Supporting Information

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SI Materials and Methods

Vision Test. In experiment 2, to verify that vision could not guide behavior when the lights were off, six rats were trained, initially in the light, to find food located directly adjacent to an object (20- × 2.5- × 2.5-cm tower constructed from Legos). If the rats could use vision to guide performance with the lights off, then they should be able to locate the object (and the food) as quickly with the lights on as with the lights off. During 2 d of habituation, rats were placed on the table with all boxes closed and allowed to explore for 10 min with the lights on. Beginning on the next day, rats were placed in a start box and given five trials each day for 25 d. A food pellet was placed directly in front of the object. The location of the object and the start box was changed for every trial. A trial began when the rat exited the box and ended when it located the food. Next, an additional 25 d of testing was given with the lights off.

Surgery. Surgery was designed to remove the entire hippocampus (H group). Anesthesia was maintained throughout surgery with isoflurane gas. Isoflurane concentration (delivered in O_2 at 1 L/min) was varied from 0.8–2.0% throughout surgery to maintain an optimal plane of anesthesia. The rat was placed in a Kopf stereotaxic instrument, and the incisor bar was adjusted until Bregma was level with Lambda. Bilateral excitotoxic hippocampal lesions were produced by local microinjections of ibotenate acid (IBO; Biosearch Technologies). IBO was dissolved in 0.1 M PBS to provide a solution with a concentration of 10 mg/mL, pH 7.4. IBO was injected at a rate of 0.1 μL/min with a 10-μL Hamilton syringe mounted on a stereotaxic frame and held with a Kopf Microinjector (model 5000). The syringe needle was lowered to the target coordinate and left in place for 1 min before beginning the injection. Following the injection, the syringe needle was left in place for a further 2 min to reduce the spread of IBO up the needle tract (for coordinates, see ref. 1). The procedure for the sham-operated control (CON) group was the same as for the lesion groups, with the exception that the dura was not punctured and IBO was not injected. Once awake and responsive, each rat was returned to its home cage in the colony room for a 14-d recovery period.

Odor Test. A probe trial was given each day following the four standard trials to assess if rats were using odor trails to guide them back to the start box. On these trials, a food pellet was placed near the middle of the table on the fixed, central platform. When the rat located the food pellet, the table was rotated by 90° (both clockwise and counterclockwise rotations were used). This procedure displaced odor cues by 90° relative to the location of the start box. If a rat were following an odor trial, then its return path should be biased toward the direction of rotation.

For data analysis, we calculated how often the rat returned to the original start box (now displaced by 90°) and how often the rat returned to the box that now occupied the same spatial location as the box where the rat began the trial. We also calculated how often the rat returned to the box opposite to the displaced box.

Histology. At completion of testing, rats were administered an overdose of sodium pentobarbital and perfused transcardially with buffered 0.9% NaCl solution followed by 10% formaldehyde solution (in 0.1 M phosphate buffer). The brains were then removed and cryoprotected in 20% glycerol/10% formaldehyde. Coronal sections (50 μm) were cut with a freezing microtome beginning at the level of the anterior commissure and continuing caudally through the length of the hippocampus. Every fifth section was mounted and stained with thionin to assess the extent of the lesions. All sections from the anterior commissure to the posterior-most section of the hippocampus (at least 11 sections for each rat) were examined to assess the locus and extent of damage in the hippocampus and adjacent structures. The percent of hippocampal damage was calculated from four coronal sections (2) (Bregma −2.8 to −5.8 mm in 1-mm intervals).

1. Broadbent NJ, Squire LR, Clark RE (2004) Spatial memory, recognition memory, and the hippocampus. *Proc Natl Acad Sci USA* 101(40):14515–14520.

2. Paxinos G, Watson C (1998) *The Rat Brain in Stereotaxic Coordinates* (Elsevier, Amsterdam).

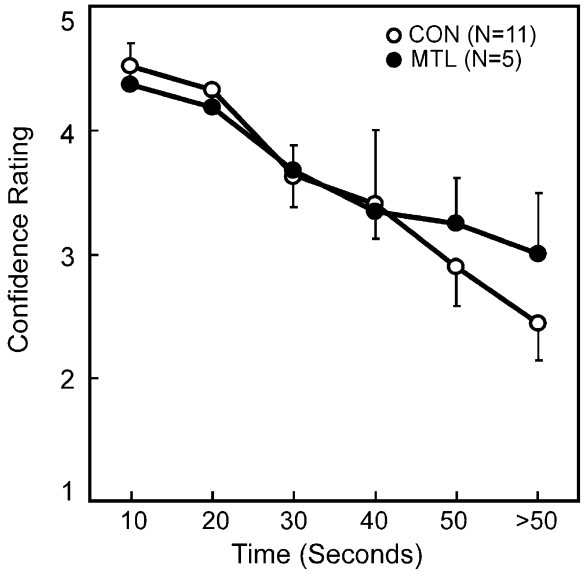

Fig. S1. Experiment 1: for memory-impaired patients [i.e., damage to the medial temporal lobe (MTL)] and controls (CON), confidence in the accuracy of the return path declined as a function of how much time was needed to find the tile. Brackets show SEM.

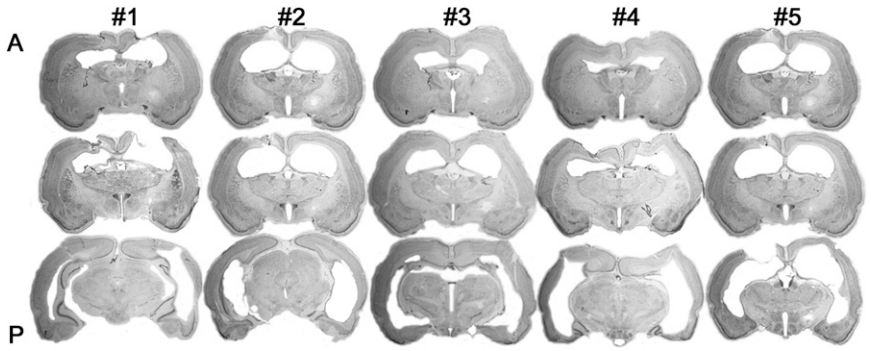

Fig. S2. Photomicrographs of the histological sections for each rat (1–5) showing each hippocampal lesion at three anteroposterior levels. The sections in each column are from the same rat with the most anterior (A) sections at the top and the most posterior (P) sections at the bottom.

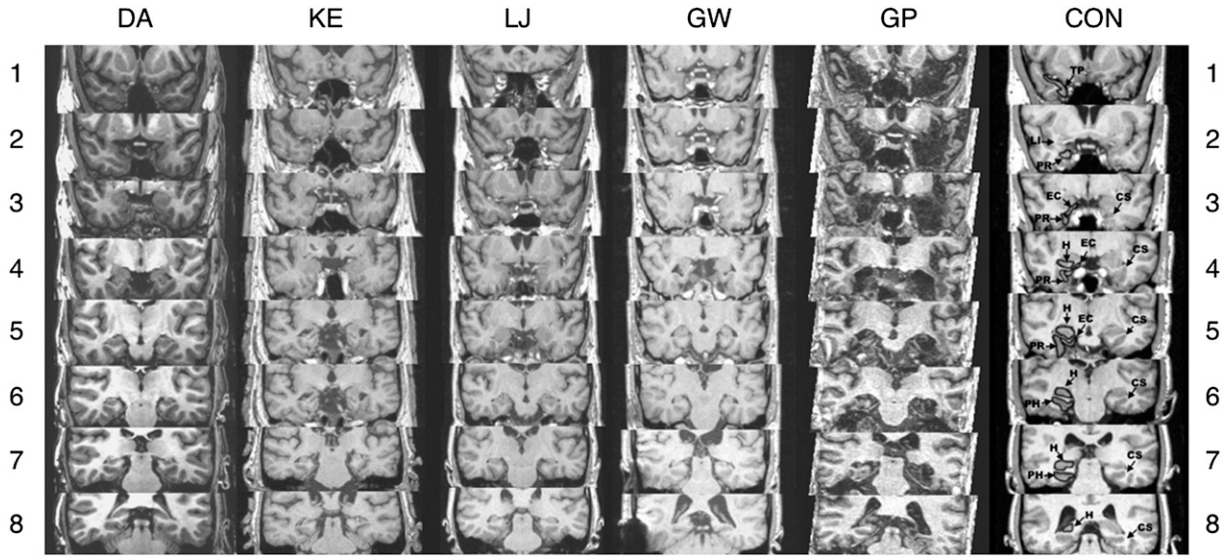

Fig. S3. Structural MRIs for each patient in experiment 1. Series of eight T1-weighted coronal images of four patients with limited hippocampal lesions (D.A., K.E., L.J., and G.W.), one with large medial temporal lesions (G.P.), and one control (CON) are illustrated. The sections proceed in 7-mm intervals from the temporopolar cortex in the top section (with the exception of G.W., whose top section is at the level of the perirhinal cortex). The left side of the brain is on the right side of each image. As described by Insausti et al. (1), temporopolar cortex (TP) extends medially from the inferotemporal sulcus to the fundus of the temporopolar sulcus. TP extends rostrally from the tip of the temporal pole caudally to the limen insula (LI), which approximates the border between the TP and perirhinal cortex. Caudal to TP, the collateral sulcus (CS) is the most important structure for the identification of medial temporal lobe cortices. At its most rostral extent, the CS is surrounded entirely by perirhinal cortex (PR). Caudally, entorhinal cortex (EC) extends from the midpoint of the medial bank of the CS to the subiculum, whereas PR extends laterally from the midpoint of the medial bank of the CS to the inferotemporal cortex. Two millimeters caudal to the disappearance of the gyrus intralimbicus of the hippocampus (H), the CS is surrounded by parahippocampal cortex (PH). The caudal border of the posterior PH is defined as lying 1.5 mm posterior to the crus of the fornix at the point where the fimbria turns upwards to continue as the posterior pillars of the fornix and posterior to the pulvinar nucleus of the thalamus (2). The top section shows the TP. Note that the portion of the temporal lobe missing in GP corresponds to TP and involves the lateral temporal lobe to a minimal extent (~10%). None of the patients with limited hippocampal lesions has damage evident at this level. For L.J., only the tip of the temporal pole is visible at this level. For G.W., the PR, not the more rostral TP, appears in this section. The second section shows the PR surrounding the CS and the LI, which is the region where the cortex of the insula is continuous with the inferior cortex of the frontal lobe. The LI appears on the left side in D.A., but is evident only on the right side in the control brain and in G.W. In the other brains, it appears caudal to this section. The third section shows the CS and surrounding perirhinal and entorhinal cortices. For D.A., bilateral damage to the globus pallidus is evident at this level, presumably secondary to heroin overdose. For G.P., no CS or surrounding tissue is evident. The fourth section shows the anterior hippocampus and the adjacent perirhinal and entorhinal cortices. The hippocampus is absent bilaterally in G.P., and no CS or surrounding tissue is evident. D.A. and G.W. have extensive damage to the hippocampus at this level. K.E.'s hippocampal damage is not evident at this level, but small bilateral lesions in the basal ganglia secondary to toxic shock syndrome are apparent (and to a lesser extent in section 3). The fifth section shows the hippocampus and the adjacent perirhinal and entorhinal cortices. G.P. has no medial temporal lobe tissue at this level. Extensive hippocampal damage is evident at this level in D.A., K.E., and G.W. The CS and the surrounding perirhinal and entorhinal cortices appear normal in all of the hippocampal patients. The sixth section shows PR on the lateral bank of the CS near the perirhinal/PH border. No medial temporal lobe tissue is evident in G.P. at this level. Also at this level, damage is evident in the hippocampal region of all of the hippocampal patients. The PR appears normal in D.A. and L.J., and the PH appears normal in D.A. and G.W. For K.E., the cortex adjacent to the hippocampus (near the perirhinal/PH border) also appears normal. The seventh section shows the hippocampus and the CS, surrounded by PH. G.P. has little normal medial temporal lobe tissue in either hemisphere. The patients with limited hippocampal lesions have moderate damage to the hippocampus at this level but the PH appears entirely normal. The warping artifact in the right lateral temporal lobe of G.W. on this section as well as on the eighth section, did not interfere with the assessment of his damage. The eighth section also shows the hippocampus. The PH appears normal at this level in K.E. and L.J. These two patients have moderate hippocampal damage at this level. For patients with limited hippocampal lesions, no damage is evident posterior to this level. For G.P., volume reductions were not recorded at this level, but some sulcal widening is apparent.

1. Insausti R, et al. (1998) MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am J Neuroradiol* 19(4):659–671.
2. Frankó E, Insausti AM, Artacho-Pérula E, Insausti R, Chavoix C (2012) Identification of the human medial temporal lobe regions on magnetic resonance images. *Hum Brain Mapp*, 10.1002/hbm.22170.