements, is marked by re-experiencing some aspect of the encoding episode (e.g. the examiner's voice or a mental association the subject might have made upon hearing the definition). The second type, corresponding to 'know' judgements, pertains to familiarity of the definition as old, but without recollection of any aspect of the encoding episode. To avoid the confusion inherent in the terms 'remember' and 'know' the two types of memory were designated as memory type A and B. Therefore, after each item judged as old, subjects indicated whether or not they could mentally re-experience the encoding episode by classifying it as 'memory type A' or 'memory type B.' To ensure that subjects understood the distinction, they were intermittently asked to explain why they made their designations.

All subjects gave informed consent. The studies were approved by the ethics committee of Baycrest Centre for Geriatric Care and a University of Toronto committee.

Results

MRI

A cluster of hypointensities in the right ventral frontal cortex and white matter was visible on both the T_1- and T_2-weighted images (see Fig. 1). The presence of hypointensities on the T_1-weighted images indicates actual loss of brain tissue, as opposed to just the presence of haemosiderin deduced from T_2-weighted images. Two hypointensities were at the ventrolateral cortical surface of the inferior frontal gyrus (Brodmann area 47) and extended into white matter. The

third was in white matter deep to frontal cortex. Comparison with white matter pathway maps (Déjérine, 1895; Talairach and Tournoux, 1988) (see Fig. 1) suggests interruption of the ventral frontal aspect of the right uncinate fasciculus.

As expected with severe TBI, there were additional pathological foci, although none were of similar size to the right ventral frontal damage. Most appeared as hypointensities on T_2 and gradient echo images and were indicative of haemosiderin deposits. These were noted in the genu of the left anterior internal capsule, bilaterally at the cortical–subcortical junction in the posterior superior frontal lobes and bilaterally in the occipital lobes. Additionally, a small hyperintense lesion was noted in the white matter deep to the left frontal lobe on the T_2-weighted images. The full MRI will be made available electronically to readers upon request.

While there were no lesions in medial temporal lobe structures, we sought confirmation of the integrity of these structures through volumetric analyses (Kidron *et al*., 1997; Köhler *et al*., 1998). This was accomplished by computing the volumes of the left and right hippocampi, parahippocampal gyri and amygdalae by planometric tracing of coronal slices on MRI, and comparing these volumes with those from an age-matched (33-year-old) healthy control subject. As seen in Fig. 2, the volumes of M.L.'s medial temporal lobe structures are normal.

PET

Behavioral data

Performance on the PET cued-recall task for healthy control subjects (from S. Kapur *et al*., 1996; Cabeza *et al*., 1997), TBI control subjects and M.L. is summarized in Table 3. Performance was broadly consistent across subjects, suggesting that the task was within their abilities. In particular, it is noted that M.L.'s performance was not impaired. In comparison with the healthy control subjects, the TBI control subjects showed a non-significant decline in recall during the retrieval scans.

Imaging data

In the earlier studies of the healthy subjects, a reading condition served as a baseline for encoding and retrieval (S. Kapur *et al*., 1996; Cabeza *et al*., 1997). In the following analyses, encoding was used as a comparison for retrieval and vice versa. Before interpreting the results from patient M.L. and the TBI subjects, we verified that the pattern of activations previously reported for encoding and retrieval held when the data from healthy control subjects were re-analysed (with encoding and retrieval serving as comparisons for one another).

For the sake of comparison with the above analyses and completeness, we next report M.L.'s encoding/retrieval differences. It is more appropriate, however, to analyse differences in M.L.'s and healthy control subjects' encoding/retrieval differences as interactions within a single design (Friston *et al*., 1995). These interactions, which indicate regions in which the pattern of M.L.'s encoding/retrieval activations were statistically different from those of control subjects, are reported next. These are followed by replication of the critical findings with TBI control subjects. Finally, regions-of-interest analyses of the hippocampal activations are reported.

Replication of previous results in healthy control subjects. Consistent with prior research (Tulving *et al*., 1994; Nyberg *et al*., 1996*a*), encoding was associated with left frontal activation and retrieval was associated with right frontal activation (see Table 4). In the encoding/retrieval comparison (Table 4, top), the maximum of the left inferior frontal activation was within 10 mm of that reported for the encoding/reading comparison in the same subjects (S. Kapur *et al*., 1996). Also activated were lateral temporal regions bilaterally, right occipital and parahippocampal regions, the right cerebellum and the right inferior parietal lobe. In the retrieval/encoding comparison (Table 4, bottom), the maximum of the right inferior frontal activation was also within 10 mm of the previously reported peak (Cabeza *et al*., 1997). Additionally, we found a large right superior frontal/anterior cingulate activation. The thalamic, striatal and brainstem activations found here were also noted in the earlier report, although our striatal findings were on the left, whereas the previous ones were on the right. In contrast to the previous report, our retrieval/encoding comparison yielded right temporal-parietal, left insular and posterior cingulate activations. The correspondence of these findings with those reported previously (S. Kapur *et al*., 1996; Cabeza *et al*., 1997) indicates that it is reasonable to predict the HERA pattern when encoding and retrieval are used as comparisons for one another.

Encoding/retrieval differences for patient M.L. M.L.'s encoding/retrieval activations were similar to those of control subjects, although more posterior (see Table 5, top). Left anterior activations were found in the precentral/postcentral gyri and the insular cortex. Right occipital and cerebellar activations were noted, as was a small left middle temporal gyrus activation.

In contrast to the healthy control subjects' pattern of right lateralized retrieval/encoding activations (see Table 4, bottom), M.L.'s retrieval/encoding activations were left-lateralized (see Table 5, bottom). Although there were small right inferior frontal activations, the most prominent activations were in the left cuneus, the left cerebellum and the left anterior cingulate gyrus.

Qualitative comparison of healthy control subjects' and M.L.'s encoding/retrieval differences (i.e. comparison of Tables 4 and 5) suggests that the expected frontal hemispheric encoding/retrieval asymmetry is attenuated in M.L. As noted above, however, this comparison is more appropriately addressed through statistical analysis of interactions between

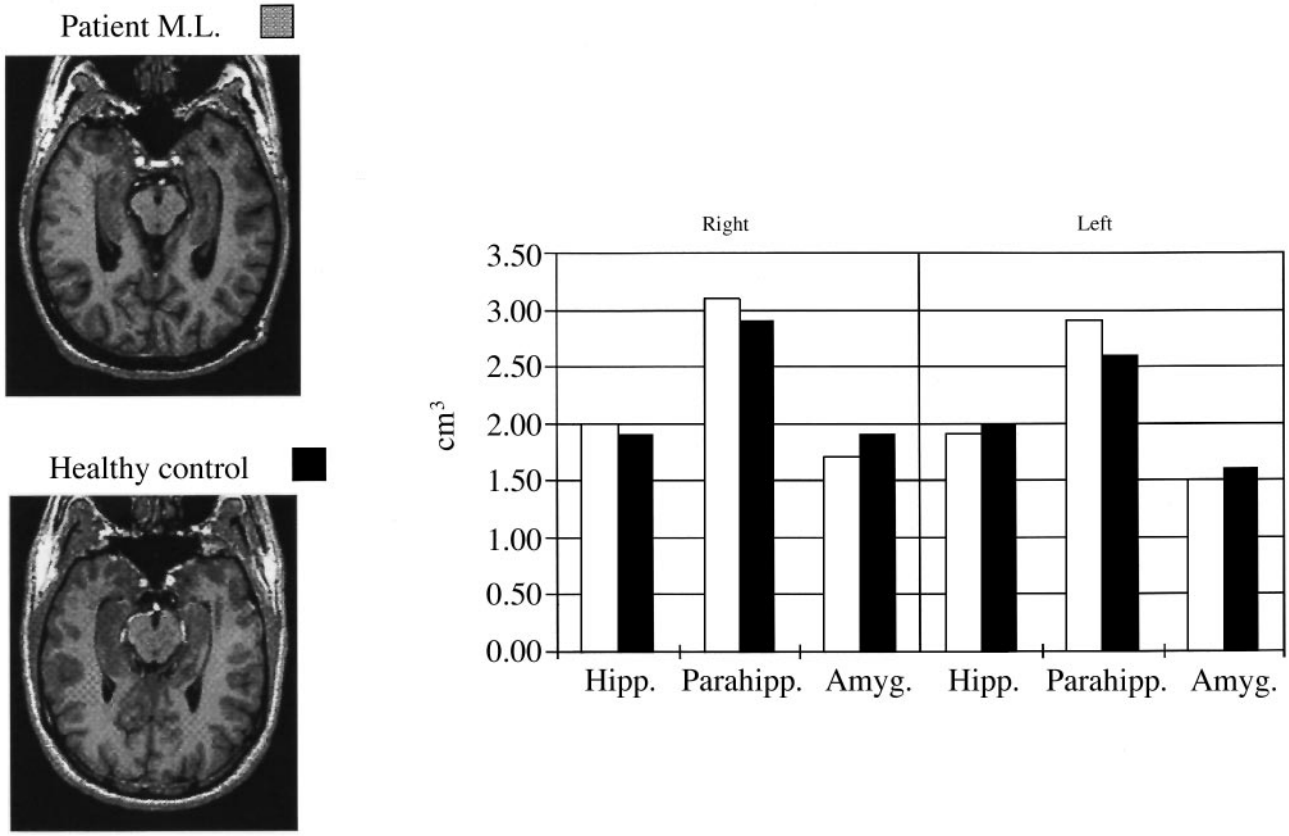

Fig. 2 Volumetric analysis of M.L.'s medial temporal lobe structures in comparison with an age-matched (33-year-old) healthy control subject. Hipp. = hippocampus; Parahipp. = parahippocampal gyrus; Amyg. = amygdala.

Table 3 *Proportion of word pairs correctly recalled*

	Healthy control subjects (mean ± SD)	TBI patients (mean ± SD)	M.L. (mean)
Recall during scans*	0.78 ± 0.20	0.71 ± 0.24	0.81
Recall after scans†	0.39 ± 0.21	0.40 ± 0.07	0.42

*Recall of the stimuli presented in the inter-scan interval prior to the retrieval scans. †Recall of the stimuli presented during the encoding scans, tested after all scans were completed.

encoding/retrieval differences of M.L. and those of healthy control subjects.

Interactions between M.L. and healthy control subjects. The observation of altered frontal asymmetry was reinforced by the results of the interaction analyses (Table 6). In two right middle frontal gyrus regions, the right anterior cingulate and the left caudate, M.L. showed less activation in retrieval than in encoding (see Table 6, top). In a left-lateralized medial/inferior temporal system including the hippocampus and the lingual gyrus, M.L. showed greater activation in retrieval than in encoding. The left and right cunei, and right superior temporal gyrus were also included (see Table 6, bottom). Healthy control subjects showed the opposite pattern: greater right frontal activations in retrieval than in encoding and less left inferomedial temporal activation in retrieval than in encoding.

Replication with TBI control subjects. The above interaction analyses were consistent with our hypotheses of reduced right frontal functioning and increased left medial temporal functioning during retrieval in M.L. However, because TBI affects systems mediating mnemonic processes, it is possible that these findings are not specific to M.L.; they may be more generalized manifestations of TBI. Therefore, we sought to replicate the critical right frontal and left hippocampal findings by conducting interaction analyses in which M.L.'s encoding/retrieval differences were statistically compared with those of TBI control subjects (without isolated retrograde amnesia) who were carefully matched to M.L. for background characteristics and injury severity.

As seen in Fig. 3, the results of these analyses provided further support for our hypotheses. The upper right portion of Fig. 3 shows a right frontal area of interaction (in Talairach space: $x = 34$, $y = 56$, $z = 12$) in which M.L. showed less activation in retrieval than in encoding ($Z = 3.24$). The lower

Table 4 *Encoding and retrieval activations in healthy control subjects*

Side/region (Brodmann area)	Size (pixels)	*Z*-value	*x*	*y*	*z*
Encoding minus retrieval					
L Superior temporal, inferior frontal gyri (41, 44)	1459	4.46	–56	–20	12
		4.11	–48	0	20
L Middle frontal gyrus (6, 9)	203	4.32	–32	12	44
		3.80	–30	32	32
L Inferior frontal gyrus (47)	134	3.93	–40	34	0
L Middle temporal gyrus (37)	207	3.92	–42	–66	8
R Superior temporal, postcentral gyri (40, 41, 22)	736	4.19	52	–22	8
		4.12	52	–28	20
		3.45	50	–2	4
R Middle occipital gyrus (37)	73	3.84	46	–70	4
R Parahippocampal gyrus (35)	48	3.56	28	–28	–20
R Cerebellum	73	3.54	42	–66	–16
R Inferior parietal lobe (40)	59	3.10	36	–32	36
Retrieval minus encoding					
R Inferomedial frontal lobe middle frontal gyrus, putamen (25, 9)	662	5.19	26	18	–4
		4.19	10	22	–16
		4.09	42	16	36
R Superior frontal gyrus, anterior cingulate (9, 32)	1220	4.44	10	56	28
R Thalamus (medial dorsal nucleus)	214	4.32	4	–10	4
R Angular gyrus (39)	165	4.99	42	–64	32
		3.89	0	36	16
R Brainstem	108	4.23	4	–32	–4
R Middle temporal gyrus (21)	148	3.91	58	–34	–12
Cingulate (23)	59	3.33	0	–28	32
L Caudate/putamen	87	3.76	–10	22	0
		3.49	–14	12	–8
L Insula	30	3.52	–34	12	–4
L Thalamus (pulvinar)	46	3.46	–14	–28	8

L = left; R = right.

Table 5 *Encoding and retrieval activations in M.L.*

Side/region (Brodmann area)	Size (pixels)	*Z*-value	*x*	*y*	*z*
Encoding minus retrieval					
L Postcentral, precentral gyri (2, 4)	198	3.95	–56	–20	28
		3.83	–54	–16	36
L Insula	101	3.30	–42	–10	12
L Middle temporal gyrus (21)	15	3.20	–62	–16	–8
R Middle occipital gyrus (19)	18	3.27	38	–78	–8
R Cerebellum	58	3.76	42	–70	–20
R Lingual gyrus (17)	74	3.44	14	–92	–12
Retrieval minus encoding					
L Cerebellum	280	4.14	–8	–52	–12
L Cuneus (18)	444	3.87	–8	–80	28
L Cingulate (32)	334	3.81	–12	26	32
L Middle temporal gyrus (39)	60	3.68	–28	–62	24
R Inferior frontal gyrus (45)	68	3.59	50	14	20
R Insula	86	3.30	32	8	–8

L = left; R = right.

Table 6 *Regions in which M.L.'s encoding/retrieval differences were significantly greater than those of healthy control subjects*

Side/region (Brodmann area)	Size (pixels)	*Z*-value	*x*	*y*	*z*
Retrieval < encoding (M.L)					
R Middle frontal gyrus (8)	18	3.15	38	22	40
R Middle frontal gyrus (10)	14	3.14	32	58	12
R Cingulate (32)	14	3.13	18	32	24
R Fusiform (18)	61	3.46	12	–94	–16
L Caudate	43	3.25	–10	18	–4
Retrieval > encoding (M.L.)					
L Hippocampus	48	3.40	–30	–20	–12
	29	3.68	–38	–32	0
L Lingual gyrus (17)	189	3.71	–16	–78	4
L Cingulate (32)	24	3.12	–12	24	28
L Cuneus (18, 19)	26	3.59	–8	–80	28
R Superior temporal gyrus (42)	53	3.26	56	–28	16
R Cuneus (18, 17)	290	3.65	6	–92	12

L = left; R = right.

right portion shows the left hippocampal area of interaction ($x = –30$, $y = –20$, $z = –12$) in which M.L. showed more activation in retrieval than in encoding ($Z = 3.53$). As seen in the charts on the left side of Fig. 3, each of the four TBI control subjects showed the opposite pattern to M.L.: more right frontal activation in retrieval than encoding and less hippocampal activation in retrieval than encoding. The coordinates of these interactions are exactly the same, or very close to, those reported for the comparison with young subjects (Table 6). Thus, M.L.'s rCBF patterns in response to anterograde episodic retrieval tasks were unique, even among individuals who have sustained moderate to severe TBI. Furthermore, given the close correspondence between the coordinates of these interactions and those of the healthy control subjects, these findings are extremely unlikely to be attributable to factors specific to the TBI control subjects, such as a lesion-related normalization artefact.

Regions-of-interest analyses. To verify that the hippocampal findings could not be accounted for by an artefact due to spatial transformation, we analysed global mean adjusted PET counts taken from hippocampal regions of interest anatomically defined on the MRIs of M.L. and TBI control subjects. Consistent with the above findings,

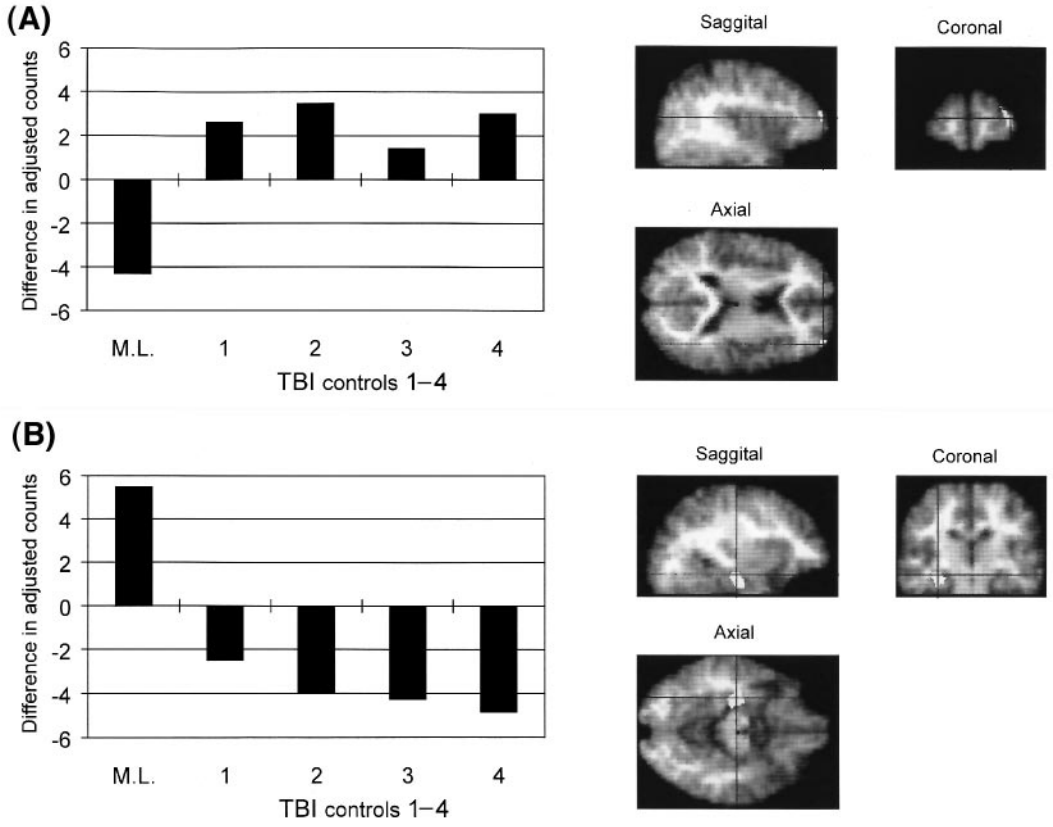

Fig. 3 (**A**) Right frontal and (**B**) left hippocampal regions in which M.L.'s retrieval-minus-encoding differences were greater than TBI control subjects. On the left, differences in adjusted counts (retrieval-minus-encoding) are plotted for M.L. and the four TBI control subjects. On the right, the areas of interaction (thresholded at $P = 0.01$ for the purposes of display) are plotted via SPM on composite brain images in standard space. The right side of the brain is depicted on the right side of the image. The coordinates of maxima in standard space (Talairach and Tournoux, 1988) are $x = 34$, $y = 56$, $z = 12$ (right frontal) and $x = –30$, $y = –20$, $z = –12$ (left hippocampal). For the right frontal interaction, $Z = 3.24$. For the left hippocampal interaction, $Z = 3.53$.

M.L. showed greater left hippocampal rCBF in retrieval than in encoding. The global mean adjusted PET counts were 0.96 ± 0.024 (SEM) and 1.0 ± 0.017 for encoding and retrieval, respectively, whereas TBI control subjects showed the opposite pattern: 1.05 ± 0.031 and 1.0 ± 0.033. The reliability of these differences was supported by a significant interaction between group (M.L. versus TBI control subjects) and condition (encoding versus retrieval) [$F(1,3) = 29.36$, $P < 0.05$] for left hippocampal global-mean-adjusted PET counts.

For the right hippocampus, the group × condition interaction was not significant, but the main effect of group was significant, with M.L.'s right hippocampus significantly less activated than the TBI control subjects' right hippocampi, in both encoding and retrieval conditions [global-mean-adjusted PET counts (± SEM) for M.L.'s right hippocampus 0.95 ± 0.029, and for control subjects, 1.06 ± 0.011; $F(1,3) = 14.88$, $P < 0.05$], suggesting that M.L.'s right hippocampus was not as responsive to the demands of the mnemonic tasks as the right hippocampi of the TBI control subjects.

Remember/know judgements

Results from the cued recall, recognition and remember/know assessments are presented in Tables 7 and 8. For the sake of simplicity, only data from the first and fourth of the four recall tests are presented. Data from the two intervening tests were consistent with these data.

M.L.'s cued recall and recognition performance was not impaired relative to that of TBI control subjects (see Table 7). At 24 h, his cued recall was relatively high, whereas recognition performance was at or near ceiling for all patients including M.L. At 2 weeks, cued recall dropped substantially for all subjects. Recognition hits were elevated for TBI control subjects, but this was attributable to a positive response bias, as seen in high false alarm rates. This bias was induced by a combination of the long delay interval, repeated and lengthy test sessions, invariance in item format and some overlapping themes across items. Correction for this bias (hits–false alarms) reveals that M.L.'s recognition accuracy was similar to that of TBI control subjects.

The cued recall and recognition results were consistent with standard neuropsychological test results showing M.L.'s

Table 7 *Recall and recognition performance for TBI control subjects and M.L.*

	Performance at 24 h				Performance at 2 weeks			
	Cued recall	Recognition hits	False alarms	Hits—False alarms	Cued recall	Recognition hits	False alarms	Hits—False alarms
Subject 2	22	33	0	33	6	28	11	17
Subject 3	25	32	8	24	9	28	8	20
Subject 4	13	32	0	32	2	30	16	14
Subject 5	19	33	7	26	1	26	6	20
TBI mean	19.8	32.5	3.8	28.8	4.5	28.0	10.2	17.8
TBI SD	5.1	0.6	4.3	4.4	3.7	1.6	4.3	2.9
M.L.	27	33	0	33	4	21	4	17

Table 8 *Remember/know responses for TBI control subjects and M.L.*

	Responses at 24 h				Responses at 2 weeks			
	Targets		Distracters		Targets		Distracters	
	R	K	R	K	R	K	R	K
Subject 2	32	1	0	0	19	9	1	10
Subject 3	31	1	0	8	15	13	3	5
Subject 4	28	4	0	0	17	13	5	11
Subject 5	33	0	4	3	15	11	1	5
TBI mean	31.0	1.5	1.0	2.8	16.5	11.5	2.5	7.8
TBI SD	2.2	1.7	2.0	3.8	1.9	1.9	1.9	3.2
M.L.	16	17	0	0	6	15	0	4

intact anterograde memory test performance. However, the R/K data suggest that the processes mediating this intact performance in M.L. differ from those in control subjects. As seen in Table 8, M.L.'s ability to re-experience the encoding episode (R responses) is significantly impoverished relative to that of control subjects. At 24 h, TBI subjects reported re-experiencing some aspect of the encoding episode for nearly all items they recognized as old, whereas M.L. did so for less than half of the items, a difference of ~7 SD. At 2 weeks, R responses declined for all subjects (see Table 8), a pattern similar to that reported by others (Tulving, 1985; Gardiner, 1988; Gardiner and Java, 1991; Knowlton and Squire, 1995). M.L.'s R responses declined at a similar rate to those of TBI control subjects over the two week period. Therefore, within the constraints of our 24 h to 2 week interval, there is no evidence of accelerated forgetting, either for overall recognition or for R responses; M.L.'s deficit in R responses was consistent across testing sessions. Additional testing at shorter delay intervals would be necessary to determine the rate of earlier decline in R responses, if any.

M.L. showed more K responses than TBI control subjects at both 24 h and 2 weeks (see Table 8). At 24 h, however, there was no opportunity for K responses in TBI control subjects because their R responses were at ceiling (R and K responses are, by definition, mutually exclusive). At 2 weeks, when M.L.'s advantage for K responses was reduced, TBI control subjects showed a positive response bias in which both targets and distracters were called old. Such false recognition responses should not be accompanied by R responses (Gardiner and Java, 1991; Rajaram, 1993) and were accordingly labelled 'K' by TBI control subjects. M.L. did not show this bias. Therefore, K responses in TBI control subjects were suppressed at 24 h due to R ceiling effects and elevated at 2 weeks due to a positive response bias. The only interpretation that is clear from these data is that M.L.'s noetic awareness (indexed by K responses) is not significantly impaired relative to TBI control subjects. On the other hand, autonoetic awareness (indexed by R responses) is impaired.

Discussion

Evidence from structural and functional neuroimaging and cognitive testing converged to support our hypotheses concerning the neuroanatomical and psychological underpinnings of M.L.'s isolated retrograde amnesia. Structural neuroimaging revealed right ventral frontal cortical and subcortical damage, including damage to fibres in the uncinate fasciculus, suggesting an association between right frontal–temporal disconnection and isolated retrograde amnesia. Reports from M.L. and other patients with isolated retrograde amnesia suggest that episodic memory dysfunction may extend to anterograde tasks, even though standard memory tests are not always sensitive to this dysfunction. The activation PET study, which showed right frontal

hypoactivation and left inferomedial temporal/hippocampal hyperactivation associated with anterograde retrieval, provided empirical support for these claims as well as a potential solution to the paradox of intact anterograde mnemonic processes with impaired retrieval of pre-injury experiences in isolated retrograde amnesia. Finally, M.L. demonstrated marked episodic impairment in comparison with carefully matched control subjects upon specific probing with the R/K technique. Taken together, the findings correspond to impoverished autonoetic awareness in M.L.

Right frontotemporal disconnection in isolated retrograde amnesia

There is now substantial evidence for the preferential role of the right prefrontal cortex in episodic memory. The HERA pattern, in which right prefrontal activation is associated with episodic retrieval and left prefrontal activation is associated with episodic encoding and semantic retrieval (Tulving *et al*., 1994), is one of the most robust findings in functional neuroimaging of cognition, replicated with a variety of stimuli in several laboratories (for reviews, see Nyberg *et al*., 1996*a*; Fletcher *et al*., 1997). While this pattern was not predicted on the basis of lesion studies, right frontal lesions are associated with deficits on retrieval tasks in which monitoring, verification and placement of information in temporal and spatial contexts are of critical importance (Milner *et al*., 1985; Stuss *et al*., 1994*a*). Reduplication, confabulation and false recognition, all disorders of faulty episodic retrieval, are associated with right frontal lesions (Stuss *et al*., 1978; Baddeley and Wilson, 1986; Hakim *et al*., 1988; N. Kapur *et al*., 1988; Schacter *et al*., 1996*b*).

The prefrontal cortex, however, does not operate in isolation. The anterior temporal, insular and ventral frontal cortex emerge from a single palaeocortical moiety originating in the olfactory cortex (Sanides, 1970; Pandya and Barnes, 1987; Pandya and Yeterian, 1996). Direct, reciprocal information transfer between these regions is mediated by the uncinate fasciculus (see Fig. 1), providing the frontal–temporal connectivity necessary for the monitoring and contextualization of temporal lobe output within the framework of one's past experience (Moscovitch, 1992). Based on HERA, the dominance of the right hemisphere in imagery and emotional processing and the presence of isolated retrograde amnesia following right frontal–temporal pathology, the right uncinate fasciculus has been proposed as being preferentially involved in retrieval of episodic autobiographical information (Markowitsch, 1995).

The other lesions noted on M.L.'s MRI could not account for his isolated retrograde amnesia. Occipital lesions, which M.L. had, have been associated with isolated retrograde amnesia (O'Connor *et al*., 1992; Ogden, 1993; Hunkin *et al*., 1995), but these patients had large cortical lesions in comparison with M.L.'s small haemosiderin deposits. An earlier isolated retrograde amnesia case (Goldberg *et al*., 1981) had damage in the ventral tegmentum. In our case, ventral tegmental damage may have occurred as a result of midline pathology that also affected the hypothalamus, as suggested by M.L.'s hunger and thirst insensitivity, but there was no evidence of this on MRI. M.L.'s bilateral superior frontal lesions were small and located in posterior frontal regions, near the parietal–frontal junction. These lesions may affect lower extremity motor and sensory functioning (present in M.L. in the right knee), but there is no a priori basis for predicting an effect of these lesions on memory functioning.

While the presence of undetected focal pathology is always an issue in severe TBI, we note that the right ventral frontal lesions represented the most significant structural pathology in M.L. (with imaging techniques that are highly sensitive to TBI-related damage). The lesion location is remarkably consistent with Markowitsch's (1995) uncinate hypothesis, and the coordinates of the lesion are within the right frontotemporal network described by Fink *et al*. (1996) activated in response to retrieval of personal past memories as measured by PET. While we agree that multifocal damage is a necessary precipitant to isolated retrograde amnesia (N. Kapur *et al*., 1996), we consider the right ventral frontal focal damage (which is itself multifocal) to be of critical importance to M.L.'s isolated retrograde amnesia. This hypothesis was supported by PET analysis of the functional consequences of his frontotemporal disconnection.

The functional neuroanatomy of preserved anterograde memory in isolated retrograde amnesia

M.L. showed right frontal hypoactivation relative to control subjects as measured by $H_2{}^{15}O$ PET during cued recall using a previously validated PET paradigm (S. Kapur *et al*., 1996; Cabeza *et al*., 1997). The focus of M.L.'s right frontal hypoactivation during retrieval was in the same location no matter which control group was used for comparison. It was in stark contrast with the expected pattern of increased right frontal rCBF in retrieval relative to encoding, a pattern that is, if anything, accentuated in TBI control subjects (see Fig. 3). The focus was in right frontal area 10, an area undercut by M.L.'s lesion that has been identified as part of the episodic retrieval system (Tulving *et al*., 1994; Buckner, 1996; Nyberg *et al*., 1996*a*). This system is impoverished in M.L., affecting his ability to re-experience episodes from his personal past that occurred in a specific time and place (including his post-injury past).

Although right frontal retrieval-related deactivation would also be consistent with the PET findings, this would require a more complex explanation involving active inhibitory processes during retrieval. If there was deactivation, however, this would not change the overall interpretation of altered right frontal functioning associated with retrieval. Hypoactivation directly in M.L.'s lesioned area was not predicted, as this area is largely located in white matter, and the size of the cortical injuries are below the spatial resolution of $H_2{}^{15}O$ PET.

M.L.'s spared performance on the cued-recall task used in the PET study (i.e. the retrieval condition) was associated with increased activation in an intact left inferomedial temporal lobe system, a finding in accord with recent evidence of functional reorganization following focal brain injury (Heiss *et al*., 1993; Engelien *et al*., 1995; Weiller *et al*., 1995; Buckner *et al*., 1996). In healthy adults, the medial temporal lobe memory system is reflexively engaged by retrieval success (Moscovitch, 1992; Grasby *et al*., 1993; Nyberg *et al*., 1996*b*; Schacter *et al*., 1996*a*; Rugg *et al*., 1997). In M.L., this system supports performance on tests of anterograde memory, but retrieval of pre-injury autobiographical episodes, initially processed by the right frontotemporal system, cannot be achieved through this system.

Our findings contrast with the early activation rCBF study of Wood *et al*. (1980*a*), where anterograde retrieval in a patient with temporally-graded isolated retrograde amnesia and left hippocampal damage was associated with preserved right hippocampal function. The two studies are consistent, however, in showing that retrieval of recently learned verbal information can be mediated by the homologous (right or left) preserved frontotemporal system. These functional neuroimaging data provide support for the proposal that anterograde learning in isolated retrograde amnesia is supported by reliance on preserved pathways, but that these pathways cannot provide access to pre-injury information (Hodges and McCarthy, 1993; Markowitsch, 1995; N. Kapur *et al*., 1996).

In interpreting both the left hippocampal temporal and right frontal PET findings, we emphasize changes associated with retrieval in comparison with encoding. From the PET data alone, however, encoding changes cannot be ruled out. In other words, encoding/retrieval differences in activation can reflect changes in association with encoding, retrieval or both. However, assuming M.L.'s encoding processes operated efficiently prior to his injury, his primary deficit is greater for retrieval than for encoding. Considering M.L.'s good performance, encoding-related left hippocampal deactivation involving active inhibition is unlikely. The demands of the encoding condition are similar to those of baseline scans used in other studies of this sort that are designed to ensure deep processing (e.g. S. Kapur *et al*., 1994). In this sense, the encoding condition can be viewed as a conservative match to the processing demands of the retrieval condition.

It is tempting to interpret M.L.'s overall right hippocampal hypoactivation (in the region-of-interest analyses) as a sign of right frontal–temporal disconnection affecting the rCBF responses to both encoding and retrieval demands. However, there was neither structural damage in the right hippocampus nor evidence of hippocampal hypoperfusion in the resting FDG PET study. More sensitive imaging techniques could potentially reveal right hippocampal damage. Firm conclusions concerning this finding should wait until these techniques become available.

Memory test performance spared 'remember'-ing impaired

M.L.'s performance on most neuropsychological tests was normal. Most notably, his performance on standard clinical and experimental measures of recall and recognition tasks was normal. There is now substantial evidence that two memory systems (episodic and semantic), each corresponding to a different level of awareness (autonoetic and noetic), contribute to performance on these tests, and that the R/K technique is a valid way to dissociate these systems (Tulving, 1985, 1989; Gardiner, 1988; Wheeler *et al*., 1997).

In accord with our hypothesis of deficient autonoetic awareness in M.L., his R responses were consistently low, indicating that he achieved normal performance without re-experiencing the encoding episode to the same extent as the TBI control subjects. The neural correlates of M.L.'s R/K performance cannot be precisely determined without functional neuroimaging concurrent with R/K testing. Although PET does not have the temporal resolution necessary for such item-by-item analyses, event related potential (ERP) studies are instructive in this regard. R responses have been consistently associated with a late frontal positivity (Smith, 1993; Mangels *et al*., 1996*b*; Düzel *et al*., 1997; Rugg *et al*., 1998). Tasks of source recall also assess recollection of encoding characteristics, they are associated with frontal function (Schacter *et al*., 1984; Shimamura and Squire, 1987; Janowsky *et al*., 1989), have the same ERP signature as R responses (Rugg *et al*., 1998) and can be considered measures of autonoetic awareness (Tulving, 1989; Wheeler *et al*., 1997). ERP studies of source recall have consistently documented late right frontal positivity associated with analysis of contextual information from the encoding episode (Wilding *et al*., 1995; Wilding and Rugg, 1996, 1997; Johnson *et al*., 1996). These ERP analyses of R responses and source recall support the association of autonoetic awareness with right frontal functioning. This research, in combination with our MRI and PET findings, suggests that M.L.'s R deficiency (and impaired autonoetic awareness) is attributable to right frontal dysfunction.

One question raised by the R/K data concerns M.L.'s increased K responses in comparison with TBI control subjects. This finding could be interpreted as evidence either for a hyperactivated left hemispheric semantic system or for a normal semantic system responding in the absence of episodic recollection. While the large retrieval–encoding left inferomedial temporal activation in M.L. could be viewed as consistent with the former hypothesis, Knowlton and Squire (1995) showed that, in healthy adults, R responses convert to K responses as episodic recollection declines over long delays. In other words, elevated K responses could simply reflect the absence of episodic recollection, rather than facilitated semantic processes. As the PET study was conducted on separate stimuli, we prefer the conservative interpretation of M.L.'s elevated K responses as evincing unimpaired (but not necessarily facilitated) noetic awareness.

Most importantly, consistent with M.L.'s reports of his own recollections of post-injury events, the information presumably retrieved via this system lacks the subjective quality characteristic of normal episodic recall of events integrated within the fabric of one's self and one's past.

Episodic memory, self-regulation and self scotomata

Remembering episodes from one's personal past is not possible in the absence of autonoetic awareness. The role of autonoetic awareness in human behaviour, however, is not limited to recollecting past episodes; it is relevant across the time dimension, encompassing both reflection on the past and projection into the future (Ingvar, 1985; Fuster, 1995; Wheeler *et al*., 1997; Stuss *et al*., 1998). In unstructured situations, autonoetic awareness supports the formulation of goals and implementation of a behavioural guidance system to achieve them. In patients deprived of this capacity, behaviour is driven by irrelevant environmental goals, or inappropriate habits or routines (Shallice and Burgess, 1993), a syndrome that we refer to as self-regulatory disorder. Therefore, patients with impaired autonoetic awareness should have impaired self-regulation as well as impaired episodic memory.

Thus far, we have supported our hypothesis of impaired autonoetic awareness in M.L. through analyses of his episodic memory functioning. The only other task on which M.L. was significantly impaired was a strategy application task designed to tap self-regulatory disorder by minimizing environmental or internal constraints typical of most neuropsychological tests (Levine *et al*., 1998; M.L.'s data were included with the TBI subjects in that study). Performance on this test was shown to be sensitive to TBI and right ventral frontal pathology (Levine *et al*., 1998).

We propose that M.L.'s impaired self-regulation (both inside and outside the laboratory) and his mnemonic deficits can be unified within the concept of impaired autonoetic awareness that affects behaviour across the time dimension. His behaviour is driven by generic information that he has learned about how one should behave, rather than by goals and intentions that arise from his own identity. The time course of his behavioural deficits is consistent with this hypothesis. His self-regulatory disorder was initially quite severe, exemplified by a number of parenting mishaps, such as letting his children play in dangerous situations. This was followed by an attenuation of the disorder with learning over time. Nevertheless, even at 5 years post-injury M.L.'s interpersonal interactions appear somewhat contrived and artificial.

One might ask why M.L.'s profile of deficits is not more commonly observed in other patients, in particular in patients with TBI and/or right ventral frontal lesions. In fact, TBI patients do have self-regulatory deficits that have profound effects on their behaviour in occupational and interpersonal situations (Lishman, 1973; Jennett and Bond, 1975; Dikmen and Temkin, 1987; Dikmen *et al*., 1995). The relationship between focal ventral frontal pathology and impaired self-regulation is also apparent in studies using tasks designed to mimic the ambiguity inherent in real-life situations (Lhermitte *et al*., 1986; Shallice and Burgess, 1991; Rolls *et al*., 1994; Bechara *et al*., 1996; Burgess and Shallice, 1996) and in case studies of impaired real-life self-regulation (Harlow, 1868; Eslinger and Damasio, 1985). Furthermore, disorders such as subarachnoid haemorrhage from anterior communicating artery aneurysms and frontotemporal dementia both involve ventral pathology and result in impaired self-regulation (as defined by specialized tests or grossly impaired real-life self-regulation; see the Lund and Manchester Groups, 1993; Miller *et al*., 1993; Alexander and Freedman, 1984). While patients in these studies typically have bilateral lesions, many of these studies specifically emphasize right ventral frontal pathology. From these observations, self-regulatory disorder, one manifestation of impaired autonoetic awareness, can be caused by ventral frontal pathology, especially in the right hemisphere.

Goldman-Rakic and colleagues (e.g. Funahashi *et al*., 1993) characterized topographically organized spatial working memory deficits in monkeys with principal sulcus lesions as mnemonic scotomata. This concept provides a potential mechanism for impaired autonoetic awareness and its behavioural manifestation as impaired self-regulation. That is, in healthy adults, referral to the self, defined here as a multimodal distributed network of associations accrued over a lifetime of experiences, gives rise to autonoetic awareness, which in turn supports the formulation of future goals, especially in unstructured situations where the goal cannot be derived from the environment or habit. Brain damage can cause mnemonic scotomata for information contained in this network, especially damage to regions important to the indexing or triggering of recollection of personal past events (i.e. anterior temporal lobes or frontal lobes), resulting in a failure of analysis or on-line maintenance of information concerning the self (or some aspect of it) as a continuous entity across time.

Dense anterograde and retrograde amnesia can be viewed as an exemplar of this syndrome, as illustrated by the following passage from Tulving (1985) describing densely amnesic patient K.C. (referred to as N.N. in that paper). [When asked, on different occasions, to describe the 'blankness' that characterizes his state of mind when he tries to think about 'tomorrow,' he says that it is 'like being asleep' or that 'it's a big blankness sort of thing.' When asked to give an analogy, to describe what it is like, he says, 'It's like being in a room with nothing there and having a guy tell you to go find a chair, and there's nothing there.' (p. 4).]

It has been argued that K.C. has no autonoetic awareness (Tulving, 1985). Even though he can describe his own personality traits when directly queried (Tulving, 1993), he cannot spontaneously hold self-specific information on-line, integrate it with mental representations of the past and future,

or use it to drive his behaviour towards personally relevant goals. M.L. most probably retains some residual autonoetic awareness, but it only operates on post-injury information, and even there less efficiently than control subjects. Other TBI patients and other patients with ventral frontal pathology may have more subtle autonoetic deficits, although evidence of this with respect to past or future events is not probed for in routine exams (Goldberg and Bilder, 1986). Furthermore, patients are not likely to register such complaints when semantic knowledge of their personal past is intact (Stuss *et al*., 1998), although they may describe personality change.

Conclusions

Taken together, the structural neuroimaging, functional neuroimaging and cognitive psychological findings converge on the hypotheses that M.L.'s clinical syndrome of isolated retrograde amnesia is related to a right frontal lesion affecting his ability to re-experience past experiences, and that this effect extends across the time continuum into anterograde learning and self-regulation of behaviour. While the results from a single case must always be interpreted with caution, the evidence presented and reviewed herein shows that brain damage affects autonoetic awareness, and that this effect can be observed through patients' behaviour with respect to their own pasts and futures.

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