INVITED REVIEW

Disorders of memory

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Summary

This paper reviews disorders of memory. After a brief survey of the clinical varieties of the amnesic syndrome, transient and persistent, selected theoretical issues will be considered by posing a series of questions. (i) What is impaired and what is spared in anterograde amnesia? (ii) Do temporal lobe, diencephalic and frontal lobe amnesias differ? (iii) How independently semantic is semantic memory? (iv) What determines the pattern and extent of retrograde memory loss? (v) Can retrograde amnesia ever be 'isolated'? (vi) Does psychogenic amnesia involve the same mechanisms as organic amnesia? (vii) How and when do false memories arise? Commonalities as well as differences across separate literatures will be emphasized, and the case for a more 'dynamic' (interactionist) approach to the investigation of amnesia will be advocated.

Introduction

'So we beat on, boats against the current, borne back ceaselessly into the past.'

(F. Scott Fitzgerald, *The Great Gatsby*, 1925.)

'The places that we have known belong now only to the little world of space on which we map them for our own convenience. None of them was ever more than a thin slice, held between the contiguous impressions that composed our life at that time; remembrance of a particular form is but regret for a particular moment; and houses, roads, avenues are as fugitive, alas, as the years.'

(M. Proust, *Remembrance of Things Past*, 1913.)

The literature on memory and its disorders has proliferated, particularly since the advent of recent neuroimaging techniques. However, controversy remains concerning certain broad issues, selected examples of which will be considered in turn in this review, following a brief survey of the clinical disorders that give rise to an amnesic syndrome. The focus of the review will be on neuropsychological studies of patients with disorders of episodic or semantic memory, and there will be only brief reference to functional neuroimaging studies of healthy individuals.

Varieties of amnesic syndrome

The *amnesic syndrome* can be defined as: 'An abnormal mental state in which memory and learning are affected out of

all proportion to other cognitive functions in an otherwise alert and responsive patient' (Victor *et al.*, 1971).

The *Korsakoff syndrome* can be defined as the same but with the following phrase added: '... resulting from nutritional depletion, notably thiamine deficiency.'

In fact, Victor *et al.* (1971) used the first description as a definition of the Korsakoff syndrome, but the present author feels that it is important to distinguish between amnesic syndromes in general (for which the Victor *et al.* definition suffices) and the particular clinical condition described by Korsakoff (1889), whose cases (with hindsight) can all be viewed as having suffered nutritional depletion, whether of alcoholic or non-alcoholic causation. Various disorders can give rise to an amnesic syndrome, including herpes encephalitis, severe hypoxia, certain vascular lesions, head injury, deep midline tumours, basal forebrain lesions and occasionally early dementia.

The Korsakoff syndrome

As just mentioned, the Korsakoff syndrome is the result of nutritional depletion, i.e. thiamine deficiency. Korsakoff (1889) described this condition as resulting from alcohol abuse or from a number of other causes, but by far the most common nowadays is alcohol abuse.

There are frequent misunderstandings about the nature of this disorder. 'Short term memory' is intact in the Jamesian sense of recall over a matter of seconds (Zangwill, 1946), but learning over more prolonged periods is severely impaired, and there is usually a retrograde memory loss which characteristically extends back many years or decades (Kopelman, 1989; Parkin *et al.*, 1990*b*). Korsakoff (1889) himself noted that his patients 'reason about everything perfectly well, draw correct deductions from given premises, make witty remarks, play chess or a game of cards, in a word comport themselves as mentally sound persons.' However, he also noted repetitive questionings, the extensive nature of the retrograde memory loss, and a particular problem in remembering the temporal sequence of events, associated with severe disorientation in time. As will be discussed below, he gave examples of confabulation that reflected the problem with temporal sequence memory, such that real memories were jumbled up and retrieved inappropriately, out of temporal context.

Many cases of the Korsakoff syndrome are diagnosed following an acute Wernicke encephalopathy, involving confusion, ataxia, nystagmus and ophthalmoplegia. Not all these features are always present, and the ophthalmoplegia in particular responds rapidly to treatment with high-dose vitamins. These features are often associated with a peripheral neuropathy. However, the disorder can also have an insidious onset (Cutting, 1978*a*), and such cases are more likely to come to the attention of psychiatrists: in these cases, there may be *either* no known history *or* only a transient history of Wernicke features. There are also reports that the characteristic Wernicke–Korsakoff neuropathology (see

below) is diagnosed much more commonly at autopsy in alcoholics than in life (Torvik *et al.*, 1982; Harper, 1983), implying that many cases are being missed.

The Korsakoff syndrome is unusual among memory disorders in that there is a distinct neurochemical pathology with important implications for treatment. Following animal research in the 1930s and 1940s, and the important observations of de Wardener and Lennox (1947) and others in malnourished prisoners-of-war, thiamine depletion was established as the mechanism giving rise to the acute Wernicke episode, and the subsequent (Korsakoff) memory impairment. However, the genetic factor, predisposing certain heavy drinkers to develop this syndrome before hepatic or gastro-intestinal complications, remains unclear. It was thought that a transketolase gene might account for this, because transketolase is the enzyme that requires thiamine pyrophosphate (TPP) as a co-factor. Such a gene has been identified (McCool *et al.*, 1993), but it does not account for all the properties of transketolase and only very weakly for predisposition to the Korsakoff syndrome. Moreover, it remains unclear how thiamine depletion produces the particular neuropathology found in Wernicke–Korsakoff patients, although Witt (1985) pointed out that six neurotransmitter systems (including acetylcholine, GABA, glutamate) are affected by thiamine depletion, either by reduction of TPP-dependent enzyme activity or by direct structural damage (see also Butterworth, 1989). Whatever the precise mechanism, treatment as soon as possible with high doses of parenterally administered multi-vitamins is essential. The Wernicke features respond well to high doses of vitamins, and such treatment can prevent the occurrence of a chronic Korsakoff state (Victor *et al.*, 1971; Lishman, 1998). The small risk of anaphylaxis is completely outweighed by the large risk of severe brain damage if such treatment is not administered.

The characteristic neuropathology in what is often known as the 'Wernicke–Korsakoff syndrome' consists of neuronal loss, micro-haemorrhages and gliosis in the paraventricular and peri-aqueductal grey matter (Victor *et al.*, 1971). However, there has been debate as to which particular lesions are critical for the chronic memory disorder to arise. Victor *et al.* (1971) pointed out that all 24 of their cases, in whom the medial-dorsal nucleus of the thalamus was affected, had a clinical history of persistent memory impairment (Korsakoff syndrome), whereas five cases, in whom this nucleus was unaffected, had a history of Wernicke features without any recorded clinical history of subsequent memory disorder. By contrast, the mamillary bodies were implicated in all the Wernicke cases, whether or not there was subsequent memory impairment. However, Mair *et al.* (1979) provided a careful pathological and neuropsychological description of two Korsakoff patients, whose autopsies showed lesions in the mamillary bodies and the anterior and midline thalamus, including the paratenial but *not* the medial-dorsal nuclei. Mair *et al.* suggested that the lesions they described might 'disconnect' a critical memory circuit running between the

temporal lobes and the frontal cortex. Mayes *et al.* (1988) obtained very similar findings in two further Korsakoff patients, who were also very carefully described both neuropsychologically and at autopsy. More recently, Harding *et al.* (2000) found neuronal loss and atrophy in the mamillary bodies and medial-dorsal thalamic nucleus of 13 Wernicke patients, whether or not they developed (Korsakoff) amnesia. Comparison of eight Korsakoff with five 'Wernicke only' patients showed differences confined to the anterior principal thalamic nucleus, suggesting that atrophy in this structure is critical for the development of amnesia.

There is also neuropathological evidence of general cortical atrophy in Korsakoff patients particularly involving the frontal lobes (Torvik *et al.*, 1982; Harper *et al.*, 1987), and this is associated with neuropsychological evidence of 'frontal' or 'executive' test dysfunction in these patients (Leng and Parkin, 1988; Jacobson *et al.*, 1990; Shoqeirat *et al.*, 1990; Kopelman, 1991).

There have been a number of neuroimaging studies in the Korsakoff syndrome. CT scan studies indicated a degree of general cortical atrophy, particularly involving the frontal lobes (Shimamura *et al.*, 1988; Jacobson and Lishman, 1990). MRI studies have indicated more specific atrophy in diencephalic and frontal structures (Jernigan *et al.*, 1991; Colchester *et al.*, 2001). The findings in single photon emission tomography (SPECT) and PET studies have been more variable, some studies showing widespread hypoperfusion and hypometabolism (Hunter *et al.*, 1989; Paller *et al.*, 1997), other studies showing very little change relative to healthy controls (Martin *et al.*, 1992). White matter and diencephalic changes have also been implicated (Reed *et al.*, 2002).

Victor *et al.* (1971) reported that 25% of Korsakoff patients 'recovered', 50% showed improvement through time and 25% remained unchanged. Whilst it is unlikely that any established Korsakoff patient shows complete recovery, the present author's experience is that substantial improvement does occur over a matter of years, if patients refrain from alcohol: it is probably correct to say that 75% of Korsakoff patients show a variable degree of improvement, whilst 25% show no change.

Herpes encephalitis

This can give rise to a particularly severe form of amnesic syndrome (Wilson and Wearing, 1995). The majority of cases are said to be primary infections, and a history of a preceding 'cold sore' on the lip is uncommon. There is characteristically a fairly abrupt onset of acute fever, headache and nausea. Seizures can occur, and there may be behavioural changes. The fully developed clinical picture with neck rigidity, vomiting, and motor and sensory deficits may take several days to emerge (Peto and Juel-Jensen, 1996). Diagnosis is by a raised titre of antibodies to the virus in the CSF, but often this is missed and a presumptive diagnosis is made on the

basis of the clinical picture as well as severe signal alteration in the temporal lobes on MRI brain imaging, associated with loss of tissue volume, haemorrhage and oedema.

Neuropathological and neuroimaging studies show that there is usually extensive bilateral temporal lobe damage (Hierons *et al.*, 1978; N. Kapur *et al.*, 1994; Yoneda *et al.*, 1994; Colchester *et al.*, 2001) although, occasionally, the changes are surprisingly unilateral (Stanhope and Kopelman, 2000). There are often frontal changes, most commonly in the orbito-frontal regions, and there is a variable degree of general cortical atrophy. The medial temporal lobe structures are particularly severely affected, including the hippocampi, amygdalae, and the entorhinal, perirhinal and parahippocampal cortices. Evidence from studies of bilateral temporal lobectomy (Scoville and Milner, 1957; Milner, 1966), as well as animal lesion studies (Zola-Morgan *et al.*, 1989; Murray *et al.*, 1993; Zola *et al.*, 2000), has indicated that these structures are particularly critical in memory formation.

The chronic memory disorder in herpes encephalitis shows many resemblances to that in the Korsakoff syndrome, consistent with the fact that there are many neural connections between the thalami, mamillary bodies and the hippocampi (Aggleton and Saunders, 1997). Encephalitis, like head injury, can also implicate basal forebrain structures, which give cholinergic outputs to the hippocampi; since these are thought to modulate hippocampal function, this may further exacerbate the damage (Damasio *et al.*, 1985; Phillips *et al.*, 1987; von Cramon and Schuri, 1992).

Contrary to what was postulated in the 1980s, there appears to be no difference between Korsakoff patients and herpes encephalitis patients in terms of forgetting rates (Kopelman and Stanhope, 1997), but herpes patients show better 'insight' into the nature of their disorder (Kopelman *et al.*, 1998*a*) and a 'flatter' temporal gradient to their retrograde memory loss (i.e. less sparing of early memories). They may have a particularly severe deficit in spatial memory, especially when the right hippocampus is implicated (Kopelman *et al.*, 1997). Semantic memory is more commonly affected in herpes patients, and this results from the involvement of the left infero-lateral temporal lobe, producing impairments in naming, reading ('surface dyslexia') and other aspects of lexical-semantic memory. Right temporal lobe damage may lead to a particularly severe impairment in face recognition memory or knowledge of people (e.g. Eslinger *et al.*, 1996).

Severe hypoxia

Severe hypoxia can give rise to an amnesic syndrome following carbon monoxide poisoning, cardiac and respiratory arrests, or suicide attempts by hanging or poisoning with the exhaust pipe from a car. Drug overdoses may precipitate prolonged unconsciousness and cerebral hypoxia, and this quite commonly occurs in heroin abusers. A recent review has provided a timely reminder that the neuropathological and cognitive consequences of hypoxia are variable and can be widespread (Caine and Watson, 2000), a point widely

accepted in clinical practice but sometimes neglected in the neuropsychological literature.

Zola-Morgan *et al.* (1986) described a patient who, following repeated episodes of hypoxia and cardio-respiratory arrest, developed moderately severe anterograde amnesia. At autopsy 6 years later, this patient was shown to have a severe loss of pyramidal cells in the CA1 region of the hippocampi bilaterally, whereas the rest of the brain appeared relatively normal. Press *et al.* (1989) reported hippocampal atrophy on MRI in three amnesic patients, and Kopelman *et al.* (2001) found medial temporal lobe atrophy in hypoxic patients although these patients also showed reduced glucose metabolism in the thalami on [^{18}H]fluoro-deoxy glucose PET (FDG PET) (Reed *et al.*, 1999; compare Markowitsch *et al.*, 1997*b*). In brief, the memory disorder is likely to result from a combination of hippocampal and thalamic changes, related to the many common neural pathways between these two structures (Fazio *et al.*, 1992; Aggleton and Saunders, 1997). A recent finding of fornix atrophy and memory deficits following carbon monoxide poisoning (Kesler *et al.*, 2001) is consistent with this view.

Vascular disorders

Vascular disorders can particularly affect memory, as opposed to general cognitive functioning, in (i) thalamic, medial temporal or retrosplenial infarction, and (ii) subarachnoid haemorrhage.

In an elegant CT scan study, von Cramon *et al.* (1985) showed that it was damage to the anterior thalamus that was critical in producing an amnesic syndrome (compare with Harding *et al.*, 2000). When the pathology was confined to the more posterior regions of the thalamus, memory function was relatively unaffected. The anterior region of the thalamus is variably supplied by the polar or paramedian arteries in different individuals, both of which are, ultimately, branches of the posterior cerebral circulation. More recently, Van der Werf *et al.* (2000), in a review of the literature, argued that it is damage to the mamillo-thalamic tract, which projects into the anterior nuclei of the thalamus, that is critical in producing an amnesic syndrome. A relatively pure lesion of the anterior thalamus produces anterograde amnesia (AA) with minimal retrograde amnesia (RA) (Graff-Radford *et al.*, 1990; Parkin and Hunkin, 1993; Kapur *et al.*, 1996*a*). Cases of more extensive RA (Hodges and McCarthy, 1993) or dementia have been described, probably reflecting the extent to which fronto-cortical projections are implicated in the infarction.

The hippocampi are supplied by the anterior and posterior choroidal arteries, branches of the internal carotid and posterior cerebral arteries, respectively (Walsh, 1987). Unilateral infarction tends to give rise to material-specific memory loss and bilateral damage to global amnesia (O'Connor and Verfaellie, 2002). The retrosplenium is also supplied from the posterior cerebral artery, and infarction or haemorrhage can produce amnesia by disrupting connections to anterior thalamus, entorhinal and parahippocampal cortices (Valenstein *et al.*, 1987; Maguire, 2001).

Subarachnoid haemorrhage following rupture of an aneurysm can result in memory impairment, whether the anterior cerebral or posterior cerebral circulation in the Circle of Willis is involved (Richardson, 1989, 1991). Ruptured aneurysms in the anterior communicating artery can implicate the basal forebrain and ventro-medial frontal structures. Gade and others have argued that it is whether or not the septal nucleus of the basal forebrain is damaged that determines whether a persistent amnesic syndrome occurs in such patients (Gade, 1982; Gade and Mortensen, 1990). Others have attributed the florid confabulation that sometimes occurs to associated ventro-medial frontal damage (e.g. De Luca and Cicerone, 1991; Moscovitch and Melo, 1997; Gilboa and Moscovitch, 2002).

Head injury

Head injury can give rise to either transient or persisting amnesia. It is important to distinguish between RA, which is usually (but not necessarily) relatively brief, post-traumatic amnesia (PTA), and 'islands' of preserved memory within the amnesic gap (Russell and Nathan, 1946; Lishman, 1968, 1973, 1998). Occasionally, PTA may exist without any RA, although this is more common in cases of penetrating lesions. Sometimes there is a particularly vivid memory for images or sounds occurring immediately before the injury, on regaining consciousness, or during a lucid interval between the injury and the onset of PTA.

PTA is generally assumed to reflect the degree of underlying diffuse brain pathology, in particular rotational forces giving rise to diffuse axonal injury. King (1997) has reported that PTA can be assessed with reasonable reliability; the length of PTA is predictive of eventual cognitive (Brooks, 1984), psychiatric (Lishman, 1968), and social outcome (Russell and Smith, 1961; Brooks, 1991). However, the duration of PTA is often not well documented in medical records, and these relationships are often weaker than is generally assumed. PTA needs to be distinguished from persisting anterograde memory impairment, which may be detected on clinical assessment or cognitive testing long after the period of PTA has ended. Levin *et al.* (1988*a*) found that, during PTA, head injury patients showed accelerated forgetting of learned information, whereas after PTA forgetting rates were normal (compare with Baddeley *et al.*, 1987).

Damage to the frontal and anterior temporal lobes by direct trauma results in contusion, haematoma and haemorrhage. Contre-coup damage, intracranial haemorrhage and hypoxia can all result (Teasdale and Mendelow, 1984). Rotational and acceleration–deceleration forces may produce shearing or tensile stretching of axons with subsequent gliosis (Strich *et al.*, 1956; Oppenheimer, 1968). The resulting intra-axonal changes lead to a failure in axoplasmic transport, axonal swelling, and, ultimately, to disconnection, de-afferentation

and loss of synaptic boutons over a matter of hours or days (Blumbergs *et al.*, 1995; Povlishock and Christman, 1995).

Memory is commonly the last cognitive function to show improvement following an acute trauma (Conkey, 1938), and patients can show the characteristic features of an amnesic syndrome (Baddeley *et al.*, 1987; Levin *et al.*, 1988*b*). Disproportionate RA has been described (see below), particularly in association with damage to the frontal or anterior temporal regions. Forgetfulness is also a common complaint within the context of mild concussion (Lishman, 1988; Fleminger, 2000). Whilst research studies show that recovery from mild head injury is typically expected 1–3 months post-injury, some patients demonstrate symptoms far beyond this time (Barth *et al.*, 1996): long periods of disability and enduring post-concussion symptoms are related, in part, to individual vulnerabilities. In such cases, complaints characteristically persist long after the settlement of any compensation issues (Merskey and Woodforde, 1972; Miller, 1979; Tarsh and Royston, 1985).

Recent controversy has concerned whether severe head injury and amnesia exclude the possibility of post-traumatic stress disorder (PTSD) symptoms. O'Brien and Nutt (1998) argued that a head injury causing coma and severe amnesia prevents the 're-experiencing' symptoms of PTSD. However, McMillan (1996) described 10 patients with head injury of varying severity, in whom PTSD arose. These 10 patients reported 'windows' of experience, in which emotional disturbance was sufficient to cause PTSD, even though PTA was of relatively long duration (three patients had PTAs of more than 2 weeks). These 'windows' involved recall of events close to impact when RA was brief (e.g. of a lorry bearing down), *or* of distressing events soon after the accident (when PTA was short) *or* of 'islands' of memory (e.g. hearing the screaming of others). Others reported distressing recollections that appeared to be self-generated or that had been reported to the patient by others. McNeil and Greenwood (1996) reported PTSD symptoms in a young traffic accident victim, who had an RA of 2 days and a PTA of 4 weeks. Despite these cases, the topic remains controversial, and some authors have even disputed whether victims of mild head injury can have PTSD (for review, see Harvey *et al.*, 2002).

Transient global amnesia

Transient global amnesia (TGA) most commonly occurs in the middle-aged or elderly, more frequently in men, and results in a period of amnesia lasting several hours. As is well known, it is characterized by repetitive questioning, and there may be some confusion, but patients do not report any loss of personal identity. It is sometimes preceded by headache or nausea, a stressful life event, a medical procedure, intense emotion or vigorous exercise. Hodges and Ward (1989) found that the mean duration of amnesia was 4 h and the maximum 12 h. In 25% of their sample, there was a past history of migraine, which was considered to have a possible aetiolo-

gical role. In a further 7%, the patients subsequently developed unequivocal features of epilepsy in the absence of any previous history of seizures. There was no association with either a past history of or risk factors for vascular disease, nor with clinical signs indicating a vascular pathology. In particular, there was no association with transient ischaemic attacks. In 60–70% of the sample, the underlying aetiology was unclear.

Somewhat similarly, Miller *et al.* (1987), in a sample of 150 men and 127 women, found that the mean duration of the episode was 6.2 h, ranging from 2 to 12 h. A seizure disorder was noted in eight patients and, as in the Hodges and Ward (1989) report, the incidence of cerebro-vascular events (stroke) was no higher than would be expected in this age group.

Where neuropsychological tests have been administered to patients during their acute episode of transient amnesia (Kritchevsky *et al.*, 1988; Hodges and Ward, 1989), the patients have shown a profound AA on tests of both verbal and non-verbal memory, but RA was variable, usually being relatively brief but occasionally prolonged, and worse for recall of episodes than facts (Evans *et al.*, 1993; Guillery *et al.*, 2000). Following the attack, Kritchevsky and Squire (1989) reported that there was complete recovery after several weeks. Miller *et al.* (1987) stated that 'a selective verbal memory deficit' was found 'in a few patients. .. [although] persisting memory complaints or frank dementia following TGA were seldom noted.' However, Hodges and Oxbury (1990), in a follow-up of 41 cases at 6 months, found statistically significant impairments on tests measuring the recall of stories, famous faces, and autobiographical memories.

The general consensus is that the amnesic disorder results from transient dysfunction in limbic-hippocampal circuits, crucial to memory formation. For example, Stillhard *et al.* (1990) reported severe bitemporal hypoperfusion during an episode of TGA using SPECT and, after recovery from the episode, cerebral perfusion returned to normal. Evans *et al.* (1993) obtained similar findings, also in a SPECT study, with recovery to normal 7 weeks later. Fujii *et al.* (1989) used FDG PET in TGA patients 3 months after the episode, obtaining normal findings in all but one of the patients. Simons and Hodges (2000) and Goldenberg (2002) have cited evidence that changes on diffusion-weighted MRI might indicate ischaemic disfunction in these brain regions.

Transient epileptic amnesia

This refers to the minority of TGA cases in whom epilepsy appears to be the underlying cause (Heathfield *et al.*, 1973; Fisher, 1982; Miller *et al.*, 1987; Hodges and Ward, 1989). The main predictive factors for an epileptic aetiology are brief episodes of memory loss (1 h or less) and multiple attacks (Miller *et al.*, 1987; Hodges and Warlow, 1990; Kapur, 1990). It is important to note that standard EEG and CT scan findings are often normal. However, an epileptic

basis to the disorder may be revealed on sleep EEG (Kopelman *et al*., 1994*a*). Kapur (1990) coined the phrase 'transient epileptic amnesia' (TEA) to describe such attacks: this is a useful term, although it does not distinguish between episodes that are *ictal* (Palmini *et al*., 1992; Vuilleumier *et al*., 1996) and those that are *post-ictal* in nature (Tassinari *et al*., 1991).

Patients with TEA may show residual deficits in between their attacks, associated with their underlying neuropathology. These may involve anterograde memory (Kopelman *et al*., 1994*a*) or aspects of remote memory (Kapur *et al*., 1986, 1989; Zeman *et al*., 1998). Most commonly, the patients complain of 'gaps' in their past memory. It seems plausible that the patients may have had brief runs of seizure activity in the past: these would have been undetected clinically but resulted in faulty (anterograde) encoding of very specific items in autobiographical memory (Kopelman, 2000*a*). An alternative interpretation is that the current epilepsy somehow prevents the retrieval of old, autobiographical memories (Kapur, 2000; Manes *et al*., 2001).

Epilepsy may, of course, give rise to automatisms or post-ictal confusional states (Logsdail and Toone, 1988; Fenwick, 1990; Lishman 1998). Where there is an automatism, there is always bilateral involvement of the limbic structures involved in memory formation, including the hippocampal and parahippocampal structures bilaterally as well as the mesial diencephalon (Fenton, 1972). Consequently, amnesia for the period of automatic behaviour is always present and is usually complete (Knox 1968; Fenwick, 1990, 1993).

Summary

The above examples do not, of course, comprise a comprehensive list of the disorders which give rise to transient or persistent amnesia. What they have in common is that temporary or permanent dysfunction or damage in medial temporal/diencephalic circuitry (or in the basal forebrain cholinergic inputs to that circuitry) produces the amnesia. The remainder of this article concerns theoretical issues that arise in our understanding of the functioning of this circuitry and its interaction with frontal lobe and temporal neocortical mechanisms.

What is impaired and what is spared in anterograde amnesia?

As is well known, a distinction is usually drawn between so-called 'working memory', which holds information for brief periods of time (a matter of seconds) and allocates resources, and secondary memory in which information is stored on a permanent or semi-permanent basis (James, 1890; Hebb, 1949; Baddeley and Warrington, 1970; Shallice and Warrington, 1970). Secondary memory can, in turn, be subdivided into an episodic (or 'explicit') component, semantic memory and implicit memory. Episodic memory refers to incidents or events from a person's past (allowing that person 'to travel back mentally in time') and it is characteristically affected in the amnesic syndrome, whereas semantic memory refers to knowledge of facts, concepts and language (Tulving, 1972). Implicit memory includes classical conditioning, the procedural learning of perceptuo-motor skills and the facilitation of responses in the absence of explicit memory known as 'priming'. Much neuropsychological research has examined which of these components are affected/spared in amnesia, and the underlying mechanisms of deficit.

Encoding, storage and retrieval

Over the years, there has been extensive debate concerning whether the primary deficit in the amnesic syndrome lies in either (i) the initial encoding of episodic memories, or (ii) some kind of physiological 'consolidation' into secondary memory, or (iii) faulty encoding and storage of contextual information, or (iv) accelerated forgetting of information, or (v) in retrieval processes (Warrington and Weiskrantz, 1970; Butters and Cermak, 1980; Meudell and Mayes, 1982).

(i) Faulty encoding

Some theories propose that there is a deficit in the psychological processes involved in the initial 'registration' or representation of information. In particular, it has been argued that, whilst Korsakoff patients are able to 'encode' the direct, sensory properties of information, they have difficulties in 'processing' its more meaningful (semantic) qualities (e.g. Butters and Cermak, 1980). For example, they perform particularly badly at learning word-pairs (e.g. hungry–thin), the recall of which is normally facilitated by thinking of semantic links between the words (Cutting, 1978*b*; Butters and Cermak, 1980). On the other hand, giving instructions or orienting tasks that encourage the extraction of meaning from a stimulus produces, at most, a relatively small enhancement in the amnesic patients' subsequent recall of that stimulus, an effect closely similar to that seen in healthy controls (Meudell *et al*., 1979; McDowall, 1981; Meudell and Mayes, 1982). Consequently, it seems unlikely that a failure to encode semantic information is the fundamental memory deficit in amnesia.

(ii) Faulty consolidation

A second type of hypothesis proposes that there is impairment in the physiological processes that are assumed to occur *shortly after* an initial representation is laid down in order to establish ('consolidate') information into some relatively permanent form (e.g. Meudell *et al*., 1979; Moscovitch, 1982). These processes were traditionally thought to involve the 'transfer' of information from primary to secondary

memory, operating during a time-period of something less than a minute. The hypothesis was suggested by the finding that span test scores and other measures of primary memory (requiring the recall of information within a few seconds) were relatively intact in Korsakoff, medial temporal lesion and head injury patients (e.g. Milner, 1966; Brooks, 1984). In one particularly intriguing study, Lynch and Yarnell (1973) interviewed six concussed American footballers within 30 s of their injury and at intervals thereafter. Although they were initially able to give a lucid account of events occurring just before the blow, they subsequently developed a 'relatively complete' RA, suggesting that their immediate memories had not been effectively consolidated. A problem with this theory is that it cannot by itself explain why RA of more than a few seconds or minutes should occur unless one postulates a distinct '*slow*' consolidation process lasting years or decades. This issue will be discussed below.

(iii) Faulty encoding or storage of contextual information

Huppert and Piercy proposed a very specific deficit in amnesic patients' acquisition of contextual (e.g. temporal/spatial) information (Huppert and Piercy, 1976, 1978), and this idea was adopted by several other groups (e.g. Mayes *et al.*, 1985). There is certainly substantial evidence of disproportionate contextual memory deficits in amnesic patients, but difficulties with this theory include (a) the fact that the pattern of contextual memory deficits may vary substantially across patient groups (e.g. Parkin *et al.*, 1990*a*), and that disproportionate contextual memory deficits are not always found (Squire, 1982; Cave and Squire 1991); and (b) such deficits have often been attributed (perhaps erroneously) to concomitant frontal lobe pathology, rather than to the medial temporal/diencephalic lesions critical to the development of anterograde amnesia. Recently, this theory has evolved into a more generalized notion of a deficit in binding complex associations (Mayes and Downes, 1997) or memory for relations between items (Cohen *et al.*, 1997). In turn, this notion relates to various distinctions to be considered below: between recall and recognition memory, remembering and knowing, and between explicit and implicit memory.

(iv) Accelerated forgetting

A fourth possibility focuses upon 'storage' (retention) rather than learning processes. On the basis of findings in a single-case (HM), Huppert and Piercy (1979) argued that patients with hippocampal lesions show accelerated forgetting, even after material has been adequately learned; however, this was not the case in patients with diencephalic pathology. Some support for this finding has been obtained in other patients with hippocampal pathology (Parkin and Leng, 1988; Frisk and Milner, 1990) and also in Alzheimer patients (Hart *et al.*, 1987). However, there were ceiling effects in the first two of

these studies, and a failure to use equivalent measures at different time-periods in the third. Moreover, Freed *et al.* (1987) failed to replicate Huppert and Piercy's original observation in HM (Huppert and Piercy, 1979) in HM when he was studied repeatedly across the same time delays; and Kopelman (1985) and McKee and Squire (1992) found no difference in forgetting between diencephalic patients and those with Alzheimer dementia or focal temporal lobe lesions. Recent studies have demonstrated an apparent difference between recognition memory, in which forgetting rates in amnesic patients were normal once initial learning had been accomplished, and recall measures in which amnesic patients showed accelerated forgetting over delays of a few minutes (Kopelman and Stanhope 1997; Christensen *et al.*, 1998; Isaac and Mayes 1999*a*, *b*; Green and Kopelman, 2002). However, there were no differences in these latter studies between patients with primarily diencephalic or temporal lobe pathology (Kopelman and Stanhope, 1997; Green and Kopelman, 2002). One interpretation of such findings is that the major deficit in amnesia involves acquisition or learning processes, since impairments in new learning can be detected on standard measures of either recognition or recall memory, but that there is an additional, more subtle impairment in retention (or 'consolidation') over a period of minutes, detectable only on recall tests (Kopelman and Stanhope, 1997, 2001; Green and Kopelman, 2002).

(v) Faulty retrieval

Two types of retrieval hypothesis have been postulated. 'Pure' retrieval hypotheses postulate a retrieval deficit arising independently of any failure of 'acquisition' processes. For example, Warrington and Weiskrantz postulated that amnesic patients are unable to suppress inappropriate responses during recall or recognition tasks (Warrington and Weiskrantz, 1968, 1970). They noted that amnesic patients sometimes respond erroneously to memory tests with what had been the correct replies to previous tasks and, secondly, that the provision of retrieval cues can improve their performance. On the other hand, it has been shown that healthy subjects also exhibit these phenomena when given recall tests at relatively long retention intervals (e.g. a week), suggesting that they may be a consequence of poor memory rather than its cause (Woods and Piercy, 1974; Mayes and Meudell, 1981). Moreover, restricting the number of choices in a recognition or cued recall test does not necessarily improve amnesic patients' performance relative to controls (Huppert and Piercy, 1976; Warrington and Weiskrantz, 1978). In recent years, the Warrington and Weiskrantz finding of a beneficial effect of cues has been reinterpreted as demonstrating preserved priming in the presence of impaired explicit memory (e.g. Shimamura, 1986), and there is also evidence that intact priming can precipitate interference effects when explicit memory is impaired (Mayes *et al.*, 1987). A modified retrieval hypothesis stresses evidence that retrieval processes are heavily dependent upon the nature of initial encoding, and

that retrieval deficits arise as a consequence of an initial encoding impairment (Tulving and Thompson, 1973). Moreover, a retrieval deficit may be important where there is an extensive RA (Weiskrantz, 1985; Kopelman, 1989; see below).

In summary, several studies point to a problem in the initial acquisition or 'consolidation' of information with a more subtle impairment in retention (forgetting) detectable only on recall testing. There may also be a secondary deficit in retrieval processes. However, the precise nature of this acquisition deficit remains ill defined. One possibility is that there is a deficit in 'binding' different types of material including contextual information, and that this relates to various distinctions drawn within episodic memory, which will now be considered.

Recall and recognition memory

There may be a differentiation between recall and recognition memory. On the basis of a meta-analysis of single case and small group studies of amnesic patients, Aggleton and Shaw (1996) claimed that patients whose pathology was confined to circuitry involving the hippocampi, fornices, mamillary bodies, mamillo-thalamic tract and anterior thalami, showed impairments on recall but not recognition testing. They argued that in such patients, memory based on familiarity judgements (recognition) was intact, whereas recall memory, involving recollection of such contextual features as time and spatial location, was impaired (see also Aggleton and Brown, 1999). They postulated that damage to other structures, such as the perirhinal cortex, was required to produce an impairment in recognition memory. A potential problem with this single-dissociation is that it might simply reflect the severity of amnesia, milder amnesic patients (with less extensive pathology) showing relatively spared performance at recognition memory. Aggleton and Shaw (1996) tried to argue against this by comparing the recognition memory scores of (i) patients with 'limbic' lesions and (ii) Korsakoff/'other' amnesic patients, where the revised Wechsler Memory Scale (WMS-R) scores of the two groups did not differ significantly. However, there were trend differences in recall scores, several of which were close to 'floor', making any interpretation equivocal.

Consistent with the Aggleton hypothesis, Vargha-Khadem *et al.* (1997) described three patients with a developmental amnesia for everyday events, resulting from brain injury in infancy or early childhood. These patients showed a pronounced loss of hippocampal volume bilaterally, and their neuropsychological test performance showed impairments on recall but not recognition memory, the latter being tested with material that included lists of words, non-words, familiar faces and unfamiliar faces. These findings suggested that, whilst recall of episodic memories (involving a temporal and spatial context) was impaired as a result of these patients' hippocampal pathology, recognition memory and semantic

memory were spared, because they do not necessarily involve recollection of temporal/spatial context: this allowed these individuals to cope within mainstream education (see also Baddeley *et al.*, 2001).

In contrast, Squire and colleagues have shown impaired performance in a series of studies on measures of recognition memory by patients whose pathology was apparently limited to the hippocampal formation: their studies included 29 measures of verbal and non-verbal recognition memory (yes/no, forced-choice; Reed and Squire, 1997) and the Doors and People test (Manns and Squire, 1999). Moreover, Zola *et al.* (2000) showed that monkeys with lesions limited to the hippocampal region were impaired on two tasks of recognition memory (but see Baxter and Murray, 2001*a, b*; Zola and Squire, 2001, on animal findings). In human amnesic patients, Kopelman *et al.* (2001) found no obvious differences between recall and recognition memory tests in the size of their correlations with an MRI measure of hippocampal atrophy.

The major difference between the Vargha-Khadem and Squire findings may be in the severity of the memory disorder in their respective patients. This is somewhat difficult to determine because different tests were employed, but the Vargha-Khadem *et al.* (1997) subjects had a mean Wechsler Adult Intelligence Scale—Revised (WAIS-R) verbal IQ minus Wechsler (Wechsler, 1945) memory quotient discrepancy of 11.67 points (SD $\pm$ 11.15), whereas the Reed and Squire (1997) patients with hippocampal lesions had a mean WAIS-R IQ minus WMS-R general memory index difference of 33.67 points (SD $\pm$ 17.92). In this connection, patient YR, reported by Mayes *et al.* is relevant (Mayes *et al.*, 2001, 2002). YR had bilateral hippocampal atrophy and a 34-point WAIS-R IQ minus WMS-R general memory discrepancy. Across 43 recognition memory tests, YR did show significant impairment relative to controls, but the impairment was very minor (mean $z = -0.5$) and clinically significant (>2 SD) in only 10% of tests. In contrast, her impairment on recall tests was disproportionately severe (mean $z = -3.6$) and clinically significant in 95% of tests.

In summary, it has been hypothesized that hippocampal damage produces a deficit only in recall memory, whereas perirhinal pathology implicates recognition memory as well. The possibility that *completely* spared recognition memory in the hippocampal cases simply reflects a relatively mild memory impairment cannot be excluded. However, there is now at least one case-report suggesting *relative* sparing of recognition memory in a patient with a fairly severe impairment of recall memory.

Remembering and knowing; recollection and familiarity

Gardiner and Richardson-Klavehn (2000) have distinguished between the subjective states of 'remembering' and 'knowing'. They defined *remembering* as 'intensely personal experiences of the past, those in which we seem to recreate

previous events and experiences with the awareness of reliving these events and experiences mentally.' *Knowing* referred to 'experiences of the past, in which we are aware of knowledge that we possess but in a more impersonal way . . . no awareness of reliving . . . [a] general sense of familiarity . . . [of] facts, without reliving them mentally.'

Various experimental studies have identified a number of factors differentiating 'remember' (R) and 'know' (K) memories (Gardiner and Java, 1990; Gardiner and Parkin, 1990; Rajaram, 1993). One issue that arises is whether R memories are (i) a special form of, and have the potential to become K memories ('redundancy'), (ii) the outcome of two overlapping ('independent') processes (one of which is 'knowing'), or (iii) the manifestation of an entirely separate process ('exclusivity'). A second issue is how these subjective states (R, K) relate to more objective measures of 'recollection' and 'familiarity'.

In amnesic patients, Knowlton and Squire (1995) found reduced R and K memories (responses) on a recognition memory test, relative to healthy controls. The controls' performance 1 week later resembled that of the amnesic patients 10 min after stimuli presentation. Moreover, many of the controls' R responses at 10 min became K responses at 1 week, implying that R and K memories were either redundant or independent, but not mutually exclusive. The authors concluded that amnesic patients show impairments in both the R and K components of explicit memory, and that K responses cannot be identified as reflecting 'implicit memory'.

Others have argued that recognition memory judgements can be made *either* on the basis of feelings of *familiarity*, which may be relatively preserved in amnesia (see above), *or* on the basis of contextual memories (e.g. when or where something happened) i.e. *conscious recollection* (e.g. Huppert and Piercy, 1978; Yonelinas, 2001). There have been various attempts to quantify these memory components: for example, Jacoby and colleagues' process dissociation procedure relies on subjects' ability/inability to include or exclude items whose source or context is recollected (Jacoby *et al.*, 1993). Yonelinas (2001) has argued that recollection and familiarity are *independent* processes with very different response characteristics. In recognition memory, recollection produces all-or-none 'high confidence' responses when the contextual information retrieved exceeds a certain threshold. Familiarity produces a much more variable pattern of responding according to trace strength (d') and response bias (B) (signal detection theory), and the pattern of these responses (hits : false alarms) at different levels of confidence (response bias) can be plotted on a so-called receiver operating characteristics (ROC) curve.

Yonelinas *et al.* (1998) emphasized the importance of controlling for response bias in both R/K and process dissociation experiments. They used a signal-detection procedure to recalculate findings from such studies in amnesia (e.g. Verfaellie and Treadwell, 1993; Schacter *et al.*, 1996*a*), and they also reported their own findings plotting ROC curves

in a small group of amnesic patients. Across all three techniques, amnesia produced a pronounced reduction in recollection memory and a smaller but consistent reduction in familiarity responses: this suggested that R and K are subjective states measuring (or reflecting) recollection and familiarity and, conversely, that objective measures of the latter can be used to predict the occurrence of these conscious states (a point contested by Gardiner, 2001).

In summary, the evidence suggests that memories based on 'recollection' (and its subjective counterpart, 'remembering') are severely impaired in amnesia, and that those based on familiarity judgements (or 'knowing') are also significantly impaired, although less severely so.

Explicit and implicit memory

Despite their severe impairment of explicit or episodic memory, many aspects of implicit memory are preserved in amnesic patients. For example, they show intact acquisition and retention of the classically conditioned eye-blink response (Weiskrantz and Warrington, 1979; Daum *et al.*, 1989), provided no interval is interposed between the offset of the conditioned stimulus and the onset of the unconditioned stimulus (Clark and Squire, 1998). Amnesic patients can also show preserved acquisition and retention of perceptuo-motor skills (procedural memory) (Corkin, 1965; Moscovitch, 1982; Cermak and O'Connor, 1983; Wilson and Wearing, 1995). In contrast, procedural memory is impaired in certain subcortical dementias such as Parkinson's disease and Huntington's disease on, for example, pursuit rotor and the 'Tower of Hanoi' tasks (Heindel *et al.*, 1988; Saint-Cyr *et al.*, 1988). More recently, Reber and Squire (1999) have demonstrated that skill learning is not a single entity: Parkinson patients were impaired at 'habit learning', implicating the neostriatum, but showed intact learning of artificial grammars and dot pattern prototypes, which were postulated to reflect brain regions outside both the neostriatum and the medial temporal lobes.

Priming refers to the facilitation of a response in the absence of conscious awareness (explicit memory) that the stimulus has occurred before. This facilitation can occur across perceptually or conceptually similar/identical stimuli. Many studies have demonstrated intact priming in amnesic patients on tasks such as stem-completion (e.g. Graf *et al.*, 1984; Shimamura and Squire, 1984; Graf and Schacter, 1985), and Hamann and Squire (1997) reported fully intact priming in a profoundly amnesic patient (from herpes encephalitis), despite his performing at chance on recognition memory tests. Such findings have been interpreted as demonstrating that priming is not dependent on diencephalic/medial temporal brain structures, but that cortical regions must be critical (e.g. Shimamura, 1986; Schacter, 1987; Alvarez and Squire, 1995; Reber and Squire, 1999).

Keane *et al.* (1995) contrasted the performance of two patients on measures of explicit and implicit memory. The first was LH, who had suffered a severe closed head injury 23

years earlier: he had undergone a right temporal lobectomy and insertion of a shunt for hydrocephalus. In addition, he had damage to the right parietal and occipital lobes and a left hemisphere white matter lesion, which extended from the inferior temporal gyrus to just below the occipital horn. The medial temporal structures were spared gross structural damage. The second patient was HM (Scoville and Milner, 1957; Corkin *et al*., 1997), who became profoundly amnesic following a bilateral medial temporal lobectomy. His MRI showed bilateral pathology including the medial temporal polar cortex, the amygdalae and the entorhinal cortex. The resection involved approximately the anterior 2 cm of the hippocampal formation, and there was atrophy in the posterior 2 cm of the hippocampal fields. The posterior perirhinal and parahippocampal cortices were only slightly damaged. Keane *et al*. (1995) showed that LH was intact at measures of (explicit) recognition memory, but impaired at perceptual priming (e.g. perceptual identification, word-completion priming). In contrast, HM showed severely impaired recognition memory, but intact perceptual priming. On the basis of these findings, Keane *et al*. (1995) argued that visuo-perceptual priming depends on the integrity of occipital circuits that were compromised in LH but were preserved in HM. In contrast, explicit recognition memory is critically dependent on intact medial temporal lobes.

An alternative view has been postulated by Ostergaard, who argued that, when a task is easy and subjects achieve high levels of baseline performance (producing the 'correct' words to cues in the absence of any primes), the possible magnitude of priming effects is constrained and may not reflect the amount of information available from the study ('priming') episode (Ostergaard, 1994, 1998, 1999). When a task was made more difficult, a significant correlation between priming and explicit memory (recognition) scores emerged in healthy subjects (Ostergaard, 1998) and amnesic patients showed a priming impairment not seen on an easier task (Ostergaard, 1999). Moreover, two studies employing quantitative structural MRI (Jernigan and Ostergaard, 1993; Jernigan *et al*., 2001) found correlations between impaired priming and medial temporal/hippocampal volume loss in mixed groups of amnesic, dementing, and healthy control subjects. Ostergaard and colleagues have concluded that amnesic patients show impaired priming, related to medial temporal damage, after controlling for baseline performance (Ostergaard, 1994, 1999). More recently, Kinder and Shanks (2001) have postulated that a single memory system may underlie apparent 'dissociations' in performance on recognition memory and priming tasks, arguing that differential rates of learning between patients and controls and differing task demands across procedures can explain the pattern of results obtained.

Gooding *et al*. (2000) have put forward a third position. They conducted a meta-analysis of studies of implicit memory for familiar or novel information in amnesic patients and healthy controls. In 36 studies involving 59 separate measures, the patients and controls showed equivalent priming on tests using familiar information (the control group doing better 11 times out of 23 investigations). However, the controls performed significantly better than the amnesic patients on priming tasks involving novel items (18 out of 23 studies) or novel associative information (e.g. unrelated word pairs such as mountain–stamp) (nine out of 13 studies). Somewhat similarly, Chun and Phelps (1999) found that amnesic patients showed normal perceptuo-motor (procedural) skill learning on a visual search task, but unlike healthy subjects, they failed to show additional benefits from contextual cueing: the benefits of this contextual cueing were 'implicit' in the healthy subjects because they could not identify the context on subsequent recognition testing. From such findings, Gooding *et al*. (2000) concluded that the hippocampi are essential for encoding and storing (or 'binding') novel information with its *associates* including context, or in making *new associations* between established items, whether implicitly or explicitly.

In summary, the conventional wisdom is that priming is spared in amnesia, and that damage to sites of pathology beyond the medial temporal lobes is required to produce impaired priming (e.g. involving occipital circuitry). However, amnesic patients do show impaired priming in certain experimental conditions, e.g. in 'difficult' tasks where baseline responding has been controlled or in associative learning. This implicates a contribution of medial temporal/diencephalic structures in priming in these circumstances.

Do temporal lobe, diencephalic and frontal lobe amnesias differ?
Lesion studies

There has been considerable interest in whether or not the pattern of memory deficits differs across patients with either medial temporal, diencephalic, or frontal pathology. As already mentioned, Huppert and Piercy (1979) argued that temporal lobe pathology gives rise to accelerated forgetting, whereas diencephalic amnesia does not, but this observation has generally not been supported. An alternative hypothesis is that the diencephalon and medial temporal lobes differ in their contribution to context memory. Parkin and others argued that diencephalic lesions produce larger deficits in temporal order memory than does medial temporal lobe pathology, whereas spatial context deficits are larger for the latter group (Parkin *et al*., 1990a; Hunkin *et al*., 1994). Other studies have provided some support for these findings, but the findings are generally much less clear-cut (Chalfonte *et al*., 1996; Kopelman *et al*., 1997).

Context memory has also been invoked as a particular role of the frontal lobes. Milner (1982) and Butters *et al*. (1994) found impairments in temporal context memory in patients with large frontal lesions, although Milner *et al*. (1991) and Kopelman *et al*. (1997) found that this deficit was confined to patients with lesions penetrating the dorso-lateral frontal cortical margins. Owen *et al*. (1990) described spatial

working memory impairments following frontal lobe lesions, and Schacter *et al.* (1984) reported that deficits in memory for the source of information were correlated with impaired performance on tests of frontal/executive function. More generally, pathology to the frontal lobes has been thought to be damaging to *executive* functions such as planning, the organization of material, monitoring of responses, the inhibition of inappropriate responses, and memory for context (e.g. Shimamura *et al.*, 1991; Shimamura, 1994; Baldo and Shimamura, 2002). Studies have drawn attention, for example, to impairment on subject-ordered tasks (Petrides and Milner, 1982), release from proactive interference (Moscovitch, 1982), or aspects of the 'executive' component of working memory (Baddeley, 1986; Petrides, 2000). This combination of planning, organizational and context memory deficits was considered to explain why, at least in some studies, patients with frontal lobe lesions showed disproportionate impairment on measures of recall memory relative to recognition (Janowsky *et al.*, 1989; Shimamura *et al.*, 1990). Furthermore, the abnormality in temporal context memory has been postulated as the basis for spontaneous confabulation sometimes found in patients with frontal lobe lesions (see below).

There are various problems with a simple notion that the frontal lobes play only a specialized 'executive' role in memory. First, it has become clear that the limbic-diencephalic memory system also contributes to various aspects of context memory, as already indicated. Studies in amnesic patients have shown that deficits in memory for temporal context (Kopelman, 1989; Parkin *et al.*, 1990*a*), spatial context (Shoqeirat and Mayes, 1991) or the modality of information (Pickering *et al.*, 1989) are often attributable to damage in the diencephalon or medial temporal lobes, rather than the frontal cortex. Secondly, some animal studies have indicated a critical role for the frontal lobes in 'target' memory (Bachevalier and Mishkin, 1986; Parker and Gaffan, 1998). Thirdly, Wheeler *et al.* (1995) re-examined the effects of frontal lesions on measures of human recall and recognition memory. In a meta-analysis of the literature, they found that, in virtually all studies, frontal lesion patients were impaired on tests of recall memory, relative to age-matched healthy controls, even if the decrement did not actually reach statistical significance in all individual studies. Moreover, there was a (lesser) degree of impairment in frontal lesion patients on tests of recognition memory in the vast majority of studies. Fourthly, individual patients have been described, in whom frontal lesions have produced a disproportionate impairment in recognition memory, resulting from a high rate of false-positive errors, rather than in recall memory, which is normally more demanding of 'executive' resources (Delbecq-Derouesné *et al.*, 1990; Parkin *et al.*, 1996; Schacter *et al.*, 1996*b*).

Following such observations, Kopelman and Stanhope conducted a series of investigations comparing groups of memory-disordered patients, whose primary pathology was either in the frontal lobes, the diencephalon or the temporal lobes. Although definite differences were found between the frontal and other groups, these were relatively subtle, and there was considerable overlap in the groups' patterns of memory impairment. Memory-disordered patients with frontal lobe lesions performed similarly to other amnesic patients in making frequency judgements (Stanhope *et al.*, 1998) and in their overall performance at recall and recognition memory measures (Kopelman and Stanhope, 1998), although their scores were enhanced by the provision of 'blocked' category cues in a way that was not seen in the other amnesic patients (Kopelman and Stanhope, 1998). Secondly, patients whose frontal lesions penetrated the dorso-lateral cortex demonstrated severe impairment on a measure of temporal context memory, but not on a measure of spatial context memory, whereas other patients with large frontal lesions showed intact performance on both measures (Kopelman *et al.*, 1997). Thirdly, diencephalic and temporal lobe patients showed accelerated forgetting, relative to controls, on measures of recall memory, whereas frontal lesion patients showed only a non-significant trend in the same direction (Kopelman and Stanhope, 1997; but also see Jetter *et al.*, 1986). Fourthly, the frontal patients showed impairment on two measures of remote memory (recall of autobiographical incidents and of famous news events), comparable in severity to other amnesic patients, but (unlike the latter group) they were not impaired in the retrieval of well-rehearsed personal facts. In the latter case, accurate retrieval presumably demands less active or 'effortful' reconstruction processes.

Neuroimaging investigations

Functional neuroimaging studies have been reviewed elsewhere (e.g. Rugg, 2002), and it is beyond the scope of this paper to provide a detailed account. One of the earliest investigations (Grasby *et al.*, 1993) pointed to the strength of frontal activations in memory encoding and retrieval. The HERA (hemispheric encoding and retrieval asymmetry) hypothesis (Tulving *et al.*, 1994*a*) was based on findings that the left frontal region was particularly involved in the encoding of episodic memories, whereas the right frontal region, together with the precuneus, was of particular importance in episodic memory retrieval (S. Kapur *et al.*, 1994; Shallice *et al.*, 1994; Tulving *et al.*, 1994*b*; Fletcher *et al.*, 1995). In contrast, a more recent functional MRI (fMRI) study has produced evidence of traditional left–right material-specific asymmetries during encoding in both the medial temporal lobes and the pre-frontal cortex (Golby *et al.*, 2001). As in lesion studies, it has become important to differentiate the role of frontal and medial temporal structures in episodic memory encoding and retrieval.

Fletcher and Henson (2001) have reviewed evidence for a subclassification of frontal functioning. They argued that ventro-lateral frontal activation is associated with the updating/maintenance of information, dorso-lateral activation with the selection/manipulation/monitoring of that information,

and anterior activation with the selection of processes/ subgoals. On the other hand, Rugg and Wilding (2000) postulated four different classes of retrieval process but argued that, to date, there is little evidence to fractionate their neural correlates.

Other studies have examined medial temporal lobe activation. For example, Schacter *et al.* (1996*c*) found that hippocampal activation was associated with the successful retrieval of episodic memories, whereas left prefrontal activation was associated with less successful but 'effortful' retrieval. Brewer *et al.* (1998) found that parahippocampal activation and a region of right dorsolateral frontal activation were predictive of subsequent remembering of pictures. Gabrieli *et al.* (1997) found that encoding of novel information activated posterior medial temporal regions, whereas successful retrieval was associated with more anterior medial temporal activations. However, on the basis of meta-analyses, Lepage *et al.* (1998) argued that *anterior* medial temporal activations were associated with memory encoding and *posterior* activations with retrieval, whereas Schacter and Wagner (1999) found that encoding activations were associated with *both* anterior and posterior activations. Wagner *et al.* (1998) have argued that the parahippocampal gyri engage general encoding mechanisms, and that the left prefrontal regions may contribute to the organization of event attributes in working memory, serving as input to the medial temporal memory system. Kopelman *et al.* (1998*b*) found that verbal encoding of new stimuli was associated with both a left hippocampal and a left prefrontal activation, but that, as incremental learning to repeated stimuli occurred, the left medial temporal activation remained but the left frontal activation disappeared. Repeated presentation of stimuli was associated with activation in a right prefrontal and precuneus 'retrieval' circuit, suggesting that 'consolidation' of learning engages both the right hemisphere circuit (to retrieve previously learned material) and the left medial temporal region (during incremental learning). Other studies have indicated that medial temporal activation may be particularly related to associative encoding. This has been found using fMRI and verbal stimuli (Mayes *et al.*, 1998), SPECT and pictures of complex scenes (Montaldi *et al.*, 1998), and the encoding of inter-item associations between pictures or words using PET (Henke *et al.*, 1997).

Summary

Recent lesion and neuroimaging studies indicate a closer interaction and overlap in function than was previously assumed between the frontal lobe and medial temporal/ diencephalic structures engaged in memory formation. Whilst a broad distinction between executive processes and encoding/retrieval mechanisms remains valid, there is considerable overlap in the effect of focal lesions involving these brain regions, and in the brain activations associated with specific memory tasks. However, lesion studies indicate that diencephalic/medial temporal patients show faster forgetting on recall tasks than frontal patients, and are less likely to respond to the provision of specific category cues, suggesting a more fundamental amnesic deficit. Similarly, some functional imaging studies suggest that medial temporal activations are more closely related to successful or incremental remembering than are frontal activations. Lesion studies indicate that there may be differences between specific sites of frontal pathology on temporal context memory and in effects upon recall and recognition memory; in functional imaging, dissociations in frontal activation patterns are currently being explored.

How independently semantic is semantic memory?

The distinction between semantic and episodic memory was made by Tulving (1972), although it had historical precedents (e.g. Gillespie, 1937). Semantic memory is the system which processes, stores, and retrieves information about the meaning of words, concepts and facts. It is affected in semantic dementia, a variant of fronto-temporal dementia, and also in herpes encephalitis, Alzheimer dementia, and occasionally in head injury. It seems to be rarely affected in cerebro-vascular disorders ('stroke') because of dual blood supply from the middle and posterior cerebral arteries to the critical regions in the left infero-lateral temporal lobe (Patterson and Hodges, 1995, 2000).

Category-specific deficits

Category-specific impairments are frequently reported in semantic memory disorders. Warrington and Shallice (1984) demonstrated that, in herpes encephalitis patients, identification of living things and foods was severely impaired, relative to the patients' ability to identify inanimate objects, and that this was independent of the modality of presentation. Other dissociations have also been postulated: for example, between physical objects and their word forms, abstract and concrete words, high and low frequency words, nouns and verbs, and content and function words (Warrington and Shallice, 1984; Caramazza, 1998).

Several problems have arisen. On the one hand, not all studies have controlled adequately for properties such as word frequency and familiarity, as pointed out by Funnell and Sheridan (1992) and Stewart *et al.* (1992), although the more recent studies have done so (e.g. Lambon Ralph *et al.*, 1998; Moss *et al.*, 1998). Secondly, unusual dissociations (e.g. patients who are severely impaired in processing animals but not other living things such as fruits and vegetables), highly specific impairments (e.g. confined to fruits and vegetables), or reversed dissociations (animals intact, inanimate objects impaired) have all been reported (Warrington and McCarthy, 1987; Caramazza, 1998). Most particularly, there is little agreement about the *interpretation* of these category-specific impairments. It has been suggested that living things may be

primarily processed in terms of their sensory properties, whereas inanimate objects are processed mainly in terms of their function (e.g. Warrington and Shallice, 1984; Basso *et al.*, 1988; Borgo and Shallice, 2001). However, Moss *et al.* (1998) reported a patient in whom the visual and functional attributes of living things were implicated equally in a naming task, whereas both types of attribute were relatively spared with respect to objects. Many alternative theories have been proposed. Not only is there disagreement about the impaired processes underlying category-specific deficits but, more generally, about whether they provide unambiguous proof of underlying brain mechanisms dedicated to those categories (Caramazza, 1998). An alternative is that category-specific deficits are simply an 'emergent property' of differences in the structure and content of concepts themselves (Tyler and Moss, 2001).

Some functional imaging studies have provided some support for a neurobiological basis to category specificity. Martin and colleagues found differing patterns of activation for generating colour words, action words and form words (Martin *et al.*, 1995, 1996; Chao *et al.*, 1999). Different classes of item were associated with activation of differing networks in discrete cortical regions: identifying and/or naming animals was associated with activations in the lateral fusiform gyrus, medial occipital cortex and superior temporal sulcus, whereas identifying and/or naming tools was associated with activations in the medial fusiform gyrus, left middle temporal gyrus and left premotor cortex. Some of these brain regions overlapped with those that are atrophied in patients with category-specific deficits (Moss *et al.*, 1998; Moss and Tyler, 2000). On the other hand, Devlin *et al.* (2002) identified a neural system common to living things and objects, but failed to find robust evidence of functional segregation by domain or category.

Semantic dementia

Warrington (1975) described three cases of a degenerative disorder, selectively affecting semantic memory. Snowden *et al.* (1989) coined the term 'semantic dementia' to describe some similar cases, and this term was subsequently adopted by Hodges *et al.* (1992) and others. Semantic dementia is really a 'temporal lobe' variant of fronto-temporal dementia or degeneration (Snowden *et al.*, 1996*b*; Hodges *et al.*, 1998). It is characterized by a progressive disorder of semantic knowledge: this involves a profound loss of meaning, encompassing verbal and non-verbal material and resulting in severe impairments in naming and word comprehension. Speech becomes increasingly empty and lacking in substantives, but output is fluent, effortless, grammatically correct and free from phonemic paraphasias. Perceptual and reasoning abilities are intact, and episodic memory is relatively preserved (Snowden *et al.*, 1989, 1996*a*; Hodges et al., 1992; Murre *et al.*, 2001). Primary progressive non-fluent aphasia is another disorder resulting from focal temporal lobe atrophy but in this, unlike semantic dementia, speech output is non-fluent, comprehension is relatively preserved (at least initially), and there are frequent phonemic errors (Snowden *et al.*, 1996*b*).

On MRI, semantic dementia patients characteristically show severe atrophy of the inferior and lateral temporal gyri with relative preservation of medial temporal structures (Snowden *et al.*, 1989; Hodges et al., 1992). A recent study using voxel-based morphometry found pronounced atrophy of the left temporal pole and left antero-lateral temporal lobe region (Mummery *et al.*, 1999). A PET activation study, examining a semantic decision task relative to a visual decision task, showed reduced activity in the left posterior inferior temporal gyrus: this was interpreted as reflecting disrupted temporal lobe connections (Mummery *et al.*, 1999). The right temporal lobe is usually affected to a lesser (but variable) degree, and it is predominantly affected in cases in whom the most prominent problems are in visual semantics (Evans *et al.*, 1995). Although the primary site(s) of cortical pathology are consistent across studies, there is variability in the histopathological findings, which may involve spongiform changes and neuronal loss (Snowden *et al.*, 1996*b*), Pick cells and bodies (Hodges *et al.*, 1998), or ubiquitin-positive tau-negative inclusion bodies identical to motor neurone disease but without involvement of brainstem or spinal cord motor neurones (Rossor *et al.*, 2000).

In semantic dementia, Warrington (1975) found that knowledge of subordinate categories (e.g. the name of a specific animal) was more impaired than knowledge of superordinate categories (e.g. animals or birds). Similar findings were obtained by Snowden *et al.* (1989) and Hodges *et al.* (1992). Hodges *et al.* (1995) monitored the deterioration of a single patient over the course of 2 years, finding that the pattern of relative preservation of superordinate knowledge was demonstrable both during a particular test session and across test sessions longitudinally. However, over the course of time, there was a progression from subordinate to superordinate errors. Warrington (1975) had interpreted this pattern of deterioration as reflecting the hierarchical manner in which knowledge is organized (compare Collins and Quillian, 1969), but Hodges *et al.* (1995) argued that superordinate words have multiple connections within the semantic network, and consequently are less vulnerable to degradation, a view that does not necessarily imply an hierarchical structure to the organization of knowledge. A third view, advocated by Funnell (1995), is that both superordinate and subordinate knowledge *are* affected, after controlling for word frequency and familiarity effects, suggesting that the apparent sparing of superordinate knowledge is an artefact of factors such as word frequency and familiarity. Other classes of knowledge, e.g. number and the ability to perform mental calculations, may be surprisingly well preserved despite the severe disruption of verbal and visual semantics in this disorder (Butterworth *et al.*, 2001; Cappelletti *et al.*, 2001).

Interaction of semantic and episodic memory in semantic dementia

In a series of publications, Snowden and colleagues have pointed to a putative interaction between autobiographical experience and semantic knowledge (Snowden *et al*., 1994, 1995, 1996*a*). They found that patients with semantic dementia recognized the names of personal acquaintances better than those of celebrities, personally familiar place names better than high frequency, impersonal place names, and personal objects better than alternative examples of the same object (Snowden *et al*., 1994). Comprehension of words in conversation tended to be limited to those aspects of meaning relevant to the patient's own life, and definitions given by a semantic dementia patient had a markedly autobiographical quality (Snowden *et al*., 1995). Furthermore, Snowden *et al*. (1996*a*) found that such patients' knowledge was better for contemporary than for past or historical celebrities, for the contemporary decimal monetary system compared with the old (imperial) British monetary system, and for recent personal facts and incidents compared with earlier ones (see below). Snowden and colleagues concluded that current autobiographical experience interacts with and facilitates the maintenance and/or retrieval of residual semantic knowledge in semantic dementia patients (Snowden *et al*., 1994, 1995, 1996*a*; Snowden, 2002). Descriptions of two more patients have provided further evidence of autobiographical cues facilitating semantic knowledge in semantic dementia patients (Funnell, 2001; Westmacott *et al*., 2001).

Graham and colleagues have contested this view (Graham *et al*., 1997, 1999, 2000). They examined knowledge of golf and bowls in two patients with semantic dementia, who were regular participants in these sports. Graham *et al*. (1997) failed to find a direct effect of autobiographical experience on previously learned knowledge of these sports, although one of their patients showed some preserved knowledge of people she saw frequently. Graham and colleagues argued that this knowledge was mediated by the hippocampi, and they characterized it as 'semantic-like' and 'highly autobiographically constrained' (Graham *et al*., 1997, 1999). In reply, Snowden *et al*. (1999) argued that this preserved knowledge is indeed 'semantic', albeit impoverished, and that what determines whether previously established knowledge is available is not the time at which it was acquired (as Graham *et al*., 1997, had suggested) but its relevance to contemporary autobiographical experience.

Dissociation of semantic and episodic memory?

Consistent with the argument of Graham *et al*. (1997), Kitchener *et al*. (1998) provided further evidence for the apparent separation of the neurobiological systems underlying semantic and episodic memory (compare Vargha-Khadem *et al*., 1997; Verfaellie *et al*., 2000). They described a severely amnesic 49-year-old man, whose MRI showed complete destruction of the left hippocampus, parahippocampal gyrus, entorhinal and perirhinal cortex. There was ischaemia in the left thalamus, and infarction involving the left medial frontal lobe and basal forebrain. There was also a circumscribed area of infarction in the right posterior hippocampus and partial atrophy in the remainder of the right hippocampus. There was relative preservation of inferolateral temporal neocortex. The patient showed severe impairment across a range of standard episodic memory tests. However, the patient did show some residual knowledge on tests involving recognition memory for personal events or personally known individuals, and on more semantic tasks involving famous faces, events, names, or premorbidly acquired vocabulary. From their findings, the authors argued that new semantic information can be acquired in the absence of 'any' significant anterograde episodic memory. They postulated that this occurs by means of a 'slow-learning' system in the (non-medial) temporal neocortex as a result of repeated presentation of the relevant information. Although some of the authors' findings were striking (for example, the patient did not know that his daughter had grown up in the last 13 years, despite knowing who Ronald Reagan was), their interpretation has to be taken with caution. The authors compared a very severely impaired episodic memory with a better but still very poor semantic memory, and there was some preservation of the right medial temporal structures. Some of the tests in which the patient performed relatively well (famous faces, famous news events) are those in which other studies have shown an important right temporal lobe contribution (Kitchener *et al*., 1999; Kopelman *et al*., 1999).

Summary

Semantic memory is severely affected in semantic dementia, and is also affected in disorders such as herpes encephalitis and Alzheimer dementia. Category-specific effects and relative preservation of superordinate knowledge have commonly been reported in these disorders. However, the underlying nature of these phenomena remains controversial, as do the degree of semantic–episodic independence in focal lesions and semantic–episodic interaction in semantic dementia.

What determines the pattern and extent of retrograde memory loss?

Temporal gradients

Ribot (1882) argued that: 'The progressive destruction of memory follows a logical order – a law . . . it begins at the most recent recollections which, being . . . rarely repeated and . . . having no permanent associations, represent organization in its feeblest form.' Since 1971, Ribot's 'law' has been tested across a number of different tasks, measuring knowledge of famous people/faces, news events and other

public information, facts about oneself (personal semantic memory), and 'autobiographical' incidents (events) from a person's past.

Sanders and Warrington (1971) administered tests of famous faces and public news events to five amnesic patients, including three alcoholic Korsakoff patients. On recall and recognition versions of their famous faces test, the amnesic group was severely impaired compared with healthy subjects, but on neither test was there any clear evidence of relative sparing of early memories, known as a 'temporal gradient'. However, subsequent studies have found such a gradient. Marslen-Wilson and Teuber (1975) obtained only mild impairment in Korsakoff patients on a famous faces test covering the 1920s to the 1950s, but severe impairment on the faces from the 1960s. Albert and colleagues (Albert *et al.*, 1979, 1981) obtained evidence of a temporal gradient extending back 30 years (from the 1970s to the 1940s) and Cohen and Squire (1981) for the most recent two decades. On a measure of the recall of autobiographical incidents, requiring subjects to retrieve memories related to a cue-word and to date them (the 'Crovitz test'; Crovitz and Schiffman, 1974), Zola-Morgan *et al.* (1983) found that Korsakoff patients had to delve much further back into their remote past in order to retrieve autobiographical memories (mean = 30.4 years) than did comparison groups of non-Korsakoff alcoholics (mean = 20.1 years) or healthy controls (mean = 12.7 years).

In general, the earlier studies in Korsakoff patients did not document the duration from the Wernicke episode until the time of testing, so that it was difficult to separate out the 'retrograde' and 'anterograde' contributions to 'recent' memory impairment. However, in the Kopelman (1989) study, the mean duration of illness was documented as 5.75 years, and there was a retrograde component to the Korsakoff patients' amnesia of 15–25 years. In addition, studies in Korsakoff patients have shown the following: (i) the severity of RA is not well correlated with the severity of AA (Shimamura *et al.*, 1986; Kopelman, 1989; Parkin, 1991; Mayes *et al.*, 1994); (ii) the impairment in recalling recent memories cannot be attributed to a specific deficit in encoding or retrieving contextual information (Parkin *et al.*, 1990*b*); and (iii) there is also RA with a temporal gradient for more purely semantic information, e.g. knowledge of words which entered the language at different times (Verfaellie *et al.*, 1995*b*).

Other groups of amnesic patients show either a temporal gradient comparable with that seen in Korsakoff patients (Squire *et al.*, 1989) or a somewhat flatter or 'gentler' gradient (Kopelman, 1989; Kopelman *et al.*, 1999). Even in Alzheimer patients, there is generally a 'gentle' temporal gradient across a number of different tasks with relative sparing of early memories (Beatty *et al.*, 1988; Sagar *et al.*, 1988; Kopelman, 1989; Greene *et al.*, 1995; Greene and Hodges, 1996). More controversial is whether there is a temporal gradient in patients with Huntington's dementia or frontal lobe pathology. Albert *et al.* (1981) and Beatty *et al.*

(1988) failed to obtain a temporal gradient in Huntington patients, as did Mangels *et al.* (1996) on recall tests in patients with frontal lobe lesions. On the other hand, Kopelman *et al.* (1999) found a statistically significant temporal gradient on a news events test in frontal patients, as did D'Esposito *et al.* (1996) on a famous faces test, and Gade and Mortensen (1990) obtained near-significance ($P = 0.053$) on a public events test.

In summary, many studies have produced evidence of a temporal gradient, consistent with Ribot's 'law'. However, the steepness of that gradient appears to differ across patient groups, generally being gentler in patients with dementia or frontal lobe atrophy than in patients with purer amnesic syndromes from, for example, hypoxia or the Korsakoff syndrome. Moreover, differing task demands may produce somewhat varying patterns of performance: retrieving auto-biographical memories in an 'unconstrained' manner to a cue-word in the Crovitz test (Sagar *et al.*, 1988), providing a 'free narrative' of important events from a person's life (Fromholt and Larsen, 1991, 1992), or retrieving autobiographical memories when constrained to particular time-periods (Kopelman, 1989; MacKinnon and Squire, 1989) may each produce somewhat different patterns of results.

Why do temporal gradients occur?

One view of the temporal gradient in Korsakoff patients was that it reflected both (i) the consequences of damage at the time of the Wernicke episode and (ii) a *progressive deterioration* in the anterograde acquisition of memories during the years of heavy drinking (Albert *et al.*, 1979, 1981). There are three pieces of evidence against the latter idea: (a) Butters and Cermak (1986) obtained a temporal gradient in an eminent scientist, PZ, who developed the alcoholic Korsakoff syndrome shortly after writing his autobiography. He was tested on information derived from this book that he had apparently been aware of at the time of writing. Nevertheless, he showed a striking temporal gradient in recalling this information after his Wernicke episode. (b) There is no significant correlation between the severity/extensiveness of the RA loss in Korsakoff patients and the estimated duration of their heavy drinking (Kopelman *et al.*, 1999). (c) Temporal gradients have also been described in non-Korsakoff amnesic patients of acute onset (Kopelman *et al.*, 1989; Squire *et al.*, 1989). To the extent that Korsakoff patients have a steeper gradient than other amnesic patients (Kopelman *et al.*, 1999), this may result from an *additional*, progressive anterograde impairment arising from their period of heavy drinking; however, this is likely to be a relatively minor factor, adding to a temporal gradient which appears acutely for other reasons (Kopelman, 1989; Parkin *et al.*, 1990*b*).

A second view is that the medial temporal and diencephalic structures are critical not only in initial memory formation, but also in the physiological '*consolidation*' of memories over 2 or 3 years or longer, after which memories are stored in neocortex and are no longer dependent upon the medial

temporal/diencephalic system ('structural reallocation'; e.g. Squire *et al.*, 1984; Squire and Alvarez, 1995; Teng and Squire, 1999). This is consistent with the finding that patients with medial temporal lobe or diencephalic lesions often show only a brief or even absent RA (Zola-Morgan *et al.*, 1986; Dusoir *et al.*, 1990; Graff-Radford *et al.*, 1990; Reed and Squire, 1998; Kopelman *et al.*, 1999). In contrast, patients with an RA extending back many years tend to have either extensive pathology beyond the medial temporal lobes/ diencephalon or an alcoholic history. Where that pathology is particularly widespread, as in Alzheimer dementia or herpes encephalitis, the RA tends to extend a long way back with a relatively 'flat' temporal gradient. Connectionist networks have been used to model the temporal gradients associated with prolonged consolidation (Alvarez and Squire, 1995; Squire and Alvarez, 1995; McClelland *et al.*, 1995; Murre, 1997). A fundamental problem for this theory is that an extensive temporal gradient, going back 20 to 30 years, would imply that physiological consolidation must continue for a very long time indeed (Nadel and Moscovitch, 1997).

A third view is that, as episodic memories are rehearsed, they adopt a more *semantic* form, losing their contextual immediacy or vividness, but *protecting* them from the effects of brain damage (Cermak, 1984). Early memories are particularly salient and well rehearsed (Cermak, 1984; Weiskrantz, 1985; Sagar *et al.*, 1988; Kopelman, 1989), and therefore protected from any retrieval deficit. There are reasons for supposing that the RA results, at least in part, from a deficit in retrieval processes, rather than from a destruction of memory storage *per se*. (a) Amnesic and dementing patients can manifest a disproportionate benefit from recognition or contextual cues (compared with healthy controls) despite very poor recall performance (Kopelman, 1989; Parkin *et al.*, 1990*a*; Verfaellie *et al.*, 1995; Kopelman *et al.*, 1999). (b) A deficit in retrieving remote memories superimposed upon an anterograde learning deficit is consistent with the observation that there are generally low and non-significant correlations between the severity of AA and RA (Shimamura and Squire, 1986; Kopelman, 1989; Parkin, 1991). (c) Significant correlations between remote memory scores and frontal/executive performance (Kopelman, 1991; Verfaellie *et al.*, 1995; D'Esposito *et al.*, 1996) suggest the putative role of frontal/neocortical mechanisms in organizing the retrieval of remote memories. To the extent that early memories are 'semanticized' or highly rehearsed, they are protected from such a retrieval deficit, and a temporal gradient results (Cermak, 1984). However, a major problem for this theory is the finding that memories which are semantic virtually from the outset, such as knowledge of the meaning of new words, can also show a temporal gradient (Verfaellie *et al.*, 1995*a, b*).

A fourth view postulated by Nadel and Moscovitch is that the hippocampi are continuously involved in the storage and retrieval (reactivation) of memory traces (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1998, 1999). In their model, a hippocampal–neocortical ensemble constitutes the memory trace for an episode, within which a distributed group of hippocampal neurones acts as an index or pointer to neocortical (or other) neurones that represent the information, binding the activations of these neurones into a coherent memory trace (compare Morton *et al.*, 1985; Murre, 1997). Because the hippocampi are always involved in encoding processes when attention is actively engaged, Nadel and Moscovitch (1997) proposed that the reactivation of a memory trace results in a newly encoded trace: repeated reactivations will produce '*multiple traces*' and the 'extraction' of factual information from an episode and its integration into pre-existing (neocortical) semantic memory stores. Retrieval becomes easier as the number of traces proliferates with rehearsal, resulting in a temporal gradient. The authors predicted that the extent of RA and slope of the temporal gradient for episodic memories would depend upon the size of a hippocampal lesion, and that complete hippocampal transection would result in a flat gradient. However, factual information (e.g. for public events and personalities) is eventually stored in neocortex independently of the (hippocampal-mediated) episode in which it was acquired: this aspect of the theory resembles 'structural reallocation' approaches and predicts a steeper gradient for 'semantic' than for autobiographical remote memories. (In the most recent accounts of this theory, the role previously attributed to the hippocampi is now accorded to the medial temporal lobes; see e.g. Fujii *et al.*, 2000.)

Nadel and Moscovitch (1997) cited a large number of studies, in which medial temporal lobe pathology was accompanied by a temporally extensive RA (see also Fujii *et al.*, 2000), and Viskontas *et al.* (2000) found a flat gradient in memory for autobiographical incidents in temporal lobe epilepsy patients, whereas there was a steeper gradient in the recall of personal semantic facts. Similarly, Cipolotti *et al.* (2001) reported an extensive RA in a patient with severe hippocampal atrophy (although there was some evidence of a gentle gradient in their data). On the other hand, virtually all of the patients cited by Nadel and Moscovitch (1997) had extensive pathology elsewhere. Other reports suggest only a brief RA in patients with medial temporal (or diencephalic) lesions (Zola-Morgan *et al.*, 1986; Reed and Squire, 1998); and Kopelman and colleagues did not find any correlation between MRI measures of medial temporal volume and the extent or gradient of RA in herpes and hypoxic patients (M. D. Kopelman, D. Lasserson, D. Kingsley, F. Bello, C. Rush, N. Stanhope *et al.*, manuscript submitted), contrary to Nadel and Moscovitch's prediction.

Reversed temporal gradients in semantic dementia

As mentioned briefly above, Snowden *et al.* (1996) found recency effects (reversed temporal gradients) in semantic

dementia patients' memory for personal facts and incidents. They contrasted this gradient with that obtained more typically in Alzheimer or amnesic patients. Graham and Hodges (1997) replicated this finding on autobiographical memory tests and Hodges and Graham (1998) on a famous names test, although the latter finding was somewhat equivocal because of 'ceiling' and 'floor' effects and the failure to report group by time-period interactions. One interpretation of these findings is in terms of structural reallocation: in semantic dementia, the temporal neocortex is severely damaged and early memories are lost, whereas more recent memories are dependent upon medial temporal structures, which are relatively preserved (Graham and Hodges, 1997). An alternative explanation is that the 'autobiographical' impairment in these patients mainly reflects their linguistic and semantic deficit, associated with left temporal damage, and that current everyday experience provides cues for the retrieval of recent autobiographical memories stored elsewhere (Moscovitch and Nadel, 1999; Kopelman, 2000), just as it helps them to make conversational use of words they cannot define (Snowden *et al.*, 1996, 1999). Consistent with this, Moss and colleagues (Moss *et al.*, 2002) have both, found a pronounced beneficial effect of cueing in autobiographical memory retrieval in semantic dementia patients, and this cueing effect was only very weakly related to time period.

Dissociable forms of retrograde amnesia

On the basis of an extensive review of the literature, Kapur (1999) proposed a 'provisional' framework, delineating major dissociable forms of neurological retrograde amnesia. He advocated a distinction between episodic RA and semantic RA, and subdivisions within these major groupings. In episodic RA, he distinguished between 'pre-ictal' and 'extended' RA, and in semantic RA between knowledge of people and events. Within 'people', Kapur argued that knowledge of names and faces can be differentially affected and, within 'faces', he differentiated knowledge of famous versus personally familiar faces.

A problem with such dissociations, as will be discussed below, is that they are largely based upon single cases and, when larger groups of patients are investigated, considerable overlap in performance can be found, and correlates of performance may emerge which might account for apparent dissociations (Kopelman, 2000*a*). Factors such as levels of education, media exposure and intelligence can strongly affect performance on semantic tests, and executive dysfunction may adversely affect performance on episodic tests: single case studies do not always examine the influence of such factors. Moreover, cognitive–brain relationships are sometimes postulated on the basis of patients with either very subtle markers of brain dysfunction (e.g. on EEG or SPECT) or patients with multiple sites of pathology, which means that the attribution of causality to a particular site of 'pathology' may be equivocal even in the presence of an apparent 'double dissociation' (Kopelman, 2000*a*). The same issue arises as in Caramazza's discussion of category-specific deficits (Caramazza, 1998): does a differential pattern of performance on cognitive tasks, even if supported by a double dissociation, necessarily imply that specific brain mechanisms should be postulated as underlying the categories affected or spared?

Despite these qualifications, Kapur's (Kapur, 1999) categorization does provide a useful framework for viewing the pattern of performance of different patients on particular *types of test*. Moreover, some general observations about localized effects can be made. Quantitative MRI evidence suggests that widespread networks within the temporal lobe, frontal neocortex and thalamus are involved in the storage and retrieval of remote memories (M. D. Kopelman, D. Lasserson, D. Kingsley, F. Bello, C. Rush, N. Stanhope *et al.*, submitted), but there are almost certainly focal or localized contributions within these regions. It seems likely that the frontal lobes contribute particularly to the planning, monitoring and organization of retrieval processes in remote memory, particularly where more 'effortful' or active reconstruction is required (Mangels *et al.*, 1996; Kopelman *et al.*, 1999). The right temporal lobe appears to be particularly important for the reconstructive processes engaging visual or multi-modal imagery necessary for retrieving autobiographical or 'event' memories (O'Connor *et al.*, 1992; Ogden, 1993; Rubin and Greenberg, 1998; Kopelman *et al.*, 1999; but contrast Kitchener *et al.*, 1999). On the other hand, the left temporal lobe may be particularly crucial for the storage and access of remote semantic and lexical-semantic information (De Renzi *et al.*, 1987; Kopelman *et al.*, 1999).

Neuroimaging of remote memory

To date, there have been relatively few activation studies of remote memory retrieval. Fink *et al.* (1996) showed widespread activation of right frontal and temporal lobe (and left medial temporal) regions when healthy subjects imagined incidents from their remote past, relative to their brain state when imagining events unrelated to their past. Maguire and Mummery (1999) required subjects to listen to statements that differed according to whether or not they constituted autobiographical or general knowledge, and whether or not they had a specific focus in time. There was enhanced activity for time-specific autobiographical events in the left hippocampus, medial prefrontal cortex and left temporal pole. Bilateral temporo-parietal regions were activated preferentially for personal memories, regardless of time-specificity. Conway *et al.* (1999) obtained left frontal, inferior temporal and occipito-parietal activations in verbal cueing of autobiographical memories and, like Ryan *et al.* (2001) and Maguire *et al.* (2001), did not obtain any medial temporal differences in retrieving remote or recent memories. In contrast, Haist *et al.* (2001) reported temporally graded medial temporal activations in retrieving the names of famous faces from different decades.

Summary

Temporal gradients of varying steepness are widely reported in RA, but their underlying basis is disputed. A progressive deterioration in acquiring new memories cannot account for temporal gradients in patients with an acute onset of amnesia. Consolidation theory requires physiological changes lasting years or decades. The semantic protection hypothesis is undermined by temporal gradients in 'purely' semantic memories. The multiple trace hypothesis has problems with cases of brief RA in patients with isolated medial temporal or diencephalic pathology. The precise role of specific brain structures in storing/retrieving remote memories is currently an active topic of research; and the neurobiological status of the many dissociations postulated in RA remains unclear.

Can retrograde amnesia ever be 'isolated'?
Case reports in the literature

In the early 1980s, a series of patients with apparently isolated RA were described (Roman-Campos *et al.*, 1980; Goldberg *et al.*, 1981, 1982; Andrews *et al.*, 1982; Rousseaux *et al.*, 1984). Of these, the most convincing study was by Goldberg *et al.* (1981), who described a 36-year-old patient with an open skull fracture associated with extensive right temporal lobe changes on CT scan and a lesser degree of left temporal abnormality. The patient had an initially 'profound' AA, but improved to a state in which a severe impairment in remote memory was accompanied by only minimal anterograde deficits.

Kapur *et al.* (1992) described a 26-year-old woman who had fallen from a horse. She had sustained left and right frontal contusions, evident on CT scan with associated regions of low attenuation. An MRI scan 18 months later showed lesions in the left and right temporal poles, with the hippocampi apparently intact. On cognitive testing, the patient had an estimated pre-morbid IQ (NART) of 105 with a current (WAIS-R) IQ of 98. Frontal/executive test performance was intact, but the patient was impaired across *all* the remote memory tests employed. Most anterograde memory tasks were performed normally, but it should be noted that the patient performed poorly at immediate logical memory (13th percentile) and on the faces component of the recognition memory test (4th percentile; Warrington, 1984).

Somewhat similarly, Levine *et al.* (1998) described a patient, ML, who had suffered a road traffic accident resulting in a right frontal lesion, involving the uncinate fasciculus, as well as left prefrontal haemorrhages. This patient had an initially severe AA, consistent with a reported post-traumatic amnesia of at least 34 days (and coma for 6 days), but this resolved leaving a verbal memory index (WMS-R) of 128 and a severe RA. However, findings on a task requiring the subject to make remember/know judgements in anterograde memory over varying delays, as well as in a PET activation study, indicated that there were, in fact, subtle impairments of anterograde memory.

A further study, commonly cited in this literature, is that by O'Connor *et al.* (1992). These authors described a patient who, following extensive right temporal lobe damage from herpes encephalitis, manifested a severe loss of autobiographical memories, relative to knowledge of public information. The patient also suffered a visual agnosia, and the authors suggested that the loss of autobiographical memories might be related to a problem in conjuring up visual imagery. The authors wrote: 'whilst she has only a mild to moderate *verbal* [my emphasis] learning deficits, she continues to demonstrate very severe retrograde amnesia.' Indeed, this patient had a severe deficit in visuo-spatial anterograde memory as well as her RA.

There are many other cases cited in this literature, which has been reviewed extensively elsewhere (Kopelman, 2000*a*). Some of these patients had definite structural brain damage (e.g. Maravita *et al.*, 1995; Evans *et al.*, 1996; Mattioli *et al.*, 1996; Carlesimo *et al.*, 1998). In other cases, the evidence for brain pathology was equivocal (Roman-Campos *et al.*, 1980; Stuss and Guzman, 1988; Starkstein *et al.*, 1997; Venneri and Caffarra, 1998), or negligible (e.g. Stracciari *et al.*, 1994; De Renzi *et al.*, 1995; Lucchelli *et al.*, 1995; Papagno, 1998). De Renzi *et al.* (1997) argued that such cases should be called 'functional amnesia' on the grounds that organic change may eventually be discovered 'at the cellular level' (see also Lucchelli *et al.*, 1995, 1998; Kapur, 1996; Spinnler *et al.*, 1996).

Critique of the literature

In a recent review of this topic (Kopelman, 2000*a*; see also Kapur, 2000; Kopelman, 2000*b*), the present author concluded such cases can be classified under a number of different categories, as follows.

(i) Some cases had severe autobiographical amnesia and have been widely cited in this literature, despite the fact that there was evidence of very poor anterograde memory, sometimes particularly for visuo-spatial material (e.g. O'Connor *et al.*, 1992; Markowitsch *et al.*, 1993; Ogden, 1993; Brown and Chobor, 1995). Such cases cannot be described as instances of 'isolated', 'focal' or 'disproportionate' RA, despite the fact that the relationship between memories for visuo-spatial material and autobiographical amnesia poses interesting theoretical questions.

(ii) There are other cases in the literature who showed poor anterograde memory in moderate or more subtle form across a number of anterograde tests, particularly logical memory, face recognition memory and tests of delayed recall (Kapur *et al.*, 1986, 1989, 1992, 1996*b*; Stuss and Guzman, 1988; Hunkin *et al.*, 1995; Maravita *et al.*, 1995; Calabrese *et al.*, 1996; Mattioli *et al.*, 1996; Carlesimo *et al.*, 1998; Gainotti *et al.*, 1998; Lucchelli and Spinnler, 1998; Zeman *et al.*, 1998). In these instances, the phrase 'disproportionate', rather than 'focal' or 'isolated', RA seems more appropriate. Moreover, these cases pose the questions of why there are such characteristic patterns, and whether 'like' has really

been compared with 'like' across retrograde and anterograde memory? Possibly the RA tasks require greater use of visual or multi-modal imagery, which may be critical for autobiographical incident recall (O'Connor *et al.*, 1992; Ogden, 1993; Brown and Chobor, 1995; Van der Linden *et al.*, 1996; Gainotti *et al.*, 1998; Rubin and Greenberg, 1998). Alternatively, remote memory tasks may be more 'effortful', requiring more spontaneous strategies and 'executive' planning and organization in retrieval (Baddeley and Wilson, 1986; Della Sala *et al.*, 1993) than do anterograde tasks. A third possibility is that the remote memory deficit reflects impaired consolidation, manifest on recall tests at prolonged delays (De Renzi and Lucchelli, 1993; Maravita *et al.*, 1995; Evans *et al.*, 1996; Kapur *et al.*, 1996b; Mattioli *et al.*, 1996). The latter is an attractive hypothesis, although insufficiently tested as yet, but it implies that the problem is *not* specific to retrograde memory. Only one recent study (Manning, 2002) has seriously addressed the issue of comparing 'like' with 'like', but the patient performed normally or near normally at standardized remote memory tasks (AMI, Dead-or-Alive).

(iii) Some of the cases in the literature showed a specific impairment in autobiographical memory (Evans *et al.*, 1996), others showed poor recall for public or semantic knowledge (e.g. Kapur *et al.*, 1986, 1989; Kapur, 1994), whilst yet others showed RA across a wide range of tasks (e.g. Kapur *et al.*, 1992). All these cases tend to get cited as instances of 'focal RA', but it is important to emphasize that they are not the same. If dissociations are to be postulated, it ought to be shown that the patient fails on more than one task reflecting a purported deficit, otherwise the findings may simply reflect chance variation in test performance. Secondly, some patterns of findings can be explained in other terms: for example, poor recall for public or semantic knowledge may reflect low intelligence or poor education and media exposure (Kopelman, 1989; Kapur *et al.*, 1999), whereas profoundly impaired autobiographical memory retrieval in the presence of surprisingly good semantic knowledge might reflect severe frontal/executive impairment (Kopelman, 2000a).

(iv) The most convincing cases in this literature have been those in whom there was an initially severe anterograde amnesia, as well as an extensive RA, particularly following head injury. The RA remained profound, whereas the AA became only moderate, mild or minimal (Rousseaux *et al.*, 1984; Goldberg *et al.*, 1981; Hunkin *et al.*, 1995; Calabrese *et al.*, 1996; Evans *et al.*, 1996; Kapur *et al.*, 1996b; Mattioli *et al.*, 1996; Carlesimo *et al.*, 1998; Levine *et al.*, 1998; Markowitsch *et al.*, 1999). In such cases, the issue is not so much whether RA can occur without AA, but *what determines differential patterns of recovery*. This is a somewhat different question, but one on which we have surprisingly little information. It is likely that *both* physiological (such as neural reorganization) and psychological factors influence recovery processes, particularly following head injury (Lishman, 1973, 1988; Newcombe, 1982). The fact that recovery from AA and RA can occur at differential rates does not necessarily mean that they are completely dissociated.

(v) A second group of patients were those with TEA, who commonly report 'gaps' in their autobiographical memory and have often been cited in this literature. Some of these cases had either moderately severe (Kopelman *et al.*, 1994a) or more subtle (Kapur *et al.*, 1989) anterograde memory impairment, and they often performed well on standardized tests of autobiographical and remote memory (Kapur *et al.*, 1986; Kapur, 1993; Kopelman *et al.*, 1994a; Zeman *et al.*, 1998; Manes *et al.*, 2001). In such cases, the most parsimonious explanation is that the patients had brief runs of seizure activity in the past, which were not detected clinically, and that these resulted in faulty (anterograde) encoding of very specific items in autobiographical memory (Kopelman, 2000a; but see Kapur, 2000).

(vi) A final group of cases were those in whom psychogenic factors might well have been predominant. Brain disease and psychiatric problems commonly co-occur (Kopelman and Crawford, 1996; Markowitsch, 1996), and psychological factors may exacerbate cognitive deficits and/or influence patterns of recovery. This may have been particularly true of patients in whom mild concussion was accompanied by disproportionate impairments in retrograde memory. In some case descriptions of focal RA, evidence of possible psychiatric factors was only briefly or scantily discussed (Roman-Campos *et al.*, 1980; Andrews *et al.*, 1982; Stuss and Guzman, 1988; Stracciari *et al.*, 1994; De Renzi *et al.*, 1995; Mattioli *et al.*, 1996), although a fuller discussion has been included in more recent studies (Barbarotto *et al.*, 1996; Lucchelli *et al.*, 1998; Papagno, 1998; Mackenzie Ross, 2000). Cases in whom RA has been reversed during an interview under sodium amytal (Stuss and Guzman, 1988; Kopelman, 2000a) add weight to the possibility that psychological factors can be crucial, even in the presence of some evidence of organic brain damage.

Summary

Disproportionate RA does occur, although 'focal' or 'isolated' RA is much more equivocal. It is an example of a postulated dissociation whose neurobiological status remains unclear. The evidence that it is related to a specific, localized brain pathology is thin, when account is taken of the above factors. Future research needs to concentrate not so much on the existence of 'dissociation', but on the determinants of differential recovery processes in head trauma, the nature of memory 'gaps' in TEA, and on the interaction of psychogenic factors and brain pathology in producing RA.

Does psychogenic amnesia involve the same mechanisms as organic amnesia?

Psychological forms of memory loss can either be 'global' or 'situation specific'. The former refers to a profound loss of

past memories, often encompassing the sense of personal identity, and the latter to memory loss for a particular incident or part of an incident.

Global amnesia

This is exemplified by the so-called 'fugue state' (Hunter, 1964), sometimes known as 'functional retrograde amnesia' (Schacter *et al.*, 1982). The fugue state refers, in essence, to a syndrome consisting of a sudden loss of all autobiographical memories and knowledge of self or personal identity, usually associated with a period of wandering, for which there is a subsequent amnesic gap upon recovery. Fugue states usually last a few hours or days only: if prolonged, the suspicion of simulation must always arise.

There appear to be three main predisposing factors for fugue episodes. First, fugue states are always preceded by a severe, precipitating stress, such as marital or emotional discord (Kanzer, 1939), bereavement (Schacter *et al.*, 1982), financial problems (Kanzer, 1939), a charge of offending (Wilson *et al.*, 1950) or stress during wartime (Sargant and Slater, 1941; Parfitt and Gall, 1944; Hunter, 1964). Secondly, depressed mood is an extremely common antecedent for psychogenic fugue states. Berrington *et al.* (1956) wrote: 'In nearly all fugues, there appears to be one common factor, namely a depressive mood. Whether the individual in the fugue is psychotic, neurotic, or psychopathic, depression seems to start off the fugue.' For example, Abeles and Schilder (1935) described a woman who deserted her husband for another man: after a week, she determined to return to her family but, as she descended into the underground railway station, she was contemplating suicide. The authors tersely reported that 'instead amnesia developed'. The third factor is a history of a transient, organic amnesia from such causes as epilepsy (Stengel, 1941), head injury (Berrington *et al.*, 1956) or alcoholic blackouts (Goodwin *et al.*, 1969). For example, Berrington *et al.* (1956) reported that 19 of their 37 fugue cases had previously experienced a head injury of some degree of severity. It appears that patients who have previously experienced a transient organic amnesia, and then become depressed and/or suicidal, are particularly likely to go into a fugue in the face of a severe precipitating stress.

The clinical and neuropsychological phenomena in such cases bear interesting resemblances to organic amnesia. For example, there may be islets or fragments of preserved memory within the amnesic gap. A woman who was due to meet her husband to discuss divorce recalled that she was 'supposed to meet someone' (Kanzer, 1939). A young man, who slipped into a fugue following his grandfather's funeral, recalled a cluster of details from the year which he described (after recovery) as having been the happiest of his life (Schacter *et al.*, 1982). The subject may adopt a detached attitude to these memory fragments, describing them as 'strange and unfamiliar' (Coriat, 1907; Markowitsch, 1996). In many cases, semantic knowledge remains unimpaired (e.g. Kanzer, 1939; Schacter *et al.*, 1982), whereas in others it is

also implicated (Coriat, 1907; Abeles and Schilder, 1935; Kanzer, 1939). Similarly, performance of verbal learning tests can be unaffected (Abeles and Schilder, 1935; Kopelman *et al.*, 1994*b*), mildly impaired (Schacter *et al.*, 1982) or more severely impaired (Gudjonsson and Taylor, 1985). Memory for procedural skills is often preserved (e.g. Coriat, 1907; Bradford and Smith, 1979) and this may also be true of other aspects of implicit memory (Campodonico and Rediess, 1996; Kihlstrom and Schacter, 2000). Deliberate cueing of memories is seldom successful (Coriat, 1907; Kanzer, 1939; Kopelman *et al.*, 1994*b*), but memory retrieval is often facilitated by chance cues in the environment (e.g. Abeles and Schilder, 1935; Schacter *et al.*, 1982). Kopelman (1995*b*) gave the example of a patient who, on seeing an author's name on the spine of a book, recalled that he had a friend of that name who was dying of cancer. On transfer to a psychiatric ward, he recollected the details of another psychiatric hospital admission from years earlier.

Situation-specific amnesia

Situation-specific amnesia can arise in a variety of circumstances, including committing an offence, being the victim of an offence or of child sexual abuse, and in a variety of other circumstances resulting in post-traumatic stress disorder (PTSD).

Offences

Offenders as well as victims of crimes commonly claim amnesia, particularly in violent offences, and psychiatrists or neurologists are often called upon to comment upon this. Amnesia is claimed by 25–45% of offenders in cases of homicide, approximately 8% of perpetrators of other violent crimes and a small percentage of non-violent offenders (Kopelman, 1987*b*, 1995*b*). Such findings have been made in different settings, including a remand prison (Taylor and Kopelman, 1984), a forensic psychiatric outpatient clinic (Bradford and Smith, 1979) and a Home Office Register of Life Offenders (Pyzsora *et al.*, 2002).

It is necessary to exclude underlying neurological factors such as an epileptic automatism, post-ictal confusional state, head injury, hypoglycaemia, sleepwalking (Howard and d'Orban, 1987; Fenwick, 1990, 1993), or REM (rapid eye movement) sleep disorder (Schenck *et al.*, 1986; Clarke *et al.*, 2000). Such pathology can be grounds for a so-called 'insane' automatism in English law (if the result of a brain disease) or a 'sane' automatism (if the consequence of an external agent). For example, the present author saw a young diabetic patient, normally obsessive in maintaining his control, who took his insulin before dinner, delayed preparing his meal when he was intrigued by a television programme and who subsequently attacked his flatmate with a bread knife. On the arrival of the police, the man showed characteristic features of hypoglycaemia. He was acquitted on the grounds of a

'sane' automatism. In other circumstances, amnesia *per se* does not constitute grounds for alleviation of responsibility.

Amnesia for an offence is most commonly associated with: (i) states of extreme emotional arousal, in which the offence is unpremeditated, and the victim usually a lover, wife, or family member, most commonly in homicide ('crimes of passion'). In such cases, there is often a preceding history of depression and, on 'coming round', the person realizes what has been done and may well call the police himself/herself (Gudjonsson and MacKeith, 1988; Kopelman, 1995*b*). (ii) Alcoholic intoxication (sometimes in association with other substances), usually involving very high peak levels as well as a long history of alcohol abuse. Alcohol can produce amnesia from a so-called 'blackout' or as a state-dependent phenomenon (Goodwin *et al.*, 1969). The offence may vary from criminal damage, through assault, to homicide, and the victim may be unknown to the offender. (iii) Florid psychotic states: occasionally, offenders describe a delusional account of what has happened (Taylor and Kopelman, 1984), quite at odds with what was observed by others, sometimes resulting in confessions to 'crimes' that the person could not actually have committed (a 'paramnesia' or 'delusional memory').

PTSD

PTSD can occur in association with head injury, road traffic accidents, being the victim of violent crime, or in major disasters (e.g. the sinking of the Herald of Free Enterprise at Zeebrugge, the King's Cross fire). As is well known, it is characterized by intrusive thoughts and memories ('flashbacks') about the traumatic experience. Brewin and colleagues have postulated a dual system of memory representation to try to account for the spontaneity and invasiveness of these flashbacks (Brewin *et al.*, 1996; Brewin, 2001). However, there may be instances of partial memory loss ('fragmentary' memories), distortions, or even frank confabulations. For example, the author saw a victim of the Herald of Free Enterprise at Zeebrugge, who described trying to rescue a close friend still on board the ship, when other witnesses reported that this close friend had not been seen from the moment the ship turned over. Although factors such as head injury or hypothermia may confound the interpretation of such cases, it is of interest that PTSD symptoms have been reported to occur even when the subject appears to have been completely amnesic for the episode (McNeil and Greenwood, 1996; Harvey *et al.*, 2002). Moreover, PTSD victims may show deficits in anterograde memory on formal tasks many years after the original trauma (Bremner *et al.*, 1993), and there are claims that they show a loss of hippocampal volume on MRI brain scan (Bremner *et al.*, 1995), which has been attributed to effects of glucocorticoid metabolism (Markowitsch, 1996). These MRI findings have to be interpreted with caution in view of the rather crude measurements employed: in the Bremner *et al.* study, even the control values were a long way out of line with those in most other investigations (see Colchester *et al.*, 2001).

A recent review documented evidence of amnesia in the victims of lightning flashes, flood disasters, pipeline explosions, earthquakes, concentration camp and holocaust survivors, refugees and traumatized soldiers from the two world wars and Vietnam (Brown *et al.*, 1999). Other reviews have cited instances of kidnap and torture (van der Kolk and Fisler, 1995). The psychological impact of a road traffic accident may also give rise to amnesia (Harvey, 2000; Kopelman, 2000*c*), although it may be difficult to separate this from the effects of concussion. Brown *et al.* (1999) also found evidence of forgetting in all 68 studies that they reviewed on the fraught issue of memory for child sexual abuse. Whilst there are indeed problems in evaluating self-reports of amnesia for child abuse, some smaller scale studies have examined the corroborative evidence for the trauma and the subsequent forgetting in some detail (Schooler *et al.*, 1997), and others have proposed mechanisms whereby such forgetting and subsequent (possibly erroneous) re-retrieval might occur (Schacter, 1996; Shimamura, 1997), particularly in relation to certain cues or triggers (Andrews *et al.*, 2000).

Mechanisms involved in psychogenic and organic amnesia

It has been claimed that situation-specific amnesia involves a narrowing of consciousness with attention focused on central perceptual details, sometimes evolving into amnesia (Christianson, 1984), and/or that emotional or traumatic events are processed differently from 'ordinary memories' (van der Kolk and Fisler, 1995). In particular, emotional memories, especially those involving fear, may implicate amygdaloid circuits, distinct from those involved in 'normal' learning (Adolphs *et al.*, 1994; Cahill *et al.*, 1995; Young *et al.*, 1995; Fine and Blair, 2000). However, it may also be the case that, when something extraordinary happens, we ask ourselves to recall far more detail than we would normally expect, and experience the shortfall as 'gaps' in memory (Kopelman, 2000*c*).

Markowitsch (1996) pointed to various commonalities between psychogenic and organic amnesia, and Kopelman (2000*a*) proposed a model to try to take account of the interplay of psychosocial factors and brain systems in producing psychogenic amnesia. In Fig. 1, social and psychological factors are indicated in the ovals, whilst the relevant brain systems are in the boxes. Whilst stress sometimes has a direct effect upon the medial temporal/ diencephalic system, thereby producing an impairment in new learning, the model postulates that, in other cases, stress predominantly affects frontal control/executive systems, such that the retrieval of autobiographical memories is inhibited. This inhibition will be exacerbated, or made more likely, when a subject is extremely aroused, very depressed, or when there has been a 'learning experience'
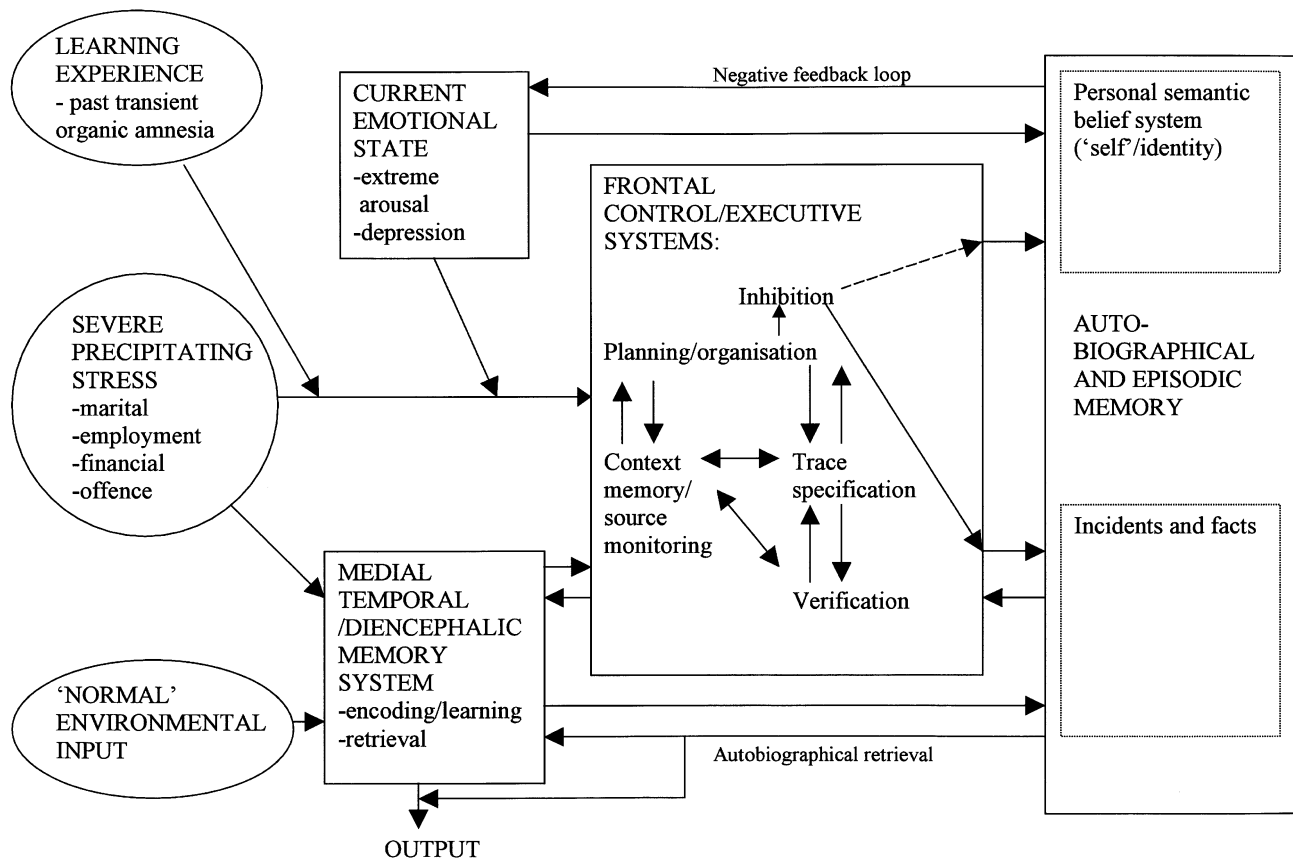
Fig. 1 Social factors and brain systems influencing autobiographical memory retrieval and personal identity. The figure shows (i) frontal lobe processes involved in confabulation (trace specification/verification; context memory/source monitoring), and (ii) social factors (in ovals) and brain systems (in rectangles) involved in psychogenic amnesia: inhibition leads to impaired retrieval of incidents and facts, and severe inhibition affects orientation in person. (Adapted from Cogn Neuropsychol 2000; 17: 585–621.)

of a past transient organic amnesia. If the stress is severe, the inhibition may even affect a postulated 'personal semantic belief system', resulting in a transient loss of personal identity (dashed arrow). If that occurs, there is 'negative feedback' in the form of a severe dampening of the current emotional state, such that a patient in fugue characteristically appears emotionally 'flat' or perplexed, instead of aroused or depressed. In such circumstances, 'new' anterograde learning in response to 'normal' environmental stimuli can still occur via the intact medial temporal/diencephalic system. In brief, this model adds to, but is broadly consistent with, knowledge of the brain systems implicated in normal memory and organic amnesia. Moreover, Anderson and Green (2001) have recently reported evidence that executive mechanisms can indeed be recruited to prevent unwanted memories from entering awareness, and that repeated use of this strategy inhibits the subsequent recall of the suppressed memories.

Summary
Psychogenic amnesia can be either local or situation specific. The brain systems modulating emotional mem-

ories are beginning to be understood, but it is essential that models of psychogenic amnesia should incorporate the psychosocial context in which it arises. That said, the dysfunction can be understood in terms of an interaction between the predisposing psychosocial factors and frontal inhibitory mechanisms operating within and upon those brain systems previously postulated in studies of normal memory and organic amnesia.

How and when do false memories arise?
Spontaneous confabulation in brain disease
In 'spontaneous' confabulation, there is a persistent, unprovoked outpouring of erroneous memories, often held with firm conviction, sometimes bizarre, and very often preoccupying. For example, patient AB (Kopelman *et al.*, 1997) believed that her parents were frequently visiting her in hospital (they had been dead 4 and 20 years), and that her brother was a doctor living on the 24th floor of the building she occupied (he was not a doctor, and she was on the top floor, the 12th). Spontaneous confabulation has most commonly been described in association with frontal lobe pathology, particularly involving the ventro-medial regions

(Luria, 1976; Stuss *et al.*, 1978; Kapur and Coughlan, 1980; Shapiro *et al.*, 1981; Baddeley and Wilson, 1986; Moscovitch and Melo, 1997). However, spontaneous confabulation can also occur in other, more generalized disorders, such as confusional states (DeLuca and Cicerone, 1991) or the generalized (metabolic) effects of carcinoma (Kopelman *et al.*, 1997). On the other hand, frontal dysfunction seems to be a necessary, but perhaps not a sufficient, condition for spontaneous confabulation (Kopelman *et al.*, 1997; Dalla Barba *et al.*, 1999): it is a truism that many patients with frontal pathology do not confabulate, and this does not seem to be related purely to the precise site of pathology.

A number of explanatory theories for spontaneous confabulation have been proposed. The first group of theories emphasizes faulty specification and verification in memory retrieval. Burgess and Shallice (1996) postulated deficits in a descriptor process, an editor process, and a mediator process, which all contribute differently to the clinical phenomena of confabulation. The 'descriptor' specifies the type of trace that would satisfy the demands of a retrieval task, and 'noisy' specification increases the chance of an inappropriate representation being produced as a candidate memory. The 'editor' checks that the output from long-term storage fits with previously retrieved memory elements and with overall task requirements. When this 'editor' is impaired, confabulators respond to a question without giving it adequate consideration, checking, or self-correction. The 'mediator' controls strategic/problem-solving operations concerning the adequacy or plausibility of retrieved memory elements; impairment results in reasoning errors and in bizarre or 'fantastic' responses (see also Burgess and McNeil, 1999). Moscovitch and Melo (1997) proposed a somewhat similar theory, also identifying a number of putative deficits in cue-retrieval, strategic search or faulty monitoring, the last resulting in erroneous memories not being edited out or suppressed. Likewise, Schacter *et al.* (1998) argued that an insufficiently 'focused' retrieval description, or an impairment in post-retrieval monitoring and verification, may give rise to confabulation. In addition, these latter authors argued that encoding impairments may make subjects more liable to confabulatory errors at retrieval.

The second group of theories emphasizes contextual memory deficits, particularly with reference to temporal sequence and/or source monitoring deficits. Korsakoff (1889) himself gave several examples of confusions in temporal sequence, resulting in confabulation, such as a woman whose account of past vacations confused journeys to Finland and the Crimea so that wholly inappropriate descriptions were given. Other authorities have also emphasized temporal context confusions as the basis of confabulation (e.g. Moll, 1915; Van der Horst, 1932; Talland, 1965; Victor *et al.*, 1971). Most recently, Schnider *et al.* (1996) found that a small group of spontaneous confabulators were differentiated from other amnesic patients and healthy controls on the basis of errors at an 'implicit' temporal context memory task, but not on other memory or executive tasks (see also Schnider

and Peak, 1999). In a variant of this hypothesis, Dalla Barba and colleagues have proposed that 'temporal consciousness' is intact but malfunctioning in confabulating patients (Dalla Barba, 1993*a*, *b*, 1999; Dalla Barba *et al.*, 1997, 1999). Such patients are aware of a past, present and future (unlike severely amnesic patients) but, in making temporal judgements, they employ only the most stable elements from their long-term memory stores. Asked what they did yesterday or will do tomorrow, the patients reply with well-established routines or the habits of a lifetime, however irrelevant to their present situation. More generally, Johnson and colleagues have argued that confabulation may result from a wider range of context, source, or reality monitoring deficits (Johnson, 1991; Johnson *et al.*, 1993, 2000). Source memory or monitoring refers to the ability to identify the 'source' of information (Schacter *et al.*, 1984), and reality monitoring to the ability to discriminate 'real' from imagined experience.

A third group of theories emphasizes that multiple deficits may contribute to confabulation. Shapiro *et al.* (1981) emphasized (i) impaired self-monitoring, (ii) a resulting failure to inhibit memory errors and (iii) frequent perseverations as the basis of confabulation: each of these deficits could be related to a different aspect of frontal/executive function. In a comparison of a confabulating patient and other patients with frontal lesions, Johnson *et al.* (1997) concluded that confabulation may reflect an interaction between (i) a vivid imagination, (ii) an inability to retrieve autobiographical memories systematically and (iii) source monitoring deficits. Kopelman *et al.* (1997) found that (i) many confabulations might plausibly result from the confounding and inappropriate retrieval of 'real' memory fragments out of temporal sequence, but that (ii) other confabulations result from perseverations, particularly in semantic memory, and (iii) yet others appear to be instantaneous, ill-considered and unchecked responses to immediate environmental and social cues.

In summary, it seems likely that temporal context and source monitoring deficits contribute to, but are not the sole basis of, the impairments of memory specification (description; focused retrieval) and verification (editing; monitoring) postulated in other theories. It seems plausible that these various deficits reflect dysfunction in differing components of frontal control mechanisms and that they interact together (see Fig. 1 and Kopelman, 1999; Gilboa and Moscovitch, 2002).

Momentary ('provoked') confabulation
Much more commonly, amnesic patients show 'momentary' or 'provoked' confabulations. These are fleeting intrusion errors or distortions made in response to a challenge to memory, such as a memory test (Berlyne, 1972; Kopelman, 1987). In amnesic patients, these intrusion errors are secondary to the memory deficit itself, rather than necessarily reflecting frontal/executive dysfunction, just as, in healthy subjects, they arise when memory is 'weak' for any reason.

Such errors reflect the essentially 'reconstructive' nature of memory retrieval: where the trace is weak (e.g. at long delays), this reconstruction becomes distorted or frankly erroneous, but this does *not* necessarily imply a conscious/deliberate attempt to 'fill in' memory gaps. The errors themselves, although fleeting, can be quite striking and surprising. Momentary confabulation in healthy subjects has been demonstrated in many experimental investigations (Bartlett, 1932; Hammersley and Read, 1986; Kopelman, 1987; Lindsay and Read, 1994; Read and Lindsay, 1997; Schacter *et al.*, 1998).

In a neuroimaging study, Schacter *et al.* (1996*d*) found that the left medial temporal (parahippocampal) memory system was activated during *both* accurate ('veridical') *and* faulty ('illusory') recognition of word stimuli. Accurate recognition was associated with significantly increased blood flow in the left temporo-parietal cortex, whereas faulty recognition was associated with activation in the prefrontal and orbito-frontal cortices and the cerebellum, which were postulated as involved in error detection. The overlap between the brain systems activated by true and faulty memories may help to explain the particular salience of false memories in many circumstances.

False memories in other contexts

False memories can also arise in many other circumstances (Kopelman, 1999). Delusional memories are a relatively rare phenomenon, displaying many of the features of spontaneous confabulation, except that they tend to revolve around a single theme and are not necessarily related to frontal/executive dysfunction (David and Howard, 1994; Kopelman *et al.*, 1995; Baddeley *et al.*, 1996). Delusional misidentification syndromes are often associated with the concurrence of bilateral frontal lobe pathology and right posterior lesions (Alexander *et al.*, 1979; Ellis and Young, 1990; Young *et al.*, 1995; Feinberg and Roane, 1997; Box *et al.*, 1999; Feinberg *et al.*, 1999). Confabulations have also been described in schizophrenic patients during story recall (Nathaniel-James and Frith, 1996; Nathaniel-James *et al.*, 1996), although it is possible that these are simply 'momentary' confabulations, coloured by the preoccupying delusional beliefs of these patients (Kopelman, 1999). There are also rare psychiatric syndromes in which patients adopt a false identity or identities, associated with 'memories' in which they have come to believe (Kopelman, 1999). These include 'pseudologia fantastica', sometimes known as 'pathological lying' (Fish, 1967), rare instances of people who adopt a new role and identity following a typical fugue episode (Kopelman *et al.*, 1994*b*; Markowitsch *et al.*, 1997*a*) and so-called multiple personality disorder (dissociative identity disorder), in which the widely varying geographical prevalence almost certainly reflects differences in the reinforcing behaviour of doctors, psychologists, and the outside world (Merskey, 1992, 1995).

Most controversial are cases of allegedly false memory for child sexual abuse. The polarized positions of official reports (Brandon *et al.*, 1998; Morton *et al.*, 1995) illustrate the unresolved and political aspects of this debate. However, certain common themes have emerged in the scientific literature on this topic. Even the most forthright protagonists of false memory have found that 19% of victims of abuse reported forgetting at some time in the past (Loftus *et al.*, 1994). Other researchers (Schacter, 1996; Schacter *et al.*, 1997; Shimamura, 1997) have suggested that memories for abuse are never actually completely forgotten, but they are retained in a vague unelaborated form, poorly located in temporal and spatial context. Such memories would be vulnerable to the normal processes of decay and interference, as well as to conscious avoidance and suppression. Appropriate cueing might result in the re-retrieval of these memories, but the 'weak trace' would make them very vulnerable to distortion and augmentation. It also seems very plausible that false memories for sexual abuse are most likely to arise in particular social contexts (Kopelman, 1999).

A related phenomenon is false confession to an offence, in which the victim is oneself rather than another. Gudjonsson *et al.* (1999) described a man whose conviction of homicide was quashed after he had served 25 years in prison. At 17 years of age, he had persuaded himself of his 'guilt' during 48 h of police interviews, in which he was in an extremely distraught and agitated state without a doctor or lawyer in attendance. Shortly before the trial, and just after it had begun, he was given three interviews under sodium amylobarbitone, which were subsequently part of the grounds for appeal. Recently, somewhat similar cases from 1952 and 1983 have had their convictions overturned (R. versus Hay Gordon, 2000; R. versus Fell, 2001). Gudjonsson and colleagues have described the circumstances in which people make such 'confessions', which they often come to believe or 'internalize' (Gudjonsson and MacKeith, 1982, 1988, 1990; Gudjonsson, 1992). In many of these cases, source memory errors (about where particular information had been learned about the offence or victim) seem to have arisen in the context of personal self-doubt (low self-esteem and/or depression) and/or external coercion by the interrogators. This resulted in a faulty attribution, held subsequently with varying degrees of conviction.

Summary

It seems that various deficits in frontal control mechanisms, involving trace specification or verification processes and context or source memory, may contribute to neurological confabulation. But false memories can also arise in the absence of brain disease, innocuously in the case of momentary confabulation, or more sinisterly in the case of false memory for sexual abuse or offences (false confessions). In these latter instances also, impairments in contextual or source memory have been postulated.

Conclusions

This review has attempted an overview of clinical memory disorders and selected theoretical controversies that arise from them. Many of the previously postulated distinctions between temporal lobe and diencephalic amnesia (e.g. in forgetting rates) have broken down. There is even substantial overlap between these forms of amnesia and that arising from large frontal lobe lesions, although important distinctions remain. Recent research in organic amnesia has emphasized impairments in 'binding' different types of material in anterograde memory, including contextual information and associations, and various distinctions have been drawn to emphasize the types of memory characteristically affected or relatively spared in AA: recall/recognition memory, remembering/knowing, recollection/familiarity and explicit/implicit memory. How these various distinctions map precisely on to one another remains controversial. One view of RA is that medial temporal/diencephalic structures are critical to memory formation, but that damage to these structures gives rise to a relatively brief (3 years or less) RA. According to this view, a superimposed retrieval deficit, related to widespread frontal and/or temporal neocortical pathology, is required to produce a temporally extensive RA (greater than 3 years) (e.g. Kopelman, 1989, 1991). Psychogenic factors could precipitate or exacerbate a retrieval deficit. However, this time-limited view of medial temporal lobe function is now contested by those who postulate a more uniform effect of medial temporal lesions upon RA and AA (Nadel and Moscovitch 1997; Fujii *et al.*, 2000; Cipolotti *et al.*, 2001).

In this review, I have tried to emphasize commonalities (as well as differences) between largely separate literatures where they exist: for example, between the mechanisms underlying the neurological and psychogenic forms of amnesia and of false memory (confabulation). An important point is that neuropsychological approaches have been heavily influenced by the success of modular models in explaining other types of cognitive disorder, such as acquired dyslexia and prosopagnosia. But this approach has sometimes led to a somewhat limiting and static perspective. There are probably only a finite number of functional dissociations to be discovered; they may have a number of alternative explanations; and their neurobiological status often remains unclear (Caramazza, 1998; Kopelman, 2000*a*; Tyler and Moss, 2001). Greater emphasis needs to be placed on a more dynamic approach which examines: (i) the interaction between different cognitive systems (and the neural networks or regions which underlie them), as in Snowden's investigations of the interplay between autobiographical and semantic memory in semantic dementia (Snowden, 2002); (ii) the determinants of differential patterns of cognitive change through time such as the relative rates of recovery of RA and AA following head injury; and (iii) the interaction of psychogenic and motivational factors with specific brain systems or pathology, e.g. following head injury, in psychogenic amnesia, or in the neurological and psycho-logical forms of false memory (confabulation). In this topic, there is still great scope for clinicians and researchers to inform and learn from one another.

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