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Anterograde and retrograde amnesia in a person with bilateral fornix lesions following removal of a colloid cyst

Amir Poreh a,∗, Gordon Winocurb, c, d, Morris Moscovitch e, f, Matti Backong, Elinor Goshen g, Zvi Ram g, Zeev Feldman g

a Cleveland State University, Department of Psychology, 2121 Euclid Avenue, Cleveland, OH 44115, United States.
b Rotman Research Institute, Baycrest Centre, Toronto, Canada
c Department of Psychology, Trent University, Canada
d Departments of Psychology and Psychiatry, University of Toronto, Canada
e Rotman Research Institute and Department of Psychology, Baycrest Centre, Toronto, Canada
f Department of Psychology, University of Toronto, Canada
g Chaim Sheba Medical Center, Israel

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Abstract

AD, a 45-year-old man, presented with a severe and global anterograde amnesia following surgery for removal of a colloid cyst. Structural neuroimaging confirmed bilateral lesions to the fornix and a small lesion in the basal forebrain. Testing for remote episodic memory of autobiographical events, and for remote semantic memory of personal and public events, and of famous people, revealed that AD had a severe retrograde amnesia for autobiographical episodes that covered his entire lifetime, and a time-limited retrograde amnesia for semantic memory. Because the fornix and basal forebrain lesions disrupted major afferent and efferent pathways of the hippocampus, it was concluded that the integrity of the hippocampus and its projections are needed to retain and/or recover autobiographical memories no matter how old they are. By contrast, hippocampal contribution to semantic memory is time-limited. These findings were interpreted as consistent with Multiple Trace Theory, which holds that the hippocampal system is essential for recovering contextually rich memories no matter how old they are, but is not needed for recovering semantic memories.

Keywords: Hippocampus; Anterograde amnesia; Medial temporal lobes; Episodic (autobiographical) memory; Semantic memory

1. Introduction

It is widely accepted that bilateral damage to the hippocampus and related medial temporal lobe (MTL) structures, the perihinal, entorhinal and parahippocampal cortices, leads to severe anterograde amnesia. However, there is considerable debate regarding the effects of damage to this region on remote memory. The debate turns on several points: (1) the location and extent of the lesion; (2) the temporal extent and severity of the deficit, and (3) the type of memory which is affected. With respect to the first two points, studies show that damage restricted to the MTL, which includes the hippocampus, leads to remote memory loss, the severity and extent being determined by the location and size of the lesion (Aggleton and Brown, 1999). Others argue that the lesion must extend to extra-MTL structures to produce a temporally extensive retrograde amnesia (Bayley, Gold, Hopkins, & Squire, 2005; Bayley, Hopkins and Squire, 2003). With respect to the type of memory deficit in patients with damage limited to the MTL, there is an emerging consensus that memory for specific personal information (episodic memory) is severely affected, with memory for general knowledge and factual information about the world and oneself (semantic memory) being relatively spared (for review see Moscovitch, Rosenbaum et al., 2005). This evidence is consistent with Multiple Trace Theory which posits that the hippocampus and related MTL structures are always needed for retention and recovery of contextually rich information, which is the hallmark of episodic memory. On the other hand, memories that are independent of the context in which they were acquired, such as semantic memories, can be mediated through extra-hippocampal structures (Nadel & Moscovitch, 1997; Rosenbaum, Winocur, & Moscovitch, 2001).
It has been difficult to evaluate the contribution of the hip-
locampus to remote memory because rarely, if ever, is damage 
restricted to this structure in humans. Furthermore, when it is, 
the hippocampal lesion is smaller than in patients whose lesions 
extend beyond this structure. In other words, we do not have 
a case where most of the hippocampus is destroyed without 
also encroaching on extra-hippocampal structures. We address 
these issues in a patient, AD, with bilateral lesions to the fornix, 
a major pathway linking the hippocampus to basal forebrain 
and diencephalic regions implicated in memory. The fornix is 
the primary efferent projection from the hippocampus to the 
manifold bodies and anterior thalamic nuclei, and also contains 
afferent cholinergic tracts from the septal nuclei in the basal 
forebrain to the hippocampus. To a lesser extent, other basal 
forebrain pathways project via the fornix to entorhinal cortex. 
Basal forebrain projections via the temporal stem, amygdala, 
and entorhinal cortex to hippocampus are relatively unaffected 
by fornix transaction (Gaffan, Parker, & Easton, 2001; Mesulam, 
Mufson, Levey, & Wainer, 1983; Ridley, Baker, Harder, & 
Pearson, 1996; Selden, Gitelman, Salamon-Murayama, Parrish, 
& Mesulam, 1998). Thus, AD’s lesion interrupts major hip-
locampal output and the primary cholinergic input into the 
hippocampus, without affecting the structural integrity of the 
hippocampus and other MTL structures themselves. Although 
there are some efferent projections from the hippocampus to 
adjacent MTL structures via other pathways, AD’s fornix lesion 
allows us to examine memory function while selectively remov-
ing a major contribution of the hippocampus and entorhinal 
cortex.

Bilateral damage to the fornix is known to impair antero-
grade memory, although there is considerable variability in the 
degree of memory loss that is reported (see reviews by 
Aggleton et al., 2000; Spiers, Maguire, & Burgess, 2001). Although 
some authors report that ablation of the anterior column of the 
fornix does not induce memory dysfunction (Bauer, Tobias, & 
Valenstein, 1993), others suggest that in certain cases, particu-
larly after the removal of a colloid cyst, anterior fornixhealthy 
cortex may cause severe anterograde amnesia (Aggleton et al., 2000; 
Carmel, 1985; Easton; Ridley, Baker, & Gaffan, 2002; Gaffan, 
1994; Gaffan, Gaftan, and Hodges, 1991; Garcia-Bengochea 
& Friedman, 1987; Maccarini, Cockburn, Anslow, & Gaffan, 
1995; Sweet, Talland, & Ervin, 1959), as it did in our patient. 
There are several reasons for such variability including, once 
again, the size and location of the lesion, type of memory tested, 
and whether the lesion is unilateral or bilateral (for review 
see Gaffan & Gaffan, 1991). There are far fewer studies on 
remote memory, but the available evidence suggests some loss, 
although the type and extent of remote memory loss is not 
well documented (D’Esposito, Verfaellie, Alexander, & Katz, 
1995; Hodges & Carpenter, 1991; Park, Hahn, Kim, Na, & 
Huh, 2000; Spiers et al., 2001). Based on the purported effects 
of fornix lesions on anterograde memory, we predicted that 
remote episodic memory would be severely impaired. We also 
predicted that remote semantic memory would be relatively spared as 
has been reported in patients with fornix lesions (Spiers et al., 
2001), and in patients with MTL/hippocampal lesions (for 
reviews see Moscovitch, Rosenbaum et al., 2005; Moscovitch, 
Westmacott et al., 2005; Moscovitch, Nadel, Winocur, Gilboa, 
& Rosenbaum, 2006).

2. Case report

AD, a right-handed 45-year-old male, was referred to the 
Neurosurgery Department of a large Israeli medical center with 
a 1-month history of excruciating headaches. An MRI T1 study 
revealed a typical high-density non-enhancing colloid-cyst situ-
ated in the anterior part of the third ventricle, with a mild degree 
of obtructive hydrocephalus (see Fig. 1). The patient had no 
complaints of memory loss, and continued working up to the 
time of the surgery. Physical examination revealed no abnor-
malities.

Surgery was performed 1 month following his initial refer-
ral. A right frontal transcortical approach to the left Foramen 
of Monro, allowed the neurosurgeon access to the cyst. A typ-
ical dense colloid cyst was identified embedded in the anterior 
portion of the third ventricle, attached to its base. The cyst was 
removed via the Foramen of Monro with no unusual operative 
complications. AD’s recovery in the immediate post-operative 
period was normal but soon after, he began to suffer from dia-
betes insipidus and became extremely confused.

Within 48 h of surgery, AD was interviewed by the first and 
second authors. He was unsure why he was hospitalized, could 
not recognize his neurosurgeon, and was unable to retain simple 
verbal material (such as three words) for more than a few min-
utes. AD’s remote memory was also impaired. He was unable 
to recall any autobiographical events that occurred in the past 
20 years. Although he recognized his wife and children, AD 
was unable to draw the exterior part of his house even though 
he had helped design it. His drawing of it was limited to a 
three-dimensional cube. After a 20-min bedside evaluation, the 
interviewers stepped out of the room. Upon their return, AD 
noted that he knew them, as he had met them “a few years ago”.

Two weeks following the operation, AD was re-evaluated and, 
although there was some general improvement, it was clear that 
he was severely amnesic.

2.1. Structural neuroimaging and lesion location

MRI brain scans were conducted 2 months post-surgery using 
an Elekta Prestige T2 machine with 5 mm thick scans. These 
scans showed no damage to the hippocampal and related medial 
temporal lobe (MTL) structures. An additional MRI was per-
formed on the same machine, with 3 mm thick scans (TE 30/80, 
TR3000, 22 cm POV). An initial inspection of the resultant MRI 
scans documented a complete transection of the left anterior 
portion of the third ventricle, attached to its base. The cyst was 
removed via the Foramen of Monro with no unusual operative 
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formed on the same machine, with 3 mm thick scans (TE 30/80, 
TR3000, 22 cm POV). An initial inspection of the resultant MRI 
scans documented a complete transection of the left anterior 
portion of the fornix at the level of the anterior commissure, 
damage to the left anterior commissure, and a tiny infarct to the 
caudate nucleus on the right (Fig. 1). Later consultations with 
Dr. Fuqiang Gao from Sunnybrook Hospital in Toronto and 
Dr. Michael Alexander of Harvard Medical School confirmed 
these observations. Additional damage to the right anterior col-
umm of the fornix was identified which, given the limitations of 
the scans, was estimated to affect 75% of the tract, just ante-
rior to the third ventricle above the anterior commissure. The
Fig. 1. Presurgical MRI scan of AD showing the colloid cyst (A-1). AD's postsurgical MRI and AD's bilateral fornix lesions can be seen in axial and coronal views of T1-weighted MRI's for the left fornix complete transection (A-2) and right fornix disruption of at least 75% (A-3). T2-weighted axial images further exemplify the fornix disruptions (A-4). AD’s basal forebrain lesion can be seen in axial and coronal views (A-3) exemplifying the minimal extent of the lesion which involves midline basal forebrain nuclei on the left and possibly minimal right sided damage.
medial part of the left basal forebrain showed a hypointense signal on the T1 and hyperintense signal on the T2, suggesting a very small lesion to the left medial basal forebrain, affecting the midline cholinergic nuclei of the basal forebrain, and sparing the lateral ones. SPECT brain scans using an Elcint XZ122 were also obtained. These scans were interpreted as showing a significant bilateral hypoperfusion of the mesial temporal regions.

2.2. Neuropsychological evaluation and anterograde memory

A month after the initial evaluation, AD became anxious and agitated about his condition. His wife noted that he often cried and wanted her to stay by his side. She also noted that each time he woke up, he reported that he was in a dream-like state. His MMPI-2 profile was elevated, with his scores on the Anxiety and Depression scales being $T = 66$ and $67$, respectively. A formal neuropsychological evaluation was then conducted on an outpatient basis.

Neuropsychological test results are summarized in Table 1. The patient’s intellectual performance, as measured by the WAIS-R, was in the higher end of the average range (IQ = 109). AD’s verbal abilities, as measured by the Boston naming test (BNT; Kaplan, Goodglass, & Weintraub, 1978), the controlled word association test (FAS) and semantic fluency (Benton, Hamsher, & Sivan 1983), were in the normal range. On the Wisconsin card sorting test, another measure of executive functioning, AD performed within the normal range for his age, achieving five categories (WCST, Berg, 1948; Heaton, 1981) but he tested in the borderline range for number of perseverative errors. Informal testing did not reveal any dyslexic or dysgraphic errors. He had no difficulty in performing complex arithmetic tasks. Working memory, as measured by both digit and spatial span, was normal, as were visual constructional abilities, as measured by the Rey Osterrieth copy figure test (ROCF, Osterrieth, 1944).

In contrast to his relatively intact intellectual functioning, AD exhibited severe verbal and visual memory deficits. He showed no improvement with repeated presentation on the auditory verbal learning test (AVLT; Rey, 1958) and following interference, recalled only 1/6 of the words he had previously recalled. After a 30 min delay, he had no recollection of the task. On long-term recognition, his responses were at chance. On the Wechsler memory scale revised (WMS-R, Wechsler, 1981) story recall subtest, he scored in the impaired range even on immediate recall. After a 3 min delay, he was unable to recall having heard the story. When he was asked to recall the ROCF after a 3-min delay, AD’s score was 0.

A follow-up neuropsychological evaluation was carried out 9 months post-surgery. During this testing, AD was also re-administered the MMPI-2 test. His profile indicated a heightened anxiety level and moderate depression. The results of the neuropsychological assessment are presented in Table 1.
Fig. 2. Autobiographical memory interview (AMI) percent scores at childhood, early adulthood and adulthood. Percentages were calculated based on a maximum score of 21 for semantic memory, and 9, for episodic memory.

It can be seen that AD’s anterograde amnesia persisted. His performance in other cognitive domains, including language, executive and working memory, also remained essentially unchanged.

2.3. Remote memory

AD’s remote memory for public and autobiographical events was assessed to determine the nature and extent of his retrograde amnesia. Memory for faces and public events was assessed using the famous Israeli faces and famous Israeli public events tests developed by the first author. Items were drawn from commonly available books, scanned into PowerPoint presentation using a color scanner, and presented using a portable computer. Whenever AD could not answer a question, the examiner provided him with several multiple choice options.

Autobiographical memory was assessed by the Autobiographical Memory Interview (AMI, Kopelman, Wilson, & Baddeley, 1989) and a set of 16 family photographs that were provided by AD’s daughter. All the stimuli were presented using a portable computer. The AMI consists of two sub-scales, Personal Semantic and Autobiographical Incidents, that sample memories from three time periods: childhood (ages 0–18), early adulthood (ages 18–30), and recent (within the past 5 years). The personal semantic sub-scale probes memory for general personal information such as names of friends and teachers, locations of schools attended, etc. The maximum score for each time period is 21 points. The Autobiographical Incidents sub-scale includes questions about specific events that require temporal and spatial contextual information for each incident. Three such incidents, such as “first day at work”, are sampled at each time period with each incident receiving a maximum of 3 points, depending on the descriptive richness of the response and its specificity as to time and place.

Fig. 2 depicts the results of the AMI. AD exhibited a general impairment in remote memory that was more severe for autobiographical incidents than for personal semantics. On the personal semantic sub-scale, AD showed a gradient in retrograde memory loss, in that the childhood score was within the normal range, whereas his early adulthood score indicated significant loss at 3 months which had recovered by 9 months. Scores for the recent time-period reflected an extensive anterograde memory deficit for personal semantics. Consequently, it is likely that memory for the most recent events draws on episodic memory as well as semantic knowledge. By contrast, memory for autobiographical episodes was severely impaired for the recent, and early adulthood periods, with borderline impairment of childhood memories. Interestingly, his childhood scores were elevated by two highly significant and emotional events that he recounts often and may constitute “personal folklore” (Cermak, 1984; Cermak & O’Connor, 1983) rather than true episodic memory.

On tests of famous faces and public events, AD was asked to name the person in the picture or identify the event during which the picture was taken. Whenever AD could not answer the question, he was prompted by a series of multiple choice options. For faces, there were 6, 6, and 7 faces from the 1970s, 1980s, and 1990s, respectively. For events, the corresponding numbers were 7, 6 and 7. He scored within the normal range for all time periods dating from the 1970s to the present. Performance on these tests was compared to that on a test of autobiographical memory in which he had to describe episodes depicted in 16 family photographs, 4, 6 and 6, for each decade. For each photograph, he was asked to provide details as to when the event occurred and who participated in the event. As seen in Fig. 3, he performed poorly on these tests relative to his performance on the famous faces and public events tests. We note, however, that he provided general semantic information related to the pictures (see below) without remembering the episodes to which they referred. His wife performed well on all of the measures and correctly identified more than 90% of the pictures. Below is a summary of some of his responses:
AD showed poor recall and poor recognition on the RAVLT, primarily because of an elevated false alarm rate. The impaired recognition differs from Aggleton et al.'s (2000) report that patients with bilateral lesions to the fornix were only impaired on recall. Studies of animals with surgical lesions to the fornix have revealed the same pattern of preserved item recognition (e.g. Aggleton & Brown, 1999; Gaffan, Shields, & Harrison, 1984; Zola-Morgan, 1989) but impaired recognition of the same items when they were embedded in unique contexts (Gaffan, 1994). The deficit was increased when the basal forebrain was implicated (Gaffan et al., 2001). The reason for the discrepancy in AD's results is not clear but it may be that AD tried to rely on general contextual cues rather than familiarity to support recognition.

By extension, the same arguments can be made with respect to retrograde amnesia following MTL damage. Two general patterns of retrograde amnesia have been reported in such patients. In one, there is a temporal gradient with recent memories being more severely affected, and very remote memories being spared, regardless of whether the memory is semantic or episodic. In the other, there is temporally extensive and severe retrograde amnesia, often dating back to early childhood, for episodic memory but a milder and temporally graded retrograde amnesia for semantic memory which is based more on familiarity (Fuji, Moscovitch, & Nadel, 2000; Moscovitch, Rosenbaum et al., 2005; Moscovitch, Westmacott et al., 2005; Moscovitch et al., 2006). AD's retrograde amnesia conforms more closely to the second of the two patterns.

On the AMI, AD showed a temporally graded retrograde amnesia for personal semantics with early childhood memories being spared, and a more severe and temporally extensive deficit for autobiographical episodes. He had no autobiographical memories dating as far back as early adulthood, and had only a few, impoverished memories for early childhood. As we noted, for the latter period, his scores were elevated by two highly significant and emotional events that had been well-rehearsed and effectively had come to exist as semantic memories (Cermak, 1984; Cermak & O'Connor, 1983).

The results from the famous faces, famous public events, and family photos tests support this interpretation. Unlike the AMI, in which personal semantics may be contaminated by autobiographical episodes, the first two of the above tests are less prone to that confound. We found that, on the public events and faces test, AD scored normally at all the remote time periods, even the most recent ones, further indicating that remote semantic memory is not dependent on the hippocampal system. These findings also suggest that the temporal gradient for semantic memory observed in other patients with MTL damage may arise either from damage to extra-hippocampal structures, or from contamination by attempts to use episodic information related to the more recent events.

By contrast, on the family photos test, AD had a retrograde amnesia that extended to early childhood with no temporal gradient. The absence of a gradient on this test is especially informative because the nature of the test diminishes the possibility that well-rehearsed memories would be produced. Unlike the AMI, the memories elicited by the photos were not self-selected.
such, they had to be based on reinstatement of autobiographical experiences in their spatial and temporal contexts rather than on "family folklore" (Cermak, 1984; Cermak & O’Connor, 1983).

Bayley et al. (2005) proposed that temporally extensive retrograde amnesia in MTL patients occurs only when the damage extends to lateral neocortex. Our results do not support this interpretation. Despite having no neocortical damage and small lesions to the fornix and basal forebrain area, AD’s retrograde amnesia for autobiographical episodes is temporally extensive and severe. It follows that the MTL, and the hippocampus in particular, are crucial for recovering autobiographical episodes, no matter how remote, and may also contribute temporarily to recovery of semantic memory. While there have been reports of patients with spared autobiographical memories following lesions restricted to MTL (Bayley et al., 2005), other investigators have found the amnesia to be far more extensive (Cipolotti et al., 2001; Moschovitch et al., 2006). The reason for these discrepancies has yet to be determined.

In addition to his fornix lesions, AD also has a small basal forebrain lesion. It is unlikely that this lesion alone caused his severe amnesia for the following reasons: (1) unilateral discrete lesions to the basal forebrain tend to produce modality specific (i.e. visual or verbal) deficits (Abe, Inokawa, Kashiwagi, & Yanagihara, 1998; Goldberg, Schuri, Gromminger, & Arnold, 1999; Morris, Bowers, Chatterjee, & Heilman, 1992), whereas AD had both visual and verbal anterograde memory deficits. (2) Retrograde memory loss is minimal or non-existent following discrete basal forebrain lesions (Abe et al., 1998; Goldberg et al., 1999; Hashimoto, Tanaka, & Nakano, 2000; Morris et al., 1992). (3) Finally, the precommissural columns of the fornix are the primary cholinergic routes from the basal forebrain to the hippocampus, with less extensive projections to neighboring MTL cortices (Easton et al., 2002; Morris et al., 1992).

Given AD’s bilateral fornix lesions, no additional effect of basal forebrain lesions on hippocampal function is likely. The results of the SPECT scan, which show hypo-perfusion only in the MTL, are broadly consistent with this interpretation. However, it should be noted, that the basal forebrain lesion may exacerbate the effects of the fornix lesion (Gaffan et al., 2001). In this case, the only contribution that the basal forebrain lesion may have made to AD’s performance is an increased susceptibility to false alarms in recognition, and intrusions in recall (Abe et al., 1998; Goldberg et al., 1999; Hashimoto et al., 2000; Morris et al., 1992). The important point to emphasize here is that only remote memory for autobiographical episodes was severely affected, whereas semantic memory was relatively spared. Although MTL extra-hippocampal structures such as the perirhinal cortex also receive cholinergic input from the basal forebrain, these are restricted to allocortical rather than neocortical regions, and they receive additional cholinergic input from lateral basal forebrain structures which were intact in AD. The relatively spared semantic memory believed to be mediated by them suggests that their function is sufficiently preserved.

The present findings add to the growing body of evidence supporting specialization within the MTL, with the hippocampus being crucial for re-experiencing episodic events (recollection) and extra-hippocampal structures, such as the entorhinal and perirhinal cortex, for familiarity (Aggleton & Brown, 1999; Eichenbaum, 2001). Our finding that autobiographical memories, which rely on recollection, are impaired, whereas familiarity-based semantic memories are spared, indicate that this view applies as much to remote memory as to anterograde memory. These findings, together with converging evidence from other studies on humans (e.g. see Gilboa, Winocur, Grady, Hevenor, & Moschovitch, 2004; Moschovitch, Rosenbaum et al., 2005; Moschovitch, Westmacott et al., 2005; Moschovitch et al., 2006) and animals (Frankland & Bontemp, 2005; Rosenbaum et al., 2001; Winocur, Moschovitch, Fogel, Rosenbaum, & Sekeres, 2005), provide the basis for an emerging view, consistent with Multiple Trace Theory, that re-experiencing contextually rich memories are dependent on the hippocampal system no matter how old they are, whereas recovery of semantic memory can be accomplished independently of it (see Moschovitch, Rosenbaum et al., 2005; Moschovitch, Westmacott et al., 2005; Nadel & Moschovitch, 1997; Rosenbaum et al., 2001).

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