''Where to?'' Remote Memory for Spatial Relations and Landmark Identity in Former Taxi Drivers with Alzheimer's Disease and Encephalitis

R. Shayna Rosenbaum[1,2], Fuqiang Gao[3], Brian Richards[1], Sandra E. Black[1,3], and Morris Moscovitch[1,2]

Abstract

■ Recent research suggests that the hippocampus is not needed for the maintenance and recovery of extensively used environments learned long ago. Instead, a network of neocortical regions differentially supports memory for location-navigation knowledge and visual appearance of well-known places. In this study, we present a patient, S. B., who was diagnosed with probable Alzheimer's disease long after retiring from his 40 years as a taxi driver in downtown Toronto, a place that he has visited rarely, if ever, in the last decade. His performance was compared to that of two other retired taxi drivers, L. R., who developed encephalitis after retirement, and I. L., who is without neurological illness, and a group of eight healthy control participants who were never taxi drivers but all of whom worked or lived in downtown Toronto until at least 10 years ago. Despite S. B.'s widespread atrophy, which has affected mainly his hippocampus and part of his occipitotemporal cortex, he performed at least as well as all other participants on remote memory tests of spatial location and mental navigation between well-known Toronto landmarks. Unlike the comparison populations, however, he was unable to discriminate between the appearances of landmarks that he had visited frequently in his many years as a taxi driver from unknown buildings. This profound deficit extended to famous world landmarks but not to famous faces and does not appear to be semantic in nature. These findings add further support to the claim that the hippocampus is not necessary for mental navigation of old environments and suggest that expertise is not sufficient to protect against landmark agnosia. ■

INTRODUCTION

As mobile organisms, we can learn the layout of new environments for wayfinding, but as creatures of habit, we more often navigate within well-known places. To lose our bearings suddenly in previously familiar surroundings would be disabling to everyday life, particularly if our job demands topographical expertise. We now know that spatial disorientation can result from lesions to one of a number of dissociable structures in the brain, suggesting that distinct mechanisms of cognitive dysfunction may give rise to what on the surface would seem to be a unitary syndrome of losing one's way. However, surprisingly little is known about the necessary roles of these structures, especially the hippocampus, in the storage and recovery of long-standing topographical knowledge. To gain a better understanding of the cognitive and neural substrates of long-term spatial memory, we examine the patterns of topographical disturbance in two patients who were once expert navigators but who have different lesion profiles.

Spatial memory may be separated into retrograde and anterograde components according to whether an environment was learned before or after the onset of brain damage. These components may be divided further into ''what'' and ''where'' aspects, such that the appearance and location of landmarks are processed and represented in different ways. There are accounts of patients who, following restricted damage to ventral-stream occipitotemporal cortex, retain the capacity to locate landmarks and use them for navigation. Nevertheless, they are unable to recognize visually the unique identity of those very same landmarks, at least beyond minute features such as a mailbox or fence (e.g., Whiteley & Warrington, 1978). This loss cannot be explained by deficient elementary perceptual abilities, such as visual discrimination of one landmark from another (Bank A vs. Bank B), gross visual identification of category membership (bank vs. hotel), or category-specific semantic knowledge (recognizing Bank A from its name).

Other cases show an opposite pattern of intact and impaired function, such as an inability to relate landmarks to person-centered coordinates within a ground-level representation of space, even though the landmarks themselves continue to look familiar (e.g., Levine,

[1]Baycrest Centre for Geriatric Care, [2]University of Toronto, [3]Sunnybrook and Women's College Health Sciences Centre

Warach, & Farah, 1985). These features preclude the physical use or imagery of a linear sequence of turns along a path to reach a destination and are symptomatic of disruption to an egocentric processing system housed within a dorsal-stream posterior parietal network. Yet another group of patients present with location-navigational disturbance, but this time stemming from a failure to integrate recognizable landmarks into an overhead, maplike arrangement of an environment that is independent of body axis. This failure to represent landmarks within an allocentric reference frame is diagnostic of a lesion to one or more medial paralimbic structures that sit below posterior parietal cortex. Insult to the parahippocampal cortex eliminates the acquisition of object–place associations (e.g., Habib & Sirigu, 1987), whereas damage to the retrosplenial cortex strips landmarks of their directional significance, at least within the first few months of onset (see Maguire, 2001).

Many believe that the fluid cascade of egocentric and allocentric processing within this highly interconnected network would be disrupted without a functional hippocampus. The finding of hippocampal place cells that fire when rats occupy certain locations but not others helped to convince O'Keefe and Nadel (1978) and others thereafter that this structure behaves as the source or repository of allocentric cognitive maps. Although this theory has since evolved to accommodate episodic memory functions in humans (Burgess, Maguire, & O'Keefe, 2002), it continues to retain the central notion that populations of place cells integrate self-motion cues with a complex of visual landmarks to encode and maintain internal spatial maps of the external world. Whereas most researchers concede that, at least in humans, the role of the hippocampus is not exclusive to the acquisition and storage of spatial maps, forming and retaining topographical memories is considered one of its main functions. Accordingly, loss of this structure's functional integrity should result in the loss of cognitive maps, whether formed recently or long ago. However, only the former seems to hold, and even this may be contested (see Aguirre & D'Esposito, 1999).

Functional neuroimaging studies of topographical memory are in general agreement with this ventral versus dorsal scheme, particularly with regard to encoding and retrieval of newly encountered environments. It is relatively well established that a posterior parahippocampal-anterior lingual/fusiform sector of the occipitotemporal cortex is preferentially responsive to spatially contained layouts (e.g., Epstein & Kanwisher, 1998), whereas mental or virtual navigation with reference to these static scenes or landmarks engages medial posterior parietal cortex, retrosplenial cortex, and more anterior parts of the medial temporal lobe (MTL). The latter includes the hippocampus in some studies (e.g., Maguire et al., 1998) but not in others (Aguirre, Detre, Alsop, & D'Esposito, 1996; for a possible explanation, see Hartley, Maguire, Spiers, & Burgess, 2003). Similarly, the very few investigations of long-standing topographical knowledge that have been conducted to date have produced seemingly mixed results with respect to the hippocampus. In one such study, Maguire, Frackowiak, and Frith (1997) found selective right hippocampal activity in London taxi drivers as they figured out the shortest legal route between landmarks. Closer inspection of their data, however, reveals that the focus of activity in the MTL was not in the hippocampus itself but rather within the parahippocampal cortex. A more recent functional magnetic resonance imaging (fMRI) study of memory for old and highly rehearsed knowledge of a city's topography in nonexpert navigators also engaged structures linked to processing the identity and the allocentric and egocentric spatial relations of Toronto landmarks based on various task demands (Rosenbaum, Ziegler, Winocur, Grady, & Moscovitch, 2004). More importantly, the core of MTL activity was within the parahippocampal cortex, extending just slightly into hippocampal territory and only at thresholds uncorrected for multiple comparisons.

Reports of hippocampal amnesics with intact recall of the topographical qualities of neighborhoods in which they grew up many years before lesion onset present an even stronger challenge to the classic view of the hippocampus as always being needed for both the acquisition and long-term storage of spatial memories (Rosenbaum et al., 2000; Teng & Squire, 1999). The flexibility of the patients' remote spatial knowledge was perhaps most evident in the ease with which they invented shortcuts between well-known locations that they had rarely, if ever, traveled along. Such an achievement has long been considered the mark of a true cognitive map (O'Keefe & Nadel, 1978; Tolman, 1948), because the direction and distances among locations can be inferred without direct experience. These results call into question the belief of a perpetual responsibility of the hippocampus to spatial memory.

Given these demonstrations of preserved aspects of remote spatial memory in amnesia, we now wish to investigate whether such information would be similarly insulated following Alzheimer's disease (AD), in which degeneration of MTL structures (Braak & Braak, 1991) is associated with early and severe loss of episodic memory (Kopelman, 1985). Temporally graded patterns of memory loss broadly similar to that observed in amnesic patients have been documented in AD patients, such that the recall of earlier semantic memories is affected less than the recall of more recent memories (Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Kopelman, 1989), whereas recall of autobiographical memories is far more severe and often ungraded (Westmacott, Black, Freedman, & Moscovitch, 2004). We examined whether memory for spatial layouts of large-scale environments would be affected similarly in AD or whether there would be a severe loss, as cognitive map theory would predict.

We also thought it important to determine if memory for landmarks, which also are used in navigation, would

suffer the same fate as memory for spatial layouts. Several brain regions outside of the hippocampus are also vulnerable to the effects of AD at different stages, although the particular neuropathological trajectory of the disease often varies from patient to patient. The course of deterioration may progress to include temporal neocortex, posterior cingulate cortex, and the parietal lobes in addition to more anterior regions (Stout, Bondi, Jernigan, et al., 1999), raising the possibility of dissociable aspects of topographical function at the level of long-term storage. Therefore, studies of patients with AD with unique patterns of neural degeneration might inform us of the degree to which topographical systems fractionate in the brain.

To this end, we report a patient, S. B., with probable AD who worked for many years as a taxi driver and courier in downtown Toronto until he retired. S. B.'s performance was compared to that of another retired taxi driver, L. R., who exhibits an opposite pattern of dissociation following viral encephalitis that affected his left temporal neocortex to a greater degree than MTL regions, thereby resulting in a relatively isolated loss of lexical–semantic memory (see Tables 1 and 2 for further detail). Notably, unlike the participants included in the Maguire et al. (1997) and Rosenbaum et al. (2004) investigations, the patients' retirement over 10 years ago marked the end of their exposure to downtown Toronto, preventing contamination of remote memory from any re-encoding that might occur upon continued experience with an old environment. A related goal is to explore the possibility of dissociable ''what'' and ''where'' aspects of remote spatial memory that have been known to emerge after selective damage to topographical neocortical sites. To anticipate, S. B. presented with a severe inability to discriminate the appearance of landmarks that he had visited frequently before his retirement from those that he had never encountered, consistent with the additional atrophy detected within his occipitotemporal cortex. This deficit is extraordinary, especially in light of the multiple viewpoints of each landmark that were likely formed during his many years as a taxi driver. Patient L. R., who has significant hippocampal atrophy but less extensive damage to the occipitotemporal cortex, recognized Toronto landmarks without difficulty.

These issues were examined using specialized tests of downtown Toronto topography that enable the investigation of the many ways in which the identity and spatial relations between landmarks encountered long ago may be represented in remote memory. To control for the range of word-finding difficulties exhibited by our patients, most tests were nonverbal in nature and those with a verbal component had flexible scoring criteria, allowing for definitions, synonyms, gestures, and drawings in place of names for streets, landmarks, and directions.

RESULTS

Magnetic Resonance Imaging of Brain Pathology

The results of the volumetric analyses for all structures examined are displayed in Table 3. Visual inspection of S. B.'s brain (Figure 1) suggested that the most prominent volume reductions were in his left anterior temporal lobe and left hippocampus, the latter confirmed with quantitative analysis; his hippocampus on the right and parahippocampal cortex bilaterally were also reduced in volume but to a lesser extent. A significant reduction was also noted in fusiform and lingual gyri, particularly on the left but also significant on the right, bordering the posterior parahippocampal cortex. However, disproportionate tissue loss was not limited to occipitotemporal regions and extended into structures closely linked neuroanatomically to the hippocampus that appear to play a role in topographical functioning, such as bilateral inferior parietal cortex and anterior and posterior portions of the basal ganglia. Left medial middle and orbital areas of the frontal lobes also showed significant reductions in volume, and a small lacunar infarct was observed in the right putamen. Interestingly, his posterior cingulate was larger than normal, particularly on the left side but also on the right.

Magnetic resonance imaging (MRI) of patient L. R. revealed a pattern of diffuse brain damage that included

Table 1. Demographic Characteristics of the Patients and Control Participants

	S. B.	*L. R.*	*I. L.*	*Controls*
Age (years)	80	76	80	$M = 67.9$
Education (years)	9	12	10	$M = 12.12$
Handedness	R	R	R	R
MMSE	24	23	30	$M = 29.13$
Years as taxi driver	30 (1940–1970)	42 (1950–1992)	30 (1951–1981)	–
Years as courier	15 (1970–1985)	–	–	–

MMSE = Mini Mental State Examination.

Table 2. Performance of the Patients on a Battery of Standard Neuropsychological Tests

	S. B.	*L. R.*
Mental status		
DRS (/144)[a]	115	108
Attention (/37)	36	37
Initiation/Persevation (/37)	27	15
Construction (/6)	4	6
Conceptualization (/39)	33	32
Memory (/25)	15	18
General intellectual function		
WAIS-R (standard score)		
Full-scale IQ	81	85 (WASI)
Verbal IQ	81	70 (WASI)
Performance IQ	85	106 (WASI)
Visuomotor tracking/focused attention		
Trail Making Test, Part A (scaled score)	2	8
WAIS-III Digit Symbol (scaled score)	6	N/A
Memory		
WAIS-R Digit Span		
Forward (*Z* score/ percentile)	0	47.5th
Backward (*Z* score/ percentile)	−1.1	61.5th
KBNA Spatial Location (scaled score)	N/A	13
CVLT		
Acquisition (*T* score)	25	3 (KBNA scaled)
Short Delay Free Recall (*Z* score)	−3	N/A
Long Delay Free Recall (*Z* score)	−2	1 (KBNA scaled)
Recognition Discriminability (*Z* score)	−3	>16th (KBNA percentile)
ROCF, 30-min delay (percentile)	< 3.8th	41.5th
Benton Facial Recognition (/54)	N/A	44 (normal range)
Language		
BNT (scaled score)	3	Raw score = 6
Category Fluency[b] (*Z* score)	−2.03	−3.81
WAIS-R Vocabulary (scaled score)	7	1 (WASI)
Pyramids and Palm Trees (/50)	N/A	39
WRAT-R Reading (standard score)	105	N/A
Visuospatial function		
ROCF, Copy (percentile)	5.7th	75.5th
WAIS-R Block Design (scaled score)	7	11 (WASI)
JLO (percentile)	72nd	56th
Executive function		
Trail Making Test, Part B (scaled score)	7	8
WAIS-R Similarities (scaled score)	7	6 (WASI)
WAIS-R Matrix Reasoning (scaled score)	7	12 (WASI)
Letter Fluency[c] (*Z* score)	−0.85	−2.37
WCST	5 of 6 categories	N/A

DRS = Dementia Rating Scale; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WASI = Wechsler Abbreviated Scale of Intelligence; KBNA = Kaplan-Baycrest Neurocognitive Assessment; CVLT = California Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; BNT = Boston Naming Test; WRAT-R = Wide Range Achievement Test-Revised; JLO = Judgment of Line Orientation; WCST = Wisconsin Card Sorting Test.

[a]Normal cutoff = 123.

[b]Score is based on the number of animal names produced in 1 min.

[c]Score is based on the total number of words produced for the letters F, A, and S when given 1 min for each.

reductions in hippocampal volume, mostly on the left side (see Figure 2), as well as clear signs of atrophy to his left parahippocampal cortex. Most apparent was extensive damage to his left anterior temporal cortex and left fusiform gyrus. Other areas of damage included a large lesion to the left insula and a smaller lesion to the posterior thalamus. However, of particular relevance to the present investigation, additional structures implicated in topographical orientation, including the posterior cingulate cortex, were unaffected by the encephalitis.

Table 3. Regional Volumes with Head-size Correction for S. B., L. R., and Control Subjects

	S. B.		*L. R.*		*Controls*	
	Volume, mm^3 (Z Score)		*Volume, mm^3 (Z Score)*		*Volume, mm^3 (SD)*	
Region of interest	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
Hippocampus	254.89 (−4.69)	1785.16 (−1.96)	1409.95 (−2.65)	2286.80 (−1.18)	2914.45 (567.57)	3050.74 (646.31)
Parahippocampus	983.05 (−1.5)	1120.31 (−1.41)	1321.71 (−1.06)	1381.62 (−0.92)	2136.86 (768.13)	1869.29 (530.48)
Fusiform gyrus	1415.76 (−3.65)	1944.92 (−2.68)	2150.89 (−2.81)	3991.25 (−0.57)	4603.16 (872.72)	4540.10 (967.85)
Posterior cingulate/ retrosplenial cortex	4299.33 (3.8)	4101.76 (1.31)	2870.03 (−0.08)	3458.42 (0.43)	2899.73 (368.57)	3141.45 (735.22)

Experiment 1: Remote Memory for Landmark Location and Mental Navigation

Informal testing on sketch mapping revealed intact remote memory for the layout of the first floor of the house in which L. R. and his wife have lived for nearly 40 years and which he had not visited since his illness. Although labels were not provided for the various rooms, comparison with the actual floor plan and his wife's map shows that L. R.'s map was accurate in terms of the delineation of rooms on the floor as well as the inclusion and positioning of details within the rooms (Figure 3A). By contrast, S. B.'s sketch map of the first floor of the house in which he and a friend have lived for the past 10 years retained only the general spatial relations of the rooms to each other and otherwise lacked any detail in comparison with the sketch map produced by his housemate (Figure 3B). To establish whether such performance is predictive of intact memory for the topographical complexity of an outdoor environment that S. B. and L. R. had often traversed, participants were assessed on tests of spatial location (Where is a landmark located on an outline map?), distance (Which of two landmarks is closest to a third? What is the distance between two landmarks?), direction (What is the most direct line between two landmarks?), and route knowledge (How do you get from A to B when the most direct route is blocked?), designed to simulate the demands of negotiating through large-scale space.

Table 4 shows S. B.'s performance and that of the comparison populations, postencephalitic expert L. R., control expert I. L., and nonexpert controls. S. B. was unimpaired on all mental navigation tasks. In fact, he performed significantly better than all other participants

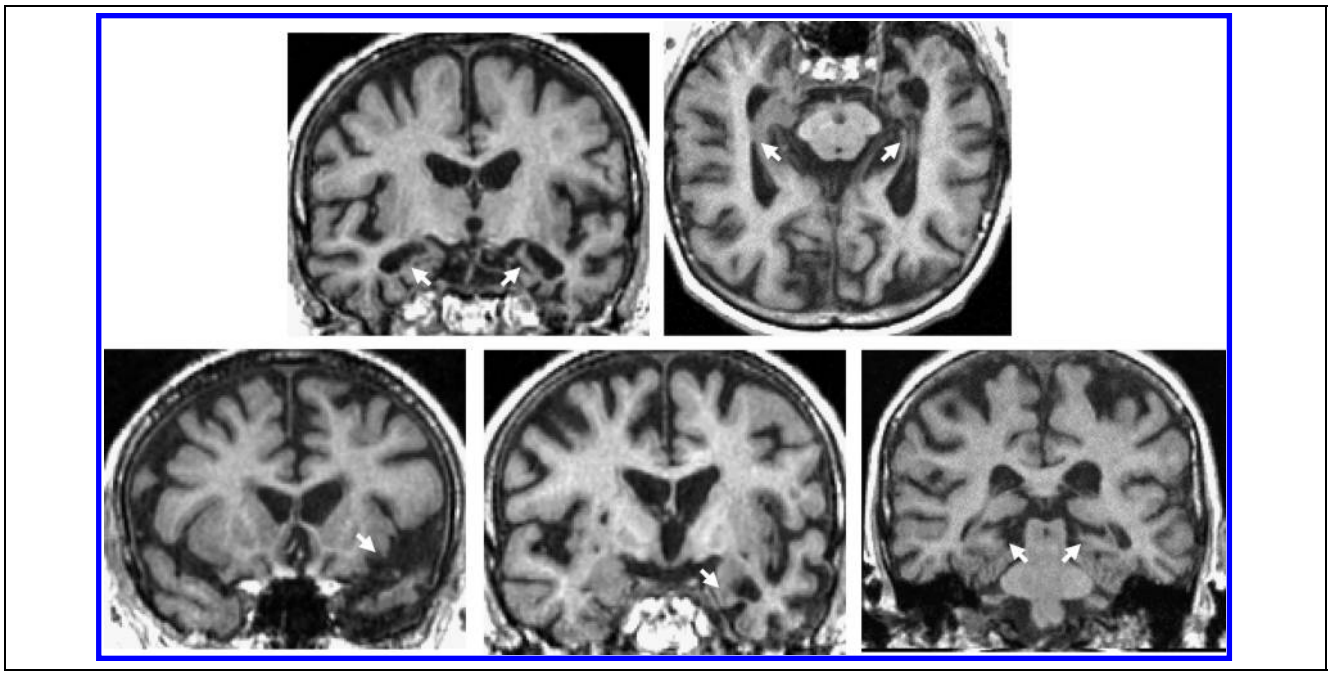

Figure 1. MRI slices showing atrophy to patient S. B.'s bilateral hippocampus in coronal (top row, left) and axial (top row, right) views and anterior temporal lobe (bottom row, left), fusiform gyrus (bottom row, middle), and anterior lingual gyrus (bottom row, right) in coronal views.

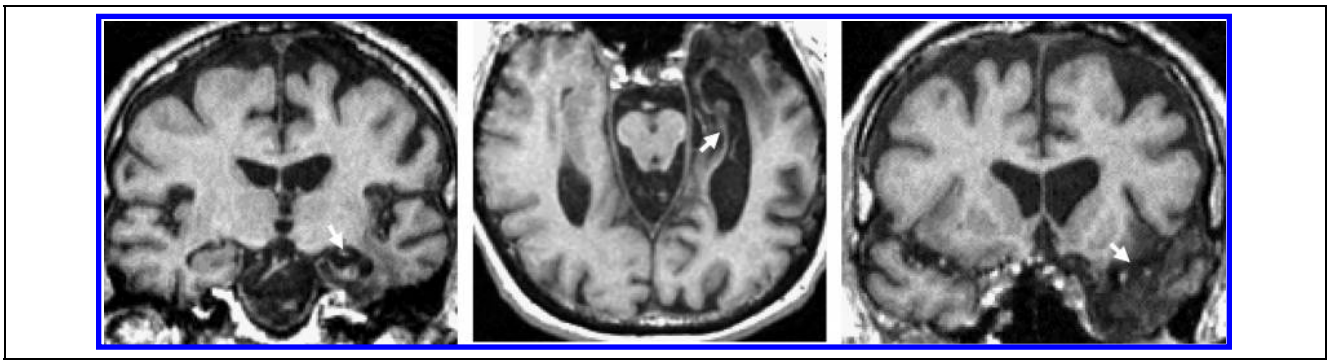

Figure 2. MRI slices showing atrophy to patient L. R.'s bilateral hippocampus in coronal (left) and axial (middle) views and left anterior temporal lobe in a coronal view (right).

in estimating the direction or "heading" between landmarks on vector mapping, which requires allocentric spatial memory and may be considered a test of retrosplenial cortex/posterior cingulate cortex function. Moreover, he, along with the healthy taxi driver, performed significantly better than L. R. and the nonexpert controls on blocked-route problem solving, a classic test of allocentric spatial ability (O'Keefe & Nadel, 1978; Tolman, 1948). However, although the demands that this task places on verbal production were reduced

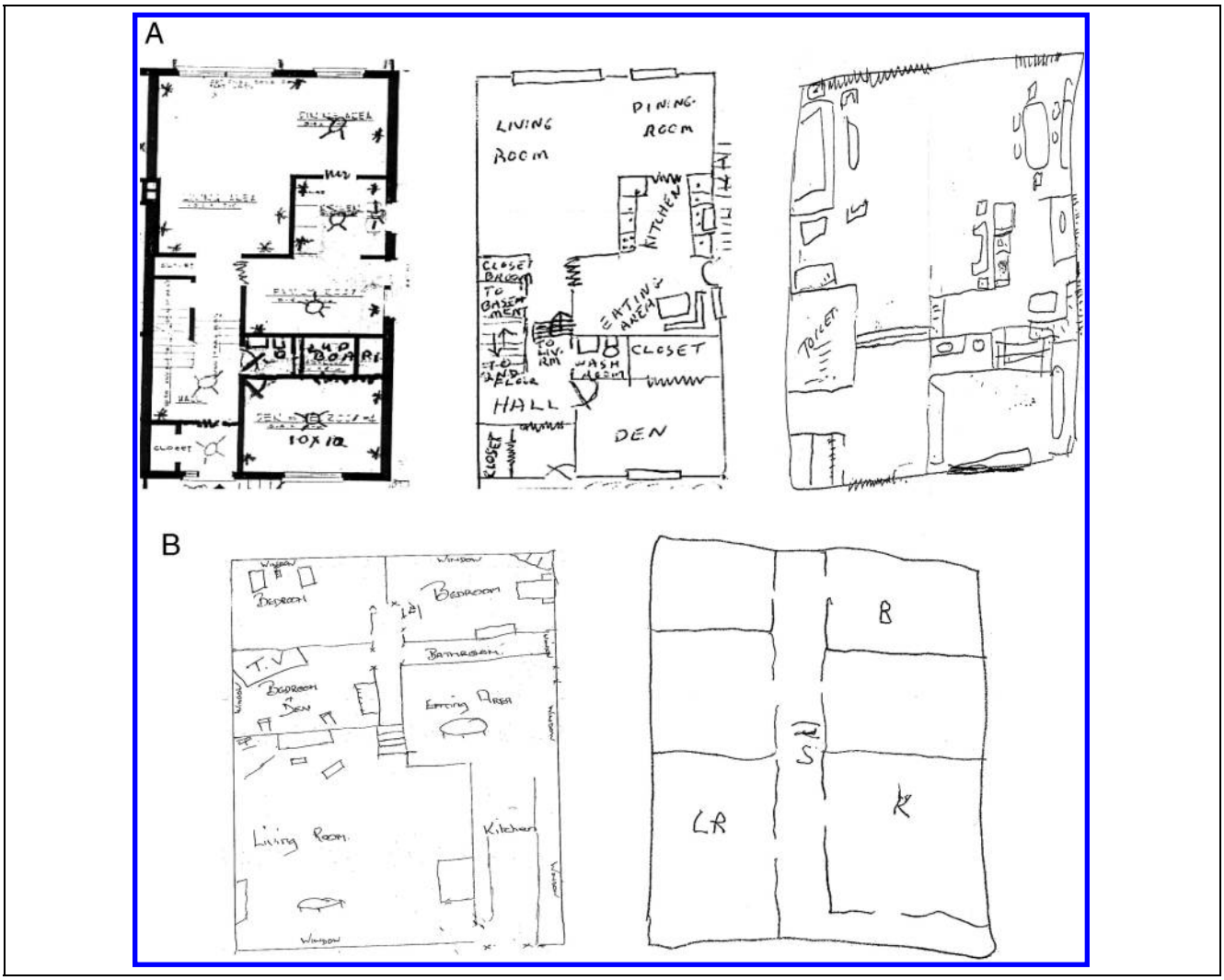

Figure 3. Sketch map of the house in which L. R. lives (A) and in which S. B. lives (B).

Table 4. Performance on Mental Navigation Tasks

Mental Navigation Tasks (Scoring Method)	*S. B.*	*L. R.*	*I. L.*	*Control Participants (SD, Range)*
Landmark localization (mean error in kilometers)	0.47	0.33	0.49	0.46 (0.09, 0.32–0.61)
Proximity judgments (% correct)	90	90	100	87.5 (14.88, 60–100)
Distance judgments (mean error in kilometers)	1.02	0.78	0.98	0.66 (0.3, 0.26–1.49)
Landmark sequencing (% correct)	100	100	90	87.5 (8.86, 70–100)
Vector mapping, distance (mean error in kilometers)	2.14	2.42	2.91	2.76 (0.54, 2.05–3.87)
Vector mapping, direction (mean error in degrees)	5.1[a]	15.5	9.4	17.7 (5.07, 10.5–22.4)
Blocked-route mental navigation (% correct)	95[a]	90	92.5[a]	70 (8.96, 57.5–80)

*SD*s and ranges in parentheses.

[a]Performance is significantly better than that of the control participants at $p < .05$.

dramatically through the use of flexible scoring criteria, they were not eliminated, making it likely that L. R.'s average-level performance represents an underestimate of his true ability.

Experiment 2: Visual Appearance of Landmarks

Recognition and Identification of Toronto Landmarks

As predicted, there was no retrograde amnesia for the locations of landmarks and mental navigation within a large-scale environment as a consequence of acquired MTL damage. However, there was some suggestion from the sketch-mapping task that S. B. might not be able to recover all aspects of an old environment, particularly the visual appearance of landmarks. As a more formal test of ventral-stream integrity, participants were required to distinguish photographs of well-known Toronto landmarks from comparable-looking distracters that were unfamiliar in a yes/no recognition task and, if possible, to identify the Toronto landmarks. Despite S. B.'s proficiency in representing the locations of well-known landmarks and navigating accordingly, he was unable to distinguish visually between those landmarks

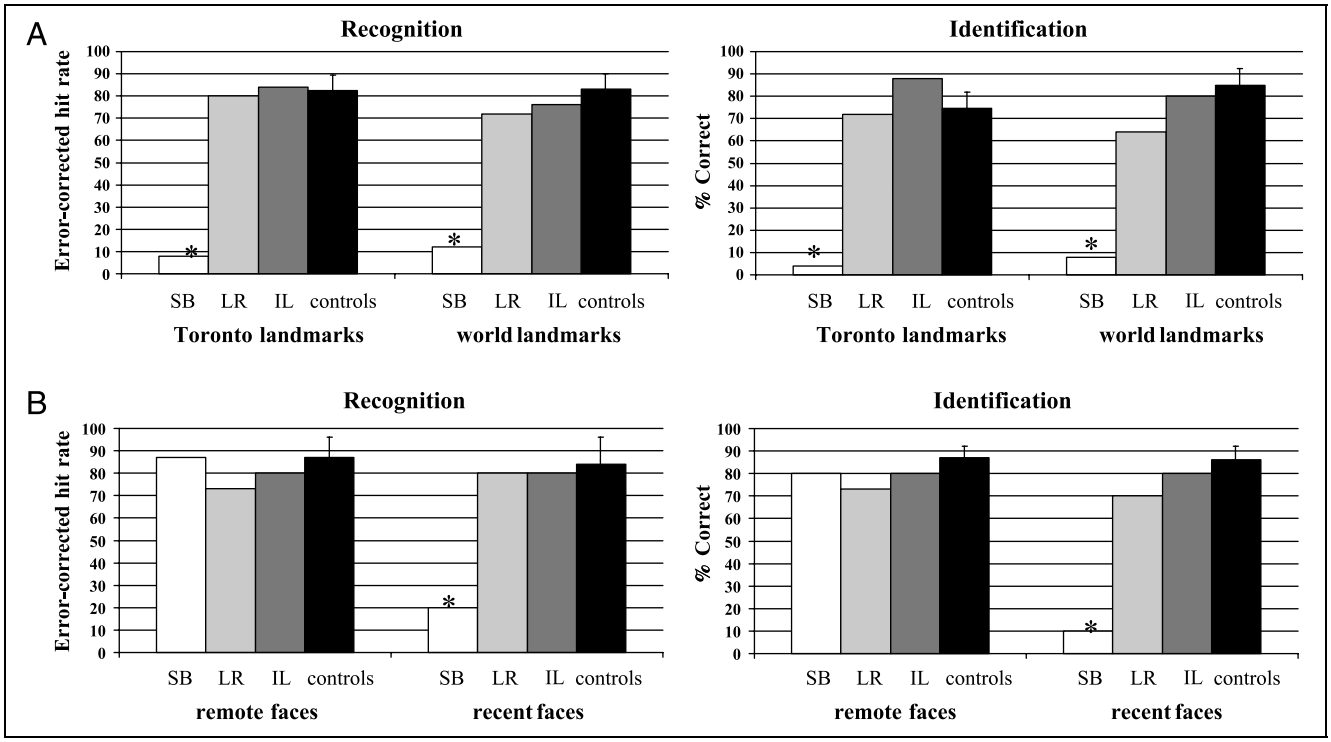

Figure 4. Percentage of famous Toronto and world landmarks (A) and famous remote and recent faces (B) accurately recognized (left) and identified (right), corrected for guessing using the standard formula. Asterisk indicates significant difference between patient S. B. and the controls.

from unknown buildings. As illustrated in Figure 4a, S. B. judged most of the landmarks and distracter buildings to be located in downtown Toronto. Furthermore, he was unable to name or identify by location any one of the landmarks that he recognized as familiar with the exception of the CN Tower, which he ''reckon[ed] is such because of its height and nearness to the lake [Lake Ontario].'' Although L. R. had difficulty naming the landmarks that he correctly distinguished from distracters, he was very eager to supply the precise intersections as well as related personal happenings in response to their visual appearance. The control participants, who were better than L. R. at retrieving landmark names, also recognized and identified the locations of many of the landmarks, while commenting that they had never seen the unfamiliar buildings.

Recognition and Identification of World Landmarks

So far, we have shown that a decline in memory for navigating an environment learned long ago is not an inevitable outcome of damage to MTL regions or to the temporal neocortex but that memory for landmarks and possibly other visual details contained within that environment may be at risk. One possibility is that both taxi drivers' knowledge of the visual features of landmarks that they visited became highly personalized and integrated into their episodic memory of unique incidents, which is compromised after hippocampal damage (Westmacott et al., 2004). If so, S. B.'s poor performance on the previous recognition task may reflect his severe episodic memory deficit, whereas L. R.'s intact performance may resemble the relative preservation of those semantic memories that have greater autobiographical significance, as observed in patients with semantic dementia. Support for this proposal would be indicated by a dissociation opposite to that for Toronto landmarks and specific to world landmarks that were never visited. If, on the other hand, S. B. shows that he generally is unable to recognize world landmarks from their visual appearance that he nevertheless knows by name, it would provide additional evidence for a visual agnosia for landmark stimuli.

To test these predictions, participants were asked to distinguish photographs of world-famous landmarks from those of unknown buildings, just as they had for Toronto landmarks. As Figure 4A shows, the results of this task replicate and extend those of the previous task, indicating that S. B. alone is impaired at recognizing the unique identity of famous landmarks. Again, S. B. was unable to tell apart famous landmarks from unknown buildings, whereas L. R. recognized and provided the correct locations of as many landmarks as controls, although he retrieved significantly fewer names.

Perceptual Matching of Landmarks

Besides intact performance on neuropsychological tests of line orientation and visuospatial construction, informal assessment of landmark perception showed that S. B. could describe many of the visual features depicted in each photograph, including the basic shape (e.g., more rounded), textures (e.g., brick), and minute details (e.g., fencing). His further ability to trace the outline of the landmarks with the back end of a pen indicated that the landmarks are perceived as discontinuous from their background. To test visuoperceptual ability with more rigor, we designed and administered a visual matching task using the same building stimuli as used in the recognition tasks. Participants were required to match photos of the same building, taken from different views, to one another but not to a similar distracter. The results from this task lend support to anecdotal evidence that S. B.'s landmark recognition deficit is unlikely to be attributable to a more basic perceptual disturbance. Indeed, both patients clearly were able to distinguish between landmarks that were similar in appearance but not identical, as indicated by the perfect score (10 of 10) attained by each participant. The patients further were able to identify a specific landmark as the same even when photographed from a different angle, with S. B. providing a correct response to four of the five such trials and all other participants performing flawlessly.

Visual Imagery of Landmark Size, Shape, and Color

S. B.'s performance in Experiment 1 reveals that his ability to image the spatial location of landmarks is reasonably well preserved, but his ability to image the appearance of those same landmarks remains unknown. There is much evidence to suggest that visual perception and visual imagery draw on some of the same

Table 5. Performance on Tests of Visual Imagery for Landmark Size, Shape, and Color

Visual Imagery Tasks (Maximum Score)	*S. B.*	*L. R.*	*I. L.*	*Control Participants (SD, Range)*
Imagery of relative size (/5)	2[a]	5	5	4.7 (0.48, 4–5)
Imagery of relative shape (/5)	2[a]	5	5	4.8 (0.42, 4–5)
Color imagery (/10)	2[a]	8	9	8.8 (0.92, 7–10)

[a]Performance is significantly worse than that of the control participants at $p < .001$.

underlying mechanisms for processing objects (e.g., O'Craven & Kanwisher, 2000). It is therefore possible that S. B.'s landmark perception deficit is accompanied by one in imagery. To evaluate this possibility, a set of tests known to be sensitive to visual imagery loss were adapted to assess the ability to inspect in the mind's eye the visual appearance of landmark features from long-term memory. Table 5 shows that unlike the other patient and control participants, S. B. has lost his ability to conjure up in imagery the size, shape, and color of features of known places. That his internal landmark images are as impoverished as his visual recognition of external landmark stimuli in the absence of more basic perceptual deficits is suggestive of an agnosia that is associative in nature.

Recognition and Identification of Famous Faces

To examine whether S. B.'s agnosia for landmarks in Toronto and the world also extends to other complex visual stimuli, he was asked to recognize faces of people who became famous in different decades, from 1950 onward either by naming them or providing identifying information. S. B.'s difficulty with well-known landmarks was found not to extend to visual recognition of faces, indicated by his ability to identify by name and occupation many of the faces that he recognized as famous. However, he did show effects of time on this semantic-like test of remote memory, with better face recognition for people who achieved fame when the patients were younger compared to more recently (see Figure 4B). These findings rule out the possibility that the landmark agnosia is the result of a generalized amnesia associated with hippocampal damage.

Experiment 3: New Spatial Learning

As described above, loss of tissue in MTL regions should compromise learning of environments encountered after the onset of brain damage, much as it impedes the ability to acquire other kinds of new declarative knowledge. To place the preserved navigational abilities in perspective, it is important to establish that S. B. is impaired at new spatial learning. Cursory observation suggests that S. B. has been unable to acquire new spatial representations after his illness. At initial interview, he and his friend agreed that he often gets lost in new places, and he could not retrieve the spatial layout of a retirement home where he has lived for the past 6 months despite sincere efforts to do so. Coupled with his greater right-sided hippocampal volume loss and the results of formal neuropsychological testing, we expected S. B. to have greater difficulty than L. R. in learning the layout of a new environment on a more formal test of navigation along a quarter-mile route (Figure 5).

S. B. performed at chance levels on all trials with the exception of the second immediate condition on the second day, on which his performance improved to five errors. However, his performance reverted to seven errors after a 30-min delay, and his inability to identify an alternate route between the start and end points was further evidence that he did not acquire a flexible, mental representation of the hospital layout. This was in stark contrast to L. R., who made five errors only in the first immediate test condition, improved to one error by the first delay condition, and received a perfect score on all trials of the second day. Moreover, L. R.'s formation of an allocentric map of the hospital layout was made clear well before his effortless use of a detour on formal testing; by the end of the first day, he pointed in the direction of the shortcut and commented, "This is sooner."

DISCUSSION

In this study, we examined the status of remote topographical memory in two taxi drivers who later developed different patterns of tissue loss in medial and neocortical parts of the temporal lobe, relating in one case to probable AD (S. B.) and in the other to encephalitis (L. R.). In so doing, we show the following: (1) Hippocampal loss in AD does not lead to a decline in the ability to store and recover old, allocentric spatial memories but may be needed for the acquisition of new layouts; likewise, memories of recently learned faces is impaired, but not memories of old faces. (2) Not all old memories are spared; occipitotemporal damage leads to loss of memories for landmarks (landmark agnosia), suggesting that a dorsal–ventral dissociation is a possible consequence of AD. Together, the results show that some, but not all, aspects of an environment learned years ago continue to benefit from prior expertise, even in the face of brain lesions. These findings are discussed in turn.

Topographical Disorientation in AD: Implications for Hippocampal Function

Remote Memory

It is widely believed that the tendency for disorientation in AD relates to memory failure from the reduction of hippocampal volume that occurs early in the disease (e.g., Burgess et al., 2002). Although this may be true of newly encountered places, as will be discussed shortly, it cannot fully explain instances of getting lost in environments that are familiar from many years before onset. Specifically, the results of our experimental investigation showed that despite extensive damage to S. B.'s hippocampus bilaterally, he performed at least as well as the other patients and controls on a range of mental navigation measures based on the topography of a city for which he was once an expert. This was true of a second, encephalitic patient L. R. who, like S. B., accurately positioned the spatial locations of landmarks on a street map of downtown Toronto. The two patients were also

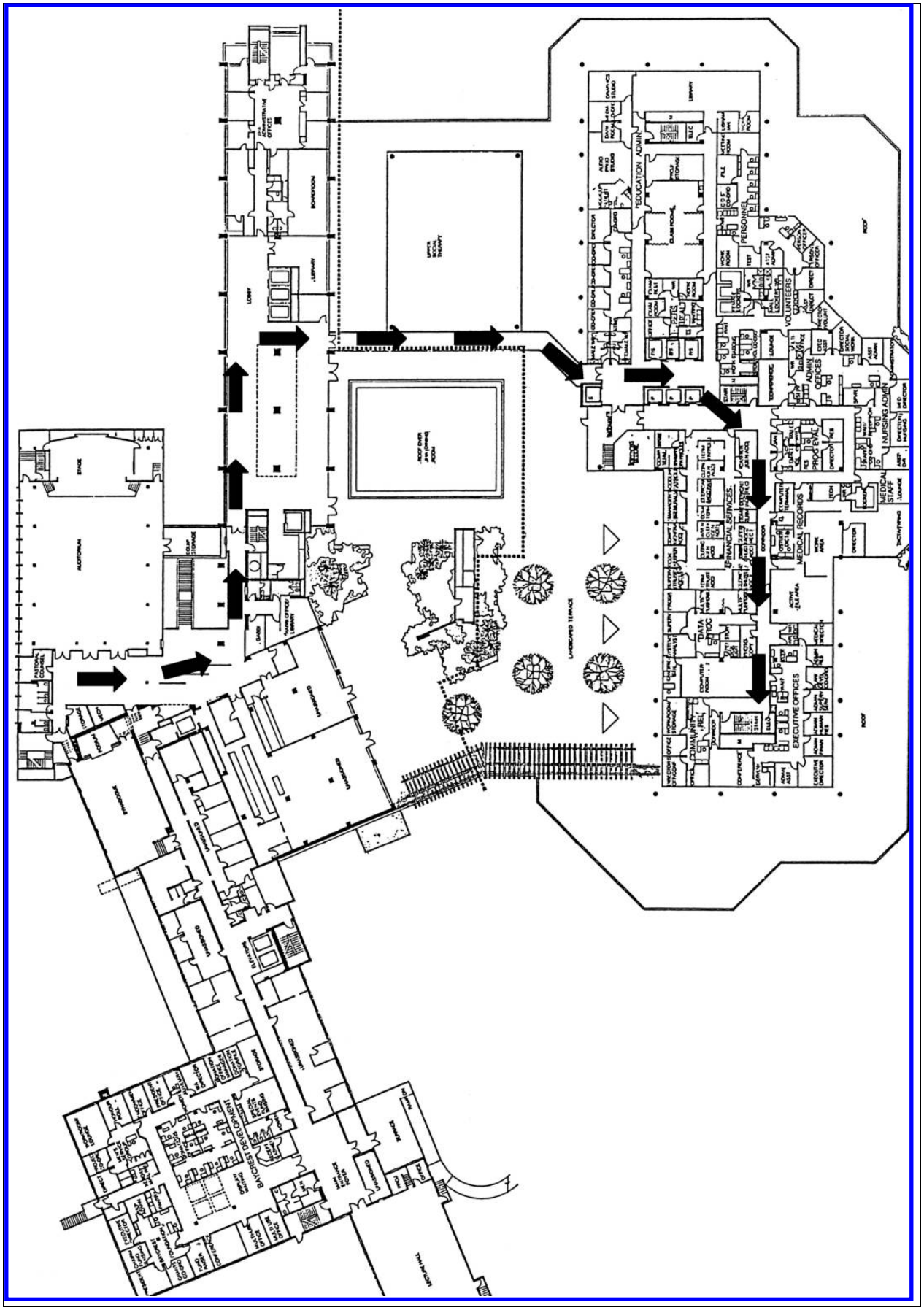

Figure 5. Aerial view of the second floor of the hospital route used for the new spatial learning task.

able to represent the spatial relations of landmarks within allocentric and egocentric coordinates as indicated by intact estimation of distance on measures of proximity judgments, distance judgments, and vector mapping, and by correct sequencing of landmarks along a route. In fact, S. B. outperformed L. R., who performed at the level of the nonexpert controls, on a more complex test of devising an alternate route to avoid a detour, and even surpassed the ability of the expert control on a vector-mapping test of orientation. Both tests require the flexible integration of allocentric and egocentric frames, with the former, in particular, thought to be specific to the domain of hippocampal operations.

That performance was well preserved despite extensive hippocampal damage suggests that the hippocampus is not needed for navigation based on remote spatial memory. This is in line with what was found of two amnesic patients with massive lesions to their hippocampus bilaterally, relating to a closed-head injury in one case (Rosenbaum et al., 2000) and to viral encephalitis in the other (Teng & Squire, 1999). Both patients performed at the level of controls on the range of remote spatial memory tasks that were used in the present study, but that were based on a neighborhood that the patients had lived in for many years before lesion onset.

Rather than focus on the hippocampus, our study suggests that representations of spatial layouts learned and practiced extensively long before lesion onset is mediated by a network of primarily dorsal regions that are intact in S. B. These include the parietal and retrosplenial cortex, which were activated in our recent fMRI study of mental navigation in healthy, young adults that used the same tests as in this study with patients (Rosenbaum et al., 2004). The possibility remains, however, that the representations of spatial layouts learned and practiced premorbidly were transformed in the process so that they no longer code for allocentric spatial information that depends on the hippocampus (Hartley et al., 2003). Although we concede this possibility, we think it is unlikely insofar as many of our tests, such as the blocked-route and vector mapping tests, are considered diagnostic of the allocentric spatial representations that form cognitive maps.

Recent Memory

Although unlikely to be the permanent repository of old spatial memories or to be needed to retrieve them, the hippocampus and related MTL structures contribute to the formation and retention of new knowledge, including cognitive maps of environments. In contrast to L. R., who has less extensive hippocampal damage, S. B. was profoundly amnesic for a new route after extensive training, let alone for abstraction of a more efficient shortcut. Together with his spared remote spatial memory, S. B.'s profile is strikingly similar to the behavior of the two amnesic patients with bilateral hippocampal lesions who also exhibit impaired encoding of indoor (Rosenbaum et al., 2000) and outdoor (Teng & Squire, 1999) layouts and yet possess intact memory for comparable layouts that were experienced premorbidly. The same is true of H. M., although he could also retain a postmorbid environment after extensive experience with it (Corkin, 2002).

Because S. B.'s damage extends beyond his MTL, his spatial impairment may result from atrophy to other regions, such as the parietal cortex. For example, in a recent study of route learning in an outdoor setting, the nature of impaired performance in a group of patients with AD was linked to a fundamental disturbance of parietal-mediated spatial processing (Cherrier, Mendez, & Perryman, 2001). However, other studies of parietal lobe contributions to disorientation that also assessed remote spatial memory (Levine et al., 1985), including an earlier study of patients with AD (de Leon, Potegal, & Gurland, 1984), extend the deficit to representations of previously familiar environments. Although S. B.'s parietal cortex shows clear signs of atrophy, the scope of his spatial deficit is limited for the most part to novel places, which casts doubt on a parietal explanation.

An alternative to the hippocampal interpretation of S. B.'s deficit in learning new locations is that he failed to learn to recognize static topographical stimuli or complex scenes that aid in signaling one's whereabouts after damage to the ventral visual cortex. In a recent study using a test of new spatial learning similar to ours, patients with damage to the right inferotemporal cortex and right or left occipitotemporal cortex were as impaired as patients with MTL lesions, presumably as a result of an inability to process indoor ''landmarks'' visually (Barrash, Damasio, Adolphs, & Tranel, 2000). S. B.'s inability to learn a new hospital route may also stem from damage to a similar set of brain structures, either alone or in combination with MTL dysfunction, as suggested by a selective visual recognition deficit that he exhibits and to which we now turn.

Fractionation of ''What'' and ''Where'' in an Expert Navigator: Landmark Agnosia

Despite S. B.'s mental navigation capabilities, his recognition memory for the visual appearance of landmarks was strikingly poor, suggesting that he has an agnosia for landmarks. This was true not only of landmarks that occupy locations that S. B. remembered well on mental navigation testing and that he had seen on a regular basis as a taxi driver, but also of ones that are world famous and that he had never visited. S. B.'s landmark recognition deficit thus cannot only result from loss of autobiographical episodic significance owing to hippocampal damage, as occurs in some patients with AD (Westmacott et al., 2004). If it did, only landmarks at which specific personal events were experienced would

have been lost from memory. In a similar vein, it is unlikely that autobiographical significance, mediated by L. R.'s hippocampus and associated with specific personal memories, served to protect the identity of Toronto landmarks, as occurs in some patients with semantic dementia, because world landmarks, which are more akin to semantic concepts, did not fall prey to his disproportionate loss of temporal neocortex.

The severity and uniqueness of S. B.'s deficit is highlighted further when considered alongside the intact landmark recognition demonstrated by patient L. R. The two patients have in common atrophied hippocampi, but only S. B. has additional damage to medial fusiform and inferior lingual gyri, regions implicated in landmark processing. This suggests that compensation may not be possible if a neural region is essential to a particular processing domain, even in a patient with sophisticated experience with that domain. S. B.'s performance also differs from that of two patients studied by Epstein, De Yoe, Press, Rosen, and Kanwisher (2001) who had lesions to the parahippocampal gyrus, close to but not touching the anterior lingual boundary, in addition to more posterior lesions to inferior lingual and medial fusiform gyri. These patients had no difficulty in recognizing the same set of world landmarks as used in the present study. Rather, the deficient performance observed in these patients was confined to the encoding into memory of novel scenelike configurations. This profile of impairment is similar to that observed in two patients described by Habib and Sirigu (1987) and one patient described by Pai (1997), whose lesions converge on the parahippocampus, but is unlike the time-independent landmark deficit often seen in patients with more posterior lesions (Aguirre & D'Esposito, 1999).

Functional segregation, therefore, might exist along the parahippocampal–lingual axis, with a more anterior medial-temporal portion dedicated to the perceptual integration of static topographical features at encoding and a more posterior ventral portion dedicated to the identification of well-learned landmarks, which also can be used to aid navigation. This localization of function is consistent with our recent fMRI finding of an anterior area of the parahippocampal cortex that responds to buildings irrespective of familiarity, and that is separate from activity in a more posterior parahippocampal-anterior lingual site that responds to well-known Toronto landmarks but not to unknown buildings (Rosenbaum et al., 2004).

The presence of additional atrophy to S. B.'s left anterior temporal lobe raises the added possibility that his landmark recognition deficit extends beyond the visual modality and represents a category-specific semantic loss of landmark knowledge as was discovered of the McCarthy, Evans, and Hodges (1996) patient, S. E. However, this alternative is made doubtful by S. B.'s intact performance to verbal referents of those landmarks for which he generates the exact locations, coupled with his tendency to offer facts about the landmarks such as their history and function, even when not made obvious from their names. Furthermore, L. R., who has more extensive damage to his temporal neocortex, readily demonstrates intact recognition of photographs of landmarks, despite his inability to name them or provide semantic information about them.

The most likely interpretation of S. B.'s deficit is that it represents a material-specific visual agnosia for landmarks caused by damage of the posterior parahippocampal gyrus bordering on the medial fusiform and lingual gyri. The specificity of this agnosia to landmarks is indicated by S. B.'s ability to recognize and identify famous faces. A pattern of relatively preserved elementary visual perception on neuropsychological testing and on a landmark-matching task, coupled with impaired imagery for the visual features of those landmarks that were unrecognizable by names but not from their photographs, suggests an associative form of agnosia (Farah, 1990). Unlike apperceptive agnosics who would fail to describe the visual properties of a landmark that is physically present, much less distinguish a landmark from its background, the breakdown in associative agnosia is at the level of long-term visual representations or access to them, preventing the assignment of meaning to a unique topographical percept that was experienced in the recent or remote past. Therefore, one reason that patients with AD lose their way in familiar environments is that they have lost their visual knowledge of landmarks with which to orient, and not that they have a deficient cognitive map with which to navigate.

Conclusion

We presented a series of detailed experiments with a patient with AD, retired taxi driver of 40 years in an attempt to understand better the brain regions responsible for preserved and impaired aspects of remote topographical memory in an expert navigator. Through comparisons with another expert patient and expert and nonexpert controls, we learned that memory for the locations of well-known landmarks and the spatial relations among them can survive significant atrophy to the hippocampus, a structure that many researchers believe to be essential to the formation, storage, and recovery of allocentric spatial maps of environments (e.g., O'Keefe & Nadel, 1978). Although it is possible that any residual hippocampal tissue in S. B. is responsible for such preservation, observations in other patients with more extensive damage to this structure (Rosenbaum et al., 2000; Teng & Squire, 1999), coupled with findings from a recent fMRI study in healthy, young adults (Rosenbaum et al., 2004), argue against this alternative. Nevertheless, although repetitive exposure is not needed to maintain proficiency in mental navigation, topographical expertise is not enough to guard against landmark agnosia associated with ventral visual-stream damage.

METHODS

Participants

The performance of the two patients, S. B. and L. R., who have previous experience as taxi drivers, was compared to that of an age-matched retired taxi driver who is free from neurological illness (I. L.) and a group of eight neurologically healthy controls without such navigational exposure (see Table 1). All participants worked or lived in downtown Toronto for a minimum of 20 years until at least 10 years ago, and have since visited a maximum of six times per year. Participants gave informed, written consent to be involved in the study, which was approved by the Baycrest Centre for Geriatric Care and the University of Toronto ethics committees.

Patients

S. B. was 80 years old at the time of testing. He is a right-handed man with 9 years of formal education. He worked for 30 years in downtown Toronto as a taxi driver and then as a courier for 15 years until his retirement in 1985. Soon after, he moved to a suburb just north of Toronto where he had lived with a friend until this past year and has since visited the downtown district only a handful of times. At the time of presentation, S. B. had met the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for probable AD (McKhann et al., 1984) and *Diagnostic and Statistical Manual of Mental Disorders, 3rd revision*, criteria for dementia (American Psychiatric Association, 1987) with no evidence of vascular change (see below). He had a 2-year history of misplacing items, poor day-to-day memory, and difficulties in remembering facts and events from the recent past, including finding his way in new places. Word-finding difficulties were reported as mild and visuospatial ability as intact. Remote medical history included a blow to the head sustained from boxing in his early 20s without apparent change to cognitive function.

The results of a neuropsychological assessment performed in June 2000, within 6 months of experimental testing, are summarized in Table 2. Performance on a test of cognitive screening for dementia (Dementia Rating Scale [DRS]) fell below the cutoff for dementia, mostly accounted for by impaired performance on tests of verbal initiation and memory. General intellectual ability was within the low average range on the Wechsler Adult Intelligence Scale-Revised (WAIS-R), consistent with S. B.'s educational and occupational background. Performance was satisfactory on the WAIS-R Digit Span test of primary memory (forward and backward span) but was compromised on tests of visuomotor tracking and focused attention (WAIS-III digit-symbol substitution and Trails A number sequencing). With respect to verbal memory, performance on the California Verbal Learning Test (CVLT) was markedly impaired on acquisition, short delay recall, long delay recall, and recognition discriminability. Visual memory for the Rey–Osterrieth Complex Figure (ROCF) was impaired following a 30-min delay. Language examination revealed anomia but relatively intact semantic memory. Poor performance was noted on an animal-naming test of semantic fluency and on the Boston Naming Test (BNT), with a moderate benefit from phonemic cueing. Semantic memory was in the low average range on the WAIS-R Vocabulary subtest and in the average range on the Wide Range Achievement Test-Revised (WRAT-R) Reading subtest. Reproduction of the Rey Figure was impoverished as a result of poor organization, but visuospatial perception (Judgment of Line Orientation [JLO]) and reconstruction (WAIS-R Block Design) were otherwise intact. On tests of executive function, concept formation and mental flexibility were within normal limits for age on the Wisconsin Card Sorting Test (WCST, five categories completed), but S. B. produced a high number of perseverative responses. Performance was in the low average range on phonemic fluency (FAS), verbal and nonverbal tests of abstract reasoning (WAIS-III Similarities and Matrix Reasoning), and speeded alternation between numbers and letters (Trails B).

L. R. was a 76-year-old, right-handed man with 12 years of education who worked as a taxi driver in downtown Toronto for 41 years. After his retirement in 1992, he had visited downtown only to go directly to the theater or to a restaurant (not more than five times a year) and has not returned since his encephalitis. He continues to live with his wife in a house north of the city proper to which they moved in 1963. In April 2002, L. R. was admitted to hospital and treated with acyclovir for viral encephalitis after presenting with a 2-day history of increasing flulike symptoms, confusion, and memory loss. Although his day-to-day nonverbal memory had resolved to near-normal levels, the encephalitis left him with a severe anomia accompanied by occasional phonemic paraphasias, although comprehension is fairly good and speech is fluent and grammatical. Interestingly, to compensate for his inability to retrieve names, L. R. identifies people that he knew from before his injury according to where they live and those whom he has met since arriving at the hospital according to the location of their room or office. He does so by using the names of streets and house numbers or room numbers, the only words that he continues to retrieve with ease. MRI performed in April 2002 revealed bilateral temporal lobe involvement that was greater laterally than medially and that was much worse on the left. Atrophy was also observed in the posterior thalamus and inferior frontal cortex on the left.

Neuropsychological testing was performed in October 2002 contemporaneous with experimental testing, while L. R. was still in hospital. Throughout testing, L. R. was alert, appropriate, cooperative, and exhibited little

difficulty understanding test instructions. He demonstrated good insight into his difficulties and was easily frustrated by his test performance. Despite the need to administer an abbreviated battery, the assessment confirmed profound compromise to L. R.'s verbal abilities despite well-preserved nonverbal memory and visuospatial function (see Table 2). Mental status as measured by the DRS was below the cutoff for dementia because of impaired verbal initiation and memory. Overall, general intellectual ability was estimated to be in the low average range as measured on the Wechsler Abbreviated Scale of Intelligence (WASI), with a significant discrepancy between impaired verbal ability and average nonverbal ability. Accordingly, he was impaired at learning and recalling after a 20-min delay the 12 items from the Word-List subtest of the Kaplan–Baycrest Neuropsychological Assessment (KBNA). However, digit span on the WAIS-III subtest fell in the average range and replication of an array of dots of increasing size from primary memory on the KBNA Spatial Location subtest fell in the high average range. L. R. also retained most of the details of the Rey Figure after a 30-min delay and successfully discriminated a set of incidentally encoded objects from new objects after a 20-min delay on the KBNA Picture Recognition subtest. Nonetheless, phonemic fluency and semantic fluency were both severely impaired. Confrontation naming on the Boston Naming Test was also severely impaired, and though phonemic cueing did not facilitate word retrieval, it was clear from gestures and descriptions that L. R. recognized many of the objects that he was unable to name. Semantic memory loss was indicated by impaired performance on the Vocabulary subtest of the WASI and on the picture–picture version of the Pyramids and Palm Trees test (Howard & Patterson, 1992), a nonverbal test of semantic access on which age-matched controls perform invariably at ceiling (Hodges & Graham, 1998). Nevertheless, L. R. shows no evidence of difficulties in visuospatial ability; his copy of the Rey Figure and perception of angles on the JLO test are both within the average range of performance. Performance was likewise intact on speeded number–letter sequencing (Trails B) and nonverbal abstract reasoning (WASI Matrix Reasoning) tests of executive function but not on a verbal test of reasoning (WASI Similarities).

Control Participants

Comparisons were made with I. L., an 80-year-old right-handed man with 10 years of education who worked as a taxi driver for 30 years until his retirement just over 10 years ago. Eight right-handed older adults (half of whom were men) who never worked as taxi drivers or couriers or in any other profession that places heavy demands on navigation within the city (e.g., delivery, postal worker) also served as controls. Mean age was 69 years (range, 65–74 years) and mean education in years was 12.12 (range, 10–16 years). All control participants were without a history of neurological or psychiatric illness. Analysis of the patients' test score against norms derived from the control group was conducted with a modified *t* test method that treats each individual patient and small group as a sample of sufficient size (Crawford & Garthwaite, 2002). For the volumetric analysis, the images of a second group of 45 control participants (25 male) were selected from a database of scans at the same unit where the patients were scanned. All controls were right-handed, free from medical illness, and never worked as taxi drivers (age: mean, 70.9 years; range, 56–81 years; years of education: mean, 14.5 years; range, 10–19 years).

Magnetic Resonance Imaging: Acquisition and Analysis

The patients and controls were scanned with a 1.5-T magnet with a standard coil (Signa, General Electric Medical Systems, Waukesha, WI). Standard high-resolution, T1-weighted images were acquired using a volumetric 3-D sequence covering the whole brain (TR = 5 msec, TE = 24 msec, NEX = 1, flip angle = 35°, acquisition matrix = 256 × 192; FOV = 22 cm; 124 axial slices; slice thickness = 1.4 mm). T2-weighted images, used to rule out significant vascular disease and for head size correction, were acquired in the transverse plane using an 11.4-min, interleaved, dual spin–echo sequence (TR/TE1/TE2 = 3000/30/80 msec; NEX = 0.5; acquisition matrix = 256 × 192; FOV = 20 cm; slice thickness = 3.0 mm). All T1-weighted images were transferred to a SUN ULTRA 3 workstation (SUN Microsystems, Mountain View, CA). Images were then reformatted parallel to the anterior commissure–posterior commissure (AC–PC) plane of Talairach and Tournoux (1998) and the skull was removed for viewing the cerebral surface using ANALYZE AVW software (version 2.5, Mayo Foundation, Rochester, MN). The volumes of the hippocampus, parahippocampal cortex, fusiform gyrus, and posterior cingulate were quantified according to a recently published protocol (Callen, Black, Gao, Caldwell, & Szalai, 2001) and corrected for interindividual differences in head size using the procedure described by Kovacevic et al. (2002). All traces were drawn blind to patient diagnosis. Mean regional volumes from the control participants were used to calculate *Z* scores, which generally indicated disproportionate volume loss in several regions of interest in each of the patients but also increased volume in at least one other region.

Experiment 1: Remote Memory for Landmark Location and Mental Navigation

The following tasks included as stimuli either single or pairs of names of downtown Toronto landmarks that were selected by participants as most familiar on a ques-

tionnaire administered 1 month before testing. Before each test, participants were reminded of the streets bordering the area of downtown Toronto relevant to the study as well as the north–south distance of this area. Tasks were presented in a fixed order and followed the progression of mental representations from simply locating individual landmarks in space (Task 1), to representing landmarks in relation to other landmarks and the self (Tasks 2–4), to more complex integration of allocentric and egocentric frameworks (Tasks 5 and 6).

Task 1: Landmark Localization

Participants were presented with a map containing only the streets bordering downtown Toronto and were asked to draw a dot on the map representing the location of each of 10 specified landmarks. Deviation of each landmark from its true location was measured.

Task 2: Proximity Judgments

In a test of relative distance judgments, participants indicated which of two landmarks was closest in distance to a third, reference landmark. The actual distance among the 10 sets of landmarks varied from trial to trial, and half of the trials were more demanding (i.e., the difference in distance between the reference and choice landmarks was less than 1 km).

Task 3: Distance Judgments

Participants were asked to provide numerical judgments of absolute distance between each of 10 pairs of landmarks. The actual distances between landmarks were varied and randomly intermixed across trials. The mean deviation of the judged distances from the actual distances was calculated.

Task 4: Landmark Sequencing

Ten randomly ordered names of landmarks located along a north–south route were presented, and participants were to order the landmarks in the sequence that would be passed during a mental walk of the route.

Task 5: Vector Mapping

Participants were asked to draw arrows indicating the correct distance and direction from a location specified by a mark to an unmarked landmark on 10 maps that included only the northern- and southernmost borders. Deviation of estimates from actual directions and distances was calculated for each trial and averaged to derive error scores.

Task 6: Blocked-Route Mental Navigation

In a paradigmatic test of cognitive mapping, participants were asked to simulate taking shortcuts in a task requiring a change of route from the most direct route between a pair of landmarks. There were five such trials, each consisting of four choice points at which to turn right or left, for a maximum score of 20.

Experiment 2: Visual Appearance of Landmarks and Faces

Recognition and Identification of Toronto and World Landmarks

For the Toronto landmark task, 25 black-and-white photographs of downtown Toronto landmarks, and of buildings that are structurally similar to those located in Toronto but that have never been encountered by the participants, were presented one at a time in random order. All photographs were taken from an unobstructed view and were digitally scanned and adjusted for luminance and contrast. In a separate world landmark task, participants viewed the set of 25 randomly ordered black-and-white photographs of famous world landmarks (e.g., Eiffel Tower) and 25 visually matched unknown buildings used by Epstein et al. (2001) in their investigation of the parahippocampal place area in patients. For each photograph, participants were to decide if the landmark is familiar, and if so, to identify it by name and location, or by some other means if necessary (e.g., type of building, decade in which it was established, and function).

Perceptual Matching of Landmarks

This task included photographs of known and unknown buildings that were paired with either an identical photograph (10 trials), a photograph of the same building taken at a different orientation (5 trials), or a photograph of a different building (15 trials). The three types of pairings were presented in random order, and for each, participants were to judge whether the photographs were of the same or different buildings.

Visual Imagery of Landmark Size, Shape, and Color

Imagery for the relative size and shape of landmark stimuli was first examined. The names of 10 pairs of Toronto landmarks were read aloud, and participants were instructed to form a mental image of the two landmarks. For each of the first five pairs, participants decided which of the two landmarks is larger, taking into account height, width, and depth. For the remainder of the stimuli, participants chose the landmark in each pair that is the most curved in shape. The second part of the imagery test involved the presentation of 10 of the black-and-white photographs of Toronto landmarks

from the recognition test and 10 crayons. For each landmark, participants were to choose the crayon that best represents the color of the landmark.

Recognition and Identification of Famous Faces

Participants viewed black-and-white photographs of 25 public figures who achieved fame in one of the last five decades, randomly intermixed with 25 matched nonfamous faces (Epstein et al., 2001). For each face, participants were to provide the name of the person or, if unable to do so, supply semantic information, such as the person's occupation (e.g., former U.S. President) or someone with whom the person was closely affiliated with (e.g., Hillary for Bill Clinton).

Experiment 3: New Spatial Learning

Using a real-world protocol similar to the one designed by Barrash et al. (2000), S. B. and L. R. received training along an approximately quarter-mile route in an open-concept hospital complex that was rich in visual detail. The route continued along two floors and contained 15 salient visual features that possess navigational value (e.g., located at corners, serving a functional purpose such as a cafeteria) but that were without obvious verbal cues, and 15 choice-turn points (Figure 5). There were two training-test sessions that took place on two separate days that were a week apart. At the beginning of each test session, the patients were told that they would learn a route so that they could navigate to future appointments unassisted. The patients were then guided along the route by the examiner, who pointed out and commented on each ''landmark.'' Way-finding performance was then tested on two consecutive trials immediately after each training session and again after a 30-min delay, with the examiner redirecting the patient after any wrong turn. The route that was devised also allowed participants to engineer a shortcut from the start point (hospital entrance) to the final destination (Neurology Department) that would reduce travel time by more than half. The ability to create such a detour was tested at the end of the second session. The total number of incorrect turns at choice turn points was recorded for the immediate, delay, and detour trials.

Acknowledgments

We are grateful to the patients and their families for their assistance. We thank Russell Epstein for his generosity in offering his world landmark stimuli for use with our patients, Cheryl Grady and Gordon Winocur for providing very insightful comments at all stages of this project. This study was supported by Canadian Institutes of Health Research (CIHR) grants to M. M. and S. E. B. and a CIHR doctoral award to R. S. R. The research reported in this manuscript was completed in partial fulfillment of requirements for R. S. R.'s doctoral dissertation at the University of Toronto.

Reprint requests should be sent to R. Shayna Rosenbaum, Rotman Research Institute, Baycrest Centre for Geriatric Care, Toronto, Ontario, Canada M6A 2E1, or via e-mail: srosenbaum@rotman-baycrest.on.ca.

REFERENCES

Aguirre, G. K., & D'Esposito, M. (1999). Topographical disorientation: A synthesis and taxonomy. *Brain, 122,* 1613–1628.

Aguirre, G. K., Detre, J. A., Alsop, D. C., & D'Esposito, M. (1996). The parahippocampus subserves topographical learning in man. *Cerebral Cortex, 6,* 823–829.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: American Psychiatric Association.

Barrash, J., Damasio, H., Adolphs, R., & Tranel, D. (2000). The neuroanatomical correlates of route learning impairment. *Neuropsychologia, 38,* 820–836.

Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica, 82,* 239–259.

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron, 35,* 625–641.

Callen, D. J. A., Black, S. E., Gao, F., Caldwell, C. B., & Szalai, J. P. (2001). Beyond the hippocampus: MRI volumetry confirms widespread limbic atrophy in AD. *Neurology, 57,* 1669–1674.

Cherrier, M. M., Mendez, M., & Perryman, K. (2001). Route learning performance in Alzheimer disease patients. *Neuropsychiatry, Neuropsychology, and Behavioural Neuroscience, 14,* 159–168.

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience, 3,* 153–160.

Crawford, J. R., & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia, 40,* 1196–1208.

de Leon, M. J., Potegal, M., & Gurland, B. (1984). Wandering and parietal signs in senile dementia of Alzheimer's type. *Neuropsychobiology, 11,* 155–157.

Epstein, R., De Yoe, E. A., Press, D. Z., Rosen, A. C., & Kanwisher, N. (2001). Neuropsychological evidence for a topographical learning mechanism in parahippocampal cortex. *Cognitive Neuropsychology, 18,* 481–508.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 392,* 598–601.

Farah, M. J. (1990). *Visual agnosia: Disorders of object recognition and what they tell us about normal vision.* Cambridge: MIT Press.

Habib, M., & Sirigu, A. (1987). Pure topographical disorientation: A definition and anatomical basis. *Cortex, 23,* 73–85.

Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. *Neuron, 37,* 877–888.

Hodges, J. R., & Graham, K. S. (1998). A reversal of the temporal gradient for famous person knowledge in semantic dementia: Implications for the neural organization of long–term memory. *Neuropsychologia, 36,* 803–825.

Howard, D., & Patterson, K. (1992). *Pyramids and palm trees: A test of semantic access from pictures and words.* Bury St Edmunds, Suffolk: Thames Valley Test Company.

Kopelman, M. D. (1985). Rates of forgetting in Alzheimer-type

dementia and Korsakoff's syndrome. *Neuropsychologia, 23,* 623–638.
Kopelman, M. D. (1989). Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia, 27,* 437–460.
Kovacevic, N., Lobaugh, N. J., Bronskill, M. J., Levine, B., Feinstein, A., & Black, S. E. (2002). A robust method for extraction and automatic segmentation of brain images. *Neuroimage, 17,* 1087–1100.
Levine, D. N., Warach, J., & Farah, M. (1985). Two visual systems in mental imagery: Dissociation of ''what'' and ''where'' in imagery disorders due to bilateral posterior cerebral lesions. *Neurology, 35,* 1010–1018.
Maguire, E. A. (2001). The retrosplenial contribution to human navigation: A review of lesion and neuroimaging findings. *Scandinavian Journal of Psychology, 42,* 225–238.
Maguire, E. A, Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: A human navigation network. *Science, 280,* 921–924.
Maguire, E. A., Frackowiak, R. S., & Frith, C. D. (1997). Recalling routes around London: Activation of the right hippocampus in taxi drivers. *Journal of Neuroscience, 17,* 7103–7110.
McCarthy, R. A., Evans, J. J., & Hodges, J. R. (1996). Topographic amnesia: Spatial memory disorder, perceptual dysfunction, or category specific semantic memory impairment? *Journal of Neurology, Neurosurgery, and Psychiatry, 60,* 318–325.
McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. *Neurology, 34,* 939–945.
Nestor, P. J., Graham, K. S., Bozeat, S., Simons, J. S., & Hodges, J. R. (2002). Memory consolidation and the hippocampus: Further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia. *Neuropsychologia, 40,* 633–654.
O'Craven, K. M., & Kanwisher, N. (2000). Mental imagery of faces and places activates corresponding stimulus-specific brain regions. *Journal of Cognitive Neuroscience, 12,* 1013–1023.
O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map.* Oxford: Clarendon Press.
Pai, M. C. (1997). Topographic disorientation: Two cases. *Journal of the Formosan Medical Association, 96,* 660–663.
Rosenbaum, R. S., Priselac, S., Köhler, S., Black, S. E., Gao, F., Nadel, L., & Moscovitch, M. (2000). Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nature Neuroscience, 3,* 1044–1048.
Rosenbaum, R. S., Ziegler, M., Winocur, G., Grady, C. L., & Moscovitch, M. (2004). ''I have often walked down this street before:'' fMRI studies on the hippocampus and other structures during mental navigation of an old environment. *Hippocampus, 14,* 826–835.
Stout, J. C., Bondi, M. W., & Jernigan, T. L., (1999). Regional cerebral volume loss associated with verbal learning and memory in dementia of the Alzheimer type. *Neuropsychology, 13,* 188–197.
Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme Medical Publishers.
Teng, E., & Squire, L. R. (1999). Memory for places learned long ago is intact after hippocampal damage. *Nature, 400,* 675–677.
Tolman, E. C. (1948). Cognitive maps in rats and man. *Psychological Review, 55,* 189–208.
Westmacott, R., Black, S. E., Freedman, M., & Moscovitch, M. (2004). The contribution of autobiographical significance to semantic memory: Evidence from Alzheimer's disease, semantic dementia, and amnesia. *Neuropsychologia, 42,* 25–48.
Whiteley, A. M., & Warrington, E. K. (1978). Selective impairment of topographical memory: A single case study. *Journal of Neurology, Neurosurgery, and Psychiatry, 41,* 575–578.

This article has been cited by:

1. Alessandro O. Caffò, Antonella Lopez, Giuseppina Spano, Fabrizio Stasolla, Silvia Serino, Pietro Cipresso, Giuseppe Riva, Andrea Bosco. 2020. The differential effect of normal and pathological aging on egocentric and allocentric spatial memory in navigational and reaching space. *Neurological Sciences* **41**:7, 1741-1749. [Crossref]
2. Elizabeth S. Paul, Shlomi Sher, Marco Tamietto, Piotr Winkielman, Michael T. Mendl. 2020. Towards a comparative science of emotion: Affect and consciousness in humans and animals. *Neuroscience & Biobehavioral Reviews* **108**, 749-770. [Crossref]
3. Jessica Robin, Josée Rivest, R. Shayna Rosenbaum, Morris Moscovitch. 2019. Remote spatial and autobiographical memory in cases of episodic amnesia and topographical disorientation. *Cortex* **119**, 237-257. [Crossref]
4. Michiel H. G. Claessen, Martine J. E. Zandvoort, Frans S. S. Leijten, Ineke J. M. Ham. 2019. Memory for novel and familiar environments relies on the hippocampus: A case study on a patient with a right anteromesial temporal lobectomy. *Hippocampus* **29**:9, 869-875. [Crossref]
5. E Zita Patai, Amir-Homayoun Javadi, Jason D Ozubko, Andrew O'Callaghan, Shuman Ji, Jessica Robin, Cheryl Grady, Gordon Winocur, R Shayna Rosenbaum, Morris Moscovitch, Hugo J Spiers. 2019. Hippocampal and Retrosplenial Goal Distance Coding After Long-term Consolidation of a Real-World Environment. *Cerebral Cortex* **29**:6, 2748-2758. [Crossref]
6. Maddalena Boccia, Antonella Di Vita, Sofia Diana, Roberta Margiotta, Letizia Imbriano, Lidia Rendace, Alessandra Campanelli, Fabrizia D'Antonio, Alessandro Trebbastoni, Carlo de Lena, Laura Piccardi, Cecilia Guariglia. 2019. Is Losing One's Way a Sign of Cognitive Decay? Topographical Memory Deficit as an Early Marker of Pathological Aging. *Journal of Alzheimer's Disease* **68**:2, 679-693. [Crossref]
7. Daniel N. Barry, Eleanor A. Maguire. 2019. Remote Memory and the Hippocampus: A Constructive Critique. *Trends in Cognitive Sciences* **23**:2, 128-142. [Crossref]
8. Antonella Lopez, Alessandro O. Caffò, Giuseppina Spano, Andrea Bosco. 2019. The Effect of Aging on Memory for Recent and Remote Egocentric and Allocentric Information. *Experimental Aging Research* **45**:1, 57-73. [Crossref]
9. Signy Sheldon, Alexa Ruel. 2018. The many routes of mental navigation: contrasting the effects of a detailed and gist retrieval approach on using and forming spatial representations. *Psychological Research* **82**:6, 1130-1143. [Crossref]
10. Antonella Lopez, Alessandro O. Caffò, Andrea Bosco. 2018. Topographical disorientation in aging. Familiarity with the environment does matter. *Neurological Sciences* **39**:9, 1519-1528. [Crossref]
11. Jessica Robin. 2018. Spatial scaffold effects in event memory and imagination. *Wiley Interdisciplinary Reviews: Cognitive Science* **9**:4, e1462. [Crossref]
12. Edwige Pissaloux, Ramiro Velázquez. On Spatial Cognition and Mobility Strategies 137-166. [Crossref]
13. Tamas Madl, Stan Franklin, Ke Chen, Robert Trappl. 2018. A computational cognitive framework of spatial memory in brains and robots. *Cognitive Systems Research* **47**, 147-172. [Crossref]
14. Jessica Robin, Morris Moscovitch. 2017. Details, gist and schema: hippocampal–neocortical interactions underlying recent and remote episodic and spatial memory. *Current Opinion in Behavioral Sciences* **17**, 114-123. [Crossref]
15. Ineke J.M. van der Ham, Marieke A.G. Martens, Michiel H.G. Claessen, Esther van den Berg. 2017. Landmark Agnosia: Evaluating the Definition of Landmark-based Navigation Impairment. *Archives of Clinical Neuropsychology* **32**:4, 472-482. [Crossref]
16. Michiel H.G. Claessen, Ineke J.M. van der Ham. 2017. Classification of navigation impairment: A systematic review of neuropsychological case studies. *Neuroscience & Biobehavioral Reviews* **73**, 81-97. [Crossref]
17. R. Shayna Rosenbaum, Alice S.N. Kim, Stevenson Baker. Episodic and Semantic Memory 87-118. [Crossref]
18. Ming-Chyi Pai, Chih-Chien Lee. 2016. The Incidence and Recurrence of Getting Lost in Community-Dwelling People with Alzheimer's Disease: A Two and a Half-Year Follow-Up. *PLOS ONE* **11**:5, e0155480. [Crossref]
19. Hélène Sauzéon, Bernard N'Kaoua, Prashant Arvind Pala, Mathieu Taillade, Pascal Guitton. 2016. Age and active navigation effects on episodic memory: A virtual reality study. *British Journal of Psychology* **107**:1, 72-94. [Crossref]
20. Branden S. Kolarik, Kiarash Shahlaie, Abdul Hassan, Alyssa A. Borders, Kyle C. Kaufman, Gene Gurkoff, Andy P. Yonelinas, Arne D. Ekstrom. 2016. Impairments in precision, rather than spatial strategy, characterize performance on the virtual Morris Water Maze: A case study. *Neuropsychologia* **80**, 90-101. [Crossref]
21. Tânia Rocha, Hugo Fernandes, Hugo Paredes, João Barroso. Combining NFC and 3D Mapping to Enhance the Perception of Spatial Location for the Blind 607-615. [Crossref]
22. R. Shayna Rosenbaum, Benjamin N. Cassidy, Katherine A. Herdman. 2015. Patterns of preserved and impaired spatial memory in a case of developmental amnesia. *Frontiers in Human Neuroscience* **9**. . [Crossref]

23. Katerina Sheardova, Jan Laczó, Martin Vyhnalek, Ross Andel, Ivana Mokrisova, Kamil Vlcek, Jana Amlerova, Jakub Hort. 2014. Famous Landmark Identification in Amnestic Mild Cognitive Impairment and Alzheimer's Disease. *PLoS ONE* **9**:8, e105623. [Crossref]
24. R. Shayna Rosenbaum, Asaf Gilboa, Morris Moscovitch. 2014. Case studies continue to illuminate the cognitive neuroscience of memory. *Annals of the New York Academy of Sciences* **1316**:1, 105-133. [Crossref]
25. Sung-Wook Jung, Heung-Yeol Kim, Tack-Hoon Kim. 2013. The Effects of a Way-finding Exercise using a Map on the Cognitive Function and Performance of Activities of Daily Living in Patients with a Stroke. *The Journal of the Korea Contents Association* **13**:10, 434-443. [Crossref]
26. Gilyana G. Borlikova, Margarita Trejo, Alexandra J. Mably, Jessica M. Mc Donald, Carlo Sala Frigerio, Ciaran M. Regan, Keith J. Murphy, Eliezer Masliah, Dominic M. Walsh. 2013. Alzheimer brain-derived amyloid β-protein impairs synaptic remodeling and memory consolidation. *Neurobiology of Aging* **34**:5, 1315-1327. [Crossref]
27. Marnie Hirshhorn, Cheryl Grady, R. Shayna Rosenbaum, Gordon Winocur, Morris Moscovitch. 2012. Brain regions involved in the retrieval of spatial and episodic details associated with a familiar environment: An fMRI study. *Neuropsychologia* **50**:13, 3094-3106. [Crossref]
28. Hélène Sauzéon, Prashant Arvind Pala, Florian Larrue, Gregory Wallet, Marie Déjos, Xia Zheng, Pascal Guitton, Bernard N'Kaoua. 2012. The Use of Virtual Reality for Episodic Memory Assessment. *Experimental Psychology* **59**:2, 99-108. [Crossref]
29. Marnie Hirshhorn, Cheryl Grady, R.Shayna Rosenbaum, Gordon Winocur, Morris Moscovitch. 2012. The hippocampus is involved in mental navigation for a recently learned, but not a highly familiar environment: A longitudinal fMRI study. *Hippocampus* **22**:4, 842-852. [Crossref]
30. Ming-Chyi Pai, Chih-Chien Lee, Ya-Chi Yang, Yen-Ti Lee, Kuang-Chi Chen, Shu-Han Lin, Sheng-Siang Jheng, Pei-Wen Sun, Pei-Ju Cheng. 2012. Development of a Questionnaire on Everyday Navigational Ability to Assess Topographical Disorientation in Alzheimer's Disease. *American Journal of Alzheimer's Disease & Other Dementiasr* **27**:1, 65-72. [Crossref]
31. Myung-Won You, Dong Kyun Lee, Jong-Min Lee, Sun-Mi Kim, Chang-Woo Ryu, Eui Jong Kim, Geon-Ho Jahng. 2012. Structural and Functional Changes of Hippocampus in Long Life Experienced Taxi Driver. *Journal of the Korean Society of Magnetic Resonance in Medicine* **16**:2, 124. [Crossref]
32. Lawrence E. M. Grierson, John Zelek, Isabel Lam, Sandra E. Black, Heather Carnahan. 2011. Application of a Tactile Way-Finding Device to Facilitate Navigation in Persons With Dementia. *Assistive Technology* **23**:2, 108-115. [Crossref]
33. Terence V. Sewards. 2011. Neural structures and mechanisms involved in scene recognition: A review and interpretation. *Neuropsychologia* **49**:3, 277-298. [Crossref]
34. M. Mapstone, C. J. Duffy. 2010. Approaching objects cause confusion in patients with Alzheimer's disease regarding their direction of self-movement. *Brain* **133**:9, 2690-2701. [Crossref]
35. Gordon Winocur, Morris Moscovitch, Bruno Bontempi. 2010. Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal–neocortical interactions. *Neuropsychologia* **48**:8, 2339-2356. [Crossref]
36. Kim S. Graham, Morgan D. Barense, Andy C.H. Lee. 2010. Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia* **48**:4, 831-853. [Crossref]
37. Oliver Baumann, Edgar Chan, Jason B. Mattingley. 2010. Dissociable neural circuits for encoding and retrieval of object locations during active navigation in humans. *NeuroImage* **49**:3, 2816-2825. [Crossref]
38. Oliver Hardt, Einar Örn Einarsson, Karim Nader. 2010. A Bridge Over Troubled Water: Reconsolidation as a Link Between Cognitive and Neuroscientific Memory Research Traditions. *Annual Review of Psychology* **61**:1, 141-167. [Crossref]
39. Lawrence E. M. Grierson, John Zelek, Heather Carnahan. 2009. The Application of a Tactile Way-finding Belt to Facilitate Navigation in Older Persons. *Ageing International* **34**:4, 203-215. [Crossref]
40. Sheng-Siang Jheng, Ming-Chyi Pai. 2009. Cognitive map in patients with mild Alzheimer's disease: A computer-generated arena study. *Behavioural Brain Research* **200**:1, 42-47. [Crossref]
41. Roland Beisteiner, Kay Drabeck, Thomas Foki, Alexander Geißler, Andreas Gartus, Eva Lehner-Baumgartner, Christoph Baumgartner. 2008. Does clinical memory fMRI provide a comprehensive map of medial temporal lobe structures?. *Experimental Neurology* **213**:1, 154-162. [Crossref]
42. M. A. Parra, S. Abrahams, K. Fabi, R. Logie, S. Luzzi, S. D. Sala. 2008. Short-term memory binding deficits in Alzheimer's disease. *Brain* **132**:4, 1057-1066. [Crossref]

43. R. Shayna Rosenbaum, Gordon Winocur, Cheryl L. Grady, Marilyne Ziegler, Morris Moscovitch. 2007. Memory for familiar environments learned in the remote past: fMRI studies of healthy people and an amnesic person with extensive bilateral hippocampal lesions. *Hippocampus* **17**:12, 1241-1251. [Crossref]
44. H.J. Spiers, E.A. Maguire. 2007. The neuroscience of remote spatial memory: A tale of two cities. *Neuroscience* **149**:1, 7-27. [Crossref]
45. Ilana J. Hepner, Armin Mohamed, Michael J. Fulham, Laurie A. Miller. 2007. Topographical, Autobiographical and Semantic Memory in a Patient with Bilateral Mesial Temporal and Retrosplenial Infarction. *Neurocase* **13**:2, 97-114. [Crossref]
46. Larry R Squire, Peter J Bayley. 2007. The neuroscience of remote memory. *Current Opinion in Neurobiology* **17**:2, 185-196. [Crossref]
47. Jason D. Warren, Elizabeth K. Warrington. Chapter 14 Cognitive Neuropsychology of Dementia Syndromes 329-380. [Crossref]
48. Lisa Cipolotti, Chris M Bird. 2006. Amnesia and the hippocampus. *Current Opinion in Neurology* **19**:6, 593-598. [Crossref]
49. John R. Crawford, Paul H. Garthwaite. 2006. Methods of testing for a deficit in single-case studies: Evaluation of statistical power by Monte Carlo simulation. *Cognitive Neuropsychology* **23**:6, 877-904. [Crossref]
50. Morris Moscovitch, Lynn Nadel, Gordon Winocur, Asaf Gilboa, R Shayna Rosenbaum. 2006. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Current Opinion in Neurobiology* **16**:2, 179-190. [Crossref]
51. Kathryn M. Gill, Sheri J. Y. Mizumori. 2006. Context-dependent modulation by D_1 receptors: Differential effects in hippocampus and striatum. *Behavioral Neuroscience* **120**:2, 377-392. [Crossref]
52. 2005. Current awareness in geriatric psychiatry. *International Journal of Geriatric Psychiatry* **20**:9, 903-910. [Crossref]
53. Morris Moscovitch, R. Shayna Rosenbaum, Asaf Gilboa, Donna Rose Addis, Robyn Westmacott, Cheryl Grady, Mary Pat McAndrews, Brian Levine, Sandra Black, Gordon Winocur, Lynn Nadel. 2005. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *Journal of Anatomy* **207**:1, 35-66. [Crossref]