

The Eyes Remember It: Oculography and Pupillometry during Recollection in Three Amnesic Patients

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Abstract

■ Two patients (TC and SS) with lesions that included the hippocampal regions (predominantly on the left side) were severely impaired in their recall of simple, verbally stated facts. However, both patients remembered spatial information that was temporally associated with semantic information. Specifically, TC and SS could not recall explicitly the content of an episode, but their spontaneous oculomotor behavior showed that they retained some information about the event as their gaze automatically returned to the locations on the computer screen where visual information had been paired to verbally presented information. Thus, this spatial information is implicit, automatically retrieved, and eye-based, as when one patient (TC) was asked to point with the finger to the same positions he was impaired. In addition, in an old/new recognition task, TC and SS and an additional patient, OB, showed

significant changes in eye pupil diameter when viewing novel visual stimuli compared to stimuli that they had previously seen, also when they (incorrectly) declared with confidence that an old item was new. The spared memory of these patients, despite severe amnesia for the learning episodes, is characterized by a re-enactment of previous eye fixations that were associated with each (forgotten) episode and physiological responses (as indexed by pupillometry) to previously seen stimuli. Such spared memory can be seen as a type of “snapshot” memory, which automatically processes eye-based spatial information and whose content remains implicit. Finally, we surmise on the basis of the neuroanatomical findings of these patients, that neural substrates in the spared (right) hemisphere might support both the eye fixations’ re-enactment and implicit visual pattern recognition. ■

INTRODUCTION

Following brain damage, some patients retain the very abilities they think they have lost (Weiskrantz, 1997). For example, some patients with agnosia for faces, or *prosopagnosia*, can show marked autonomic responses or brain potentials to unrecognized familiar faces (Tranel & Damasio, 1985). Patients with large scotoma can show *blindsight* for visual stimuli presented within the blind field (Weiskrantz, 1986); that is, they can show good visual discrimination capacity for contours’ orientations and motion within the blind field in the absence of any acknowledged experience. Moreover, patients with *amnesia* can learn to categorize visual patterns into new classes, although they cannot recognize the individual patterns as having been seen previously (Squire & Knowlton, 1995). Several recent studies have garnered more evidence that patients with amnesia can show

learning in the absence of awareness of having learned (e.g., Vandenberghe, Schmidt, Fery, & Cleeremans, 2006; Fleischman, Vaidya, Lange, & Gabrieli, 1997). The presence of “islands” of spared cognitive functions in the context of a severe deficit has attracted much attention from the research community. These phenomena force researchers to review their theories about the cognitive architecture of the human brain as well as help to better define the role of the brain structures damaged or preserved by the lesion.

In the present study, we present evidence for “islands” of spared memory functioning from three patients who are unable to either remember the “content” of an episode (e.g., a simple fact or what spatial position a previously seen object occupied) or to recognize a visual item as previously seen. Despite their severe amnesic problems, these patients showed evidence that information was registered within the visual system, as either their oculomotor or pupillary responses were consistent with a memory record of each event. Specifically, patient TC suffered from bilateral lesions in the hippocampal and extrahippocampal regions, but a careful

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analysis of his oculomotor behavior shows that he has learned something about the “context” of the event because his gaze returns to the location of the computer screen where visual information had been presented simultaneously to the spoken sentences. A similar oculomotor behavior, in the presence of severe amnesia, was shown by SS, a young female patient who suffered from a tumor located within the anterior medial region of the left temporal lobe. This patient was tested after surgical macroscopic extirpation of the tumor. For both patients, eye fixations reveal the ability of verbal cues in activating a rather specific memory about the learning event in the absence of the ability to retrieve explicitly the verbal/semantic information. In addition, TC, SS, and a third patient, OB, a male patient with a tumor located in the region of the left lateral ventricle and hippocampus, were tested with an old/new recognition task of realistic color drawings of single-object items and faces. All three patients showed significant changes in eye pupil diameter (i.e., an autonomic index of object recognition) when viewing novel visual stimuli compared to stimuli that they had previously seen, although they all confidently declared that every previously seen stimulus was novel.

The findings of the present study are of particular interest when seen in the light of recent research on normal participants on the relationship between gaze and memory. That is, when an observer is visually attending a scene, the eye fixations and scanpaths can provide a system of coordinates for spatially indexing information that will be needed at a later stage. In other words, the human brain might make use of spatial indexes in the form of oculomotor or eye-based coordinates. Such eye-based spatial indexes can provide “pointers” to visual information that either exceeds working memory load (Chun & Nakayama, 2000; Ballard, Hayhoe, Pook, & Rao, 1997; O’Regan, 1992) or that it is not presently seen but needs to be retrieved from memory in the form of a mental image (Mantyla & Holm, 2006; Altmann, 2004; Laeng & Teodorescu, 2002; Spivey & Geng, 2001; Brandt & Stark, 1997). The existence of such mechanisms reflects a limitation in the brain’s capacity to process visual information from the whole field of vision. This limitation is not simply sensory; in fact, as already proposed by Yarbus (1967), saccadic eye movements reflect the operation of other cognitive mechanisms and the part of the visual field within the fovea during a fixation corresponds to that area from which the observer is currently abstracting information or “attending to” (Loftus, 1972).

Most actions of everyday life require monitoring the scene through gaze (Karn & Hayhoe, 2000; Land, Mennie, & Rusted, 1999; Ballard et al., 1997). Thus, given the relevance of gaze in action control, it would seem likely that whenever we are involved in some form of action, gaze information would be automatically or reflexively registered. One important question is whether gaze information would be automatically or reflexively

registered also in circumstances in which (1) actions are not required, (2) the location information is irrelevant to the current task, or (3) there is no intention to learn the spatial information. A study by Richardson and Spivey (2000) with normal participants provides some initial answers to the above questions. In their study, participants were requested to learn a series of verbal facts being spoken to them while an unrelated event would be simultaneously visible in one of the quadrants of the computer screen. When queried about each of the facts, the eye-tracking method revealed more eye fixations on the (empty) region of space where the visual information had occurred during the learning of the semantic information than in other locations on the screen. Remarkably, location was irrelevant to the memory task, but gaze during recall indicates the observers’ automatic encoding of spatial information. Several other studies provide converging evidence; for example, when participants view pictures of scenes and the same scene is shown again by occasionally removing features or objects; although the subjects of this study were typically unable to report the missing feature, there was a strong tendency to make saccades to the location previously occupied by an object (Henderson & Ferreira, 2004). Explicit memory of the absent object is apparently not required in order for eye movements to be normally elicited (Ryan, Althoff, Whitlow, & Cohen, 2000). Chun and Nakayama (2000) have proposed that an “implicit visual memory system” keeps traces of past views and can guide attention and eye movements to allow for effective access (indexing) to a scene’s detail.

Thus, eye movements could provide a coordinate frame that can be used in the memory encoding of information about the external world. Eye-based spatial coordinates or “pointers” would use the external world itself as a readily available source of information or an “outside memory” (O’Regan, 1992); this, in turn, can reduce the amount of visual information that needs to be held in short-term memory at any time. If so, the details in the visual world ought to be accessed by a set of “deictic” primitives, markers, or pointers (Xu & Chun, 2005; Chun & Nakayama, 2000), and these visual implicit memory mechanisms should retain very little conscious information across views but allow specific visual information from scenes to persist across image changes and over time. In other words, spatial pointers are included in the episodic trace associated with each learned item, and when the trace is activated, then the encoded location of the item is also necessarily activated; this component can automatically drive the eyes toward that location (Altmann, 2004).

In addition, current theories of visual imagery (Kosslyn, 1980, 1994) give a central role to visual images as useful when recalling properties and relations that may have never been encoded explicitly as such (as, for example, when answering a question like: “What shape are a German Shepherd’s ears?”) but are retrievable on the

basis of information implicitly contained in the image. Laeng and Teodorescu (2002), Spivey and Geng (2001), and Brandt and Stark (1997) have also shown that, during visual imagery, there occur spontaneous eye movements that closely reflect the content and the spatial arrangement of the original scene. Hence, it can be concluded from the above evidence that eye movements do constitute an important component of memory processes.

In Experiments 1 and 2 of the present study, we hypothesized that, although the patients may show no explicit memory for the “content” of the facts they were requested to remember, they would show implicit memory for the “context” of a previous learning episode as indexed by the direction of gaze while attempting to recall a specific fact. Because mentally reinstating the image of the picture concurrently presented with the fact would not be helpful in the condition where the facts and the pictures were not related semantically, the occurrence of such a reinstatement of eye fixations or spared oculomotor memory would suggest that this form of memory can occur in a mechanistic and reflexive manner and that it can also survive extensive damage to the hippocampal regions.

In a final experiment (Experiment 3), three patients’ (TC, OB, and SS) incidental memory for the pictures was tested in an old/new recognition task, where previously presented pictures were presented again individually, together with an equal number of novel, foil pictures. Pupillary changes were measured during this recognition task. Pupillometric evidence that an amnesic patient responds differently to familiar versus novel pictures would indicate that this autonomic index of object recognition could be dissociated from the explicit memory for specific episodes.

EXPERIMENT 1

In the present study, we used a paradigm similar to that originally designed by Spivey and Geng (2001) and Richardson and Spivey (2000). That is, TC and SS and their matched control participants were requested to learn blocks of four little known or fictional facts (while one colored picture appeared in one of the screen’s quadrants) and a few minutes later the investigator probed the memory for each of the facts. Irwin (1996) has estimated that between three and six elements of a visual pattern can normally be maintained in memory across each eye movement.

The experiment was divided in two blocked conditions, where the facts and the images presented could be unrelated or bear some semantic relatedness to the pictures. Importantly, eye fixations were recorded both in the “learning” as in the “recall” phase. Spivey and Geng (2001) and Richardson and Spivey (2000) have shown that eye fixations to previous locations occurred in tasks in which the visual and verbal information were not semantically related. However, it is plausible to think

that such an effect might be stronger when the two types of information are related, as the relatedness might prompt the forming of a visual image, which in turn might require re-enacting the eye movements during its generation (Laeng & Teodorescu, 2002). We hypothesized that the patients would show memory of the location of images associated with the verbally presented facts and their gaze while attempting to recall a fact would express such a memory. Because mentally reinstating the image of the picture concurrently presented with the fact would not be helpful in the condition where the facts and the pictures were not semantically related, spared oculomotor memory in this condition would suggest that this form of memory occurs in a mechanistic and reflexive manner and that can also be spared after extensive hippocampal damage (as for the case of TC).

Methods

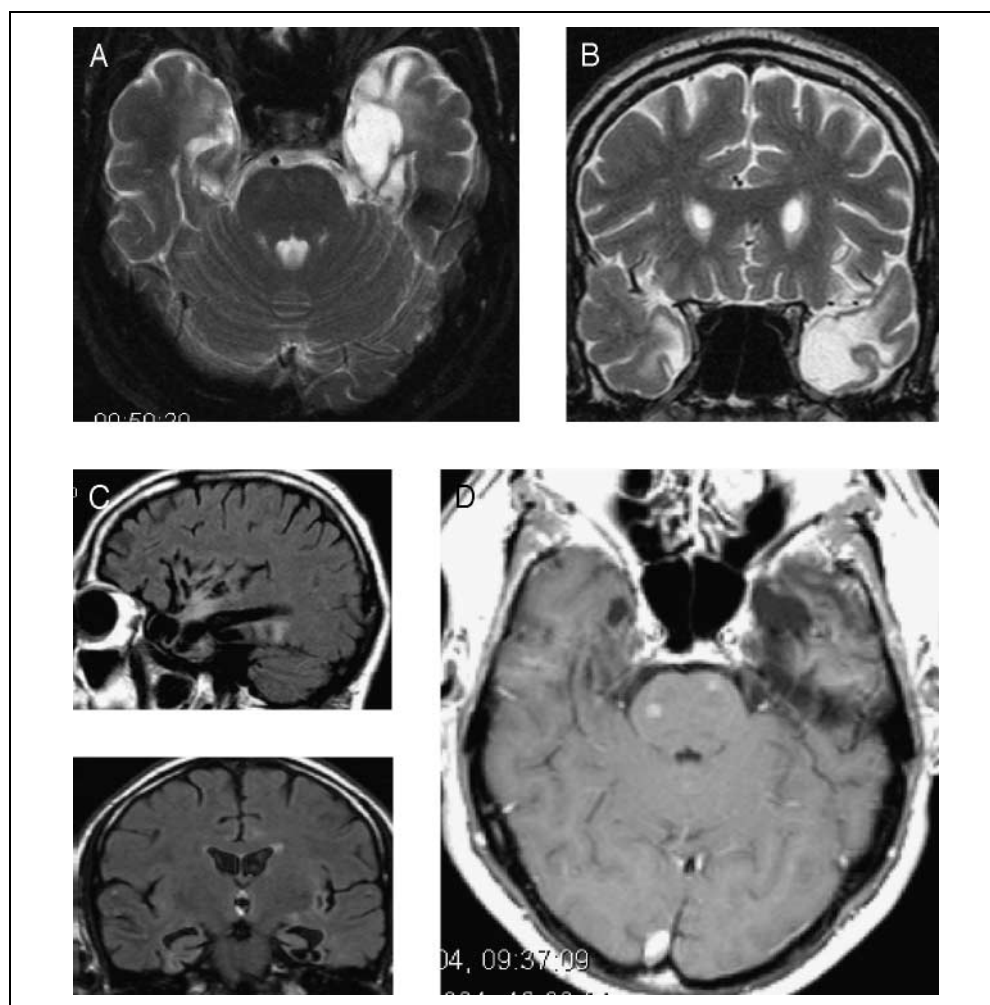
Participants

Patient TC, a 53-year-old right-handed man, and 10 neurologically healthy individuals (9 men) matched by educational level and age to TC (age range: 44–56 years; mean age = 49.8 years; *SD* = 3.8), were tested. About a year later, patient SS, a 21-year-old right-handed woman, and 10 neurologically healthy individuals (all women) matched by educational level and age to SS (age range: 20–25 years; mean age = 22.7 years; *SD* = 1.9), were also tested.

Clinical Histories

In July 2002, TC was diagnosed as having myelomatosis and transferred to the Hematological Department at the University Hospital of Northern Norway, Tromsø. In September 2002, induction treatment with VAD (Vincristine-Adriamycin-Dexamethasone) was started. During this therapy, he developed acute loss of memory. Ten days after debut of symptoms, a magnetic resonance (MR) scan of the brain showed enhanced signals in the hippocampus region and the amygdala on the left side. On the right side, the changes were more discrete (see Figure 1). The condition was judged as encephalitis. The patient’s nearly total loss of episodic memory has persisted and represents a considerable handicap in daily life of living. TC quickly forgets having met an individual if the person happens to leave the room for a few minutes. In one session, he arrived with one hand heavily bandaged but he could not explain how he got injured (chopping wood the previous day). He also shows a remarkable retrograde amnesia, given that he cannot remember details of his marriage and honeymoon (which both took place abroad) that occurred 10 years before the onset of his amnesia. Historical events of recent years seem completely unknown to him (e.g., the two Iraq wars; September 11), even after probing and suggestions. However,

Figure 1. (A) A T2W axial MRI performed in 2003 shows high signal lesions in the medial aspect of the left temporal lobe, including the frontal lower subcortical area. There is some retraction on the left temporal horn of the ventricle and small lesions are visible on the right side. (B) Coronal view from a T2W MRI performed in 2004. There are increasing signal abnormalities and destruction of the left temporal lobe as well some signal increases on the right side. (C) Sagittal and coronal T1W images performed in 2004 demonstrate destruction or substance loss in the left temporal lobe as well as wide cerebrospinal fluid spaces in the insular area. (D) An axial T1W image with Gadolinium enhancement shows two small lesions in pons and inflammatory reaction.



TC is able to describe verbally and in detail many events of his life, especially remote ones. He also shows intact general semantic knowledge (e.g., he can provide correct color labels of named fruits and vegetables). He can also provide accurate verbal descriptions of how to move different pieces on a chessboard or how to change the tire of a car. A new MR scan in June 2003 (Figure 1) showed that the edematous areas in the hippocampus had been replaced by brain atrophy and gliosis. Instead, there were less extensive changes involving the anterior hippocampus in the right hemisphere. Another MR scan 9 months later showed even more loss of brain tissue bilaterally in the hippocampal region (Figure 1). The volume loss on the right temporal lobe was about 10%, and on the left temporal lobe was about 35%. Even if the polymerase chain reaction (PCR) was negative, we think that the medical history and MR findings in this patient are consistent with necrotic encephalitis caused by the Herpes Simplex virus. Clinical findings and standard neuropsychological examinations, performed at the University Hospital of Northern Norway, are summarized in Table 1.

The second patient, SS, in October 2000, at the age of 15, was hospitalized due to tonic-clonic seizures. A CT scan of the brain revealed a hypodense lesion, 2 ×

2 cm, located in the left temporal region. An MR scan performed at the Neurology Department of the University Hospital of Northern Norway showed an expansive tumor, which was located anterior and medially in the left temporal lobe. She went through surgery with macroscopic extirpation of the tumor. Histological diagnosis confirmed a pilocystic astrocytoma. A postoperative MR scan showed no tumor remnants. A tumor relapse was suspected in July 2001 and she was reoperated with resection of the tumor remnants, the remaining part of amygdala, uncus, hippocampus, and the corresponding part of gyrus parahippocampalis as well as a modest resection of the lateral cortex. A preoperative Wada test had demonstrated left-sided linguistic dominance and bilateral capacity of memory. In June 2005, the antiepileptic treatment was ceased. At this time, she worked full-time as a shop assistant. Due to relapse of epilepsy in September 2005, treatment with carbamazepine was started. In February 2006, a striking lack of memory was noticed and the patient herself also had acknowledged this for a time. She was referred to neuropsychological testing. She still had complex partial seizures, and therefore her medication was switched to oxcarbazepine. An MR scan in June 2006 showed no

Table 1. Clinical and Neuropsychological Findings for the Three Patients

<i>Patients</i>	<i>TC</i>	<i>SS</i>	<i>OB</i>
<i>Clinical Findings</i>			
Diagnosis	Myelomatosis	Tumor	Tumor
	Encephalitis (Herpes Simplex virus)	Pilocystic astrocytoma	Glioblastoma multiforme
MR findings	Enhanced signals in the left hippocampus and amygdala with more discrete changes on the right side	Hypodense lesion in the anterior and medially left temporal region	Enhanced signals deeply in the left temporo-occipital region extending into the splenium of the corpus callosum
	Atrophy and gliosis	Enhanced signals in the resection cavity in the left medial temporal lobe	MRI demonstrated progression with a diffuse infiltration and subependymal enhancement in the splenium of the corpus callosum, around the posterior horn of the left lateral ventricle and in the medial part of the left hippocampus
		Resection of tumor remnants, the remaining part of the amygdala, uncus, hippocampus, gyrus, and parahippocampalis, and modest resection of the lateral cortex	
Clinical symptoms	Nearly total loss of memory	Memory loss	Memory loss, confusion
		Complex partial seizures	Generalized epileptic seizures
			Right-sided homonymous hemianopsia
<i>Neuropsychological Examination</i>			
WAIS/WAIS-III			
T-scores:			
Information	47	41	40
Comprehension	56	44	39
Similarities	55	30	43
Arithmetic	56	42	37
Digit Symbol	42	46	31
Picture Arrangement	69	41	
Block Design	50	55	38
WMS-R			
General Memory Index	65	78	61
Attention Index	102	112	84
Verbal Memory Index	68	75	59
Visual Memory Index	81	103	97
Delayed Memory	0	12	4
Halstead-Reitan Battery			
TMT A	43	46	37
TMT B	43	45	40

Table 1. (continued)

<i>Patients</i>	<i>TC</i>	<i>SS</i>	<i>OB</i>
<i>Neuropsychological Examination</i>			
Category test	41	51	42
Seashore Rhythm test	46	49	–
Tactual Performance Test			
Time	40	48	–
Dominant hand (R)	34	37	–
No dominant hand	45	49	–
Memory	30	35	–
Location	33	37	–
COWA/FAS	41	40	41

WAIS = Wechsler Adult Intelligence Scale; WAIS-III = Wechsler Adult Intelligence Scale—third edition; WMS-R = Wechsler Memory Scale—revised; COWA = controlled oral word association.

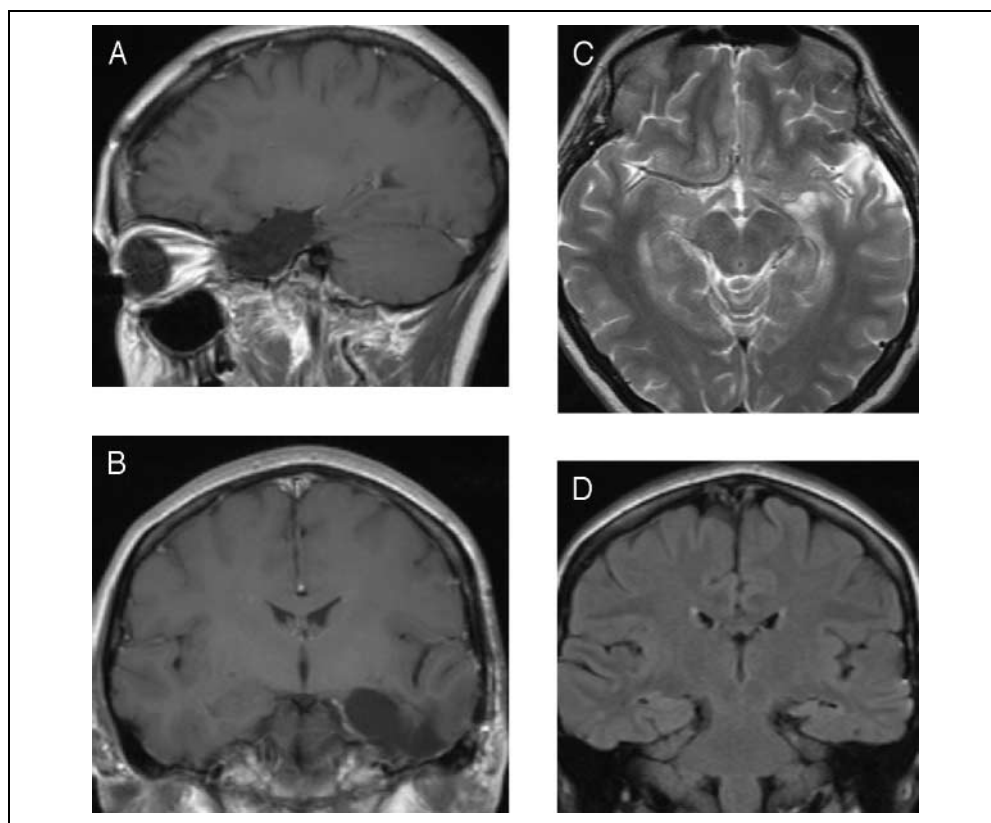
signs of tumor relapse. Clinical findings and standard neuropsychological examinations, performed at the University Hospital of Northern Norway, are summarized in Table 1.

Apparatus and Stimuli

Eye positions were recorded by means of the Remote Eye Tracking Device, R.E.D., built by SensoMotoric In-

struments (SMI, Teltow, Germany). Analyses of recordings were then computed by use of the iView software. The R.E.D.-2 can operate at a distance of 0.5–1.5 m and the recording eye tracking sample rate is 50/60 Hz, with resolution better than 0.1°. The eye tracking device operates on the basis of determining the positions of two elements of the eye: the pupil and the corneal reflection. The sensor is an infrared light-sensitive video camera typically centered on the left eye of the subject.

Figure 2. (A and B) Sagittal and coronal T1W MRI shows the resected area of left temporal lobe >4 cm from the anterior pole. The posterior part of the hippocampal tract is visible but reduced in size compared to the contralateral right. (C) Axial T2W MRI: High signal changes behind the resected temporal lobe's region affecting the more posterior medial aspect. (D) Coronal Fluid Attenuated Inversion Recovery (FLAIR) MRI at the posterior remaining part of left hippocampus, which is reduced in size, as well as the adjacent medial cortical structure with widening of the choroidal fissure.



Room lighting does not interfere with the recording capabilities of this apparatus. The coordinates of all boundary points are fed to the computer which, in turn, determines the centroids of the two elements. The vectorial difference between the two centroids is the “raw” computed eye position. The presentation of the pictorial stimuli was controlled by ACDsee 32v2.4 software and presented on a 49-cm flat color monitor. All pictures were in color, each surrounded by a white background (Figure 3). All participants positioned their heads in a chin rest at a distance of 73 cm from the screen so as to reduce head movements.

Procedure

Each participant was tested individually in a windowless room with constant illumination. The investigator read the instructions to the participant. These included the request to look at the screen at all times while listening carefully to the orally presented facts. Such requests were repeated to the patients during each block of four trials, to insure that they would not forget following the instructions. A standard calibration procedure was used at the very beginning of each session where eye position was recorded at nine standard calibration points (appearing as white plus signs on a blue background), corresponding to a regularly spaced 3×3 matrix. Every participant was told that the optical device being used was only measuring their pupil sizes and that they could move their eyes freely. The patients and the normal control participants listened to the investigator reading short sentences stating little known or fictional facts. Each of the various facts and queries could either probe knowledge of functional, perceptual, or encyclopedic

properties of objects. For example, the participant could hear that “Albert Einstein was a professor at Princeton University” or “penguins lay blue eggs.” The participant was requested to listen carefully to each sentence while looking at the computer screen and, simultaneously to the verbal information, one colored picture appeared in one of the screen’s quadrants. The visual presentation of each picture and the oral presentation occurred in synchrony, thus temporally “pairing” each fact to an image. The same pairings of sentences and images was used for every participant. After the four items were presented, the four respective questions were asked in the same order of the items. For example, the participant could be asked: “Where did Albert Einstein used to teach?” or “What is the color of a penguin’s egg?” All questions were asked one at a time, while the participant was requested to look at the computer screen. During the question phase, the computer screen showed only an empty grid. Eye recordings were taken from the time in which the subject of the question was named (e.g., when the experimenter said “penguin” until the time the subject gave a verbal response; whether this was correct, incorrect, or of the “don’t remember” type). The majority of correct answers implied only a single word response (and the maximum number of words to respond to an item was three; e.g., “World War II”). None of the questions had a 50% likelihood of being answered correctly. In order to assess what would be the chance level of answering correctly, six students at the Department of Psychology in Tromsø were asked all of the questions used in the experimental task without previous exposure to either the facts or the pictures. These results were taken as base-rates for pretest factual knowledge or “educated guessing” and were used as a comparison to the patients’ accuracy rate.

The whole task consisted of two conditions, one in which the factual (verbally presented) and the visual presentations were unrelated (44 trials; e.g., the fact about Einstein showed the picture of a honeybee or that about “penguins lay blue eggs” while being presented with a picture of an electric drill) and another condition in which the factual and the visual presentations were semantically related (36 trials; e.g., a fact about the sinking of the Vasa ship in Stockholm was accompanied by a picture of an ancient sailing vessel). The related and the unrelated trials were given in different blocks, always beginning with the unrelated ones (to avoid building assumptions of relatedness between images and facts that could have originated from presenting the related condition first). In the related condition, when the orally stated facts related to a person (e.g., “Anne works at the airport”), a face was always presented. All the faces used were novel to the participants and when names and biographical information was used in the orally presented fact, these were entirely fictional. Also, the facts always referred to aspects that were clearly visible from the photograph of the face (e.g., eye color, sex, age).

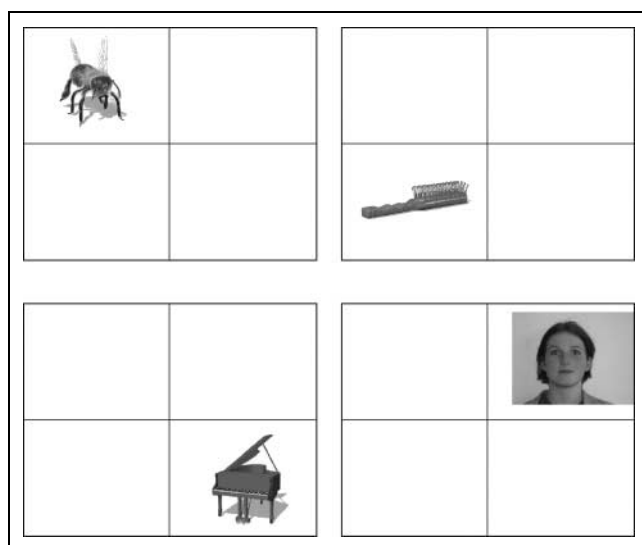


Figure 3. Examples of visual stimuli used in the experiments.

Results

Control Participants

An analysis of variance was conducted on the percentage of correct answers (averaged across all subjects) with condition (related, unrelated) as the within-subject factor. The analysis of variance confirmed this difference to be significant, $F(1, 18) = 19.9$, $p < .0001$ (mean % correct answers for related condition = 92.2, $SD = 27$; unrelated condition = 81.5, $SD = 39$).

Regarding the eye movements/fixations data, percentages of time spent looking at each of the quadrants were coded separately for each trial both during the “learning” or “perception” phase and the “recall” or “memory” phase. It was found that, during the recall phase, the quadrant that previously contained the image was looked at, on average, for 58% of the time; while the eyes spent less time within the other three quadrants (i.e., 12% of the time on average for each quadrant; range = 11–16%). Given that the chance probability that gaze will be in the “critical” quadrant (i.e., the quadrant where the picture associated with the specific fact originally appeared) would equal 25%, an average rate of 58% in the critical quadrant would then correspond to a Poisson probability of $p < .0001$, whereas an average rate of 12% in the noncritical quadrants would yield a Poisson probability of $p = .0003$. Hence, given that our hypothesis is that there will be more looks to the critical quadrant than to the other quadrants, the control participants’ gaze preference for the critical quadrant confirmed, at a highly significant level, our expectations.

In addition, simple regression analyses were run using relative time spent in each quadrant: Scores in the perception phase were used as the regressor and scores in the memory phase as the dependent variable. For the control participants’ data, we collapsed across all participants the percentage scores for perception and memory. A first analysis of trials from the related and the unrelated conditions combined revealed a slope coefficient of 0.32, $t(326) = 17.5$, $p < .0001$, $R = .68$. Two additional regression analyses showed a significant regression for unrelated trials, slope coefficient = 0.31, $t(182) = 8.3$, $p < .0001$, $R = .51$, as well as a significant regression for related trials, slope coefficient = 0.33, $t(142) = 17.4$, $p < .0001$, $R = .84$. A t test showed no difference between the regression slopes for the related condition (regression coefficient = .33, standard error = .69) and the unrelated condition (regression coefficient = .31, standard error = .85), $t(19) = 0.9$.

Patients

TC answered only 17 of the 84 questions correctly (i.e., 14.3%). However, this accuracy rate did not exceed the level of educated guessing that was estimated separately with a group of six normal participants (i.e., a mean %

correct answers of 20.2; $SD = 4.8$). For instance, TC correctly answered that “among the black widow spiders, the female is larger than the male,” which is what each of the six control person (who were not exposed to the learning phase) also answered to the same question. Regarding the eye fixations/movements data, those trials in which TC did not look at the screen either in the presentation or the questioning phase were removed (7% of trials). During the recall phase, TC’s eyes were in the quadrant that previously contained the image, on average, for 32% of the time; in contrast, the eyes spent less time within the other three quadrants (i.e., 23% of the time; range = 22–24%) that did not contain an image in each trial. Given that the chance probability that gaze will be in the “critical” quadrant is 25%, an average rate of 32% in the critical quadrant corresponds to a Poisson probability of $p = .03$; whereas an average rate of 23% in the noncritical quadrants yields a Poisson probability of $p = .07$. Hence, TC showed a significant gaze preference for the critical quadrant. In addition, regression analysis of the related and unrelated trials combined showed a slope coefficient of 0.11, $t(310) = 3.1$, $p < .0001$; and a weak correlation of $R = .17$. A separate regression analysis revealed no significant relation among eye fixations in the perception and memory phase for unrelated trials, slope coefficient = 0.06, $t(180) = 1.3$, $p < .19$, $R = .01$. However, the analysis on the related trials revealed a significant relation between the same two variables, slope coefficient = 0.18, $t(132) = 3.1$, $p < .003$; $R = .26$.

SS answered 43 of the 84 questions correctly (i.e., 51.8%). However, this accuracy rate was 17.5 standard deviations lower than that of the mean accuracy of normal participants who were matched by age and education to this patient (i.e., a mean % correct answers of 97.4; $SD = 2.6$). Regarding the eye fixations/movements data, trials in which SS did not look at the screen either in the presentation or the questioning phase were removed (3% of trials). During the recall phase, SS’s eyes were in the quadrant that previously contained the image, on average, for 41% of the time; in contrast, the eyes were within the other three quadrants for 19% of the time; range = 11–29%). An average rate of 41% in the critical quadrant corresponded to a Poisson probability of $p = .002$, whereas an average rate of 19% in the noncritical quadrants yielded a Poisson probability of $p = .03$. Hence, SS also showed a gaze preference for the critical quadrant. The regression analysis of the related and unrelated trials combined showed a slope coefficient = 0.23, $t(310) = 3.5$, $p < .0001$; and a moderate correlation of $R = .31$. Separate regressions analyses revealed significant relations among eye fixations in the perception and memory phase for both conditions [unrelated trials: slope coefficient = 0.19, $t(180) = 3.2$, $p = .0005$, $R = .27$; related trials: slope coefficient = 0.28, $t(132) = 4.1$; $p < .0001$, $R = .38$].

Discussion

Despite being unable to remember at normal levels of performance recently learned factual information, the patients' oculography results showed the presence of a memory trace of the context of each episode, as their eyes returned to the position where visual stimuli had appeared when the verbal information was originally presented. Thus, the present findings demonstrate that at least some amnesic patients can remember implicitly the location of an object that has disappeared from the scene. However, this behavior was clearly not useful for the explicit recall of the verbal/semantic information. Also, re-enactment of the ocular behavior was significantly stronger for one patient in the condition where the images had some semantic relation to the verbally presented fact. This finding seems to contradict the hypothesis that spatial information is encoded in all cases, even those in which it is irrelevant to the task. However, a correspondence between visual and verbal information might allow the formation of stronger memory traces, which in turn could result in a better re-enactment of gaze.

Interestingly, in a previous study with normal participants, Althoff and Cohen (1999) had revealed an "eye movement-based memory effect" consisting in a reduced amount of ocular scanning for previously viewed items than for novel items. Althoff and Cohen also showed that even amnesic patients, with no explicit remembering of the old items, exhibited this effect. However, a study with a group of six amnesic patients by Ryan et al. (2000) failed to observe re-enactments of eye movements to regions of a scene that were emptied of previously shown items. Yet, the patients included in that study had mixed etiology and were grouped on the basis of the presence of amnesic problems, whereas in the present study, the patients were selected on the basis of damage to the temporal lobe that affected the hippocampal regions. Also, capacity limitation might be behind the negative finding of Ryan et al. (Experiment 4) on memory for real-world scenes. In their study, the eye fixations of six amnesic patients were recorded while they viewed a given scene and then compared with their eye movements when viewing the same scene again. A key manipulation of this study was that although a scene could be repeated without changes, in some instances, the same scene could have one object deleted from the scene or another object added to it. Normal control participants showed an increase in viewing of the regions where manipulations had occurred, especially when they were also unaware that a scene had been manipulated. In contrast, the amnesic patients, as a group, did not show this effect. The authors concluded that the memory system damaged in amnesia is declarative memory for relations among the elements of a scene or "relational memory binding." We surmise that one key reason for the discrepancy between the findings

of Ryan et al. and the findings of the present study (showing a reinstatement of eye fixation on the region emptied of a previous item) might be accounted by the fact that their study manipulated the presence of an object in a scene, while all other objects remained visible and able to attract the overt attention of the patients. This procedure is then very different from presenting a blank screen, as done in the current study, where only a single object was present at the time of learning. Finally, in Ryan and colleagues' experiment, there was greater load on memory required by the displays used in their experiment (i.e., color photographs of real-world scenes). Thus, it is likely that implicit visual memory traces of previous eye fixations on specific visual contexts might have been particularly inefficient in the amnesic group when a variety of intervening complex displays occurred between the learning and recognition episodes.

EXPERIMENT 2

One possible confounding in our previous experiment was that the probing questions were asked in the same order in which the facts were originally presented. Thus, one possibility is that a patient could hold a record within spatial working memory, or some type of spatial short-term memory, of the sequence in which each series of four images were presented and this was responsible for the correspondence in eye fixations. In this account, the semantic information in each of the questions did not constitute at all a retrieval cue for the spatial information associated with each fact. In order to better explore these aspects, we decided to perform a second experiment with patient TC. This time the order of the questions did not reflect the order of the presented facts.

Experiment 2 consisted of two parts: In Experiment 2A, TC was retested with the same material used in the previous experiment after about 9 months from the previous experiment. This experiment was nearly identical to the previous one but the order of presented facts and the order of subsequent questions were different. In Experiment 2B, TC was tested a few months later with two "control" tasks that were performed off-line from the eye-tracker but with the same visual and verbal material used in the previous tasks. This time, TC was requested to respond nonverbally by pointing to images and screen position with his finger. One could suspect that correlated eye fixations on previously occupied positions might simply reflect some form of explicit spatial short-term memory. Specifically, TC once again listened to the investigator reading short sentences, stating the same facts used earlier and each coupled with the same images (from the "related facts" conditions). During the test phases of the experiment, TC was requested to point to the positions on the screen where each of the four images had previously appeared. For example, if the fact mentioned that "Tina is a nurse at the University Hospital," then the

question would be “Where did you see the picture of Tina the nurse?” In the visual recognition task, TC was shown the images of two objects side by side, one novel and one “old.” His task was to point to the one already seen.

Methods

Patient TC was the only participant in this experiment. Eye positions were recorded by means of the same SMI eye-tracker described above. Pictorial stimuli and apparatus were the same as the previous experiment, with the only change being that questions were asked in a different order than the one in which the facts were presented. The facts in the learning phase were presented in the same order as in the previous experiment. TC was requested to point to the positions on the screen where each of the four images had previously appeared. The patient was also informed that each image would appear in a different position (corner) of the screen (in other words, there was no “replacement” for each spatial choice).

Results

Experiment 2A

TC answered correctly 34.52% of the questions. This accuracy rate exceeded by 15 percentage points the previously estimated level of “prior knowledge” (20.2%). However, this improved performance, compared to TC’s performance in Experiment 1 (14.3% correct), was entirely accounted by the fact that, in Experiment 1, the delay between presentation of a fact and probing questions was held constant, whereas in Experiment 2 it was variable so that, in some trials, a question happened to probe a recently presented fact. Given the short delays between learning and memory in a certain number of trials, the improved recollection could reflect the processing of immediate short memory storage. Indeed, TC’s recollection was 100% correct in the trials where the question followed right after the presentation of the fact, 45% in the trials where there was one other question in between, and at all other delays, the percentage correctly recalled had reached the “prior to the test” knowledge level of about 20% correct. Such a rapid decay of explicit knowledge might not be surprising given that for the famous case HM (Scoville & Milner, 1957), his short-term memory was normal and that his memory deficits appeared at memorization delays that were longer than 16 sec.

Regarding the eye fixations/movements data, in 4% of the trials, TC did not look at the screen either in the presentation or in the questioning phase. Importantly, in the remaining trials, TC looked at the critical quadrant that previously contained the image, on average, for 39% of the time; instead, the eyes spent less time within the other three quadrants that did not contain an image (i.e., 20% of the time; range = 18–22%). Again, the

chance probability that gaze will be in the “critical” quadrant is 25%, an average rate of 39% in the critical quadrant corresponds to a Poisson probability of $p = .004$, whereas an average rate of 20% in the noncritical quadrants yields a Poisson probability of $p = .04$. Hence, once again, TC showed a significant gaze preference for the critical quadrant.

A regression analysis of the related and unrelated trials combined showed a slope coefficient of 0.30, $t(336) = 10.3$, $p < .0001$; and a moderate correlation of $R = .49$. Separate regression analyses were also performed on the unrelated and related data. The analysis on the unrelated trials revealed a significant relation among eye fixations in the perception and memory phase, slope coefficient = 0.27, $t(192) = 6.7$, $p < .0001$, $R = .45$. Moreover, the analysis on the related trials revealed a significant relation among the same two variables [slope coefficient = 0.28, $t(144) = 6.8$, $p < .0001$, $R = 0.48$]. In addition, we performed regression analyses on only those trials in which TC showed no explicit recollection of the facts. The regression analysis of the related and unrelated trials combined showed a slope coefficient of 0.24, $t(220) = 6.7$, $p < .0001$, and a moderate correlation of $R = .42$. Separate regression analyses for the unrelated and related data showed significant relations among eye fixations in the perception and memory phase [Unrelated: slope coefficient = 0.29, $t(140) = 6.4$, $p < .0001$, $R = .48$; Related: slope coefficient = 0.17, $t(80) = 3.1$, $p = .003$; $R = .33$].

Experiment 2B

In the pointing to objects’ positions task, TC pointed to the correct position in 56% of the cases. The Poisson Probability of Observed (Count = 18) versus Expected Events (Chance = 16) was $p = .338$. Note that, in this case, chance is not 25% because the task requires four consecutive choices “without replacement.” In the visual recognition task, TC pointed to the correct (old) object in 54% of the cases. In this case, the Poisson Probability of Observed (Count = 45) versus Expected Events (Chance = 42) was $p = .342$.

Discussion

In this second experiment, despite a severely impaired memory for recently learned factual information, TC’s eyes tended to return to the position where visual stimuli had appeared when the verbal information was originally presented. Indeed, the regression function between eye position during learning/perception and during recall explained about 24% of the variance in eye fixations. Moreover, in this experiment, the re-enactment of the ocular behavior of learning episodes occurred also in the condition where the images had no semantic relation to the verbally presented facts but were entirely arbitrary. This finding suggests that spatial information can be encoded in all cases, even those in which

it is irrelevant to the task, as suggested by several researchers (e.g., Pouliot & Gagnon, 2005; Hommel, 2002; Caldwell & Masson, 2001; Richardson & Spivey, 2000; Hasher & Zacks, 1979; Mandler, Seigmiller, & Day, 1977). Importantly, the present results rule out the possibility that the patient's oculomotor behavior simply reflected a memory of the order of presentation of the visual stimuli. Questions in Experiment 2 were posed in a different order than the facts. Hence, the questions themselves were able to provide the retrieval cues for the spatial information uniquely associated with each fact.

In sum, the amnesic patient's performance did not differ from chance when asked to point to a position on screen corresponding to a previously seen object or to the corresponding image. Hence, TC appears to have no explicit memory of spatial positions and visual content, nonetheless, his ocular responses reveal a spared form of implicit, eye-based, spatial memory. Thus, such knowledge cannot be made explicit, neither through verbal nor nonverbal responses. TC's eye-based spatial memory also seems highly specific and not transformable into other spatial coordinates (e.g., hand-based) that would allow him to indicate to the correct locations of previously seen objects.

EXPERIMENT 3

Previous studies have shown that patients with visual agnosias can show pupillary responses that are also characteristic of individuals with normal vision (Lê, Raufaste, Roussel, Puel, & Démonet, 2003; Weiskrantz, Cowey, & Barbur, 1999). Thus, in a final experiment, we decided to test three amnesic patients (SS, TC, and a new patient OB) in a visual recognition task where the pictures originally used in the factual learning task were presented intermixed with an equal amount of pictures of animals, objects, and faces that had not been previously shown. Importantly, while the patients performed the recognition task, changes in pupillary diameter were recorded. The patients were only asked to provide a yes/no answer to the question "seen before?" and not to remember something about the learning episode itself (cf. Yonelinas, 2002). For two of the patients, we also collected confidence scores. The question was whether, in the absence of explicit recognition, the patients would show autonomic responses (as indexed by pupillometry) that would distinguish familiar from novel information.

Methods

Participants

Patients SS and TC, as well as OB, a 73-year-old right-handed man, participated in this experiment.

OB's Case History

In December 2005, OB was admitted to the Department of Neurology at the University Hospital of Northern

Norway, Tromsø, due to generalized epileptic seizures. At arrival, he presented with a right-sided homonymous hemianopsia. An MR scan without contrast showed increased signals deeply in the left temporo-occipital region extending into the splenium of corpus callosum. A new MRI scan with contrast demonstrated considerable progression with a diffuse infiltration and subependymal contrast enhancement in the splenium of the corpus callosum, around the posterior horn of the left lateral ventricle and in the medial part of the left hippocampus (see Figure 4). A stereotactic intracranial biopsy was performed and the histological examination showed a glioblastoma multiforme. The patient was transferred to the Department of Oncology for radiotherapy and chemotherapy. OB was subjected to standard neuropsychological examinations at the University Hospital of Northern Norway and the findings are summarized in Table 1.

Procedure

Presentation of stimuli as well as the recording of the pupil diameter was controlled by Presentation software. The experimenter pressed a key at the beginning of each trial, which triggered the appearance of a visual stimulus at the center of the screen. Another keypress of the experimenter, when the patient gave a response, interrupted the recording of the pupil size and caused the visual stimulus to be replaced by a blank screen. Patients OB and SS, who were both tested after TC, were requested to provide an estimate about how confident they were of their judgment of having seen earlier (or not seen) the same picture (1 = sure "old" to 6 = sure "new"). Moreover, a microphone switch recorded vocal onsets of these two patients' verbal responses so as to obtain reaction times (RTs) from the onset of each picture. Patient OB went through the same procedure used in Experiment 1 with Patients SS and TC when measuring their eye fixations; however, for technical reasons, OB's eye movements were not recorded at that time. In addition, for Patient SS, pupillary diameters were also recorded during the presentation of a blank screen between two consecutive pictures, so as to provide a baseline measurement to compare the pupillary changes to old and new pictures. Importantly, the learning procedure and the stimuli used in the present experiment were the same for all patients.

Results

TC responded without hesitations "new" to every picture presented to him in the visual recognition task; thus, showing no explicit visual recognition whatsoever. However, the pupillometric data collected during the same task showed a difference in pupil size between the pictures that were actually new and those that were old. Specifically, the mean pupillary diameter for new pictures was 3.65 mm ($SD = 0.18$), whereas the mean

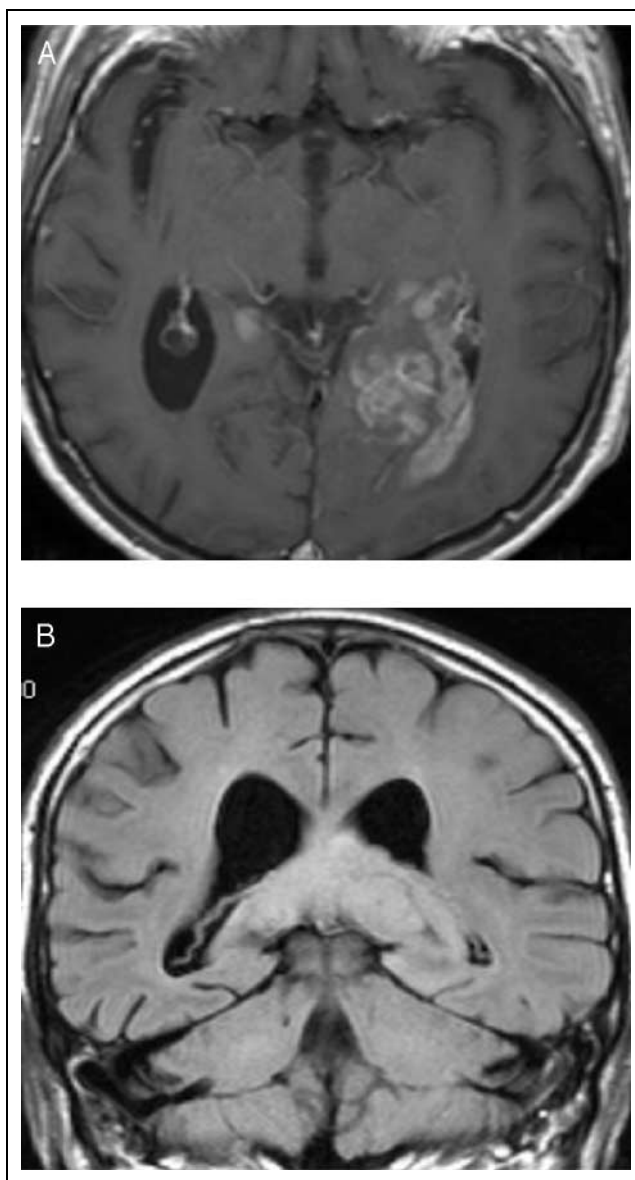


Figure 4. (A) Axial T1W MRI with Gd contrast demonstrates enhancing tumor infiltration in the medial aspect of the left temporal lobe, splenium corpus callosum crossing the midline, and also a tumor in the posterior medial aspect of the contralateral right temporal lobe. (B) Coronal FLAIR MRI: The infiltrating tumor affects the posterior part of left medial temporal lobe and the limbic tract, whereas the anterior part is intact. There is a retraction of the right anterior lateral ventricle with loss of substance in the right caudate nucleus.

pupillary diameter for old pictures was 3.23 mm ($SD = 0.15$). Both means were outside of the 95% confidence intervals of the other mean (95% CI = $3.61 < \text{mean} < 3.68$; and 95% CI = $3.19 < \text{mean} < 3.26$, respectively). Given that TC classified every single image as new, there was no explicit memory of the pictures or awareness of their repetition.

OB answered correctly only 46.4% of the time. Thus, he also showed poor explicit visual recognition. However, there was also a difference in pupil size for new

pictures compared to old ones. Specifically, the mean pupillary diameter for new pictures was 3.57 mm ($SD = 0.09$), whereas the mean pupillary diameter for old pictures was 3.45 mm ($SD = 0.11$). Both means were outside of the 95% confidence intervals of the other mean (95% CI = $3.51 < \text{mean} < 3.63$; and 95% CI = $3.39 < \text{mean} < 3.51$, respectively). An analysis of RTs for all responses (i.e., disregarding their accuracy) showed no significant difference between new and old pictures, $F < 1$. Finally, OB was confident in his responses, given that his average confidence score for misses (i.e., old pictures judged as new) was 5.2 ($SD = 1.1$).

SS answered correctly 70.2% of the time. That is, she answered “new” to the majority of the pictures presented to her, which resulted in a correct performance for 95.3% of the pictures that were actually novel. However, she correctly recognized previously seen pictures as “old” only in 43.9% of the cases, thus showing impaired visual recognition. The mean pupillary diameter for new pictures was 3.89 mm ($SD = 0.69$), whereas the mean pupillary diameter for old pictures was 3.63 mm ($SD = 0.55$). Both means were outside of the 95% confidence intervals of the other mean (95% CI = $3.5 < \text{mean} < 3.76$; 95% CI = $3.76 < \text{mean} < 4.02$). Interestingly, SS’s mean pupillary response to the blank screen appearing between pictures (mean pupil size = 3.65 mm; $SD = 0.42$) was smaller than her pupillary response to the new pictures but it fell within the confidence intervals of the pupillary responses to the old pictures. An analysis of RTs for all responses (i.e., disregarding their accuracy) showed also a significant difference between new and old pictures, $F(1, 82) = 4.9$, $p = .02$. RTs were faster for new pictures (mean RT = 3312, $SD = 504$) than for old pictures (mean RT = 3740, $SD = 1144$). Finally, SS was also confident in her responses, given that her average confidence score for misses was 4.9 ($SD = 1.4$).

Discussion

These pupillometric findings reveal that the patients’ recognition memory is able to differentiate novel from previous views of an object despite the absence of explicit awareness of “knowing” the pictures already. The present finding of increased pupillary diameter with novel images (compared to old images or no images) is also consistent with the typical pupillary responses of normal participants to novel stimuli (Andreassi, 1995).

As pointed out by Weiskrantz (1998), given that the eye pupil is controlled by the autonomic nervous system, it might be surmised that the pupillary response is generated by a “primitive,” adaptive system that is especially tuned to the detection of novel occurrences and its selectivity of activation could, normally, provide the impetus for action (Peters, 2000). Weiskrantz et al. (1999) have also shown that, in a blindsight patient (GY), the pupillary response occurs even when awareness is

eliminated, although the size of the response is reduced. Hence, novel stimuli might trigger an attentional response that is then reflected in the autonomic response of pupillary dilation (Paulsen & Laeng, 2006; Beatty & Lucero-Wagoner, 2000; Kahneman, 1973; Kahneman & Peavler, 1969; Hess & Polt, 1960).

It has been proposed that implicit memory reflects increased efficiency in carrying out the same set of perceptual procedures a second time (Kolers & Roediger, 1984). Schacter, Tharan, Cooper, and Rubens (1991) and Tulving and Schacter (1990) have proposed that many priming effects reflect the operation of a “presemantic” perceptual representation system. One can surmise that in the present study, the limited previous exposure to the figures was sufficient for our amnesic patient to form perceptual “object tokens” (cf. DeSchepper & Treisman, 1996) that were automatically retrieved when these matched a currently presented stimulus, resulting in a reduced pupillary response to the “primed” versus “unprimed” visual stimuli.

GENERAL DISCUSSION

The patients’ oculomotor and pupillary responses provide examples of “islands” of spared memory functions in the context of a severe amnesic syndrome. Specifically, on one hand, an amnesic patient can have severe explicit memory impairment for the content of facts and events presented either verbally or visually. On the other hand, the same patient can show intact memory of the specific learning contexts and contents, as indexed by eye movements and pupillary changes during recall or recognition situations. This form of spared memory is *implicit* (i.e., not conscious to the patient himself), given that the patient still fails to recognize explicitly visual stimuli that were previously presented. In sum, the re-enactment of eye fixations occurred (1) without explicit knowledge of the spatial positions of the visual stimuli and (2) after verbal cueing. Remarkably, in the case of TC who had suffered bilateral hippocampal damage, despite the extensive damage to the left hemisphere’s temporal structures (about 35%) and the total loss of its medial structures, the linguistic input was clearly able to activate memory representations that included the oculomotor responses originally associated with them.

The above findings of re-enactment of eye fixations prompt us to examine some of the current views about the cognitive architecture of memory in the human brain. In particular, it is known that humans and non-human primates with damage to the hippocampus are impaired in object–place memory tasks (e.g., Parkinson, Murray, & Mishkin, 1989). Rolls (2000) has proposed that this spatial processing involves a “snapshot” type of memory and that this memory may be considered as a special case of episodic memory, which involves an arbitrary association of a set of spatial and/or non-spatial events that describe a past episode. According

to several current models of hippocampal function, this brain structure plays a key role in learning (rapidly) arbitrary associations among various elements of specific events and experiences (Eichenbaum, 2004; McClelland, McNaughton, & O’Reilly, 1995). In fact, patients with hippocampal amnesia can show normal rates of learning of verbal labels for new visual patterns that resemble already known objects, in incidental learning situations where the use of such nonarbitrary labels constitutes the “common ground” of verbal communication exchanges (Duff, Hengst, Tranel, & Cohen, 2006). Burgess, Becker, King, and O’Keefe (2001) have explicitly made a distinction between “content” and “context” in the memory for events, and stressed the role of the hippocampus as the central player in the neural support of the rich spatial context of an event. Several models have stressed the relevance of the hippocampal system in forming memories involving spatial information, places, or environmental locations (O’Keefe & Nadel, 1978) as, for example, in remembering that a particular stimulus occurred in a particular place (Burgess et al., 2001; Eichenbaum, 2000; Vargha-Khadem et al., 1997; Parkinson et al., 1989). Finally, within the temporal lobe, hippocampal damage is sufficient to cause anterograde amnesia, but the disruption of other temporal areas can increase the scale of the amnesia (Squire et al., 2004).

In light of the above-described accounts, it is relevant to discuss our patients’ ability to re-enact past eye fixations. This could be described, using Rolls’s (2000) terms, as a spared form of “snapshot” memory, involving arbitrary association of a set of spatial and/or non-spatial events that describe a past episode. On the basis of the present findings, it would seem that extensive left-sided damage hippocampal or medial-temporal lobe damage does not interfere with such a memory mechanism that spatially “tags” (by eye position) verbal/semantic information. Both Patients TC and SS in the present study had left temporal damage, with no right-sided damage for SS or, for TC, additional (but less extensive) damage on the right side. However, both patients TC and SS showed memory for the locations of a few objects presented in succession, as revealed by their oculomotor behavior. Most interestingly, these spatial memories could be triggered by verbal/semantic cues that were arbitrarily paired to visually presented objects. Indeed, temporal lobectomy affects spatial memory more when it is performed on the right side of the human brain than on the left (Nunn, Graydon, Polkey, & Morris, 1999; Smith & Milner, 1981). Moreover, both split-brain patients and healthy subjects, when tested for their memory of pictures with tachistoscopically lateralized images, have shown a right hemisphere’s advantage (Laeng, Øvervoll, & Steinsvik, 2007; Metcalfe, Funnell, & Gazzaniga, 1995; Phelps & Gazzaniga, 1992). Several studies with rodents and nonhuman primates have also found that the (posterior) hippocampus is preferentially involved in spatial navigation (e.g., Moser,

Moser, Forrest, Andersen, & Morris, 1995). Brain imaging evidence has shown that navigation-related structural, volumetric changes in human subjects with extensive navigation experience are greatest in the posterior hippocampus and, in particular, of the right hemisphere (Maguire et al., 2000). Moreover, Rolls has specifically proposed that the primate (monkey) hippocampus contains specialized cells, called "spatial view cells," for the encoding of the place where the animal is looking (instead of the place where the animal is); thus, spatial view cells could provide the spatial representation required to perform object-place memory (i.e., associating a spatial representation with a representation of a person or object), and might be unique to the primates' highly developed visual system and eye movement control system. In sum, one might hypothesize that the hippocampus provides a network for events or episodes for which a spatial component provides part of the context (e.g., Burgess et al., 2001; Rolls, 2000; Robertson, Rolls, & George-Francois, 1999) and that such function is mainly supported by the right hemisphere's hippocampus (Smith & Milner, 1981) and, in particular, by the posterior portion of the right hemisphere's hippocampus (cf., Colombo, Fernandez, Nakamura, & Gross, 1998) as well as by extra-hippocampal areas of either hemisphere (e.g., parahippocampal cortex and perirhinal cortex; cf. Miyashita, 2000; Ploner et al., 1999, 2000; Higuchi & Miyashita, 1996).

Given that TC's damage on the right side of the brain was limited to the anterior region of the hippocampus, evidence from this patient could suggest that spared regions of the medial and inferior temporal structures on the right side might be sufficient to support the encoding of specific spatial views and their retrieval at the presentation of the auditory cues contained in the questions. Intriguingly, even small blocks of spared hippocampus seem sufficient to support adequate performance in spatial tasks in other mammals; for example, removing 40% of the hippocampus of rats does not impair their new learning of a water maze and 70% of intact hippocampus is required to retrieve a spatial task that was originally encoded with an intact brain (Moser & Moser, 1998). Indeed, an fMRI study of a patient with bilateral hippocampal atrophy affecting about 50% of the neural tissue (Maguire, Vargha-Khadem, & Mishkin, 2001) has revealed, during recall tasks, hippocampal activations that were similar to those of control subjects; thus, supporting the view that the remaining tissue in the human hippocampus can be functional and can participate in memory tasks.

Nevertheless, several other areas of the brain than those contained in the temporal lobe could support the rapid learning of an object's position and use this information, at a later stage, as a spatial index for the recovery of other types of information. Specifically, areas within the parietal and frontal lobes, which jointly direct eye movements as well as visual attention shifts (Corbetta, 1998), could spatially index events (i.e., objects and their locations) as they are attended or gazed

(cf. Xu & Chun, 2005; Shimozaki et al., 2003; Andersen, Essick, & Siegel, 1985) and keep track of sequences of eye movements (Grosbras et al., 2001). Such spatial indexes could be eye-based and used at a later stage as "pointers" to positions in the external world as an available source of information or an "outside memory" (O'Regan, 1992). However, very little detailed visual information is explicitly retained across views (Henderson & Hollingworth, 2003), although long-term visual memory for details of a scene increases linearly as a function of the total time of viewing (Melcher, 2006). Chun and Nakayama (2000) suggest that the continuity of visual processing is afforded by *implicit* visual memory traces of previous views or specific visual contexts. That is, these implicit traces of past views guide attention and eye movements to allow for effective access (indexing) to a scene, hence, providing context and continuity (Karn & Hayhoe, 2000). Such an indexing system might not encode within itself the "content" of visual information, as pointers can be, per se, empty of content (Scholl & Pylyshyn, 1999) and all they may do is to direct to a source (location) of information. In a metaphor, the brain might have internalized the "method of loci" mnemonic strategy; that is, by coding spatial information that is temporally related to objects and events, the content of a past experience can be more efficiently accessed.

The perirhinal area remains a likely cortical area that could have been responsible for the autonomic system's responses to previously seen stimuli in all of the three patients examined in the present study. Although there are no studies of patients with lesions confined to this area, studies with nonhuman primates have shown that about 25% of the neurons in the perirhinal area respond strongly to the sight of novel objects (Baxter & Murray, 2001; Brown & Aggleton, 2001; Murray & Bussey, 1999; Brown & Xiang, 1998), and lesions of the perirhinal cortex of monkeys disrupt the visual recognition of patterns (Meunier, Bachevalier, Mishkin, & Murray, 1993). The perirhinal cortex is also positioned earlier in the information processing hierarchy than the hippocampal formation (Suzuki & Amaral, 1994). One can surmise that, in all three of our patients, the perirhinal cortex was spared (in the right hemisphere) and this was sufficient for resulting in response reductions to the presentation of previously seen stimuli (Aggleton & Brown, 2006), which in turn was expressed as an autonomic system's adaptation response; whereas there was increased attention to the novel stimuli resulting, in turn, in an increased pupillary response. Moreover, there is also evidence from studies of either normal individuals or patients that the right hemisphere plays a particular important role in the memory of specific visual patterns (e.g., Laeng et al., 2007; Garoff, Slotnick, & Schacter, 2005; Metcalfe et al., 1995; Phelps & Gazzaniga, 1992), either explicit or implicit (e.g., Vaidya, Gabrieli, Verfaellie, Fleischman, & Askari, 1998; Swick & Knight, 1995); however, this does not necessarily mean that occipital areas

of the left hemisphere do not participate in visual implicit memory (cf., Yonelinas et al., 2002).

As a final note, the present findings may have some implications for programs to remedy specific problems of everyday life attributable to the memory deficit (e.g., Schacter & Glisky, 1986). For example, amnesic patients can learn vocabularies and skills within particular domains of knowledge or ability, such as operating a personal computer (e.g., Glisky, Schacter, & Butters, 1994). Based on the evidence of the present study, one aspect of preserved learning ability may often involve spatial indexing; if so, providing systematic and consistent spatial locations, for instance, on a computer screen, to particular hints and operations might be particularly effective (e.g., an operation of a certain type could always be cued on a given part of the screen, whereas a different operation could be performed on another). More generally, amnesics should benefit from an ordered environment where spatial locations of relevant objects remain consistent.

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