Current Trends in
Neurology
Vol. 10, 2016

Original Communication

The effects of selective amygdalo-hippocampectomy on different spatial orientation skills

Giuseppe Iaria[1,*], Gertruida M. Wentzel[1], Jacqueline Boon[1], Ford Burles[1], Irene Liu[1] and Paolo Federico[2]

[1]NeuroLab, Departments of Psychology and Clinical Neurosciences, Hotchkiss Brain Institute and Alberta Children's Hospital Research Institute; [2]Departments of Neuroscience, Radiology and Clinical Neurosciences, Hotchkiss Brain Institute and Seaman Family MR Centre, University of Calgary, Canada.

ABSTRACT

Topographical orientation refers to the ability of the individuals to find their way around by using a variety of cognitive strategies during navigation. Here, we report six case studies of patients who underwent selective amygdalo-hippocampectomy (as treatment for severe temporal lobe epilepsy) in order to shed more light on the role of the medial temporal lobe (MTL) in adopting different strategies useful for orientation. Patients were submitted to a comprehensive assessment of topographical orientation skills in which they were asked to perform different spatial orientation tasks. The performance of each patient is discussed within his/her neurological context in order to provide a better understanding of the effects of amygdalo-hippocampectomy on the human ability to orient. The general conclusions support the critical role of medial temporal lobe structures in processing allocentric spatial information useful for creating cognitive maps, as opposed to the use of egocentric spatial information that are mostly involved in navigating while relying on body turns and sequences. These findings may have significant implications in developing rehabilitation programs for patients undergoing selective amygdalo-hippocampectomy.

KEYWORDS: cognitive map, getting lost, hippocampus, path integration, spatial orientation

*Corresponding author: giaria@ucalgary.ca

INTRODUCTION

Topographical orientation refers to the ability of individuals to orient and navigate within the environment [1]. This complex and important function relies on several cognitive processes such as memory, attention, perception, mental imagery and decision-making skills, all of which play important roles in spatial cognition [2-9]. The proper function of these cognitive processes allows individuals to become familiar with the environment and adopt a variety of strategies useful for orientation [1, 10]. For instance, one may reach a target location by using the landmarks available within the environment and their spatial relationships (e.g., "the liquor store is between the cinema and the pharmacy"). Alternatively, one may use directions from single landmarks (e.g., "turn right at the bank, and right again at the cinema"), or make choices with respect to distances and body motions (e.g., "two blocks ahead, then make a right turn, and a right turn again). Of the various orientation strategies, however, the formation of a mental representation of the environment based on the spatial relationships between landmarks (i.e., a cognitive map) is the most flexible strategy allowing successfully navigation in the surrounding [11]. The use of cognitive maps is, indeed, the only strategy that allows individuals to reach a target place starting from all possible locations within the environment.

In addition to widespread neurodegenerative disorders as in the case of patients with Mild Cognitive Impairment (MCI) [12, 13] or Alzheimer's Disease (AD) [14, 15] and more selective neuropsychological reports [16], topographical disorientation has been also documented in individuals who underwent surgical treatment for severe temporal lobe epilepsy [17-19]. Evidence of topographical disorientation in patients with temporal lobe resection is provided in both ecological [18] and virtual [19] environments, and is commonly interpreted as a consequence of the surgical resection of regions in the temporal lobe, especially the hippocampal complex. Although the evidence of spatial deficits in these patients is consistent with the well-known role of medial temporal lobe (MTL) regions in spatial learning and memory, as largely supported by studies in both rodents (i.e. [11, 20-23] and humans [24-27], to date, the topographical defects following surgical treatment for severe temporal lobe epilepsy remains incompletely characterized. The reason behind this may rely on the fact that wayfinding and spatial navigation in novel environments can be indeed accomplished by using a variety of orientation strategies, only some of which are dependent on the hippocampus complex [28, 29]. Here, we report six case studies of patients who underwent selective amygdalo-hippocampectomy (SAH) in which they performed a comprehensive battery of tests assessing different spatial orientation skills: we tested the hypothesis that such a surgical treatment results in the impaired use of allocentric-based orientation strategies (mostly relying on the ability to form cognitive maps) and does not affect the ability to use egocentric-based orientation strategies as the ones involving body turns and distances travelled while navigating.

CASE REPORTS

The patients described below received surgery in the form of SAH in either the left or right temporal region as part of treatment for severe epilepsy. Performances of patients at various orientation tests (see below) were compared to a group of participants including 120 healthy volunteers (102 females, 18 males) who were matched for age (M = 42.3, SD = 14.42) and education (M = 16.1, SD = 3.97) to the patient group [30]. Each patient was administered a complete neuropsychological battery to evaluate general cognitive skills following surgical treatment (see Table 1). Hereafter is a detailed description of each patient included in the study.

Patient L-SAH1 is a 62-year-old left-handed female who completed a Grade 12 education. She began to experience seizures at the age of 53, and underwent a left SAH six years prior this testing. At the time of testing, she was still prescribed medication to treat recurring seizures. The post-operative neuro-radiological examination reports a focal area of post surgical encephalomalacia and chronic gliosis in the left temporal lobe. As shown in table 1, post-operative neuropsychological evaluation estimated that her premorbid intelligence was in the high average range. Her post-operative intellectual abilities were found to be within the average to above average range, with working memory in the normal range. The patient demonstrated impairments on tests of memory (both immediate and delayed) for verbal material and object naming. Visuospatial memory was found to be normal on all measures. Post-operative MRI images documenting selective amygdalo-hippocampectomy in the left hemisphere are reported in figure 1. These images are representative of all patients included in the SAH groups since they all underwent the same surgical procedure and resection.

Patient L-SAH2 is a 57-year-old right-handed female who completed Grade 12 and four years of post-secondary education. She began to experience seizures at age 3, and received surgery four years prior this testing. At the time of testing, she was not taking any medication for seizure control, nor was she experiencing any seizures. The post-operative neuro-radiological examination reports a fluid-filled surgical cleft is seen at the operative left temporal site, extending through the temporal lobe to the medial aspect. Her post-operative neuropsychological evaluation (as reported in table 1) estimated her premorbid intelligence as in the high average range. Her post-operative intelligence was within the average range. The patient demonstrated impairments on measures of immediate and delayed verbal memory as well as object naming, and delayed recognition in the domain of visuospatial memory. Performance in all other cognitive domains was normal. The only

Table 1. SAH patients' neuropsychological assessment. **Bold** text indicates impaired performance.

	L-SAH1	L-SAH2	L-SAH3	L-SAH4	R-SAH1	R-SAH2
PREMORBID INTELLIGENCE [46]						
NAART errors	22	22	23	18	39	58
Predicted FSIQ	111	111	110	114	97	83
Predicted VIQ	109	109	108	113	94	77
INTELLIGENCE [47]						
Composite IQ (percentile)	102 (55)	93 (32)	106 (66)	106 (66)	89 (23)	**70 (2)**
Verbal IQ (percentile)	94 (34)	95 (37)	102 (55)	112 (79)	91 (27)	**71 (3)**
Nonverbal IQ (percentile)	110 (75)	92 (30)	110 (75)	99 (47)	88 (21)	**67 (1)**
WORKING MEMORY [48, 49]	40/40	34/40	39/40	36/40	**14/40**	**12/30**
VERBAL MEMORY [49, 50]						
CVLT-II						
Recall Trial 1-5 (T-score)	**26 (25)**	**33 (32)**			47 (42)	**28 (28)**
Short delay free recall (Z-score)	**1 (-3.5)**	**4 (-2.5)**			9 (-1)	**5 (-2.5)**
Long delay free recall (Z-score)	**2 (-3.5)**	**3 (-3)**			10 (-1)	**8 (-1.5)**
Short delay cued recall (Z-score)	**2 (-4)**	**7 (-2)**			12 (-0.5)	**9 (-1.5)**
Long delay cued recall (Z-score)	**2 (-3.5)**	**6 (-2.5)**			**10 (-1.5)**	**9 (-1.5)**
Recognition hits (Z-score)	**12 (-2)**	16 (0.5)			16 (0)	
WMS-III						
Auditory immediate index (percentile)	**77 (6)**	**80 (9)**	97 (42)	94 (34)	99 (47)	84 (23)
Auditory delayed index (percentile)	83 (13)	**74 (4)**	97 (42)	102 (55)	102 (55)	83 (13)
Auditory recognition delay index (percentile)	120 (91)	**75 (5)**	90 (25)	90 (25)	95 (37)	85 (16)
VISUOSPATIAL MEMORY [49, 51, 52]						
BVMT-R						
Total recognition (percentile)	21 (34)	17 (10)			**11 (<1)**	
Delayed recognition (percentile)	8 (34)	**6 (7)**			**4 (<1)**	
Recognition hits (percentile)	5 (11-16)	5 (11-16)			**5 (6-10)**	
RCFT						
Immediate recall (percentile)	12 (12)	15 (18)			**6 (<1)**	**5 (<1)**
Delay recall (percentile)	13 (14)	14.5 (16)			**7 (<1)**	**6 (<1)**
WMS-III						
Visual immediate index (percentile)	88 (21)	88 (21)	97 (42)	118 (88)	100 (50)	**62 (8)**
Visual delay index (percentile)	**78 (7)**	84 (14)	109 (73)	112 (79)	91 (27)	**65 (1)**
EXECUTIVE FUNCTIONS [53-55]						
COWAT						
Total words						
WCST	42	42	33	59	40	19

Table 1 continued..

	L-SAH1	**L-SAH2**	**L-SAH3**	**L-SAH4**	**R-SAH1**	**R-SAH2**
Categories completed (percentile)	6 (>16)	6 (>16)	6 (>16)	6 (>16)	6 (>16)	5 (11-16)
Trials administered	77	79	86	82	91	128
Perseverative responses (percentile)	7 (87)	6 (55)	7 (66)	11 (39)	6 (66)	17 (27)
Perseverative errors (percentile)	7 (84)	6 (55)	7 (61)	8 (53)	6 (63)	16 (25)
Nonperseverative errors (percentile)	3 (96)	5 (61)	5 (66)	6 (61)	6 (58)	19 (14)
Failure to maintain set (percentile)	0 (>16)	1 (>16)	1 (>16)	0 (>16)	**2 (6-10)**	**3 (2-5)**
Design Fluency						
Free condition (Z-score)	18 (0.4)	21 (0.9)	17 (0.2)	50 (5.7)	35 (3.1)	10 (-0.9)
Four lines condition (Z-score)	12 (-1.23)	16 (-0.5)	20 (0.2)	31 (2.2)	19 (0)	**7 (-2.1)**
READING [56]	12/30	14/30	17/30	14/30	15/30	**7/30**
OBJECT NAMING [57] BNT–60 (T-score)	**39 (20.2)**	**39 (12.8)**	**47 (36.7)**	56 (50.9)	52 (40.1)	**22 (<16.2)**
LANGUAGE COMPREHENSION [58]	58/62	58/62	60/62	62/62	62/62	**57/62**
VISUO-PERCEPTION [53]	31	24	26	28	24	**17**
VISUO-CONSTRUCTION [59, 60] *Free Drawing (clock, bicycle, cube)* *RCFT Standard copy (percentile)*	Normal 33 (>16)	Normal **31 (2-5)**	Normal 33 (>16)	Normal 35 (>16)	Normal **29.5 (<1)**	**Impaired** **31 (2-5)**

cognitive difficulty reported by the patient post-surgery was word-finding.

Patient L-SAH3 is a 39-year-old right-handed female who completed Grade 12 and two years of post-secondary education. She began experiencing seizures at age 10, and received surgery to the left hemisphere 7 years prior this testing. Since surgery she has been completely seizure-free and is not currently taking any medication. The post-operative neuro-radiological examination confirms the resection of the amygdala and anterior hippocampus. The residual posterior region of the hippocampus is reported to be atrophic with increased T2 signal within it, consistent with hippocampal sclerosis. The patient’s post-operative neuropsychological evaluation (details displayed in table 1) indicated that her intelligence was within the average range. No premorbid intelligence estimate was made. The patient displayed impairment in object naming, but all other measures (including working memory and executive functions) were found to be within the average range.

Patient L-SAH4 is a 43-year-old right-handed female who completed Grade 12 as well as one year of post-secondary education. She began having seizures at age 10, and received surgery eight years prior testing. She has been seizure-free since surgery, and is currently not taking any medication. The patient’s post-operative neuro-radiological examination reveals findings consistent with mesial temporal sclerosis on the left hemisphere and abnormal appearance of the left anterior temporal lobe consistent with cortical dysplasia. As reported in table 1, post-operative neuropsychological evaluation estimated her premorbid intelligence as being in the high average range. Her intelligence at the time of evaluation was found to be in the above average to average range. Her cognitive abilities were found to be mostly intact.

Patient R-SAH1 is a 44-year-old right-handed female who completed Grade 12 as well as five years of post-secondary education. She began experiencing seizures at age 9, and received

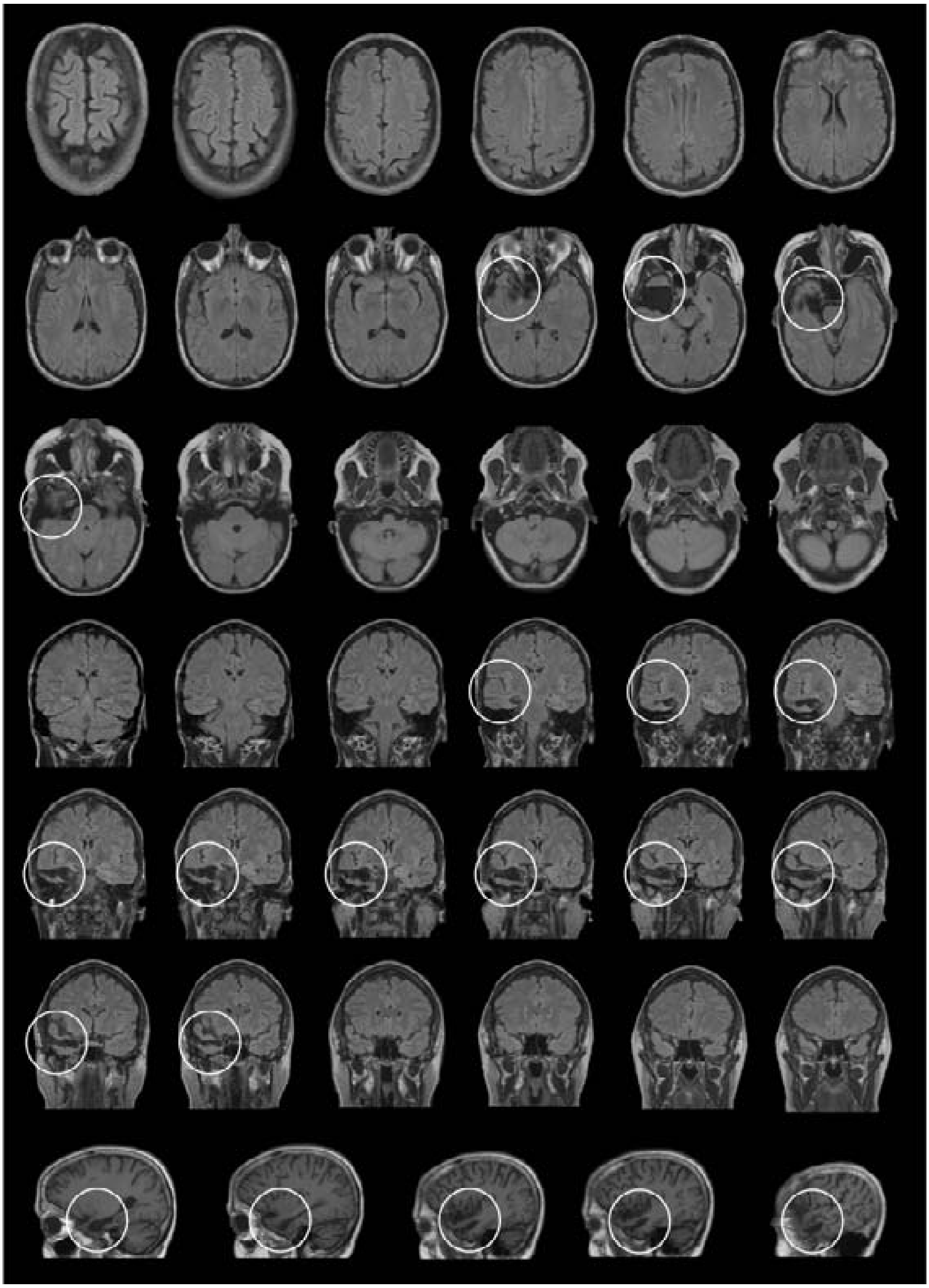

Figure 1. Neuroradiological examination. Axial, coronal and sagittal view of post-operative MRI images documenting left selective amygadalo-hippocampectomy. The white circles highlight the surgical resection and resulting damage. As shown in the sagittal section (bottom row) the damage following the resection included the temporal cortex laterally as well as the perirhinal cortex in the medial region.

surgery four years prior testing. She has been seizure-free since surgery, and is not currently taking any medication. The post-operative neuro-radiological examination confirms the resection of the right hippocampus with a residual small amount of it in the posteromedial aspect. Post-operative neuropsychological evaluation (as shown in table 1) estimated a premorbid intelligence within the average range. Intelligence at the time of testing was also assessed within the average range. Other results indicate impairments on tests of working memory, acquisition and recall of visuospatial material, semantic word fluency and bilateral motor dexterity.

Patient R-SAH2 is a 47-year-old right-handed male who completed a Grade 12 education. He began experiencing seizures at the age of 18, and received surgery eight years prior testing. Since surgery, he has experienced very few seizures separated by a minimum of 6-month period. He is currently taking medication to minimize further seizures. The post-operative neuro-radiological examination confirms a partial resection of the anteromedial temporal lobe, with part of the hippocampus remaining at its most posterior aspect. The brain appears mildly and diffusely atrophic and the lateral and third ventricles appear moderately enlarged. Post-operative neuropsychological evaluation (shown in Table 1) estimated his premorbid intelligence as being in the low average range. His intelligence at the time of evaluation was found to be within the well-below average range. The patient demonstrated impairments on tests of working memory, verbal memory (long delay cued recall), visuospatial memory, word fluency, visuoconstruction, visuoperception, reading speed, object naming, right-hand grip strength, left-hand dexterity and somatosensory extinction. This particular patient had a history of hydrocephalus and the results of most measures were comparable to pre-operative evaluations.

MATERIALS AND METHODS

Participants completed a battery of tests consisting of six subtests appositely designed for assessing a variety of orientation skills in virtual environments [30]. Before beginning the first test, all participants completed a demographic questionnaire. Each participant then completed all six subtests, which were administered in a randomized order. Hereafter is a detailed description of each test.

Landmark recognition test

This test assessed participants' ability to recognize abstract landmarks encountered during navigation. Each trial consisted of a 30-second video clip showing, from a first-person perspective, an individual navigating through a virtual environment and encountering three sign-post "landmarks" displaying abstract images (see figure 2 for samples of images). After each clip ended, participants were presented sequentially with six similar abstract images (three of which were novel images), and asked for each image whether or not it was encountered while navigating in the virtual environment as shown in the video clip. This procedure was repeated for six unique trials randomly administered, each including novel landmarks encountered along novel pathways. We recorded the number of correct responses. The choice of using abstract images as landmarks in this test (as well as in the test described below) relies on the opportunity to assess recognition skills independently of previous knowledge acquired in real life.

Heading orientation test

This test was designed to measure participants' ability to make associations between left and right body turns with respect to given landmarks. In each trial, participants viewed a first-person perspective video clip similar to those in the previous task. Three signpost landmarks displaying abstract images (novel but similar to the ones used in the previous test) were seen in each video clip (samples of abstract images are displayed in figure 2). At each landmark, the individual in the video clip made either a left or a right turn. After the clip was viewed, participants were randomly presented with pictures of each landmark they encountered, and asked to indicate whether the individual turned left or right at each particular landmark. This test consisted of six trials randomly administered, each including novel landmarks encountered along different pathways within the environment. We recorded the number of correct responses.

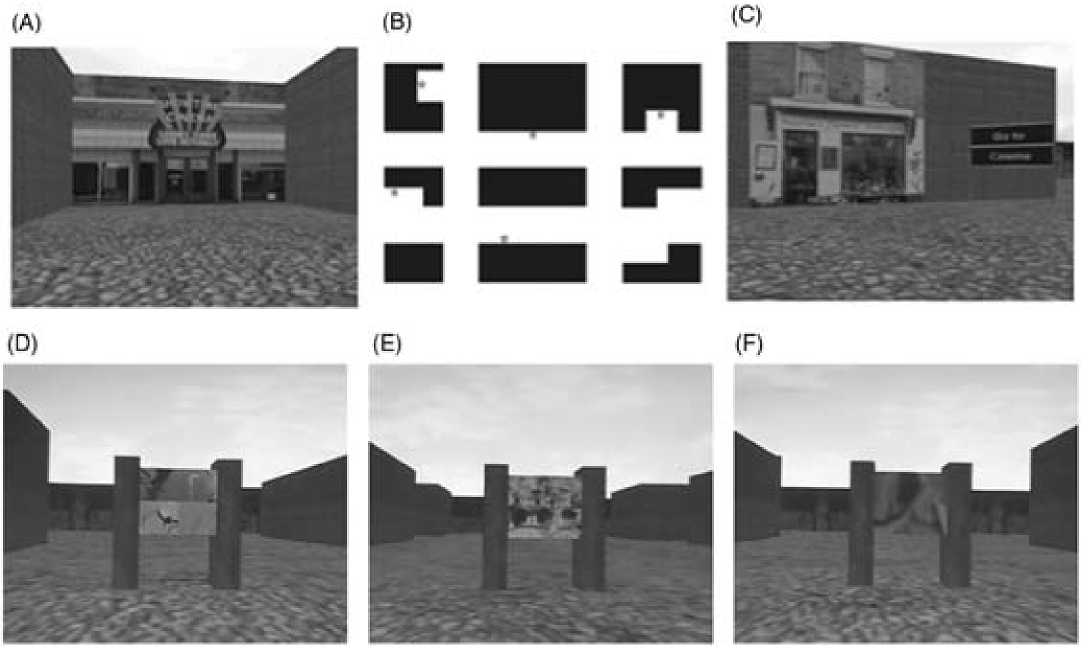

Figure 2. Cognitive map test. (A) An example of the four landmarks located in the virtual environment. (B) The top-view map of the environment; here we indicated the locations of the four landmarks but this information was not available to the participants while solving the task. (C) The first view of one of the trials in the cognitive map use test. In this specific trial the individual in the clip is facing the flower shop and required to reach the cinema. (D, E, F) Sample of abstract images used in the landmark recognition and heading orientation tests.

Left-right orientation test (no landmarks)

This test assessed the ability of the individuals to remember a sequence of turns in a maze-like virtual environment in which no relevant information and landmarks are available for orientation. The test consisted of six trials randomly administered. In each trial, participants viewed two separate 30-second clips of an individual navigating through a virtual environment similar to the ones used in the previous task. In each clip, the individual in the video made a series of three randomized left-right turns but no landmarks were encountered while performing the pathway in the environment. After each set of two clips was shown, participants were asked to indicate whether the path traveled in the second clip was identical to that traveled in the first one (i.e. whether the individual followed the same pathways in the two clips). We recorded the number of correct responses.

Path reversal test (no landmarks)

This test assessed participants' ability to recognize a path when traveled in reverse direction. As for the test described above, no landmarks are available in the environment and participants are required to memorize a series of left and right turns. In each of the six randomized trials, the participant viewed a clip in which an individual navigate in a virtual environment by following a given sequence of turns for about 30 seconds, then turning around and moving in the opposite direction for about 30 seconds by making the same number of turns. After the clip ended, participants were asked to indicate whether the individual in the clip turned around and retraced the original pathway or took a different one. This test requires additional effort as compared to the previous test since left and right turns would need to be reversed in order to make a decision on whether or not the individual navigating in the video travels the same pathway in both directions. We measured the number of correct responses.

Cognitive map formation test

The cognitive map formation test aimed to assess the ability of the individuals to form cognitive maps. The test consisted of a series of trials in which the participants viewed a clip, from a first-person perspective, of an individual moving through a virtual environment. The virtual environment in this test included four easily identifiable landmarks (a flower shop, a cinema, a restaurant, and a hotel), each located on a different building available in the environment (see figure 2). All four landmarks were visited in the first clip, after which the number of landmarks visited in each clip varied pseudo-randomly from 1 to 3 in order to control for the equal duration of each clip. All landmarks were visited in the first clip to give participants the opportunity to solve the task from the very first trial (see below). Subsequent trials were generated pseudo-randomly with the same number of visits for each landmark across clips throughout the entire test. After each clip, the participant was shown a top-view map of the environment (Figure 2), and asked to indicate, by dragging and placing icons depicting each landmark, where each of the landmarks was located within the environment. Each landmark placement was considered correct if the icon was located on the block indicating the actual building (see figure 2B). If the participant placed incorrectly one of any four landmarks, another clip was shown to help further familiarize him/her with the environment and the landmarks located within it. Participants were allowed to perform up to 20 trials (each consisting of one clip and one attempt to place the four landmarks on the map) to successfully complete the task (a limited number of trials was used to avoid frustration if unsuccessful in solving the task). The task was concluded either when the participant successfully placed all four landmarks in the correct positions in two consecutive trials, or after 20 unsuccessful attempts. To minimize the possibility of guessing, participants were given no feedback over the course of this task. In case of successful completion, we recorded the number of trials that were necessary in order to form a cognitive map of that environment. On the other hand, if participants were unsuccessful, they were presented with the map that included the correct locations of the landmarks and allowed to study it before performing the test described below. In this test, we measured the number of trials required to solve the task, and therefore higher scores refer to worse performance.

Cognitive map use test

This test assessed participants' ability to make use of the cognitive map as formed in the test described above. The test consisted of six trials and it was performed within the same environment in which participants performed the cognitive map formation test described above. In each trial, the participant was shown a video clip starting with the camera facing one of the landmarks available in the environment and a sign-post indicating a target location to be reached (Figure 2C); then, the camera traversed a path ending at the target landmark indicated on the signpost. At this specific time, the video clip ended and the participants were asked whether or not the individual followed the shortest possible pathway while reaching the target location. In half of the trials, the individual in the video follows the shortest pathway; in the other half the individual follows a longer one. This task required participants to make use of their mental representation of the environment in order to estimate whether the shortest pathway is followed while moving from one place to another. We recorded the number of correct responses.

RESULTS

We considered a patient's performance impaired if his/her score was below two (or more) standard deviations from the mean's score of controls. Table 2 displays individual scores of each patient, as well as cut-off score, mean and standard deviation scores as derived from the control group at each test.

The results revealed that patient R-SAH2 was the only participant showing a significant impairment in solving the landmark recognition test (due to technical issues, data for the performance of patient L-SAH3 were not recorded). With respect to the heading orientation test, patients with resections in the right hemisphere (i.e., R-SAH1 and R-SAH2) scored at cut-off, which was suggestive of impairment in both cases. Performance of patients L-SAH1 and R-SAH2 was impaired while solving the left-right orientation test, whereas none of the six patients showed impairments when performing the path reversal test. The cognitive map formation test resulted to be the most challenging task for all patients except patient L-SAH4:

Table 2. Control group and SAH patients' scores at each test (* indicates impairment).

	Landmark recognition	**Heading orientation**	**L-R orientation**	**Path reversal**	**CM formation**	**CM use**
Controls mean	33.81	15.9	5.55	5.01	5.09	5.54
Controls SD	2.53	2.38	0.73	1.04	3.96	0.83
Cut-off score	*29*	*11*	*4*	*3*	*13*	*4*
L-SAH1	30	12	**4***	5	**20***	N/A
L-SAH2	30	15	5	4	**20***	**4***
L-SAH3	N/A	12	6	4	**14***	6
L-SAH4	35	16	5	5	3	6
R-SAH1	30	**11***	6	4	**15***	5
R-SAH2	**21***	**11***	**3***	4	**20***	**3***

patients L-SAH1, L-SAH2 and R-SAH2 did not solve the task even after performing all 20 possible trials, whereas patient L-SAH3 and R-SAH1 required a significant higher number of trials (as compared to controls) in order to solve the task, which indicates an impairment in the ability to form cognitive maps. Finally, the cognitive map use test resulted to be impaired in patient L-SAH2 and patient R-SAH2 (due to technical problems, data for patient L-SAH1 were not recorded).

DISCUSSION

In this study we aimed at investigating the consequences of SAH in adopting different orientation strategies while navigating in the environment. To achieve this goal, we performed a comprehensive assessment of orientation skills in six patients who underwent selective amygdalo-hippocampectomy as surgical treatment for temporal lobe epilepsy. Hereafter, we will first provide the individual analysis and discussion of patients' performances at our spatial orientation tests within their clinical history and neuropsychological outcomes; then, we will discuss the contribution of our findings more generally to the field of spatial cognition, hoping to shed some light on the role of MTL structures on the complex ability of orienting and navigating in spatial surroundings.

We will start our analysis with patient L-SAH4, who performed as well on all our tests as the healthy controls. According to the neuropsychological evaluation, her post-surgical intelligence was measured in the above average to average range. She also reportedly demonstrated intact cognitive abilities in all domains. Although she suffers from a significant lesion to the left hippocampal region, it is possible that neural plasticity as well as other behavioural mechanisms have allowed her to compensate for the loss. Research by Tanriverdi and colleagues [31] suggests, in fact, that several factors influence the outcome of selective amygdalo-hippocampectomy on measures of memory, including age at surgery, duration of seizures, and seizure control after surgery. Given such findings, it can be reasoned that the fact that this patient underwent surgery at the relatively young age of 35, and has been seizure-free since surgery, may contribute significantly to the positive memory outcomes, possibly due to neuroplasticity. Her above average IQ likely also contributed to her relatively intact abilities for spatial reasoning, as even a relative decrease in verbal and spatial reasoning abilities after surgery may not have resulted in a measurable impairment. Upon questioning, this patient reported that throughout her life she has always had strong orientation skills, though relying almost exclusively on a keen memory for landmarks to navigate in new and familiar environments.

From a neuropsychological perspective, patient L-SAH1 and L-SAH2 reported an overlapping outcome. They both performed poorly in the domain of verbal memory and object naming, and performed similarly while solving our tests. They both were unable to solve our cognitive map formation test; their performance was similar to controls in the path reversal test, as well as the heading orientation and landmark recognition tests. Their performance differ though in the left-right orientation test with patient L-SAH1 performing worse than controls and L-SAH2. These results may suggest that although it is not surprising that lesions to the left MTL result in greater deficits in verbal memory [32], such a deficit may or may not affect the encoding of spatial information relying on sequences of left and right body turns. One may speculate that the inconsistent finding between these two patients may rely on the fact that the encoding of left-right body turns may occur with or without the involvement of verbal memory skills.

Patient L-SAH3 showed impairments only in the cognitive map formation test. The neuropsychological evaluation done post-surgery estimated her intelligence within the average range, and did not indicate any cognitive deficits other than object naming. This suggests that the ability to name objects (and therefore landmarks) may affect performance when that ability is required while creating a cognitive map of the surrounding. However, in this specific patient, it is important to note that although she scored within the impaired range in the cognitive map formation test, she eventually solved the test. In fact, with the exception of one other participant, this patient required the fewest trials of all in the patient group to solve this task. This suggests that although the hippocampal lesion may have impacted her orientation abilities, she may employ some compensatory strategies to learn spatial relationships. As described earlier, the outcome of amygdalo-hippocampectomy may be influenced by various factors including age at surgery [31]: since this patient underwent surgery at age 32, she experienced a relatively short lifetime seizure duration in comparison to the other participants in the patient group. If, as suggested by Tanriverdi and colleagues [31], younger patients undergoing SAH tend to recover cognitive capacities to a greater degree than older patients, her young age may have allowed for a higher level of neuroplasticity, thus positively influencing her memory outcomes on several measures after surgery. Her impairment on the cognitive map formation test may be related to the hippocampal lesion affecting a component necessary for cognitive map formation that is unrelated to verbal or visuospatial memory.

Patient R-SAH1 scored within the impaired range on the heading orientation and cognitive map formation tests. These selective deficits are consistent with the patient's post-surgical neuropsychological assessment, which reported deficits in working and visuospatial memory despite an IQ within the average range. Such a deficit in visuospatial memory is not surprising given well-documented evidence that lesions in the right MTL affect visuospatial memory to a greater degree than verbal memory [32]. The two tasks with which she experienced difficulty all require the ability to learn and memorize complex visuospatial information in relationship to spatial layout and directions. As documented by Laeng and colleagues [33], the right MTL and associated areas such as the hippocampus play a crucial role in the learning and memory for the type of visual information that cannot easily be verbalized. These findings may explain in part why this particular patient experienced difficulty when trying to relate the abstract landmarks to directions.

Patient R-SAH2 scored within the impaired range on all measures of spatial orientation expect for the path reversal test. These rather pronounced deficits could be understood in the context of his post-operative neuropsychological assessment. It is noted in the assessment that his intellectual abilities were measured to be within the well-below average range. As previously reported, this patient shows deficits in several areas of memory, perception, and other cognitive functions. It is possible that these impairments, as well as the surgical lesion, contributed in large to the low scores on most of the measures in the current test. With demonstrated deficits in memory, it can be understood that this participant experienced difficulty with complex tasks such as cognitive map formation, which requires various resources and a high degree of cognitive effort. Since the right MTL and associated hippocampal regions are vital for the initial learning stages of novel spatial information [34], the lesion to the right hemisphere may have impacted the participant's ability to memorize the spatial relationships between the landmarks in the cognitive map formation task. An inability to properly commit novel visuospatial information (in this case, the map of a virtual environment) to memory to begin with, even after being shown the correct locations of the landmarks, would contribute heavily to the continuing deficit demonstrated in the cognitive map use task. This inability to commit spatial relationships to memory may also be related to effects of the lesion on the patient's ability to use mental imagery for means of topographical orientation. There is evidence that many individuals suffering from orientation deficits report difficulty envisioning familiar environments [16]. Furthermore, an inability to perform mental rotations or imagine oneself moving within an environment has been related to difficulties in forming cognitive maps [35]. The fact that this patient is currently still prescribed medication and periodically experiences seizures may also negatively influence his memory outcomes, as greater seizure frequency and less successful seizure control are related to the deterioration of memory function [31]. In addition, it should be noted that this particular patient had a history of hydrocephalus; although the MRIs show no signs of extended brain damage we cannot exclude that the presence of hydrocephalus might have impacted on his cognitive skills and brain functioning in general.

The overall performance of the six patients described in this study supports the hypothesis that lesions in the MTL severely affect the ability of the individuals to solve a task that heavily relies on the processing of allocentric spatial information, such as the spatial relationships between landmarks available in the environment, which allows for the formation of cognitive maps. On the other hand, damage in the MTL does not seem to affect the ability of the individuals to process egocentric spatial information as engaged in left-right body turns and distances travelled (i.e. left-right orientation and path reversal tests), as well as in the ability to recognize short-cuts (i.e. cognitive map use test). Some of these findings are consistent with the well-known role of the MTL in processing landmark-based spatial information related to the ability of forming cognitive maps [24-27], suggesting that alternative non-landmark-based orientation strategies may be available when structures in the temporal lobe are damaged [18].

Spatial learning and memory defects in patients with unilateral temporal lobe resection or amygdalo-hippocampectomy have been documented in a variety of tasks in different experimental settings. Some studies show that MTL patients are impaired in remembering the locations of objects on a table top [36-38], or in a scene [39, 40], or while performing a variety of spatial mazes originally designed for rodents [41-43]. However, the use of large-scale environments to investigate topographical orientation and navigation in MTL patients has been limited. Maguire and colleagues [17] used film footage of someone walking in a real environment to assess the ability of patients to correctly identify scenes and environmental landmarks (and their spatial relationships) from the surrounding, as well as their ability to recall the correct sequence of landmarks encountered along the route and the ability to draw a map of the environment. The results showed that both patients with left or right MTL damage were impaired in solving all navigational tasks, with the only exception of left MTL patients being able to judge proximity between two landmarks. In a different study, Spiers and colleagues [44] used a large-scale virtual town to investigate the effects of unilateral temporal lobectomy on topographical and episodic memory. Patients with either left or right MTL damage were asked to explore the virtual town; while navigating in the environment, participants experienced events in which they participated actively in order to simulate a real-life situation. Following the exploration phase, patients were tested on a variety of topographical tasks such as map drawing, wayfinding (i.e., navigating between different locations in the town) and scene recognition, as well as an episodic memory task in which they were tested on the events occurred in the virtual town. The results of this study revealed an important dissociation between the right and left MTL on their critical role for topographical and episodic memory, respectively; importantly, however, although topographical memory was severely affected in right MTL patients, patients with left MTL damage performed significantly worse than controls as well. Our findings are only in part consistent with both these studies: the patients we described here with either left or right SAH are impaired in topographical orientation tasks in which the use of environmental landmarks is critical for forming a cognitive map of the environment; however, the impairment is not as evident when patients are asked to recognize short-cuts while performing our cognitive map use test, which according to previous literature still relies on MTL structures. There may be two explanations for this inconsistency. First, it may be possible that our cognitive map use test is not entirely assessing the ability to make use of a cognitive map as investigated traditionally in the literature. The test that we used here, in fact, does not require active navigation, and it consists of a series of video clips that participants watch in order to identify short-cuts. Therefore the test may be engaging other cognitive processes for successful performance, rather than the ones involved in making use of cognitive maps. The second explanation may refer to the engagement of other brain areas in support of allocentric memory. In a very recent study, in fact, Zhang and Ekstrom [45] provide evidence that the retrieval and utilization of an allocentric representation engage brain regions that are not in the MTL such as the retrosplenial cortex, the superior posterior parietal cortex and the precuneus. The authors found that these regions were particularly engaged when participants navigated in the surrounding after studying overview maps of the environment, suggesting that they may play a critical role in navigating by means of allocentric memory. Our findings seem to support this recent evidence suggesting that in the absence of MTL structures other regions may be sufficient for navigating and performing short-cuts, as well as for navigating by using egocentric spatial information that are mostly required in using body turns and distances travelled.

It is important to highlight some limitations of this study. First, the six case studies described in this study include patients presenting with a significant heterogeneity in their clinical history, with different premorbid onset, duration of epilepsy, pre-surgical cognitive status and neuropsychological outcomes following the resection. This limits our findings to these selective patients with their specific clinical history and does not allow the findings to be generalized to the entire clinical population undergoing SAH; as case reports, however, they do provide insights into the possible outcomes of SAH within the spatial cognition domain. The second major limitation of our study refers to the limited number of trials to be performed in some of our tests (i.e., left-right orientation, path reversal and cognitive map use tests). In each of these tests, participants are required to perform a total of six trials; this low number of trials does not provide the opportunity to detect a large range of variance in performance, which may limit the sensitivity of these tests in detecting moderate cognitive impairments. A third limitation of our study refers to the use of virtual environments and abstract images for assessing spatial orientation skills. Although there are obvious advantages in creating tests in virtual environments, mostly consisting of having total control of the experimental environments, these tests lack the contribution of proprioceptive, somatosensory and vestibular information, which are critical while navigating in ecological surroundings.

ACKNOWLEDGEMENTS

This study was supported by the Natural Science and Engineering Research Council of Canada (NSERC) under Discovery Grant (#RT735872). We would like to thank Lisa Partlo for helping with the neuropsychological evaluations.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Gallistel, C. R. 1990, The Organization of Learning. Cambridge: Bradford Books/MIT Press.
2. Berthoz, A. and Viaud-Delmon, I. 1999, Curr. Opin. Neurobiol., 9, 708-712.
3. Brunsdon, R., Nickels, L. and Coltheart, M. 2007, Neuropsychol. Rehabil., 17, 34-52.
4. Burgess, N., Trinkler, I., King, J., Kennedy, A. and Cipolotti, L. 2006, Rev. Neurosci., 17, 239-251.

5. Corbetta, M., Kincade, J. M. and Shulman, G. L. 2002, J. Cogn. Neurosci., 14, 508-523.
6. Davis, S. J. C. and Coltheart, M. 1999, Neuropsychol. Rehabil., 9, 1-30.
7. Farah, M. J. 1989, The Neuropsychology of Mental Imagery, F. Boller and J. Grafman (Eds.), The Handbook of Neuropsychology, Disorders of Visual Behavior, Amsterdam, Elsevier, 395-413.
8. Lepsien, J. and Nobre, A. C. 2006, Brain Res., 1105, 20-31.
9. Riddoch, M. and Humphreys, G. 1989, Finding the way around topographical impairments, J. W. Brown (Ed.), Neuropsychology of visual perception, Hillsdale, Lawrence Erlbaum Associates, 79-103.
10. Bures, J. and Fenton, A. A. 2000, News Physiol. Sci.,15, 233-240.
11. O'Keefe, J. and Nadel, L. 1978, The Hippocampus as a Cognitive Map. Oxford, Clarendon.
12. Hort, J., Laczo, J., Vyhnalek, M., Bojar, M., Bures, J. and Vlcek, K. 2007, Proc. Natl. Acad. Sci. USA, 104, 4042-4047.
13. Lim, T. S., Iaria, G. and Moon, S. Y. 2010, J. Clin. Neurol., 6, 204-211.
14. Jheng, S. S. and Pai, M. C. 2009, Behav. Brain Res., 200, 42-47.
15. Pai, M. C. and Jacobs, W. J. 2004, Int. J. Geriatr. Psychiatry, 19, 250-255.
16. Aguirre, G. K. and D’Esposito, M. 1999, Brain, 122, 1613-1628.
17. Maguire, E. A., Burke, T., Phillips, J. and Staunton, H. 1996, Neuropsychologia, 34, 993-1001.
18. Bohbot, V. D., Iaria, G. and Petrides, M. 2004, Neuropsychology, 18, 418-425.
19. Astur, R. S., Taylor, L. B., Mamelak, A. N., Philpott, L. and Sutherland, R. J. 2002, Behav. Brain Res., 132, 77-84.
20. O'Keefe, J. and Dostrovsky, J. 1971, Brain Res., 34, 171-175.
21. O'Keefe, J. and Speakman, A. 1987, Exp. Brain Res., 68, 1-27.
22. White, N. M. and McDonald, R. J. 2002, Neurobiol. Learn. Mem., 77, 125-184.
23. Wilson, M. A. and McNaughton, B. L. 1994, Science, 265, 676-679.
24. Iaria, G., Chen, J. K., Guariglia, C., Ptito, A. and Petrides, M. 2007, Eur. J. Neurosci., 25, 890-899.
25. Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D. and O’Keefe, J. 1998, Science, 280, 921-924.
26. Maguire, E. A., Frackowiak, R. S. and Frith, C. D. 1997, J. Neurosci., 17, 7103-7110.
27. Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. and Frith, C. D. 2000, Proc. Natl. Acad. Sci. USA, 97, 4398-4403.
28. Hartley, T., Maguire, E. A., Spiers, H. J. and Burgess, N. 2003, Neuron, 37, 877-888.
29. Iaria, G., Petrides, M., Dagher, A., Pike, B. and Bohbot, V. D. 2003, J. Neurosci., 23, 5945-5952.
30. Iaria, G. and Barton, J. J. 2010, Exp. Brain Res, 206, 189-196.
31. Tanriverdi, T., Dudley, R. W., Hasan, A., Al Jishi, A., Al Hinai, Q., Poulin, N., Colnat-Coulbois, S. and Olivier, A. 2010, J. Neurosurg., 113, 1164-1175.
32. Milner, B. 2003, Epilepsy Behav., 4, 799-812.
33. Laeng, B., Overvoll, M. and Ole Steinsvik, O. 2007, Brain Cogn., 63, 136-144.
34. Jones-Gotman, M., Zatorre, R. J., Olivier, A., Andermann, F., Cendes, F., Staunton, H., McMackin, D., Siegel, A. M. and Wieser, H. G. 1997, Neuropsychologia, 35, 963-973.
35. Palermo, L., Iaria, G. and Guariglia, C. 2008, Behav. Brain Res., 192, 248-253.
36. Nunn, J. A., Graydon, F. J., Polkey, C. E. and Morris, R. G. 1999, Brain, 122, 47-59.
37. Smith, M. L. and Milner, B. 1981, Neuropsychologia, 19, 781-793.
38. Smith, M. L. and Milner, B. 1989, Neuropsychologia, 27, 71-81.
39. Baxendale, S. A., Thompson, P. J. and van Paesschen, W. 1998, Neuropsychologia, 36, 591-602.
40. Pigott, S. and Milner, B. 1993, Neuropsychologia, 31, 1-15.
41. Abrahams, S., Pickering, A., Polkey, C. E. and Morris, R. G. 1997, Neuropsychologia, 35, 11-24.
42. Bohbot, V. D., Kalina, M., Stepankova, K., Spackova, N., Petrides, M. and Nadel, L. 1998, Neuropsychologia, 36, 1217-1238.

43. Goldstein, L. H., Canavan, A. G. and Polkey, C. E. 1989, Neuropsychologia, 27, 167-177.
44. Spiers, H. J., Burgess, N., Maguire, E. A., Baxendale, S. A., Hartley, T., Thompson, P. J. and O'Keefe, J. 2001, Brain, 124, 2476-2489.
45. Zhang, H. and Ekstrom, A. 2013, Hum. Brain Mapp., 34, 1070-1087.
46. Blair, J. R. and Spreen, O. 1989, The Clinical Neuropsychologist, 3, 129-136.
47. Kaufman, A. S. and Kaufman, N. L. 1990, Kaufman Brief Intelligence Test manual, Circle Pines, MN, American Guidance Service.
48. Dobbs, A. R. and Rule, B. G. 1989, Psychology and Aging, 4, 500-503.
49. Wechsler, D. 1997, Wechsler Adult Intelligence Scale-Third Edition, San Antonio, Psychological Corporation.
50. Delis, D. C., Kramer, J. H., Kaplan, E. and Ober, B. A. 2000, California Verbal Learning Test - Second Edition, Adult Version, San Antonio, TX, The Psychological Corporation.
51. Benedict, R. H. B. 1997, Brief Visuospatial Memory Test – Revised, Odessa, Fla, Psychological Assessment Resources.
52. Osterrieth, P. 1944, Le test de copie d'une figure complexe, Les Archieves de Psychologie, 31, 206-356.
53. Benton, A. L., Hamsher, K. D. and Sivan, A. B. 1944, Multilingual Aphasia Examination (3rd Ed.), San Antonio, TX, Psychological Corporation.
54. Grant, D. A. and Berg, E. A. 1948, J. Exp. Psychol., 38, 404-411.
55. Jones-Gotman, M. and Milner, B. 1977, Neuropsychologia, 15, 653-674.
56. Chapman, J. C. 1924, Chapman-Cook Speed of Reading Test, Educational Test Bureau.
57. Kaplan, E. F., Goodglass, H. and Weintraub, S. 2001, The Boston Naming Test (2nd Ed.), Philadelphia, Lippincott Williams & Wilkins.
58. Spreen, O. and Benton, A. L. 1969, 1977, The Neurosensory Center Comprehensive Examination for Aphasia, Neuropsychology Laboratory, University of Victoria, Victoria, BC, Canada.
59. Osterrieth, P. 1944, Archives de Psychologie, 30, 206-356.
60. Rey, A. 1941, Archives de Psychologie, 28, 286-340.