Hippocampal Contributions to Recollection in Retrograde and Anterograde Amnesia

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ABSTRACT: Lesions restricted to the hippocampal formation and/or extended hippocampal system (hippocampal formation, fornix, mammillary bodies, and anterior thalamic nuclei) can disrupt conscious recollection in anterograde amnesia, while leaving familiarity-based memory relatively intact. Familiarity may be supported by extra-hippocampal medial temporal lobe (MTL) structures. Within-task dissociations in recognition memory best exemplify this distinction in anterograde amnesia. The authors report for the first time comparable dissociations within recognition memory in retrograde amnesia. An amnesic patient (A.D.) with bilateral fornix and septal nuclei lesions failed to recognize details pertaining to personal past events only when recollection was required, during recognition of episodic details. His intact recognition of generic and semantic details pertaining to the same events was ascribed to intact familiarity processes. Recollective processes in the controls were reflected by asymmetrical Receiver's Operating Characteristic curves, whereas the patient's Receiver's Operating Characteristic was symmetrical, suggesting that his inferior recognition performance on episodic details was reliant on familiarity processes. Anterograde and retrograde memories were equally affected, with no temporal gradient for retrograde memories. By comparison, another amnesic person (K.C.) with extensive MTL damage (involving extra-hippocampal MTL structures in addition to hippocampal and fornix lesions) had very poor recognition and no recollection of either episodic or generic/semantic details. These data suggest that the extended hippocampal system is required to support recollection for both anterograde and retrograde memories, regardless of their age.

KEY WORDS: remote memory; retrograde amnesia; recollection; generic memories; hippocampus

INTRODUCTION

Patients with extensive damage to the medial temporal lobe (MTL) show deficits on recall and recognition tests of anterograde memory (Scoville and Milner, 1957; Milner, 1972; Yonelinas et al., 2002). One view of MTL function maintains that the hippocampus and neighboring extra-hippocampal MTL structures are required for acquisition and retention of all declarative memories with the extent of deficit determined by the amount of damaged tissue (Squire, 1992; McClelland et al., 1995; Murre, 1996; Kapur and Brooks, 1999; Kopelman and Kapur, 2001; Squire et al., 2004). Others have suggested that distinct subregions within the MTL have dissociable memory functions (Eichenbaum et al., 1994; Aggleton and Brown, 1999). According to one such view, the hippocampal formation (CA fields, dentate gyrus, and subiculum) is specifically implicated in recollective aspects of memory retrieval (Aggleton and Brown, 1999; Yonelinas et al., 2002; Fortin et al., 2004), whereas extra-hippocampal MTL structures (perirhinal, entorhinal, and parahippocampal cortices) are sufficient to support familiarity-based memory judgments, but not recollection (Aggleton and Brown, 1999; Yonelinas et al., 2002). Recollection is the process required for the recall of associative elements of knowledge or specific contextual details of a previous event (Norman and O'Reilly, 2003) that allow one to reexperience or relive the past (Tulving, 1983, 2002), whereas familiarity involves memory decisions based on the match between the retrieval cue and memory representations, in the absence of a recollective experience (Norman and O'Reilly, 2003). Thus, patients with lesions limited to the hippocampus are severely impaired on tests of recall, which typically entail recollection. However, such patients are impaired on tests of recognition if recollection is required but not if the test can be performed on the basis of familiarity (Holdstock et al., 2002; Mayes et al., 2002; Holdstock et al., 2005; Barbeau et al., 2005b; but see Reed and Squire, 1997; Buffalo et al., 1998; Stark and Squire, 2001; Stark et al., 2002).

In the animal literature, these distinctions are captured by contrasts between relational/configural or context-rich memories on the one hand, and nonrelational or item-specific memory on the other (Rudy and Sutherland, 1989; Eichenbaum et al., 1994; Norman and O'Reilly, 2003; Fortin et al., 2004). Like humans, animals with lesions restricted to the hippocampus are impaired only on tests of the former type (for a review see Aggleton and Brown, 1999; but see Squire et al., 2004 for an opposing view). For example, rats with hippocampal lesions are impaired in forming and retrieving context-rich representations, but not in making item-

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specific associations (Winocur, 1992, 1997). It has recently been shown that rats with hippocampal lesions, like humans, are specifically impaired on recollective processes (Fortin et al., 2004). To our knowledge, no one has examined whether these distinctions within recognition memory also apply to retrograde memories.

In this paper, we show for the first time that recollection is selectively impaired in remote recognition memory as it is in anterograde memory in a patient, A.D. (Poreh et al., 2006), with severe memory problems resulting from a bilateral lesion to the fornix and septal nuclei. The fornix is a critical pathway that connects the hippocampus to the diencephalon and, through it, to other cortical regions. It contains both afferent cholinergic tracts from septal nuclei and the primary efferent projections from the hippocampus to the mammillary bodies and anterior thalamic nuclei (Aggleton and Brown, 1999). By contrast, fornical pathways to and from extrahippocampal MTL structures are extremely sparse. A.D.'s lesion to the septal nuclei further deprives the hippocampal formation of its cholinergic input, while sparing cholinergic input from the horizontal limb of the diagonal band of Broca and nucleus basalis of Meynert to the rest of the cortex (Mesulam, 2000; Parent and Baxter, 2004). Thus, A.D., by virtue of his lesion, which effectively isolates the hippocampus from other limbic and diencephalic memory structures, can provide crucial information about the unique role of the extended hippocampal system in retrograde amnesia (RA), independently of other MTL structures.

Studies of humans and animals with lesions to the fornix provide important support for the distinctive role of the hippocampus in recalling specific events in anterograde memory (Gaffan, 1994; McMackin et al., 1995; Aggleton and Brown, 1999; Aggleton et al., 2000; Easton et al., 2002). In humans, Aggleton and collegues (2000) have shown that patients with bilateral lesions to the fornix were more impaired on tests of recall than on tests of recognition that relied on familiarity. When familiarity could not be used as a cue to distinguish targets from foils on recognition tests, fornix patients were severely impaired. Furthermore, on a delayed matching to sample task, simple recognition was intact in fornix patients. However, severe impairments were observed when the stimuli were set in their own unique background or scene, i.e., when recollection of a unique context was required to perform the recognition task. Studies of animals with surgical lesions to the fornices have revealed the same pattern of preserved item recognition (e.g., Gaffan et al., 1984; Zola-Morgan, 1989) but impaired recognition of the same items when they were embedded in unique contexts (Gaffan, 1994).

There have only been a handful of studies of the effects of fornix lesions on retrograde memory (Hodges and Carpenter, 1991; D'Esposito et al., 1995; Park et al., 2000). Retrograde memory was judged to be relatively preserved in comparison with anterograde memory, but, importantly, none of these studies investigated differences between processes of recollection and aspects of remote memory such as general familiarity or between episodic context-rich memory and decontextualized self-related knowledge. In this study, we address this deficiency by comparing free recall, cued recall, and recognition tests of anterograde and retrograde autobiographical memory. Within recognition, we distinguish between memory based on recollection and memory based on general familiarity. As previously reported (Poreh et al., 2006), on tests of recall, A.D. exhibited severe anterograde and retrograde episodic memory deficits and graded retrograde memory impairment for personal semantics. Our autobiographical recognition task demonstrated that his memory performance was largely dependent on familiarity, which allowed him normal recognition of semantic/generic details, but could not support recognition of episodic details which depends on recollective processes.

An additional question addressed by this study is whether the deficit in retrograde episodic memories (and hence recollective processes) extends to all memories regardless of their age, or whether recent memories are affected more than remote ones. Both patterns have been reported in patients with MTL damage, but the reason for the discrepancy is still unknown. Some investigators have attributed the extent and severity of RA to the size and location of the lesion to hippocampal and extra-hippocampal structures. They argue that restricted lesions lead to a temporally graded RA for all declarative memories in accordance with the unitary functional view of the MTL system mentioned earlier (Squire, 1992; Squire et al., 2004). Extensive RA with no temporal gradients is obtained only following damage to lateral neocortical structures. Other investigators, however, have posited that the extent and severity of RA depend not only on the type of lesion, but crucially also on the type of memory that is tested. They draw a distinction between episodic and semantic memories, with the former being dependent on the MTL, and the hippocampus in particular, regardless of age, and the latter benefiting from the MTL for a period following acquisition, after which they can exist independently of this region (Nadel and Moscovitch, 1997). One possibility explored in the present study is that the dependence of episodic memories on the hippocampus regardless of their age stems from a deficit in the recollective processes required for their retrieval, rather than from their unique content per se. That is, extensive RA should be observed independent of the memory's age on all tests that have a recollective component.

If lesions restricted to the hippocampus cause specific deficits in recollective aspects of retrograde recognition memory, as it does in anterograde amnesia (AA), it would suggest that the hippocampus performs similar functions during retrieval of remote memories as it does during acquisition and retrieval of recent memories. By testing recognition, we also circumvent problems associated with motivation and retrieval that may confound results obtained from tests of free and cued recall in amnesia. A.D.'s performance was compared with that of healthy matched controls and with that of patient K.C. who has extensive bilateral MTL lesions, which included hippocampal and perihippocampal areas (Rosenbaum et al., 2005). We predicted that A.D., whose fornix damage affected only the hippocampal component of the MTL, would be impaired only on tests requiring recollection, whereas K.C., whose damage extends to

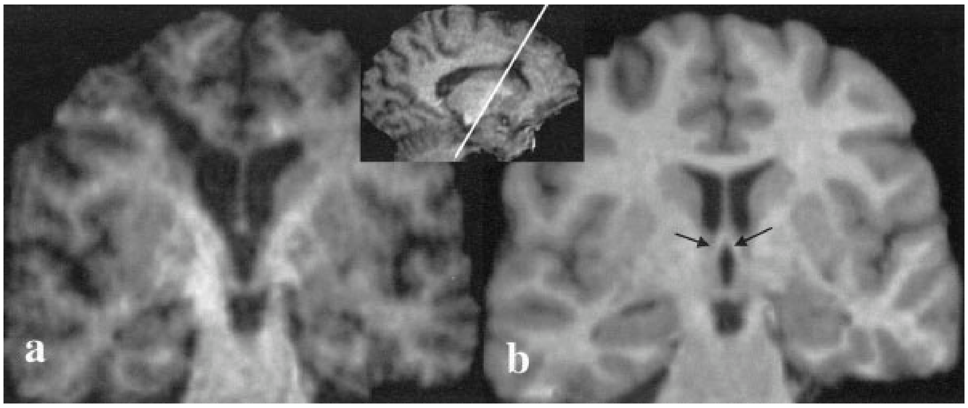

FIGURE 1. MRI 3D-T1 scans of A.D. (a) and an age-matched normal control (b) passing through the anterior fornix [black arrows in (b)] in coronal oblique sections. The two scans were coregistered to each other and oriented parallel to the long axis of the surgical pathway at the same section indicated by the line inside the inset picture in the sagittal plane. The fornix cannot be seen in (a) compared with the corresponding location as shown in (b), indicating severe injury.

extra-hippocampal structures, would be impaired on all tests of autobiographical memory.

PARTICIPANTS

Patient A.D.

A.D. was 51 years old at the time of testing. Four years earlier, in 1999, he underwent surgery for removal of a colloid cyst in the third ventricle. Clinical presurgical neurological presentation included seizures, headaches, dizziness, and nausea. Presurgical magnetic resonance imaging (MRI) demonstrated a typical T1 high-density nonenhancing colloid-cyst situated in the anterior part of the third ventricle, with a mild degree of obstructive hydrocephalus (Poreh et al., 2006). The cyst was removed via a transcortical approach. MRI images 6 months postsurgery showed hypointense tracts from the right frontal region to the anterior part of the third ventricle, representing the stereotactic paths. Coronal images showed that the left anterior part of the fornix was completely disrupted at the level immediately posterior to the anterior commissure. The right anterior fornix was judged to be severely disrupted (approximately 75%) just anterior to the third ventricle above the anterior commissure. It also appeared smaller than normal on both axial and coronal views. The medial part of the left basal forebrain showed hyperintensity on T2 images and hypointensity in T1, suggesting involvement of the midline cholinergic basal forebrain nuclei (septal nuclei). No other structural damage was evident; however, single photon emission computed tomography images acquired at the time revealed bilateral mesial temporal hypoperfusion (Poreh et al., 2006).

For the purpose of the present study, a new set of images was acquired using a 3T GE Signa Horizon scanner. Scans were affected by movement artifacts resulting from A.D.'s tendency to wake up not knowing where he was, and needing constant reminders of the exam. To allow better assessment of the extent and location of damage in A.D., an age- and sex-matched 3D-T1 MRI was warped to the ACPC aligned 3D-T1 MRI of A.D., illustrating the findings by comparison with normal anatomy. Images showed that the colloid cyst was completely removed from the anterior third ventricle region by the stereotactic surgical procedures. A lesion, consistent with postsurgical encepholomalacia from the stereotactic pathway, with low T1 and high T2 signal intensity originated from the right anterior superolateral frontal region, passed through medial surface of the right anterior caudate, entered the right frontal horn of the lateral ventricle, and extended to the anterior inferior third ventricle. Along the stereotactic pathways, a coronal MRI (3D-T1, 0.86-mm slice thickness) revealed disruptions of the left and right anterior fornix at the level of the anterior commissure (Figs. 1 and 2). Demyelinization of the fornices was observed compared with the scan performed 6 months postsurgery (Poreh et al., 2006), as well as mild cortical and hippocampal atrophy. In addition, the anterior commissure (Fig. 3a) was disrupted and the midline septal nuclei severely damaged (Fig. 3a). A lesion showing low T1 and high T2 signal intensity was seen in the vertical limb of the diagonal band of Broca of the left basal forebrain, suggesting injury to this region as well (Fig. 3c).

Before the surgery, A.D. worked as a security officer in a large organization, and prior to that, he served as an officer in the army for more than 20 years. He has 12 years of formal education and military training in practical engineering. A.D.'s clinical picture several weeks after surgery was characterized by severe depression (Poreh et al., 2006). At the time of the present testing, his depression was controlled pharmacologically and his functional status (with regard to Activities of Daily Living, employment, etc.) greatly improved following rehabilitation, which may also have contributed to his current relatively stable, mood. Formal assessment demonstrated minimal to mild levels of depression (BDI score of 17). The severe amnesia observed is thus unlikely the result of A.D.'s depression.

Neuropsychological assessment at the time of the present investigation largely confirmed the findings obtained several months after his surgery. A.D.'s intellectual performance was within the average range, as determined by the Raven's Standard Progressive Matrices (total score: 31; 50th percentile). His language skills were also well

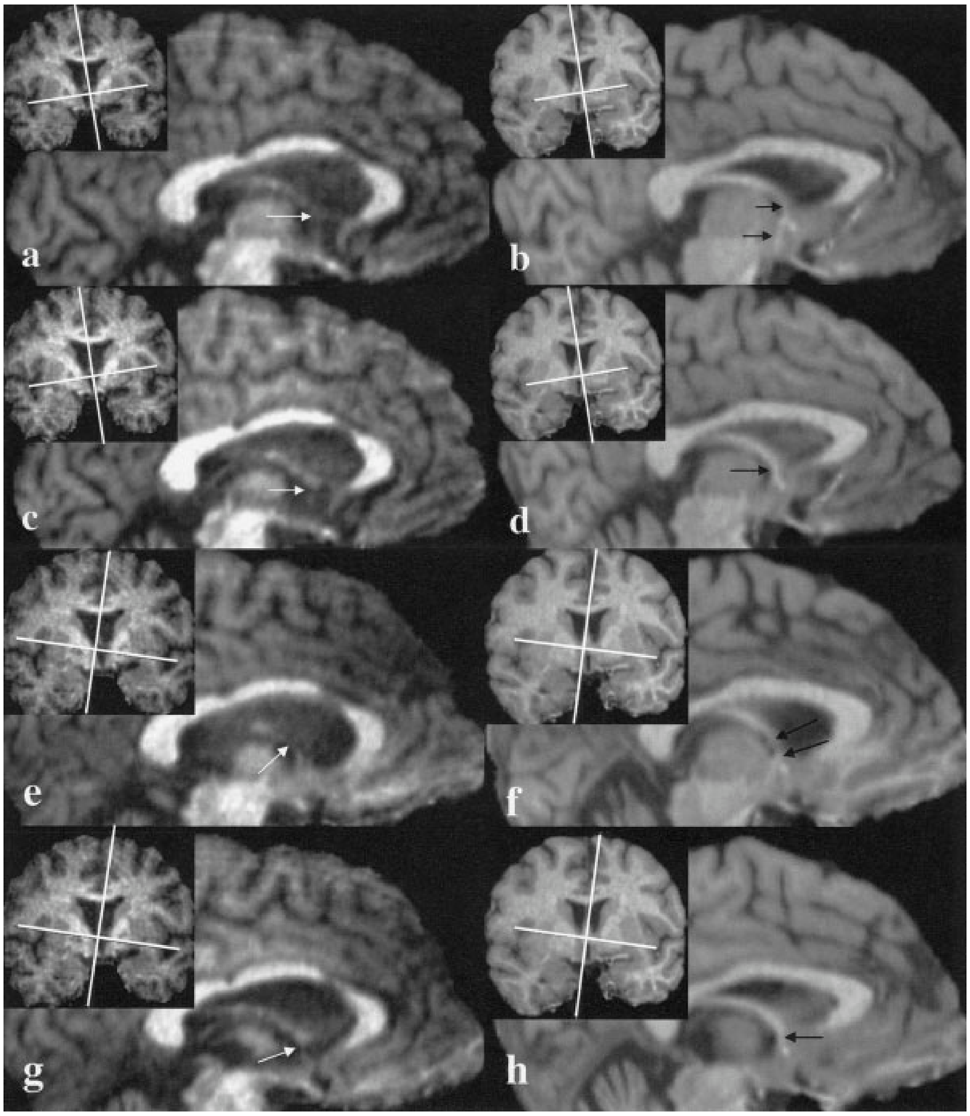

FIGURE 2. MRI 3D-T1 scans of A.D. (left hand column) and an age-matched normal control (right hand column) passing through the vertical axis of the left anterior fornix [black arrows in (b) and (d)] and the right anterior fornix [black arrows in (f) and (h)] in the sagittal oblique sections. The scans of the two subjects were coregistered to each other at the sections indicated by the vertical lines inside the inset pictures in the coronal plane. The complete disruption of the left and right anterior fornix in A.D. is demonstrated (white arrows) by comparison with the corresponding locations of NC.

preserved, and a previously noted reduced performance on verbal fluency had resolved (phonemic fluency: $Z = -0.79$; semantic fluency: $Z = -0.9$). There were also no deficits on attentional/executive functioning (Stroop interference score: $Z = -0.26$; Trails Making Test ratio score: $Z = -0.96$; Digit span: Scaled score = 11), although his performance was somewhat slower on more complex tasks (e.g., Trails part *A*: $Z = 0.45$; part B: $Z = -1.06$).

His performance on tests of anterograde memory depended on the method of testing (i.e., recall vs. recognition) and on duration of delay, but not on the modality of the material (i.e., visual vs. verbal). For example, his immediate memory for paragraphs was average ($Z = -0.41$), but he was unable to recall any detail from the stories after a delay of twenty minutes ($Z = -2.75$). His delayed recognition, on the other hand, was better: 60% correct in a four-choice forced choice paradigm (no norms available). Similarly, during acquisition trials of the Rey Auditory Verbal Learning Test, A.D.'s performance was in the average to low-average range, reflecting mostly his intact immediate span. By contrast, his delayed performance was impaired. Delayed recognition, however, was better but still in the borderline range (see Table 1). The same pattern was revealed in visual memory, using the Rey-Osterieth complex figure test. On this test, A.D.'s scores were average on copy, low average on immediate testing, and impaired on delayed recall, but with a normal delayed recognition score (Table 1). His total correct score on the Benton Visual Retention Test was also impaired ($Z = -2.46$), as was the number of errors on this test ($Z = -4.31$). Note that this pattern is different from the one reported by Poreh et al. (2006) 5 years prior to the current testing. At that time, A.D. displayed chance performance on the Auditory Verbal Learning Test recognition, primarily

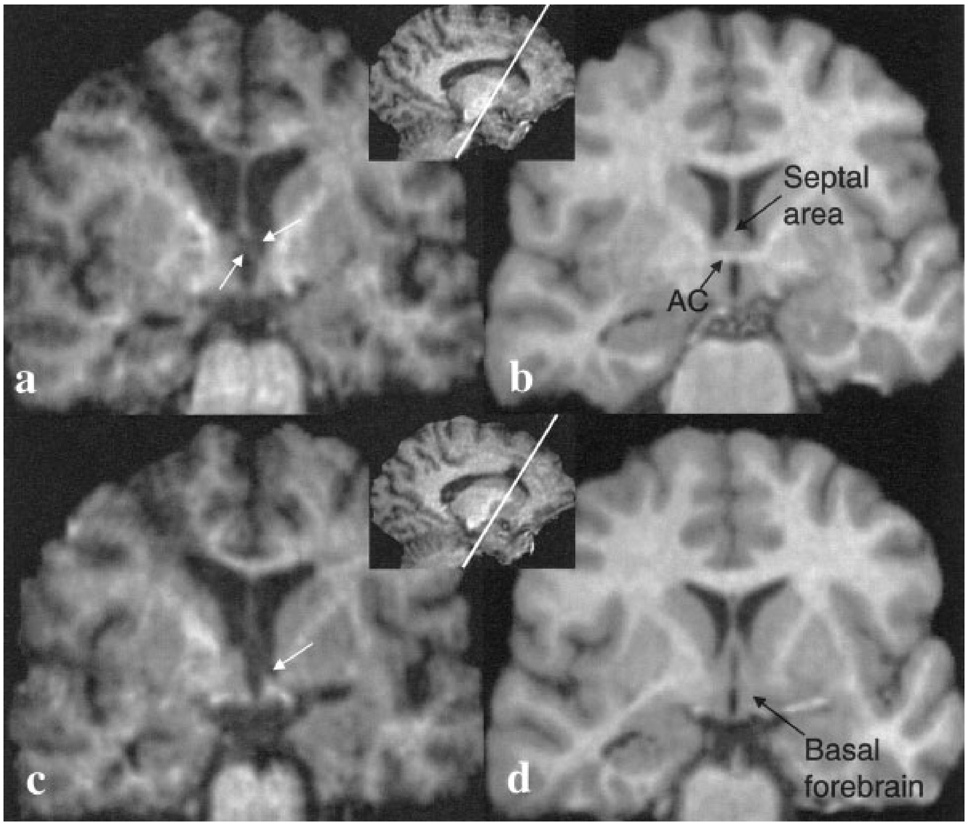

FIGURE 3. MRI 3D-T1 scans of A.D. (left) and an aged-matched normal control (right) passing through the septal area and the anterior commissure [black arrows in (b)] and vertical limb of the diagonal band of Broca the basal forebrain [black arrows in (d)] in coronal oblique sections. The septal area and the anterior commissure cannot be seen in (a) (white arrows) and the left medial basal forebrain shows low signal (white arrow) compared with the corresponding structure in (d), indicating injury. The two scans were coregistered to each other and oriented parallel to the long axis of the surgical pathway at the same section indicated by the line inside the inset pictures.

because of a high false alarm rate. The reason for this difference in performance is not clear, but may be related to altered response criteria used by A.D. because of the prolonged duration of his memory impairment and an improved ability to make familiarity-based memory judgments.

Patient K.C.

Patient K.C. was 52 years old at the time of the study; he has 16 years of formal education. Twenty-two years ago, at the age of 30, he was involved in a motorcycle accident and suffered a severe closed head injury (72 h loss of consciousness) that left him densely amnesic. K.C.'s severe AA and RA have been extensively studied, establishing his inability to acquire declarative (explicit) memories and his loss of premorbid memories which affects primarily remote episodic information, while personal and general semantic information are relatively spared (Tulving et al., 1988; Rosenbaum et al., 2000; Westmacott et al., 2001; Rosenbaum et al., 2005). K.C.'s neuropathology is quite extensive and diffuse (Tulving et al., 1988; Rosenbaum et al., 2000; Rosenbaum et al., 2005) as is to be expected by the nature of his injury. His brain lesions include almost complete obliteration to the right and left hippocampi and extensive atrophy of his left and right parahippocampal gyri (more pronounced on the left) (Fig. 4). The mammillary bodies, the septal area, and the fornices are also noticeably atrophic. Neocortical damage includes a large lesion in left occipital-temporal cortex, which extends into retrosplenial cortex, as well as lesions to medial occipital–temporal–parietal, and left frontal–parietal regions. Neuropsychological assessment conducted 6 months before the present study (Rosenbaum et al., 2005) revealed largely invariant levels of performance compared with previous reports, attesting to the stability of K.C.'s neuropsychological status. His intellectual performance is average, and equivalent on both performance and verbal subsections of the test. His language skills are also well preserved, except for a markedly reduced performance on verbal fluency. His performance on tests of anterograde memory is at floor, both in the verbal and visual domains, and regardless of method of testing (recall, cued recall, recognition, Table 1). In particular, he was unable to retain any information over delays as short as 20 min, and his immediate memory was also extremely poor; he retained only a few items on paragraph recall, and performed at chance on recognition memory for faces and words.

Controls

Ten healthy adults (four males), matched for age and education to patients A.D. and K.C., served as controls for the first part of the study (free and cued recall). The average age of the

TABLE 1.

Patients' Z Scores on Standardized Memory Tests Including the AMI

	A.D.	K.C.
Rey auditory verbal learning test		
Immediate recall	−0.24	−0.75
Sum of trials 1–5	−**2.01**	−**1.98**
Delayed recall	−**3.85**	−**3.84**
Delayed recognition	−1.41	−**5.46**
Rey's complex figure test		
Copy	−0.32	−1.19
Delayed recall	**−2.65**	**−3.16**
Delayed recognition	0.81	**−3.81**
AMI (semantic/event)(Kopelman et al., 1990)		
Childhood	1.5/−**1.92**	−1.0/−**4.23**
Early adulthood	**−2.25/−5.38**	**−2.75/−3.84**
Recent (AA)	**−2.75/−4.28**	**−4.3/−5.76**

Performance is reported in *Z* scores compared with published norms. Scores reflecting significant impairment (>1.64) are bolded. AMI, autobiographical memory interview; AA, Anterograde Amnesia.

control group was 50.85 [standard deviation (SD) = 6.3], with an average of 14.2 years of education (SD = 2.66). For the autobiographical recognition test, six males matched for age and education to the patients served as controls. Their average age was 51.5 (SD = 2.07) and average years of education was 14 (SD = 1.67). Control participants had no history of substance abuse, neurological or psychiatric abnormalities.

MATERIALS AND METHODS

Part 1: Free and Cued Recall of Autobiographical Memory

Modified Crovitz personal remote memory test

This test, which was only administered to A.D., requires participants to recall personally experienced events from any remote time period when cued with 10 high frequency words (Crovitz and Schiffman, 1974): angry, break, dog, find, play, happy, letter, lonely, make, river. Incomplete responses were prompted with general prompts ("tell me more," "can you think of a specific instance") and the patient was asked to date the memory. Responses were scored on a 0–3 scale, depending upon the degree of specificity to time and place as described by several previous authors who have used this method (Zola-Morgan et al., 1983; Hodges and Carpenter, 1991). Two independent raters scored the memories (interrater agreement: 0.83) The average of the two scores was taken as A.D.'s score for the present report. A.D.'s performance was compared with that of healthy controls, as well as to that of the healthy controls described by Hodges and Carpenter (1991).

Autobiographical memory interview

This test was administered and scored according to the procedures described in the test manual. The autobiographical memory interview (AMI) (Kopelman et al., 1990) consists of two subscales (Personal Semantic and Autobiographical Incidents) and probes memory from three time periods: childhood (ages 0–18), early adulthood (ages 18–30), and recent (within the past 5 years). In the Personal Semantic subscale, participants are probed for information such as names of friends and teachers, locations of schools attended, home addresses, dates, and so forth. Each time period had a maximum score of 21 points. The Autobiographical Incidents subscale includes questions about specific events that occurred during each of the three time periods. Participants are required to provide temporal and spatial contextual information for each incident in order to receive full credit. Three such incidents are sampled at each time period, and specifications such as "first day at work" are used as probes in some cases, whereas in other cases the probes are more open-ended allowing for any memory to be retrieved. Each incident can receive a maximum of 3 points, depending on the descriptive richness of the response and its specificity as to time and place. K.C.'s and A.D.'s performance on this test was compared with the normative data available for the AMI (Kopelman et al., 1990).

Family photos and autobiographical interview

The stimuli consisted of five photographs from each of five time periods (25 in all) ranging from when the participant was 5 years of age until the present time. The five age ranges tested were as follows: childhood (ages 5–11), adolescence (ages 11–18), early adulthood (ages 18–30), late adulthood (ages 30–45), and

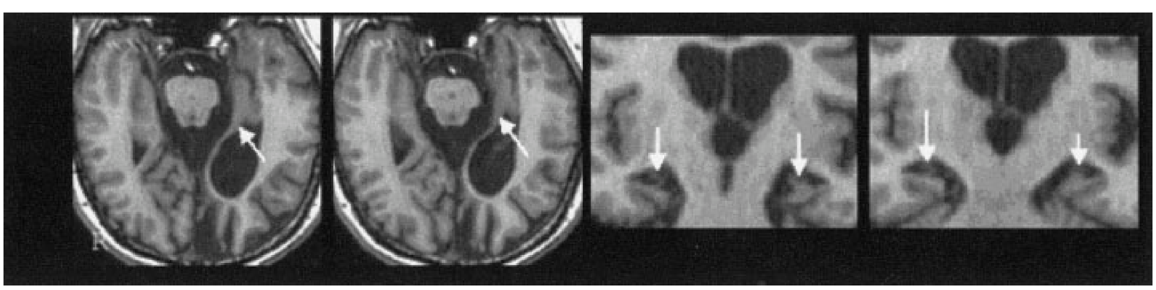

FIGURE 4. Patient K.C.'s MRI displaying the extensive damage to the hippocampi and extra-hippocampal MTL cortices bilaterally.

recent (past 5 years). For K.C. and A.D., the late adulthood period was varied to capture the 2 years just prior to their injury. Photos from ages 28–30 were selected for K.C. and from ages 45–47 for A.D. We, therefore, compared K.C.'s scores with the scores of controls for both the early adulthood and late adulthood periods, as both corresponded to his "late adulthood" period in terms of memory's age. We compared A.D.'s late adulthood scores with controls' scores on both late adulthood and recent for the same reason.

Only photos depicting events, as opposed to portraits, were selected. Participants rated all pictures for vividness, which was defined as the extent to which they were able to recall the event and relive it. The vividness scale ranged from 0, when there was no recollection of the depicted event, to 6, when a highly detailed reexperiencing of the event could be achieved. Participants were asked to distinguish in their ratings between context-rich recollections and highly visual, but not context-specific memories, such as generic memories of past events. Only the former were rated high on vividness. Ten of the photos, the two most vividly recollected from each time period, were then selected for a further extensive semistructured autobiographical interview (Levine et al., 2002). This method of selection of memories circumvents the common problem of biased self selection, which can lead to recall of highly practiced "family folklore" type of memories.

An adaptation of Levine et al.'s (2002) autobiographical memory questionnaire, which includes free recall and cued recall items, was administered with the photos serving as cues. Participants were asked to provide detailed descriptions of their memories related to the events depicted in their pictures. Three levels of cueing were used: free recall ("tell me about the event"), general probing (e.g., "anything else you can tell me about it?"), and specific probing that includes a set of predetermined questions relating to different aspects of the experience (e.g., "what was the weather like?"). Interviews were recorded and transcribed, and transcriptions were segmented into informational bits relating to a one-time occurrence, observation, or thought that are often demarcated by a clause (for example: "/Mike and I were living together at the time./But my aunts wanted me to sleep at my grandmother's house/ with my aunts/ and some of my cousins/"). Each detail was then classified as "internal" (episodic; related directly to the main event described, specific to time and place, and conveying a sense of episodic reexperiencing) or "external" (semantic/generic; tangential or unrelated to the main event, semantic facts) as well as repetitions, or other metacognitive statements or editorializing according to the procedure outlined in Levine et al. (2002).

Part 2: Autobiographical Recognition

RA and AA were probed in K.C. and A.D. using two events from each of four life periods covering childhood, late teens/early twenties, and early adulthood (up to 2 years prior to injury) and recent years (2 years prior to testing). Two highly significant events per time period were selected to ensure that the patients at least had gist knowledge of the event. This was confirmed through preliminary interviews with the patients and more extensive interviews with family members (K.C.'s mother, A.D.'s wife), who also supplied event details. Events included moves to new neighborhoods, siblings' weddings, funerals, injuries sustained by the patients (excluding the injury causing the amnesia), memorable trips and vacations, etc. Dated events, matched in time to those of the patients, were also collected for the six control participants through interviews with family and/or friends. Based on the interviews, 30–40 sentences describing details of each of the events were created, half of which were true and half were false. There was a total of approximately 240–280 sentences per person, 60–70 sentences per time period. Prior to testing, each sentence was labeled as "episodic," "generic," or "semantic." Episodic details were defined as those details that would require reexperiencing or recollection of the event for veracity judgments. These were details unique to the event and context in which the event occurred, such as the people who were present, things that were said or done during the event, the sequence of elements in the event, etc. Generic details are details associated with either extended or repeated experiences that are not unique to the target event but are nonetheless associated with it (e.g., common recurring features of vacations at one's cottage, or visual features of an often-visited place). Finally, personal semantics included abstract, self-related information that is not particularly associated with repeated or extended events, such as one's address, names of relatives, etc. For the analyses reported here, personal semantics and generic details were combined to equate them with the number of episodic sentences/details.

The categorization system often depends on knowledge of the context of the events. For example, in the context of choosing a puppy at the pet store, a sentence such as "one puppy was brown" can be scored as episodic. However, if the puppy was purchased by the participant and was the family dog for 15 years, this statement becomes a generic or visual semantic detail. Thus, during the interview family members were asked to indicate which information was unique to the event and which was generic in nature. Categorization was done by the persons who conducted the interviews and were aware of that background information. Twenty-eight events (totaling 952 sentences or event-details) were selected from across the participants to test for interrater categorization agreement. Proportions of interrater agreement ranged from 88% (RSR and RW) to 94% (AG and RSR).

To ensure that sentences could not be correctly identified as true or false simply by guessing, we asked three controls who did not know any of the patients to try to guess the correct answer for each of the event details. For K.C., subjects had an average of 51% accuracy for episodic details and 52% accuracy for generic semantic details. For A.D., controls had 54% accuracy for episodic details and 48% for semantic details. This suggests that the two types of sentences were not inherently different from each other with regard to their construction and did not contain cues as to the correct answer.

During testing, the event-title was presented on a computer screen, and the examiner made sure that the subject remembered the event and could describe it in general terms. Then, event details were presented on the screen, one at a time, and subjects were required to indicate by a key-press whether the sentence was true or false. The event title appeared on the top of the screen throughout, along with reminders for the coding of the keys as true or false. There was no time limit, but participants were encouraged to respond after delays of more than 10 s. Following each sentence, a rating scale of 0 to 5 appeared, during which subjects rated their confidence in their response, with zero indicating a guess and five indicating absolute certainty in one's response. These ratings were used to produce Receiver's Operating Characteristic (ROC) curves for events from the RA period based on all sentences (regardless of their age).

To assess the discriminability of participants' responses to both true and false sentences, d′ index of discriminability was used separately for each time period. This measure takes into account the hit rate and the false alarm rate, and so reflects in a single score participants' ability to judge the truthfulness of the sentences presented to them.

RESULTS

Free Recall and Cued Recall

A.D.'s score on 10 memories from the modified Crovitz test (range 0–3 per memory) was 25. This score is 1.81 SDs lower than controls' mean score of 28.8 (SD = 2.1) and also 1.7 SDs lower than Hodges and Carpenter's (1991) controls' mean score of 28.3 (SD = 1.9) and the scores reported by these authors for two patients with fornix lesions. Three of the ten memories were from the previous 5 years, which is similar to the distribution reported in controls and in the patients.

On the personal semantic schedule of the AMI, both K.C. and A.D. showed a gradient in retrograde memory loss, in that their childhood score was within normal range, whereas their early adulthood score reflected substantial loss (Table 1). Their scores on the recent time-period of the AMI reflected an extensive anterograde memory deficit for personal semantics, which was larger for K.C. It is important to note that the information included in the recent section of the personal semantics schedule also involves knowledge of events, such as "last Christmas" or "a recent vacation," that likely require more than just semantic knowledge. Their pattern of performance on the event memory schedule was somewhat different. K.C. showed the well-documented flat gradient for personal autobiographical memories that characterizes him (Rosenbaum et al., 2005). A.D., on the other hand, had only borderline impairment of childhood memories, compared with severe deficits on personal memories from later periods, confirming findings from his previous testing (Poreh et al., 2006). His childhood score was elevated by biased self-selection of two highly significant and emotional events that he recounts often ("personal folklore").

Family photos

To compare the scores of internal and external details provided by A.D. and K.C. in response to the events depicted in their photos, we used a *t*-test developed by Crawford and colleagues (Crawford and Howell, 1998) for comparing scores obtained by single subjects to those of small groups of healthy controls. To account for multiple comparisons, a Bonferoni correction was used, setting the significance threshold at $P < 0.004$ for each patient. Tests were performed for the scores obtained using all three levels of probing to equate test-taking strategies and propensity for providing detailed accounts. Both patients provided significantly fewer internal (episodic) and external (semantic/generic) details for all periods of RA and for the AA period compared with controls (see Fig. 5). The age of events from K.C.'s "late adulthood" period (2 year prior to injury, age 28–30) fell at the top end of the "early adulthood" age range of controls. K.C.'s late adulthood scores were significantly lower than controls' early adulthood for both internal

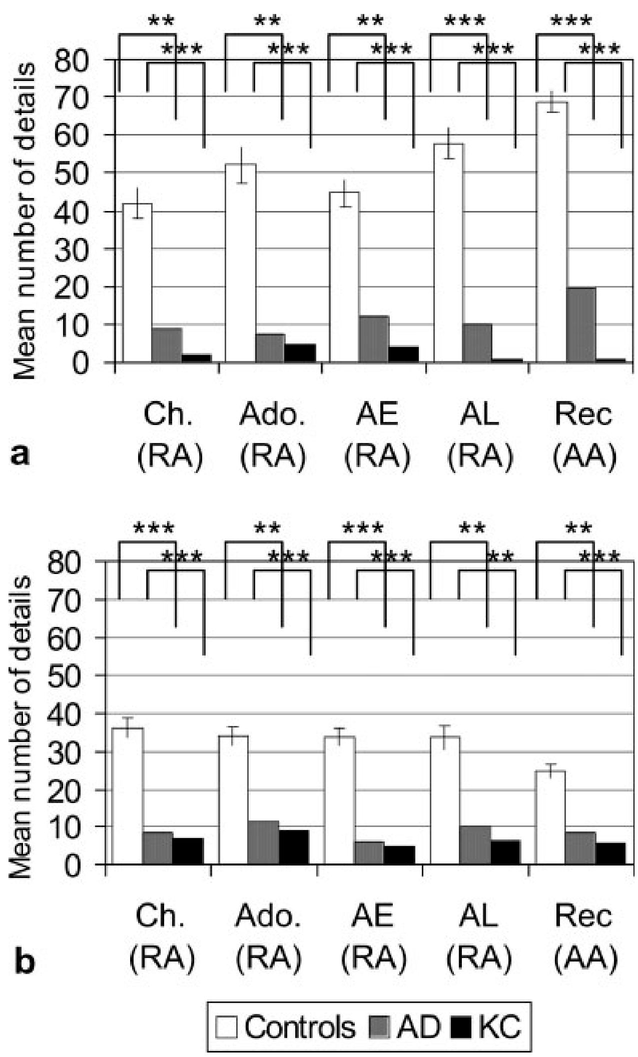

FIGURE 5. Number of internal (episodic) details provided by controls, A.D. and K.C. with all three levels of probing (a). Number of external (semantic/generic) details provided by controls, A.D. and K.C. with all three levels of probing (b). *Note:* AA, anterograde amnesia; Ado., adolescence; AE, Adulthood, Early; AL, Adulthood, Late; Ch., Childhood; RA, retrograde amnesia; Rec., Recent. **$P < 0.004$; ***$P < 0.001$.

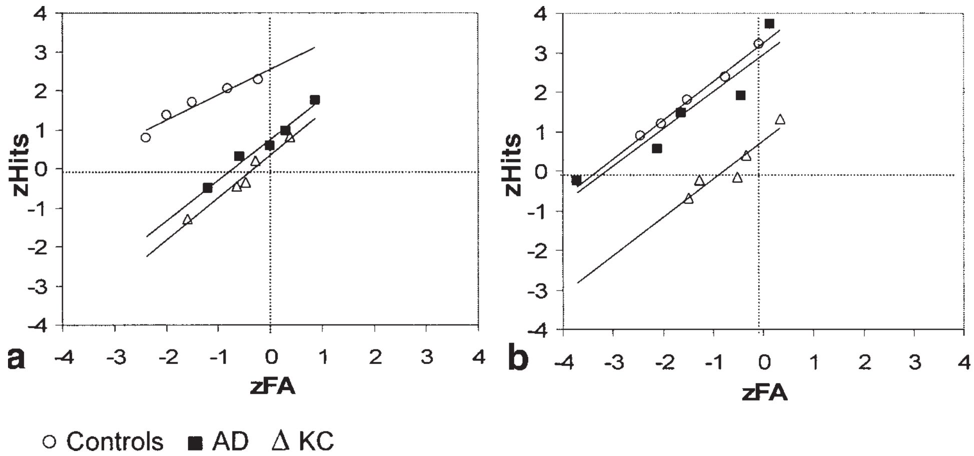

FIGURE 6. **Linear trends in zROC space. Plotted are the *z*-transformed data and best fitting linear trend for the control group and for patients A.D. and K.C. for episodic (a) and for semantic/generic (b) details.**

($t_{(9)} = -6.1$, $P < 0.001$) and external details ($t_{(9)} = -4.08$, $P < 0.004$). Similarly, the age of events from A.D.'s "late adulthood" period was just outside the range of normal controls' (ages 45–47). His scores were significantly lower than those of controls' recent events for both internal ($t_{(9)} = -10.24$, $P < 0.001$) and external ($t_{(9)} = -6.08$, $P < 0.001$) details.

Autobiographical Recognition

Recognition by confidence level

In the initial analysis of the autobiographical memory recognition, we plotted zROCs as a function of response confidence for all of the events, regardless of age. Confidence ratings were collapsed into three levels of confidence (low: ratings 1 and 2; medium: rating 3; high: ratings 4 and 5). Stimuli were collapsed across age and across rating categories to ensure there were sufficient responses within each confidence category. The hit and false alarm rates of each control participant at each confidence level were converted to Z scores and the Z scores corresponding to the area under the normal distribution for each hit and false alarm rate were fitted with a linear regression and the shape of the corresponding z-ROC was plotted. The same procedure was followed for A.D. and K.C. individually. Figure 6 presents the zROC slopes for episodic and generic/semantic sentences, separately.

It has been previously shown that the presence of recollective processes is associated with asymmetrical ROC curves, whereas familiarity alone produces symmetrical ROCs (Yonelinas et al., 1998; Yonelinas et al., 2002; Fortin et al., 2004). Symmetrical ROCs have a slope of 1.0 in z space (Yonelinas et al., 1998; MacMillan and Creelman, 2004) whereas asymmetric ROCs have a slope less than 1.0. Semantic/generic sentences produced zROCs with slopes very close to 1.0 for controls, A.D. and K.C. (0.98, 0.94, and 0.97, respectively). By contrast, the slope for controls' episodic details was 0.65 whereas A.D. and K.C. again showed slopes very close to 1.0 (1.03 and 1.08, respectively). To test whether the slopes of the zROC were significantly different than 1.0, we ran the regressions again, but this time for (zHits–zFA) with zFA as the predictor in each of the conditions. The only coefficient that was significantly different from 0 in that analysis (i.e., suggesting a slope significantly different from 1.0) was the one involving controls' performance on the episodic details ($t = -6.38$; $P < 0.01$).

Put another way, changes in zFA predicted changes in d′ value only for the episodic sentences, producing an asymmetrical ROC and reflecting recollective processes (Yonelinas et al., 1998). It could be argued that the symmetry observed in the amnesics' episodic details ROCs is due to floor effects, but this cannot be said about controls' or A.D.'s generic/semantic details performance, which was very high but still symmetrical.

As can be observed in Figure 6, the two patients differed considerably with regard to their zROC slopes on the two types of details. While K.C. was very poor at recognition of both semantic and episodic details, A.D. showed a clear distinction between his generic/semantic scores, which were equivalent to those of controls, and his episodic scores which were equivalent to K.C.'s.

Recognition by memory age

To examine performance separately for the anterograde and the three retrograde time periods, d′ scores for each time period were computed (regardless of confidence ratings). Both patients had very low d′ scores for retrograde episodic details regardless of their age compared with controls (Fig. 7). For episodic anterograde memory details, K.C. was at floor, while A.D.'s score was still considerably lower than that of controls' though higher than his retrograde scores. For generic/semantic details, K.C. was at floor for all time periods, whereas A.D.'s scores were equivalent to those of controls, regardless of memory age or whether they were anterograde or retrograde events.

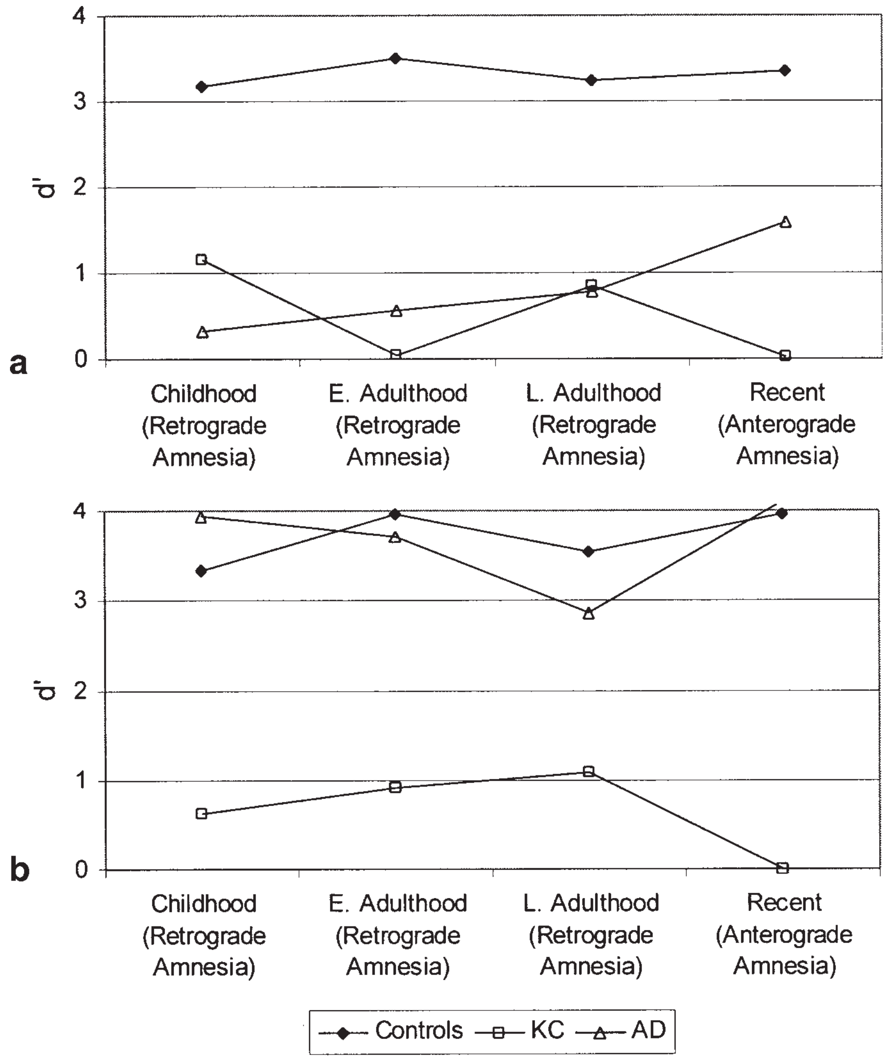

FIGURE 7. Autobiographical recognition d′ scores for A.D., K.C., and controls (n = 6). Discriminability scores on autobiographical recognition (d′) for episodic details (a) and for generic/semantic details (b) as a function of age of events. Discriminability scores were determined from participants' hit rate and false alarm rate for each sentence type. Childhood = ages 5–18; early adulthood = ages 19–28; late adulthood = 2 years prior to injury (K.C.: 28–30; A.D.: 45–47); Recent = within the last 2 years.

DISCUSSION

This study of patient A.D. is the first detailed description of a dissociation between recollection and familiarity processes in retrograde autobiographical amnesia. This dissociation partially corresponds to the different patterns of preservation and loss of personal semantic vs. episodic memory, highlighting the close correspondence between memory processes and memory content but also their dissemblance.

Episodic and Semantic Memory

On traditional, free, and cued recall tests of autobiographical memories, such as the Galton-Crovitz test and the AMI, A.D. showed severe deficits when autobiographical events were sampled. Importantly, on the AMI a temporal gradient was observed for personal semantics, but not for unique events memory, confirming a previous report (Poreh et al., 2006). One apparent discrepancy to this pattern was A.D.'s performance on the family photographs task where both the number of episodic and the number of semantic details were significantly reduced. However, on this task the number of semantic/generic details partially depends of the ability to relate an episode from the past, to which the generic/semantic details serve as a backdrop. A.D.'s failure to associate the photos with any event from his life has led to laconic responses lacking in detail of any kind. A more appropriate way to test semantic/generic details on this task would be to ask directly about such details (as is done in the AMI). The dissociation between semantic and episodic memory was most apparent on the autobiographical recognition task. A.D.'s remote memory was as severely impaired as his recent memory only for episodic details, which always require recollection, while his memory was normal in both cases on generic/semantic recognition where he could rely on familiarity. By contrast, patient K.C., whose lesion extends to extra-hippocampal MTL cortices, was severely impaired on all tests, even those requiring familiarity. The comparison between patients, however, should be done cautiously because both were at floor for many of the measures we used, which could mask true memory performance differences between them.

The Extended Hippocampal System and Recollection

Because it is difficult to distinguish between recollection and familiarity on tests of recall, we devised a recognition test of remote memory, modeled on anterograde memory tests, which have proven successful in distinguishing between the two. The pattern of results we obtained is consistent with theories of functional dissociations within the MTL (Eichenbaum et al., 1994; Aggleton and Brown, 1999; Mayes et al., 2002; Yonelinas et al., 2002), some of which posit that the hippocampus proper mediates recollection whereas adjacent MTL structures mediate familiarity. As predicted, A.D.'s performance on standard visual and verbal clinical tests of anterograde memory, like that of other patients with selective bilateral fornix lesions (McMackin et al., 1995; Aggleton et al., 2000), was worse on recall than on recognition, a pattern not shared by K.C. According to these theories, following selective hippocampal lesions performance on recall tests tends to be significantly poorer than performance on recognition tests, because recall depends primarily on recollection, whereas recognition depends on either recollection or familiarity (Yonelinas et al., 1998; Mayes et al., 2002; Yonelinas et al., 2002; Holdstock et al., 2005; Barbeau et al., 2005b) but see (Reed and Squire, 1997; Buffalo et al., 1998; Stark et al., 2001; Stark et al., 2002; Manns et al., 2000a). This has been confirmed by several studies of AA that have shown that it is possible to dissociate familiarity from recollection on recognition tests. On tests using Remember/Know and Process Dissociation Paradigms, patients with hippocampal lesions perform normally when recognition memory is based on familiarity but are impaired when recollection is required (Yonelinas et al., 1998; Mayes et al., 2002; Yonelinas et al., 2002). The same pattern was also apparent on the anterograde part of the autobiographical memory recognition task, suggesting the anterograde recollection-specific deficit in AD extends to the autobiographical domain.

The present study was the first to investigate whether similar dissociations exist also for retrograde memory. Our recognition task reflected comparable dissociations between recollection and familiarity for retrograde and anterograde time periods, suggesting that the role of the hippocampus in recollection is consistent across time. Correct recognition of unique details, which entails mental time-travel and reexperiencing, was taken as a measure of recollective processes. Familiarity, on the other hand, was measured by recognition of details that are generic or semantic, which could be identified correctly without reexperiencing the event itself. Indeed, whereas controls' performance on both types of event details was exceptionally accurate, A.D. was accurate only in recognizing generic/semantic details, whereas his performance on the episodic details was as poor as K.C.'s. This dissociation between familiarity and recollection in A.D.'s performance for both anterograde and retrograde memory is compatible with his performance on clinical tests of anterograde recall and recognition.

The dissociation between recollection and familiarity was also evident in the retrieval dynamics associated with each process in the RA period. Several studies of humans (Yonelinas et al., 1998; Yonelinas et al., 2002) and one in rats (Fortin et al., 2004) have argued that recollection involves a threshold process that is characterized by asymmetrical ROCs with a slope smaller than 1.0 in z space, whereas familiarity has a graded memory strength function with a slope equal to 1.0. Indeed, the zROC slope produced by controls for episodic details was smaller than 1.0, reflecting the involvement of a recollective component in recognition memory for these event details. This was not the case for generic/semantic details in which the pattern of responses suggested a graded memory strength function, providing important support to the way we classified the sentences. Put another way, in terms of a pure signal detection model, the generic/semantic condition requires only a single memory parameter (d') to describe performance. This parameter would appear to be disrupted in the K.C., but is perfectly normal in A.D. In contrast, for the episodic condition, two memory parameters are required to account for the control subjects' ROC (d' and old/new variance ratio), whereas only one (d') is needed to account for both patients' ROCs (but see Wais et al., 2006).

Our data from the recognition task suggest that recollection depends on the Extended Hippocampal System for both anterograde and retrograde memories (as further discussed below). Kapur and Brooks (1999) also examined recognition of retrograde personal events in a patient, BE, with restricted hippocampal lesions. Their findings can be interpreted as consistent with our own. Patient BE correctly identified 15/17 places he had visited together with his wife prior to his lesion, presumably reflecting intact retrograde memory (Kapur and Brooks, 1999). However, he erroneously selected 10 other places, which he had visited without her, as places they had visited together. This suggests BE had only generic memories of having visited certain locations, but was missing contextual information such as who accompanied him or even in what era of his life he had visited these places (i.e., before or after he had met his wife).

Our definition of recollection in autobiographical memory closely matches definitions of recollection in standard anterograde memory studies, and in fact the latter are usually an attempt to mimic the process that allows autobiographical reexperiencing under laboratory conditions. Generic/semantic memories, on the other hand, can be supported by familiarity because such memory representations are decontextualized. Familiarity is often defined as recognition in the absence of recollection, i.e., without an association to a specific context, that depends on an exact match between the retrieval cue and a memory trace (Huppert and Piercy, 1976; Yonelinas et al., 1998; Aggleton and Brown, 1999; Yonelinas et al., 2002).

With regard to the present study, memories of frequently repeated events retain the gist of those events without the characteristics that distinguish one occurrence from another. A sense of familiarity can arise in response to a recently encountered stimulus (which is the basis for familiarity processes in list learning paradigms), but also in response to frequently experienced stimuli, not associated with a specific event. This is consistent with Huppert and Piercy's (1976) finding that amnesic patients, who presumably rely on familiarity and memory strength, could not distinguish between frequently presented stimuli and recently presented ones. It is also consistent with Norman and O'Reilly's (2003) model of MTL cortex learning. This model posits that cortically supported familiarity judgments in the MTL are based on the sharpness of representations and sharpness is established by repeated exposures to stimulus representations. However, the MTL cortex in Norman and O'Reilly's model cannot support recall of details from specific events because of its low learning rate and its inability to differentiate well the representations of different events from one another. Thus, generic representations in remote memory possess the required attributes for familiarity processes.

At the anatomical level, it appears that generic autobiographical memories are spared following damage to the Extended Hippocampal System because familiarity can be supported by extra-hippocampal MTL structures. When familiarity is compromised following more extensive MTL damage, as seen in K.C., generic representations can no longer be supported. Recently, Barbeau et al. (2005a) reported that electrical stimulation of the perirhinal cortex elicited highly vivid generic memories in a patient with epilepsy. These authors emphasized that the memories elicited were of repeated experiences (e.g., seeing a neighbor go by on his motorbike) and unrelated to a specific episode in the patient's past (Barbeau et al., 2005a). This intriguing finding suggests that the perirhinal cortex indeed plays a role in the representation of remote generic memories, as suggested by the present study.

In addition to his fornix lesions, A.D. also has a midline basal forebrain lesion, which probably contributes to his memory deficits (Parent and Baxter, 2004) through cholinergic depletion in the hippocampus, as reported in monkeys (Easton et al., 2002) and humans (Morris et al., 1992). This lesion also specifically affects the Extended Hippocampal System, because the midline basal forebrain nuclei are the primary cholinergic route to the hippocampus through the precommissural columns of the fornix whereas the neighboring MTL cortices are only weakly connected with this system and receive their primary cholinergic input from lateral basal forebrain nuclei which are intact in A.D.

Potentially, A.D.'s pattern of results could arise because episodic details are more difficult to retrieve than generic ones. This cannot be ruled out entirely, though it should be noted that controls found it easy, as reflected by their level of performance, to distinguish between the distinctly true or false details provided by their family members. As an additional control, we had, normal participants who were unfamiliar with either patient's history, try to guess the answers to the sentences administered to the patients. They performed at chance for both detail types, suggesting the sentences were not inherently different from one another.

To conclude, A.D.'s performance on both anterograde and retrograde memory tasks reflects a dissociation between recollective processes and nonrecollective memory components. His restricted bilateral fornix and midline basal forebrain lesions suggest the role of the Extended Hippocampal System in anterograde and retrograde memory is the same, namely, it mediates recollection which supports the ability to reexperience events from the past.

The Extended Hippocampal System and Remote Memory

An important feature of the present data is that the dissociation between recollection and familiarity seen in patient A.D. was maintained across all periods of RA including childhood. This suggests recollection processes in recognition memory are always dependent on the hippocampal system, contrary to ideas of standard consolidation theories (Squire, 1992; McClelland et al., 1995; Murre, 1996; Squire et al., 2004). A.D.'s severe and ungraded deficits on recognition of episodic details, and on recall of events from his photographs, differed from his performance on standard tests of autobiographical memory such as the Crovitz cue word test (which was borderline) and the AMI, which showed some temporal gradient (although less apparent for the event memory section). These differences reflect the impact that testing methods may have on the ability to detect patterns of preservation and loss in autobiographical memory. When unconstrained free recall is used, patients can resort to retrieval of highly semanticized or well-rehearsed memories that are fundamentally different from autobiographical reexperiencing (Cermak, 1984; Neisser, 1988; Moscovitch et al., 2000; Levine et al., 2002; Piolino et al., 2002).

Most studies of memory dysfunction after fornix lesions have not examined retrograde memory at all (e.g., McMackin et al., 1995; Aggleton et al., 2000) or have only examined it informally (e.g., D'Esposito et al., 1995). Two studies have reported intact retrograde memory following fornix lesions using the cue-word test (Hodges and Carpenter, 1991) and the AMI (Park et al., 2000). However, all three patients described in these studies, also differed from A.D. in their anterograde memory performance which was characterized by severe verbal memory loss but relatively preserved visuospatial memory at the chronic stage, suggesting at least partial functional sparing of the hippocampal-fornix system. This partial sparing may have been sufficient to support remote memory performance, especially if the test was not sensitive enough to detect autobiographical memory loss, as discussed earlier.

As in the anterograde memory literature, the idea that only certain types of remote memories always depend on the hippocampal system is contentious. Traditional consolidation theory suggests that all declarative memories become independent of the hippocampus as they age, regardless of whether they are semantic (Manns et al., 2003b) or episodic (Bayley et al., 2003), a stance that is closely associated with the idea that the

MTL is a unitary declarative memory system (Squire, 1992; Squire et al., 2004). Our data are more consistent with evidence that the MTL, and in particular the hippocampus, is always needed for retrieval of remote personal memories which are vivid and detailed, whereas semantic memories, including personal semantics, become independent of the hippocampus. Patients with lesions restricted to the hippocampus have been shown to have retrograde memory loss for vivid autobiographical episodes that extended their lifetime (Nadel and Moscovitch, 1997; Hirano and Noguchi, 1998; Cipolotti et al., 2001; Mocovitch et al., 2006), but see Bayley et al. (2004) for contrary evidence. The multiple trace theory accounts for findings of lifelong loss of personal memories by proposing that context-rich memories always are mediated by a hippocampal–neocortical ensemble, whereas semantic memories become independent of their MTL component as they lose their contextual qualities and event-specificity over time (Nadel and Moscovitch, 1997; Rosenbaum et al., 2001) or due to repetition as is the case for generic representations. The present study suggests that the crucial hippocampally mediated factor may be the process of recollection and its associated experiential quality. The distinctiveness of unique context-rich events requires recollective processes at retrieval regardless of the method of testing. Generic/semantic content can be retrieved based on either recollective or familiarity processes, whereas richly detailed episodic content can only be retrieved based on the recollective processes.

The original neuroanatomical focus of multiple trace theory, however, was on the MTL memory system (i.e., hippocampus and surrounding cortices), with only a suggestion of possible functional specialization within that system. In light of what we now know about the possible role of the hippocampus proper in AA, and in light of the data presented here, it may be useful to revise our ideas of the role of the hippocampus and of the parahippocampal cortices in remote memory [cf. (Gilboa et al., 2005; Moscovitch et al., 2005)]. Rather than focus on the hippocampus as the hub of remote recollective experiences, it may be more accurate to ascribe such a function to the whole extended hippocampal system, including the fornix, mammillary bodies, and anterior thalamic nuclei (Aggleton and Brown, 1999) although not all of them would necessarily have the same function. In addition, the possible role of extrahippocampal MTL structures in supporting the retrieval of generic autobiographical memories through familiarity processes should also be carefully considered.

To conclude, these data show that lesions confined to the extended hippocampal system, as in A.D.'s case of bilateral fornix resection, specifically impair recollection in both AA and RA, regardless of memory age. This is consistent with neuroimaging studies that have shown that hippocampal activation for remote memories was specifically associated with recollection in a patient with developmental amnesia (Maguire et al., 2001) and in neurologically intact people (Gilboa et al., 2004). The data converge to support two major theories of hippocampal function, namely, that it is specifically needed for recollection (Aggleton and Brown, 1999), and that recollective aspects of remote memories always depend on the hippocampal system, regardless of the memory's age (Nadel and Moscovitch, 1997).

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