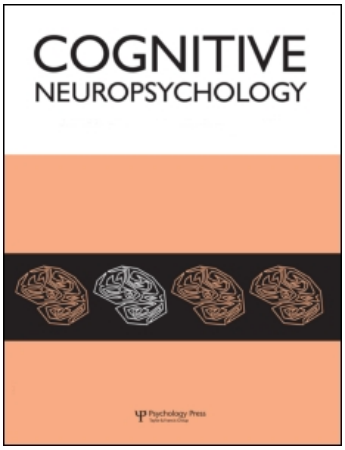

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Focal retrograde amnesia and the attribution of causality: An exceptionally benign commentary

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FOCAL RETROGRADE AMNESIA AND THE ATTRIBUTION OF CAUSALITY: AN EXCEPTIONALLY BENIGN COMMENTARY

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Kopelman offers an invaluable and comprehensive review of empirical and theoretical issues relating to focal retrograde amnesia and related conditions. He makes two main points: (1) That many of the published cases of focal retrograde amnesia in fact showed significant anterograde memory impairment, and thus should strictly not be classified as cases of focal retrograde amnesia; (2) that there are hazards in attributing causality in patients with retrograde amnesia, especially those with a major autobiographical component. In the case of his first point, I suggest that his observations are a matter of interpretation, essentially revolving around the defining criteria for the selection of memories to be compared and for regarding one set of memories as "disproportionately impaired" compared to the other. With regard to the second point, however, I largely concur with his observations, adding some reservations of my own. I conclude that although some patients with focal retrograde amnesia may represent a diagnostic dilemma when it comes to attributing causality, those who are shown to have a clear neural basis to their memory loss provide an avenue for exploring the brain's plasticity in accommodating the formation of new memories despite the loss of equivalent old memories.

Does focal retrograde amnesia exist as a valid neurological entity? I welcome the article by Kopelman (2000, this issue, pp. 585–621), which addresses important issues relevant to answering this question. His review is well-written, comprehensive, illuminating, valuable, and exceptionally critical.

In my commentary, I will initially consider matters of terminology. Next, I will deal with issues relating to definition and mechanisms as they apply to cases of focal retrograde amnesia (focal RA). I will then examine the issue of causality. Finally, I will consider Kopelman's conclusions and try to come to my own conclusions to the question posed at the beginning of this commentary.

TERMINOLOGY

Problems in terminology and definition are not unique to brain-based memory systems and are also found in areas such as immunological memory (see Doherty, 2000). As I will indicate later, the terms "retrograde amnesia" and "anterograde amnesia", which date back to the late nineteenth century (see Schacter, 1996, p. 312), may themselves be rather unsatisfactory. In the case of the term "focal retrograde amnesia", we first used the term in the Discussion (Kapur, Heath, Meudell, & Kennedy, 1986, p. 219), but not in the title, of a paper relating to our patient who had attacks that subsequently turned out to be epilepsy-related. We used the

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phrase "focal retrograde amnesia for verbal material." The reason for using the term "focal retrograde amnesia" was simply that the patient performed poorly on tests that had traditionally been used to assess retrograde amnesia in amnesic populations, but performed relatively well on tests that had traditionally been used to assess anterograde memory in the same amnesic populations. We subsequently used the term in the title, but not in the content, of a paper (Kapur, Young, Bateman, & Kennedy, 1989) where the same patient was described. He showed a similar distinction in his pattern of memory performance. There was something of a contrast between his normal performance on the Autobiographical Memory Interview and a patchy loss of memory for major personal events (major surgery that he and his wife underwent), but we concluded that his autobiographical memory was relatively preserved. In both of these papers, therefore, the term "focal retrograde amnesia" was used to describe a contrast between relatively poor performance on certain retrograde memory tests dealing with public events, famous personalities, etc. and relatively good performance on certain anterograde memory tests.

In the case of the review article that I wrote a few years later (Kapur, 1993), I implicitly referred to four relatively distinct sets of observations that I thought contributed to the viability of coining the term "focal retrograde amnesia" and defining it as a neurological entity: (1) The definition inherent in our original papers on the patient ED with a form of temporal lobe epilepsy (Kapur et al., 1986, 1989), where we contrasted performance on public events retrograde memory tests and performance on standard anterograde memory tests; (2) somewhat analogous to this were reports in the literature of transient episodes of memory loss, where there was a temporary loss of knowledge, coupled with preserved ongoing episodic memory, such that the patient subsequently had a fairly clear recollection of his/her loss of well-established memories (e.g., Damasio, Graff-Radford, & Damasio, 1983; Schott, Courjon, Trillet, & Rahme, 1970); (3) the time-limited (months to a few years) autobiographical episodic memory loss, such as that documented by Williams and Smith (1954) in patients who had recovered from TB meningitis and who had made a good recovery in terms of anterograde memory; (4) the dense, temporally extensive and temporally ungraded autobiographical amnesia, coupled with relatively spared anterograde memory, associated with cases of acute brain pathology, such as the study published by Goldberg et al. (1981).

While I therefore had in mind a fairly eclectic approach and considered all four sets of observations when introducing the term "focal retrograde amnesia", in recent years the term has mainly been associated with the last of the four entities, i.e., severe loss of autobiographical episodic memories in the context of relatively spared performance on standard anterograde memory tasks. This has resulted in the unfortunate consequence of allowing the possible inclusion of cases where psychogenic factors might be at work—marked autobiographical amnesia as a presenting symptom is a common feature of psychogenic memory loss, but I do not know of any case of pure semantic retrograde amnesia that has a solely psychogenic basis (few patients will present in clinical settings complaining that they cannot remember any past famous personalities or news events!).

The term "retrograde amnesia" itself is arguably rather unsatisfactory, since it can convey one of at least six different meanings—loss of immediately pre-ictal/pre-traumatic episodic memories, longer-term loss of memory for personally experienced events, memory loss for personal semantic information, loss of memory for "singular" knowledge (e.g., public events), loss of memory for "generic" knowledge (e.g., semantic memory loss), and loss of memory for skills (cf. Meltzer, 1983). In discussions relating to retrograde amnesia in general and focal RA in particular, the term "retrograde amnesia" is often used as the converse to "anterograde amnesia", but the two sets of memory domains are usually quite distinct. Whenever we refer to comparisons between pre-illness and post-illness memories, perhaps we should use the prefix "retrograde" and also a novel term, such as "postgrade", and supplement these with the domains of memory in question, leaving the term "anterograde memory" to refer to performance on standard tests of episodic retention. Thus, we would talk of "retrograde

semantic memory" compared to "postgrade semantic memory", or "retrograde autobiographical memory" compared to "postgrade autobiographical memory". I further suggest that the terms "pretraumatic amnesia/pre-ictal amnesia" be used to refer to the loss of memory for events immediately preceding a brain insult.

There are three main areas of memory functioning that have usually been included when comparisons have been made in studies of focal RA: factual knowledge (usually tested in the form of memory for public events, famous personalities, etc.), autobiographical memories, and performance on standard anterograde memory tests. As indicated earlier, and as noted by Kopelman, most of the comparisons that are made in such studies are seldom "like for like", in terms of memory domains, time periods sampled, retention test procedures, etc. In addition to these differences, there has never been any clear indication as to what would operationally be defined as "disproportionate" when different sets of memory measures are compared. The threshold that is adopted is obviously critical, for it may decide whether there is sufficient contrast in performance to justify a label such as focal RA.

DEFINITION

Much of Kopelman's review of past cases of presumed focal RA deals with showing that there was a "significant" degree of anterograde memory impairment and/or that psychological factors may have been prominent in the cases in question. There is little doubt that most, if not all, of the reported cases of focal RA had *some* anterograde memory impairment, but whether this is regarded as "significant" or "disproportionate" to retrograde memory loss may in some cases be open to interpretation unless some a priori criteria have been established. I would see the question of "like for like" comparisons between anterograde and retrograde memory as an important but separate issue from the presence of marked or subtle anterograde memory impairments, and similarly the question as to the mechanisms that may have determined an outcome as being separate from how that outcome is characterised.

Considering some sample cases, Kopelman comments (p. 595) on the patient reported by Carlesimo, Sabbadini, Loasses, and Caltagirone (1998) by noting the Full Scale IQ of 88 and the Wechsler Memory Quotient of 89, and observing that these scores were interpreted as showing "mild anterograde memory impairment." However, of the 10 measures of anterograde memory that were presumably used by the authors to come to this conclusion (Table 1 of their paper, p. 452), all the scores were within normal limits in the case of testing carried out 13 months after the onset of the illness. Although it could well be argued that some of these scores, including the Memory Quotient of 89, have to be considered in the light of the patient's educational background, the same could be said for her performance on the retrograde memory tests that were also given. Similarly, the patient reported by Levine et al. (1998), showed a clear contrast between normal or near normal scores on most anterograde memory test and marked loss of pre-injury autobiographical memories. Thus, in terms of the criteria that Kopelman has applied to earlier cases in the same section, this type of case should be classifiable as an example of focal RA, regardless of any presumed underlying deficit in "re-awareness" that may be common to both pre-injury and post-injury memories.

Kopelman goes to some length to offer his interpretation of the O'Connor, Butters, Miliotis, Eslinger, and Cermak (1992) paper, which he says is a "much misquoted paper." He comments on the very poor visual nonverbal memory scores of the patient. However, to be fair to O'Connor et al., they probably saw their primary dissociation as being between normal or near-normal *verbal* memory test scores and markedly impaired performance on retrograde memory tests that had a high *verbal* loading. Thus, they were trying to compare "like" with "like", something that Kopelman himself advocates in his article.

Ideally, similar sets of memory domains that are sampled over similar time periods should form the basis of classifying a case as one of focal RA. In our 1996 report of two cases of disproportionate mem-

ory loss (Kapur et al., 1996), for the first of the two cases (patient GR) it was precisely the fact that we were able to make autobiographical memory comparisons over comparable time periods (i.e., similar sets of "retrograde" and "postgrade" autobiographical memories) that made her case so interesting. In the case of the accelerated forgetting that we found in the patient SP, the fact that she scored at floor level after 6 weeks for delayed story recall and delayed design recall suggests that, if anything, we may have underestimated her rate of forgetting. Although I agree that there may be "immense variability" in the forgetting rates of control subjects and patient groups, this is an empirical issue that one has to face within a single study when deciding at which point to stop collecting more data from control subjects. Kopelman notes the papers by Lucchelli and Spinnler (1998) and by O'Connor, Sieggreen, Ahern, Schomer, and Mesulam (1997) by further reference to variability in forgetting rates. An important aspect of these two papers is that they provide fairly good examples of focal retrograde amnesia, where this is strictly defined in the terms that Kopelman applies to many of the studies—relative performance on standard anterograde and retrograde memory tests—e.g., the patient studied by O'Connor et al. (1997) had a Delayed Memory Quotient of 111, in spite of poor performance on retrograde memory tests.

In the section of his paper, "*Only brief retrograde memory loss*" (p. 589), Kopelman plays down the importance of cases of "brief" retrograde memory loss, such as the papers by Yoneda, Yamadori, Mori, and Yamashita (1992) and by Hokkanen, Launes, Vataja, Valanne, and Iivanainen (1995), making the reasonable point that the theoretical issues raised by these two papers "are quite different from those raised by the (more common) descriptions of RA extending back many years" (Kopelman, pp. 589–590). It was in fact a similar series of patients, who had suffered TB meningitis (Williams & Smith, 1954), and who appeared to have a similar profile of residual memory loss to these two cases, which in part stimulated me to write the 1993 review article. Although I agree that these cases are likely to be qualitatively different from those where there is claimed to be a dense, temporally extensive, retrograde amnesia, they may nevertheless represent an important prototype of time-limited focal retrograde amnesia that could form the basis for useful theoretical formulations and comparisons with other sources of data, such as animal lesion studies. Where time-limited focal RA is associated with more discrete, unilateral temporal lobe damage, this may complement cases of more severe retrograde amnesia associated with bilateral pathology and help to contribute to our overall understanding of anatomy-memory relationships as far as retrograde amnesia is concerned.

For cases of dense retrograde amnesia following minor concussion, my own views on these types of cases (Kapur, 1999) are very similar to those of Kopelman, and I regard such cases as being a distinct entity from cases where the cerebral pathology is more substantive.

MECHANISMS AND OUTCOME

It seems to me to be important to distinguish statements about empirical outcome from statements about putative mechanisms/determinants, whether this be the role of retrieval processes in patients with semantic dementia (Kopelman, p. 596), or differential rates of recovery after head injury (Kopelman, p. 588). The primary issue is whether certain patients satisfy criteria for the presence of focal retrograde amnesia, and although I have reservations that criteria have never been spelled out clearly enough, this issue needs to be considered on its own merits, and separately from issues relating to mechanisms.

In the case of patients who have the syndrome of semantic dementia (Hodges, Patterson, Oxbury, & Funnell, 1992), Kopelman refers to the Hodges and Graham (1998) paper. Differences between earliest and most recent time periods were found by the authors on famous names identification, as indicated on p. 810 of their paper, and the overall conclusions in that report were based on both the single-case study described in the paper and on data sets where no floor or ceiling effects were found. His main argument is that different explanations

may be feasible for the patterns of memory performance that emerge in patients with semantic dementia. Although these differing explanations are plausible, with the strengths and weaknesses of alternative viewpoints having been debated in detail elsewhere (Graham, 1999; Moscovitch & Nadel, 1999), this does not detract from the basic pattern of more preserved recent memories compared to older memories that was found by Snowden, Griffiths, and Neary (1996) and by Graham and Hodges (1997). In the latter study, Graham and Hodges provided autobiographical memory data on their patient AM, which showed clear time-specific differences in recall of autobiographical memories, using similar sets of cue words, making it unlikely that the better retrieval of recent memories were due to poor conceptual/linguistic skills.

Similarly, for the case reported by Evans, Breen, Antoun, and Hodges (1996), Kopelman refers to differential recovery mechanisms as being critical, though—as I indicated earlier—I suggest that this is confusing empirical outcome with putative mechanism. He also makes comments on the model espoused by the authors, and offers predictions from that model, and this again has to be seen to be independent of whether the empirical data on this patient support a claim that it represents a case of "focal retrograde amnesia".

POSSIBLE ROLE OF EPILEPTIC MECHANISMS

The possibility of epileptic mechanisms contributing to the occurrence of cases of focal RA was first raised in the paper by Roman-Campos, Poser, and Wood (1980). Kopelman is critical of that paper, and in my 1993 review paper, I was also rather critical of that report. I specifically commented on the unusual duration of loss of memory and on the patient's disinhibited behaviour, though I did not comment on the manic features of the case in the same detail. Kopelman indicates that "Consistent with this syndrome [TGA], the woman was much improved after 12 hours" (Kopelman, p. 588). However, apart from being oriented for place after 12 hours, there is no evidence in the paper that after 12 hours (which is around twice as long as a normal TGA episode—Hodges, 1991) her anterograde memory had improved—the authors report that she "was still disoriented to time and unable to recall 3 out of 3 objects" (p. 510). Although it is quite possible that a manic episode will result in amnesia for the time of the disturbed behaviour, there is no evidence of which I am aware that a manic episode in itself may result in a permanent retrograde amnesia for a number of years. Since a discrete period of retrograde amnesia may occasionally be associated with temporal lobe epilepsy (e.g., case PO in Kapur, 1997), it may be premature to dismiss this case as partly or wholly psychogenic, in spite of its undoubted unusual features. It therefore remains possible that the patient did in fact have an unusual temporal lobe epileptic seizure which had both mnestic and behavioural manifestations, and which resulted in a period of relatively isolated retrograde amnesia.

Our own studies (Kapur et al., 1986; Kapur et al., 1989) further raised the possibility of epileptic mechanisms being important in focal RA. In discussing our two papers, Kopelman describes the attacks that our patient suffered as being "identical to TGA" (Kopelman, p. 590). One of the main points about our case was that the attacks did *not* fit with the classical features of TGA. First, as we noted in the first paper, there were "20 episodes of transient amnesia, lasting 15 minutes to several hours, over the previous six years....Following the attack, he could recollect some information about events during the attack, although this was patchy" (1986, p. 216). The number of episodes, duration of episodes and incomplete loss of memory for the attack itself, marked the clinical features out from classical descriptions of TGA (Hodges, 1991). In the second article on this patient (Kapur et al., 1989), we specifically described three distinct forms in which the attacks were manifest, and these were even more different from TGA. Later in his article (pp. 609–610), Kopelman refers to the Kapur et al. (1986) paper as attributing "disproportionate retrograde amnesia to a relatively subtle and common EEG abnormality." However, in that paper we specifically indicated (p. 216) that "standard and 48-hr EEG investigations were all normal." We did note

in our subsequent paper (Kapur et al., 1989, p. 389) that there was EEG evidence of a left temporal lobe abnormality, together with a few instances of isolated spike discharges from the right temporal region. However, at no place in that second paper did we try to "attribute disproportionate retrograde amnesia to a relatively subtle and common EEG abnormality." What might the mechanism be that could have contributed to impaired retrograde memory performance in our patient? Kopelman (p. 590) hypothesises that "it seems highly plausible that the patients may have had brief runs of seizure activity in the past, which were undetected clinically, and these resulted in faulty (*anterograde* [his emphasis]) encoding of very specific items in autobiographical memory." This may explain faulty memory for events that occurred *after* the presumed onset of epileptic activity, but it cannot explain loss of memory for more distant events, unless one concludes that epileptic activity was taking place for decades before it became clinically apparent—in our patient (Kapur et al., 1989) there was impairment for items dating back to the *1940s*. Kopelman considers the related articles by Lucchelli and Spinnler and by O'Connor et al. (1997) simply in the context of accelerated forgetting in the anterograde domain. However, the important feature of these two papers, and to some extent the paper by Zeman, Boniface, and Hodges (1998), is that they provide a possible framework by which it may be possible to understand how more distant memories may be disrupted in the context of normal retention over periods of hours. The reader is referred to the detailed discussion by Lucchelli and Spinnler on this issue. To summarise, it would appear that disruption of neocortically-based neuronal networks may occur as a result of periodic episodes of clinical and subclinical epileptiform activity. Repeated bursts of such activity over months and years may result in degradation of networks that act as storage or retrieval sites for long-term memories. The source of such pathology may be in areas of the medial temporal lobe that are not critical for the shorter-term retention of new memories over periods of hours, perhaps in anterior or posterior areas of the hippocampus that are not specifically concerned with the memory processes required for the particular tasks in question, or the pathology may be in critical structures but may simply not be severe enough to disrupt performance on anterograde memory tasks. In either case, there would be sufficient reserve in the limbic-diencephalic system to support new learning over limited time periods. Thus, one does not necessarily have to hypothesise that hippocampally-based consolidation processes are actively continuing for decades, and that these become disrupted by an intrinsic lesion within the hippocampal system. Rather, sufficient degradation takes place to the connectivity between neuronal networks that underlie retrieval of remote memories to result in their failure to reach a sufficient level of activation in response to particular memory task demands. The fact that most of the patients in the Zeman et al. study had TEA episodes on awakening also raises the possibility of nocturnal epileptic activity that may have interfered with sleep-related consolidation mechanisms.

In a discussion of cases of transient epileptic amnesia, Kopelman criticises Zeman et al. (1998) for mis-citing his case (Kopelman, Panayiotopoulos, & Lewis, 1994) as an instance of focal retrograde amnesia, although they do not make any such specific reference. They do, perhaps, overemphasise the mild impairments on the Autobiographical Memory Interview found by Kopelman by referring to memory performance on that test as an example of a "pronounced persisting impairment of retrograde memory" (Zeman et al., 1998, p. 442), but that is different from calling it an example of focal retrograde amnesia. Kopelman also states that Zeman et al. did not find any significant differences between the TEA group and a control group on any formal test of retrograde memory. However, this is only part of the picture—7 of the 10 patients studied by Zeman et al. were reported to have had impaired performance on at least one neuropsychological test, and all but one of these tests related to retrograde memory. Thus, anterograde memory was relatively preserved in these patients. They therefore represent an important series of patients, although I think it likely that longer-term consolidation of new memories would also be disrupted to some degree in such cases, and

the extent to which such disruption is less than that for pre-illness onset memories would determine whether a diagnostic classification of focal RA could be made in such a setting. On the basis of the data from Zeman et al. and other cases with an epileptic aetiology (e.g., Kapur et al., 1989; Lucchelli & Spinnler, 1998; O'Connor et al., 1997), it would seem that of the various candidate mechanisms for focal retrograde amnesia, one of the more attractive pathophysiological models would appear to be one that is based on multiple, temporally distributed, episodes of epileptogenic activity that interfere with the neocortical representation of long-term memories, or with mechanisms that access such representations, while leaving relatively undisturbed those brain structures that allow for the shorter-term consolidation of new memories.

ATTRIBUTION OF CAUSALITY

In the second part of his paper, Kopelman deals with clinical and theoretical issues relating to the attribution of causality in organic and psychogenic amnesia. In this part of the paper, Kopelman provides an incisive analysis of the complex interactions between psychogenic and organic amnesia. He highlights critical issues that arise when one tries to attribute causality in patients with retrograde amnesia, and he has offered some very useful practical and conceptual guidelines for the way forward. Although I agree with his caution in adopting the view that the psychogenic–organic distinction is largely redundant, and with his reservation about a third, more neutral, category of "functional amnesia" being introduced, it is worth noting the significant overlap between the areas of pathology (anterior fronto-temporal) noted in many cases of focal retrograde amnesia and the similar areas of abnormal activation in functional imaging of psychogenic memory loss (see Markowitsch, 1999, for a review of such studies). It therefore remains possible that in some cases of focal retrograde amnesia there may be a dual contribution to the retrograde memory deficits that are found, that this arises from overlapping brain regions, and that the reversible (metabolic) component of the brain disturbance arising from psychosocial determinants may interact or merge with the structural lesion to result in apparently irreversible changes to brain integrity in this region (cf. Costello, Fletcher, Dolan, Frith, & Shallice, 1998). The patient we originally reported in 1992 (Kapur, Ellison, Smith, McLellan, & Burrows, 1992) may also be one in point. This case has turned out to be an intriguing one, in that it does now seem that this patient had more underlying psychological disturbance than we originally thought. After our initial neuropsychological investigations, the patient moved from our area and was lost to neuropsychological follow-up for a period of time, but we have since learned that she has in recent years developed significant psychosomatic symptoms, including unexplained left-sided weakness, in the context of a major depressive disorder. Some of these symptoms appeared to be precipitated by the break-up of a long-standing relationship with her boyfriend. Our patient received a number of sessions of psychotherapy in her own locality, and these sessions have recently come to an end. These sessions highlighted psychodynamic factors that might have contributed to a loss of past memories, such as a teenage pregnancy that was terminated, and yielded additional observations, such as a failure to recognise some family members at various points after her injury. However, her psychotherapist reported no return of lost autobiographical memories during or after her period of psychotherapy, and felt on the basis of his sessions that her memory loss was organic rather than psychological. Although it would be unusual, but not impossible, for a psychogenic retrograde amnesia to last for so long (over 8 years), and to be resistant to psychotherapeutic intervention, the possibility of a psychological contribution to her previously reported retrograde memory loss needs to be borne in mind in view of her psychosomatic symptoms. Her current psychiatric condition has precluded any further detailed neuropsychological assessment.

I also have some reservations relating to the case reported by Goldberg et al. (1981). Whereas Kopelman refers to a subsequent article on the same case in the following year (Goldberg, Hughes, Mattis, & Antin, 1982), a further article appeared

several years later in which the same patient was described (Goldberg & Bilder, 1986). I am concerned by the fact that the patient showed an age-disorientation of 20 years, something that is relatively uncommon in neurological disease (Zangwill, 1953), his failure (reported in Goldberg & Bilder, 1986, p. 57) to recognise his wife and his children, and the implication (op. cit., paragraph 1) that for a period of time he also suffered a loss of personal identity.

In terms of the role of psychogenic factors that could play a significant role in patients with focal RA, Kopelman has powerfully brought home Teuber's aphorism (1975, p. 166) that "absence of evidence is not evidence of absence", and that careful detective work may be needed to unearth information relating to psychological variables. However, the converse is equally valid—that the "presence of evidence is not evidence of primacy"—not only where there is a structural brain lesion that may mistakenly be attributed a role in amnesic deficits, but also where psychodynamic factors have been unearthed and have automatically been presumed to determine loss of memory in a particular patient with marked retrograde amnesia.

I myself have a few general reservations in relation to recent research on focal retrograde amnesia.

1. *Negative cases*. The issue of negative cases is not new in neuropsychology and not confined to retrograde amnesia (cf. the debate on Broca's area and Broca's aphasia; Mohr, 1976). "Positive" single cases tend to be seized upon and reported. "Negative" single cases tend either to be passed unnoticed, or to be actively ignored. Anterior frontal lobe and anterior temporal lobe damage has been implicated in a number of cases of focal retrograde amnesia. However, researchers such as J.T.L. Wilson, Hadley, Wiedman, and Teasdale (1992) have reported that combined bilateral anterior temporal and frontal polar lesions are not an uncommon occurrence in cases of severe blunt head injury, yet those patients do not appear to develop a severe, focal retrograde amnesia. Perhaps such an amnesia is present but not detected by clinicians, but this appears unlikely. Perhaps the particular pattern of anterior lesions in their cases are somehow distinct from those reported in the case of patients with focal RA. This is difficult to prove. The same argument could be seen to apply to cases of herpes simplex encephalitis (HSE), where one might have expected that group studies (e.g., Kapur et al., 1994a; Kopelman, Stanhope, & Kingsley, 1999; Utley, Ogden, Gibb, McGrath, & Anderson, 1997) would have yielded at least a few patients with a similar lesion profile to those HSE cases of focal RA that have been reported in the literature.

2. *Lesion heterogeneity*. I am also concerned at the heterogeneity of the lesion profiles that have been associated with reported cases of focal retrograde amnesia. In the case of focal anterograde amnesia, which is a fairly noncontentious amnesic profile, there is a consistent lesion picture that emerges—discrete lesions to structures within the limbic-diencephalic system will result in significant anterograde memory loss but only mild retrograde amnesia (e.g., Guinan, Lowy, Stanhope, Lewis, & Kopelman, 1998; Isaac et al., 1998; Zola-Morgan, Squire, & Amaral, 1986). Why should it be that there is an absence of such lesion consistency in focal retrograde amnesia? Lesion locations have been embarrassingly wide-ranging, from bilateral temporal and frontal involvement, to right posterior neocortical involvement, to discrete lesions that involve the uncinate fasciculus in the right frontal region. In some cases there is a complete mirror-image in the lesion profile—right temporal with limited left temporal lobe involvement in the case reported by O'Connor et al. (1992), but left temporal with limited right temporal lobe involvement in the two cases reported by Kapur et al. (1996). It could be argued that retrograde memories are by their nature more widely distributed, and that all of these areas play a role in performance on retrograde memory tasks—that lesions will cause similar patterns of disruption to a fairly common set of neural networks regardless of the actual site of the pathology, but this does sound as special pleading. On the basis of well-documented cases of dense retrograde amnesia (Damasio, Eslinger, Damasio, Van Hoesen, & Cornell, 1985; B.A. Wilson, Baddeley, & Kapur, 1995), the recent study by Kopelman et al. (1999), and recent functional imaging studies of

autobiographical memory (Maguire & Mummery, 1999), the most likely candidate for a dense focal autobiographical retrograde amnesia should be a lesion profile that includes bilateral anterior temporal lobe and bilateral anterior frontal lobe pathology, perhaps with a greater left temporal lobe bias, and with relative sparing of medial temporal lobe structures. Because of the lesion heterogeneity between cases of focal RA, it is also difficult to see how some forms of focal RA can be readily accommodated within current models of memory consolidation. For example, Nadel and Moscovitsch (1998) have argued that the hippocampal complex is always necessary for retrieval of personally experienced episodes, and it would therefore seem from their viewpoint that for a dense autobiographical amnesia to occur there would need to be substantive bilateral damage to hippocampal structures. Although it is possible that different structures within the hippocampal complex contribute separately to anterograde and retrograde memory functioning, with parahippocampal and rhinal areas playing a greater role in the latter, and the hippocampus proper more important for the former, there remains a need for a coherent anatomical framework that will incorporate the various lesion sites associated with focal RA. So far, the most attractive hypotheses have been based around fronto-temporal networks (e.g., Kroll, Markowitsch, Knight, & Von Cramon, 1997) rather than medial temporal areas, and this anatomical divergence needs to be resolved.

3. *Possible bias in sex distribution*. My final concern is the impression I have that in certain aetiologies there may be a disproportionate number of female cases with focal RA. For example, of four cases with encephalitis who have a marked autobiographical amnesia as part of their focal RA (Calabrese et al., 1996; Carlesimo et al., 1998; O'Connor et al., 1992; Tanaka, Miyazawa, Hashimoto, Nakano, & Obayashi, 1999), all are women. The reason for some concern at a possible bias in the ratio of female to male cases is that in Western society the prevalence of dissociative disorders, which would usually include psychogenic amnesia, is substantially higher for women than for men (Gelder, Mayou, & Geddes, 1999).

COMMENTS ON KOPELMAN'S CONCLUSIONS

1. Kopelman concludes that some of the cases of severe autobiographical amnesia are accompanied by very poor anterograde memory, especially for visuospatial material, and that such cases cannot be described as instances of "isolated", "focal" or "disproportionate" retrograde amnesia. Although I would partly agree with this conclusion, I would reiterate my earlier point that even within some of these reports, verbal anterograde memory is usually not "very poor" and does stand in contrast with autobiographical memory (usually verbally cued and with a verbal response), which could be described as "very poor" (e.g., Markowitsch et al., 1993; O'Connor et al., 1992).

2. Kopelman appears to accept around 12 cases as exemplifying "disproportionate" RA, although his preference not to use the term "focal RA" for such cases could be seen to be one of semantics. He then notes that one is seldom comparing "like" with "like" across retrograde and anterograde memory domains, and that remote autobiographical memory tasks are in general more "effortful" than anterograde memory tests. The issue of comparability across "retrograde" and post-injury/illness domains is a critical one, as I have pointed out earlier in this article, but it is separate from the issue of whether particular reports satisfy criteria that have been set for classifying cases as acceptable examples of focal RA. In addition, unless one has some independent measure of effort, such statements must remain rather subjective, as there surely are anterograde memory tests that could be described as effortful (e.g. paired-associate learning tasks or delayed recall of a story after several days).

3. Kopelman's next conclusion is that not all forms of focal RA are the same, and that alternative explanations should be sought before attribution to particular sites of pathology. I do not have any qualms with this point.

4. Kopelman then makes the point, which I have queried earlier, that because a certain outcome (focal RA) may be due to a certain cause (differential rate of recovery), the outcome is somehow flawed.

5. Similarly, his preferred explanation for a certain outcome (reversed temporal gradient in remote memory) in semantic dementia patients is plausible, but does not change the fact of the outcome.

6. Kopelman's "parsimonious explanation" of the remote memory loss shown by patients with transient epileptic amnesia has difficulty in accounting for the failure to remember episodes that occurred many years *before* the presumed onset of any epileptic activity.

7. His argument with regard to the role of psychogenic factors, and their careful documentation, is well taken, and I would accept in its entirety.

MY CONCLUSIONS

Does focal retrograde amnesia exist as a valid neurological entity? The answer to this question probably revolves around how one defines "focal retrograde amnesia". The ideal contrasts are those where comparisons of "retrograde" and "postgrade" memory functioning are based on tasks that are closely matched on all pertinent variables, including memory domains, task complexity, response demands, time periods sampled, etc.

At the beginning of this commentary, I identified four ways in which focal retrograde amnesia was implicitly defined in my original review article (Kapur, 1993). I shall now take a subset of questions that incorporate these definitions:

1. *Does focal retrograde amnesia exist as a purely neurological entity, when it is defined as markedly abnormal performance on standard retrograde memory tests, that include items such as public events, famous personalities, etc., and relatively spared performance on standard anterograde memory tests?*—The answer would appear to be *Yes*, allowing for the possibility that in some cases longer-term anterograde forgetting may be compromised. Such a dissociation was the context in which we originally used the term "focal retrograde amnesia" (Kapur et al., 1986, 1989), and has been noted by O'Connor et al. (1997) and by Lucchelli and Spinnler (1998), where the retrograde amnesia also included some element of autobiographical memory loss. Such a dissociation accords with the many findings of a low correlation within patient groups between performance on retrograde memory tests and standard anterograde memory tests (Greene & Hodges, 1996; Kopelman, 1989, 1991; Schmidtke & Vollmer, 1997; Shimamura & Squire, 1986). It also accords with recovery-of-function studies that show a contrast between the recovery profiles for the two memory domains (Jones, Grabowski, & Tranel, 1998; Kapur, Millar, Abbott, & Carter, 1998). The study by Jones et al. is of particular interest since it provides neuroanatomical support for distinguishing the two sets of memories (neocortical for public events memories and autobiographical memories, medial temporal for new episodic memories).

2. *Does focal retrograde amnesia exist as a valid neurological entity, when it is defined as a period of autobiographical memory loss for a period ranging from months to a few years, coupled with good recovery of anterograde memory?*—The answer would appear to be *Yes*. The studies by Yoneda et al. (1992) and by Hokkanen et al. (1995) substantiate the early reports by Williams and Smith (1954) that I reviewed in my 1993 article.

3. *Does focal retrograde amnesia exist as a valid neurological entity, when it is defined as transient loss of knowledge, coupled with relatively preserved ongoing episodic memory?*—The answer would appear to be *Yes*, in the light of reports such as those of Schott et al. (1970); Ashcraft (1993), Cammalleri et al., (1996), Damasio et al. (1983), Hodges (1997), Kapur, Katifi, El-Zawawi, Sedgwick, and Barker (1994b).

4. *Does focal retrograde amnesia exist as a purely neurological entity, when it is defined as dense, temporally ungraded and temporally extensive autobiographical retrograde amnesia, in the context of normal or near–normal performance on standard anterograde memory tests?*—The best answer is *We do not yet know*. I agree with Kopelman that there are published cases with this pattern of memory functioning which have been diagnosed as solely neurological, but which may be partly or wholly psychological in origin. Although it is right to be sceptical that a neurological entity of pure, dense,

temporally extensive and temporally ungraded autobiographical retrograde amnesia exists or can exist, I think it would be premature to throw the baby out with the bathwater, at least until we are sure there are no well-documented cases that have satisfied the strict psychiatric criteria set out by Kopelman (p. 611). As indicated earlier, I take the view that epilepsy-related cases of focal RA may represent a more satisfactory prototype than other aetiologies of focal RA. In this context, it is worth pointing out that the patient reported by Lucchelli and Spinnler (1998) did have a fairly dense, relatively ungraded, autobiographical amnesia, in the context of relatively mild impairment on standard anterograde memory tests. Perhaps the most important question is—*Does focal retrograde amnesia exist as a purely neurological entity, when it is defined as disproportionate "retrograde" to "postgrade" memory performance, where the domains of memory function, methods of testing, time periods sampled, and all other critical variables are as comparable as one can make them?*—The answer is *We do not yet know*. I myself have some reservations as to whether a marked, as opposed to a mild, dissociation might be found, since one would have to postulate distinct neural networks playing a role in memory formation and retrieval for sets of memories that are otherwise identical apart from differing in terms of their temporal relationship to the onset of cerebral pathology. Bearing in mind this type of reservation, there is some suggestive evidence in the animal lesion literature that the brain does incorporate sufficient plasticity to allow for similar patterns of memory performance to arise (Thornton, Rothblat, & Murray, 1997). In the field of human retrograde amnesia, one could argue that autobiographical memories may be coded either in terms of verbal scripts or in a more nonverbal form that includes extensive use of visual imagery. Where brain pathology disrupts past memories that have been primarily coded in one form, then there may be sufficient neural flexibility to allow new autobiographical memories to be encoded in an alternative form. This possibility is implicit in the cases of "visual-deficit" amnesia described by Rubin and Greenberg (1998), who point out that "these patients could gradually compensate for their deficits, allowing emotion and nonvisual sensory data to play a greater role" (p. 5414). The converse scenario was also noted by Eslinger (1998) to account for the disproportionate preservation of post-illness autobiographical memories, compared to loss of pre-illness memories, in a case of herpes simplex encephalitis (patient EK). He noted that "over the past seven years, she clearly encodes and retrieves more recent events, with a strong visual imagery emphasis but impoverished verbal semantic knowledge" (p. 488). In this case, the patient did appear to have a mild-moderate anterograde memory impairment, with a Wechsler Delayed Memory Quotient of 88, but by the more satisfactory criteria where "like retrograde" memories are compared with "like postgrade" memories, she might be classifiable as a good example of focal RA.

One of the possible reasons for the major discrepancies amongst studies reviewed by Kopelman is simply that in most clinical studies of retrograde amnesia we have no means of knowing, or having any control over, the encoding parameters for the test stimuli/events in question. In the case of public events memory tests, trying to get a handle on exposure to the original stimuli in question was one of the reasons why we developed a simple media exposure questionnaire (Kapur, Thompson, Kartsounis, & Abbott, 1999). The fact that we found a more significant correlation between that measure and public events memory performance than we did with predicted IQ, and the fact that none of the studies reviewed by Kopelman or by myself have, to my knowledge, even tried to formally control for degree of media exposure, casts at least some doubt on the reliability of published data to date on some aspects of retrograde amnesia. In the case of autobiographical memory, an inability to offer any recollections of personally experienced episodes usually has to be accepted at face value, even though such absence of response may be due to multiple reasons, ranging from genuine memory loss to malingering. Even where detailed autobiographical responses are offered by subjects, corroboration may not always be available (e.g., for early child-

hood events) and the corroboration itself may occasionally be unreliable.

For reasons such as these, it could be argued that we need to place more emphasis in retrograde amnesia research on lines of inquiry where we are more certain what we are measuring—in the clinical sphere, we may have to look more carefully at settings such as recovery-of-function paradigms where there is an additional set of corroborative data in the form of the patient's responses after recovery. Meaningful data may also emerge from other paradigms that potentially allow for controlled exposure of stimuli prior to treatment, such as ECT, transcranial magnetic stimulation, direct brain stimulation, etc. A major source of valuable data is of course from animal studies, and this set of evidence may eventually have some bearing on the neural viability, in terms of plasticity limits, of some forms of focal retrograde amnesia (see Spear & Riccio, 1994, for a review of studies up to that time). Lesion or other sources of data that postulate the viability of a form of focal retrograde amnesia should also ideally be in harmony with functional brain imaging data from normal subjects (Fink et al., 1996; Maguire & Mummery, 1999), as would appear to be the case in the form of the frontotemporal hypothesis (Kroll et al., 1997), and should also be consistent with computational models that incorporate focal retrograde amnesia within their predictive framework (e.g., Murre, 1997).

In conclusion, certain contrasts in memory performance may occur in neurological disease that permit a classification of "focal retrograde amnesia", though this very much depends on the specific contrasts that are made and the criteria for deciding whether two sets of memory performance are "disproportionate". Whereas some patients with focal retrograde amnesia may represent a diagnostic dilemma when it comes to attributing causality, those who are shown to have a clear neural basis to their memory loss provide a unique opportunity to explore the brain's plasticity in accommodating the formation of new memories despite the loss of equivalent old memories.

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