

SPECIAL ISSUE

THE IMPACT OF DISRUPTED CORTICO-CORTICO CONNECTIVITY: A LONG-TERM FOLLOW-UP OF A CASE OF FOCAL RETROGRADE AMNESIA

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ABSTRACT

We report a long-term follow-up study of case JM, who demonstrated a focal retrograde amnesia (FRA) as a consequence of cerebral vasculitis. The present study showed that, several years post-onset, JM experienced considerable impairment in episodic retrograde memory, with normal anterograde autobiographical memory. Further investigations demonstrated that she showed no evidence of accelerated forgetting, unlike some other cases of FRA. Knowledge of people, pre- and post-illness, was also normal. Her ability to recall details of famous public events was good (though weaker for pre-illness events). JM's pattern of impairment is discussed in the context of other recent cases of FRA and developments in models of normal memory function.

Key words: autobiographical memory, anterograde memory, forgetting, cerebral vasculitis

INTRODUCTION

Despite the existence of several case studies (see Kapur, 1993 and Wheeler and McMillan, 2001 for reviews) the status of focal retrograde amnesia remains controversial for several reasons (see Kopelman, 2000; Kapur, 2000). The first is that many of the cases reported as examples of *focal* retrograde amnesia (FRA) are better described as *disproportionate* retrograde amnesia in that they do have a degree of anterograde amnesia. In a summary table of such cases presented by Kapur (1999) approximately 75% were reported to show some persisting anterograde memory deficits. Some cases have had significant perceptual difficulties (Ogden, 1993). Kopelman (2000) argued that in several other cases the possibility of psychogenic aetiology was not adequately ruled out. Identifying the conditions under which focal retrograde amnesia may occur continues to be an important task.

Evans et al. (1996) described a patient, JM, who presented with a severe retrograde amnesia for autobiographical events in the context of normal anterograde memory, following recovery from cerebral vasculitis. Here, we present data from a follow-up study of JM, carried out some six years post-illness. Being rare, the condition presents a useful test of models of long-term memory. If such models are to be useful, they must be able to account for how brain lesions can result in the loss of the ability to recall information, often

stretching back many years, in the context of a retained ability to learn and remember new information.

Evans et al. (1996) demonstrated that JM's retrograde amnesia was largely confined to autobiographical events or episodes from over the previous thirty to forty years (she was aged 61 at the time of her illness). To examine autobiographical memory Evans et al. (1996) used a modified version of the autobiographical recall task designed by Crovitz and described by Hodges and Ward (1989). This involved subjects being asked to recall memories of events in their lives in response to a set of cue words (e.g. car, arm, boy). In that version, subjects were able to recall items from any period in their lives. One of the limitations of this free-recall version is that, because subjects are free to choose the time period from which to retrieve memories, it may be that only memories from the periods where recall is easy will be chosen. It is not therefore possible to conclude that the subject cannot recall, or even has more difficulty recalling, memories from particular time periods unless the subject is asked to constrain their recall to those time periods. Therefore in the present study a version of the Crovitz task (the Time-Constrained Crovitz task) was used which involved the same basic task format, but required the subject to try to recall memories from specified lifetime periods (see Graham and Hodges, 1997). The first aim of the present study was to establish whether JM still showed the same impairment in autobiographical retrograde memory when the period from which memories should be retrieved was constrained.

What was most striking about JM on previous testing was the level of detail, accuracy, and confidence associated with her recall of post-illness or anterograde events. However, one possibility not formally explored in the previous study was that JM would show accelerated forgetting. A number of studies have described patients with apparent intact initial learning rate, and normal recall after a short delay (e.g. 30 minutes) but an abnormally fast forgetting rate over a period of days or weeks (O'Connor et al., 1997; De Renzi and Lucchelli 1993; Kapur et al., 1996, 1997; Lucchelli and Spinnler, 1998). A number of these patients also demonstrated significant problems recalling events from the past and have been described as cases of *disproportionate* retrograde amnesia. It is therefore critical to establish whether JM showed any evidence of accelerated forgetting that might impact on her ability to retain information over longer periods.

Levine et al. (1998) describe the case of patient ML, who developed a focal retrograde amnesia following a head injury. Like JM, he showed impairment in pre-injury autobiographical recall (with preserved recall of general personal semantic knowledge), in the context of excellent performance on standardized tests of anterograde memory such as the Wechsler Memory Scale- Revised and word list learning tasks. ML's FRA was attributed to a lesion in his right ventral frontal cortex and underlying white matter including the uncinate fasciculus, with a resultant deficit in the strategic retrieval of autobiographical memories. Although ML's performance on tests of anterograde memory was normal, Levine et al. note that he, "reported a feeling of subjective distance from recall of events occurring after his recovery" (p. 1956). JM did not report such a feeling. Data collection for the previous study of JM, however, took place within the first one/two years post-injury. Although there was evidence that she

was remembering post-illness events in a way that would be expected of someone who presented with normal performance on standardized anterograde memory tests, we were keen to establish whether she was retaining information over several years, with a normal level of detail (i.e. such that events were recalled as personally experienced) rather than perhaps being more superficially recalled. This is clearly critical for adjudicating between a general retrieval disorder, which would be expected to effect both pre- and post-morbid memories or alternative explanations for the genesis of FRA (see later for a fuller discussion).

Kapur (1999) argues that evidence from a number of single cases points to a double dissociation between retrograde amnesia for episodic material and retrograde amnesia for semantic knowledge. Within the category of semantic retrograde amnesia, knowledge of people and events also appear to dissociate. JM's recall, or at least recognition, of famous people and events from over the same period was much better than her recall of personal events. A degree of lack of detail or uncertainty, however, was associated with her recall of famous events (p. 7). For example in describing the 'Camp David Agreement', she said it was "an agreement between Israeli's and Arabs brokered by the US, can't remember which people were involved.... wasn't Gadaffi was it... or was it Egypt?" and in describing the 'Chappaquidick Episode' she said, "it was the death of a mistress of one of the Kennedy's, not too sure if it was Robert...did she fall or was she pushed....think it was a car accident....or did she drown...could have done both". Thus although she was broadly accurate in her recall, the level of error and uncertainty seemed greater than might have been expected from someone who takes a very great interest in news and politics. In the present study we explored this issue in more detail, probing JM's knowledge of famous people and events, both pre- and post-illness.

This study was therefore designed to answer the following questions:

Investigation 1: Would JM show ongoing impairment in recall of pre-illness autobiographical information?

Investigation 2: Would JM show any evidence of abnormally fast forgetting?

Investigation 3: Would JM recall her post-illness autobiographical history?

Investigation 4: Would JM show impairments in her knowledge of famous people and famous events?

CASE REPORT

Detailed case history information on JM was provided by Evans et al. (1996). In brief, she was born in 1930 and retired from her job of university administrator in 1989. In 1991 she developed cerebral vasculitis, which was successfully treated first with prednisilone together with cyclophosphamide and then azathioprine. Between April 1992 and mid-1999 she remained well, living at home independently. She pursued interests in Russian language, other adult education learning opportunities and theatre during that time. Sadly, in 1999 she developed an undifferentiated bladder carcinoma which was resistant to therapy and she died. Post-mortem examination was not performed.

A 3D-MRI scan carried out in October 1993 demonstrated a degree of bi-frontal and left parietal atrophy with dilation of the posterior part of the left lateral ventricle. The left sylvian fissure was also enlarged. The right temporal lobe appeared normal. On the left, there was evidence of a mature infarct involving the left temporal pole. The hippocampal complex appeared normal in size and configuration bilaterally. An HMPAO SPECT scan revealed generally patchy uptake of tracer in the frontal lobes with areas of more focal hypoperfusion in the left temporal and parietal regions.

General cognitive testing carried out in 1992 and afterwards, revealed preserved general intellectual performance as well as good executive, perceptual and language skills. JM's anterograde memory performance was intact, as demonstrated on tests such as the Wechsler Memory Scale - Revised (Wechsler, 1987), Rivermead Behavioural Memory Test (Wilson et al., 1995) and the Warrington Recognition Memory Test (Warrington, 1984).

The data for the studies presented here were collected approximately six years post-illness.

Investigation 1: Would JM still show impaired recall of pre-illness autobiographical information?

To address this question a modified version of the Crovitz technique (Graham and Hodges, 1997) was used.

Method

Participants were instructed to try to remember a specific event or episode in response to each of 15 cue words, from a particular lifetime period [under 18; twenties and thirties; forties and fifties; over 60]. The test used the same 15 words (e.g. holiday, accident, game, meal, hospital) for each time period. Time periods were sampled in a random order. In order to encourage the production of as much detail as possible, there was no time limit for recall and participants were prompted (e.g. "Can you tell me more about that?"; "Can you give me a specific example?") if necessary.

Responses were scored on a 6 point (0-5) scale according to the specificity of the memory (see Graham and Hodges, 1997 for details of the scoring system). JM's ratings were scored by two raters independently. It was not possible for the raters to be blind to the patient's identity, though one of the two raters was blind to any experimental hypotheses. There was good inter-rater reliability (Cronbach's Alpha = 0.947) and average ratings are presented. JM's scores were compared with published data from the three control participants used in the Graham and Hodges (1997) study. Although there was a small number of control subjects and some caution is therefore required in interpreting the data, the control participants were well matched with JM, being aged 65 at the time of testing and all being university graduates.

Results

Figure 1 shows the results from the test. A Friedman analysis (reported in Graham and Hodges, 1997, p. 85) showed that there was no significant difference

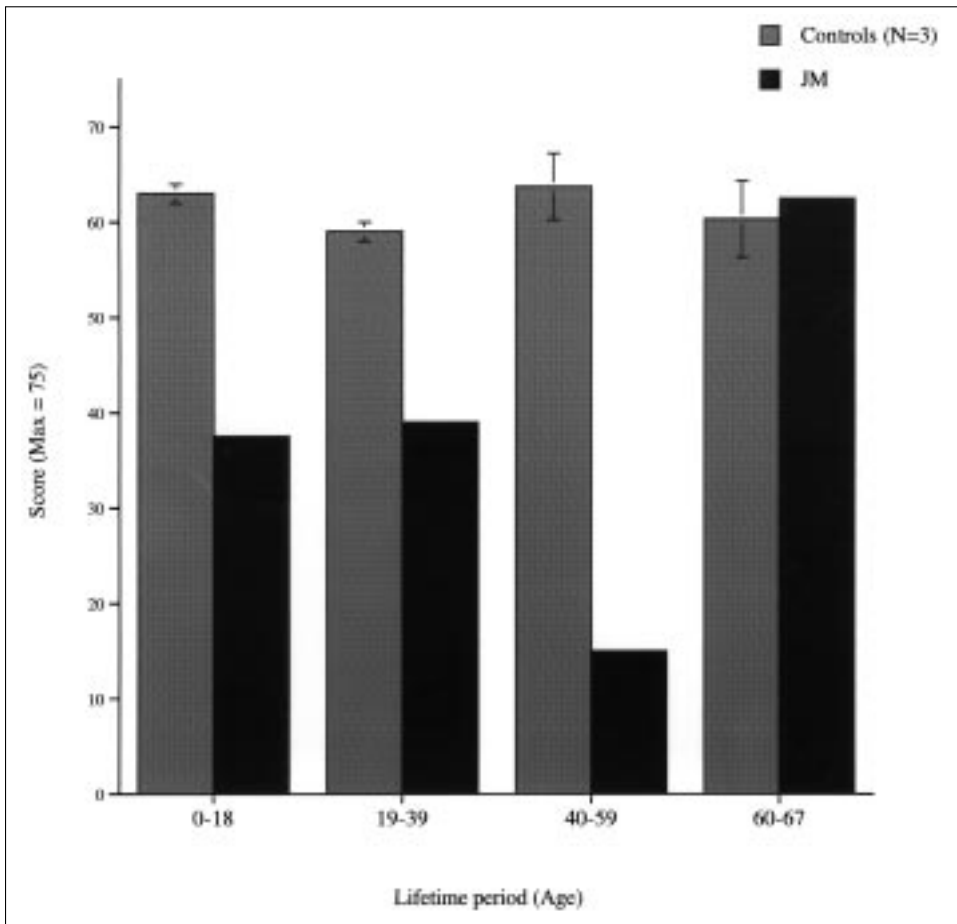


Fig. 1 – Performance of JM and three control participants (mean scores with one standard deviation bars) on the lifetime period constrained Crovitz task.

across the time periods for the control participants ($\chi^2 = 3.64$, $p = 0.30$). The performance of this group on each of the time periods was consistent with the performance of a larger group of subjects ($N = 41$) reported by Hodges and Ward (1989) on a similar, but unconstrained, Crovitz task. By contrast a Friedman analysis performed on JM's data showed a significant difference across time periods ($\chi^2 = 20.28$, $p < 0.0001$). Wilcoxon rank-sum tests showed that JM's memories were significantly less detailed than the controls for all time periods apart from the most recent (0-18: $z = -3.30$, $p = 0.001$; 19-39: $z = -2.27$, $p = 0.023$; 40-59: $z = -3.41$, $p < 0.001$; 60+: $z = -.489$, $p = 0.62$). It is noticeable that the period of 20 years immediately prior to the onset of her illness appear to be particularly badly effected. For the most recent, post-illness period, JM produced memories, as did control participants, from across the time period, suggesting there was no tendency towards accelerated forgetting of autobiographical memories within the post-illness period.

JM's contrasting recall of memories in response to the cue word 'animal' provide an illustration of the marked difference in her ability to recall pre- and post-illness events. For the time period immediately prior to her illness, in response to the cue word 'animal' JM talked of how she had come to have a cat (which she had acquired some four years prior to her illness). The following is a transcript of JM's response, which we reproduce with her permission (note that KP is the researcher who was administering the test):

KP: The next word is animal. Have you got a particular memory of something to do with an animal from the time period between the ages of 40 and 59?

JM: Oh yes, well this was when I got this cat. But again, you see, I don't remember. Except in the vaguest terms. I think I've been told what the circumstances were. And of course that overlays, and you can't...I knew that the cat had adopted me, that I could remember. I think she came... Well I thought that she had adopted me, but then I was told that it belonged... I have a whole memory of where the house is, but then it's probably a false memory, there was this young couple and they were concerned about the cat sitting on the baby. Well everyone says that's an old wives' tale, but I do think it actually was. I mean she was capable of actually sitting on my face.

KP: So they were right...

JM: So they, no, I don't know whether... quite how it worked out, whether... One version of the story, and for that person it was only a story, was that I kind of had it while the baby was kind of stopping being a baby... and that I said, "will you have it back?"... and they said "No, you keep it". But I'm not sure.

KP: You can't remember?

JM: No, but I do think, I'm sure that they didn't come and say we're having a baby, or we've got a baby, will you look after this cat? I'm sure that she came and, errm, adopted me. Yes I'm sure that's right.

KP: OK. And can you remember when it was she adopted you?

JM: Well it wouldn't have been very... because I moved with her of course in 1989, so I tend to think I'd had her 2 years.

By way of comparison, the following transcript is of JM's response to the same cue word for the post-illness period.

KP: Can you tell me anything to do with 'animal' that's happened in the last seven years?

JM: Yes, yes yes. I had a cat and it died. That was a trauma as far as I was concerned.

KP: Can you tell me about how it died?

JM: Well, yes, it was awful because I kept being concerned that it wasn't well. My cousin had a vet and... the part I remember was I went saying that I thought she had got cystitis. I think that was the first time I went. And,... I can't, but he said that it would be one of three things, ermm, but for one of them she'd have to have a blood test. I can't quite remember what the three things were, what he said they might be. But anyhow, he took the blood test and I rang up and he said that it wasn't whatever the blood test had been for. But she started to go off her food and so on, and I came back this particular day, because she wouldn't drink- that's right, and errm, this stuff that someone had suggested, this

special kind of milk for cats which was easier for them to digest. Well, then I got home and she was in a very poor way.

KP: Oh dear

JM: So my neighbour kindly agreed to take me to this vet and I took her in and I put her on the table and he said to me, "She's dying on you". Well I think he expected that I was going to leave her behind. Well I took her home for the night because it was such a shock.... my neighbour was very shocked by the vet's attitude. She actually died of kidney failure and I don't think that was one of the things he had suggested it might be. You know what I mean. I don't think anything could have been done about it if he had, because it's an irreversible thing, but if I'd had known...

KP: So did she die during the night that you had her?

JM: No, I took her in and fortunately for me he was away and it was another vet, a much nicer vet, who was acting as a locum. He's a man with his own practice, which is the practice I now go to with my new cat. And he was very nice.

KP: That's dreadful isn't it. So, when was this that she died?

JM: Well she died in '93.

These two transcripts illustrate the contrast in the level of detail and confidence in JM's recall of personally experienced events pre and post-illness. The results of the Crovitz test suggest that JM is laying down new memories post-illness and retaining those memories. The next investigation examined more formally the question of whether JM shows any evidence of accelerated forgetting.

Investigation 2: Would JM show any evidence of abnormally fast forgetting?

To investigate forgetting over time, JM and four age- and IQ-matched controls were tested on story and complex figure recall immediately following presentation, and then after a 30-minute delay and then after a six-week delay. They were also tested on an object decision recognition memory test following delays of 30 minutes, three weeks and six weeks.

Story recall

Method

The story used in this test was from Form 2 of the Coughlan and Hollows Adult Memory and Information Processing Battery (1985). This story consists of 30 idea units. The story was read to the subjects, following which the subjects were asked to recall as much of the story as possible. Participants were not told that they would be tested again. After a thirty-minute delay and then a six-week delay subjects were re-tested on their recall of the story. The story was scored according the scoring criteria described by Coughlan and Hollows.

Results

Data for each of the delay periods in terms of percentage of maximum points obtained for JM and the four controls is presented in Figure 2. It is noteworthy

that JM's recall of the story was somewhat better than the four controls. For example at immediate recall her score was 3.04 standard deviations above the control mean, with her performance being better at immediate recall than any of the controls participants. JM appeared to show a similar forgetting rate to the control group, although it is difficult to draw firm conclusions regarding this issue as a result of JM's initial recall performance being so much higher. At delayed recall, JM's performance was 1.92 standard deviations above the control mean. Within the control group there was considerable variation on the six-week delayed recall trial, particularly in relation to the percentage of the immediate recall score. Two subjects retained none of the story, one retained 24.1% of the immediate score and one recalled 70% of the immediate score. There was no apparent relationship between six-week delayed recall and either immediate or 30 minute delayed recall. The control participant with the highest immediate and 30 minute delayed recall scores was one of the two who recollected nothing at six weeks, the other being the person with the lowest immediate and three week scores. JM retained 51.0% of her immediate recall after six weeks.

Complex Figure Recall

Method

The complex figure used in this test was from Form 2 of the Coughlan and Hollows Adult Memory and Information Processing Battery (1985). Subjects were shown the figure and asked to copy it. Immediately afterwards subjects were asked to draw the figure from memory. Subjects were not told that they would be tested again. After 30-minute and six-week delays subjects were re-tested on their recall of the figure. Drawings were scored according to the scoring criteria described by Coughlan and Hollows.

Results

Data for each of the delay periods in terms of percentage of maximum points obtained for JM and the four controls is presented in Figure 2. The figure shows that JM's recall of the figure was within one standard deviation of the control mean for all three time periods.

Object Decision Recognition Memory Test

Method

This test was derived from Graham's (1993) Test of Object and Animal Decision (TOAD). The test consists of line drawings of real and non-real man-made objects and animals. The non-real 'objects' are constructed of two halves of different real objects (e.g. light bulb and screwdriver) and the non-real 'animals' consist of half of one animal with half of another (e.g. Penguin-Owl). On the first part of the test, subjects were presented with items one at a time and asked to identify whether the item was real or not. Seventy-eight items were presented in total, half of which were real and half non-real.

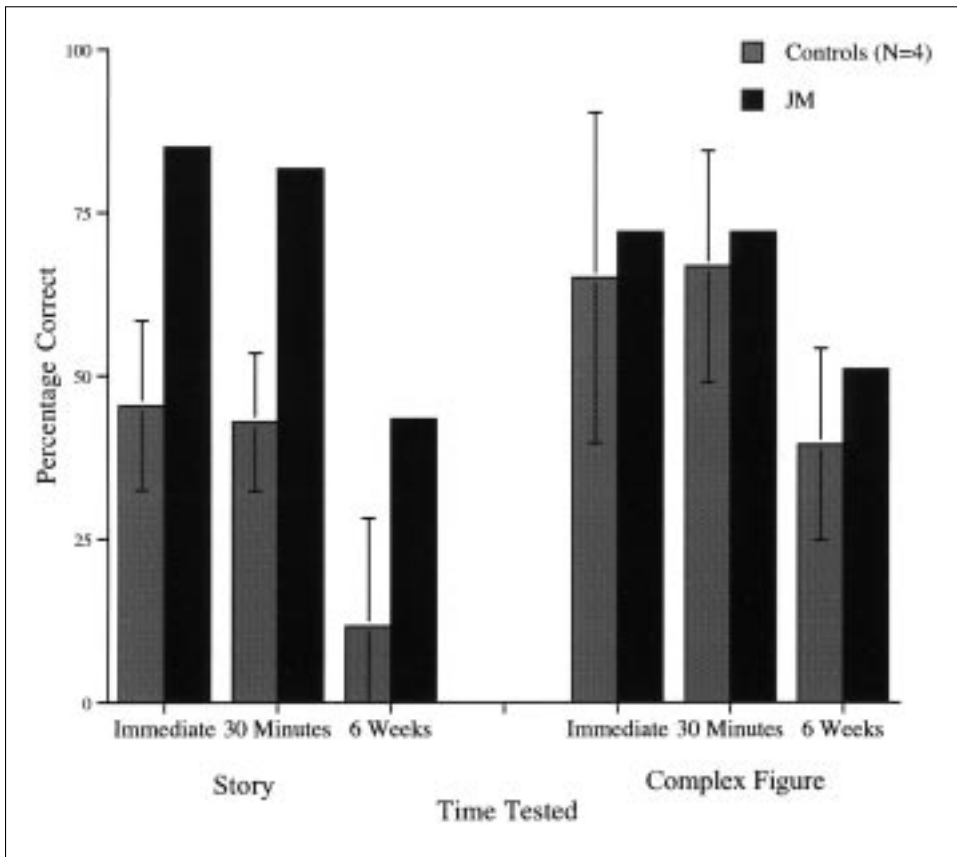


Fig. 2 – Performance of JM and four controls (mean scores with one standard deviation bars) on the Story and Complex Figure Tests.

After 30 minutes, a sub-sample of 26 items from the original list was presented along with 26 new items, not previously seen by the subject in a two-alternative forced-choice recognition test procedure. Studied items were always paired with a similar new drawing (e.g. real-real or non-real-non-real). At three weeks a further sub-sample of 26 pairs of items (half from the original sample and half new) was presented, again using a two-alternative forced-choice recognition test procedure. The same procedure was repeated at six weeks.

Results

JM's performance at identifying whether or not the objects/animals were real or not was perfect. Figure 3 shows the performance of JM and the four controls at each of the three delays for the recognition memory test. JM's performance was just above that of the control mean for each of the three time periods, suggesting that JM does not show any evidence of accelerated forgetting.

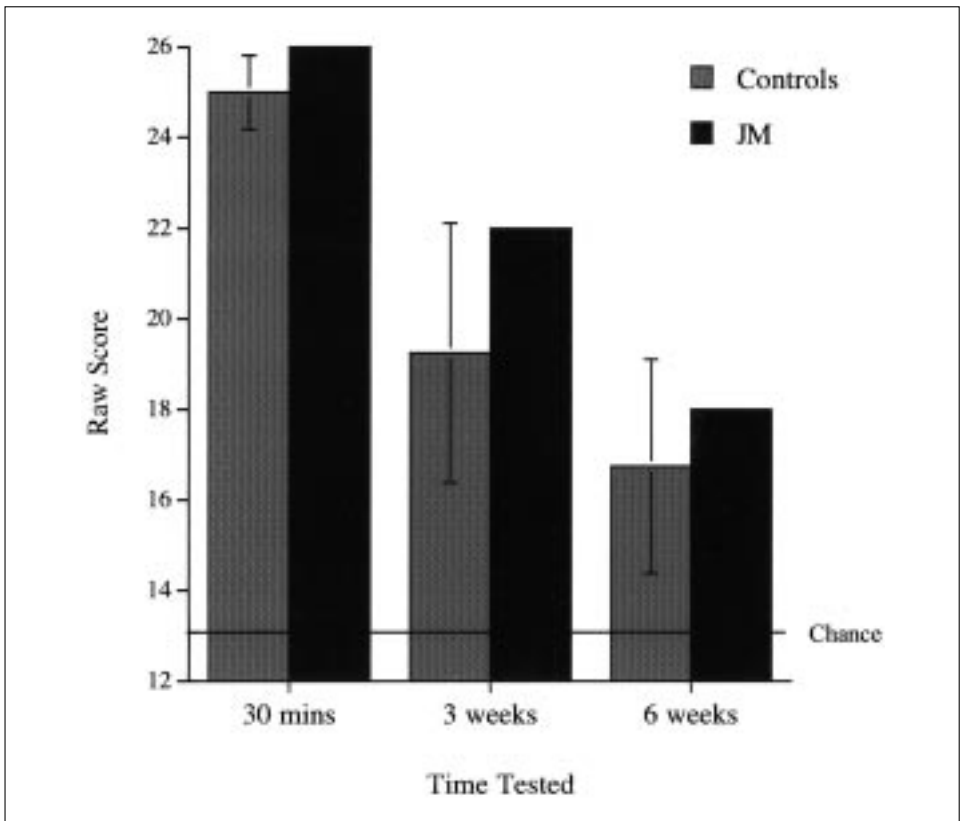


Fig. 3 – Performance of JM and four controls (mean scores with one standard deviation bars) on the recognition component of the Test of Object and Animal Recognition (TOAD; Graham 1993).

Investigation 3: Would JM recall her post-illness autobiographical history?

The Crovitz task demonstrated that JM was able to recall specific events from the post-illness period in a way that appeared normal and the forgetting tests demonstrated that JM did not show evidence of accelerated loss of anterograde information. We explored JM's recall of the post-illness period in more detail in an interview focusing on her recall of her medical history and a range of personal events which she had referred to in the intervening years (and had been noted in clinical interview notes) in order to informally identify whether she appeared to be retaining post-injury autobiographical memories.

Medical history

Key events from JM's post-illness medical history were collated from her medical notes and through discussion with treating clinicians. There were no major medical problems during this time, but she had had a number of contacts with medical practitioners relating to follow-up treatment and investigation of her condition. In an interview, JM was asked to describe her medical history.

She was able to do this in some detail, spontaneously noting all of the major events (e.g. attending outpatient vasculitis and neurology clinics, undertaking a period of counselling, having brain scans, changing her General Practitioner). She was accurate in terms of the general order of events and broadly accurate in relation to dates over a six-year post-illness period. Although no control data is available for this sort of highly individualized task, it was clear that JM does recall the relevant information accurately and furthermore she has a degree of confidence in her memories that is lacking for pre-illness events.

Personal events

A list of personal episodes (including both 'one-off' events and activities that occurred over a more extended period) was compiled by one of us (JE) who had seen JM regularly throughout the years after JM's illness up to the time of the present follow-up study. These included events surrounding attendance at Russian language classes, getting a cat, having friends to visit, getting someone to clean for her, having a burglary and attending a monthly Lunch Club. Once again control data are not available, so it is not possible to demonstrate conclusively that her remembering is entirely normal, but it was clear that she was able to recall the main details from each of these personal event areas. With regard to the Lunch Club, this is something she had attended approximately monthly for over two years, since its inception. The format for the club was that as well as lunch being provided there was a speaker who would give a presentation at each meeting. We obtained a list of all the topics (e.g. Landscape Design, Railways in Cambridge and Aerial Photography in Archaeology) and asked JM to try to recall as many as possible. She was able to spontaneously recall just over half of all the topics covered (15/27), with the topics she did recall being spread across the three years.

Investigation 4: Would JM show impairments in her knowledge of famous people and famous events?

Evans et al. (1996) tested JM on a test of famous face identification and a famous event recognition task. As noted earlier, JM performed within the normal range on these tasks, but there were hints that JM could not access the level of detail that might have been expected of her on the Famous Events test. As the Famous Events test used was scored only on the basis of recognition, there was no formal assessment of her ability to provide relevant event detail. We therefore undertook a more detailed assessment of her knowledge of famous events and people with a series of tasks, her performance on which was compared with that of a group of control participants.

(a) Famous People

Famous People I

Method

This test examined JM's knowledge of famous people from their names. The

test is described in detail in Hodges and Graham (1998) which includes details of the specific stimuli used. The names of thirty people who were primarily famous in each of the following four time periods were included: 1950's, 1980's, early 1990's and current (i.e. currently or very recently famous). Recognition and identification of the famous names was tested. The 120 items were presented in a random order. Each famous name was presented with three other non-famous names, with the position of the target famous name varying randomly throughout the test. The subject was asked to point to the famous name (the recognition element) and then, if correct, to provide as much detail as possible about the person to uniquely identify that individual. If a subject incorrectly chose a non-famous foil, the correct name was provided and the subject asked to try to produce as much information about the person as possible.

The recognition component of the test was scored simply in terms of the total number of correctly identified items (Max. = 30 per time period). For the identification task, each response was again scored according to a 4 point (0-3) scale, according to the following criteria: 0 = don't know or incorrect response; 1 = superordinate information only (e.g. sportsman, politician); 2 = a definition that accurately described the person, but did not uniquely identify that individual; 3 = a definition that uniquely identified the person. There was a maximum possible score of 120 per time period.

The test was given to JM and her performance was compared with that of six control subjects (described in Hodges and Graham, 1998). The mean age of the controls was 63 years (just slightly below JM who was 67 at the time of testing).

Results

On the recognition component of the test, JM's performance was perfect (120/120), which matched the performance of the controls.

Figure 4 shows the identification scores for each of the four time periods for JM and the six controls. A Friedman analysis showed that there was no significant difference across the time periods for the control participants ($\chi^2 = 2.83$, $p = 0.419$) or for JM ($\chi^2 = 0.690$, $p < 0.876$). Wilcoxon matched pairs signed ranks tests on each of the time periods comparing the performance of JM with the controls revealed no significant differences (50's, $z = -.786$, $p = 0.432$; 80's, $z = -1.28$, $p = 0.196$; Early 90's, $z = -.813$, $p = 0.416$, Late 90's, $z = -.148$, $p = 0.882$).

Famous People II

Method

The previous famous people test included people who were not primarily famous in connection with single events. Given JM's difficulty with pre-morbid episodic information, we wondered therefore whether she would have more difficulty with identifying people whose fame is primarily associated with a single event, or at least a limited set of events over a short time period. A test of knowledge of famous people primarily associated with particular events was constructed. The names of eight people associated with events in each of five

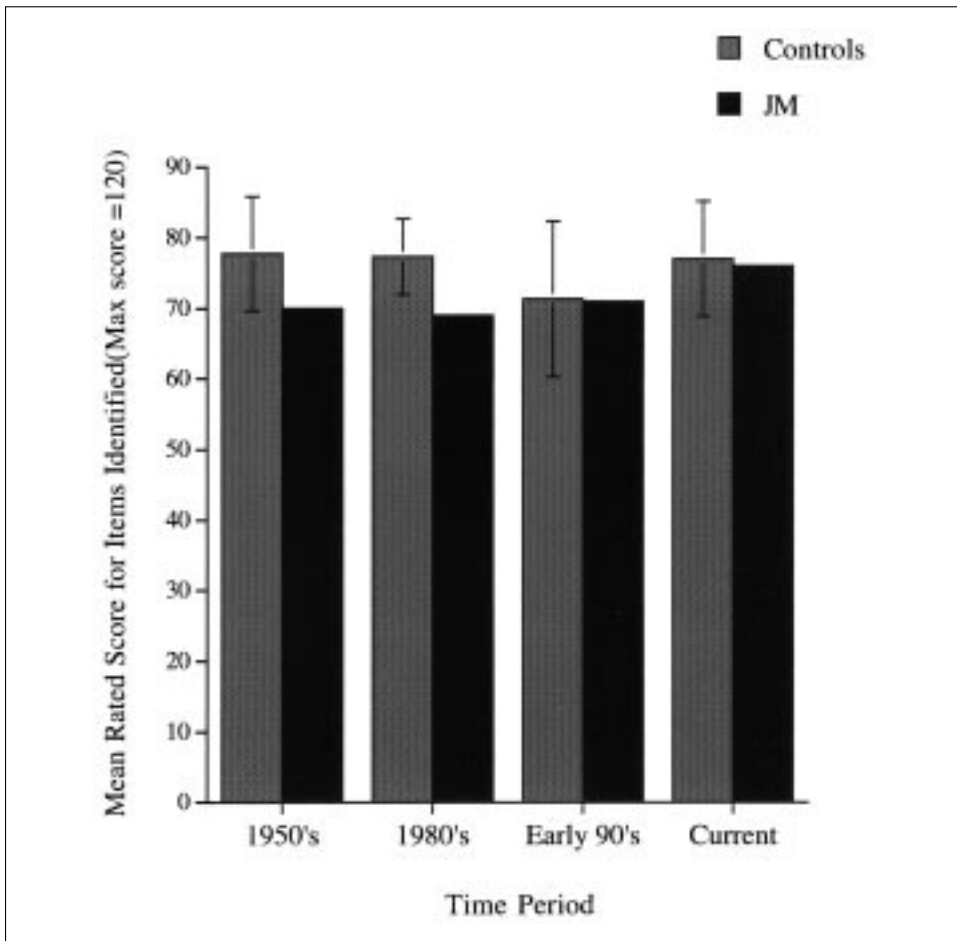


Fig. 4 – Performance of JM and six controls (mean scores with one standard deviation bars) on the identification component of the Famous People I Test.

years pre-illness (1987-1991) and five years post-illness (1993-1997) was constructed making a total of 80 names. JM became ill towards the end of 1991, and was acutely ill for a significant part of 1992, hence events from the year 1992 were excluded. A further 240 'plausible', but non-famous names were created. Recognition and identification of the famous names were tested by presenting each famous name with three non-famous names (e.g. David Koresh, Robert Purcell, Neil Reed, Adam Wall). The four names were arranged vertically on a piece of paper, with the position of the famous name (1, 2, 3, or 4) and the order of the names (with respect to year of event with which they were associated) arranged randomly. The subject was asked firstly to try to identify which of the four names was famous. If the subject correctly selected the real name she was then asked to produce as much information as possible with the aim of uniquely identifying the individual. If the subject made an error

during the recognition phase, incorrectly identifying a non-famous name as a famous name, she was told which was the real name and asked to try to produce as much information as she could about that person.

The recognition component of the test was scored simply in terms of the total number of correctly identified items. For the identification task, each response was scored according to a 4 point (0-3) scale, according to the following criteria: 0 = don't know or incorrect response; 1 = superordinate information only (e.g. sportsman, politician); 2 = a definition that accurately described the person, but did not accurately identify the event with which s/he was associated; 3 = a definition that uniquely identified the person and event with which s/he was associated. There was a maximum total score of 120 per five-year time period.

The test was given to 6 control subjects who, like JM, had been educated to degree level. They were well matched with JM for age (JM: 67 years; Controls: 67.7 years, s.d = 1.86)

Results

Figures 5a and 5b show the performance of JM and the control subjects on the recognition and identification components of this test respectively. They show that JM's performance for the recognition task was similar to that of the control participants.

On the Identification task, for the pre-illness period JM was comparable to the controls (Wilcoxon matched pairs signed ranks test, $z = -1.219$, $p = 0.223$).

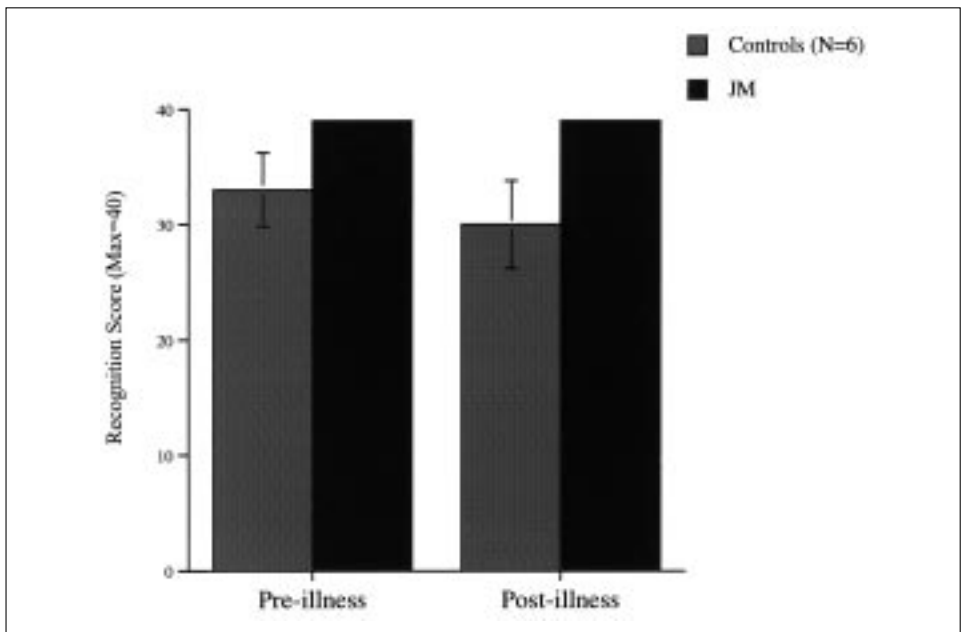


Fig. 5a – Performance of JM and six controls (mean scores with one standard deviation error bars) on the Recognition component of the Famous People II Test.

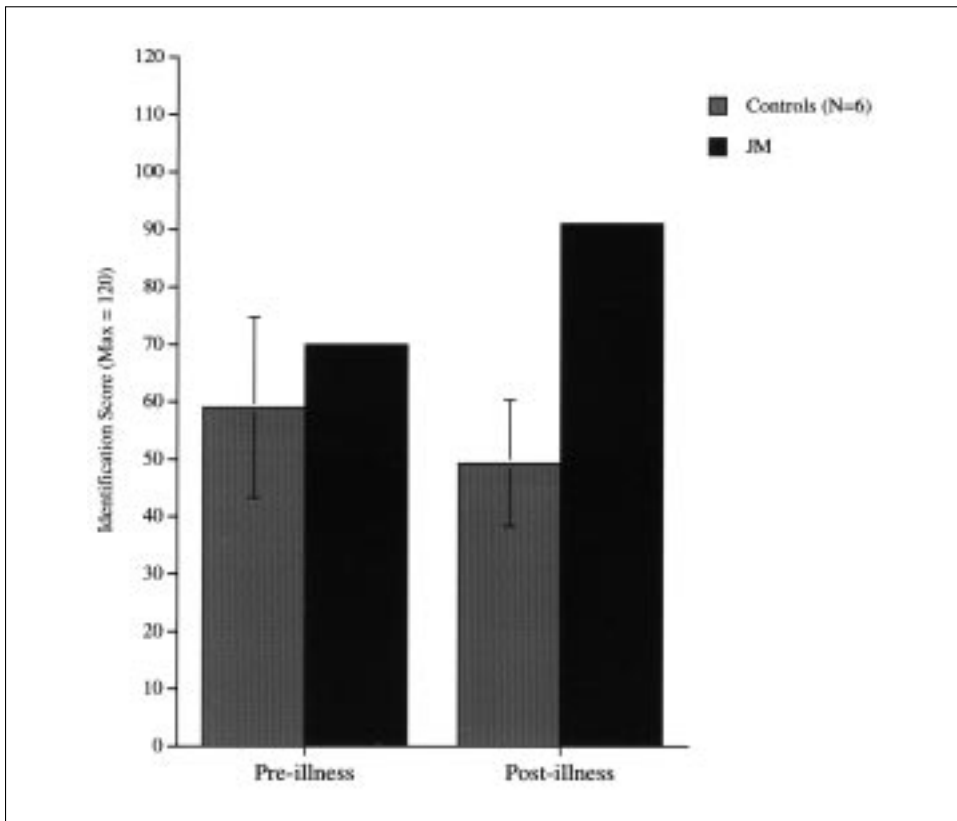


Fig. 5b – Performance of JM and six controls (mean scores with one standard deviation bars) on the Identification component of the Famous People II Test.

For the post-illness period JM's performance was significantly better than the controls (Wilcoxon matched pairs signed ranks test, $z = -2.02$, $p = 0.043$). The controls did not show any significant difference between the two time periods (Mann Whitney $U = 8$, $p = 0.347$), whilst with JM there was a trend towards a difference, though this did not reach statistical significance (Mann Whitney $U = 4$, $p = 0.07$). These data show that JM was good at identifying famous people from the pre- and post-illness periods studied. However, there was some indication that her performance from the pre-illness period was perhaps somewhat weaker relative to the post-illness period.

(b) Famous Events

The tests of JM's knowledge of famous people suggested that she retained relatively good knowledge of people, including of those people who are primarily associated with single events with the caveat that there was some indication of a very mild weakness in pre-illness knowledge. JM's knowledge of famous events was further examined in the following test. The famous events in

this test were selected as those that would be likely to be known by someone living in the UK. Eight events per year over two five-year periods (1987-1991 and 1993-1997) were selected for inclusion, making a total of 80 events. Each event was given a title designed to convey enough information about the event so that it could be recognised. A further 240 'plausible', but non-famous events were created using similar titles. Recognition and identification of the famous events were tested by presenting each famous event (e.g. The Tokyo Subway Gas Attack) with three non-famous events (e.g. The Jersey Killer Bee Invasion, The Napoleon Diaries Fraud, The Westwood Shooting). The four events were arranged vertically on a piece of paper, with the position of the famous event (1, 2, 3, or 4) and the order of the events (with respect to year) arranged randomly. The subject was asked first to identify which of the four events was real. If the subject correctly selected the real event she was then asked to produce as much information as possible with the aim of uniquely identifying the event. If the subject made an error during the recognition phase, incorrectly identifying a non-famous event as a famous event, then she was told which was the real event and asked to produce as much information as she could about that event.

The recognition component of the test was scored simply in terms of the total number of correctly identified items. For the identification component of the task, each response was scored according to a 4 point (0-3) scale: 0 = don't know or incorrect response; 1 = superordinate information only; 2 = a definition that described the event, but did not distinguish it from other similar events (i.e. did not uniquely identify the event); 3 = a definition that uniquely identified the event (see Graham et al., 1998 for illustrations of the scoring method). There was a maximum total score of 120 per five year time period.

The test was given to four control subjects who, like JM, had been educated to degree level. They were well matched with JM for age (JM: 67 years, Controls: 68.3 years, $SD=3.4$).

Results

Figures 6a and 6b shows the performance of JM and the four controls on the Recognition and Identification components of the Famous Events test. Figure 6a shows that JM's performance on the Recognition component of the test was comparable to the control participants. On the Identification task, for the pre-illness period JM was comparable to the controls (Wilcoxon matched pairs signed ranks test, $z = -.983$, $p = 0.326$). For the post-illness period JM's performance was significantly better than the controls (Wilcoxon matched pairs signed ranks test, $z = -3.24$, $p = 0.001$).

The controls did not show any significant difference between the two time periods (Mann Whitney $U = 689.5$, $p = 0.287$), whilst with JM her scores did show evidence of a difference (Mann Whitney $U = 607.5$, $p = 0.064$, tied $p = 0.036$), suggesting that JM was better at identifying events post-illness in comparison to pre-illness. Nevertheless, JM was clearly remembering details of many public events, both pre- and post-illness, and the most it seems possible to conclude is that for some of the pre-illness events there was a little less detail or confidence in recalled information. By way of example, for 'The Kuwait

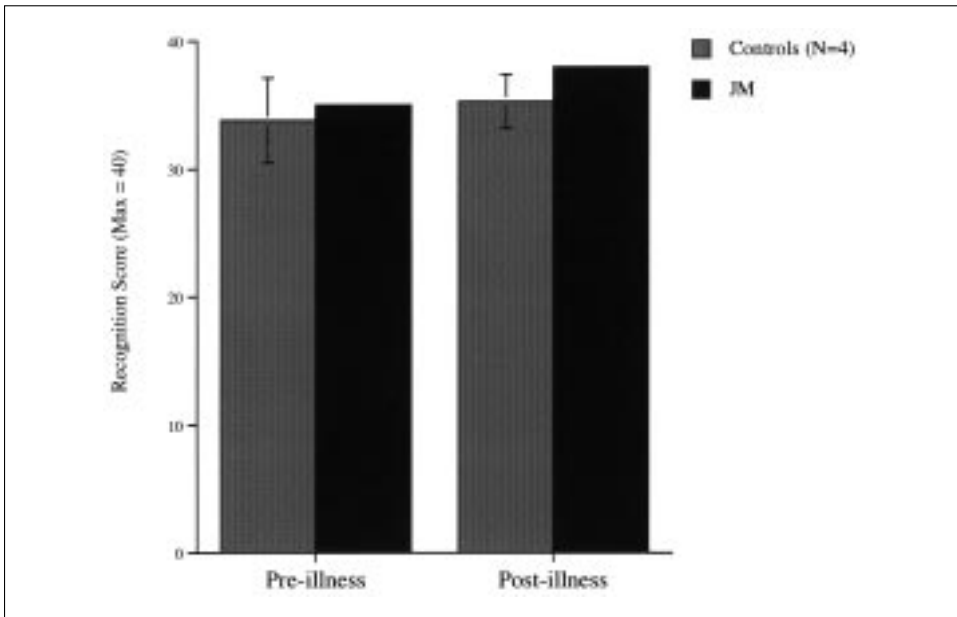


Fig. 6a – Performance of JM and four controls (mean scores with one standard deviation bars) on the Recognition component of the Famous Events Test.

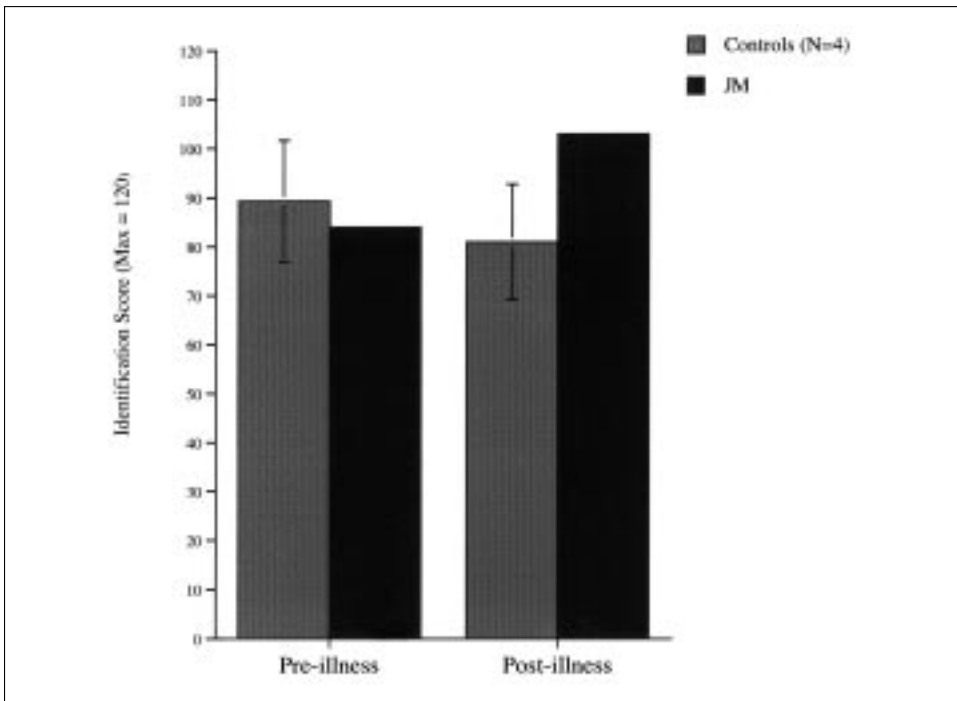


Fig. 6b – Performance of JM and four controls (mean scores with one standard deviation bars) on the Identification component of the Famous Events test.

Invasion' (from 1990), she responded, "Iraq invaded Kuwait. Was that the origin of the Gulf War? Or did we get them out of there?", and for 'The Piper Alpha Incident' (from 1988), she responded, "An oil rig disaster- it went on fire or did it sink? Large numbers of people had to be rescued". This is entirely consistent with her pattern of performance on the Famous Events Recognition test described in Evans et al. (1996). There was no evidence to suggest that she had less of an interest in news events pre-illness, although it is possible that she had more time available to her post-illness (post-retirement) with which to follow media coverage of news events.

DISCUSSION

This follow-up study of JM demonstrated that she continued to experience significant impairment in retrograde autobiographical memory in the context of intact anterograde learning. There does not appear to be any evidence of accelerated forgetting. It was not possible to draw firm conclusions on this issue from the story recall task as JM's initial recall performance was rather better than the controls. Amongst the control participants there was considerable variation in performance after a six-week delay. It is not clear what accounted for this, though the possibility of variation in rehearsal amongst the control participants cannot be ruled out. This highlights one of the difficulties in studying forgetting over extended time periods. Nevertheless, JM's performance on the non-verbal recall task and the recognition task, provided stronger evidence that she did not show accelerated forgetting. JM also appeared to have learned and retained a good record of autobiographical information since recovering from her acute illness.

JM's knowledge of people from both before and after her illness was excellent, though there was some indication that her ability to recollect information about people who were famous, but associated with more singular events was a little weaker for the pre-illness period in comparison to the post-illness period. This finding replicated the pattern with famous events from the previous Evans et al. (1996) study, and was further replicated with the famous events test in the present study.

JM's results on the Crovitz task confirmed our previous finding of a broadly U-shaped pattern with good recall of recent autobiographical events, moderate (but still impaired) recall of early life events and very poor recall of events over a period of some 20 years preceding the illness. The pattern is different from both the standard temporal gradient found in conditions such as Korsakoff's syndrome, or the reverse temporal 'step function' associated with semantic dementia (Graham et al., 1998; Graham, 1999).

To the best of our knowledge, this is the first long-term follow-up study of a patient with focal retrograde amnesia that has attempted to address the status of episodic memory in the period after the onset of brain pathology.

How should focal retrograde amnesia, and in particular JM's pattern of impairment be explained? We consider here three different hypotheses. The first hypothesis suggests that FRA can be explained in terms of a retrieval deficit

associated with frontal lobe damage. The second hypothesis is that FRA can be accounted for in terms of a temporary perturbation of medial temporal lobe structures. The third hypothesis suggests that it is the multi-focal neocortical damage that is critical to the production of the problems.

The retrieval deficit hypothesis

Levine et al. (1998) argued that their patient ML's isolated retrograde amnesia could be accounted for in terms of a retrieval deficit associated with lesions of the right ventral frontal cortex, with associated damage to the uncinate fasciculus leading to a fronto-temporal disconnection. They further argue that the preservation of anterograde memory functioning in ML can be accounted for by a degree of reorganisation of preserved pathways. In the case of ML there was evidence of hyper-activation (in comparison with controls) in the left inferomedial temporal lobe system, which they claim, was responsible for a normal performance on a cued-recall task. These 'preserved pathways' cannot, however, provide access to pre-injury information. One of the observations that Levine et al. made about ML was that he reports "a feeling of subjective distance from recall of events occurring after his recovery". Thus his anterograde recall of autobiographical events is not entirely normal and perhaps the lack of feeling of personal connection with the events reflects a lack of the ability to recall fully integrated (in terms of temporal, spatial and visual characteristics) autobiographical episodes. Whilst ML has intact anterograde memory for unimodal remembering situations (e.g. word lists, designs) he appears not to have a normal recall of events that require integrated multi-modal or multi-sensory information (i.e. autobiographical episodes). By contrast JM had normal recall of such information.

Our patient JM had MRI evidence of frontal lobe damage, though little in the way of behavioural evidence at the time of testing. The fact that JM was able to encode and retrieve personally experienced events with a normal level of detail and phenomenological experience suggests that her difficulty could not be ascribed to a general retrieval deficit, associated with frontal lobe impairment.

The temporary perturbation of medial temporal lobe structures hypothesis

Nearly all of the most recent models of memory functioning point to the close co-operation and integration of neocortical and limbic structures, including the hippocampal complex, (McClelland et al., 1995; Nadel and Moscovitch, 1997). The fact that JM could acquire, store and retrieve (post-illness) memories, including autobiographical memories rich in detail suggests that these systems were intact and functioning effectively. During the acute period of JM's illness in 1991, however, the systems were not working, evidenced by her initial presentation which included severe anterograde amnesia that has produced a dense amnesic gap encompassing the acute period of her illness. She also had one seizure during this period. Could a temporary disruption to the system account for the persisting deficits in pre-illness autobiographical memory? We noted previously that Murre's (1996) TraceLink model does predict that a temporary perturbation in the medial temporal lobe based Link system would result in a

temporally-graded focal retrograde amnesia. Within this model, the Link system is seen as acting as a temporary bridge or link between neocortical level traces (the low level features co-occurring in an event). Through rehearsal or re-experiencing over time a memory of the episode is established at the neocortical level and then does not require the medial temporal lobe system for retrieval. A number of other similar cortico-hippocampal models of memory (Alvarez and Squire 1994; McClelland et al., 1995) make the same argument. This hypothesis was, however, rejected as a complete explanation of JM's pattern of impairment because of the temporal extent of JM's retrograde amnesia- it seems improbable that this 'temporary' process would persist over a period of 20-30 years.

Nadel and Moscovitch (1997) presented a model that is similar to Murre's TraceLink model in that it also involves interactions between medial temporal lobe and wider neocortical systems to represent autobiographical memories. Their Multiple-Trace model proposes that the hippocampal complex, "acts as a pointer or index to the neocortical elements needed to provide the detailed content of the experience" (Moscovitch and Nadel, 1999 p. 87). This Multiple-Trace model differs in one important aspect related to the time scale of the hippocampal involvement. They argue that the medial temporal lobe units are needed to recover the memory for as long as it lasts. Over time, as autobiographical memories are retrieved, they are re-coded so that multiple, related memory traces are formed and dispersed over wider areas of the hippocampal complex. If the hippocampal complex is required over a lifetime of a memory, then significant disruption to the system should produce difficulty in recall over a longer time period. They note that the temporal, 'Ribot' gradient often associated with retrograde amnesia can be accommodated within their theory by the argument that older memories are represented by more traces within the hippocampal formation than more recent episodes and thus are less vulnerable to damage which does not completely destroy the whole of the medial temporal lobe region. If this model is correct, a temporary, but severe disruption to this system would be expected to cause extensive retrograde amnesia in combination with the anterograde amnesia. This difficulty recalling autobiographical memories should perhaps only last for as long as the system is disrupted and on return of functioning, recall should be normal once more. This phenomenon is seen with recovery from head injury, in that the period of retrograde amnesia shrinks over time (there is usually still a period of retrograde amnesia, though it might be very short) and also following recovery from Transient Global Amnesia (Evans et al., 1993; Simons and Hodges, 2000). This was not the case with JM, who was left with a permanent retrograde amnesia following the return to normal functioning of anterograde recall. The only other possibility here is that the temporary disruption disturbed the multiple hippocampal traces to an extent that connectivity was lost, without there being significant loss of actual neuronal tissue (as evidenced by brain imaging). The feasibility of this hypothesis, however, is not clear.

The multi-focal neocortical lesions hypothesis

The interpretation of JM's impairment that we previously favoured emphasized the importance of her multi-focal damage. A disorder such as

cerebral vasculitis produces numerous, widely distributed, but discrete lesions. All of the recent models of memory suggest that autobiographical recall is dependent upon interconnected neocortical networks. As noted above, the various models differ in whether or not the medial temporal lobe system plays a temporary (Murre, 1996) or permanent (Nadel and Moscovitch, 1997) role in the retrieval of autobiographical memories. The models of Damasio (1989), Kapur (1997) and Mesulam (1998) need also to be considered. Damasio's time-locked multi-regional retro-activation model suggests that neurone ensembles representing feature fragments converge on local and then non-local zones (including hippocampus and entorhinal cortex) which register the coincidence of feature fragments (in terms of space and time). The model is similar to that of Mesulam (1998) and Kapur (1997), the latter of whom suggests that there are two sets of representation memory units- the 'feature codes' which store the perceptual and other elementary features of past events and 'index codes', which, "provide temporal and spatial frames of reference for each event, and are laid down at the time of initial experience" (p. 126). Kapur proposes that the feature codes are located throughout the cortex, particularly in temporal, parietal and occipital areas, whilst the index codes are stored in the inferior and anterior parts of the temporal lobe and perhaps in rhinal cortices and parahippocampal gyri. Lesions throughout the cortex, even if small, are likely to disrupt the transmission of information from areas coding for feature fragments to, in Damasio's terms, convergence zones (or in Kapur's terminology, index codes) or from one (modality specific) convergence zone to another. This explanation was also favoured by Hunkin and colleagues (1995, 1997) in accounting the focal retrograde amnesia of their case, DH. Along with Hunkin et al. (1995) and Kapur et al. (1996 p. 432), we have argued that, so long as the disruption or destruction to critical tissue is not complete, then new connections can be established and so new memories laid down. An additional factor may be the role of self-repair after widespread damage. Robertson and Murre (1999) suggest that in this situation, spontaneous self-repair will lead to the development of great numbers of faulty connections so that the system regains plasticity at the expense of existing memories.

CONCLUSIONS

Evidence from a number of cases, including JM, suggests that focal retrograde amnesia actually comes in a number of forms and there are a number of different aetiologies and disruptions to cognitive processes that could cause a pattern of impairment which is then referred to as a 'focal' retrograde amnesia.

In some cases of focal retrograde amnesia, a frontal lobe-related retrieval deficit appears to account for the problem (Levine et al., 1998) In others an imagery or visuo-spatial deficit is responsible (Ogden, 1993). In both of these types of case, there is usually some disruption to anterograde learning and thus the impairment is best described as a disproportionate retrograde amnesia.

Focal retrograde amnesia could be said to occur after head injury for some people. Those individuals who experience a head injury, sufficient to induce a

period of unconsciousness and post-traumatic amnesia, but who make a good recovery may still be left with a period of retrograde amnesia. However, this is likely to be short. For this group, the temporary perturbation hypothesis would seem to provide a possible explanation.

Similarly, individuals who have suffered a Transient Global Amnesic attack may be left with a short period of retrograde amnesia (Fisher, 1982; Hodges, 1991; Kapur, 1999). Again here there may be a temporary perturbation of temporal lobe functioning (Evans et al., 1993), which then recovers to leave only a short period of retrograde amnesia.

As noted earlier, a number of cases of focal or disproportionate retrograde amnesia have been described in which the impairment in retrograde recall is combined with intact initial learning, but impaired recall of anterograde information after a longer delay, usually of the order of a few weeks (DeRenzi and Lucchelli 1993, Kapur et al., 1996, Kapur et al., 1997). The relationship between these two types of impairment is, however, not clear. The fact that FRA can occur without evidence of accelerated forgetting (as in the case of JM) suggest that the two phenomenon are not automatically linked. This does not mean, however, that in the cases where both are present that there is not a common explanation. Several of the patients studied have had epilepsy and Blake et al. (2000) demonstrated accelerated forgetting in a group of patients with epilepsy. De Renzi and Lucchelli (1993) argued that both impairments could be conceptualised as consolidation deficits, but only if it is assumed that the FRA is caused by disruption to a consolidation process that must be happening over a period of decades. As discussed earlier under the 'temporary perturbation' hypothesis, this seems an unlikely explanation.

For cases of FRA such as that of JM, who show intact anterograde learning, no accelerated forgetting, and significant impairment of autobiographical retrograde memory, we would argue that multi-focal damage to either lower level features of memories, or, perhaps more likely, the pathways that are required to connect those mnemonic fragments into an event is responsible for the pattern of impairment. This explanation also accounts for why FRA is such a rare condition; most other conditions produce either a significant lesion in one region of the brain (e.g. stroke), or global, but less discrete damage (e.g. head injury). As Kapur (1999) notes, there are many reason why retrograde amnesia has been neglected by researchers and clinicians. Focal retrograde amnesia, which may have little in the way of associated practical impairment (though considerable psychological consequences), is perhaps easy to 'miss,' in clinical practice. Its importance in helping to understand remembering processes, however, suggests that it would be helpful to look out for it, particularly in conditions likely to produce multi-focal discrete lesions.

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