Verbal Encoding Deficits in a Patient with a Left Retrosplenial Lesion

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Abstract

Over the past decade, memory impairments associated with retrosplenial damage have received increased attention among neuroscientists, although the exact role of the retrosplenial region in memory has not been clearly defined. Evidence from lesion studies and functional neuroimaging has implicated the retrosplenial region in verbal episodic memory, temporal ordering of information, and topographical memory. In addition, recent positron emission tomography studies have shown increased activation of the retrosplenial cortex during tasks involving both the encoding and retrieval of episodic information. The objective of this study was to define more clearly the nature of memory impairments observed in retrosplenial amnesia. A 47-year-old amnesic male with a left retrosplenial arteriovenous malformation, and remote memory. Despite normal performance on frontal cognitive tasks, intact memory for remote information, and a superior IQ, this individual exhibited a profound deficit in the encoding of information, evidenced by poor release from proactive interference, poor category clustering on word list recall, poor semantic encoding on a levels of processing task, and mild impairments in temporal ordering. These results imply that the retrosplenial region plays a role in the verbal encoding of information, which contributes to the profound verbal memory impairment reported in previous case studies of patients with retrosplenial damage.

Introduction

In 1987, Valenstein et al. reported a landmark case of a patient with profound amnesia following hemorrhage of an arteriovenous malformation (AVM) in a region involving the retrosplenial cortex and the cingulate bundle. This patient evidenced severe anterograde amnesia and circumscribed retrograde amnesia, with relatively intact intellectual functioning and memory for remote information. Valenstein et al. (1987) concluded that their patient's retrosplenial damage had produced amnesia by disrupting the portion of Papez' circuit which traverses retrosplenial cortex, providing one route from the left hippocampus to the left anterior thalamic nuclei. Several years later, Rudge and Warrington (1991) reported similar memory impairments in nine patients with tumors involving the splenium of the corpus callosum. These authors proposed that the observed amnesia resulted from a disconnection between the frontal and the temporal lobes, due to fornix damage rather than to a thalamohippocampal disconnection, or damage to the retrosplenial cortex itself. To date, the exact anatomical explanation for retrosplenial amnesia remains unclear, although both models seem plausible explanations for the amnesia associated with retrosplenial damage.

Clinical case studies

Since these initial reports, neuroscientists have focused more attention on elucidating the exact nature of memory impairments observed in patients with retrosplenial amnesia. Clinical case studies have shown that patients with retrosplenial damage exhibit verbal and non-verbal anterograde amnesia (Takayama et al., 1991; Katai et al., 1992; Iwasaki et al., 1993; Arita et al., 1995; Yasuda et al., 1997; Sato et al., 1998; Correa et al., 1999), time-limited retrograde amnesia (Iwasaki et al., 1993), topographical amnesia (Cammalleri et al., 1996; Sato et al., 1998), and poor acquisition of temporal information (Bowers et al., 1988; Correa et al., 1999). In addition, some case reports suggest that these memory impairments are material-specific, with loss of verbal episodic memory more profound following left retrosplenial damage and loss of memory for spatial relationships more apparent in patients with right retrosplenial damage (Maddock, 1999). For example, Valenstein et al.'s patient initially presented with both verbal and visual memory deficits associated with his left retrosplenial AVM. However, subsequent testing revealed that verbal tests alone remained consistently impaired, while tests of non-verbal memory,

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with the exception of the Rey–Osterrieth Complex Figure Test (ROCFT), were typically normal. Conversely, Takahashi *et al.* (1997) studied three patients with topographical amnesia resulting from small, focal hemorrhages involving the right retrosplenial region. These patients had intact discrimination and identification of familiar landscapes, but could not remember familiar spatial relationships between two distant locations. No verbal memory impairments were noted in these patients with right retrosplenial damage.

Other studies have described the amnesic syndrome associated with retrosplenial damage as bitemporal in nature. For example, Correa et al. (1999) presented a study of a 41-yearold male with memory deficits secondary to a glioblastoma of the splenium of the corpus callosum and retrosplenial region. Their patient showed a profound impairment in verbal and non-verbal learning and recall, as well as difficulty with the temporal ordering of information. In addition, their patient exhibited characteristics of frontal dysfunction, including perseveration, increased susceptibility to interference, and decreased verbal fluency. Katai et al. (1992) presented the case of a 73-year-old patient with impaired recent memory for both verbal and non-verbal information following a left cerebral infarction in the retrosplenial region. In addition to anterograde amnesia, this patient had severe retrograde amnesia for information up to 2 years prior to the injury. More recently, Gainotti et al. (1998) reported the case of a patient with a bilateral retrosplenial tumor whose memory impairment was characterized primarily by dense retrograde amnesia for personal events and poor visual, but relatively intact verbal learning and recall. The authors note, however, that their case cannot be considered a 'pure' case of retrosplenial amnesia, as the tumor also involved the fornix bilaterally.

In summary, a handful of cases of retrosplenial damage have been reported in the literature over the past decade. These case reports, however, are greatly limited by their anatomical variability (e.g. most involving additional damage to the splenium and fornix) and by relatively non-specific descriptions of the resulting amnesic syndrome.

Positron emission tomography (PET) studies

In addition to studies of patients with focal brain lesions, a growing functional neuroimaging literature provides converging evidence for the role of the retrosplenial area in memory (Shallice *et al.*, 1994; Tulving *et al.*, 1994; Fletcher *et al.*, 1995). Shallice *et al.* (1994) found that the acquisition of episodic memories was associated with activity in both the left pre-frontal cortex and the left retrosplenial area, whereas retrieval was associated with increased activity in the right pre-frontal cortex and pre-cuneus. Similar results were reported by Fletcher *et al.* (1995) in a study of verbal episodic encoding. Tulving *et al.* (1994) found activation of the retrosplenial cortex during encoding of novel pictures, but not familiar ones, suggesting that the retrosplenial region may be one component of a visual/spatial novelty encoding

network in the brain. Similarly, Dolan and Fletcher (1997) have implicated posterior cortex, specifically the left hippocampal formation, in the encoding of novel verbal information.

Based on evidence from case studies and functional imaging, it seems plausible that the left retrosplenial cortex and left hippocampal formation, which are richly and reciprocally connected, may be components of a complex, distributed encoding network for verbal information. It remains unclear from these studies, however, whether the retrosplenial cortex has a specific memory-related function in and of itself, or whether the amnesia results from a disconnection of mesial temporal, pre-frontal, and/or diencephalic structures important in this memory encoding system (Valenstein *et al.*, 1987; Maddock, 1999).

Current case study

The present case study represents an attempt to clarify the nature of the amnesic disturbance due to retrosplenial damage by using well-validated clinical and experimental paradigms in a patient with a discrete left retrosplenial lesion, which spared the fornix and most of the splenium. This is important, as few, if any, studies of retrosplenial damage have been reported in which the fornix and the splenium are intact. We were primarily interested in examining the extent to which our patient was impaired in the encoding and retrieval of verbal information. These parameters were of interest because recent PET research has implicated the left retrospenial region in the encoding of verbal episodic information. In addition, numerous case studies of patients with left retrosplenial damage have shown that these patients demonstrate poor acquisition and temporal ordering of verbal information (Valenstein et al., 1987; Bowers et al., 1988; Correa et al., 1999), which may reflect a more general verbal encoding deficit. Finally, retrieval of verbal information was of interest because we wished to rule out the possibility that poor memory performances were related to impaired retrieval of information.

To examine these parameters, we evaluated the degree to which our patient was impaired on tasks of automatic and directed semantic encoding, temporal ordering of verbal information, and retrieval of autobiographical/remote information. Tasks of automatic semantic encoding require that the subject spontaneously uses semantic cues to facilitate recall performance, without the instruction of the examiner. On the other hand, in directed semantic encoding the examiner instructs the subject to process information at varying levels of analysis (i.e. perceptual, phonemic, or semantic). Although the encoding of information was once conceptualized as a single process, recent views suggest that adequate encoding of new information involves at least two distinct processes (Verfaellie and Cermak, 1991). First, the individual must correctly process the to-be-remembered information. This stage involves the initial semantic analysis of information. Second, the individual must manipulate the results of semantic

analysis in order to permit adequate storage of the information (Verfaellie and Cermak, 1991). Failures during this second stage of encoding are observed in amnesic patients who correctly analyse semantic information, but continue to show memory impairments at recall. These patients do not benefit from their semantic analysis because they are unable to utilize this information in a strategic manner to improve memory performance. In addition to evaluating semantic encoding, temporal ordering of information was of interest because it is believed to reflect another aspect of encoding—the 'time-tagging' of new information in memory—and has been found to be impaired in other patients with retrosplenial damage (Bowers *et al.*, 1988; Correa *et al.*, 1999).

To summarize, we were interested in exploring whether our patient exhibited a deficit in the semantic encoding of information, as well as whether such an impairment represented a breakdown in the initial semantic analysis or subsequent cognitive manipulation of information. Second, we were interested in whether other aspects of encoding, such as temporal ordering of information, were impaired. We hypothesized that our patient would be impaired on tasks which involved the semantic encoding of information, as well as on tasks of the temporal ordering of information in memory. These hypotheses were based on previous PET research, as well as findings from previous case studies of retrosplenial damage. Third, we hypothesized that our patient would not be impaired in the retrieval of remote memories. This hypothesis was based on the assumption that our patient's memory problems were related to poor encoding of information and not to a retrieval deficit.

Case report

LC, a 47-year-old, left-handed college-educated engineer presented to our neuropsychology clinic with complaints of chronic memory impairment, difficulty sustaining attention, and poor concentration. Years earlier he had experienced an acute onset of severe headache pain which lasted for 3 days. LC was admitted to Shands Teaching Hospital on 8 March 1991, where he underwent a cerebral arteriogram and magnetic resonance imaging (MRI), which revealed an AVM medial to the trigone of the left lateral ventricle, filling from the left anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) branches. The arteriogram also revealed minor filling from the MCA on the right. A computed tomography (CT) scan with and without contrast revealed a 5 \times 5 \times 3 cm mass with associated subacute blood. There was no evidence of hydrocephalus. His past medical history and family history were noncontributory.

On admission, LC's vital signs were stable, his temperature was 39°C, and his lungs were clear to auscultation. His medical record states that he was awake, alert, and oriented times three with a normal mental status examination. Speech was fluent with normal repetition. Cranial nerves II–XII were intact and a motor examination was 5/5 for all groups.

Cerebellar examination was within normal limits except for some bilateral end gaze nystagmus noted. Deep tendon reflexes were 2+ and symmetric.

LC received three embolizations of the AVM, followed by his first stereotactic radiosurgery in 1991. He first received embolization of PCA feeders which resulted in a reduction in the volume of the AVM by one third, with a residual opacified nidus of approximately 4×2 cm. Pre- and postcompensation MRI studies demonstrated a residual flow within the AVM nidus. The first radiosurgery involved 1000 rads of radiation to the margin of his AVM through 30 and 16 mm collimators.

CT and MRI performed 6 months post-radiosurgery revealed no definite evidence of further decrease in nidus size or in overall flow through the AVM. A CT scan performed 3 years later (1 January 1994) still revealed a zone of atrophy mixed with areas of dystrophic calcification within the deep portion of the vascular malformation. There was evidence of increased vascular structures even on a non-enhanced scan. There was normal ventricular size and a reasonably normal sulcal pattern, other than areas of encephalomalacia in the region of the nidus of the AVM. An enlarged posterior cerebral artery was evident on the left side, presumably representing the afferent blood supply to the AVM. No acute hemorrhage was identified. LC received a second stereotactic surgery in 1995, to remove the remainder of the AVM. Following the second surgery, MRI revealed a thrombosed AVM with some low flow state adjacent to the trigone of the left lateral ventricle. There appeared to be leukomalacic changes in and around the radiation field associated with the surgeries. In addition, there was minimal damage to the splenium of the corpus callosum at the most lateral extent on the left, although the fornix remained intact bilaterally. Post-surgical neurological examination revealed intact cranial nerves, motor reflexes, and sensory findings. LC showed normal verbal fluency, and an intact orientation, but he was able to recall only one of three objects after a 5-min delay, suggesting an impairment in verbal memory. Figure 1 presents MRIs obtained in 1998 showing the residual of an AVM affecting retrosplenial cortex and subadjacent white matter. Figure 2 shows axial slices depicting the full extent of the retrosplenial lesion mapped according to Damasio and Damasio's (1989) anatomic atlas.

Neuropsychological evaluations

LC reportedly began to experience significant memory problems and progressive difficulties with his job following the second radiosurgery in 1995, leading to his resignation as vice-president of engineering in 1997. As a result of the perceived cognitive changes, LC was referred to our clinic where he was evaluated on three separate occasions. Detailed neuropsychological examination results are shown in Table 1. Formal neuropsychological testing was performed in January 1997 and 2 years later in January 1999. During both evaluations, LC was alert, attentive, and socially appropriate.

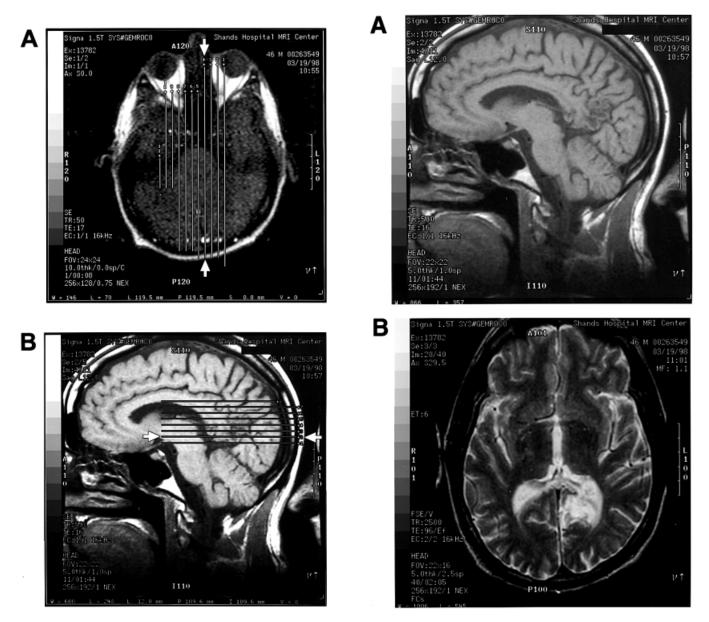


Fig. 1. Magnetic resonance images (T1- and T2-weighted images) taken in June 1998 of residual of an arteriovenous malformation in the left hemisphere with multiple abnormal vessels involving the retrosplenial cortex and subadjacent white matter. (A) T1 sagittal section 5 mm left of midline. (B) T2 horizontal plane extending through the mid-portion of the third ventricle inferior to the splenium of the corpus callosum.

He showed no signs of a thought disorder and conversational speech was fluent and grammatically correct. With the exception of changes in his memory functioning, performances on other tasks of neurocognitive abilities were similar for both evaluations.

Performances during the first evaluation, however, were confounded by the fact that LC reported heavy alcohol intake at the time. Therefore, the degree to which his neuropsychological deficits on the first evaluation were a result of his vascular malformation versus alcohol abuse cannot be determined. According to the patient and spouse report, LC was not drinking alcohol at the time of the second evaluation.

First neuropsychological evaluation

The results of both neuropsychological evaluations are depicted in Table 1. On the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), LC's full-scale IQ was 127 (superior), with a verbal IQ of 134 (very superior) and a performance IQ of 111 (high average). Confrontation naming was intact, and no signs of aphasia were present. In addition, he showed no evidence of spatial neglect or impaired facial recognition. Performances on neurocognitive tasks of executive functioning (Trail Making, Parts A and B, Stroop Interference Test and Auditory Consonant Trigrams) were also intact. The one exception

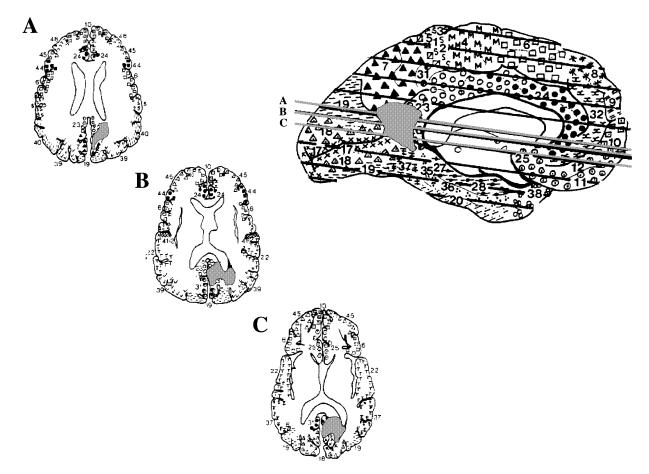


Fig. 2. Axial slices showing the full extent of the retrosplenial lesion mapped according to Damasio and Damasio's (1989) anatomic atlas. The lesion is depicted by the darkened areas.

was a borderline performance on the Halstead–Reitan Booklet Category Test (Halstead, 1947), which measures concept formation and flexibility during novel problemsolving (Spreen and Strauss, 1998).

Examination of memory functions

Verbal memory. LC's immediate recall of prose passages was average (Wechsler Memory Scale-Revised; WMS-R), while his performance after a 30-min delay fell in the low average range. Performances were well below average on a task of verbal list learning [California Verbal Learning Test (CVLT); Delis *et al.*, 1987]. LC's immediate list recall was impaired and he did not appear to benefit from repeated exposure to the list. Delayed free recall was also significantly impaired, as was category cued recall and item recognition. A significant number of intrusions and false positives were also noted across trials.

Non-verbal memory. LC's immediate recall of geometric designs was high average (WMS-R), while his recall of the same figures after a 30-min delay was in the low average range. Non-verbal memory was also significantly impaired on the ROCFT (Osterrieth, 1944). LC was able to copy a

complex figure adequately. However, his approach to the copy was disorganized, and may have led to poor encoding of the design. This is consistent with the fact that his immediate and delayed recall of the same figure were significantly impaired and lacking in detail.

Second neuropsychological evaluation

The results of the second neuropsychological evaluation indicated that LC's non-verbal memory had significantly improved, while his verbal memory remained impaired. On the WAIS-R, LC obtained a full-scale IQ of 134 (very superior)—close to the score obtained in the initial evaluation. His verbal IQ was 148 (very superior) and his performance IQ was 112 (high average). No evidence of spatial neglect was present (Judgment of Line Orientation), and all performances on neurocognitive tasks of executive functioning were intact (Stroop Interference Test, Auditory Consonant Trigrams, Booklet Category Test).

Examination of memory functions

Verbal memory. Consistent with his performance on the first evaluation, LC's immediate recall of prose passages was

Table 1. Summar	y of the neuropsychological da	ta obtained during LC's first and second clinical evaluations
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	29 January 1997		27 January 1999	
	Raw	Scaled score	Raw	Scaled score
WAIS-R				
Verbal IQ	89	134	97	148
Performance IQ	50	111	51	112
Full-scale IQ	139	127	148	134
Language				
Boston Naming Test	59	18		
	Raw	Percentile	Raw	Percentile
Frontal/executive				
Trail Making A	32'	16th		
Trail Making B	70'	31st		
Stroop Interference Test	111	69th	111	69th
Booklet Category Test	73 ers	16th	52 ers	70th
Auditory Consonant Trigrams	3'	67th	3'	86th
Frances Consonant Highans	9'	93rd	9'	80th
	18'	100th	18'	80th
Memory	10	10011	10	oour
WMS-R	25	57.1	21	244
Logical Memory I	25	57th	21	34th
Logical Memory II	14	24th	10	14th
Visual Reproduction I	36	88th	39	98th
Visual Reproduction II	20	21st	34	87th
	Raw	z-score	Raw	z-score
CVLT				
List A total 1–5	38	T = 30	39	T = 31
List A Trial 1	6	-1	4	-2
List A Trial 5	7	-3	9	-2
List B	5	-1	5	-1
List A SDFR	2	-4	3	-3
List A SDCR	9	-1	5	-3
List A LDFR	5	-2	7	-2
List A LDCR	9	-1	8	-2
Semantic cluster	2.2	0	0.3	-2^{2}
Serial cluster	3.0	1	1.2	-1
Recognition hits	10	-3	16	1
False positives	13	5	6	2
Total intrusions	32	5	23	2
	Raw	Scaled score	Raw	Scaled score
ROCFT				
Сору	64	9	63	8
Immediate recall	11	3	26	6
Delayed recall	12	3	23	6

WAIS-R, Wechsler Adult Intelligence Scale-Revised; WMS-R, Wechsler Memory Scale-Revised; CVLT, California Verbal Learning Test; ROCFT, Rey-Osterrieth Complex Figure Test.

SDFR, short delay free-recall; SDCR, short delay cued-recall; LDFR, long delay free-recall; LDCR, long delay cued-recall.

average, while his recall after a 30-min delay was low average. LC's performance on the CVLT was also consistent with his performance on the initial evaluation. LC's immediate list recall was significantly impaired and he did not appear to benefit from repeated exposure to the list. Delayed free recall was also significantly impaired, as was category cued recall. Item recognition, as calculated by recognition hits, appeared normal. LC also continued to exhibit a significant number of false positives in the recognition trial, suggesting a strong positive response bias as opposed to true recognition accuracy. A significant number of intrusions was also noted across trials. In addition, use of semantic clustering was impaired. On both evaluations, LC's best trial performance after repeated exposure to the word list was only 62% recall.

Non-verbal memory. LC's immediate recall of geometric designs on the WMS-R was very superior and his recall after a 30-min delay was superior, suggesting a significant

improvement in non-verbal memory. LC's performances remained impaired on the ROCFT, but were significantly improved relative to the initial evaluation. LC's copy of a complex figure was low average. However, his immediate and delayed recall of the same figure were borderline. Similar to the initial evaluation, his copy and reproductions of the figure were disorganized and lacking in detail.

Experimental procedures

LC returned to our clinic 4 months after his second neuropsychological evaluation at our request to complete additional memory testing. The purpose of this evaluation was to define more clearly the nature of LC's anterograde amnesia using well-validated experimental paradigms of encoding and retrieval. We examined LC's performance on neurocognitive tasks of automatic and directed encoding [e.g. levels of processing (LOP), release from proactive interference] and temporal ordering of information (e.g. temporal ordering for sentences). In addition, we administered tests of remote memory for events (Kortenkamp Remote Memory Test; KRMT) and for personal information (Crovitz Remote Memory Test; CRMT) to determine if LC showed any retrieval deficit or evidence of retrograde amnesia.

Encoding tasks

Release from proactive interference. Release from proactive interference was assessed using Wickens' (1970) category shift manipulation. This paradigm was administered in order to assess LC's automatic use of semantic cues to facilitate memory performance at recall. In this procedure, subjects are presented with eight blocks consisting of five trials of words. Each trial consists of the presentation of three words read aloud by the examiner, followed by a distraction task which requires the subjects to count backwards in threes, beginning with a specified number in order to prevent rehearsal. After the distraction task, subjects are requested to recall the previously heard words. For four of the eight blocks, words in all trials belong to a single taxonomic category. In the other four blocks, the taxonomic category is shifted in the fifth trial. Taxonomic categories include occupations, furniture, body parts, transportation, fruit, clothing, musical instruments, and geographical landmarks. Wickens proposed that if there is a decline in performance across early trials followed by a significant improvement in the shift trial, subjects are engaging in category encoding and 'releasing' from proactive interference. Failure to release from proactive interference, on the other hand, is represented by no improvement in the shift trial and suggests poor semantic analysis of the information.

LC's performance in the shift trials (66% correct) did not differ significantly from his performance in the non-shift trials (58% correct). As can be seen in Fig. 3, LC and agematched controls showed no difference in their performances in the non-shift condition (58 and 60% correct, respectively).

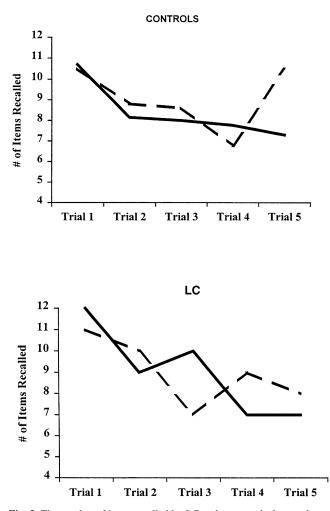


Fig. 3. The number of items recalled by LC and age-matched controls across shift (----) and non-shift (-----) trials of a release from proactive interference paradigm.

For controls, however, the change in semantic class in trial 5 of the category shift condition was associated with a significant increase in recall as compared with the no-shift condition (25% increase). LC did not show a significant increase with the shift condition (8.3% increase). This performance suggests a failure to release from proactive interference, which is likely to reflect poor semantic encoding of the taxonomic information.

LOP. The LOP paradigm (Craik and Lockhart, 1972) was administered in order to determine whether LC would benefit from depth of encoding for verbal information. In this task, the examinee is presented with 36 words on flashcards and is directed to encode each word based on either the word's perceptual (e.g. Is this word printed in upper-case letters?), phonemic (e.g. Does this word rhyme with daisy?), or semantic (e.g. Is this a type of flower?) features. Free recall for the words is assessed after a 20-min delay, followed by a multiple-choice recognition trial. Depth of encoding in this task ranges from very shallow (perceptual) to deep (semantic) analysis of the information. Deeper levels of analysis should

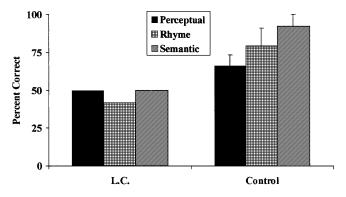


Fig. 4. Performances of LC and age-matched controls on item recognition in a levels of processing task. Error bars represent the standard deviations for the control group.

theoretically produce more elaboration, and stronger memory for information than shallow encoding of information at recall, especially over the long term.

LC's performance on the LOP was significantly impaired relative to a group of eight age-matched controls. LC was able to recall freely only one of the 36 words presented on the LOP after a 20-min delay. His recognition of these words was 50% for the words introduced with a perceptual orienting question, 42% for words introduced with a phonological orienting question, and only 50% for words introduced with a semantic orienting question. In contrast, the control group showed the expected pattern, correctly identifying 66% of the perceptually, 79% of the phonologically, and 93% of the semantically cued words. Recognition performances on the LOP for LC and the control group are shown in Fig. 4.

Temporal memory. To assess LC's ability to encode information in a temporal context, we gave a sentence discrimination task similar to that used by previous investigators (Bowers et al., 1988). A set of eight target sentences is shown (set 1) on flashcards, followed 30 min later by the presentation of a second set of eight different target sentences (set 2). Two minutes later a recognition test is given. For the recognition test, the 16 sentences from the two target sets are randomly intermixed with 16 distractor sentences, and subjects are instructed to state whether the sentences had previously been seen (recognition judgment). If so, they then indicate whether the sentence had occurred in the first or second set of sentences (i.e. temporal order judgment). Each stimulus is shown for a 2-s duration. Two separate scores are obtained for the task-recognition accuracy and accuracy of temporal order judgments. Recognition accuracy is based on the number of targets correctly identified as having been previously presented (true positives) in conjunction with the number of distractors correctly identified as not having been presented (true negatives). Percentage recognition accuracy is then derived from the formula: 'true positives + true negatives/32,' where 32 equals the total number of targets and distractors shown on the recognition test. Accuracy on temporal order judgments is based only on those targets that are correctly identified as having been presented (i.e. true

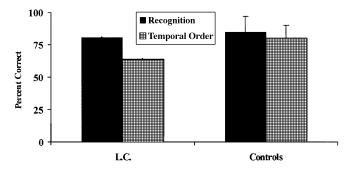


Fig. 5. Percentage of target words recognized by LC and age-matched controls relative to their temporal ordering judgments of the same words. Error bars represent the standard deviations for the control group.

positives). This score is computed from the formula: 'number of correct temporal order judgments/true positives'.

The results of LC's performance on the temporal ordering task are depicted in Fig. 5, beside the performance of the control group. As shown, LC's recognition accuracy was 81%, which is close to that of a control group (mean = 85%, SD = 12.9). In contrast, his temporal order judgments were somewhat lower (64%), falling 1.5 SD below the mean of the control group (mean = 80%, SD = 10.7).

Retrograde memory. The KRMT (Kortenkamp, personal communication) was used to assess LC's memory for information acquired before his illness. The KRMT is a 15-item multiple-choice format that includes questions about worldwide events that received significant media coverage during the 1970s (n = 5), 1980s (n = 5), and 1990s (n = 5). These questions cover events in sport and politics, as well as national disasters that are generally familiar to the American public. LC's performance on the KRMT was within normal limits (95% correct), suggesting intact remote memory for public events.

The CRMT (Crovitz and Schiffmann, 1974) was used to assess LC's memory for personal events occurring throughout his life. The CRMT is an open-ended interview that requires subjects to recall detailed information about specific events that occurred during childhood (age 1-18 years), early adulthood (age 19-30 years), and middle adulthood (age 40-60 years) (i.e. Recall a specific event from your childhood about a birthday party....). Responses on the CRMT are scored qualitatively, according to the degree of detail provided by the subject for each personal event. Responses are also compared across decades to determine if subjects are able to provide equally detailed information about events occurring in each of the age ranges identified. LC's performance on the CRMT suggests intact memory for autobiographical information throughout his life. He was able to recall and elaborate on specific events occurring during childhood and adolescence, young adulthood, and middle adulthood with appropriate detail and affective response. Therefore, LC did not appear to exhibit a generalized or time-limited retrograde amnesia.

Discussion

The results of this case study are largely consistent with our hypotheses and with other cases of retrosplenial amnesia reported in the literature (Valenstein et al., 1987). On the initial clinical evaluation, our patient exhibited severe anterograde amnesia, marked by poor learning and recall of both verbal and visual information. At follow-up, however, LC's memory impairment was primarily for verbal information, which is consistent with his left-sided lesion. The exception was that LC continued to perform poorly on the ROCFT at follow-up. Although this finding suggests residual non-verbal memory impairment, research has shown the ROCFT to discriminate poorly between patients with right versus left hemisphere dysfunction (Barr et al., 1997). This is probably related to the fact that the scoring of the ROCFT is largely influenced by the presence or absence of details within the figure, which is more dependent on intact left hemisphere functioning. Consistent with this interpretation, LC maintained the gestalt of the figure in his reproductions, but omitted many of the details. It is also possible that LC maintained a more subtle visual memory impairment that was detected only by the ROCFT-the more difficult of the two non-verbal tasks with higher organizational demands.

The results of the experimental testing revealed three major findings. First, our patient exhibited a profound deficit in the semantic encoding of information, evidenced by poor release from proactive interference on Wickens' paradigm and poor semantic encoding on a LOP task. These results were complimented by poor semantic clustering on the CVLT evidenced in the clinical evaluations. While LC was able to retain an intact semantic analysis of verbal information (i.e. he was able to answer correctly semantic orienting questions related to verbal stimuli in the LOP paradigm), he appeared unable to utilize the results of this semantic analysis to improve effectively his memory performance. Therefore, our patient exhibited an impairment in the cognitive manipulation of semantic information, suggesting a deficit in the second stage of encoding. Inability to utilize cognitive strategies spontaneously to facilitate encoding of information has been described in patients with frontal lobe damage (Squire, 1982; Shimamura, 1995). On the other hand, patients with frontal pathology are generally able to employ semantic encoding strategies when instructed by the examiner (Butters and Cermak, 1980), as this method facilitates retrieval of the to-be-remembered information. Our patient, however, was impaired on tasks of both automatic and directed encoding, perhaps suggesting involvement of both frontal and hippocampal systems.

Our second major finding from the experimental testing was that LC showed a mild impairment in the temporal ordering of verbal information. While his ability to order verbal information in memory was less impaired than his use of semantic encoding strategies, he performed correctly in only 64% of the trials, compared with the 80% accuracy obtained by age-matched control subjects. Previous researchers have found similar temporal ordering impairments in patients with retrosplenial damage (Bowers *et al.*, 1988; Correa *et al.*, 1999) and have hypothesized that this defect occurs in the early stages of acquisition, such that incoming stimuli are not initially encoded or 'time-tagged' in terms of their temporal properties. It is interesting that our patient also exhibited a significant number of intrusions on the CVLT, a finding which may also reflect an inability to 'timetag' information according to discrete episodes (i.e. list A versus list B words). This finding is consistent with the hypothesis that our patient exhibited a rather generalized deficit in the encoding of new verbal information captured by tests of semantic and temporal encoding.

Our third major finding was that LC was unimpaired in the retrieval of remote memories. This suggests that LC's retrosplenial damage resulted in a severe anterograde amnesia, with no apparent retrograde amnesia or retrieval deficit. Evidence against a retrieval deficit hypothesis of LC's impairments is also reflected by the fact that category cueing and item recognition on the CVLT did not facilitate LC's recall of verbal episodic information.

In summary, the results of this case study suggest that the retrosplenial region plays a role in memory functioning, specific to the encoding of new verbal information. Our patient was impaired in initial 'time-tagging' of information, as well as semantic encoding at the level of cognitive manipulation, and not at the level of the initial semantic analysis. Therefore, our case is consistent with previous cases of amnesia following retrosplenial damage, in addition to recent functional imaging research implicating the retrosplenial cortex in verbal episodic encoding. It is noteworthy that PET studies have cited activated voxels during verbal episodic encoding in Brodmann's (BA) 29, as well as in areas 23 and 31, which the authors refer to as the retrosplenial portion of the posterior cingulate gyrus (Shallice et al., 1994; Fletcher et al., 1995). Our patient's most extensive damage was to BAs 29 and 30, although the damage extended more anteriorly and superiorly into BAs 23 and 31. Brodmann describes areas 29 and 30 as human retrosplenial cortex [Brodmann (1994) cited in Morris et al. (2000)], which is most consistent with the location of our lesion. Other researchers, however, also include areas 23 and 31 as part of retrosplenial cortex (Fletcher et al., 1995; Maddock, 1999). Therefore, our patient's damage did overlap with activations from PET research, although expert opinions are divided as to whether activations in areas 23 and 31 should be defined as in the retrosplenial cortex (Vogt et al., 2000).

Valenstein *et al.* (1987) suggested that lesions of the cingulum and retrosplenial cortex may cause amnesia by disrupting input from the anterior nucleus of the thalamus to the hippocampus. Von Cramon and Schuri (1992) further proposed that disruption of a septal–hippocampal route including the posterior cingulum, the supracommissural hippocampus and the proximal fornix may contribute to cases involving more persistent forms of amnesia. Additionally, Rudge and Warrington (1991) have argued that amnesia may

result from a disconnection between the frontal and temporal lobes, due to fornix damage, which prevents the cognitive mediational memory system (within the frontal lobes) from providing meaningful input to the medial temporal memory system.

The results of our study suggest that retrosplenial damage causes severe and persistent anterograde amnesia, characterized by poor temporal ordering and semantic encoding in the absence of identifiable frontal lobe pathology. While a frontotemporal disconnection may have contributed to our patient's verbal amnesia, he performed normally on tests of frontal executive ability which are believed to rely on dorsolateral pre-frontal cortex (Fuster, 1997). Second, our patient demonstrated poor recognition memory more characteristic of patients with medial temporal dysfunction (Scoville and Milner, 1957) than of patients with frontal lobe impairment. Third, LC did not benefit from category cueing as would be expected following frontal lobe pathology or possibly from a frontotemporal disconnection. Therefore, we feel that LC's amnesia more likely reflects a disconnection of diencephalic from medial temporal structures, similar to the mechanisms described by Valenstein et al. (1987) in their original paper.

Other factors may have also contributed to LC's severe anterograde amnesia. It is possible that LC's alcohol use contributed largely to the memory impairments observed in the first evaluation. This explanation, however, is unlikely as his profile closely resembles the profiles from other case reports of patients with retrosplenial damage (Valenstein *et al.*, 1987; Correa *et al.*, 1999). Furthermore, his verbal memory deficits were markedly impaired at the time of the second and third evaluations, despite reported long-term abstinence from alcohol. As mentioned, frontal lobe involvement cannot be ruled out as dorsolateral pre-frontal cortex is richly connected with medial temporal structures and retrosplenial cortex and may have contributed to features of our patient's amnesic syndrome.

Finally, we cannot completely rule out the possibility that slight damage to the splenium did not contribute to LC's memory impairment. Although the fornix was intact bilaterally, there was mild damage to the most lateral extent of the splenium on the left. Few studies of memory impairment following splenial damage, however, have been reported in the literature. Rudge and Warrington (1991) studied nine patients with splenial tumors and reported severe memory deficits, as well as impairments in visual perception, in all patients. This study was limited, however, by significant anatomic variability in the placement of the tumors and the authors concluded that it was actually damage to the fornix subjacent to the splenium that accounted for the persisting amnesia. To our knowledge, no studies have been reported in the literature of amnesia following damage restricted to the splenium of the corpus callosum. Additionally, damage to the splenium in our patient was very minimal, making this hypothesis even more unlikely.

It is important to highlight that the fornix was intact

bilaterally in our patient. This information is paramount as the fornix, which has often been implicated in memory functioning itself, is most often damaged in patients with retrosplenial lesions. Fornix involvement in memory would seem likely as this structure forms a vital bridge between medial temporal and medial diencephalic regions implicated in anterograde amnesia (Aggleton and Brown, 1999). Research from the animal literature (Squire and Zola-Morgan, 1991), as well as from the human clinical literature (Garcia-Bengochea and Friedman, 1987), however, has not provided convincing evidence that fornix damage produces amnesia. In fact, Aggleton and Brown (1999) provide a review of the animal and human literature and conclude that the number of studies of fornix damage with intact memory functioning far outnumber the cases in which fornix damage has been associated with amnesia. Other researchers, however, have found evidence of memory impairments in patients with fornix damage (Heilman and Sypert, 1977; Hodges and Carpenter, 1991). The present case provides evidence that not all of the memory deficits observed following retrosplenial damage can be attributed to damage of the fornix. Nevertheless, additional case reports of patients with circumscribed retrosplenial damage, as well as additional functional imaging research are needed to provide more conclusive evidence regarding the role of retrosplenial cortex in memory and cognition.

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References

- Aggleton JP, Brown MW. Episodic memory, amnesia, and the hippocampalanterior thalamic axis. Behavioral and Brain Sciences 1999; 22: 425–44.
- Arita K, Uozumi T, Ogasawara H, Sugiyama K, Ohba S, Pant B *et al.* A case of pineal germinosa presenting with severe amnesia. No-Shinkei-Geke 1995; 23: 271–5.
- Barr WB, Chelune GJ, Hermann BP, Loring DW, Perrine K, Strauss E *et al.* The use of figural reproduction tests as measures of nonverbal memory in epilepsy surgery candidates. Journal of the International Neuropsychological Society 1997; 3: 435–43.
- Bowers D, Verfaellie M, Valenstein E, Heilman KM. Impaired acquisition of temporal information in retrosplenial amnesia. Brain and Cognition 1988; 8: 47–66.
- Butters N, Cermak L. Alcoholic Korsakoff's syndrome: an informationprocessing approach to amnesia. New York: Academic Press, 1980: 69–95.
- Cammalleri R, Gangitano M, D'Amelio M, Raieli, V, Raimondo D, Camarda R. Transient topographical amnesia and cingulate cortex damage: a case report. Neuropsychologia 1996; 4: 321–6.
- Correa DD, Relkin NR, Ruge MI, Schiff N, DeAngeles LM, Hirsch J. Retrosplenial amnesia: a multimodal investigation. Poster session presented at the annual meeting of Cognitive Neuroscience, Washington, DC, 1999.
- Craik F, Lockhart R. Levels of processing: A framework for memory research. Journal of Verbal Learning and Verbal Behavior 1972; 11: 671–84.
- Crovitz HF, Schiffmann H. Frequency of episodic memories as a function of their age. Bulletin of Psychological Society 1974; 4: 517–8.
- Damasio H, Damasio AR. Lesion analysis in neuropsychology. New York: Oxford University Press, 1989.
- Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test, research edition. Manual. San Antonio: Psychological Corporation, 1987.
- Dolan RJ, Fletcher PC. Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature 1997; 388: 582-5.

- Fletcher PC, Frith CD, Grasby PM, Shallice T. Brain systems for encoding and retrieval of auditory verbal memory: An *in vivo* study in humans. Brain 1995; 118: 401–16.
- Fuster JM. The prefrontal cortex: anatomy, physiology, and neuropsychology of the frontal lobe. New York: Lippincott-Raven, 1997.
- Gainotti G, Almonti S, Di Betta AM, Silveri MC. Retrograde amnesia in a patient with retrosplenial tumour. Neurocase 1998; 4: 519–26.
- Garcia-Bengochea F, Friedman WA. Persistent memory loss following section of the anterior fornix in humans. Surgical Neurology 1987; 27: 361–4.
- Halstead WC. Brain and intelligence. Chicago: University of Chicago Press, 1947.
- Heilman KM, Sypert GW. Korsakoff's syndrome resulting from bilateral fornix lesions. Neurology 1977; 27: 490–3.
- Hodges JR, Carpenter K. Anterograde amnesia with fornix damage following removal of IIIrd ventricle colloid cyst. Journal of Neurology, Neurosurgery, and Psychiatry 1991; 54: 633–8.
- Iwasaki Ś, Arihara T, Torii H, Hiraguti M, Kitamoto F, Nakagawa A *et al.* A case of splenial astrocytoma with various neuropsychological symptoms (in Japanese). No-To-Shinkei 1993; 45: 1067–73.
- Katai S, Maruyama T, Hashimoto T, Yanagisawa N. A case of cerebral infarction presented as retrosplenial amnesia. Rinsho-Shinkeigaku 1992; 32: 1281–7.
- Maddock RJ. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. Trends in Neuroscience 1999; 22: 310–6.
- Morris R, Paxinos G, Petrides M. Archetectonic analysis of the human retrosplenial cortex. Journal of Comparative Neurology 2000; 421: 14–28.
- Osterrieth R. Le test de copie d'une figure complexe. Archives de Psychologie 1944; 30: 206–356.
- Rudge P, Warrington EK. Selective impairment of memory and visual perception in splenial tumours. Brain 1991; 114: 349–60.
- Sato K, Sakajiri K, Komai K, Takamori M. A patient with amnestic syndrome with defective route finding due to left posterior cerebral artery territory infarction. No-To-Shinkei 1998; 50: 69–73.
- Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry 1957; 20: 11–21.
- Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak SJ, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature 1994; 368: 633–5.
- Shimamura A. Memory and frontal lobe dysfunction. In: Gazzaniga M, editor. The cognitive neurosciences. Massachusetts: MIT Press, 1995: 803–13.
- Spreen O, Strauss E. A compendium of neuropsychological tests, 2nd edn. New York: Oxford University Press, 1998.
- Squire LR. Comparisons between forms of amnesia: Some deficits are unique to Korsakoff's syndrome. Journal of Experimental Psychology: Learning, Memory, and Cognition 1982; 8: 560–71.
- Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991; 253: 1380–6.
- Takahashi N, Kawamura M, Shiota J, Kasahata N, Hirayama K. Pure topographic disorientation due to right retrosplenial lesion. Neurology 1997; 49: 464–9.
- Takayama Y, Kamo H, Ohkawa Y, Akiguchi I, Kimura J. A case of retrosplenial amnesia. Rinsho-Shinkeigaku 1991; 31: 331–3.
- Tulving E, Markowitsch HJ, Kapur S, Habib R. Novelty encoding networks in the human brain: Positron emission tomography data. Neuroreport 1994; 5: 2525–8.
- Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, Watson RT. Retrosplenial amnesia. Brain 1987; 110: 1631–46.
- Verfaellie M, Cermak LS. Neuropsychological issues in amnesia. In: Martinez JL, Kesner RP, editors. Learning and memory: a biological view, 2nd edn. San Diego: Academic Press, 1991.
- Vogt BA, Absher JR, Bush G. Human retrosplenial cortex; where is it and is it involved in emotion. Trends in Neuroscience 2000; 23: 195–7.
- Von Cramon DY, Schuri U. The septo-hippocampal pathways and their relevance to human memory: A case report. Cortex 1992; 28: 411–22.
- Wechsler D. Wechsler Adult Intelligence Scale-Revised. Manual. Cleveland: Psychological Corporation, 1981.
- Wickens D. Encoding categories of words: An empirical approach to meaning. Psychological Review 1970; 77: 1–15.
- Yasuda Y, Watanabe T, Tanaka H, Tadashi I, Akiguchi I. Amnesia following infarction in the right retrosplenial region. Clinical Neurology and Neurosurgery 1997; 99: 102–5.

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Verbal encoding deficits in a patient with a left retrosplenial lesion

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Abstract

Over the past decade, memory impairments associated with retrosplenial damage have received increased attention among neuroscientists, although the exact role of the retrosplenial region in memory has not been clearly defined. Evidence from lesion studies and functional neuroimaging has implicated the retrosplenial region in verbal episodic memory, temporal ordering of information, and topographical memory. In addition, recent positron emission tomography studies have shown increased activation of the retrosplenial cortex during tasks involving both the encoding and retrieval of episodic information. The objective of this study was to define more clearly the nature of memory impairments observed in retrosplenial amnesia. A 47-year-old amnesic male with a left retrosplenial arteriovenous malformation was examined on neurocognitive tasks of automatic and directed encoding, temporal ordering of information, and remote memory. Despite normal performance on frontal cognitive tasks, intact memory for remote information, and a superior IQ, this individual exhibited a profound deficit in the encoding of information, evidenced by poor release from proactive interference, poor category clustering on word list recall, poor semantic encoding on a levels of processing task, and mild impairments in temporal ordering. These results imply that the retrosplenial region plays a role in the verbal encoding of information, which contributes to the profound verbal memory impairment reported in previous case studies of patients with retrosplenial damage.

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Primary diagnosis of interest

Verbal anterograde amnesia

Author's designation of case

Key theoretical issue

- Verbal encoding deficit following damage to the left retrosplenial cortex
- Episodic memory impairments resulting from disruption of Papez circuit

Key words: retrosplenial amnesia; verbal encoding deficit; Papez circuit; episodic memory

Scan, EEG and related measures

Magnetic resonance imaging (T1- and T2-weighted sequences)

Standardized assessment

Wechsler Adult Intelligence Scale-Revised (WAIS-R), Boston Naming Test, Trail Making Test (A and B), Stroop Interference Test, Halstead–Reitan Booklet Category Test, Auditory Consonant Trigrams, Wechsler Memory Scale-Revised (WMS-R; selected subtests), California Verbal Learning Test (CVLT), Rey–Osterrieth Complex Figure Test (ROCFT)

Other assessment

Release from proactive interference (Wickens, 1970), levels of processing (LOP; Craik and Lockhart, 1972), Kortenkamp Remote Memory Test (KRMT), Crovitz Remote Memory Test (CRMT; Crovitz and Schiffmann, 1974)

Lesion location

• Left retrosplenial area and subadjacent white matter, left splenium

Lesion type

Hemorrhagic arteriovenous malformation (AVM)

Language

English