Episodic memory in transient global amnesia: encoding, storage, or retrieval deficit?

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Abstract

Objectives—To assess episodic memory (especially anterograde amnesia) during the acute phase of transient global amnesia to differentiate an encoding, a storage, or a retrieval deficit.

Methods—In three patients, whose amnestic episode fulfilled all current criteria for transient global amnesia, a neuropsychological protocol was administered which included a word learning task derived from the Grober and Buschke’s procedure.

Results—In one patient, the results suggested an encoding deficit, and in two others, a storage deficit.

Conclusions—The encoding/storage impairment concerning anterograde amnesia documented in our patients stands in clear contrast with the impairment in retrieval which must underlie the retrograde amnesia that also characterises transient global amnesia. This dissociation in turn favours the idea of a functional independence among the cognitive mechanisms that subserve episodic memory.

Keywords: encoding; storage; retrieval; anterograde amnesia; retrograde amnesia; episodic memory

Transient global amnesia (TGA) is a neurological syndrome the operational definition of which is purely clinical: a massive amnesia with an abrupt onset, without accompanying neurological deficit, which lasts a few hours. The patients, aged around 50 or over, remain alert and communicative with no loss of personal identity. Neuropsychological examinations made during the acute phase have shown that TGA is a selective disorder of episodic memory with no impairment of general cognitive functions, or of other components of memory, such as short-term memory, semantic memory, procedural memory, and priming. This selective impairment of episodic memory manifests itself as both retrograde and anterograde amnesia. However, the exact nature of the impairment within episodic memory processes—encoding, storage, or retrieval—remains unknown. As pointed out by Baddeley, “any system for storing information...will need (1) to be able to encode...information; (2) to store it; and subsequently (3) to retrieve that information. While these three stages are closely linked...n-
Episodic memory in transient global amnesia

Methods

SUBJECTS

Control subjects
The control group consisted of 40 subjects aged between 45 and 75 (mean 57.7 (SD 9.1) years). To allow subsequent matching to prospectively recruited TGA patients, this control group was further subdivided into four subgroups of 10 subjects each according to age (two age ranges: 45–60 and 61–75 years) and educational level (for the young group: above or below 10 years of education; for the old group: above or below 8 years of education; the class boundary being different to lessen cohort effects).

Patients
Over a period of 1 year, we had the opportunity of examining eight patients suspected of having an episode of idiopathic TGA in the emergency department of the University Hospital of Caen. Six of them satisfied the operational criteria established by Caplan and modified by Hodges and Warlow, but three had already entered the recovery stage when the neuropsychological tests were carried out. The protocol could be completed in its entirety during the acute phase by three patients. Their results are the basis of this study. There were two women (patient A and patient B), aged respectively 71 and 68 years, both with a good educational level and a man of 54 years, patient C, with a low educational level.

NEUROPSYCHOLOGICAL PROTOCOL

The neuropsychological protocol was specially designed for this study. It is modular and can be applied in the form of short sequences interleaved with medical examinations.

General cognitive assessment
The general cognitive assessment included the following subtests: orientation in time and space,23 problem solving, and copying of geometric figures (taken from the cognitive assessment battery23), short term memory, assessed by the forward span,21 and semantic memory, assessed by means of categorical fluency (names of animals) and orthographical fluency (names beginning with the letter p). In both cases the patient must provide a maximum number of names in 2 minutes.22

Assessment of episodic memory

Procedure—The battery for episodic memory was designed specifically to differentiate between encoding, storage, and retrieval, while accounting for the presence of massive anterograde amnesia during the tests. It consists of one list of 16 words belonging to 16 different semantic categories—presented one by one orally together with an instruction for memorisation—which the subject is required to reproduce explicitly. The words are concrete nouns of 5 to 8 letters, with a lexical frequency ranging from 100 to 10 000, selected from the Brulex lexical data bank.25 Our paradigm is derived from Grober and Buschke’s procedure26 and uses the encoding depth principle of Tulving and Thompson,27 according to which the greater the depth of the processing of information the better it is recalled (generally semantic processing would be involved). To control the level of processing, the subject is first asked to process each word in depth by generating a sentence containing the word. Then, to ensure the actual carrying out of deep encoding, a task of immediate cued recall is given by providing the appropriate semantic category. This task is carried out every two words, the time elapsing between the presentation of the target word and the cued recall task thus remaining within the limits of working memory (appendix). Therefore, after processing for example, the first two words of the list (turnip, museum), the subject must recall each one of them in response to the presentation of their respective semantic cues (vegetable and public place respectively). This procedure is repeated throughout the whole list providing the score of immediate cued recall. If the subject fails in the immediate recall task, he or she is reminded of the word, again requested to make a sentence containing the target, and to recall it in response to its categorical cue. This procedure therefore ensures that even if the instruction to memorise is forgotten during the test, the items have been processed and therefore should leave a memory trace, if encoding is preserved. Immediately after the processing of the 16 words, retrieval is assessed according to both free recall and recognition. In the free recall procedure, the subject has to engage in a strategic search process which is not necessary in the recognition task because each target item is provided for him or her together with three distractors from the same semantic category the position of which was randomised.

Analysis of the score profiles

The battery produces three scores—namely, immediate cued recall, free recall, and recognition scores. The analysis of the score profiles makes it possible to infer the nature of the disturbance responsible for the anterograde amnesia. Thus, in the case of an encoding disturbance, patients will not be able to recall the target words in immediate cued recall28 and therefore both free recall and recognition will be defective. In the case of a storage disturbance, despite adequate processing and preserved immediate cued recall in the encoding task, performances in free recall and recognition will be significantly affected. In fact, neither semantic processing nor recognition help at the stage of recall whenever encoding or storage are deficient. The comparison between free recall and recognition tasks is a standard method for showing specific disturbances in retrieval.29 Thus, where there is a selective retrieval disorder, performances should be clearly better in recognition than in free recall. This procedure should, therefore, make it possible to deduce whether the disorder is...
Table 1 Neuropsychological results of the control subjects on the two sessions: data shown are mean scores (SD)

<table>
<thead>
<tr>
<th>Cognitive functions</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Session 1</td>
<td>Session 2</td>
</tr>
<tr>
<td>Orientation in time (5)</td>
<td>4.90 (0.32)</td>
<td>5§</td>
</tr>
<tr>
<td>Problem solving (12)</td>
<td>11.70 (0.67)</td>
<td>11.70 (0.48)</td>
</tr>
<tr>
<td>Copying of geometric figures (12)</td>
<td>11.40 (1.07)</td>
<td>11.50 (0.84)</td>
</tr>
<tr>
<td>Forward memory span</td>
<td>5.90 (0.87)</td>
<td>5.90 (0.74)</td>
</tr>
<tr>
<td>Categorical fluency</td>
<td>33.90 (5.15)</td>
<td>35.50 (5.10)</td>
</tr>
<tr>
<td>Correct responses</td>
<td>0.90 (0.99)</td>
<td>0.8 (0.79)</td>
</tr>
<tr>
<td>Perseverative errors</td>
<td>25 (5.25)</td>
<td>25.30 (4.11)</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>0.2 (0.42)</td>
<td>0.4 (0.52)</td>
</tr>
<tr>
<td>Episodic memory:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate cued recall (16)</td>
<td>16§</td>
<td>16§</td>
</tr>
<tr>
<td>Free recall (16)</td>
<td>7.90 (1.37)</td>
<td>8.40 (2.59)</td>
</tr>
<tr>
<td>Recognition (16)</td>
<td>15.70 (0.67)</td>
<td>16§</td>
</tr>
</tbody>
</table>

*Group 1 is matched with patients A and B.
†Group 2 is matched with patient C.
‡SD=0.
§Group 2 is matched with patient C.

Results

CONTROL SUBJECTS

Table 1 gives the results of the control subjects (first group matched with patient A and patient B and the second group matched with patient C) for the battery of neuropsychological tests on two occasions at an interval of 1 month.

PATIENTS

Clinical findings

Patient A, a 71 year old right handed woman, without any medical history other than arterial hypertension (treated for several years with β blockers and diuretics) and hypercholesterolaemia, was at a swimming pool with a friend on 11 June 1996. At around 3:00 pm, as she came out of the pool, having swum 300 metres, her friend noticed that her behaviour was unusual; she asked repetitive questions about her presence at the pool, the day, the hour, and the date. Accompanied by her friend, patient A went to her daughter, a pharmaceutical chemist. Her daughter called the family doctor, who noted an arterial blood pressure of 170/90. She was referred to the University Hospital of Caen and arrived there accompanied by her husband at about 6:00 pm. Neurological examination did not show any focal abnormality other than that of memory. An ECG showed no significant abnormality and routine blood testing was normal. Brain CT was normal. Neuropsychological testing started at 8:00 pm while the patient was still deeply amnesic. The psychologist noted memory impairment until she left at 10:45 pm. Retrograde amnesia was estimated at about 2 months. Patient A had forgotten the death of a close friend and was astonished when her husband confirmed that the friend had in fact died 2 months previously. The next day the patient showed no signs of memory disturbance apart from a lacunar amnesia concerning the day of the attack. An ultrasound investigation of the cervical arteries with B-mode scanning and transcranial Doppler ultrasonography were normal.

Patient B, a 68 year old right handed woman, without any medical history apart from previous arterial hypertension treated with β blockers and diuretics, was at home with her husband and grandchildren on 4 December 1996. At around 11:30 am she started repetitive questioning concerning the date and her short term plans. When seen at the emergency ward at 12:45 pm, neurological examination disclosed disorientation for time but not for space, anterograde amnesia with persistence of repetitive questioning but normal awareness, and no other focal neurological abnormality. Cardiac examination was normal, ECG showed a sinusal rhythm, and routine blood testing was normal. Brain CT showed mild diffuse cortical atrophy and one lacunar hypodensity on the lateral part of each putamen, as well as grade I leukoaraisis. Neuropsychological examination started around 5:00 pm. At this time patient B still had both severe anterograde and retrograde amnesia covering the previous weekend. She knew that some of her grandchildren were at her house but not which of them; she did not remember her activities of the previous day and seemed anxious and very intrigued at the presence of a necklace around her neck. This indicated that she had had to leave home but was not connected with any specific memory. She had forgotten that she took her grandchildren back to their house the same day. Around 7:00 pm the recovery phase began but memory disturbances persisted for the entire evening. The next day the patient presented no memory impairment apart from lacunar amnesia going back to the final hours of the day before. An EEG and a Doppler examination of the supra-
aortic and intracranial vessels, as well as carotid ultrasonography, were normal. T2 weighted MRI showed no additional lesions.

Patient C, a 54 year old right handed man without any medical history other than migraine without aura, was at home on 7 November 1996. At about 10 30 am, after sexual intercourse, he questioned his wife repetitively, asking her why he had to change his clothes (he was invited to lunch). He had forgotten what he had done during the morning, particularly a gym session, which had finished at 10 00 am. His family doctor reported memory disturbances without any associated neurological disorder. On his arrival at the University Hospital of Caen at 11 30 am, accompanied by his wife and son, a neurological examination showed normal awareness, mnestic disturbance, disorientation in time without disorientation in space, and no other abnormality. Brain CT was normal and ECG and routine blood testing showed no special features. The neuropsychological examination began around 1 30 pm when the patient still had severe anterograde amnesia and total disorientation in time. The retrograde amnesia seemed to concern several months; in particular he had forgotten a trip to Canada in August 1996. The next day the patient had no memory disturbance other than lacunar amnesia concerning the day of the attack (lasting from 10 00 am until the evening). During his stay in hospital, arterial hypertension with a maximum of 250 mm Hg was found. Doppler examination of supra-aortic and transcranial vessels was normal, and the EEG only showed slowed bifrontotemporal reactivity during hyperventilation.

Neuropsychological scores during TGA

Table 2 gives the three patients’ scores for the battery of neuropsychological tests during the attack. Orientation in time was significantly disturbed in all three patients. Reasoning (assessed by problem solving), visuoconstructive abilities (copying geometric figures), and short term memory (verbal forward span) were preserved in all cases. The number of correct responses in both verbal fluency tasks was significantly low for patient A and on the borders of significance for patient C. These two patients produced several perseverative errors both in categorical and letter fluency. These results stand in contrast with those of patient B who, despite a normal number of correct responses, produced a great number of perseverative errors in both fluency tasks.

For the episodic memory test, the three patients carried out the semantic processing task correctly (making a sentence). The sentences were produced quickly and without error but patient A was able to recall only eight of 16 words on the first trial and the ensuing eight on the second trial in the immediate cued recall. Her performances were also significantly impaired in both free recall and recognition. Taken together for patient A, these results suggest an encoding impairment. For the other two patients, immediate cued recall was either strictly normal (patient B) or just below maximal score (patient C) indicating effective encoding, which contrasted with low free recall and recognition scores, suggesting a storage impairment even if recognition scores were higher than free recall scores.

Neuropsychological results the day after TGA

The battery of neuropsychological tests carried out about 1 month after the attack gave normal results for all the patients (table 3). A medical and psychological follow up of these patients several months after the attack showed that all were in good health, had not had any new neurological episode, and did not complain of any memory difficulties.

Discussion

We have carried out what is to be the best of our knowledge the first prospective study especially designed to examine the cognitive characteristics of anterograde amnesia in idiopathic TGA using a procedure derived from Grober and Buschke. The results obtained favour the idea of a disturbance in the encoding in one patient (A) and the storage of information for the other two patients (B and C).

CLINICAL CONSIDERATIONS

Each of the three patients satisfied the operational criteria for transient global amnesia proposed by Caplan and modified by Hodges and Warlow. Epilepsy, stroke, and head injury were ruled out by means of a reasonably extensive investigation. The follow up several months after the episode showed them to be in good health with no complaints of memory disturbance. During the attack, anterograde amnesia was severe and was associated with disorientation in time, contrasting with main-
Our three patients had disturbed verbal fluency both in number of correct responses (during the acute stage for patient A, or the next day for patient C, but in C, the score obtained during the episode was close to the pathological threshold) and in number of perseverative errors. At follow up, all these scores became normal. Impaired verbal fluency (either categorical or letter) has previously been reported during9, 62, 9 or after 30 a TGA episode. The low correct response score has been interpreted as reflecting impaired strategy of retrieval from semantic memory. The perseverative errors are in keeping with the severe episodic memory deficit rather than with an impairment of semantic memory, the preservation of which has previously been demonstrated during TGA. In the same way, the normal ability of our patients to generate sentences from words in the episodic memory test argues in favour of preserved semantic memory.

The day after the episode, the performances in episodic memory tests were normal in all patients. Only few investigators have reported the persistence of a clinically undetectable episodic memory impairment on the day after TGA.11, 12

ANTEGRADE AMNESIA

The principal objective of this prospective study was to analyse the mechanisms of the anterograde amnesia that characterises the acute phase of TGA. A protocol was purposely designed to allow the distinction between disturbances in encoding, storage, or retrieval of information in the episodic memory. This protocol, based on verbal material, controlled for both the type of semantic processing used at the encoding stage (deep encoding) and the type of processing used at retrieval (free recall or recognition). Our three patients presented two distinct impairment patterns. Whereas all three patients showed accurate semantic processing of the items, as established by good sentence production, only two of them (patient B and patient C) performed correctly at the immediate cued recall task. The last patient (A) gave only half of the items on the first trial (and the remaining on the second trial). This may reflect difficulties in simultaneously carrying out two tasks (maintaining a word and making a sentence with another word), an ability that depends on the central executive component of working memory.33 This may result in defective elaborate encoding that requires items not only being deeply processed, but also meaningfully associated with knowledge already stored in long term memory.34 Nevertheless, the other components of working memory (including the phonological loop) would be intact; hence the normal forward digit span in patient A. This encoding deficit in turn would readily explain patient A’s poor performances in free recall and recognition (see33, 34 for discussion in permanent amnesia).

The two other patients did encode the verbal material, but were impaired at both free recall and recognition, although recognition scores were better preserved. This pattern would not fit the hypothesis of a predominance of a retrieval problem. The better performance in recognition relative to recall tasks may reflect implicit processes,63 which are preserved in TGA. All things considered, the lack of efficacy of deep semantic processing and recognition does suggest a preferential storage disturbance (see64 for a discussion of permanent amnesia). The fact that the performance of patient C at the immediate cued recall was just below the maximal score (table 2) could suggest a participation of some encoding impairment as well.

As has been shown recently by Kapur et al,10 even massive anterograde amnesia does not prevent encoding, storage, and retrieval of new information when implicit tasks are involved. These authors showed intact priming effects not only during the TGA episode,65, 66 but also 7 days later for information encoded during the episode. If results of Kapur et al and ours are considered together, it emerges that the disturbance in either encoding or storage during TGA is restricted to explicit memory. Future studies examining the speed of forgetting

Table 3  Neuropsychological results the day after the TGA episode and at follow up: data shown are raw scores (and corresponding z scores)

<table>
<thead>
<tr>
<th>Cognitive functions:</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation in time (s)</td>
<td>5 (+0.31) ††</td>
<td>5 (+0.31) ††</td>
<td>5† 5†</td>
</tr>
<tr>
<td>Problem solving (12)</td>
<td>ND 12 (+0.62)</td>
<td>12 (+0.47) 12 (+0.62)</td>
<td>12 (+0.47) 12†</td>
</tr>
<tr>
<td>Copying of geometric figures (12)</td>
<td>12 (+0.56) 12 (+0.59)</td>
<td>12 (+0.56) 11 (+0.59)</td>
<td>12 (+0.57) 12 (+0.62)</td>
</tr>
<tr>
<td>Forward memory span</td>
<td>7 (+1.26) 7 (+1.49)</td>
<td>7 (+1.26) 6 (0.13)</td>
<td>6 (+0.29) 6 (+0.13)</td>
</tr>
<tr>
<td>Categorical fluency:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct responses</td>
<td>ND 46 (+2.06)</td>
<td>49 (+2.93) 57 (+4.21)</td>
<td>16 (−2.47)† 25 (−1.01)</td>
</tr>
<tr>
<td>perseverative errors</td>
<td>0 (+1.01)</td>
<td>2 (+1.11) 0 (+1.01)</td>
<td>1 (−1.93)* 0 (+0.62)</td>
</tr>
<tr>
<td>Letter fluency:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct responses</td>
<td>ND 22 (−0.8)</td>
<td>44 (+3.62) 44 (+4.55)</td>
<td>16 (−0.95) 24 (+0.35)</td>
</tr>
<tr>
<td>perseverative errors</td>
<td>0 (+0.77)</td>
<td>0 (+0.48) 0 (+0.77)</td>
<td>0 (+0.44) 0 (+0.62)</td>
</tr>
<tr>
<td>Episodic memory:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate cued recall (/16)</td>
<td>16† 16†</td>
<td>16† 16†</td>
<td>16† 16†</td>
</tr>
<tr>
<td>Free recall (/16)</td>
<td>7 (−0.65) 11 (+1.00)</td>
<td>12 (+2.99) 10 (+0.62)</td>
<td>10 (+0.37) 9 (+0.34)</td>
</tr>
<tr>
<td>Recognition (/16)</td>
<td>16† (+0.45) 16†</td>
<td>16 (+0.45) 16†</td>
<td>16 (+0.45) 16†</td>
</tr>
</tbody>
</table>

*p<0.05. †Normal performance (see table 2). ND=not done.
should be able to clarify whether the disturbance in consolidation manifests itself during the passage from working memory to episodic memory or within episodic memory itself. 

RETROGRADE V’ ANTEROGRADE AMNESIA

In our patients, retrograde amnesia was not as systematically assessed as anterograde amnesia because of methodological restrictions due to the brevity of the attack. However, certain clinical elements indicate that retrograde amnesia did exist in all, and was even extensive in two of our three cases. In addition, several prospective studies have assessed retrograde amnesia, emphasising its extensiveness and the fact that it essentially involves episodic memory.13 As TGA occurs suddenly and as the memories preceding the episode (but inaccessible during it) may be recalled when the episode is over, the most likely mechanism to explain retrograde amnesia in TGA is impairment in the retrieval of episodic information. As our results indicate that anterograde amnesia in TGA is due to either or both an encoding or a storage deficiency, it follows that in TGA anterograde and retrograde amnesia are caused by different mechanisms. Previously, Hodges and Ward10 suggested this hypothesis, but on the basis of clinical arguments only—such as the severity of anterograde amnesia as compared with a more erratic nature of retrograde amnesia. This variability in the extent of retrograde amnesia from patient to patient could reflect the commensurate variability in the time the evaluation is carried out within the course of the episode. Indeed, there exists a point in time in the recovery phase when anterograde amnesia is still significant but retrograde amnesia has already almost vanished.40 A difference in the intensity of the two types of amnesia has also been emphasised in permanent amnesic syndromes,41 the clearest dissociation having been found in focal retrograde amnesia.84 However, these studies have only pointed out quantitative differences in the duration of retrograde versus anterograde amnesia, without going into the mechanisms involved. The present work provides experimental evidence for dissociated impairment within episodic memory processes and gives further support to the idea of functional independence of these processes. Such a dissociation in the mechanisms of anterograde and retrograde amnesia has been extensively discussed by Evans et al.84 in a case report of focal retrograde amnesia after primary cerebral vasculitis. The authors qualified this dissociation and discussed the pattern of impairment of their patient in the framework of connectionist models of memory and amnesia.85 Further prospective studies in TGA are required, using protocols specifically designed to assess the fine grained mechanisms of both anterograde amnesia and retrograde amnesia, notably about the temporal gradient.

We thank the physicians of the Emergency Department of the University Hospital of Caen, and especially Dr Bruno Le Chevalier, for help in this project.

Appendix: Episodic memory task

List of 16 words (roman case) and corresponding cues (italics, the semantic category provided by the examiner in the immediate cued recall task that takes place every two words):

1. navet (turnip)
2. musée (museum)
3. légume (vegetable)
4. buffet (sideboard)
5. maitre de maison (household)
6. raisin (grapes)
7. mouton (sheep)
8. pomme (apple)
9. célébrer (celebrate)
10. dîner (dinner)
11. ventre (stomach)
12. arbre (tree)
13. argent (silver)
14. voilier (sailing ship)
15. couteau (knife)
16. poisson (fish)


