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Retrieval of old memories: the temporofrontal hypothesis

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Summary

Extensive neuropsychological testing is reported on two chronic patients with combined temporopolar and prefrontal damage, dominantly left-hemispheric, and, as control, one chronic patient with bi-hemispheric prefrontal damage. The principal finding is that combined temporofrontal damage, but not substantial prefrontal damage alone, results in marked retrograde memory deficits while leaving intelligence and new learning relatively unimpaired. Although their general world knowledge was good, the temporopolar patients demonstrated retrograde memory impairments on several tests of past events and faces of previously famous people. With respect to retrograde autobiographical memory, one of the temporopolar patients was severely impaired and the other was judged to be moderately impaired. The control patient appeared to be normal. These results, together with corresponding data from related single case and dynamic imaging studies, strongly support a crucial role of the temporofrontal junction area in the ecphory of old memories.

Keywords: retrograde amnesia; episodic memory

Abbreviations: BA = Brodmann area; SI = signal intensity

Introduction

Functional localization is a major aim in brain research of the anatomical substratum for memory (Alzheimer, 1896; Lashley, 1950; Squire, 1987). It is likely that a number of network-like interacting brain structures subserve mnemonic processing. Indeed, a number of nodal points, or bottleneck structures, for the encoding of mnemonic information into long-term storage have been described. These can be clustered into a medial diencephalic, a medial temporal lobe, and a basal forebrain system (Markowitsch, 1995*a*).

Information is usually first encoded as an episode, i.e. an event that is specific to time and locus. The resulting 'episodic' old memories are composed of information from our own past to which we can fix a date or a locus which are not necessarily of particular significance (Tulving, 1995). Disturbances in the recollection of such events occur from many causes, including dementia, transient global amnesia, direct interference (via electrical or chemical means), thiamine deficiency, focal brain damage or psychogenic amnesia.

Repetition of information may induce other forms of memory. For example, the knowledge system (frequently referred to as 'semantic memory') represents our knowledge of the world, including grammar, calculus, persons of history and geography. Other memory systems represent abilities, e.g., to drive a car or to play polo ('procedural memory'), or to be prepared to react on a later occasion to the same stimuli ('priming') (Tulving, 1995). An alternative classification includes episodic and semantic memory within a single 'declarative memory system' (Squire, 1987).

There is disagreement over whether patients with anterograde amnesia are deficient only with respect to encoding new episodic memories, or are also deficient in their encoding of new information at the knowledge level. A recent study supports the hypothesis of combined impairments (Verfaellie and Cermak, 1994).

Until recently, 'the hypothesis that anterograde and retrograde amnesia might result from separate and independent impairments' was regarded as 'unproven'

(Meudell, 1992, p. 67) and Squire and Alvarez (1995) formulated that 'retrograde memory loss almost always occurs in association with anterograde amnesia' (p. 169). A few years earlier, Squire *et al*. (1989) reported similar degrees of retrograde amnesia in patients with amnesia due to Korsakoff's disease, anoxia or ischaemia, thalamic infarction, and an unknown aetiology. This led them to suggest that 'the structures damaged in amnesia support memory storage, retrieval, or both, during a lengthy period of reorganization, after which representations in memory can become independent of these structures' (p. 828).

Single case descriptions, however, suggest that certain cortical regions are relevant for recall, but not for information encoding. The present work provides further evidence of retrograde memory loss without learning impairment. It also addresses hemisphere-specific information retrieval and the role of frontal and temporal cortices.

Qualitative and quantitative measurements of retrograde amnesia are among the most difficult endeavours in neuropsychological testing (Markowitsch, 1992). This is due to a combination of factors. (i) The personal history of an individual is frequently difficult to determine. (ii) Estimating losses from world knowledge can be just as difficult; people have individual preferences and interests so that, in the absence of pre-tests, their pre-morbid knowledge is largely unknown. (iii) Some autobiographical events may have been transferred into the knowledge system over time and with repetition. (iv) It may be impossible to know the conditions under which knowledge was obtained. Greene and Hodges (1996) gave the example of seeing a politician while on holiday in London and seeing the same politician on the television news. (v) The mode of testing (e.g. recall versus recognition) can influence the outcome (e.g. Chatterjee *et al*., 1993; von Cramon *et al*. 1993). (vi) In some cases the memory disturbance may be quite selective, for example only affecting the memory of names of people, famous animals, buildings, and product names (Ellis *et al*., 1989; Hittmair-Delazer *et al*., 1994; N. Kapur *et al*., 1994*b*; Reinkemeier *et al*., 1997). (vii) Finally, there are continued debates on possible gradients in retrograde amnesia (Sanders and Warrington, 1971; Mair *et al*., 1979; Butters, 1984; Squire *et al*., 1989; Gaffan, 1993) (*see* below).

Forms of retrograde amnesia

Time and content-specific forms of retrograde amnesia have been reported in numerous studies. The reported subdivisions and results depend in part on the patients' aetiologies, and in part on the respective nomenclature and fine tuning in the subdivisions applied.

Time-specific memory problems have been noted most regularly in temporal sequencing and ordering. These have been reported in patients with basal ganglia (Sagar *et al*., 1988), dorsolateral prefrontal (Shimamura *et al*., 1995), and in diencephalic damage as in Korsakoff's psychosis (van der Horst, 1923; Bouman and Gruenbaum, 1929; Krauss, 1930; Grünthal, 1932, 1939; Kleist, 1934; Benedek and Juba, 1940, 1941; Williams and Zangwill, 1950). A loss in the feeling of time was also reported for a 67 year old patient who had focal atrophy in the orbitofrontal cortex and numerous Pick bodies in medial temporal lobe structures (Hodges and Gurd, 1994). At the beginning of his memory deterioration, he had selective deficits in recalling context-rich and time-specific autobiographical events. The authors suggest that fronto-striatal pathway damage was responsible for the deficit.

Mention should also be made of the symptom of 'chronotaraxis' which was reported after mediodorsal stereotaxic thalamotomy (Spiegel *et al*., 1955, 1956; Wycis, 1972). 'Chronotaraxis is characterized by an inability to identify the date; the patient may not know the time of the day, may make incorrect statements regarding the season of the year though this is obvious if he looks through the window' (Spiegel *et al*., 1956, p. 97).

Content-specific forms of retrograde memory loss have, on the one hand, been found in cases with focal brain damage (Markowitsch, 1995*b*), and, on the other hand, in demented cases (Hodges *et al*., 1992; Greene and Hodges, 1996).

Some patients with a dominant damage focus in temporofrontal regions of one hemisphere, together with minor damage in the other, show a clear-cut division between preservation of (world) knowledge and a loss of autobiographic (episodic) information or vice versa (De Renzi *et al*., 1987; N. Kapur *et al*., 1992; Markowitsch *et al*., 1993*c*; Calabrese *et al*., 1996). Other patients with still more selective damage or with damage in more posterior cortical regions may manifest more subtle forms of retrograde amnesia. For example, dissociations were described between preserved knowledge of people, but impaired knowledge of events (e.g. regarding to what happened to these people) (Ellis *et al*., 1989; McCarthy and Warrington, 1992) or vice versa (Reinkemeier *et al*., 1997).

Demented patients in particular may manifest an impairment in semantic memory as defined by Hodges *et al*. (1992). That is, they may demonstrate severe anomia, a reduced vocabulary and a major impairment in single-word comprehension (cf. Hodges *et al*., 1994; Hodges and Patterson, 1995). More recently, Greene and Hodges (1996) suggested a further fractionation of remote memory in dementia, namely that in autobiographic memory versus famous person knowledge. Deficits in the identification of famous names and faces were attributed to a loss of semantic knowledge regarding famous persons, while a retrieval deficit contributed to the proper name anomia, which was in addition to the semantic deficit (Greene and Hodges, 1996). With respect to remote memory processing, Graham and Hodges (1997) recently found that patients with Alzheimer's disease show a temporally graded loss with poor recall of recent memories; whereas patients with semantic dementia showed the reverse pattern.

Findings obtained in normal subjects with dynamic imaging techniques argue for a hemisphere-specific dissociation between retrieval of information from the episodic and the

knowledge domains, with the first being associated with the right and the second with the left hemisphere (Markowitsch, 1995*b*; Nyberg *et al*., 1996). Considered collectively, these data speak for a modular representation of memory, probably with some commonly shared components.

Preferred brain loci in cases with selective retrograde amnesia

By selective retrograde amnesia, we mean severe and lasting retrograde amnesia in the presence of the ability to acquire new episodic information. N. Kapur (1993) introduced the term 'focal retrograde amnesia' to describe the deficit in such patients. Usually, patients with selective retrograde amnesia have some disturbances in anterograde memory domains as well; however, their preserved ability to acquire new long term declarative information distinguishes them from other amnesics.

The first cases of major retrograde amnesia with no, or only minor, anterograde memory disturbances were reported in the early 1980s (Roman-Campos *et al*., 1980; Goldberg *et al*., 1981, 1982; Andrews *et al*., 1982). Goldberg and co-workers had an early CT-scan of their patient's brain. The trauma-induced damage was widespread, extending from the right posterior temporal lobe down to the pontine–mesencephalic junction area. The 36-year-old patient considered himself to be between 16 and 18 years old and recognized neither wife or children, nor other details of his former private or professional background. However, this case's behaviour closely resembles that of patients with psychogenic amnesia (cf. Markowitsch, 1990) and may, therefore, not be relevant to the present discussion.

N. Kapur *et al*. (1989, 1992) reported two cases with retrograde amnesia as a prominent syndrome. In patient L.T., the trauma-caused (horse riding accident) lesion was bilateral, but predominantly right-sided, and affected the temporopolar and the orbitofrontal cortex. Her brain damage closely resembles that of case E.D. of Markowitsch *et al*. (1993*a*, *b*), discussed below.

Other cases with temporal damage and retrograde amnesia have been reported. O'Connor *et al*. (1992) reported a case resulting from a herpes simplex encephalopathy, and De Renzi and Lucchelli (1993) reported a case resulting from a severe trauma. Both of these cases were characterized by the ability to learn new information (though De Renzi and Lucchelli's case was an abnormally fast forgetter) and both had their main deficits on the autobiographical old memory level. In addition, Yoneda *et al*. (1992) briefly described a case of a 21-year-old right handed patient with isolated retrograde amnesia after encephalitis-based dysfunction of the left temporal lobe.

Case E.D., of Markowitsch *et al*. (1993*a*, *b*), was similar to that of N. Kapur *et al*. (1992). E.D. had fallen from a horse and had the same combination of lesioned structures; the lesion was bilateral, but dominantly on the right side, and damage involved the temporopolar and portions of the orbitofrontal cortex; i.e., regions which are combined by the uncinate fascicle (Ebeling and von Cramon, 1992). Also E.D. closely resembled case L.T. behaviourally, having a preserved ability to learn episodic information anew, but being grossly impaired in the ability to retrieve old episodic information.

Recently, Calabrese *et al*. (1996) provided detailed neuropsychological information on a patient with a severe and enduring loss of old autobiographical memories after herpes simplex type I infection. The patient was examined neuropsychologically, 2 years after the infection, with MRI and single photon emission computerized tomography. Brain damage was found mainly in the right temporofrontal region, but minor left-sided damage to this region appears possible. The patient manifested severe retrograde memory deficits with respect to episodic old memories and more moderate deficits in tests of general knowledge.

Mention should also be made of the reports of Della Sala *et al*. (1993) on cases with frontal lobe damage. Their patients had problems with the retrieval of autobiographical events from the past. They concluded that the prefontal cortex is involved in the effortful retrieval of remote information, without being solely responsible for them. In addition, Lucchelli *et al*. (1995) reported on two patients who recovered unexpectedly from major retrograde amnesia. One of them had had a left thalamic infarction, the other mild head trauma.

It should be noted that recent evidence from PET studies with normal subjects, testing episodic memory processing, pointed to an involvement of the prefrontal cortex in episodic memory (S. Kapur *et al*., 1994; Tulving *et al*., 1994*a*, *b*, *c*, 1996). However, due to technical limitations, a possible contribution from the temporopolar cortex could not be excluded. The PET studies resulted in another important finding which Tulving *et al*. (1994*a*) termed the 'hemispheric encoding, retrieval asymmetry (HERA)'. They found that for encoding of episodic information the left prefrontal cortex was differentially activated whereas,for retrieval, the right prefrontal cortex was activated. These findings correspond quite well to the predominance of right-sided brain damage in cases with selective episodic retrograde amnesia (Goldberg *et al*., 1981, 1982; N. Kapur *et al*., 1992; Morris *et al*., 1992; O'Connor *et al*., 1992; Markowitsch *et al*., 1993*a*, *b*). However, patients with focal damage in the right prefrontal cortex do not have retrieval deficits, raising some questions about the functional meaning of the PET activation studies (Swick and Knight, 1996).

The patient of N. Kapur *et al*. (1994*a*), with mainly semantic memory disorders, had symmetrical bilateral brain damage, mainly in the lateral temporal lobes. The authors suggested that his 'right anterior temporal lesion played a part in his poor autobiographical memory for specific episodes', while his 'poor performance on pre-1980 items on the Dead-or-Alive test was related to the left anterior temporal lobe damage' (p. 34). (The Dead-or-Alive test is a semantic memory test.) Yoneda *et al*. (1994) described a correlation between atrophy of the parahippocampal gyrus

and the density of retrograde amnesia in encephalitis patients. Hokkanen *et al*. (1995) found isolated retrograde amnesia for autobiographical material in a patient with acute left temporal encephalitis.

Finally, we would like to comment on 'semantic dementia' which, of course, includes intellectual disturbances beyond retrograde amnesia. A dissociation between relatively preserved autobiographical memory and semantic retrograde amnesia can frequently be found in these cases, in which atrophy of the inferolateral temporal lobe often involves predominantly the left hemisphere (Hodges *et al*., 1992, 1994; Hodges and Patterson, 1995).

Case descriptions

We investigated the intellectual and memory abilities, particularly the older memory, of three male, right-handed Caucasian patients of average intelligence. All of them had had traumatic brain injury in young adulthood: Patient A.A. at the age of 24 years (bike/car accident, 1974); Patient B.B. at the age of 30 years (knocked off his bike by somebody with a club and robbed, 1975) and Patient C.C. at the age of 24 years (motorcycle accident, 1977). At the time of testing, Patient A.A. was 44, Patient B.B. 49, and Patient C.C. 41 years old. Patients A.A. and B.B. were both veterans. They were tested over more than a dozen sessions each at the VA Medical Center in Martinez, California. Many of the tests used can be found in Lezak (1995) and in Spreen and Strauss (1991). Most of the others, especially the German-language ones, were described in our previous publications (Markowitsch *et al*., 1993*a*, *b*,*c*, 1994; von Cramon *et al*., 1993). Written informed consent was obtained from all three subjects.

In addition to the three patients, a group of 18 healthy control adults were tested on some of the tests which lack published norms. These subjects were contracted via a newspaper advertisement and were tested in the University Psychology Laboratories in Davis, California. There were seven males and 11 females who ranged in age from 40 to 70 years with a mean age of 56.7 years. All subjects were paid $10/h for their participation and written informed consent was obtained from all subjects. The study was approved by the Human Subjects Review Committee, University of California, Davis.

Patient A.A.

Patient A.A. had 12 years of schooling; he is unemployed, but does volunteer work in a hospital. His coma duration after the accident had been 4 days. It was reported that he had been disoriented for an extended period after his accident. For example, he did not know who was the President (of the USA), nor similar kinds of basic knowledge. His sister reports that when she saw him several weeks after the accident, he first assumed that her girl friend (whom he had not seen before) was his sister. During the interview, he stated that he can remember 'big' moments from his youth, but he had to relearn many of his relatives. His memories seem 'flat' or overlearned. He stated that his memories for recent events are much better now than they were during the first years after his accident, but that he still tends to forget 'quite a bit.'

Neuroradiological examination

Patient A.A.'s brain damage can be seen in Fig. 1. Both ventral frontal poles and temporopolar regions were damaged. In addition, most of the anterior two-thirds of his left temporal cortex was damaged. MRI was carried out in February 1992 (i.e., 18 year post-injury) using a (Vista) 0.5 Tesla scanner. MRI comprised sagittal and coronal T_1-weighted (TR 550; TE 20) and transverse T_2-weighted (TR SE 3000; TE 100) 10 mm sequences.

Coronal T_1-weighted images. Sections through the polar region of the frontal lobes reveal low signal intensities (SI) in the frontomarginal region of both prefrontal cortices. Whereas on the right the shallow hypointensity seems limited to the frontoorbital margin, the hypointense area on the left extends to the anterior gyrus rectus encroaching on the olfactory bulb and reaches medially to the superior rostral sulcus.

On sections through the anterior third of the temporal lobes, low SI are seen in both temporal lobes, but particularly in the left. The temporopolar cortices are altered on both sides. The anterior 1.5 cm of the right temporal pole is lesioned, whereas the extent of the left-sided hypointensity measures ~5–6 cm from the temporal pole comprising the middle and inferior temporal gyri, parts of the para-hippocampal gyrus, the anterior fusiform gyrus, and the lateral and inferior temporal white matter. With respect to the first temporal gyrus, only the anterior third appears altered; the temporal isthmus seems largely spared.

The left inferior horn is enlarged to a transverse diameter of >2 cm and its presumably maximally widened tip merges with the surrounding hypointense area. The tip of the right inferior horn is at best slightly enlarged.

The left-sided amygdaloid complex and the hippocampal formation is largely spared. The left hippocampus appears 'isolated' from lateral temporal and other brain structures because the white matter compartment under the floor of the maximally enlarged inferior horn reveals a low SI.

Transverse T_2-weighted images. The T_2-weighted images are characterized by homogeneous fronto-orbital and temporal hyperintesities that appear more extensive than the corresponding hypointense area in the T_1-weighted mode. The nearly symmetrical hyperintense area comprises the anterior half of the medial aspect of the orbital gyri including the gyrus rectus on both sides. A 'wedge-shaped' extension reaches dorsally in the deep frontal white matter and posteriorly to the anterior horns of the lateral ventricles. The

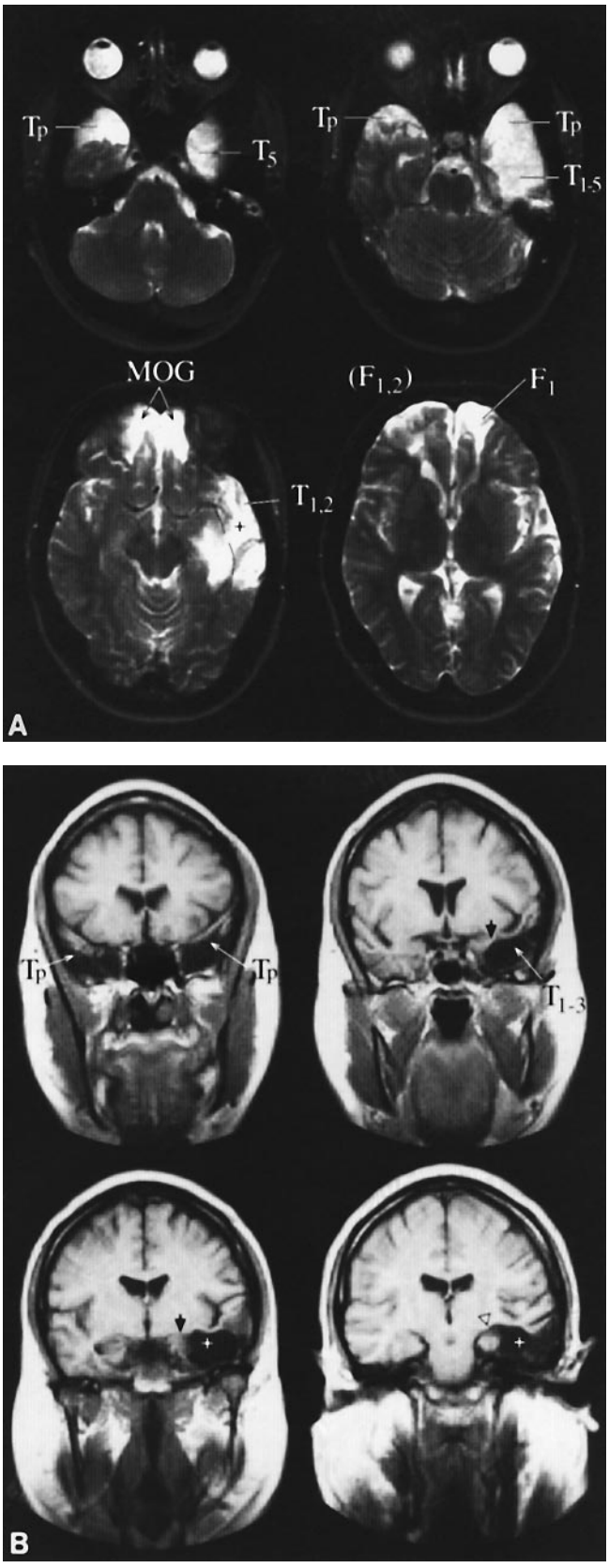


Fig. 1 Patient A.A. (**A**) T_2-weighted horizontal sections. (**B**) T_1-weighted coronal sections. Spared mediotemporal structures: gyrus semilunaris, ambiens; amygdala; uncus (arrows); parahippocampal gyrus (arrowhead). For abbreviations, *see* Table 1.

left frontal pole is more affected than its counterpart of the right.

As previously suggested, tissue alteration to the right temporal lobe is restricted largely to the temporopolar region. Correspondingly, the tip of the inferior horn is only slightly widened.

With respect to the left temporal lobe, the anterior half seems involved. The medial border of the left-sided hyperintense area is clearly demarcated by the (lateral) outline of the amygdaloid complex and the hippocampal formation. Medial parts of the anterior parahippocampal gyrus may also be spared. The remainder of the brain appears inconspicuous.

Summary of MRI findings. The MRI, carried out 18 years post-injury, reveals bilateral frontotemporal tissue damage which can be attributed to the bike/car accident Patient A.A. had suffered in 1974.

As indicated by the T_1-weighted images, the frontal tissue damage primarily affects the medial portion of lower Brodmann area (BA) 10, and on the left side anterior parts of BA 11 and 12. More extensive gliotic tissue repair, presumably as a consequence of diffuse axonal injury and traumatic oedema, is observed in both frontal lobes involving the frontoorbital and the dorsally adjacent white matter compartment. Gliotic scarring reaches far beyond the rather small lesion area in the fronto-orbital region.

With respect to the temporal lesions, it is noteworthy that only the temporopolar region (BA 38) is damaged on both sides. On the left side, anterior lateral and basal structures of the temporal lobe (BA 20, 21, 22, 35, 36) are severely injured except for the amygdaloid complex, the hippocampal formation and, presumably, parts of the parahippocampal gyrus. The anterior temporal white matter is substantially reduced. The hippocampal formation seems deprived of its neocortical target sites in the convexity cortex, but afferent and efferent fibre connections between the amygdaloid complex and the septal area via the ventral route (amygdalofugal pathway, diagonal band of Broca) should be preserved.

Patient B.B.

Patient B.B. had 12 years of schooling; he is currently unemployed. After completing high school he joined the army and was stationed in Korea at the time of his injury. His head injury resulted in 3 weeks of unconsciousness and was followed by meningitis and a second operation.

Neuroradiological examination

MRI revealed extensive frontal and left temporal encephalomacia, affecting a large amount of the prefrontal cortex bilaterally and substantial ventro-anterior portions of the temporal lobes (Fig. 2). As with Patient A.A., Patient B.B.'s left temporal cortex was damaged along more than its anterior half. The medial temporal cortex was largely spared.

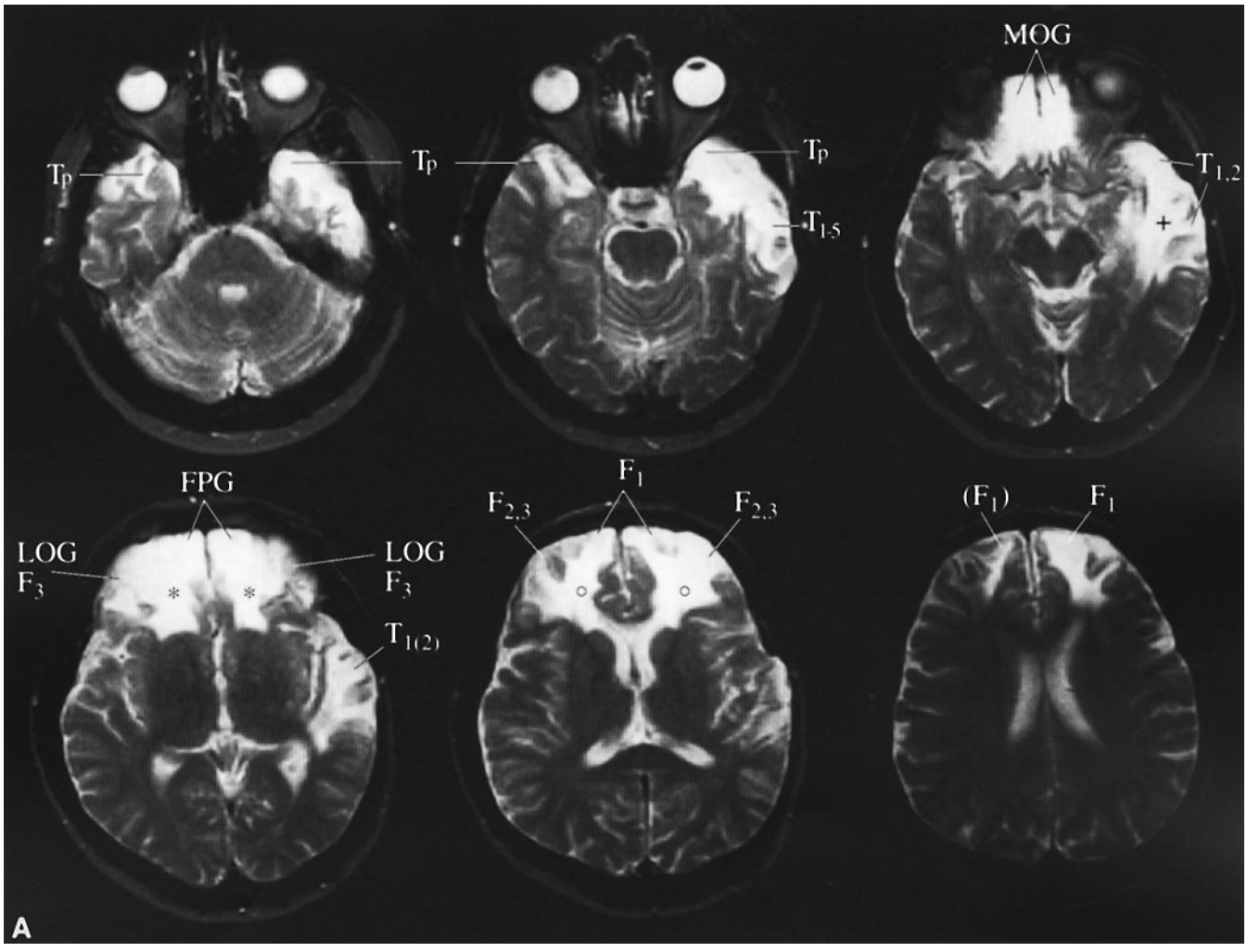
An EEG from the same time period was interpreted as demonstrating a left temporal lobe focus with possible seizure disorder. MRI was carried out in September 1993 (i.e. 18 years post-injury) using a 0.5 Tesla scanner. MRI comprised coronal T_1-weighted (TR 600; TE 20) and transverse T_2-weighted (TR SE 3000; TE 100) 10-mm sequences.

Coronal T_1-weighted images. Sections through the preventricular frontal lobe show extended, bilateral hypointensities involving the frontopolar cortex and the anterior fronto-orbital cortex (including the gyrus rectus and the medial portions of the orbital gyri). The fronto-orbital white matter compartment below the anterior radiation of the corpus callosum is likewise altered. On the right side, the area of low SI reaches the posterior part of the medial orbital gyri.

It is questionable whether the right temporal polar region is affected. If so, there are only spots of decreased SI. The extent of low SI in the left temporal lobe, however, is considerable and measures ~4–5 cm from the pole. It includes the superior, middle and inferior temporal gyri, the anterior and lateral part of the fusiform gyrus, as well as the deep temporal white matter including the temporal isthmus. Despite extensive hypointensities in the left temporal lobe, the corresponding inferior horn seems only slightly enlarged.

The left-sided amygdaloid complex, the hippocampal formation, a major portion of the parahippocampal gyrus and the lateral bank of the collateral sulcus (fusiform gyrus) appear unaltered.

Transverse T_2-weighted images. The T_2-weighted images reveal bilateral, completely homogeneous hyperintensities in the frontoorbital white matter. They are sharply demarcated on three sides: (i) laterally by the inferior frontal and anterior insular cortex; (ii) posteriorly by the nucleus accumbens, the anterior putamen and the head of the caudate nucleus; (iii) medially by the frontomedial cortex. The polar and anterior frontolateral cortex, however, is part of the hyperintensive area. The same holds true for the anterior radiation and the genu of the corpus callosum. In more dorsal parts of the frontal white matter, the area of high SI shrinks until, on a section through the body of the caudate nucleus, it is restricted to a wedge-shaped area involving the upper portion of the frontal polar cap, to the gyral stalks of both superior frontal gyri and to that of the second frontal gyrus on the right side.



In contrast to the T_1-weighted images, there is no doubt that a small area of high SI also affects the right temporal pole, especially its basolateral aspect. The corresponding inferior horn is hardly widened. On the left side, the hyperintensive area, largely coincides with that in the T_1-weighted mode. Further evidence is provided that a substantial part of the left parahippocampal gyrus, especially the anterior portion, seems preserved. On the other hand, the left anterior hippocampus may be at least partially altered. The left inferior horn is most likely considerably enlarged.

The remainder of the brain appears inconspicuous.

Summary of MRI findings. The MRI, carried out 18 years post-injury, reveals extended frontotemporal tissue damage which can be attributed to the blunt head trauma Patient B.B. suffered in 1975.

In comparison with Patient A.A. (*see* above), the virtually symmetrical frontal lesions are considerably larger, affecting not only the medial and lateral fronto-orbital cortex (anterior BA 11 and 12) and the frontal polar cap (BA 10), but also the fronto-orbital white matter. As with Patient A.A., gliotic tissue repair reaches far beyond the true lesion area, involving some parts of the frontolateral cortex (possibly even BA 9/64, 46 and 47/12), a large portion of the deep frontal white matter compartment, and the anterior radiation/genu of the corpus callosum.

Although tissue damage to the left polar (BA 38), anterior lateral and basal (BA 20, 21, 22 and 36) temporal cortices, and anterior temporal white matter is substantial, the tissue alteration in the right temporal pole (BA 38) appears relatively insignificant. Nevertheless, a bilateral lesion of BA 38 can be assumed. It should be emphasized that the left temporomesial structures (including the amygdaloid complex and the anterior parahippocampal gyrus) are largely spared. However, the left anterior hippocampus may be partially damaged.

Patient C.C.

Patient C.C. had 10 years of schooling, plus some junior college. He describes himself as 'self-educated' and is currently unemployed (disabled); previously he was a car mechanic. He is currently medicated with anti-convulsants. He talks easily, confidently, consistently and realistically about his early life.

Neuroradiological examination

MRI revealed extensive bilateral frontal damage; however, the temporal lobes were totally unaffected (Fig. 3). MRI was

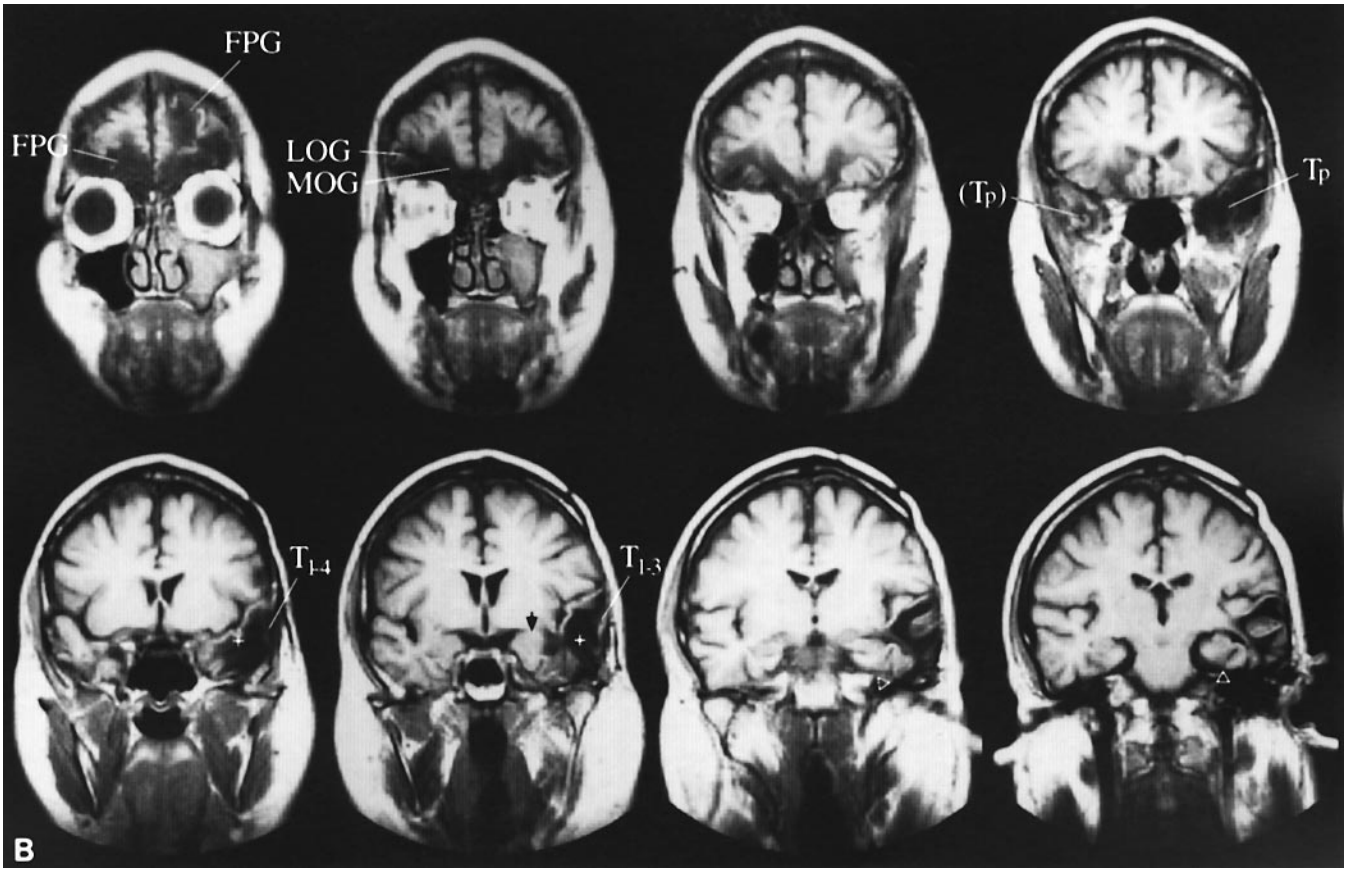


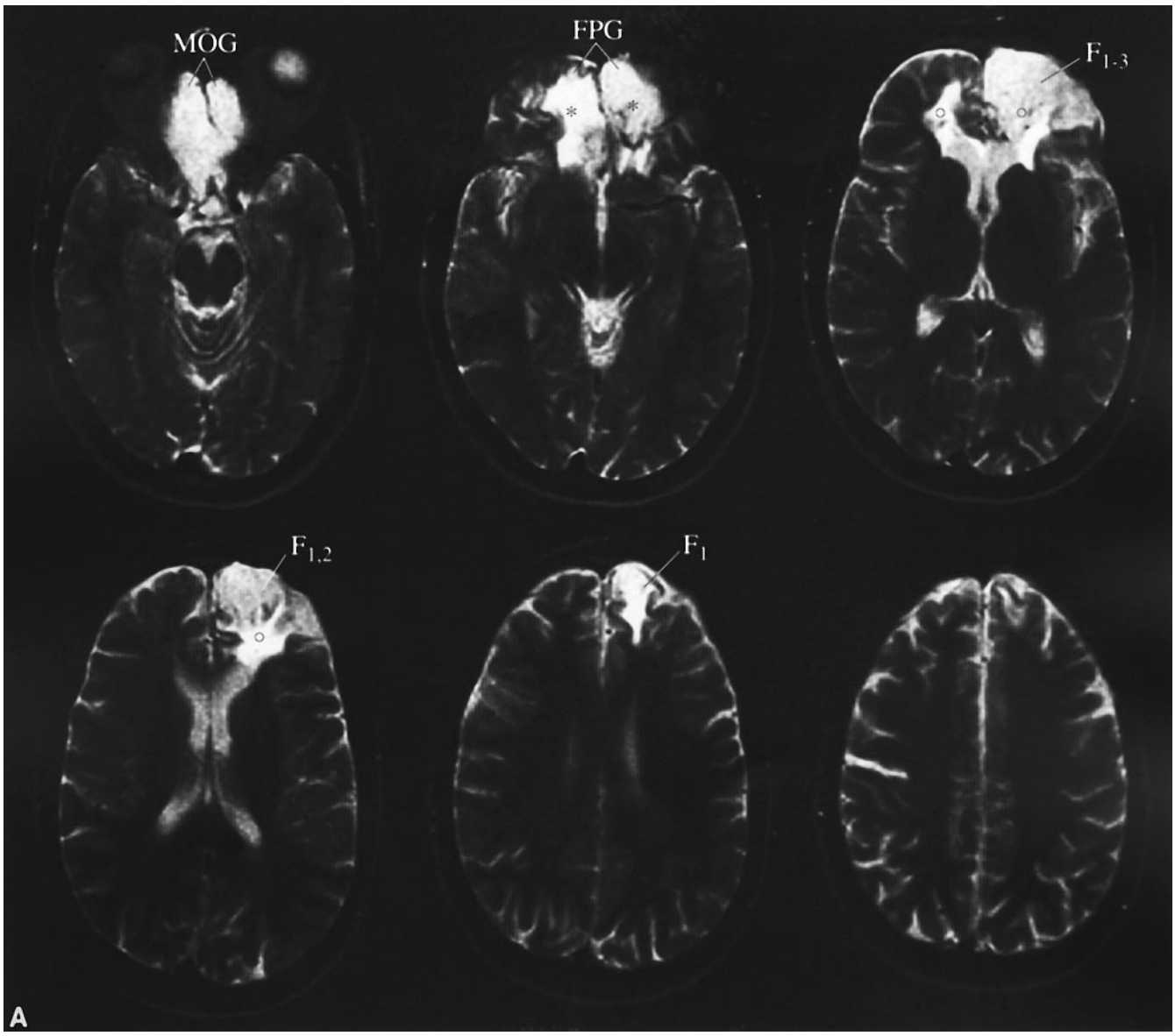
Fig. 2 Patient B.B. (**A**) T_2-weighted horizontal sections. (**B**) T_1-weighted coronal sections. Spared mediotemporal structures: gyrus semilunaris, ambiens; amygdala; head of the hippocampus (arrows); body of the hippocampus; parahippocampal gyrus (arrowhead). For abbreviations, *see* Table 1.

carried out in January 1996 (i.e. 19 years post-injury) using a 0.5 T scanner. MRI comprised coronal and transverse T_1-weighted (TR 500; TE 20) 5-mm sequences.

Coronal and transverse T_1-weighted images. A section through the optic chiasm demarcates the posterior border of a large tissue area of low signal intensity in the right frontal lobe. The cortical contours of the entire polar cap, the inferior frontal gyrus (with the exception of a small strip of its opercular portion), the anterior insula and the orbital and frontobasal cortices are no longer discernible. This also holds true for the underlying frontal white matter and for a major portion of the head of the caudate nucleus, the anterior limb of the internal capsule and the anterior putamen/nucleus accumbens. The destruction of the anterior substantia innominata and other sublenticular structures can be assumed. Less marked hypointensities involve the frontodorsal white matter expanding into the gyral stalks of the first and second frontal gyri. A small hypointensive strip, largely restricted to the cortical band, seems to involve the right temporopolar region and the anterior temporal operculum.

On the left side, a significantly less hypointense tissue area is primarily focussed on the frontoorbital structures. The cortex of the gyrus rectus, and of the adjacent orbital gyrus, is affected. A hypointense tissue zone reaches from the inferior polar cap through the orbital white matter posteriorly to the anterior horn of the lateral ventricle, presumably involving the most anterior parts of the left neostriatum and, in particular, the head of the caudate nucleus.

In comparison with an age-matched group of controls, the anterior horns of the lateral ventricles, the frontal interhemispheric fissure and the frontal sulci appear mildly (to moderately) widened. The concavely sunken dorsolateral convexity of the right frontal lobe should be emphasized.



The remainder of the brain appears inconspicuous.

Summary of MRI findings. The MRI, carried out 19 years post-injury, reveals extended tissue damage in the right frontal lobe due to a, presumably haemorrhagic, contusion and surgical debridement following the patient's motorcycle accident in 1977. Frontopolar, ventrolateral, orbital and basal frontomedial cortices (corresponding with BA 10, 11, 12, 44, 45, 46 and 47), the anterior insular region and a substantial compartment of the frontal white matter appear largely destroyed. The partial destruction of the right neostriatum and of some sublenticular nuclei, as well as the interruption of the anterior limb of the internal capsule and sublenticular pathways interconnecting the septal region with mediobasal temporal structures, may play an additional role in the lesion pattern.

In contrast, the mildly hypointense areas in the frontodorsal white matter, reflecting gliotic tissue repair following regional traumatic oedema or axonal degeneration, may be of minor importance. The lesion of the right anterior temporal operculum appears quite insignificant compared with the much more extended temporal lesions in Patients A.A. and B.B.

The left frontal lesion is less substantial regarding both its extent and the degree of tissue damage. It is centred on parts of BA 10 and 11 and the underlying fronto-orbital white matter which, together with the head of the caudate nucleus, may be the only bilaterally damaged brain structures in this patient.

A summary of the lesion sites in all three of the patients is presented in Table 2. Patients A.A. and B.B. have bilateral but dominantly left-hemispheric temporopolar and prefrontal damage, while Patient C.C., a person of similar age and background, has bi-hemispheric prefrontal damage.

Table 1 *List of anatomical abbreviations and symbols used in Figs 1–3*

FPG	Transverse frontopolar gyri, frontomarginal gyrus
MOG	Gyrus rectus, medial orbital gyrus
LOG	Anterior, posterior orbital gyrus
*	Orbitofrontal white matter
F1	Superior frontal byrus
F2	Middle frontal gyrus
F3	Inferior frontal gyrus
o	Deep frontal/frontodorsal white matter
Tp	Temporopolar region
T1	Superior temporal gyrus
T2	Middle temporal gyrus
T3	Inferior temporal gyrus
T4	Fusiform gyrus
T5	Parahippocampal gyrus
+	Deep temporal
( )	Questionable lesion

Neuropsychological testing

Attention and concentration

The d2-Concentration Endurance (described in Markowitsch *et al*., 1993*a*), Trail Making and Stroop tests were used to

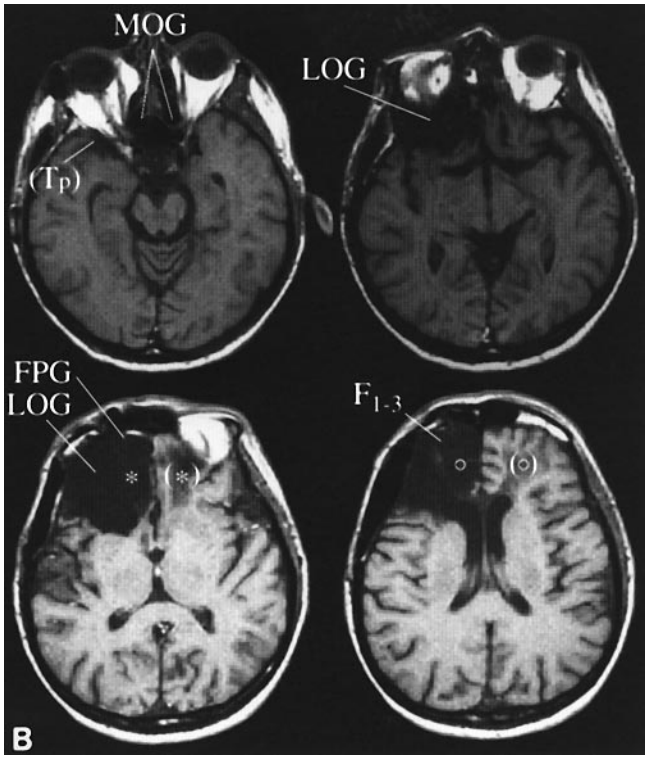


Fig. 3 Patient C.C. (**A**) T_2-weighted horizontal sections. (**B**) T_1-weighted horizontal sections. For abbreviations, *see* Table 1.

Table 2 *Summary of lesion sites in the three patients*

Patients	A.A.	B.B.	C.C.
Frontal lobe			
Gyrus rectus, medial orbital gyrus	Bilateral	Bilateral	Bilateral
Anterior, posterior orbital gyrus	–	Bilateral	–
Orbitofrontal white matter	Left	Bilateral	Bilateral
Frontomarginal, transverse frontopolar gyri	Left	Bilateral	Bilateral
Superior frontal gyrus (anterior portion)	Left	Bilateral	Left
Middle frontal gyrus (anterior portion)	–	Bilateral	Left
Inferior frontal gyrus	–	Bilateral	Left
Deep frontal white matter	Left	Bilateral	Bilateral
Caudate nucleus (head)	–	–	Left
Temporal Lobe			
Temporopolar region	Bilateral	Bilateral	Right?
Superior temporal gyrus	Left	Left	–
Middle temporal gyrus	Left	Left	–
Inferior temporal gyrus	Left	Left	–
Fusiform gyrus (anterior portion)	Left	Left	–
Parahippocampal gyrus	Left	Left?	–
Amygdaloid complex (gyrus semilunaris, ambiens)	–	–	–
Hippocampus proper	Left?	–	–

test attentional and concentration abilities. Patient A.A. scored within normal range on all three tests. Patient B.B. had some difficulty with attentional tasks which had a more cognitive load. He was slowed by the verbal interference in the Stroop Test and by the need to maintain dual alternating sequence on Part B of Trail Making, and he was more than a standard deviation below average on the d2-test. However, he was able to complete all three tasks accurately and without undue prompting or redirection. Patient C.C. was quite slow on the Trail Making Task (Part A = 50 s, Part B = 98 s). Part of his difficulty might be due to his poor eyesight. On the d2-Test, where 'tunnel-vision' is not a handicap, Patient C.C. scored at the 46th percentile. Although Patient C.C. was able to read all 112 words under the time constraints of the Stroop test, he was only able to name 39 of the colours, an extremely low score.

Intelligence and conceptual ability

Intelligence

All three patients were of normal intelligence on the Wechsler Adult Intelligence Scale—Revised (Patient AA: verbal IQ (VIQ) = 96, performance IQ (PIQ) = 115, full scale IQ (FSIQ) = 102; Patient B.B.: VIQ = 116, PIQ = 89; FSIQ = 104; Patient C.C.: VIQ = 106, PIQ = 94; FSIQ = 100).

Cognitive flexibility/rule generation

In the Wisconsin Card Sorting Test (original version), Patient A.A. reached only two categories, Patients B.B. and C.C. six. In the Fibonacci series (*see* Markowitsch *et al*., 1993*c*), Patients A.A. and C.C. discovered the rule by the end of the first five number-string. Patient B.B. required three full sequences of five to figure out the rule. In the Category test (long version) (*see* Lezak, 1995), Patients A.A. and C.C. behaved normally, Patient B.B. was mildly impaired.

Concept comprehension

In the Concept Comprehension test (Cronin-Golomb, 1986), none of the patients had any problems with the concrete concepts. With the abstract concepts Patients A.A. and B.B. made two errors, and Patient C.C. one error (which seemed to be more likely a misinterpretation than a true error). Application of a Test of Simple Calculations (Markowitsch *et al*., 1993*c*) and a Transformation test (writing out numbers; Tegnér and Nybäck, 1990) resulted in a nearly error-free performances from all three subjects. In the Cognitive Estimate Questions (Shallice and Evans, 1978), all three made adequate judgments. In the Tower of Hanoi test with four disks, Patient A.A. required 22, Patient B.B. 16, and Patient C.C. 25 moves; our healthy controls averaged 23.1 moves (minimum number of moves required to solve the problem is 15).

Language

Language and word-fluency abilities of the three patients were average on the Boston Naming Test, Sentence Comprehension Test, and Controlled Oral Fluency Test, with the exception of Patient B.B. who scored in the Low Average range of the Boston Naming Test.

Skill learning and priming

Four tests were used to measure non-declarative memory abilities. In a Mirror Reading Task, subjects attempted to read mirror-images of words as quickly as possible. Words

were presented in nine blocks of 40 with blocks two to eight containing 20 new words and 20 words that were repetitions of new words from the previous block. Block nine contained 20 words from block eight and the 20 words from block one that were not repeated in block two. All patients improved over trials in this skill-learning test and appeared quite similar to the control subjects.

In an Incomplete Pictures test (Henke *et al*., 1993; Kessler *et al*., 1993) subjects see a fragmented picture and attempt to name the object represented. Additional pictures are presented, each one more complete than previous one in the series, until the subject reports seeing the correct object. The number of pictures needed before the subject reports the correct object is recorded. The version we used had one practice- and 10 test-objects with seven possible steps for each object. Each subject received three trials (the second trial being 15 min after the first, and the third 5 days later). All three subjects showed normal perceptual priming performance. Similarly, the normal priming pattern (same modality score > different modality score > baseline score) was found in a Word Fragment Completion test, in which subjects first see or hear a list of 20 eight-letter words (two lists presented visually, two auditorily) and, after each, sees a list of 40 eight-letter word fragments (20 'old', 20 'new').

Learning and memory

Subjective Memory Questionnaire (Bennett-Levy and Powell, 1980). Patient A.A. usually rated himself well within the lower half of the normal range. The tester had, however, the impression that Patient A.A. was either being overly hard on himself or tended to overestimate how well other people can do things. Patient B.B. usually rated himself within the upper half, rating himself as being only really bad at remembering telephone numbers. The tester, however, had the impression that Patient B.B. was overestimating his own abilities on at least some measures. For example, Patient B.B. rated himself as 'average' in remembering spatial routes, yet he always had difficulties in finding his way from the testing room, and his sisters reported that he had always had difficulties in learning new routes (note that this difficulty apparently preceded his accident). Patient C.C. usually rated himself as 'very good' or at least 'good', with a few exceptions.

Wechsler Memory Scale—Revised

Patient A.A. was in the normal range, only his Delayed Recall Index was borderline (85). This decline over time was most evident in his memory for the short stories. Patient B.B. was able to learn the new verbal material presented in the short stories for immediate recall with only minor distortion, but the clarity of his memory fell off rapidly with delay. Patient C.C. was in the normal range. Table 3 summarizes the patients' results on the Wechsler Memory Scale—Revised.

Table 3 *Performance of the three patients on the Wechsler Memory Scale—Revised*

Patient	Memory			Attention-concentration	Delayed recall
	Verbal	Visual	General		
A.A.	90	126	92	100	85
B.B.	107	91	99	95	95
C.C.	110	92	103	100	109

Paired associate learning

An A–B, A–C study–test procedure was used (Shimamura *et al*., 1995). Subjects first received three study–test blocks of 12 word pairs (A–B), with mild pre-experimental associations (e.g. 'lion–hunter'). Then they receive three study–test blocks of 12 new word pairs consisting of the same stimuli, but new responses (A–C, e.g. 'lion–circus'). The results are presented in Table 4 along with those of the prefrontal patients and normal controls tested by Shimamura *et al*. (1995). In general, all three patients performed similarly to normal controls, learning the second list quickly with no intrusions from the first list.

Verbal learning

The California Verbal Learning test entails the learning of categorized lists, each list consisting of 16 words taken from four semantic categories, four words per category. The test involves five presentations and free recall tests with List A, followed by one presentation and a free recall test with List B, followed by free recall and recognition testing with List A. Consecutive recall of words from the same category (semantic clustering) reflects the extent to which an examinee has actively imposed an organization on the list based on semantic features. All three subjects are noticeably impaired in both the recall and recognition portions of this test which requires both semantic organization and list discrimination to do well. The main results for the three patients on the California Verbal Learning test are given in Table 5.

Picture recognition

In a Picture Recognition test, 10 pictures of male and female faces were presented; after a 3-day delay, these were presented again together with 30 distractors (cf. von Cramon *et al*., 1993). Our controls scored 9.1 hits and averaged 2.3 false alarms. Patient A.A. had 9 hits and 2 false alarms. When two of the 30 distractors were presented twice (once early in the test and then again at the end), Patient A.A. immediately spotted these as 'within list repetitions'. Patient B.B. had only 3 hits, but he had 6 false alarms, and did not respond to the 'within list repetitions'. Patient C.C. had 9 hits and 6 false alarms, and noticed the two 'within list repetitions'. Thus, Patient A.A. had normal hit and false alarm rates, Patient B.B. had both fewer hits and more false alarms than any of our control subjects, and Patient C.C. had a normal

Table 4 *Performance of the patients and of brain-damaged and healthy controls in an A–B, A–C paired-associate learning test*

Subject	Percentage correct						Percentage		Intrusions
	List A–B			List A–C			Final recall		
	1	2	3	4	5	6	B	C	A–C
Frontal patients*	79	92	100	63	76	92	77	92	1.67
Normal controls*	87	99	100	85	98	100	98	100	0.17
A.A.	83	99	100	83	100	100	100	100	0.0
B.B.	83	92	100	75	100	100	92	100	0.0
C.C.	83	92	100	83	92	100	92	100	0.03

1, 2 and 3 refer to blocks. *As reported in Shimamura *et al*., 1995.

Table 5 *Performance of the patients in the California Verbal Learning Test*

Patient	A.A.		B.B.		C.C.	
	Raw score	Standard/ T-score*	Raw score	Standard/ T-score*	Raw score	Standard/ T-score*
Recall measures						
List A, trials 1–5 total	38	(24)	58	(56)	49	(40)
List A, trial 1	4	(–2)	9	(+1)	6	(–1)
List A, trial 5	11	(–1)	13	(0)	14	(+1)
List B	3	(–3)	8	(+1)	6	(–1)
List A, short-delay FR	5	(–3)	6	(–2)	10	(–1)
List A, short-delay CR	8	(–2)	8	(–2)	12	(0)
List A, long-delay FR	6	(–3)	8	(–1)	12	(0)
Recall errors (lists A and B)						
Perseverations† (free and cued recall total)	0	(–1)	0	(–1)	4	(0)
FR intrusions (total)†	3	(0)	2	(0)	6	(+1)
CR intrusions (total)†	1	(0)	8	(+2)	5	(+2)
Recognition measures						
Hits	13/16	(–2)	14	(–1)	15	(0)
Discrimination	84%	(–2)	89%	(–1)	89%	(–1)
False positives†	4/28	(+1)	3	(+1)	4	(+1)
Response bias	0.1	(0)	0.2	(+1)	0.6	(+2)

The standard scores are derived from a sample of normal subjects who have not had a history of neurological, psychiatric, or other systemic medical disorder. For all variables, except for 'List A, trials 1–5 total' which uses a 'T-Scale', the standard scores have a mean of 0 and a standard deviation of 1. The 'T-Scale' has a mean of 50 and a standard deviation of 10. All of the standard scores are non-normalized, i.e. any skew in a raw score distribution is preserved in the corresponding standard score distribution. FR = free recall; CR = cued recall. *Standard and T-score equivalents of raw scores based on age and sex. †On these measures, + indicates worse, and – better, than the normal group.

number of hits, but more false alarms than any of our control subjects.

All three patients reproduced the Rey–Osterrieth Figure normally both under immediate and delayed conditions.

Behavioural memory

As in the Rivermead Behavioural Memory Test (Wilson *et al*., 1985), we hid three objects, moving the second object after hiding the third, and asked the subject to remember where they were hidden. All patients recalled all three objects and their locations after 1 h; Patients A.A. and C.C. did so without, and Patient B.B., with some hesitation. After one week Patient A.A. could describe the task, the objects and their places, Patient B.B. had difficulties recalling them, and Patient C.C. was about intermediate between Patients A.A. and B.B.

Semantic retrograde memory

Several tests were given to assess semantic retrograde memory abilities: a headlines memory test (kindly provided by A. Shimamura); a *Time* magazine news test; a transient events test; a general knowledge test (kindly provided by K. Schmidtke, *see* Markowitsch *et al*., 1993*a*); and a famous faces test.

Headlines memory test

This test was updated by us for the time period 1986–1992. It has three forms (A, B and C), each consisting of 38

Table 6 *Performance of the patients in the Headline Memory Test*

	Decade/period					
	1950s	1960s	1970s	1980–4	1985–9	1990s
	Questions (*n*)					
	18	24	20	25	18	9
A.A.						
Recall	0	16.7	20	16	11.1	33.3
Recognition	16.7	33.3	40	44	33.3	55.6
B.B.						
Recall	22.2	25	20	8	11.1	22.2
Recognition	44.4	66.7	65	56	50	44.4
C.C.						
Recall	27.8	41.7	30	12	16.7	22.2
Recognition	44.4	66.7	65	60	55.6	44.4
Healthy control subjects						
Recall	34.6	45.5	38.0	23.5	25.3	44.4
Recognition	53.3	71.7	68.2	66.7	58.4	66.7

The scores represent the percentage correct after combining Form A (1st week), Form B (2nd week) and Form C (3rd week)

questions about 'headline news,' largely taken from Almanacs. First, a recall test without feedback is given, then later a four-choice recognition test of the same items. Forms B and C are used in later sessions. (Unfortunately, although the test relates to the question of when the event happened, the subject may have learned of it later, e.g. a movie may be re-shown on television, a news show may relate a current event to a previous event. In fact, for some of his answers, Patient A.A. suggested that his memory of these older events was not from the original event itself, but from seeing something related to it recently on TV.) Table 6 gives the outcome of the Headlines Memory Test for each of our patients and for our healthy controls.

Transient events test

This test (from M. O'Connor, personal communication) includes 40 questions, one per year from 1950 to 1990. Each question is phrased in a way that maximizes the individual's chance of answering correctly. The most salient aspect of an episode is embedded in the question, so, rather than asking for the name of the school teacher who died in the Challenger explosion, the subject is provided with the name Christa McAuliffe and asked what the name brings to mind. Two specific facts about each event have been identified as critical for a correct answer. Concerning the Christa McAuliffe example, the individual must mention that she was a school teacher and that she was involved in the shuttle explosion in order to receive a score of '2' on the free-recall portion of the test. If the subject can provide only one key fact, she/he receives a score of '1'. If no correct information is elicited, the score is '0'. If the subject does not obtain a full score of '2', a pair of recognition questions are administered. These questions are in the forced choice format and are arranged in a hierarchical fashion so that the first question provides more general information (e.g. 'Did she die in the Challenger explosion or was she a news anchorwoman who filed a sexual discrimination suit?'), while the second question focuses on specific details (e.g. 'Was she an elementary school teacher or a psychologist?'). Results are given in Table 7 for each of our patients and for O'Connor's control subjects.

Time *news test*

Time magazine reported the results of a general news test that they had just given people in various countries. The example questions that they reported, and the percentage of the American people knowing the answer, is given in Table 8, along with the patients' answers. The reason for giving this test was to have some indication as to the attention they were paying to current news stories to compare how well they remembered news stories of the past. Their results seem to indicate that they are, if anything, somewhat more aware of current affairs than is the general American public.

General knowledge of the world

This test included capitals, currencies, automobile brands, famous people and animals (*see* Markowitsch *et al*., 1993*a*). Their correct-recall scores were: Patient A.A. >90%, Patient B.B. 84%, and Patient C.C. 86%. On recognition tests for the questions incorrectly recalled, Patients A.A. and C.C. recognized the correct answers for all of the remaining items and Patient B.B. recognized the correct answers for all but two of remaining 16%.

Famous faces test

Pictures from news magazines were obtained from 1936 onwards, and from three contexts: cultural (movie stars, singers, authors, etc.); political (military and political leaders); and sports. Two points were given for saying the person's name upon seeing the face. One point if either (i) the person was described in some detail, and/or (ii) the name was supplied after various hints (occupation, first name). In addition to our 18 healthy control subjects, five control patients were tested, each of whom had unilateral hippocampal damage and some indication of anterograde amnesia. Note that the faces from the very early magazines represent a kind of baseline for famous people our subjects would have learned about in school or in later life, while the faces from 1956 onwards represent faces that our subjects should have been seeing in the concurrent news media (Table 9).

Autobiographical retrograde memory

The following tests were applied: Old Memories, a Crovitz-form test, Twelve Significant Events, Autobiographical

Table 7 *Performance of Patients A.A., B.B. and C.C. and O'Connor's control subjects on the Transient Events Test*

Time questioned	Patient A.A.		Patient B.B.		Patient C.C.		Controls*
	Recall	Recognition	Recall	Recognition	Recall	Recognition	Recall
1955–9	0	6	0	5	0	7	2.1
1960–4	0	5	1	6	1	7	3.1
1965–9	0	5	0	7	2	6	4.2
1970–4	2	5	1	8	2	8	4.5
1975–9	4	6	3	5	3	10	7.0
1980–4	4	9	2	7	3	8	7.5
1985–90	6	9	4	10	1	8	7.5

*The control group consisted of 12 subjects in the 40–49-year age-group. As most of them had had at least some college education their averages might be higher than those which would have been found with a group more representative of the social/educational class of our subjects. Both recall and recognition scores are from totals of 10 questions per time period. Thus a recognition score of 5 represents chance performance. Patient A.A.'s recognition responses for 1955–74 were accompanied by his saying 'Guessing' or 'Just saw that on TV'. After 1975, he was more likely to say 'I remember that.' Patient C.C. explained his low scores by saying that he had never paid that much attention to current affairs.

Table 8 *Questions from* Time *magazine's 'News Test' with the patients's answers (and the percentage of the American people knowing the answer)*

(1) 'What's the name of the ethnic group that has conquered much of Bosnia and has surrounded the city of Sarajevo?' (Correct answer: Serbs 28%)
A.A.: Serbs
B.B.: Did not know, but recognized the correct answer while tester listed possibilities (rejected Baltics and Slavs).
C.C.: Serbs

(2) 'What's the name of the group with which the Israelis recently reached a peace accord?' (Correct answer: Palestinians 40%)
A.A.: Palestinians
B.B.: Palestinians
C.C.: Jordanians (also right by the time Patient C.C. was tested)

(3) 'Who's the President of Russia?' (Correct answer: Yelsin 50%)
A.A.: Yelsin
B.B.: Did not know, but recognized the correct answer (rejected Kruschev and Andropov)
C.C.: Did not know, but recognized the correct answer (rejected Kruschev and Andropov)

(4) 'Who's Boutros Boutros-Ghali?' (Correct answer: Secretary-General of UN 13%)
A.A.: In charge of UN.
'What country is he from?' (our addition): Switzerland (Correct answer: Egypt)
B.B.: One of the leaders of the Middle East.
C.C.: No idea

Our added questions

(5) 'Why was Dan Rostenkowski in the news lately?' (Correct answer: Running for re-election to the House of Representatives from Chicago despite being accused of malfeasance related to the congressional post office)
A.A.: Senator from east coast running for re-election, he did something bad with the post office or banking.
B.B.: No idea
C.C.: No idea

(6) 'Why was Tonya Harding in the news lately?' (Correct answer: Skater accused of having another skater injured)
A.A.: Skater who had another skater hurt.
B.B.: Skater
C.C.: Skater who had another skater injured

(7) 'What is 'Schindler's List'?' (Correct answer: Movie then about to be released about the holocaust)
A.A.: Movie set in Nazi Germany, I want to see it.
B.B.: World war two movie, looking forward to seeing it.
C.C.: Nazi Germany movie, didn't see it.

Table 9 *Performance on the Famous Faces Test of Patients A.A., B.B. and C.C., five control patients with unilateral hippocampal damage and some evidence for anterograde amnesia, and 18 healthy control subjects*

Subjects	Healthy controls	Patient controls	A.A.	B.B.	C.C.
Birth	1925–1955	1921–1950	1949	1945	1953
Trauma	–	1975–1988	1974	1975	1977
Performance on Famous Faces Test, during years					
1936–45	48.7	49.5	35.2	33.6	11.7
1946–55	47.9	48.5	17.8	23.3	23.6
1956–65	59.1	57.8	27.8	41.7	34.8
1966–75	65.7	63.3	27.8	41.1	66.7
1976–85	58.8	53.3	37.8	40.6	56.1
1986–93	57.2	50.5	51.7	52.8	56.1

Events and an Autobiographical Memory Interview. In order to have a solid basis for asking Patients A.A. and B.B. about their personal pasts, two of each of their sisters were interviewed, and relevant details from their pasts were recorded in detail. Unfortunately, Patient C.C. did not have family members living in the reachable area.

Old Memories Test

In the Old Memories Test, there was a huge discrepancy between Patient A.A.'s memories from the recent past and those from the time before his brain damage. He had no problems remembering the first meeting with the examiner and details of the testing procedure. On the other hand, he had only very few, isolated memories from his childhood and youth, at least some of which had been told to him after his injury. Of those isolated events he seemed to remember, all seemed to be of a quite emotional nature, e.g. burning his family's house and consequently being spanked with a razor strap by his father, and when he had to move to the front of the class in grade school because his eyesight had deteriorated, and he could no longer see the board from the back of the room (later he suggested that he had been told of the 'moving to the front of the class' incident). He could neither remember his favourite special toy from his childhood, even after several hints were added, nor a number of his close associates of his youth. He was very concerned about not being able to remember any interactions with one younger sister, though both of his older sisters interviewed told how he used to defend her at school.

We asked a number of questions from his personal past, including some related to his previous occupation. He remembered very little and, from those few items he did remember, he was frequently uncertain as to whether he had been told about them after his accident or whether he remembered the actual event. However, it seems that he has some isolated memories from his pre-trauma phase. He termed these items as 'little bits and pieces that don't really connect with each other.' He also had the impression that things from the very recent past 'seem more likely that they really happened to me'. On the other hand, he was able to describe in some detail various tasks that he had performed while in the navy.

Two of Patient B.B.'s sisters (one older and the other his twin) were interviewed extensively to get an idea about events in the patient's early life. Patient B.B. is not as introspective as Patient A.A. and has a tendency to joke and confabulate in order to give what appear, on the surface, to be answers to questions about his early life. Many of these confabulations are quite obvious. For example, he brags about having been the favourite travelling companion and beer-drinking buddy of his commanding officer while he was stationed in Germany, supposedly because of his command of the German language. When the interviewer started speaking to him in German, Patient B.B.'s German proved to be virtually non-existent.

Patient B.B. appears to have much more information about his early life than does Patient A.A., although it is not clear how much may have been 're-learned' after his injury, but there also appear to be many 'holes' in his memories. Many incidents described by his sisters were not remembered at all by Patient B.B. He did, however, seem to have a good grasp of names of early friends, and names of many of the locations which were significant to his childhood, at least for that period of his life after the age of ten.

It was not possible to interview any of Patient C.C.'s family members, but he talks quite normally about his early life. His statements made a consistent story and those statements that were possible to verify were reasonably accurate.

Crovitz-form test

In the Crovitz-form test (cf. O'Connor *et al*., 1992; Hodges and McCarthy, 1993), 10 high-frequency nouns are administered and the patient is asked to describe personal experiences of a unique episode relating to each word. The instructions were: 'Relate personally-experienced life events from any time-period evoked by each of the following words...' and 'Now estimate the date of this occurrence.' The first 10 words constitute the 'unconstrained condition' where the subject is allowed to relate memories from any

age. The second 10 words constitute the 'early condition' where the subject is asked to relate memories from before the age of 17 years. The final 10 words constitute the 'middle condition' where our subjects were asked to relate memories from between the ages of 20 and 30 years. The whole procedure was repeated 7 days later.

Under the unrestrained time condition Patient A.A. produced no memories from the time prior to his injury. When there was a restraint to the time before the age of 17 years, he gave five short answers on five events ('got a car'; 'there was a tree beside our home'; 'shot my dad's shotgun'; 'stepped on nail'; 'killed my brother's pet pigeon'). For the time period between the ages of 25 and 35 years, he had even fewer memories. When this whole testing procedure was repeated a second time, he presented exactly the same early memories, but did add a few new details.

Under the unrestrained time condition, Patient B.B. produced only one memory from the period prior to his accident, and that had a definite 'story' tone to it. When asked for early memories, the earliest memory he produced was from the age of 10 years. While his early memories were ostensibly the same across sessions, the details were often dramatically different. His unrestrained and middle memory reports tended to be different across sessions.

Under the unrestrained time condition, Patient C.C. produced one memory from the age of 4 years, one from the age of 12 years, one from the age of '16 or 17 years', and five recent memories (he claimed to be unable to produce memories for the words 'happy' or 'successful'). On the second test, one of the recent memories was replaced by an even more recent memory of something that had happened to him on the way to the testing session. The remaining memories under this condition were basically the same. Under the early condition, Patient C.C. produced nine memories (his response to 'clumsy' was simply: 'I wasn't clumsy then, not until my accident.'). In the second session, one of the words produced a different memory. In the middle condition, he produced nine memories, but one was a bit fanciful (involving a rather unlikely fight scene). The fanciful one was not repeated in the second session. Under all conditions, the details and perspectives changed on some memories from the first to the second session, but these changes were not in conflict.

Twelve Significant Events

Each subject was asked about 12 significant autobiographical events.

Patient A.A.'s answer to the question 'What is your first memory?' was 'Needing a shave in the military hospital' (immediately after his brain damage). He did not remember the name of his first grade teacher, nor any toy that he received during childhood.

When asked for his first memory, Patient B.B. started telling about an event that occurred to him in Korea. This turned out to be a misunderstanding. He thought he was being asked to talk about the first thing that came to mind. When asked to try to remember something from early childhood, he reported a story from fifth grade (when he was ~10 years old). Of the six questions designed to elicit early childhood memories, Patient B.B. could not answer the two specifically asking for the first two years of school and answered the other four with memories about fifth and sixth grade.

When asked for his first memory, Patient C.C. responded being in a tree on a corner in Chicago, ~3.5 years old, hiding from his older brothers. He was also able to answer questions easily about his first toy, the first time he drove a car, his first girl friend, his first colour TV set, etc.

Autobiographical memory interview

The autobiographical memory interview of Kopelman *et al*. (1990) is divided into three sections, Childhood, Early Adult Life and Recent Life, each of which is then subdivided into 'semantic' and 'autobiographical' questions. The section on Recent Life in Kopelman's original version, assumes that the patient's trauma and resulting hospitalization has been recent. Our patients had had their traumas ~20 years previously. Consequently, we modified the autobiographical memory interview to have four sections, Childhood, Early Adult Life, Immediately After Trauma and Recent Life, but kept the general format as similar as possible to the original version.

The autobiographical memory interview is probably not measuring memory for Patient A.A. the way it was meant to measure memory. Many of the items, especially many of the 'episodic' memories, were things that he has re-learned since his accident. He was sometimes uncertain as to whether these were original memories or re-learned memories. At other times, he seemed more certain that they were re-learned. Sometimes he switched with the same 'memory' from one meeting to the next, being certain one time that it was an original memory, and equally certain at another time that it was a re-learned memory.

Patient B.B. could not relate any incidents about his life prior to fifth grade. His scores for events after this time were quite high, although, as with most of his answers, it was difficult to separate true memories, re-learning and confabulations.

Patient C.C. scored very high on the autobiographical memory interview. He lost a few points in childhood by not being able to name three friends before starting school ('I was very lonely then.') and a few points because he couldn't name his grade-school teachers ('I went to Catholic School; they were all called 'Sister'!'), but otherwise got practically every possible point.

Table 10 provides a summary of the autobiographical memory interview subscores and Table 11 provides a summary of the principal neuropsychological test results.

Discussion

We have described detailed neuropsychological testing, with particular emphasis in the memory domain, of two chronic

Table 10 *Autobiographical Memory Interview Subscores*

Section	Maximum score	Patient		
		A.A.	B.B.*	C.C.
Childhood				
Semantic	21	9	18	18
Autobiographical	9	5–9†	6	9
Early adult life				
Semantic	21	6.5	21	21
Autobiographical	9	0	8	9
Immediately after trauma		(1974)	(1975)	(1977)
Semantic	21	16	21	21
Autobiographical	9	3	6	9
Recent life				
Semantic	21	21	21	21
Autobiographical	9	9	9	9

*It is difficult to know how much to trust Patient B.B.'s autobiographical memories. Patient B.B. has a tendency to confabulate and the autobiographical memories are impossible to check. He was not to be able to remember many of the details of his childhood related by his sisters. †Exact score depends on criteria used. Patient A.A. suggested that many of these 'memories' were probably re-learned after his trauma.

patients with combined and dominantly left-hemispheric temporopolar and prefrontal damage and in one chronic patient with bi-hemispheric prefrontal damage. The principal finding is that combined temporofrontal damage, but not substantial prefrontal damage alone, results in marked retrograde memory deficits while leaving intelligence and anterograde memory relatively unimpaired. All three patients manifested average values in intelligence and general memory, were able to describe concrete and abstract concepts, to build up strategies, to show normal priming, and to behave normally in several standard learning tasks. In the quite demanding California verbal learning test, however, all three were impaired; none of them seemed to be able to take full advantage of the potential semantic organization in the word list. Their general knowledge of the world was good, but they demonstrated retrograde memory impairments in several other tests. Impairments were obvious in the Headlines Memory Test, the Transient Events Test, and the Famous Faces Test. Although, of course, it is not possible to know if these subjects had much interest in current events when they were young. With respect to retrograde autobiographical memory, Patient A.A. was severely impaired in all four tests applied, Patient B.B. was moderately impaired, and Patient C.C.'s memory was intact.

These findings confirm and extend previous results from single cases with retrograde memory impairments. First, the brain damage is centred around the inferolateral prefrontal and anterolateral temporal cortices, as had been observed previously (N. Kapur *et al*., 1992; Markowitsch *et al*., 1993*a*, *b*). Secondly, the patients had a traumatic aetiology for their brain damage, a finding stressed decades ago for cases with retrograde memory disorders (Russell 1935, 1971; Russell and Nathan 1946; Whitty and Zangwill, 1977). Thirdly, Patients A.A. and B.B. are able to learn information anew and store that information long-term, a finding again paralleling that of cases L.T. and E.D. of N. Kapur *et al*. (1992) and Markowitsch *et al*. (1993*a*, *b*).

It has been suggested that whenever the relevant brain damage is predominantly right-sided, episodic old memories are affected, whereas semantic old memories are affected when the damage is predominantly left-sided (Markowitsch, 1995*b*). This relationship holds for L.T. and E.D., as well as De Renzi and Lucchelli's (1993) case, who suffered mainly right-hemispheric damage, and for the cases of De Renzi *et al*. (1987) and Grossi *et al*. (1988), who suffered mainly left-hemispheric damage. Exceptions are the more cursorily described patients (Yoneda *et al*., 1992, 1994; Hokkanen *et al*., 1995), who appeared to suffer autobiographical memory loss after left-hemispheric brain damage).

Patients A.A. and B.B. had bilateral damage which may explain their substantial deficits in both the episodic and the knowledge systems. The distinction between episodic and semantic memory may need to be viewed more on a continuum since semantic information may include generalized, repeated episodic information (Hodges, 1994), and generalized (i.e. episodic plus semantic) encoding deficits in brain-damaged patients (Verfaellie and Cermak, 1994) may hold for retrieval as well.

The episodic memory system may be more sensitive to brain damage than the knowledge system since episodic information is unique (Damasio, 1990), while semantic memories may derive from episodic events with generalization and repetition (Hodges, 1994) and may be associated with more cues. Furthermore, the ecphory (triggering stimulus) required by episodic memories may often need a synchronized activation of affect-coding structures of the limbic system (amygdala) (Markowitsch, 1996). ('Ecphory' is used by Tulving, 1983, to describe the process by which retrieval cues interact with stored information during the reconstruction of the information in question.)

The lateral temporopolar-orbitofrontal cortices may not be the locus of the engrams, but appear to be a necessary mediator (Markowitsch, 1995*b*). This fact has been stressed for decades. Penfield wrote in 1968 (p. 839): 'This should not suggest to us that the engram and its thread of facilitation are localized in the temporal cortex beneath the surgeon's electrode. Indeed it suggests only that there is a scanning mechanism, in the temporal cortex, that is capable of activating the thread of facilitation at a distance.' Single unit results from human patients suggest that 'a large proportion of neurons in the lateral temporal cortex are dedicated to... the initial retrieval from memory' (Haglund *et al*., 1994, p. 1513). Emphasizing the initial retrieval is in line with our view that the lateral temporal cortex is not the principal storage site of episodic memory, but the one which triggers cortical storage sites to provide memory output. This interpretation seems also to be corroborated by the outcome

Table 11 *Overview of the principal neuropsychological testing results in the patients*

Test	Patient		
	A.A.	B.B.	C.C.
Intelligence (WAIS-R)	102	104	100
Wisconsin Card Sorting Test, categories	2*	6	6
Concept Comprehension Test, errors	2	2	1
Tower of Hanoi (four-disk version): number of moves	22	16	25
Boston Naming test	Average	Low average	Average
Mirror Reading Task: % improvement, 1st/repeat	40%	46%	28%
Incomplete Pictures Test: % improvement, 1st/3rd day	130%	55%	40%
Word Fragment Completion:			
visual priming–baseline	26%	30%	23%
auditory priming–baseline	11%	5%	10%
Wechsler Memory Scale—Revised	92	99	103
Paired-associate learning: blocks 3 and 5, final recall	100	100	100
California Verbal Learning Test	Impaired*	Impaired*	Impaired*
Picture Recognition Test (hits/false alarms)	9/2	3*/6*	9/6*
Rey–Osterrieth Figure: immediate, delayed	Normal	Normal	Normal
Headline Memory Test: 1960s recall; controls = 45.5%	16.7%†	25%†	41.7%
Transient Events Test: 1960–69 recall; controls = 7.3	0*	1*	3*
General Knowledge of the World	90%	84%	86%
Famous Faces Test: 1966–75; controls = 65.7%	27.8%*	41.1%*	66.7%
Old Memories Test	Isolated memories*	Some memories†	Probably normal
Crovitz Test	Strongly impaired*	Strongly impaired*	Probably normal
Twelve significant events questions	Strongly impaired*	Impaired*	Probably normal
Autobiographical memory interview	Impaired*	Probably impaired†	Normal

WAIS-R = Wechsler Adult Intelligence Scale—Revised. *Significantly worse than normals. †Value likely to be worse than normals (or Patient C.C.).

of single unit recordings in animals (Gochin *et al*., 1994; Nakamura *et al*., 1994).

Retrograde amnesia is a multi-facetted phenomenon which can accompany various kinds and loci of diseases (e.g. Albert *et al*., 1981; Hodges and Gurd, 1994), and which can occur after damage to quite divergent brain loci (e.g. N. Kapur *et al*., 1992; Hodges and McCarthy, 1993; Markowitsch *et al*., 1993*a*; Ogden, 1993). Consequently, retrograde amnesia may either be the consequence of widespread cortical damage, as in cases with dementia, where the stored representations or engrams are actually lost (Hodges *et al*., 1992), or in cases with hypoxia-induced widespread cortical dysfunction (Markowitsch *et al*., 1997). Or, as in the present cases, it may (like anterograde amnesia) be a disconnection syndrome which can occur after interruption of major memory processing pathways in the temporofrontal cortex. For this kind of damage then, the engrams may still exist, but access to them is interrupted due to the specific locus of cortical damage (Markowitsch, 1995*b*).

One of our reviewers asked us to explain, given that this distribution of injury is relatively common, why is isolated retrograde amnesia is so rarely reported. There are probably a number of reasons contributing to this. For example, only modern medicine may enable these patients (with weeks of coma) to survive and still regain their other intellectual and motor–sensory abilities. Another contributing factor could be that doctors may not usually test for it. Retrograde amnesia is a variable phenomenon which may often be mistaken for a confused state, especially as the patient is able to fill in some of the gaps with semantic memory and will be re-learning the past through interactions with relatives.

The role of the frontal cortex in retrieval

Results from studies in patients with selective prefrontal damage usually do not indicate significant retrieval deficits. Only the active, effortful engagement in ecphorizing information may be disturbed (Jetter *et al*., 1986; Gershberg and Shimamura, 1995). Other features of mnemonic information processing which are altered after prefrontal damage include aspects of metamemory and memory for the temporal order of events (Shimamura *et al*., 1990).

Furthermore, the prefrontal cortex is viewed as active in the monitoring of environmental stimulation (Shallice, 1982; Knight, 1984), and in the application of strategies (Shallice and Burgess, 1991).

All of these functions have, however, a closer affinity to the dorsolateral than to the orbitofrontal aspects of the frontal lobes. Damage to the orbitofrontal region is assumed to induce changes in personality and emotional behaviour (Röhrenbach and Markowitsch, 1997).

Subcortically, the mediodorsal thalamus contributes substantially to memory processing, both with respect to encoding and retrieval (Hodges and McCarthy, 1993; Markowitsch, 1993*a*, 1995*a*). It is not surprising that a number of reports point to anatomical–behavioural interactions between the mediodorsal thalamus and the prefrontal cortex. Goldenberg *et al*. (1991) found a lasting hypometabolism after transient global amnesia which initially had resulted in medial thalamic dysfunction. Related to this, Baron *et al*. (1994) noted prefrontal hypometabolism in transient global amnesia. Hennerici *et al*. (1989), Pepin and Audary-Pepin (1993) and Szelies *et al*. (1991) similarly found prefrontal dysfunction after focal thalamic damage.

In conclusion then, the prefrontal cortex contributes to memory retrieval both by providing the impetus or trigger for an active search of the engrams (Markowitsch, 1995*b*, 1996) and by its capacity as a temporal organizer. As mentioned in the Introduction, autobiographical memory is composed of personally significant knowledge and temporal knowledge (Anderson and Conway, 1993). The temporal structuring or temporal ordering of information is apparently necessary for its successful ecphory and retrieval. Results from single cases with prefrontal damage strongly support this view (Dall'Ora *et al*., 1989; Della Sala *et al*., 1993).

The role of the temporal cortex in retrieval

Descriptions of memory related changes in patients with temporal lobe epilepsy provide one major source for the idea that the temporal lobes are memory-sensitive structures. However, as the major cause of temporal lobe epilepsy lies in prolonged febrile seizures in infancy or in birth complications (Penfield, 1975; Miller *et al*., 1993), it can be assumed that the brain of most temporal lobe epileptics has undergone changes from the early postnatal stage onward. Consequently, it is likely that there is a considerable rewiring and functional shift in the brains of such patients. This makes an interpretation of memory-related changes difficult, whether or not there has been a surgical intervention. Nevertheless, we will discuss data from this approach.

Electrical stimulation

Penfield (1958, 1968, 1975) elucidated many of the phenomena occurring during electrical stimulation of the temporal lobe. One of his major findings was the appearance of what he called 'psychical responses', i.e. reproductions of past personal experiences (Penfield, 1958); 'The subject relives a period of the past, although he is still aware of the present' (Penfield, 1958, p. 23). While he attributed these to the (lateral) temporal cortex, Gloor *et al*. (1982) and Fish *et al*. (1993) later emphasized that the stimulation of limbic regions was responsible. Halgren *et al*. (1978, 1985) were also able to elicit numerous responses of this kind in epileptic patients. Furthermore, Halgren *et al*. (1985) found that the disruption of medial temporal lobe activity for >1 s during recognition also resulted in deficits, suggesting that the stimulated structures might also be engaged in retrieval. (It should, however, be noted that there was only a small delay period between original encoding and retrieving, so that consolidation might not have been completed for these stimuli.)

An additional source for an involvement of the lateral temporal lobes in memory retrieval comes from studies on semantic dementia. Patients with semantic dementia frequently have damage predominantly in these regions and show an inability to retrieve world knowledge information (Hodges *et al*., 1992, 1994; Hodges and Patterson, 1995). Furthermore, there seems to be some indication for a hemispheric asymmetry, with left temporal damage being more closely related to semantic retrograde amnesia and right temporal lobe damage to a retrieval deficit of public figures (cf. also Evans *et al*., 1995; Greene and Hodges, 1996).

In summary then, case descriptions of epileptic patients with temporal lobe involvement indicate a role of lateral temporal portions in memory retrieval.

Why is there successful retrieval of memories acquired after the temporofrontal damage?

As is also demonstrated by Patients A.A. and B.B., patients with selective temporofrontal damage are still able to acquire new information after the insult and subsequently recall it from long-term memory. This recall must therefore occur via routes independent of the damaged temporofrontal areas. While we do not know the reason for this, speculations on the plasticity of the nervous system which may lead to rewiring or rerouting of information acquired after brain damage appear appropriate (Treadway *et al*., 1992). Another idea, formulated by Squire *et al*. (1993), is that the process of consolidation may last for years and may therefore allow a recall via limbic regions over this time period. One might also assume the existence of hierarchically ordered recall systems, similar to the models proposed for memory encoding after damage of relevant bottleneck structures (Markowitsch, 1988). With respect to the differential retrieval of information acquired after brain damage (but not before brain damage), the additional requirement is that the process of information consolidation implies the immediate establishment of a retrieval path. In the intact brain this retrieval path would principally and primarily involve the temporofrontal junction areas. In the brain with damage to this region an immediate

retrieval path would be established to other, intact structures, lower in hierarchy, and less accurate and precise in retrieval.

Several authors have proposed the idea, implicitly or explicitly, that the storage of memory content is composed according to landmarks (e.g. around an important event such as the second world war). This could then result in the inability to recall events which occurred prior to the landmark of the brain damage, while not affecting those stored thereafter (Treadway *et al*., 1992; Hodges and McCarthy, 1993). This view might also be in accordance with Wolpaw's (1971) hypothesis that brain damage which is especially traumatic (the dominant aetiology for retrograde amnesia) may disrupt the association between memories due to the 'missing link' (temporofrontal junction area) which is necessary for the organized triggering of (frontal portion) and access to (temporal portion) the engrams. The temporofrontal junction area is composed of the inferolateral prefrontal cortex (portions of BAs 10, 11, 12 and 47) and the temporopolar cortex (BA 38 and possibly immediately adjacent areas). This region is intimately interconnected via the ventral branch of the uncinate fascicle (Ebeling and von Cramon, 1992) and both the prefrontal and the temporal portion (BA 38) receive afferents from the thalamic mediodorsal nucleus (Markowitsch *et al*., 1985). As our present findings confirm, this region may constitute a unity with respect to its involvement in ecphorizing (Calabrese *et al*., 1996) information from the past.

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