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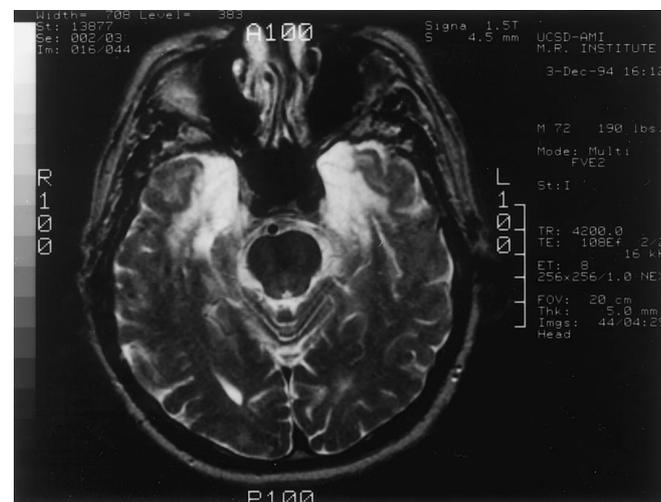
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## Memory for places learned long ago is intact after hippocampal damage

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The hippocampus is part of a system of structures in the medial temporal lobe that are essential for memory<sup>1–3</sup>. One influential view of hippocampal function emphasizes its role in the acquisition and retrieval of spatial knowledge<sup>4,5</sup>. By this view, the hippocampus constructs and stores spatial maps and is therefore essential for learning and remembering places, including those learned about long ago. We tested a profoundly amnesic patient (E.P.), who has virtually complete bilateral damage to the hippocampus and extensive damage to adjacent structures in the medial temporal lobe. We asked him to recall the spatial layout of the region where he grew up, from which he moved away more than 50 years ago. E.P. performed as well as or better than age-matched control subjects who grew up in the same region and also moved away. In contrast, E.P. has no knowledge of his current neighbourhood, to which he moved after he became amnesic. Our results show that the medial temporal lobe is not the permanent repository of



**Figure 1** An axial T2 weighted image through the temporal lobes of patient E.P. The extent of damage to the bilateral medial temporal lobe can be seen; it extends caudally from the temporal pole and includes the hippocampal region (dentate gyrus, cell fields of the hippocampus proper and subicular complex), the entorhinal cortex, the perirhinal cortex, the parahippocampal cortex and the amygdaloid complex. The lesion also extends laterally to include the anterior portion of the fusiform gyrus. Damage to the hippocampal region is virtually complete, except for a small fragment of tissue in the lateral ventricle bilaterally. The adjacent cortical structures of the medial temporal lobe are extensively damaged, possibly sparing the caudal portion of the parahippocampal cortex.

spatial maps, and support the view that the hippocampus and other structures in the medial temporal lobe are essential for the formation of long-term declarative memories, both spatial and non-spatial, but not for the retrieval of very remote memories, either spatial or non-spatial<sup>3,6</sup>.

Patient E.P., a 76-year-old former laboratory technician, became amnesic in 1992 after an episode of herpes simplex encephalitis. He has extensive bilateral damage to all the components of the memory system of the medial temporal lobe, including the hippocampus<sup>7</sup> (Fig. 1). E.P.'s amnesia is so severe that he fails to recognize his examiners, even after 40 visits to his house in one year, and he scores at chance on a variety of verbal and non-verbal tasks of recognition memory<sup>8,9</sup>. He also has severe difficulty recalling facts and events that occurred during the 40 years before his illness<sup>7</sup>.

E.P. grew up in the Hayward-Castro Valley area of California during the 1930s and 1940s (Fig. 2). He moved away from the area at the age of 28 and has returned only occasionally. We identified five other individuals who attended E.P.'s high school during this same period, lived there for about as long as E.P. did (controls, 26 years; E.P., 22 years), and then moved away from the area. We tested all six subjects on four tests of topographical memory that assessed their spatial knowledge of the region in which they grew up. They were asked to describe how they would navigate from their homes to different locations in the area (familiar navigation), between different locations in the area (novel navigation), and between these same locations if a main street were blocked off (alternative routes). They were also asked to imagine themselves in a particular orientation at certain locations and then to point towards specific landmarks (pointing to landmarks).

E.P. scored well on all four tests (Fig. 3). His poorer performance on the first administration of 'pointing to landmarks' was due to



**Figure 2** Street map of a portion of the Hayward-Castro Valley region from the 1940s (Thomas Bros. Map Co.). The locations of four representative landmarks used in the topographical memory tasks are shown: A, Bret Harte School; B, Hayward Union High School; C, Hayward Theatre; D, Castro Valley Grammar School. The locations used in the four topographical memory tasks encompassed an area of approximately 50 square miles, a larger area than is shown here.

two instances in which he reported the corrected heading verbally (for example, southwest) but then pointed in a different direction. When these two questions were omitted, his median error on this first administration of the task was 35 degrees. Based on all the questions in both testing sessions, his median pointing error was 38 degrees (control median, 34 degrees), and his mean heading vector relative to the correct heading was significantly above chance ( $P < 0.05$ , Rayleigh's test<sup>10</sup>) and not significantly different from the correct heading ( $P > 0.10$ , Stephen's test<sup>10</sup>). The mean heading vectors for four of the five control subjects were also significantly above chance and were statistically indistinguishable from the correct heading.

In Fig. 3a, responses in the verbal navigation tasks were scored as correct if they included the correct sequence and direction of turns, even if specific street names were not recalled. E.P.'s performance was indistinguishable from that of the controls. When a different scoring criterion was used, which required both the correct sequence of turns and the correct street names, E.P. continued to perform either above or within the control range on all three verbal navigation tasks (E.P. scored 57%, 75% and 38% against control ranges of 50–100%, 20–71% and 25–100%, respectively).

Although the specific questions used to assess topographical memory differed across subjects (because not all subjects were familiar with exactly the same locations), there were 3–6 questions for each test that were given to E.P. and at least four of the five control subjects. For this common set of questions, E.P. averaged 70% correct on the 'familiar navigation' task (control mean, 80%), 92% correct on the 'novel navigation' task (control mean, 81%) and 88% correct on the 'alternative routes' task (control mean, 88%). On the 'pointing to landmarks' task, E.P.'s average pointing error was 40 degrees (control mean, 36 degrees).

According to the spatial hypothesis of hippocampal function, the spatial maps stored in the hippocampus enable flexible navigation by encoding several routes to the same destination<sup>4</sup>. However, E.P.'s performance on the 'alternative routes' task was slightly better than that of the control subjects, indicating that flexible navigation through environments learned long ago is possible despite virtually complete hippocampal damage.

We also asked all six subjects to describe how they would navigate from the homes in which they currently reside to each of five different locations in the neighbourhood. All control subjects were able to provide accurate directions in response to each question (100% correct), but E.P., who moved to San Diego County in 1993, after he became amnesic, was unable to provide any response at all

to any of the questions (0% correct).

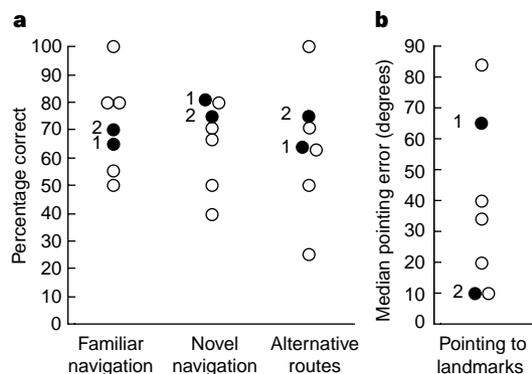
The idea that the hippocampus or related structures in the medial temporal lobe are important for spatial cognition is based on the discovery of place cells in the rodent hippocampus<sup>11</sup>, findings of impaired spatial learning in human patients<sup>12–14</sup> and animals<sup>5,15</sup> with hippocampal damage, and neuroimaging studies that find activation of these regions in tasks of spatial navigation<sup>16–19</sup>. E.P.'s failure to acquire new spatial knowledge about his current neighbourhood is consistent with these findings. It has also been supposed that damage to the medial temporal lobe might impair all autobiographical memories and spatial memories, regardless of when they were acquired<sup>20</sup>. Yet patient E.P., despite almost complete damage to his medial temporal lobe, has intact memory for remote autobiographical episodes<sup>7</sup> and, as shown here, has intact memory for remote spatial information. Our findings therefore support the view that the medial temporal lobe is essential for the formation of long-term declarative memories, both spatial and non-spatial, but not for the retrieval of very remote spatial or non-spatial memories<sup>3,6</sup>. Case studies of patients with topographical amnesia, defined<sup>21</sup> as "when the patient loses his bearings in a well-known environment and is not able to give a verbal or graphic description of familiar routes or places", have consistently reported damage to posterior cortical regions, particularly the parietal and retrosplenial cortices<sup>22–27</sup>, indicating that these may be the brain regions that maintain long-term spatial maps of learned environments. □

## Methods

E.P.'s performance was compared with the performance of healthy subjects (three men and two women) who attended the Hayward Union High School (Hayward, California) at the same time as E.P. They were matched to E.P. with respect to age (control mean, 75 years; E.P., 76 years) and duration of education (12 years). They had lived in the Hayward-Castro Valley region for an average of 26 years (range, 11–52 years; E.P., 22 years), and had then lived elsewhere in California for an average of 44 years (range 24–50 years; E.P., 51 years). They have occasionally returned to the area for visits but, with the exception of one control subject, not within the past two years. E.P.'s most recent visit to the region was in 1993. The five controls had intact memory functions (mean Wechsler Memory Scale-III subtest scores were 11.0 for Logical Memory and 10.6 for Verbal Paired Associates with an age-matched score for the normative sample of 10.0) (ref. 28).

E.P. was tested twice, once before any of the control subjects were tested and again after all the control subjects were tested. Through interviews before formal testing, approximately 20 familiar locations in the Hayward-Castro Valley region of California in the 1930s and 1940s were identified for each subject. These locations were then used to construct four tasks.

In the 'familiar navigation' task, subjects were asked to describe a route from their childhood home to different locations in the region (E.P. was asked 10 questions; control mean, 9.8); for example: "Can you tell me how to get from your house to the Bret Harte School?". In the 'novel navigation' task, subjects were asked to describe a route from one location to another (E.P., 8 questions; control mean, 7.8); for example: "Can you tell me how to get from the Hayward Union High School to the Hayward Theatre?". Next, after navigating a route between these two locations, subjects were asked to find an alternative route to the same destination, assuming that one of the major streets that they had just used was now blocked off (alternative routes task). Responses to these questions were scored using printed transcripts of the testing sessions. For example, in patient E.P.'s transcript, his response to the 'novel navigation' question was: "Make a left out of the high school. To A Street. Make a right on A Street, down to Castro. A left on Castro, and then in the middle of the block is the Hayward Theatre." Finally, in the 'pointing to landmarks' task, subjects were asked to imagine themselves in a given location, facing a particular direction, and then to point in the direction of another location (E.P., 9 questions; control mean, 8.6); for example: "You are standing in front of the Hayward Union High School, facing Foothill Boulevard. Can you point in the direction of the Castro Valley Grammar School?" Performance on this task was measured as the error (in degrees) between the correct heading and the direction to which the subject pointed.



**Figure 3** Performance on four tasks of topographical memory. Open circles, scores of five control subjects; filled circles, E.P.'s scores on two different occasions separated by 9 months. Numbers next to the filled circles indicate scores for E.P.'s first and second test sessions. **a**, Percentage correct on three verbal navigation tasks that required negotiating either familiar routes, novel routes or alternative routes (when the most direct route was blocked). **b**, Median error in degrees on a task in which subjects pointed to particular locations while imagining themselves oriented at other locations in the area.

Although the specific locations used in these tests varied between subjects, 3–6 of the same questions on each test were administered to E.P. and at least four of the five controls. In addition, the ‘familiar navigation’ and ‘novel navigation’ tasks were matched across subjects with respect to the distance travelled (mean, 3.0 and 3.3 miles, respectively) and the number of turns needed (mean, 3.0 and 2.7 turns, respectively) to reach each destination. The routes that subjects reported in the verbal navigation tasks were scored as correct if they incorporated the correct sequence and direction of turns necessary to reach the destination. All subjects typically reported street names as they navigated their routes. However, presumably because of his anomia (Boston Naming Test score, 42; maximum score, 60, mean of four control subjects, 54.5)<sup>7</sup>, E.P. omitted street names more frequently than did the control subjects (0.5 omissions per question compared with 0.3 omissions for controls; range, 0.1–0.5). Accordingly, we also used another scoring method, which required both a correct sequence of turns and correct street names. An independent scorer who was blind to subject identity scored all transcripts using both scoring criteria. Average inter-scorer reliability across both scoring criteria was 0.91.

The five verbal navigation questions for current neighbourhoods were administered in the same way as the ‘familiar navigation’ task. Across subjects, the questions were similar with respect to the distance travelled and the number of turns needed to reach location (mean, 6.5 miles and 5.5 turns, respectively).

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## A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus

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The subthalamic nucleus of the basal ganglia (STN) is important for normal movement<sup>1,2</sup> as well as in movement disorders<sup>3–5</sup>. Lesioning<sup>6</sup> or deep-brain stimulation<sup>7,8</sup> of the STN can alleviate resting tremor in Parkinson’s disease. The STN<sup>5</sup> and its target nuclei<sup>9,10</sup> display synchronized oscillatory burst discharge at low frequencies, some of which correlate with tremor, but the mechanism underlying this synchronized bursting is unknown. Here we show that the excitatory STN and inhibitory, external globus pallidus (GPe) form a feedback system that engages in synchronized bursting. In mature organotypic cortex–striatum–STN–GPe cultures, neurons in the STN and GPe spontaneously produce synchronized oscillating bursts at 0.4, 0.8 and 1.8 Hz. Pallidal lesion abolishes this bursting, whereas cortical lesion favours bursting at 0.8 Hz. Pallidal bursts, although weaker than STN bursts, were required for synchronized oscillatory burst generation by recruitment of subthalamic rebound excitation. We propose that the STN and GPe constitute a central pacemaker modulated by striatal inhibition of GPe neurons. This pacemaker could be responsible for synchronized oscillatory activity in the normal and pathological basal ganglia.

To test our proposal that the STN and GPe produce synchronized oscillatory bursts, we developed an *in vitro* model<sup>11</sup> in which both nuclei were co-cultured with the cortex and striatum, their main extrinsic input sources, to ensure proper maturation. The STN and GPe were obtained from rats at postnatal day 0–2 and cultured with frontomedial cortex and dorsolateral striatum. After  $38 \pm 1$  days *in vitro* ( $n = 58$  cultures), spontaneous single- and multi-unit activities were recorded from the STN and GPe with one or two extracellular electrodes.

Spontaneous activity in the STN showed distinctive, stereotypic periods of oscillatory burst discharge that lasted for 10–15 s (Fig. 1a). Intra-burst firing rates reached several hundred spikes per second, and the bursts oscillated at low frequencies. Between bursts, STN units were either silent or fired irregularly at low rates. The burst activity of STN units was phase-locked and synchronized with other STN and GPe units (Fig. 1b, c), showing that it reflects population activity across both nuclei. Spontaneous synchronized bursting occurred regularly every 1–2 min and with occasional shifts in main frequency (Fig. 1d).

Based on correlation analysis and frequency plots using continuous periods of spontaneous spiking ( $324 \pm 135$  s per neuron), about half of STN (83/181) and a third of GPe units (31/102) fired in oscillatory bursts with frequencies between 0.1 and 4 Hz (20 ms time resolution). Similarly, 61% of STN–STN (46/76), 44% of STN–GPe (33/75), and 23% of GP–GPe (4/17) neuronal pairs displayed synchronized oscillatory bursts in that frequency range.

The STN–GPe system showed clear preferences for particular frequencies during synchronized bursts. The relative power spectrum analysis revealed two main population frequencies at  $f_{01} = 0.44$  Hz and  $f_{02} = 0.79$  Hz, respectively (Fig. 2a). A third

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