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The loss of episodic memories in retrograde amnesia: single-case and group studies

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Retrograde amnesia in neurological disorders is a perplexing and fascinating research topic. The severity of retrograde amnesia is not well correlated with that of anterograde amnesia, and there can be disproportionate impairments of either. Within retrograde amnesia, there are various dissociations which have been claimed—for example, between the more autobiographical (episodic) and more semantic components of memory. However, the associations of different types of retrograde amnesia are also important, and clarification of these issues is confounded by the fact that retrograde amnesia seems to be particularly vulnerable to psychogenic factors. Large frontal and temporal lobe lesions have been postulated as critical in producing retrograde amnesia. Theories of retrograde amnesia have encompassed storage versus access disruption, physiological processes of 'consolidation', the progressive transformation of episodic memories into a more 'semantic' form, and multiple-trace theory. Single-case investigations, group studies and various forms of neuroimaging can all contribute to the resolution of these controversies.

Keywords: episodic memory; retrograde amnesia; autobiographical memory; semantic memory

1. INTRODUCTION

The nature of retrograde amnesia (RA) in brain disease is a particularly intriguing problem. Recent research has emphasized differing patterns (dissociations) of memory loss in RA. Less emphasis has been placed upon important associations (correlates) of retrograde memory loss, which may contribute to or explain these differing patterns. There can also be differential patterns of deficit in the retention of 'old' memories (RA), on the one hand, and the acquisition of 'new' memories (anterograde amnesia (AA)), on the other. One obvious factor which may putatively influence these varying patterns of deficit is the site or sites of focal brain pathology. However, psychological factors are increasingly recognized to have an important influence on the retrieval of 'old' memories; RA seems to be particularly vulnerable to psychogenic phenomena. In this article, these various factors will be reviewed, and current theories of RA will be considered in the light of them.

2. DISSOCIATIONS WITHIN RA

(a) *Autobiographical versus semantic remote memory*

The most common distinction employed in this literature is that between episodic or autobiographical memory and semantic memory. Autobiographical memory refers, characteristically, to a person's recollection of past incidents and events, which occurred at a specific time and place. Episodic memory is a somewhat broader term, encompassing autobiographical memories as well as performance on certain learning tasks such as recall of a word-list. However, the terms 'autobiographical' and 'episodic' are often used interchangeably. Semantic memory is commonly defined as referring to knowledge of language, concepts, and facts, which do not have a specific time or location. ('Paris is the capital of France' may once have been learned at a particular time and place, but these contextual aspects are seldom retained.) Many authors have postulated dissociations between the autobiographical and semantic aspects of remote memory, and these will be reviewed below. However, it is possible that there is simply a continuum of knowledge across these domains: for example, autobiographical 'facts', often known as 'personal semantic memory' (e.g. knowledge of the names of school teachers, addresses where someone has lived, etc.), fall midway between the two. Moreover, performance on many existing retrograde memory tasks—e.g. recognizing and identifying pictures of famous faces or famous news events (such as Margaret Thatcher leaving office)—may involve both autobioraphical ('I was on business in Edinburgh when Thatcher lost office') as well as more purely semantic knowledge. It is difficult to develop equivalent tests of autobiographical and semantic remote memory for comparative purposes.

De Renzi *et al.* (1987) reported the case of a 44-year-old woman who, following an episode of herpes encephalitis, displayed a severe impairment of semantic knowledge,

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contrasting with normal memory for autobiographical events. She was impaired at tasks demanding the retrieval of words or of their meaning, such as (i) a confrontation naming test, (ii) a sentence verification test, and (iii) a task requiring classification of items to categories. More particularly, she was impaired at knowledge of famous people (including Hitler, Mussolini and Stalin) and on knowledge of public events. For example, she was unable to provide any information about either the Second World War or the assassination of the Italian Prime Minister, Moro, a recent event at the time she was tested. Cueing helped her in some instances, but she was never able to achieve precise recollection. By contrast, it was apparent that not only did she remember personal incidents that had occurred before and after the acute stage of her disease, but she was well informed on current issues in her family, and she could recall the bulk of what had been done from testing session to testing session. A 20-item questionnaire was constructed about autobiographical memories, and her performance was generally very satisfactory. A magnetic resonance imaging (MRI) scan showed a wide irregular area of increased signal density extending over the inferior and anterior part of the left temporal lobe, above and lateral to the temporal horn (which was enlarged), involving the amygdala, the uncus, the hippocampus and the parahippocampal gyrus. The frontal lobes and the language areas of the temporal and parietal lobes were spared. In the right hemisphere, there were minimal signs of increased signal density in the white matter of the inferior temporal lobe.

Grossi *et al.* (1988) reported similar losses of remote semantic knowledge in a patient who had a large left parietal lesion evident on computed tomography (CT) scan, following a head trauma. This patient was also impaired on logical memory and failed to learn a word-list to criterion. Semantic memory deficits extended to vocabulary, arithmetic and geographical knowledge, and appreciation of concepts such as geometrical forms; but recollection of personally experienced events from the age of 6 to 18 years was excellent. Disproportionate impairment of public knowledge compared with autobiographical memories has also been noted in patients with left temporal lobe epilepsy or temporal lobectomy (Barr *et al.* 1990; Kapur *et al.* 1989). This has also been noted in two cases of irradiation necrosis to anterior and inferior temporal lobe structures (Kapur *et al.* 1994; Yasuda *et al.* 1997). A particular group in whom there may be disproportionate semantic memory loss is patients with semantic dementia, usually resulting from left temporal lobe atrophy. However, the interpretation of their remote memory loss is controversial: some studies report preservation for 'recent' but not distant autobiographical memories (Snowden *et al.* 1996; Graham & Hodges 1997), whereas others find a more uniform loss, largely secondary to their semantic memory deficit (Moss *et al.* 2000).

Other patients have shown the opposite pattern of performance. Dalla Barba *et al.* (1990) described a female Korsakoff syndrome patient, who manifested a severe impairment of autobiographical memory but preserved semantic memory. Despite her episodic memory problems, she was intact in detecting semantic anomalies, defining words, identifying inanimate from animate objects, and category naming. She also performed well when asked questions about famous people or events. It is of interest that she had a lower intelligence quotient (IQ) than the De Renzi *et al.* (1987) patient (92 versus 108), but much better semantic memory.

O'Connor *et al.* (1992) described a patient who had extensive damage to right temporal lobe structures, which resulted in a disproportionately severe impairment in the recall of autobiographical incidents, relative to remote semantic information. This patient also exhibited severe visuoperceptual deficits, and the authors argued that she may have had a particular difficulty in conjuring up the visual images necessary for the retrieval of past autobiographical experiences. There was only moderate impairment in memory for public events which had occurred in the 5-year period before the encephalitis, and knowledge of earlier public events was preserved, whereas the loss of autobiographical incidents was extensive and showed little evidence of earlier memories being spared. Similarly, Ogden (1993) reported severe autobiographical memory loss, prosopagnosia and visual agnosia in a head injury patient, who had relative preservation of remote semantic knowledge. In this case, the pathology was more posterior, but projections from the right occipital to the right temporal lobe were disrupted. Ogden also suggested that a failure in visual imagery might be contributing to the autobiographical memory loss. Both patients (O'Connor *et al.* 1992; Ogden 1993) also had a severe impairment of visual, anterograde memory. Rubin & Greenberg (1998) reviewed a series of similar cases, in whom 'visual memory-deficit amnesia' gave rise to disproportionate impairments in autobiographical memory.

Partial dissociations of autobiographical and semantic memory have also been claimed. For example, Hodges & McCarthy (1993) reported a case of amnesia following bilateral thalamic infarction, in which there was dense autobiographical memory loss, together with memory loss for public events, but in whom knowledge of famous personalities was relatively intact. Mackenzie Ross & Hodges (1997) reported a patient who was severely impaired at autobiographical memory and knowledge of public events, but whose ability was surprisingly preserved at a famous faces task. As the patient had presumed cerebral hypoxia following a cardiac arrest with a normal CT scan, it is difficult to relate this finding to focal pathology.

Moreover, group studies have indicated that this simple left–semantic versus right–autobiographical distinction, postulated in single-case reports, does not necessarily hold good. Kopelman *et al.* (1999) did indeed find particularly severe autobiographical memory loss in patients with right-sided temporal lobe damage from herpes encephalitis, relative to patients with left-sided pathology, consistent with several studies cited above (O'Connor *et al.* 1992; Ogden 1993; Rubin & Greenberg 1998). However, the right-sided patients were also particularly impaired on a measure of famous news events, particularly when these images involved perception of famous faces, perhaps reflecting both 'episodic' and face recognition components to the task. Left-sided patients were particularly impaired when they had to 'complete' the names of famous people from the past from word-stems: this was interpreted as reflecting a deficit in the lexical–semantic labelling of remote memories. This double

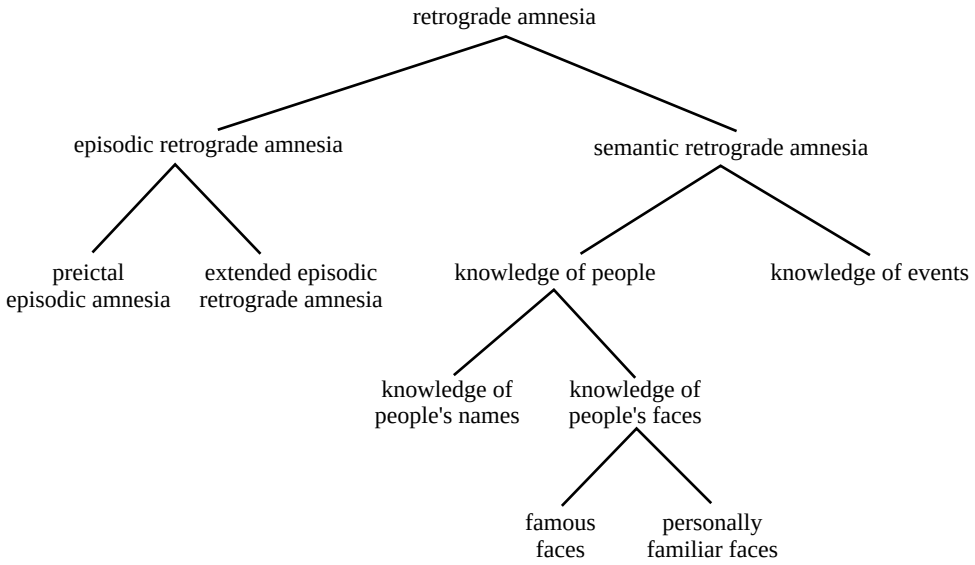

Figure 1. A provisional framework outlining the major forms of neurological RA, taken from Kapur (1999). Episodic RA refers to loss of memory for personally experienced events. Semantic RA refers to loss of specific forms of acquired knowledge. The framework is not meant to represent a comprehensive taxonomic classification—for example, more general forms of loss of knowledge (dysphasia, apraxia, etc.), psychogenic RA, and loss of personal semantic verbal knowledge, are not included.

dissociation was statistically significant. By contrast, Eslinger (1998) also examined patients with left or right temporal lobe pathology, finding that left medial temporal lobe lesions caused time-limited retrograde autobiographical memory changes. More extensive left temporal lobe pathology impaired personal semantic memory, but did not affect recollection of autobiographical incidents. However, right temporal lobe lesions did not appear to affect either personal semantic or autobiographical incident recall. Bilateral temporal lobe lesions seemed to be required to cause extensive autobiographical memory deficits, and Eslinger (1998) postulated that interactions between prefrontal cortex and diverse temporal lobe regions were involved in autobiographical memory retrieval.

In summary, there is evidence that the more semantic remote memories are dependent upon left temporal lobe function, that the retrieval of autobiographical incidents is more dependent upon the integrity of right temporal lobe structures, and that bilateral damage is probably more harmful than unilateral. Figure 1 is taken from Kapur (1999) and illustrates further proposed dissociations within autobiographical and semantic remote memory. However, the autobiographical–semantic distinction is by no means clear-cut, perhaps reflecting the fact that performance on many remote memory tasks involves aspects of both types of memory.

(b) *Explicit versus implicit remote memory*

There have been several attempts to identify an implicit component in RA, although this is much more difficult and vulnerable to criticism than in AA.

A novel dissociation in remote memory was reported by Warrington & McCarthy (1988) and McCarthy & Warrington (1992). They described a 54-year-old man who had suffered herpes encephalitis, resulting in bitemporal damage that was worse on the right. He showed extensive retrograde memory loss for autobiographical episodes and also for knowledge of public events, famous faces and famous names. Despite this, he performed within normal limits at a word-completion task (completing a name when given a stem cue) for famous names and at familiarity judgements for famous faces. The authors proposed a dual system for the semantic representation of names and faces: a vocabulary-like fact memory which was preserved in this patient, and a cognitive mediational memory system, which was impaired. The implication seemed to be that the former was analogous to so-called 'implicit' memory, which is preserved in AA.

Eslinger *et al.* (1996) compared the performance of two post-encephalitic patients on several tests, similar to those employed by Warrington and McCarthy (1988). A patient who had sustained left inferior and anterior medial temporal lobe pathology, together with a small right temporal polar lesion, was substantially impaired at a name-completion task when the cue was paired with a famous face. By contrast, a patient with right inferior and anterior medial temporal lobe pathology showed only very mild impairment at this task.

In a group study, Kopelman *et al.* (1999) obtained results consistent with those of Eslinger *et al.* (1996). Two patients with unilateral left temporal lobe pathology following herpes encephalitis were severely impaired at a name-completion task, whereas herpes patients with predominantly right temporal lobe pathology were virtually intact at this test, consistent with the Warrington & McCarthy (1988) findings. Taken together, these results suggest that the 'vocabulary-like fact memory' is sensitive only to certain types of left temporal lobe damage. However, Reed & Squire (1998) found impairment in patients with temporal lobe lesions at a more difficult task, in which only the names were presented for completion (in the absence of the associated famous faces),

indicating that task difficulty needs to be taken into account in evaluating such findings.

Two further studies (Tulving *et al.* 1988; Lhermitte & Serdaru 1993) have shown that progressive priming or prompting in training sessions over a number of days or weeks can help to restore a number of personal semantic memories, but that this procedure fails to alter loss of memory for autobiographical incidents.

In addition, at least three studies of psychogenic amnesia (see § 6) have addressed this issue. Kopelman *et al.* (1994) described a patient with psychogenic amnesia, who failed to show word-completion priming of the names of people and places known to her preceding the onset of her amnesia, whereas she showed normal priming of the names of people and places that she had learned only since the onset of her disorder. However, this patient may have been simulating by the time she was tested on this task. Markowitsch *et al.* (1997) used a word-stem completion task involving the names of people and companies that a psychogenic amnesic patient had worked with in the past. This patient performed very badly at this task. Again, there were issues of possible simulation, and incidental statements by this patient suggested that the task was not, in fact, measuring implicit memory in this case. Campodonico & Rediess (1996) examined this issue using tests of semantic knowledge in a patient with 'profound psychogenic RA'. On a measure of indirect remote memory, their patient showed more rapid learning of famous identities relative to novel ones, compared with control subjects, despite having been unable to name the famous faces at baseline. She also learned the names and occupations of famous people better than she did those of unknown people. The authors interpreted their findings as evidence for preserved 'implicit' remote semantic knowledge, despite impaired 'explicit' recall of the same material.

In summary, the idea that there might be a preserved 'implicit' component in RA, as many studies have found in AA, is indeed attractive. Such a finding might also be valuable in differentiating authentic or 'hysterical' psychogenic amnesia from simulated or factitious amnesia. However, it is much harder to demonstrate unequivocally an implicit component in RA than it is in AA. There have been few studies to date, and the findings so far remain vulnerable to alternative interpretations.

(c) *Brief versus extensive episodic RA*

Various authors have argued for qualitatively different types of RA, broadly related to the time-span (temporal extensiveness) that it covers (e.g. Williams & Zangwill 1952; Symonds 1966; Squire *et al.* 1984; Kapur 1999). The nature of RA may vary according to whether it covers a matter of (i) seconds, minutes or hours; (ii) days, weeks or months up to a period of 2 to 3 years; or (iii) an extensive retrograde memory loss covering years or decades.

Kapur (1999) distinguished two classes of RA, which he called 'pre-ictal amnesia' and 'extended episodic RA', respectively. Kapur (1999) put forward four arguments in favour of this distinction:

(i) The delayed onset of certain types of brief RA. Lynch & Yarnell (1973) studied American footballers who had incurred a mild head injury. These footballers were initially able to describe what had happened just before the blow, but, when reinterviewed some minutes later, they were unable to recall these events. This has usually been interpreted as a failure of memory consolidation following the blow, resulting in a brief period of RA lasting a matter of minutes. Consistent with this, Russell & Nathan (1946) also noted that in some patients pretraumatic events were briefly recalled in the first few minutes following a head injury, but then were rapidly forgotten.

(ii) Following a closed head injury, an extensive RA characteristically shrinks to a much briefer period, which may be a matter of minutes, hours or days, depending upon severity of the injury (Russell & Nathan 1946; Williams & Zangwill 1952; Wasterlain 1971). Kapur (1999) also noted that, following episodes of transient global amnesia (TGA), there is commonly some residual 'pre-ictal RA', lasting a matter of minutes or (exceptionally) hours (Fisher 1982; Hodges 1991; Kapur *et al.* 1998).

(iii) There are qualitative discontinuities in the density of pre-injury memory loss reported by patients. For example, following head injury, there is commonly a short, virtually complete RA lasting a matter of minutes or hours. In some cases, there is also a far less dense loss of memories for incidents or events over the preceding few weeks (Russell & Nathan 1946; Williams & Zangwill 1952).

(iv) Some experimental studies also support this distinction. Electrical stimulation (under local anaesthetic) of temporal lobe regions in epileptic patients with complex partial seizures produces a period of pre-ictal RA, ranging from a few minutes to a few days or weeks (Bickford *et al.* 1958). Bickford *et al.* (1958) also found that the longer the duration of electrical stimulation, the more extensive was this brief or pre-ictal RA. Electroconvulsive therapy (ECT) also gives rise to a brief RA lasting a matter of days (Squire *et al.* 1981) and complaints of memory loss which may go back to 2–3 years (Squire & Slater 1983).

A fifth argument is that there is at least some evidence that patients with lesions confined to the diencephalic or medial temporal structures have an RA which may extend back 2–3 years but no further (Milner 1966; Zola-Morgan *et al.* 1986; Dusoir *et al.* 1990; Graff-Radford *et al.* 1990; Snowden *et al.* 1996; Graham & Hodges 1997; Guinan *et al.* 1998). As will be discussed below (§ 5), cortical damage seems to be required for a more extensive RA, going back years or decades as is seen in (for example) the Korsakoff syndrome, herpes encephalitis, or Alzheimer dementia (e.g. Albert *et al.* 1981; Kopelman 1989; Wilson *et al.* 1995; Kopelman *et al.* 1999). This distinction between a brief or short RA (2–3 years) and much longer RA (years or decades) has also been made in connection with the literature on focal RA (Kopelman 2000*a*).

In brief, there are several reasons for attempting to distinguish the mechanisms which underlie these different components of RA. The precise boundaries of these different types of RA, and whether they should be

differentiated into two, three, or more subtypes, remain unclear. To date, most neuropsychological literature has concentrated on understanding the nature of an extensive RA.

3. ASSOCIATIONS OF RA

Important factors to consider in assessing and interpreting the 'temporal gradient' of RA, i.e. the relative sparing of early memories, are the duration (time since onset) of the amnesia and the age of the subject. Surprisingly, the duration of amnesia was seldom reported in the earlier quantitative studies from the 1970s and 1980s. The age of the subject is obviously important in reviewing the items in any given remote memory task. Furthermore, there is some evidence that older amnesic patients (aged 40 or over) are more likely to show a steep temporal gradient than patients under 40, particularly in recalling facts about themselves (Kopelman *et al.* 1989). This finding does not appear to be related to the severity, rate of onset or duration of amnesia, but suggests that older subjects may encode new memories in a way which makes them more vulnerable to the effects of brain damage than are new memories in younger subjects.

Second, other factors which determine performance on remote memory tasks include intelligence, education and media exposure. Kopelman (1989) found significant correlations between full-scale IQ and measures of 'semantic' remote memory—tests of famous news event recall and recognition, and a test involving famous personalities. However, correlations with IQ were not significant for measures of autobiographical incidents and 'personal semantic' facts. Likewise, Kapur *et al.* (1999) found a trend in the same direction in healthy subjects between estimated premorbid IQ and a public events remote memory measure. Moreover, Kapur *et al.* (1999) also found that this fairly typical test of retrograde memory correlated even more closely with an estimate of media exposure, based on how often a subject watched the television news, read newspapers, etc.

Third, a subject's ability at executive or 'frontal' tests may also be an important predictor of remote memory performance. This may be particularly the case for autobiographical recall, where active reconstruction or recollection is required, but significant correlations with executive test scores are not confined to episodic RA tests. Kopelman (1991) found that six out of eight executive or frontal tests correlated significantly with retrograde memory performance, but only one out of eight tests correlated significantly with a 'composite' measure of anterograde memory performance. Whereas anterograde test scores predicted only 21% of the variance in retrograde memory scores, a regression equation based on three of the executive or frontal tests predicted 64% of the variance. There were significant correlations with news event recall and recognition scores as well as with memory for autobiographical incidents and facts. Similarly, Verfaellie *et al.* (1995*b*) obtained a significant correlation between a measure of more purely semantic memory (words which had come into the vocabulary at different times) and a 'composite' measure of frontal function. Moreover, D'Esposito *et al.* (1996) contrasted subarachnoid haemorrhage patients who performed well or badly on executive tests, finding that only patients with severe executive impairment showed RA on a famous faces test, and that improvement in executive scores was correlated with improvement in RA.

Fourth, the extent of cortical pathology is probably also important, as will be discussed further below (§ 5). Schmidtke & Vollmer (1997) developed a 'new' test of semantic memory, requiring subjects to retrieve 81 items of well-rehearsed semantic knowledge across various domains: scores on this test were interpreted as an index of neocortical-dependent memory representation. Scores on the Wechsler Memory Scale (WMS) were assumed to reflect hippocampal-dependent memory. On the basis of regression analyses, remote autobiographical memory scores and performance on a test of memory for famous people were found to be predicted by the measure of 'neocortical' function, according to these criteria. Other potentially important correlates of remote memory performance include direct, quantitative measures of brain volume on MRI, brain metabolism on positron emission tomography (PET), and cerebral perfusion on single-photon emission computed tomography, as will be considered below (§ 5).

In summary, there are a number of important correlates of performance on measures of retrograde memory, which are apparent in larger-scale group studies. Understandably, these factors tend to be ignored in single-case reports, but they may help to account for some of the dissociations which are reported. Amongst patients with memory disorders, the combination of low IQ, poor education, limited media exposure and relatively mild amnesia may give the impression of disproportionate impairment on the 'more semantic' remote memory tests (Kapur *et al.* 1999; Kopelman 2000*a*). The opposite pattern—severe autobiographical memory loss in someone with good background semantic knowledge (high IQ and education)—will give a pattern of performance the other way round. Before dissociations are claimed in particular patients and attributed to differing sites of pathology, it is always necessary to control for such factors.

4. RA VERSUS AA

As already mentioned (§ 3), there is generally a poor correlation between scores on retrograde and anterograde memory tests. This has been shown in Korsakoff syndrome patients by Shimamura & Squire (1986), Kopelman (1989, 1991) and Parkin (1991), in a mixed group of amnesic patients by Mayes *et al.* (1994), and in Alzheimer dementia patients by Kopelman (1989, 1991) and Greene & Hodges (1996). In the Kopelman (1989) study, only one out of five measures of RA showed a significant correlation with a composite measure of AA, and shared variance between RA and AA was only 21%. Somewhat similar findings were obtained by Mayes *et al.* (1997), although these authors also observed that higher correlations were found between anterograde and retrograde tests where the tasks were similar in format and in the kind of information tapped.

It is widely accepted that AA can occur with minimal or no RA—for example, in some cases of TGA (Hodges & Ward 1989), head injury (particularly if mild or

penetrating) (Russell & Nathan 1946; Dusoir *et al.* 1990), some cases of thalamic infarction (Dall'Ora *et al.* 1989; Graff-Radford *et al.* 1990; Parkin *et al.* 1994; Winocur *et al.* 1984), and in certain deep midline tumours (Kapur *et al.* 1996; Guinan *et al.* 1998). In particular, penetrating lesions to the brain often arise in the absence of any RA, despite the presence of moderate or severe post-traumatic amnesia (Russell 1948; Lishman 1968; Teuber 1969, 1975; Teuber *et al.* 1968; Grafman *et al.* 1985).

Much more contentious is the nature of disproportionate RA, sometimes known as 'focal' or 'isolated' RA. Kapur *et al.* (1992) described a 26-year-old woman who had fallen from a horse, sustaining left and right frontal contusions, evident on CT scan, and subsequent signal alteration on MRI at the left and right temporal poles. The patient was impaired across all remote memory tests employed, with normal or only moderate impairment at various anterograde tests. Similarly, Levine *et al.* (1998) described a patient who was involved in a road traffic accident, resulting in a right frontal lesion involving the uncinate fasciculus as well as prefrontal haemorrhages. The patient had an initially severe AA, but this resolved leaving a (Wechsler Memory Scale—Revised) verbal memory index of 128 and a severe RA.

The present authors have debated the underlying nature of focal RA elsewhere (Kopelman 2000*a*,*b*; Kapur 2000). Patients with disproportionate RA often have an initially severe or moderately severe AA, which subsequently subsides, and the importance of this is disputed. Second, they may have some degree of residual AA, which begs the question of whether measures of retrograde and anterograde memory are strictly comparable. Third, patients with specific deficits in autobiographical memory, or public semantic knowledge, or both, are commonly labelled as instances of 'focal RA', and it is important to remember that they differ. More specifically, patients with transient epileptic amnesia—TGA with an epileptic aetiology—commonly complain of 'gaps' in their autobiographical memory. The explanation for these gaps could be either that current epileptic activity has caused impaired retrieval of much earlier encoded memories, or that previously undetected 'subclinical' ictal activity resulted in faulty (anterograde) encoding of specific memories. Likewise, patients with semantic dementia have been reported to show a 'reversed' temporal gradient, analogous to that seen in focal RA (Snowden *et al.* 1996; Graham & Hodges 1997), but there are a number of alternative explanations for this, including the fact that difficulty in retrieving 'old' memories may reflect these patients' linguistic or semantic disorder. Finally, it is important to remember that psychogenic amnesia can produce temporal gradients which resemble those in focal RA (Kopelman *et al.* 1994; Kritchevsky *et al.* 1997). Psychiatric and psychogenic factors may be important, even in the presence of brain pathology (see § 6).

In summary, the severity and extent of RA is poorly correlated with the severity of AA, although most investigations of this topic have looked at the more extensive forms of RA rather than the briefer forms mentioned in § 2. While AA can exist alongside little or no RA, the interpretation of disproportionate retrograde impairments remains controversial and several different types of factor may produce this phenomenon.

5. STRUCTURAL BRAIN PATHOLOGY AND RA

There is little doubt that a variety of sites of pathology can give rise to RA, as has been reviewed in detail elsewhere (Kopelman 1993, 2000*c*).

Large temporal lobe lesions can produce an extensive RA. As already considered, there is a differing pattern of deficit across left- and right-sided lesions. Left-sided lesions tend to produce damage to semantic remote memory (De Renzi *et al.* 1987), right-sided lesions to autobiographical memory (O'Connor *et al.* 1992), and bilateral lesions affect both (Wilson *et al.* 1995). Cermak & O'Connor (1983), studied a patient S.S., who had suffered herpes encephalitis resulting in bitemporal pathology and a severe AA. On a test of famous faces (Albert *et al.* 1979), he showed a marked impairment with a temporal gradient, i.e. relative sparing of early memories. During follow-up over a number of years, there was substantial improvement. Asked about events from his past life (from the 1930s to the 1970s) on a questionnaire, he showed impairment for the two most recent decades only. Given cue-words, and asked to describe specific episodes from his past relating to these words, S.S. seemed to display only a 'personal pool of generalized knowledge about himself, i.e. his own semantic memory'. On the other hand, his past knowledge about physics and laser technology (his profession) appeared to be intact, although he was not able to retain information encountered in a new article about the subject. A further study showed that he was impaired in recalling and recognizing the meaning of words which had come into the language only since the onset of his amnesia (Verfaellie *et al.* 1995*a*).

Large frontal lobe lesions can also produce retrograde memory loss, particularly if bilateral. Baddeley & Wilson (1986) described impaired retrieval of autobiographical memories in two such patients, and florid confabulation in autobiographical memory retrieval in two others. Larger group studies in patients with neuroradiologically delineated frontal lesions have also demonstrated severe impairments in autobiographical memory retrieval (Della Sala *et al.* 1993; Kopelman *et al.* 1999), public or news event knowledge (D'Esposito *et al.* 1996; Mangels *et al.* 1996; Kopelman *et al.* 1999), and famous faces (Mangels *et al.* 1996).

Findings in patients with diencephalic lesions are variable. There is little doubt that Korsakoff syndrome patients generally show an extensive RA with a relatively steep temporal gradient (Zola-Morgan *et al.* 1983; Butters & Cermak 1986; Kopelman 1989; Kopelman *et al.* 1999). Squire *et al.* (1989) compared the performance of seven patients with the alcoholic Korsakoff syndrome with that of five patients of more acute onset on six tests of remote memory. In both groups, there was a temporal gradient to the RA extending across a period of about 15 years, and the gradient was closely similar between the two groups. Verfaellie *et al.* (1995*b*) examined remote memory for semantic information in Korsakoff syndrome and other amnesic patients, using a test of vocabulary for words which had come into the language between 1955 and 1989. They found an impairment in the Korsakoff syndrome group in the recall of these words, and that there was a temporal gradient such that their knowledge of recent words was more impaired than that of remote

words. However, it seems to be the concomitant presence of some degree of frontal lobe pathology which contributes to this. This was first postulated on the basis of correlations between RA scores and frontal or executive test performance by Kopelman (1991), and it appears to be corroborated by subsequent studies (e.g. Hodges & McCarthy 1993; Kopelman *et al.* 1999). Hodges & McCarthy (1993) found severe impairment of autobiographical memory in a patient with bilateral paramedian thalamic infarction, whereas other studies of patients with thalamic infarction have found preserved remote memory (e.g. Winocur *et al.* 1984; Graff-Radford *et al.* 1990): it seems likely that the extent of involvement of frontal projections from the thalamus may determine the severity and extent of RA. Similarly, Kopelman *et al.* (1999) compared Korsakoff syndrome patients with a degree of frontal atrophy and patients who had focal diencephalic pathology, resulting from pituitary tumours and their treatment: only the former group showed an extensive retrograde memory loss.

Most controversial is the issue of whether damage confined to the medial temporal lobes produces an extensive RA. Following a bitemporal lobectomy, patient H.M. appeared in initial studies to have an RA of only 2–3 years (Milner 1966, 1972), and this appeared to be confirmed on tests of famous faces and famous news events (Marslen-Wilson & Teuber 1975; Gabrieli *et al.* 1988). Similarly, Zola-Morgan *et al.* (1986) found a 2-year RA in a patient with moderately severe AA following hypoxic brain damage to the CAl regions of the hippocampi bilaterally. In contrast, Nadel & Moscovitch (1997) have reviewed the literature, and have suggested that hippocampal pathology alone can produce an extensive RA. Unfortunately, many of the studies which they reviewed involved patients with extensive temporal lobe pathology, confounding the interpretation of the findings. Two of the better studies were by Victor & Agamanolis (1990) and Kartsounis *et al.* (1995). These authors described single cases who showed either a relatively specific loss of neurons in the hippocampi bilaterally (Victor & Agamanolis 1990) or signal alteration on MRI in the hippocampi bilaterally in the CAl and CA2 fields (Kartsounis *et al.* 1995), respectively. (Quantified MRI evidence of severe hippocampal atrophy in the latter patient has recently been provided by Cipolotti *et al.* (2001).) However, it is of interest that both patients had a history of heavy drinking, although the authors stated that this had not been true in recent years.

Kopelman *et al.* (1999) carried out the first study comparing groups of patients with temporal lobe, frontal or diencephalic lesions across several RA tasks, including recall of autobiographical incidents, personal semantic facts, and famous news events. As already stated, Korsakoff syndrome patients (with combined diencephalic and frontal pathology) showed severe RA across all tasks with a relatively steep temporal gradient, whereas patients who had been treated for pituitary tumours extending into the diencephalon showed severe AA but no evidence of RA. Patients with temporal lobe pathology also showed a severe RA, although their temporal gradients appeared to be 'flatter' than those of Korsakoff syndrome patients. Patients with frontal lobe lesions showed severe impairment in the recall of autobiographical incidents and famous news events, but were relatively intact in the retrieval of well-rehearsed personal semantic facts—i.e. this latter group seemed to be particularly impaired where 'effortful' or organized retrieval processes were required for reconstructing 'old' memories. In general, patients with bilateral frontal lesions performed worse than did patients with unilateral frontal lesions. Subsequent analysis has shown significant correlations with quantitative MRI measures of the volume of specific brain structures in these patients, such that 60–68% of variance on autobiographical memory tasks could be accounted for by these brain volume measures.

In summary, large temporal lobe or frontal lesions can produce an extensive RA. Diencephalic lesions appear to contribute to an extensive RA where there is concomitant frontal pathology. The contribution of medial temporal lobe pathology in isolation remains controversial. Somewhat different patterns of RA are found between left and right temporal lobe lesions, and between frontal and temporal lobe pathology.

6. PSYCHOGENIC INFLUENCES ON RA

Psychological forms of RA can be relatively 'pure', in that there is no known evidence of cerebral pathology, or they can occur in the context of either minor or major brain disorder (Kapur 1999). However, even in 'pure' cases, which are the ones usually referred to as 'psychogenic amnesia', there is commonly a past history of a transient organic memory loss (Stengel 1941; Berrington *et al.* 1956; Kopelman 1987, 2000*a*,*c*; Markowitsch 1996). Psychogenic amnesia can be situation-specific, e.g. loss of memory for an offence (including child sexual abuse) by either the perpetrator or the victim: in these cases, there is a brief gap in memory for the episode, presumably as a result of compromised anterograde memory encoding (Kopelman 1987, 2000*c*). Alternatively, psychogenic amnesia can be 'global', encompassing the whole of a person's past, as occurs in a so-called 'fugue' episode, also known as 'functional RA'.

Schacter *et al.* (1982) described a young man who developed 'functional RA' after attending the funeral of his grandfather, to whom he had been very close. When asked to retrieve autobiographical memories to cue-words, the median age of his retrieved memories was very short (i.e. recent), relative to both healthy controls and his own subsequent (post-recovery) performance. However, there were some preserved 'islands' of autobiographical memory from the happiest period of his life. He recovered his memories after seeing a television programme in which a funeral was shown.

Kopelman *et al.* (1994) reported a 'reverse' temporal gradient on autobiographical and public event remote memory tasks in a patient with psychogenic amnesia. Anterograde memory test scores were normal. Following a marital crisis, this woman disappeared from her home, flew across the Atlantic, and 'came round' in the London Underground. There was a persistent amnesic gap for a 1-week period, which was thought to reflect an authentic fugue state, although this lady was shown to be at least partially simulating some 3 months after first being seen.

Kapur & Abbott (1996) described a 19-year-old male university student, who was found in a city park a few

days before his university examinations were due to start. In addition to the likely stress resulting from his pending examinations, the patient's grandmother had died 8 months earlier, and the patient had been quite close to her. Witness accounts were obtained from people who had observed the episode from the onset, and the authors monitored the acute stages of recovery of memory function over the next 4 weeks. The memory loss was characterized by impaired performance on both autobiographical and public events memory tests, in the context of normal anterograde memory scores. Shrinkage of RA took place over a 4-week period, with the autobiographical and public events components of retrograde memory recovering at the same rate.

Kritchevsky *et al.* (1997) obtained a pronounced recency effect on a cued autobiographical memory task in nine patients with functional RA, similar to that obtained in the Kopelman *et al.* (1994) patient. This gradient was in stark contrast to a conventional 'Ribot' temporal gradient (i.e. sparing of early memories) obtained in patients during a TGA episode.

Markowitsch *et al.* (1997) described a 37-year-old man, who experienced a 'fugue' episode lasting 5 days when out bicycling, and who then had a persistent loss of autobiographical memory, lasting 8 months or more. During this period, the patient was required to listen to sentences containing information about his past, either preceding or following the onset of amnesia, while undergoing an oxygen-15 PET scan. The authors found reduced right hemisphere activation, relative to healthy controls performing a similar task.

Costello *et al.* (1998) described a man in his 40s who, following a left superior dorsolateral prefrontal haemorrhage, developed a dense RA for the 19 years preceding his stroke. However, the authors considered that 'a purely organic account of the condition does not seem very plausible'. They also carried out PET activation study, in which the subject attempted to recall events using family photographs as stimuli in three conditions—events for which he was amnesic but at which he had been present, events from the amnesic period at which he was not present, and events outside the amnesic period. In the 'amnesic–present' condition, activation was diminished in both the right ventrolateral frontal cortex and a region close to the site of the haemorrhage. The finding of reduced right frontal activation is broadly consistent with the finding of Markowitsch *et al.* (1997) of diminished right hemisphere activation.

These last two studies suggest that there may be common pathways which are affected in both neurological and psychogenic forms of RA (cf. Markowitsch 1996). However, Kapur (1999) has pointed out that there may be differences in the influences that psychosocial variables can have on functional anatomy in these cases. Furthermore, much more common than cases of 'pure' psychogenic amnesia are patients in whom psychosocial factors are combined with mild or moderate degrees of brain pathology to produce an RA which is very much disproportionate to what would be expected on the basis of the cerebral pathology alone. Kopelman (2000*a*) described several such cases, including 'Patient E' who experienced a minor cerebral ischaemic episode, but whose autobiographical memory loss was quite disproportionate to this: it was probably related to the severe employment and marital problems that he was undergoing at the time. The effect of psychogenic factors can also be seen in patients with more severe brain pathology, as described by Stuss & Guzman (1988) and Binder (1994).

Kopelman (2000*a*) argued that even patients with clear-cut brain pathology can 'use' that pathology to differing ends, and that there may be variable degrees of awareness in psychological forms of amnesia. Taking account of various known associates of psychogenic amnesia—a severe precipitating stress, depression or extreme arousal, and a past history of a transient organic amnesia—Kopelman (2000*a*) proposed a model to suggest how psychosocial factors interact with brain systems known to be involved in memory. Figure 2 illustrates this model. The relevant social and psychological factors are indicated in the ovals, and the brain systems in rectangular boxes. The model postulated that stress can affect frontal control or executive systems such that there is inhibition in the retrieval of autobiographical and episodic memories. This inhibition is exacerbated, or made more likely, when a subject is extremely aroused, very depressed, or when there has been a past 'learning experience' of transient amnesia. When such stresses are severe, the inhibition may even affect a 'personal semantic belief system', resulting in a transient loss of knowledge of self and identity (see dotted arrow)—as is characteristic of 'fugue' states. If this occurs, there is negative feedback to the emotional state, such that the subject is commonly described as appearing 'flat' or perplexed. Despite this suppression of autobiographical memory retrieval by these frontal inhibitory mechanisms, anterograde learning (and 'new' episodic memory retrieval) can occur from 'normal' environmental stimuli via the intact medial temporal or diencephalic system, as illustrated in figure 2.

7. THEORIES OF RA

Theories of RA have traditionally focused on three issues. The first is whether the problem is essentially a failure of access or retrieval or a loss of storage. The second concerns the nature of the temporal gradient which characterizes RA in most forms of organic amnesia. The third concerns the respective roles of specific brain structures in storing and accessing remote memories, and how these structures interact.

There are several reasons for supposing that the RA in amnesic or dementing patients might result, at least in part, from a retrieval deficit—or from a disruption in the organization of retrieval processes—rather than from a destruction of memory storage itself. Various studies have shown that amnesic or dementing patients manifest a remarkably good response to recognition or contextual cues, compared with their very poor recall memory performance (Kopelman 1989; Parkin *et al.* 1990; Verfaellie *et al.* 1995*b*; Kopelman *et al.* 1999). Weiskrantz (1985) pointed out that a marked response to recognition testing or cueing for memories long preceding the onset of an illness must be indicative of a retrieval component to the RA, whatever the slope of the remote memory curve. A deficit in retrieving remote memories, superimposed upon an anterograde learning deficit, is consistent with the finding that there are generally low

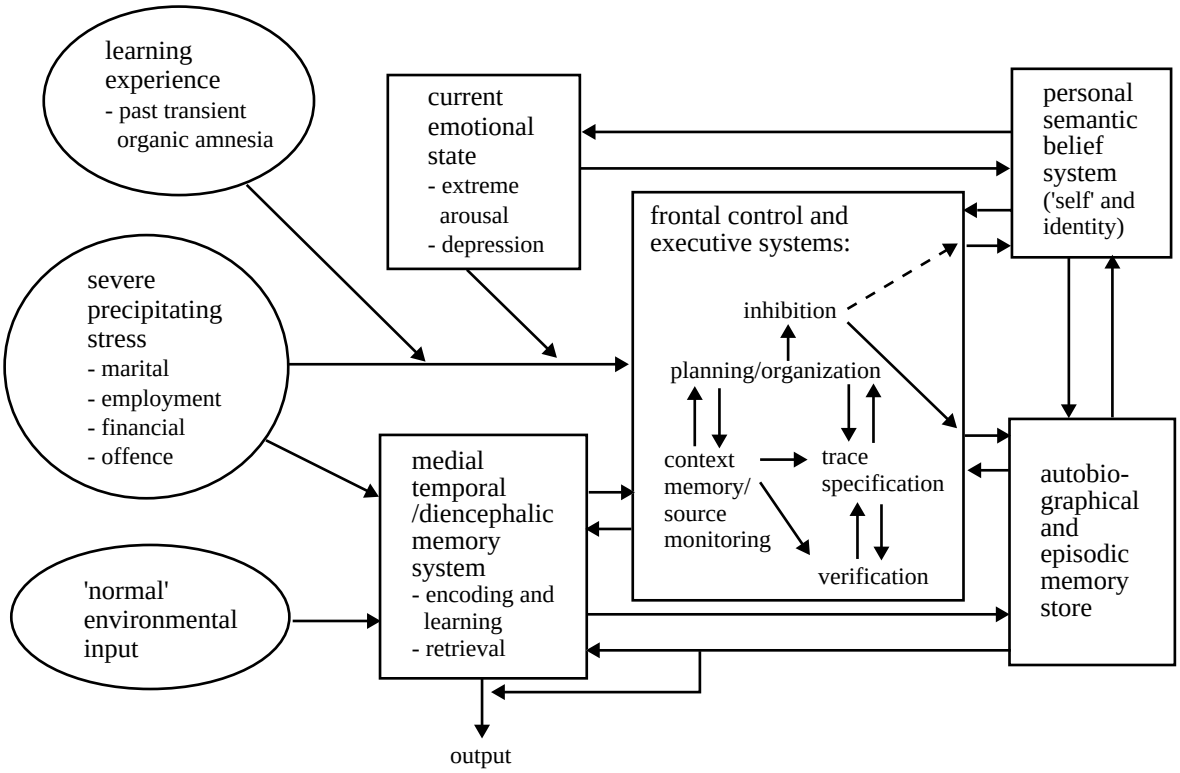

Figure 2. Social factors and brain systems influencing autobiographical memory retrieval and personal identity. The relevant social and psychological factors are indicated in the ovals. The brain systems are indicated in the rectangular boxes. Severe stress affects frontal control and executive systems, thereby inhibiting the retrieval of autobiographical or episodic memories. This is more likely if the subject is extremely aroused, very depressed, or if there is a past experience of a transient organic amnesia. If the stress is severe, there may even be a transient loss of knowledge of self and identity (dashed arrow). From Kopelman (2000*a*).

and non-significant correlations between the severity of AA and performance on various tests of RA (Shimamura & Squire 1986; Kopelman 1989, 1991; Parkin 1991; Mayes *et al.* 1994, Greene & Hodges 1996). In addition, there are sometimes inconsistencies in the retrieval of past memories by individual patients (Cermak & O'Connor 1983; Sagar *et al.* 1988). Obviously, where RA shrinks (as in head injury, following ECT, and in TGA), there must have been an important retrieval component to the deficit (Kapur 1999). However, this does not exclude the possibility that loss of actual storage might occur in certain forms of focal brain atrophy or dementia. Moreover, as Kapur (1999) pointed out, it may be more important to identify at which point in a network of associations a breakdown has occurred than simply to pursue dichotomies, such as retrieval versus storage.

Various theories have been postulated to account for the temporal gradient in RA. One view is that there is a prolonged process of physiological consolidation of memories, during which memories are initially dependent upon the medial temporal lobe system but gradually become established in other areas of the brain ('structural reallocation'). According to this view, there is a gradual reorganization of memory storage, whereby memories that are initially dependent upon the medial temporal lobes eventually do not require this system. A more permanent memory, independent of the medial temporal lobes, gradually develops, presumably in neocortex (Alvarez & Squire 1994; Murre 1997). However, very extensive temporal gradients, extending over 20–30 years, provide a problem for this theory, as they imply that this process of physiological consolidation must continue for a very long time indeed.

A second approach emphasizes that, as episodic memories are rehearsed through time, they adopt a more semantic form, which protects them against the effects of brain disorder (e.g. Cermak 1984; Weiskrantz 1985; Sagar *et al.* 1988). In other words, the contextual components of these memories become attenuated or lost, making the memories feel much less immediate and vivid, but they are better preserved. This hypothesis is not incompatible with the notion of structural reallocation, proposed in consolidation theory. Although an attractive idea, the problem with this view is that the notion of 'semanticization' is poorly specified and therefore somewhat unsatisfactory. Moreover, it does not explain why knowledge which is semantic virtually from the outset, such as knowledge of the meaning of new words, also shows a temporal gradient (Verfaellie *et al.* 1995*b*).

A third approach is multiple-trace theory, proposed by Nadel & Moscovitch (1997). These authors accept that the hippocampi and related structures in the medial temporal lobes and diencephalon are involved in a short-term consolidation process, that they call 'cohesion', which is critical to memory formation. However, they argued against a notion of long-term consolidation, lasting years or even decades. They postulated that the hippocampi or medial temporal lobe structures are continuously involved

in the storage and retrieval of memories, both new and old, in interaction with neocortex. They argued that an ensemble of hippocampal neurons acts as a pointer or index to those neocortical neurons that represent information, and this ensemble serves as a mechanism for binding information into a coherent memory trace. The entire hippocampus–neocortical ensemble constitutes the memory trace for an episode. Each reactivation of this memory trace occurs in an altered neuronal and experiential context, resulting in the creation of a newly encoded trace. The creation of multiple, related traces facilitates the 'extraction' of factual information from an episode and its integration with pre-existing semantic memory stores. Hence, facts about the world are separated from an episode and ultimately stored independently of it. However, the spatial and temporal contextual information that conveys the episodic quality to a memory depends, according to Nadel & Moscovitch (1997), upon the continuing involvement of the hippocampi (for spatial context) and the frontal cortex (for temporal context). Consequently, autobiographical memory always depends upon the hippocampal complex and its provision of contextual information.

According to Nadel & Moscovitch (1997), as memories age, they are either forgotten or they benefit from the formation of multiple traces in the hippocampal complex and neocortex. Thus, older episodic memories will be associated with a greater number of traces, and retrieval will become easier as the number of traces proliferates, in parallel with the number of access routes to them. However, because neural connections in the hippocampi are sparse, even minimal damage in the hippocampal formation will affect the retention and recovery of memory traces. Newly acquired traces will be particularly vulnerable, whereas older memories, which are multiply represented, will be able to withstand the loss of more hippocampal tissue. This gives rise to the temporal gradient. The extent of the RA and the slope of the gradient will depend upon the size of the hippocampal lesion.

This theory, which has resemblances to Morton's 'headed records' model (Morton *et al.* 1985), makes the prediction that temporal gradients will be steeper in semantic memory, where some structural reallocation can occur, than in episodic memory. Support for this is provided in a study by Viskontas *et al.* (2000), who showed steeper gradients for personal semantic facts, compared with the recall of autobiographical incidents, in a study of patients with temporal lobe epilepsy. However, the theory cannot account for the finding that some patients with medial temporal lobe or diencephalic pathology and severe AA have only a brief (2–3 year) RA, and many of the studies reviewed by Nadel & Moscovitch (1997) involved patients whose pathology extended far beyond the medial temporal lobes.

The third theoretical issue mentioned above—namely, the relative contribution of specific brain structures to RA and their interaction—is closely tied to the first two theoretical topics. Controversies concern whether structural reallocation occurs or whether the hippocampi are continuously involved in memory, whether that structural reallocation applies more to semantic than autobiographical memory, whether damage to the hippocampal system alone can produce an extensive RA, and whether there are distinct functional roles of the frontal lobes and of the left and right temporal lobes in maintaining and retrieving 'old' memories. Kapur (1999) concluded that, although the representation of old memories may be widely distributed as multiple neural networks, this does not exclude the possibility that some regional specialization of function can occur. Similarly, Kopelman (2000*c*) concluded that, while there is evidence that widespread networks underlie the storage of old memories, there is also evidence of functional specialization.

8. CONCLUSIONS

There is a need for both single-case and group studies in investigating RA. Single-case investigations permit the identification of dissociations in RA, but group studies are required to corroborate and quantify these differing patterns of performance and also to establish the correlates (associations) of performance at different tasks. There is much evidence that there is a broad distinction between the autobiographical and semantic aspects of RA, but this distinction is not always clear-cut and its relationship to specific sites of damage (e.g. right versus left temporal lobe) is not entirely consistent across different studies. Large lesions in the temporal or frontal lobes produce RA, but precise delineation in terms of specific structures has not proved possible: it is most likely that the storage and retrieval of old memories depend on a widespread network of neural connections. Similarly, the specific role of the hippocampi and other medial temporal lobe structures remains highly controversial. This latter point relates to controversies concerning the nature of the temporal gradient in RA—whether it results from physiological consolidation and structural reallocation, memories acquiring a more semantic form, or the acquisition of multiple traces within the hippocampal system. Moreover, investigation of all these issues is confounded by psychological factors, which frequently contribute to, bias, or exaggerate patterns of RA in particular patients. Nevertheless, advances in our understanding of RA in the last 30 years have been considerable.

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