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Recovery of function processes in human amnesia: evidence from transient global amnesia

NARINDER KAPUR,*†‡ JOHN MILLAR,* PAT ABBOTT* and MICHAEL CARTER*

*Wessex Neurological Centre, Southampton General Hospital, Southampton SO16 6YD, U.K.; †Department of Psychology, University of Southampton, Southampton, U.K.

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Abstract—There are few clues as to the processes that underlie recovery of function from human amnesia. Evidence is offered from the perspective of a study of recovery of function during an episode of transient global amnesia (TGA) that occurred as a complication of a cerebral angiographic procedure being carried out in a neurosciences centre, and where there was therefore a unique opportunity to examine acute changes in memory function. This allowed us to conduct the first quantitative study where shrinkage of anterograde and retrograde memory loss was plotted at four separate intervals throughout the acute recovery process, and also 24 hr later. Recovery of retrograde amnesia preceded recovery from anterograde amnesia. Resolution of a naming deficit more closely paralleled recovery from retrograde amnesia rather than anterograde amnesia. Within retrograde amnesia for public events, there was a temporal gradient of memory loss, with more recent events affected to a greater degree than earlier events. Within anterograde amnesia, picture recognition memory preceded recovery of story recall memory. On the basis of these findings, and related observations in the published literature, it is proposed that recovery from some types of human amnesia, such as that associated with TGA, follows a 'lateral-to-medial' rule—lateral inferotemporal areas that play a major role in retrograde amnesia recover first from hypometabolism related to the TGA attack, followed by 'interface' areas such as the rhinal and parahippocampal cortices that are considered to have a role in both anterograde and retrograde memory functioning, with the last areas to recover physiological integrity being discrete limbic–diencephalic structures such as the hippocampus.

Key Words: amnesia; transient global amnesia (TGA); recovery of function.

Introduction

Our understanding of recovery of function in human memory disorder, especially in the acute stages of recovery, is very sparse. This may be due in part to the limited number of neurological conditions that readily lend themselves to a study of recovery of function, to the small range of assessment tools that are currently available to examine recovery of memory functioning over short or long time periods, and perhaps also to a relative lack of awareness amongst memory researchers of the potential value of recovery-of-function paradigms for amnesia research.

Transient global amnesia (TGA) is one of the most common forms of acute, transient memory disorders seen after cerebral pathology. TGA provides a unique opportunity to examine some aspects of amnesia, and in particular recovery of memory functioning. Recent years have seen several contributions to our knowledge relating to transient amnesic states [12, 19, 34], but few studies have addressed the issue of recovery of memory function. Among the advantages of using TGA as a model for studying recovery of function are the fairly dramatic change in memory status over a relatively short time period, and the fact that patients can effectively act as their own control after they have recovered from the TGA episode—this helps to overcome a major problem associated with the interpretation of autobiographical and public knowledge memory tests, namely how to control for individual differences in pre-illness/injury level of functioning for such tests. The density and purity of the amnesia that patients suffer, the limbic focus of brain abnormalities that have been found in clinical studies [7] and the hippocampal focus that has been implicated in experimental studies [29] render TGA a particularly important neurological condition for the study of the evolution and resolution of pure amnesia.

An oft-quoted study of recovery from retrograde amnesia [5] claimed that shrinkage of retrograde amnesia

‡ Address for correspondence: Wessex Neurological Centre, Southampton General Hospital, Southampton SO16 6YD, U.K.; tel.: 01703 796576; fax: 01703 796085; e-mail: n.kapur@soton.ac.uk.

occurred largely in parallel with shrinkage of post-traumatic amnesia, though with the latter rather more rapid than the former. However, this report was mainly based on clinical observations, and only a minimal amount of test data was reported to support these observations. In addition, the cerebral dysfunction in this case may have been due to a combination of factors that included head injury and alcohol intoxication, together with a possible subdural haematoma.

At the level of longer-term recovery of function, Hodges and Oxbury [14] noted that there was evidence of a mild verbal memory impairment, on both anterograde and retrograde memory tasks, 6 months after recovery from an episode of TGA. At the more acute level, Kazui *et al.* [27] offered clinical observations to suggest that retrograde amnesia may shrink before anterograde amnesia, in contrast to the claim made by Benson and Geschwind [5]. Russell and Nathan [45] had observed that in head injury patients shrinkage of retrograde amnesia was characterized by older memories returning before more recent memories. Kazui *et al.* [27] reported similar observations, but noted occasional exceptions to this in their two TGA patients. They found that in a few cases events which are important/emotionally significant to the patient may return sooner than other memories. Kazui *et al.* pointed out that the stage at which recovery is assessed may be critical to the profile of memory loss that is found.

In the study reported in this paper, we were in the relatively unique position where the TGA attack occurred in a neurosciences centre itself, and where it was possible to examine the patient throughout the recovery period. The purpose of the present study was to shed light on some of the processes underlying recovery of memory function by attempting to answer the following questions:

1. Does retrograde amnesia show the same pattern of shrinkage as anterograde amnesia?
2. Do different anterograde memory functions recover at the same rate?
3. Does a form of Ribot's law govern the profile of retrograde amnesia, such that early memories are relatively spared compared to more recent memories?

Clinical history

SG (born 5 August 1957) is a right-handed caterer who was admitted in July 1996 for investigations relating to a suspected arteriovenous malformation (AVM). He had suffered for 2 years from severe headaches, but with no cognitive symptoms, and a magnetic resonance imaging scan had shown an AVM in the left posterior temporal region.

He underwent cerebral angiography under local anaesthetic and light sedation (20 mg temazepam, 1 hr prior to the procedure). The vessels examined were in the order: left internal carotid, left vertebral and finally right common carotid. At the time of the investigation, building work was being carried out in the area and the air-conditioning came on with noticeable dust contamination of the air during the final right carotid study. The possibility of low-level contamination throughout the procedure could not be excluded, and we believe that this may well be implicated in the complication that subsequently came to light. The procedure was otherwise uneventful. There had been no dialogue with the patient throughout the procedure, but after removal of the catheter and during preliminary discussion of the results of the angiogram with him, he was found to be profoundly amnesic. He did not know his occupation, the name of the Prime Minister or the month. He knew his name. He knew the name of the hospital, but he did not know why he was receiving investigations or for how long he had been in hospital.

No neurological deficit was apparent during or shortly after the angiographic procedure, and the angiograms themselves did not show any evidence of arterial spasm or occlusion.

Neuropsychological investigations

Due to the limited time available for neuropsychological testing of a transient condition such as TGA, assessment was restricted to those memory and related functions that were of relevance to this particular study. The onset of the amnesic episode was around 12.30 p.m. SG was assessed on five occasions: 3 p.m., 5 p.m., 7 p.m., 9 p.m. and 24 hr after the episode (around 12 p.m. the following day). Where possible, we chose tests that could be administered in the brief time period available, that had parallel forms and that had established normative data. For this purpose, we chose two subtests from the Rivermead Behavioural Memory Test [51]: the story recall subtest and the picture memory subtest (for practical reasons, this latter test could not be given on the first two test sessions). In the story recall test, immediate and 10 min delayed recall are tested. In the picture memory test, a series of 10 pictures is shown, with an exposure duration of 5 sec per picture. After an interpolated task (delayed story recall), picture recognition memory is tested by presenting a series of 20 pictures, the 10 originals and the 10 distractors. Distractor and original items are taken from the same pool of line drawings of common objects (see [51] for further details). SG was also assessed for current awareness orientation for place, day, year, month and Prime Minister. For the assessment of retrograde memory, SG was given a short form of the Dead-or-Alive Test [25] and a short form of a Verbal News Events Test [24]. In this version of the Dead-or-Alive Test, the patient was presented with 143 names of personalities who had been famous over the past 40 years and was asked to circle those who had died. In the Verbal News Events Test, SG was given a list of 44 events, 22 of which had taken place

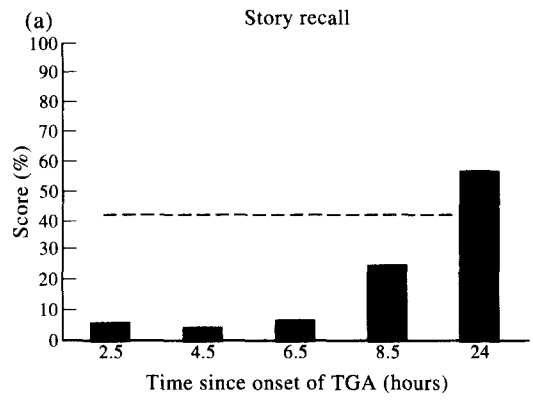
over the past 40 years and 22 of which were fictitious. He had to circle those events that he thought had actually taken place. We also administered a picture naming test [36] as a test of 'semantic memory', in view of our earlier observation of a mild naming deficit in a case of TGA [21].

For the retrograde memory tests, SG's performance was compared with that of a group of five age-, sex- and education-matched control subjects (mean age = 41 years, range = 37–45 years).

Results

Recovery of anterograde memory functioning

Figure 1 shows SG's performance over the five time periods on the story recall test and over three time periods on the picture memory test. As can be seen, by 8–9 hr after the attack, his picture recognition memory was close to normal, but his immediate and delayed story recall were still significantly impaired. By 24 hr after the attack, both sets of memory functions had returned to normal.



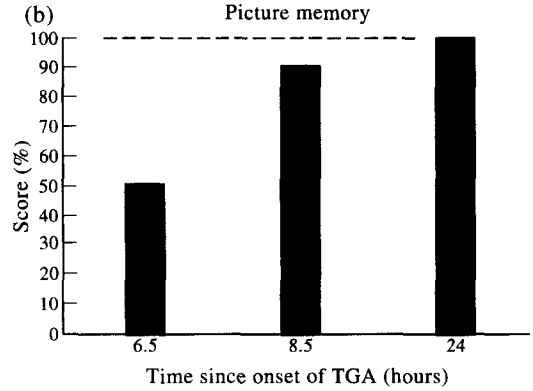
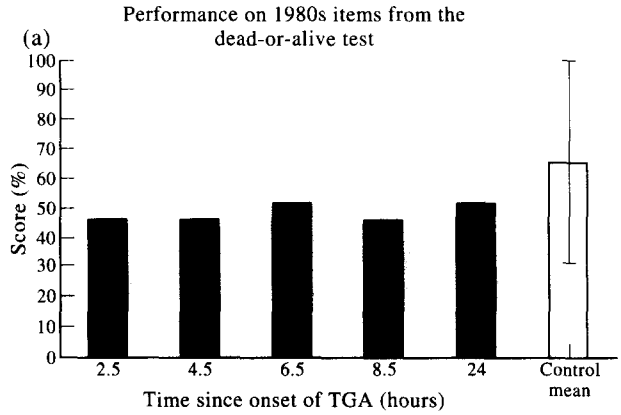


Fig. 1. Performance of SG on the story recall (a) and picture memory (b) tests from the Rivermead Behavioural Memory Test. The hatched lines indicate cut-off scores for normal control subjects' story recall performance and picture memory performance [52].

Recovery of retrograde memory functioning

Figure 2 shows SG's performance over the five time periods on the Dead-or-Alive Test. As can be seen, SG did not have any impairment for 1980s items (Fig. 2a) but he did have an initial retrograde amnesia for 1990s items. This retrograde amnesia shrank in a stepwise fashion over the subsequent few hours, with performance continuing to show an improvement up to 24 hr after the onset of the attack of amnesia. A similar, though less dramatic, profile was found for performance on the Verbal News Events Test (Fig. 3).

We assessed recovery of function for autobiographical amnesia by carrying out structured interviews with SG



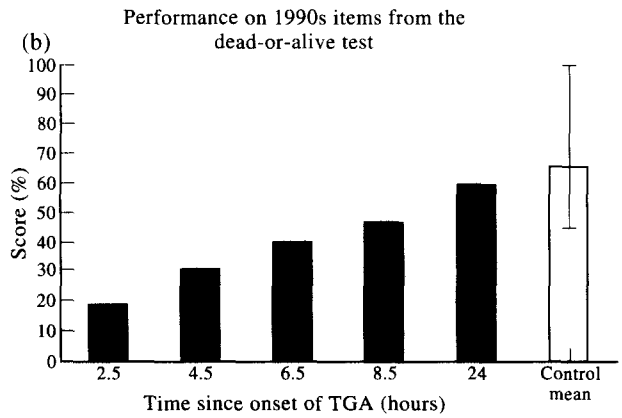
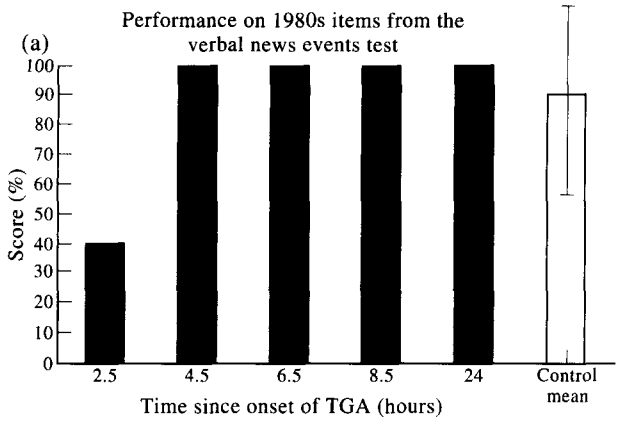


Fig. 2. (a) Performance of SG and matched control subjects on 1980s items from the Dead-or-Alive Test of retrograde amnesia, over the five time periods after the onset of the TGA attack. Bars indicate two standard deviations. (b) Performance of SG and matched control subjects on 1990s items from the Dead-or-Alive Test of retrograde amnesia, over the five time periods after the onset of the TGA attack. Bars indicate two standard deviations.



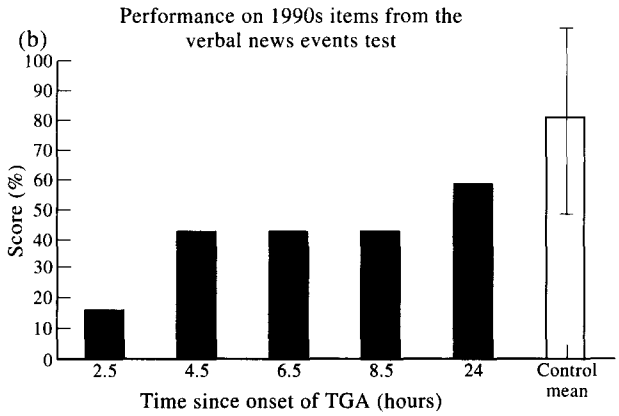


Fig. 3. (a) Performance of SG and matched control subjects on 1980s items from the Verbal News Events Test of retrograde amnesia, over the five time periods after the onset of the TGA attack. Bars indicate two standard deviations. (b) Performance of SG and matched control subjects on 1990s items from the Verbal News Events Test of retrograde amnesia, over the five time periods after the onset of the TGA attack. Bars indicate two standard deviations.

about jobs that he had held, together with his schooling before starting work. We also assessed memory for houses in which he had lived. Fortunately, over the past 20 years he had held a number of different jobs and had lived at a number of different addresses—this provided a good opportunity to assess loss of discrete retrograde memories. SG's responses during the interviews were recorded and transcribed, and we obtained corroborative information from his fiancée. Using a simple scoring system that allocated 0, 1 or 2 points for absent, vague and clear recollections, we were able to build up a profile of his autobiographical memory loss at different stages of recovery. He initially showed marked autobiographical amnesia, stretching back to around 22 years. As can be seen from Fig. 4, this amnesia showed a steady recovery over the 8 hr after the onset of the TGA episode, though with the greatest degree of recovery occurring between 2.5 and 4.5 hr after the attack. Within the shrinkage of

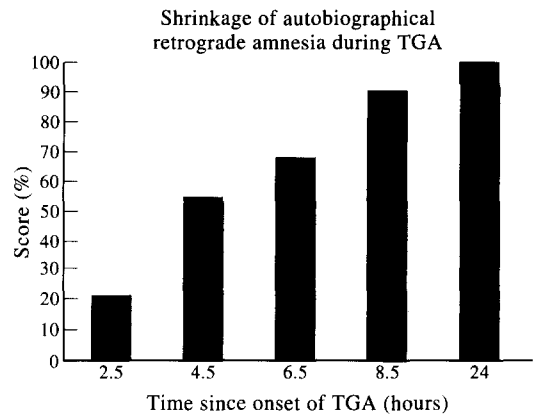


Fig. 4. Recovery of autobiographical retrograde amnesia.

autobiographical memories, there was a variable picture in respect of which memories came back first, with no fixed chronological order determining recovery of function. This may have been due to at least two factors: firstly, different autobiographical memories had different salience or 'trace strength', depending on factors such as the time spent, emotional significance, etc.; secondly, SG's fiancée was with him during the early recovery period, and it is quite possible that she told him about recent events in his life to help reduce his feelings of disorientation and confusion.

Recovery of semantic memory functioning

Figure 5 shows SG's performance over the five time periods on the picture naming test [36]. As can be seen, resolution of a mild naming deficit took place in the first half of the recovery period, with normal performance by 4–5 hours post-amnesia onset.

Other cognitive testing

At the last test session (24 hr post-TGA), SG was also given a more comprehensive neuropsychological examination that included, in addition to the memory tests outlined above, a short form of the Wechsler Adult Intelligence Scale—Revised [49], the visual and verbal paired-associate learning subtests of the Wechsler Memory Scale—Revised [50], the modified card sorting test [40], the FAS verbal fluency test [33], the Recognition Memory Test [48], copy of the Rey complex figure [33], and the National Adult Reading Test [41]. As can be seen in Table 1, on all of these tests SG performed well, with little in the way of cognitive impairment.

Clinical course

SG subsequently underwent repeat cerebral angiography and there was also an attempt to embolize his

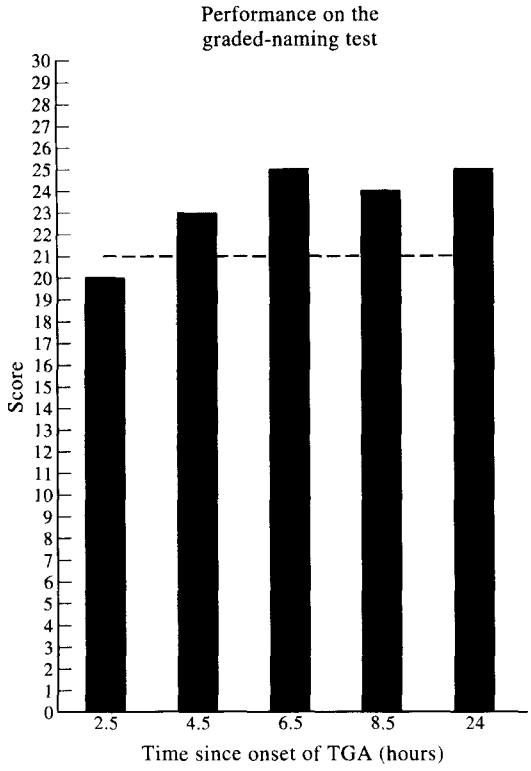


Fig. 5. Performance of SG on the picture naming test, over the five time periods after the onset of the TGA attack. The hatched line indicates the mean score of five matched control subjects.

AVM. The lesion was partially embolized following negative superselective amytal testing, but further embolization was not possible, since on subsequent superselective sodium amytal testing SG developed a transient right homonymous upper quadrantinopia. At the end of the procedure, it became apparent that there was a fixed deficit which was smaller than the initial quadrantinopia and which was presumed to be a complication of the embolization. At 2-month follow-up in clinic, this deficit had fully resolved. SG is now being considered for stereotactic radiosurgery for his AVM. His severe headaches remain as a persistent neurological symptom.

Discussion

Our patient with TGA showed a distinct profile of recovery of function as the attack of amnesia resolved. Recovery of retrograde amnesia occurred before recovery of anterograde amnesia. Within retrograde amnesia for public events, there was a temporal gradient of memory loss, with more recent events affected to a greater degree than earlier events. Within anterograde amnesia, picture recognition memory preceded recovery of story recall memory. Resolution of a mild naming deficit more closely paralleled recovery from retrograde amnesia rather than anterograde amnesia.

In some respects, the recovery profile shown by our patient is similar to the clinical observations noted by Kazui *et al.* [27]. They also reported that retrograde amnesia recovered earlier than anterograde amnesia. Our findings also reinforce the conclusions reached by Hodges and Ward [15] relating to the separability of anterograde and retrograde amnesia on the basis of their observations of memory functioning during TGA. In the light of recent findings relating to the anatomical basis of persistent, focal retrograde amnesia, and post-mortem data relating to patients with focal anterograde amnesia or a more global amnesia, it is possible to offer a tentative hypothesis to explain the specific recovery profile shown by our TGA patient. Focal retrograde amnesia has been linked with the presence of both focal and diffuse pathology, with the focal lesions affecting inferior, anterior and lateral areas of the temporal lobes [20, 23, 35]. Retrograde amnesia in some forms of more global memory loss has been linked to pathology in the entorhinal cortex [44], or has been associated with damage to the parahippocampal gyri [54]. In the latter study, the anatomical boundary that encompassed the parahippocampal gyrus also subsumed the entorhinal cortex. The entorhinal cortex has also been implicated as contributing towards the severity of anterograde memory loss in patients with dense amnesia [6]. Focal anterograde amnesia has been associated with discrete hippocampal or mammillary body lesions [22, 57]. Naming difficulties and picture recognition memory have both been linked to anterior–

Table 1. SG's cognitive functioning 24 hr after transient global amnesia episode

	Raw score	Statistic score
WAIS-R Verbal IQ	—	104
WAIS-R Performance IQ	—	113
WAIS-R Full Scale IQ	—	108
WMS-R Verbal P.A. Subtest Trials 1–3	19/24	(within normal limits)
WMS-R Non-verbal P.A. Subtest Trials 1–3	18/18	(within normal limits)
Recognition Memory Test—Faces	45	11
Recognition Memory Test—Words	47	10
Modified Card Sorting Test	5/6 categories	(within normal limits)
Rey Complex Figure	36/36	(within normal limits)
FAS Fluency Test	54	(within normal limits)
National Adult Reading Test	23 errors	102

inferior parts of the temporal lobe [16, 38], areas that overlap with those implicated in focal retrograde amnesia. We would therefore propose that recovery from acute amnesia, such as that associated with TGA, follows a 'lateral-to-medial' rule—lateral inferotemporal areas that play a major role in retrograde amnesia recover first from hypometabolism related to the TGA attack, followed by interface areas such as the entorhinal cortex that have a role in both anterograde and retrograde memory functioning, with the last areas to recover physiological integrity being medial temporal lobe structures such as the hippocampus. This formulation would account for the differential shrinkage of anterograde and retrograde amnesia that we found and that was also noted by Kazui *et al.* [27]. There is some support from functional imaging studies for the anatomical separability of anterograde and retrograde memory functioning. While some studies of TGA patients have noted frontal [4] or thalamic [9] reductions in blood flow, most studies have implicated medial temporal lobe structures such as the hippocampus (e.g., [13, 26, 47]). Recent positron emission tomography studies of autobiographical memory in normal subjects [3, 8] have noted the greater involvement of lateral than medial temporal lobe structures.

Our finding of differential recovery profiles for anterograde and retrograde amnesia further reinforces the practical point made by Kazui *et al.* [27] with regard to the importance of documenting the time of assessment of patients during the acute episode of transient memory loss. At any one time point, the relative severities of anterograde and retrograde amnesia will vary. Thus, in some studies, such as the one recently reported by Harting and Markowitsch [11], there may be the impression of a focal anterograde amnesia, with minimal retrograde memory loss, and this may be interpreted as reflecting the typical profile in TGA. We did in fact observe such a profile, but only late in the recovery period. In the more acute phase, both anterograde memory and retrograde memory were significantly impaired. A further practical point relates to the distinction between measures of anterograde amnesia and measures of post-ictal/post-traumatic amnesia. These measures are not synonymous [53], and previous studies that have contrasted different recovery rates for retrograde amnesia and post-traumatic amnesia (e.g., [5]) cannot be readily compared with studies such as the present one, where formal tests of anterograde memory function were used, rather than more general measures of 'post-traumatic confusion'.

At the neurophysiological level, there are a range of possible mechanisms that may underlie the pattern of induction of deficit and recovery of function seen in TGA. It is clear that, in the case of shrinking retrograde amnesia, there is not abolition of past memories but temporary disruption of access to these memories. The pathological process therefore needs to be a reversible one that causes cell dysfunction rather than major cell loss. A variety of mechanisms have been hypothesized to play a part in producing deficits in the acute stages of brain injury/cerebral ischaemia [28], and the spontaneous resolution of these pathophysiological factors may play a role in the recovery of function that is observed. These factors include: reduction of cerebral blood flow, with an ischaemic penumbra around a critical region that has suffered the most reduction in flow; cerebral oedema; diaschisis; spreading depression of cortical electrical activity [42], perhaps related to glutamate activity; intracellular calcium influx, perhaps also related to glutamate activity; and the accumulation of free radicals. At present, there do not appear to be any empirical means of evaluating the relative roles of these factors in conditions such as TGA. It also remains to be established whether the distinctive patterns of memory disorder and recovery of function seen in TGA reflect variability in the degree of blood flow reduction across brain structures, perhaps in turn related to variability in arterial architecture, or to differences in individual susceptibility of particular structures to the effects of reduction in blood flow; e.g., the hippocampus is often considered to be more susceptible than neocortical areas to the adverse effects of a reduction in blood flow.

Within recovery from retrograde amnesia, there was differential memory loss—for public events items, distant memories were less affected than more recent memories, but there was a more variable pattern for autobiographical memories. 'Ribot's law' has been interpreted as stating that when retrograde amnesia occurs, it will affect recent memories more than distant memories. However, as Zangwill [56] pointed out, Ribot himself postulated that temporal factors were only one of a number of variables that contributed towards the differential vulnerability of stored information to the effects of brain injury or disease. Other factors, such as frequency of usage, were considered to be equally as important. Zangwill [56] reported a case study by Abercrombie [1], where events that took place shortly before the accident recovered sooner than events of the previous day. Zangwill [55], in a study of shrinkage of retrograde amnesia after blunt, relatively mild, head injury, reported that "very seldom, however, did memories appear to return in strict chronological order...Although it remains true that recent memory is relatively more vulnerable than remote, the order of return of memories in recovery from amnesia does not suggest that age of memory is the only factor governing its accessibility" (pp. 220–221). Kazui *et al.* [27] noted some exceptions to the general pattern of retrograde amnesia shrinkage: detailed memory of the Gulf War recovered sooner than memory for a Japanese Prime Minister, even though the latter event preceded the former. Kazui *et al.* [27] argued that Gulf War memories may have been more robustly encoded than some other temporally adjacent memories, and that this may have explained their preferential recovery. Kritchevsky and Squire [31] and Kritchevsky *et al.* [32] also reported variability within a period of retrograde amnesia—although an overall temporal gradient was evident in the memory loss for past events, some later memories were retained

and there was occasional evidence of loss of memories from more distant periods for which memory was otherwise intact. In general, older memories have greater 'trace strength' than more recent memories, and the reasons for this may be diverse: more frequent rehearsal, greater likelihood of incorporation into 'semantic memory', longer period for consolidation processes to operate, etc. It would therefore seem that a reformulation of Ribot's law in terms of an overall variable such as 'trace strength' may help to explain recovery of function profiles in retrograde amnesia more easily than simple temporal parameters. We therefore suggest that a 'trace strength' law rather than a simple chronological law will underlie the pattern of shrinkage of retrograde amnesia. A wide range of variables may contribute towards the strength of a particular trace in memory. Such variables include the following. (1) The time since acquisition of the memory (allowing long-term consolidation processes to operate). (2) The duration of exposure to the relevant stimuli and learning experiences; e.g., the number of times the skill has been practised. (3) The meaningfulness of the original learning experiences; e.g., whether they were novel, interesting, etc. (4) The emotional valence of the stimuli; e.g., whether they were life-threatening. (5) The pattern of temporal distribution of any repetition of the experience or similar experiences; e.g., spaced versus massed repetition of learning experiences. (6) The number of modalities in which the experience was represented at time of acquisition. (7) The number and distribution pattern of retrievals of the experience. (8) The 'richness' of the encoding experience at the times of presentation and retrieval.

We found that our patient had an initial mild naming deficit that resolved at approximately the same rate as the shrinkage of retrograde amnesia. Our finding of a naming deficit replicates a similar observation in two earlier TGA studies [21, 31]. However, Hodges [13] did not find a naming deficit in his two TGA cases. It is possible that differences in difficulty level of the respective naming tasks may partly explain this discrepancy. It is also possible that time of testing is critical; in the present study, the naming deficit was only evident in the first half of the recovery phase. The presence of a naming deficit points to left neocortical temporal lobe dysfunction, perhaps in anterior–inferior regions, and this naming deficit may contribute to impairments on tests of retrograde amnesia with a recall component. For example, Kritchevsky and Squire [31] reported an error by one of their TGA patients in recalling the name of a school teacher—it is possible that this simply reflected a naming deficit rather than a primary loss of remote memory for that particular time period.

TGA has been noted in association with cerebral angiographic procedures (see [12] for a review of cases reported up to 1990). Two recent papers [17, 18] have reported TGA using a similar non-ionic contrast agent (iohexol) to that used in the present case. In the report by Jackson *et al.* [17], the authors considered that arterial spasm was triggered by a higher than normal injectate temperature. The relative rarity of TGA in association with angiographic procedures, (Hodges [12] indicated that no cases had been recorded in 8 years experience within his local radiology unit, and we have had a similar experience in this centre) points to some atypical feature of the agent at the time rather than individual susceptibility to TGA as a result of anomalous vascular architecture.

At a more general level, our findings confirm the dissociability of anterograde and retrograde amnesia. We found distinct recovery profiles, with retrograde amnesia showing an earlier and more progressive recovery curve than anterograde amnesia. Patients with very discrete lesions of the limbic–diencephalic system, such as after mammillary body lesions [22] or focal hippocampal pathology [57], show significant anterograde memory impairment but relatively mild retrograde memory loss. A number of studies have documented patients with focal retrograde amnesia [43]. Group studies of alcoholic Korsakoff patients (e.g., [30, 46]) have generally found relatively low correlations between severity of anterograde and retrograde amnesia. Studies of anterograde and retrograde memory functioning in patients with semantic dementia and Alzheimer-type dementia have pointed to dissociations between the learning of new material and the recall of equivalent, well-established material [10]. Some computational models of memory have also allowed for similar patterns of dissociation in memory performance [2, 37, 39]. Functional imaging studies in normal subjects have shown greater lateral than medial temporal lobe activation during autobiographical memory retrieval tasks [3, 8]. Our own data add to this catalogue of dissociability, and strengthen the argument for separate memory networks for the consolidation of new information and the retrieval of well-established information.

The available neuropsychological methodology and tools for studying recovery of function remain relatively crude, and future research needs to be carried out to refine experimental designs and test instruments. In the case of the present investigation, some methodological limitations that need to be addressed in further studies include having anterograde and retrograde memory tests that are matched in terms of retention test format. For example, the different recovery profiles that we found for story and picture memory may have been related to recall versus recognition mode of testing. An example of a potential difficulty in monitoring recovery of function is that created by repeated memory testing where the same distractors are used on the different tests, as in the Verbal News Events Test given in this study. If patients are asked to make familiarity judgements on each occasion, the effects of implicit learning/proactive interference from earlier trials may be such that they will be liable to show a 'false fame' effect and make false positive responses to distractor items. We did not find this to be the case in our patient, perhaps due to the severity of his amnesia or

the nature of the particular memory test, but such a potential problem needs to be borne in mind when developing tests *de novo* in future recovery-of-function studies.

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