Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory

Christian F. Doeller*, John A. King†, and Neil Burgess*

Institute of Cognitive Neuroscience, University College London, London WC1N 3AR, United Kingdom

Communicated by Mortimer Mishkin, National Institutes of Health, Bethesda, MD, February 20, 2008 (received for review October 31, 2007)

How the memory systems centered on the hippocampus and dorsal striatum interact to support behavior remains controversial. We used functional MRI while people learned the locations of objects by collecting and replacing them over multiple trials within a virtual environment comprising a landmark, a circular boundary, and distant cues for orientation. The relative location of landmark and boundary was occasionally changed, with specific objects paired with one or other cue, allowing dissociation of learning and performance relative to either cue. Right posterior hippocampal activation reflected learning and remembering of boundary-related locations, whereas right dorsal striatal activation reflected learning and remembering of landmark-related locations. Within the right hippocampus, anterior processing of environmental change (spatial novelty) was dissociated from posterior processing of location. Behavioral studies show that landmark-related learning obeys associative reinforcement, whereas boundary-related learning is incidental [Doeller CF, Burgess N (2008) *Proc Natl Acad Sci USA* 105:5909–5914]. The distinct incidental hippocampal processing of boundaries is suggestive of a ''geometric module'' or ''cognitive map'' and may explain the hippocampal support of incidental/observational learning in ''declarative'' or ''episodic'' memory versus the striatal support of trial-and-error learning in ''procedural'' memory. Finally, the hippocampal and striatal systems appear to combine ''bottom-up,'' simply influencing behavior proportional to their activations, without direct interaction, with ''top-down'' ventromedial prefrontal involvement when both are similarly active.

cognitive map | functional MRI | incidental | learning | procedural

Memory is not a unitary process but rather consists of different systems relying on separate brain structures. Evidence for parallel "declarative," "relational," or "episodic" systems centered on the hippocampus and "procedural" systems centered on the dorsal striatum has been obtained in animals and humans (1–9). These systems are proposed to serve different functions: rapid acquisition of experience (supporting "episodic memory") and slower cumulative trial-and-error acquisition of skills and habits, respectively (5, 9–12). Distinct processing by either system is seen particularly clearly in studies of spatial memory, with hippocampal-dependent learning of environmental layout ("place" or "locale" learning), and striatal-dependent learning of responses to individual stimuli ("response" or "taxon" learning) (2, 4, 13–15).

How these two systems act and interact to support learned behavior poses several important questions.

Do both systems simply learn over different time courses or is each biased to process specific types of stimuli? In the spatial domain, the rodent hippocampus has been identified with environment-centered representations of location, whereas the dorsal striatum has been associated with approach responses to a single landmark (2, 8, 13, 16–18). Consistent with this idea, the firing of hippocampal place cells is determined by the environmental boundary (19, 20) to a much greater extent than by discrete intramaze objects (21), whereas neuronal firing in the striatum reflects egocentric responses (22) and the stage of task (10).

How do the systems interact during learning? The hippocampal and striatal systems are often differentially involved in different tasks (e.g., refs. 6 and 7), in different stages of the same task (initially hippocampal dependent, becoming striatal dependent with practice) (e.g., refs. 13 and 14), or in individuals with different strategies (e.g., refs. 15, 23, and 24). However, direct within-subjects investigation of the development and interaction of learning within both systems is not possible across different tasks or different subjects and is confounded by variation in novelty across different stages of the same task [e.g., hippocampal activation can result from novelty *per se* (25)].

Here, we seek to answer some of these questions in the context of human spatial memory. We designed a naturalistic task during which both memory systems are recruited in parallel, with similar time courses and task contingencies, and in which their relative involvement can be read out from behavior. This task allows fair, trial-by-trial, evaluation of: (*i*) differential involvement of neural systems, (*ii*) differences in the characteristics of learning in each system, and (*iii*) interactions between the two systems during learning or performance of a single task.

Our task was inspired by rat experiments in the Morris watermaze (17, 26), in which learning to find the submerged platform is hippocampal dependent (26), with the distance from the wall of the tank being a strong cue (27). However, if the platform is located at a constant distance and direction from an intramaze landmark and both landmark and platform are moved together within the tank between sessions, rats with hippocampal lesions outperform control rats at the beginning of each session (17). These results suggest that hippocampal processing concerns environmental geometry rather than intramaze landmarks, consistent with the place cell responses discussed above: control rats are biased toward the (incorrect) location predicted by the boundary in the previous session, whereas rats with hippocampal lesions follow the landmark alone. Finally, the definition of locations relative to the wall of the tank, or to the intramaze landmark, also requires orientational information that was provided by distal cues and presumably mediated by the head-direction system (ref. 28 and see ref. 29).

We created an object-location memory task, in which some objects maintained a fixed location relative to the environmental boundary, whereas others maintained a fixed location relative to a single intramaze landmark. Functional MRI (fMRI) was used to examine the neural bases of learning and remembering the locations of the objects. Participants explored a first-person perspective virtual reality arena, navigating through it by pressing buttons to move the viewpoint. The arena was bounded by a circular wall, contained a single landmark, and was surrounded by distant cues for orientation. During initial exploration participants encountered four objects in different locations. On each subsequent trial they

Author contributions: C.F.D., J.A.K., and N.B. designed research; C.F.D. J.A.K., and N.B. performed research; C.F.D. analyzed data; and C.F.D. and N.B. wrote the paper.

The authors declare no conflict of interest.

*To whom correspondence may be addressed. E-mail: c.doeller@ucl.ac.uk or n.burgess@ucl.ac.uk.

†Present address: Department of Clinical, Educational and Health Psychology, University College London, London WC1E 6BT, United Kingdon.

This article contains supporting information online at www.pnas.org/cgi/content/full/0801489105/DCSupplemental.

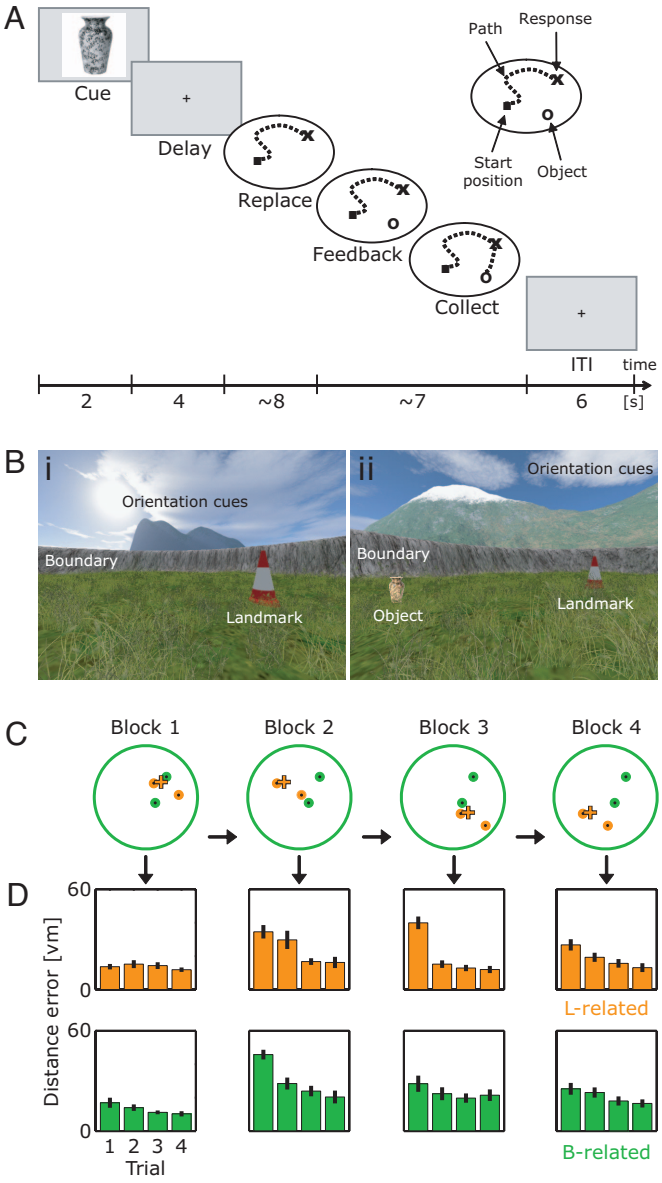

Fig. 1. Virtual reality task and behavior. (*A*) Trial structure (after initial collection of objects). Participants replace the cued object after a short delay phase and received feedback (object appears in correct location immediately after the response and is collected). (*B*) Virtual arena from the participant's perspective [replace phase (*i*) and feedback phase (*ii*); different viewpoints] showing the intramaze landmark (traffic cone), the boundary (circular wall), the extramaze orientation cues (mountains, which were projected at infinity), and one object (vase). (*C*) Participants learned four object-locations over four blocks, the landmark (orange +) and boundary (green circle) moving relative to each other at the start of each block (columns). Two objects were paired with the landmark (orange dots), and two objects were paired with the boundary (green dots). (*D*) Participants learned the associations to landmark and boundary within and across blocks 2–4 at similar rates. Neither learning nor performance differed significantly between landmark-related and boundary-related objects. Bars show the "distance error" of the response location from the correct location for each trial, averaged over the two objects paired with each cue, in virtual meters (vm). Error bars show SEM; ITI, intertrial interval.

saw a picture of an object on a blank background (the cue phase) and indicated its location within the arena by navigating to it from a variable start location and making a button-press response (the replace phase), the object then appeared in its correct location and was collected (the feedback phase; see Fig. 1 *A* and *B*). The replace phase reflects memory retrieval, whereas spatial learning occurs during the feedback phase. Each set of 16 trials (four per experimental object) comprised a block, with four blocks in total. Critically, the landmark and boundary were moved relative to each other between blocks, with two objects maintaining their location relative to the boundary and two relative to the landmark (Fig. 1*C*).

Within each block, participants gradually learned the relationships between object locations and landmark or boundary by using the feedback provided. Performance was measured as the proximity of the response location to the correct location, whereas learning during the feedback phase was measured as the improvement in performance on the next trial with the same object. The relative influence of boundary versus landmark on responding in blocks 2–4 was measured as the relative proximity of the response location to the locations predicted by either cue. Both cues played functionally equivalent roles in the task and were not distinguished in the instructions. The distant orientation cues were projected at infinity so that they could be used for orientation but not location. In separate behavioral studies we formally tested the associative characteristics of learning of locations relative to the landmark or boundary within this paradigm (30).

Results

Behavioral Results. Performance in block 1, in which both cues indicate the same location for each object, was noticeably better than in blocks 2–4, in which the relative movement of landmark and boundary causes the two cues to indicate different locations. In blocks 2–4, participants' responses were influenced by both cues when replacing objects formally paired with either, with performance corresponding closely to the relative influence of the correct cue (explaining 83.3% of the variance, in blocks 2–4, $P < 0.001$) [see Fig. 1*D* and supporting information (SI) Fig. S1]. Improving performance indicated that participants learned the associations to landmark or boundary within ($F_{3,45} = 84.85$, $P < 0.001$) and across ($F_{2,30} = 8.07$, $P < 0.01$) blocks 2–4. Neither performance levels (overall: $F_{1,15} = 3.51$; $P > 0.08$; block 1: $F_{1,15} < 1$) or their rate of improvement (within-block: $F_{3,45} = 2.12$, $P > 0.1$; across-block: $F_{2,30} < 1$) differed significantly between boundary-related and landmark-related objects. Debriefing after the experiment indicated that the majority of subjects were aware of the association of each object to either cue (see *SI Text*).

Imaging Results. fMRI data were fitted by a general linear model containing separate regressors for the cue phase, the replace phase, and the feedback phases of boundary-related and landmark-related objects (one regressor for each object type in the feedback phase). To model variations in activation across boundary-related feedback phases that might reflect learning about the boundary, we included a copy of the boundary-related feedback-phase regressor whose amplitudes were parametrically modulated by the amount learned in each trial. A similar parametric modulation of the landmark-related feedback-phase regressor was included to capture landmark-related learning. To model variations in activation across replace phases according to the relative influence of boundary versus landmark on behavior in that trial, we included a parametric modulation of the replace-phase regressor by the relative influence of boundary versus landmark on the replacement location (see Fig. S2). Finally, we included parametric modulations of the feedback-phase and replace-phase regressors by time-within-block (exponential decay across trials 1–4 for each object) to capture any effects of novelty-within-block that might otherwise confound apparent effects of learning or the influence of either cue. The resulting coefficients were analyzed across participants using SPM2, with regions showing significant effects (threshold $P = 0.001$, uncorrected) being referred to as activations below. See *Methods* and *SI Text* for details.

During the feedback phase of blocks 2–4, learning of landmark-related locations corresponded to increased activation of the right

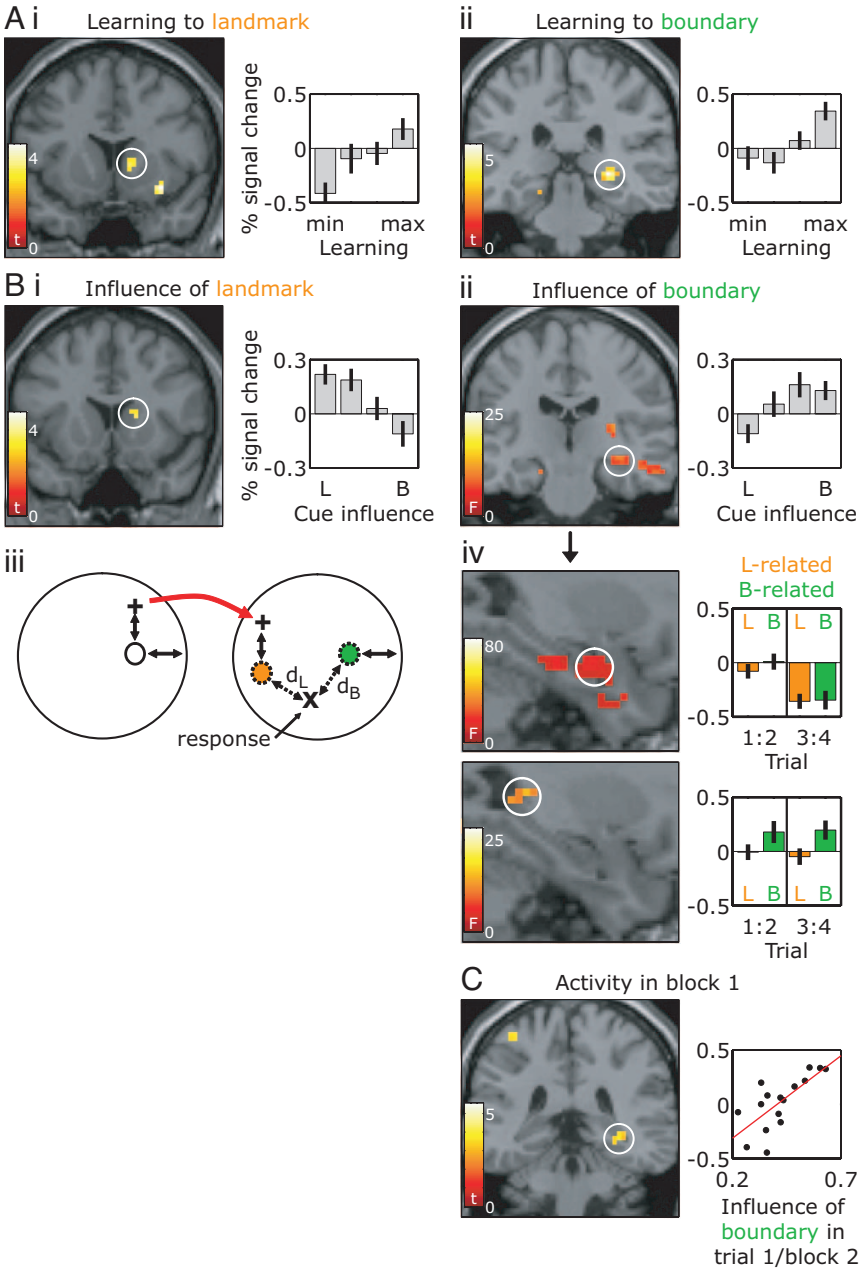

Fig. 2. Distinct neural bases support learning relative to landmark or boundary in right dorsal striatum and right posterior hippocampus, respectively, and independent of a right anterior hippocampal response to spatial novelty. (*A*) Extent of learning during the feedback phase (performance increase in next trial with that object in blocks 2–4) corresponds to activation of right dorsal striatum for landmark-related objects [peaked in head of caudate: Montreal Neurological Institute (MNI) coordinates 12/12/3] (*i*) and right posterior hippocampus for boundary-related objects (27/−30/−3) (*ii*). (*B*) After relative movement of landmark and boundary (i.e., in blocks 2–4), we measured the relative influence of boundary versus landmark on replacement location as $d_L/(d_L + d_B)$, where d_L is the distance of the response from the location predicted by the landmark and d_B is the distance from the location predicted by the boundary (see *iii*). (*i*) Replacement of objects relative to the landmark corresponds to activation of right dorsal striatum (peaked in head of caudate: 18/15/9). (*ii*) Activity in the right hippocampus (33/−21/−9) reflected the influence of the boundary combined with an effect of trial-within block. (*iv*) Dissociation of novelty and boundary processing along the long axis of right hippocampus. An object-type (landmark-related vs. boundary-related) × trial-within-block (1–2 vs. 3–4) ANOVA revealed independent main effects of trial anteriorly [36/−9/−21 (*Upper*)] and object-type posteriorly [30/−39/3 (*Lower*)]. Both images are shown at $x = 30$. (*Left*) Plots show fMRI activation on aligned SPM structural template (coronal sections; sagittal sections in *Biv*). (*Right*) Bar plots show mean percentage fMRI signal change (+/− SEM) in feedback or replace phase (*y* axis), binned by the measure of learning, influence of cue, or trial (*x* axis). (*C*) (*Left*) Activity in right posterior hippocampus (33/−36/−6) in block 1 predicts each participant's bias toward using the boundary in the first trial of block 2. (*Right*) Percentage signal change in block 1 versus the influence of the boundary in trial 1 of block 2, averaged over the four objects. Each dot represents one participant. This activation reflects overshadowing of the landmark by the boundary in block 1 (see ref. 30). For display purposes, images are thresholded at $P < 0.005$ in *A–C* or $P < 0.00025$ in *Biv*, uncorrected.

dorsal striatum (peaked in the caudate head), whereas learning of boundary-related locations corresponded to activation of the right posterior hippocampus. Higher activation corresponded to greater performance increase in the next trial with the same object, as indicated by significant positive coefficients for the respective parametric modulations in the two brain regions. See Fig. 2*A* and Table S1 for details, including activations in nonhypothesized areas. Thus boundary-related learning and landmark-related learning

appear to be supported by distinct neural systems in the right posterior hippocampus and dorsal striatum, respectively.

During the replace phases in blocks 2–4, the influence of the landmark on response locations corresponded to activity in the right dorsal striatum (peaked in the caudate head), as indicated by a significant coefficient for the replace-phase regressor parametrically modulated by the influence of the landmark versus the boundary (Fig. 2*Bi*). We did not observe a response in the hippocampus simply reflecting the influence of the boundary. Rather, activity in the right hippocampus reflected the influence of the boundary combined with an effect of trial-within block (Fig. 2*Bii*, as indicated by an F test assessing the joint effect of the influence of the boundary and the decay of activation across trial-within-block, see *Methods* and Fig. S2 for details). A follow-up object-type (landmark-related vs. boundary-related) × trial-within-block (trials 1–2 vs. 3–4) ANOVA revealed a posterior–anterior dissociation within the right hippocampus during the replace phase: a posterior response to boundary-related relative to landmark-related objects and an anterior response to spatial novelty (decaying within blocks after a new landmark/boundary configuration had been introduced; Fig. 2*Biv*). Additional parametric analyses showed that this within-block anterior right hippocampal response to novelty was independent of the object's association to landmark or boundary, specific to the replace phase and specific to spatial change, not occurring in block 1 (before any change) or across blocks (see *SI Text* for details).

In addition to concurrent effects of boundary-related learning or memory, an individual's bias toward using the boundary to replace objects when boundary and landmark are first moved relative to each other (i.e., at the start of block 2) was predicted by their right posterior hippocampal activation during the replace phase of block 1 (Fig. 2*C*), as indicated by a significant across-subject correlation between bias and hippocampal activity. This finding corresponds to overshadowing of learning to the landmark by learning to the boundary in block 1: the higher the posterior hippocampal activity during block 1, the greater the influence of the boundary on responding at the start of block 2 (see ref. 30 for the corresponding behavioral experiment).

How do the hippocampal and striatal systems interact to control behavior? Do they compete via mutual inhibition, or does activation in each independently signal suitability for behavioral control? We used dynamic causal modeling (31) to test for direct interaction between hippocampal and caudate activity during the feedback and replacement phases of blocks 2–4. In model 1, activation in hippocampus or caudate simply reflects learning relative to (during the feedback phase) or influence of (during the replace phase) boundary or landmark respectively. Model 2 allows, in addition, direct interaction between activity in the two regions. Bayesian model selection favored the simpler, independent, model in all participants during both phases (Bayes factor 6.94 during replacement, 7.17 during feedback; see *SI Text* and Fig. 3*A*). Thus the two systems appear to operate independently in parallel. However, ventromedial prefrontal activity correlated with temporary fluctuations in the covariance of hippocampal and caudate activation during the replace phase. Prefrontal activity increased when hippocampus and caudate were similarly activated or deactivated (positive covariance), whereas prefrontal activity decreased whenever hippocampal and caudate activity had negative covariance. Thus ventromedial prefrontal cortex may mediate between the conflicting behavioral responses indicated by both systems when similarly active (see Fig. 3*B* and *SI Text*). No such correlation was found during the feedback phase, when learning can occur in parallel.

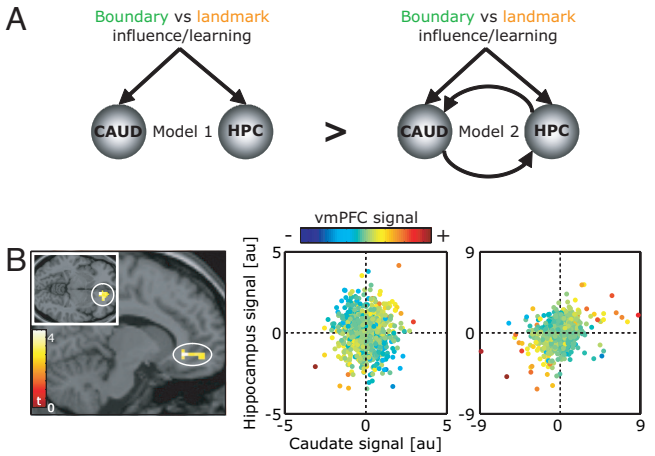

Fig. 3. Dorsal striatum and hippocampus independently influence behavior according to their activation, with ventromedial prefrontal involvement when both are similarly active. (*A*) Alternative models of the activity in caudate and hippocampus during replacement and feedback phases. (*Left*) Model 1: inputs solely reflecting behavior (influence of boundary versus landmark during replacement; learning about boundary versus landmark during feedback). (*Right*) Model 2: additional inputs reflecting the influence of activity in the other structure. Bayesian model selection favors model 1, indicating that caudate and hippocampal activity reflect the influence of landmark and boundary on replacement location and learning, but do not interact directly. (*B*) (*Left*) Activity in ventromedial prefrontal cortex [12/33/−6; shown on sagittal section; (*Inset*) axial section] correlates with fluctuations in covariance between hippocampal and caudate activity, increasing whenever they are similarly activated or deactivated. (*Center* and *Right*) Mean-corrected prefrontal activity during object-replacements plotted as color against mean-corrected hippocampal and caudate activity for two representative subjects. au, arbitrary units. For display purposes, the statistical image is thresholded at $P < 0.005$, uncorrected.

Discussion

Our findings strongly support the idea of parallel memory systems centered on the hippocampus and dorsal striatum (1–9). Our paradigm provides a sensitive means of detecting the relative involvement of the two systems on a trial-by-trial basis and allows their distinct functional characteristics to be examined. Differential activity in the hippocampus and caudate corresponded to the acquisition and expression of information about locations derived from environmental boundaries or landmarks, respectively.

Our behavioral experiments (30) indicate that the striatal landmark-related learning obeys associative reinforcement with a single prediction-error signal (32, 33), whereas the hippocampal boundary-related learning appears to be incidental, occurring independent of error. Thus the two systems' distinct roles may result from differences in the learning rule implemented by each and not necessarily differences in learning rate. Our results provide well controlled confirmation of some previous theories of hippocampal function (1–3) and are consistent with studies in animals (34–36) and humans (37–39) showing that striatal activity follows the predictions of reinforcement learning, and with observations that striatal dysfunction impairs feedback-based learning (compared to observational learning) (6, 40).

The apparent specialization of the right posterior hippocampus in memory for spatial locations is consistent with a specifically spatial role for this region in humans (41) and with spatial specialization of the dorsal portion of the rat hippocampus (corresponding to the posterior human hippocampus) where a higher precision coding of spatial location (42) is found and where lesions have a greater impact on spatial memory (43). The additional specialization for representations of location relative to environmental boundaries is consistent with the dependence of place cell firing on boundaries (19, 20) and with apparent specialization of the human hippocampus for processing environmental geometry rather than other aspects of visual scenes (44).

The processing of environmental boundaries by a specific neural system with a specific type of learning rule is reminiscent of the idea of a dedicated geometric module (45, 46) for processing the surface geometry of the local environment, albeit for determining location

rather than orientation. It also supports a specific role for the hippocampus in incidental learning of spatial layout (2) and emphasizes the importance of boundaries in this process. Consequently, environmental boundaries may have a privileged role in the hippocampal contribution of spatial context to episodic memory (2). More generally, the different types of learning may explain the two systems' differential roles in memory. Striatal-dependent learning controlled by a single error signal may underlie procedural memory and other forms of learning by trial and error (5, 10), whereas incidental hippocampal-dependent learning may be more appropriate for maintenance of a flexible mental model (9), mediating representation (47) or cognitive map (2, 48), and for efficient encoding of experience into episodic memory (5, 49) (see also ref. 30).

The anterior hippocampal response to spatial novelty agrees with findings in rodents that hippocampal lesions disrupt the exploration of changes to spatial layout (e.g., ref. 50) and that place cell activity is modulated by spatial, but not nonspatial, novelty (51). Our results suggest that, in the rat, the ventral hippocampus might be the primary source of this novelty signal. In humans, a recent fMRI study (52) found anterior hippocampal activity to correlate with the formation of a survey representation of a new virtual reality (VR) environment, possibly reflecting incorporation of new landmark information into a boundary-based representation. Our results are also consistent with numerous fMRI studies showing an anterior hippocampal novelty response (e.g., ref. 25). Interestingly, the posterior parahippocampal cortex responded to both spatial novelty and processing of the boundary, consistent with its role in representing spatial scenes (53).

What distinguishes a landmark from a boundary in terms of ability to activate the two systems? We cannot be sure, but place cell firing appears to reflect a matching of distances to the nearest obstacle in all directions around the rat (19, 20). Thus, the influence of a given object on the hippocampal representation of location might be simply proportional to the horizontal angle subtended by it at the participant, with extended obstacles having a greater influence than discrete ones. However, our results are not explained by previous findings of striatal versus hippocampal processing of proximal versus distal cues (4, 8, 16). We used a variety of object locations so as to include boundary-related objects initially nearer to the landmark and landmark-related objects initially nearer to the boundary. Conversely, the proximal–distal dissociation may reflect differences in the type of processing required rather than the distance of the cue from the goal *per se*. Distal cues are important for orientation [via the head-direction system (28)], and tasks that test memory for location relative to a boundary often also require orientation, whereas tasks involving a proximal cue actually at the goal location can be solved by a simple association (cue approach) and do not require orientation. In our task, navigation relative to landmark or boundary both require orientation and neither can be solved by cue approach.

How did the two systems interact to support behavior within a single task? When put into conflict, each system's influence on behavior corresponded to its activation level, without direct activation-based competition between systems. Thus a system's suitability to control behavior may be signaled bottom-up by its activation. This interpretation would be consistent with effects of locally injected anesthetic in biasing behavior to follow a hippocampal place strategy when injected into the striatum and to follow a striatal response strategy when injected into the hippocampus (13). In addition, top-down ventromedial prefrontal mediation may be required when both systems are similarly active (54, 55). More generally, the effect of having two independent systems may appear competitive or cooperative according to the situation (7, 8, 13, 24, 56). Overall, our paradigm appears to be highly sensitive to the relative activation of the two systems, and so may provide a useful indicator of damage, e.g., in Huntington's (24) or Alzheimer's (23) diseases.

In conclusion, our findings, together with behavioral experiments using the same paradigm (30), indicate that learning locations relative to an intramaze landmark is supported by the dorsal striatum and obeys associative reinforcement, whereas learning locations relative to a boundary is supported by the right posterior hippocampus and is incidental. Both types of learning occur in parallel within the same task and do not reflect differences in the time course of learning, performance levels, instructions, or in the proximity, salience, or novelty of stimuli that would otherwise confound identification of the characteristics of the two systems. Indeed, spatial novelty produced anterior hippocampal activation unrelated to the boundary-related learning in posterior hippocampus. Finally, the two systems appear to influence behavior proportionally to their activation, with ventromedial prefrontal involvement when both are similarly active.

Methods

Participants. Sixteen male participants (aged 20–31, mean age 23.8 years) gave written consent and were paid for participating, as approved by the local Research Ethics Committee. All were right-handed with normal or corrected-to-normal vision and reported to be in good health with no history of neurological disease. All had experience of playing first-person perspective video games.

Virtual Reality Environment. We used UnrealEngine2 Runtime software (Epic Games) to present a first-person perspective view of a grassy plane surrounded by a circular cliff with a background of mountains, clouds, and the sun (created by using Terragen; Planetside Software) projected at infinity, to provide orientation but not location within the arena. A traffic cone was used as an intramaze landmark. Both the boundary (cliff) and landmark (cone) were rotationally symmetric, leaving the distal cues as the main source of orientation. Participants moved the viewpoint by using their right hand to operate keys to move forward and turn left or right. The viewpoint is ≈2 virtual meters above ground, the boundary is ≈180 virtual meters in diameter, and the virtual heading and location were recorded every 100 ms. Participants practiced in an unrelated virtual environment before performing the experiment (see *SI Text*).

Stimuli, Task, and Trial Structure. Participants initially familiarized themselves with the arena by exploring for 2–3 min. Next, everyday objects were presented sequentially (once each) within the arena; participants collected the objects by running over them and were instructed to remember their locations. At the beginning of each subsequent trial, a picture of an object was presented on a blank background for 2 s (the cue phase), followed by a variable delay period (fixation cross; 2–6 s; mean 4 s). Participants then started at a random position within the arena and had to move to where they thought the cued object had been (the replace phase; mean duration 8.32 s). After participants had indicated their response by a button press, feedback was provided, i.e., the object appeared in its correct position and participants collected it by running over it (the feedback phase; mean duration 6.59 s). Participants could use the feedback phase to (re)learn the object positions. A fixation cross was then presented for a variable intertrial interval (2–10 s; mean 6 s), before the start of the next trial.

Details of Procedure and Design. Participants performed four blocks. Each block comprised 16 trials with the four experimental objects (four trials each) in pseudorandom order. Trials with one control object were interspersed with regular trials (see *SI Text*). The landmark and boundary were moved relative to each other between blocks, with two experimental objects maintaining a fixed position relative to the landmark and two relative to the boundary (see Fig. 1*C*). There were four arena configurations, with the landmark roughly in the middle of the northeast, southeast, southwest, and northwest sectors of the arena, as defined by the distal cues. Arena configuration to block assignment was counterbalanced across participants. There were four initial object positions in block 1, which were assigned to landmark- or boundary-related objects, counterbalanced across participants, such that one object of each type was close to the landmark in block 1 (and one of each type distant from it).

Characterizing the Relative Influence of Either Cue on Replace Location. For blocks 2–4, we attempted to quantify the relative influence of either cue on each response location. In a pilot study, we noticed that incorrect responses tended to be clustered around locations previously associated with the incorrect cue: either during block 1 or during the immediately preceding block. Accordingly, we calculated the relative influence of boundary versus landmark in blocks 2–4 as $d_L/(d_L + d_B)$, where d_L is the distance of the response from the location predicted

by the landmark and d_B is the distance from the location predicted by the boundary. This measure varies between 0 (using the landmark) and 1 (using the boundary). On the basis of our pilot data the incorrect cue potentially predicts two different locations in blocks 3 and 4 (reflecting the object's positions relative to it in the preceding block and in block 1): we used whichever was closest to the response location. This measure was used to create a parametric regressor for analysis of fMRI data in the replace phase (see Fig. S2).

Acquisition and Analysis of fMRI Time Series. Functional images were acquired on a 3T scanner and analyzed by using SPM2, including standard preprocessing procedures. fMRI time series were modeled by a general linear model including regressors for the cue, replace, and feedback phases, and parametric modulations of these regressors reflecting trial-by-trial behavioral measures and time of trial within block. We also modeled effects related to VR movements by including parametric modulations of the replace- and feedback-phase regressors by speed and signed and unsigned rotation following ref. 14. All regressors were convolved with the SPM hemodynamic response function. Data were high-pass filtered (cut-off period = 128 s). Coefficients for each regressor were estimated for each participant by a least-mean-squares fit of the model to the time series. Linear contrasts of coefficients for each participant were entered into a second-level random-effects analysis. Based on our strong *a priori* hypotheses with respect to the hippocampus and striatum we have chosen an uncorrected statistical threshold of $P = 0.001$. Nonhypothesized activations outside of the hippocampus and striatum are reported in Table S1. Coordinates of brain regions are reported in MNI space. See *SI Text* for details.

ACKNOWLEDGMENTS. We thank N. Weiskopf for MR sequence development; E. Featherstone, C. Hutton, and T. Hartley for technical help; R. Spiers for help during scanning; P. Dayan, J. Driver, C. Frith, U. Frith, M. Lengyel, E. Maguire, M. Mishkin, and J. O'Keefe for useful discussions; and M. Mishkin for carefully reading this manuscript. This work was funded by the Biotechnology and Biological Sciences Research Council and the Medical Research Council U.K.

1. Hirsh R (1974) The hippocampus and contextual retrieval of information from memory: A theory. *Behav Biol* 12:421–444.
2. O'Keefe J, Nadel L (1978) *The Hippocampus as a Cognitive Map* (Oxford Univ Press, Oxford).
3. Mishkin M, Malamut B, Bachevalier J (1984) Memories and habits: Two neural systems. *Neurobiology of Learning and Memory*, eds Lynch G, McGaugh JL, Weinberger M (Guilford, New York), pp 65–77.
4. Packard MG, Hirsh R, White NM (1989) Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. *J Neurosci* 9:1465–1472.
5. Squire LR, Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci USA* 93:13515–13522.
6. Knowlton BJ, Mangels JA, Squire LR (1996) A neostriatal habit learning system in humans. *Science* 273:1399–1402.
7. Poldrack RA, *et al.* (2001) Interactive memory systems in the human brain. *Nature* 414:546–550.
8. McDonald RJ, White NM (1994) Parallel information processing in the water maze: Evidence for independent memory systems involving dorsal striatum and hippocampus. *Behav Neural Biol* 61:260–270.
9. Eichenbaum H, Cohen NJ (2001) *From Conditioning to Conscious Recollection: Memory Systems of the Brain* (Oxford Univ Press, Oxford).
10. Barnes TD, Kubota Y, Hu D, Jin DZ, Graybiel AM (2005) Activity of striatal neurons reflects dynamic encoding and recoding of procedural memories. *Nature* 437:1158–1161.
11. Packard MG, Knowlton BJ (2002) Learning and memory functions of the basal ganglia. *Annu Rev Neurosci* 25:563–593.
12. Yin HH, Knowlton BJ (2006) The role of the basal ganglia in habit formation. *Nat Rev Neurosci* 7:464–476.
13. Packard MG, McGaugh JL (1996) Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiol Learn Mem* 65:65–72.
14. Hartley T, Maguire EA, Spiers HJ, Burgess N (2003) The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. *Neuron* 37:877–888.
15. Iaria G, Petrides M, Dagher A, Pike B, Bohbot VD (2003) Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: Variability and change with practice. *J Neurosci* 23:5945–5952.
16. Packard MG, McGaugh JL (1992) Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: Further evidence for multiple memory systems. *Behav Neurosci* 106:439–446.
17. Pearce JM, Roberts AD, Good M (1998) Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. *Nature* 396:75–77.
18. McGregor A, Hayward AJ, Pearce JM, Good MA (2004) Hippocampal lesions disrupt navigation based on the shape of the environment. *Behav Neurosci* 118:1011–1021.
19. O'Keefe J, Burgess N (1996) Geometric determinants of the place fields of hippocampal neurons. *Nature* 381:425–428.
20. Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J (2000) Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus* 10:369–379.
21. Cressant A, Muller RU, Poucet B (1997) Failure of centrally placed objects to control the firing fields of hippocampal place cells. *J Neurosci* 17:2531–2542.
22. Berke JD, Breck JT, Eichenbaum H (2007) Distinct striatal and hippocampal single-unit representations during win-stay maze task performance. *Soc Neurosci Abstr* 840.8/TT31.
23. Middei S, Geracitano R, Caprioli A, Mercuri N, Ammassari-Teule M (2004) Preserved fronto-striatal plasticity and enhanced procedural learning in a transgenic mouse model of Alzheimer's disease overexpressing mutant hAPPswe. *Learn Mem* 11:447–452.
24. Voermans NC, *et al.* (2004) Interaction between the human hippocampus and the caudate nucleus during route recognition. *Neuron* 43:427–435.
25. Strange BA, Fletcher PC, Henson RN, Friston KJ, Dolan RJ (1999) Segregating the functions of human hippocampus. *Proc Natl Acad Sci USA* 96:4034–4039.
26. Morris RGM, Garrud P, Rawlins JN, O'Keefe J (1982) Place navigation impaired in rats with hippocampal lesions. *Nature* 297:681–683.
27. Maurer R, Derivaz V (2000) Rats in a transparent Morris water maze use elemental and configural geometry of landmarks as well as distance to the pool wall. *Spatial Cognit Comput* 2:135–156.
28. Taube JS (1998) Head direction cells and the neuropsychological basis for a sense of direction. *Prog Neurobiol* 55:225–256.
29. Wilton LA, Baird AL, Muir JL, Honey RC, Aggleton JP (2001) Loss of the thalamic nuclei for ''head direction'' impairs performance on spatial memory tasks in rats. *Behav Neurosci* 115:861–869.
30. Doeller CF, Burgess N (2008) Distinct error-correcting and incidental learning of location relative to landmarks and boundaries. *Proc Natl Acad Sci USA* 105:5909–5914.
31. Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. *NeuroImage* 19:1273–1302.
32. Rescorla RA, Wagner AR (1972) A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. *Current Research and Theory*, eds. Black AH, Prokasy WF (Appleton-Century-Crofts, New York), pp 64–99.
33. Sutton RS, Barto AG (1988) *Reinforcement Learning: An Introduction* (MIT Press, Cambridge, MA).
34. Balleine BW, Delgado MR, Hikosaka O (2007) The role of the dorsal striatum in reward and decision-making. *J Neurosci* 27:8161–8165.
35. Williams ZM, Eskandar EN (2006) Selective enhancement of associative learning by microstimulation of the anterior caudate. *Nat Neurosci* 9:562–568.
36. Schultz W (2002) Getting formal with dopamine and reward. *Neuron* 36:241–263.
37. O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ (2003) Temporal difference models and reward-related learning in the human brain. *Neuron* 38:329–337.
38. McClure SM, Berns GS, Montague PR (2003) Temporal prediction errors in a passive learning task activate human striatum. *Neuron* 38:339–346.
39. Corlett PR, *et al.* (2004) Prediction error during retrospective revaluation of causal associations in humans: fMRI evidence in favor of an associative model of learning. *Neuron* 44:877–888.
40. Shohamy D, *et al.* (2004) Cortico-striatal contributions to feedback-based learning: Converging data from neuroimaging and neuropsychology. *Brain* 127:851–859.
41. Burgess N, Maguire EA, O'Keefe J (2002) The human hippocampus and spatial and episodic memory. *Neuron* 35:625–641.
42. Jung MW, Wiener SI, McNaughton BL (1994) Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *J Neurosci* 14:7347–7356.
43. Moser MB, Moser EI, Forrest E, Andersen P, Morris RGM (1995) Spatial learning with a minislab in the dorsal hippocampus. *Proc Natl Acad Sci USA* 92:9697–9701.
44. Hartley T, *et al.* (2007) The hippocampus is required for short-term topographical memory in humans. *Hippocampus* 17:34–48.
45. Gallistel R (1990) *The Organization of Learning* (MIT Press, Cambridge, MA).
46. Cheng K, Newcombe NS (2005) Is there a geometric module for spatial orientation? Squaring theory and evidence. *Psychon Bull Rev* 12:1–23.
47. Gluck MA, Meeter M, Myers CE (2003) Computational models of the hippocampal region: Linking incremental learning and episodic memory. *Trends Cogn Sci* 7:269–276.
48. Tolman EC (1948) Cognitive maps in rats and men. *Psychol Rev* 55:189–208.
49. Morris RGM, Frey U (1997) Hippocampal synaptic plasticity: Role in spatial learning or the automatic recording of attended experience? *Philos Trans R Soc London Ser B* 352:1489–1503.
50. Save E, Poucet B, Foreman N, Buhot MC (1992) Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. *Behav Neurosci* 106:447–456.
51. Lenck-Santini PP, Rivard B, Muller RU, Poucet B (2005) Study of CA1 place cell activity and exploratory behavior following spatial and nonspatial changes in the environment. *Hippocampus* 15:356–369.
52. Wolbers T, Buchel C (2005) Dissociable retrosplenial and hippocampal contributions to successful formation of survey representations. *J Neurosci* 25:3333–3340.
53. Epstein R, Kanwisher N (1998) A cortical representation of the local visual environment. *Nature* 392:598–601.
54. Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24:167–202.
55. Killcross S, Coutureau E (2003) Coordination of actions and habits in the medial prefrontal cortex of rats. *Cereb Cortex* 13:400–408.
56. Foerde K, Knowlton BJ, Poldrack RA (2006) Modulation of competing memory systems by distraction. *Proc Natl Acad Sci USA* 103:11778–11783.

Supporting Information

Doeller *et al*. 10.1073/pnas.0801489105

SI Text

Details of Procedure and Design. Delay and intertrial interval (ITI) durations were selected randomly for each trial with the constraint that the overall distribution (and by this the overall duration) of delay and ITI times were identical for each object. Within experimental blocks, trials were separated into mini-blocks (unknown to the participants), each object occurring once per mini-block. Object order within the mini-blocks was randomized with the constraint that no object appeared in two successive trials across mini-block boundaries. Trials across mini-block boundaries were separated by the same average ITI as the other trials.

Training. To prepare the participants for the experiment and familiarize them with the task, participants underwent training immediately before the experiment. To prevent any unspecific learning effects the training environment differed from the experimental environment with respect to the shape of the environment (square vs. circle), the ground (desert-like vs. grass), the intramaze landmark (bush vs. traffic cone), the global configuration of the background mountains and the objects. Participants learned the initial position of four training objects and then performed two trials per object.

Control Trials. During control trials, participants were cued by a picture of an object followed by a short delay and then had to collect the object from an infinite grassy plane with blue background on which it was clearly visible (mimicking the feedback phase, but with all spatial cues removed). Thus, this condition did not require spatial memory, or spatial processing of environmental location. Cue, delay, and ITI durations were identical to the experimental trials.

fMRI Acquisition. BOLD-sensitive T2*-weighted functional images were acquired on a 3T Siemens Allegra scanner using a gradient-echo EPI pulse sequence with the following parameters: TR = 2,600 ms, TE = 30 ms, flip angle = 90°, slice thickness = 2 mm, interslice gap = 1mm, in-plane resolution = 3×3 mm, FoV = 192 mm^2, 40 slices per volume. The first five volumes were discarded to allow for T1 equilibration. The sequence was optimized to minimize signal dropouts in the medial temporal lobes (1). In addition, a field map using a double echo FLASH sequence was recorded for distortion correction of the acquired EPI images (1) (see below).

Image Preprocessing. EPI images were spatially realigned to the first image in the times series and were corrected for distortions based on the field map (2) and the interaction of motion and distortion using the Unwarp routines in SPM (2, 3). Then images were normalized to the standard EPI template (MNI reference brain). Finally, the normalized functional images were spatially smoothed with an isotropic 8-mm FWHM Gaussian kernel.

Details of fMRI Analyses. In the main analyses we focussed on blocks 2–4, because the separation of both object types became established at the beginning of block 2 when the landmark was moved relative to the boundary for the first time. All general linear models (GLMs) included regressors for the cue, replace, and feedback phase and included parametric modulations of the replace and feedback phase regressors by speed and signed and unsigned rotation to model unspecific effects caused by virtual reality (VR) movements.

The basic model for the fMRI data included regressors for the cue and replace phase for all experimental objects and parametric modulations of the replace phase regressor by the influence of boundary or landmark on the response. Separate regressors were included for the feedback phase of landmark-related and boundary-related objects, as the object's location in this phase determines an object's association to either cue, and parametric modulation of the feedback phase regressors by the amount learned (i.e., the reduction in the distance between the replacement location and the correct location on the next trial with the same object). Parametric modulation by the time of trial within block [exponential decay across trials 1–4 for each object with time constant 1, i.e. a mean corrected parameter proportional to exp(−trial number)] was also included for the feedback and replacement phase regressors to capture any effects of novelty-within-block (4). Finally, separate regressors for the cue phase and the navigation phase of the control object were included.

All parametric modulations are normalized to have zero mean so that the parametrically modulated regressor is orthogonal to the unmodulated regressor (5). Thus, e.g., the relative influence of boundary versus landmark on replacement location (a number between 0 and 1) varies between −0.5 (following the landmark) and +0.5 (following the boundary) after normalization. All regressors (parametrically modulated or not) were convolved with the canonical hemodynamic response function (HRF) in SPM before entering the GLM.

We conducted an F test of the combined effect of influence-of-boundary and trial-within-block modulations of the activation during the replacement phase for the hippocampus (see Fig. 2*Bii*). To dissociate these effects, we conducted an ANOVA with the factors object type (landmark-related vs boundary-related) and trial (trials 1–2 vs. 3–4) (see Fig. 2*Biv*). This model included separate regressors for trials 1–2 and 3–4 in each block for landmark-related and boundary-related objects (replace phase) and for the control object (navigation phase). In addition, the cue phase of all objects and the feedback phase of the experimental objects were modeled with two additional regressors.

In a separate across-subject analysis we looked at the correlation between activity during the replace phase of block 1 (irrespective of object type) and the initial influence of boundary/landmark in trial 1 of block 2 (see Fig. 2*C*). This model included separate regressors for the cue, replace, and feedback phase of the experimental objects, and for the cue and navigation phase of the control object for block 1.

In separate models we tested the specificity of the observed decay of hippocampal activity in the replace phase of blocks 2–4. First, we compared decay effects between landmark-related and boundary-related objects in blocks 2–4 and found no difference. We also looked at decay effects in the feedback phase of blocks 2–4. Then we looked at decay effects in the control trials within blocks 2–4. For the experimental objects, we also examined decay effects within block 1 (before any spatial change). In additional analyses we looked at decay effects across blocks (parametric function decaying across but not within blocks) and across the entire experiment (parametric function decaying from trial to trial). We did not observe any decay effects in the hippocampus in these additional analyses (all P 0.01, uncorrected), supporting the view that the decay of anterior hippocampal activity in the replace phase of blocks 2–4 is specific to spatial novelty, i.e. a response to the new landmark-boundary configuration during navigation.

For the visualization of the parametric responses to learning relative to boundary or landmark and influence of boundary or landmark, we grouped trials into four bins reflecting quartiles of the respective parametric values and calculated the % signal change separately for each bin. See bar plots in Fig. 2.

Dynamic Causal Modeling. We used dynamic causal modelling (6) to test whether direct interactions between caudate and hippocampus could provide significant explanation of these two regions' activation levels in addition to the behavioral variables revealed in the above basic GLM. In this analysis (Fig. 3*A*) we first extracted the hippocampal and caudate BOLD time series for each participant separately for the replace and feedback phase by extracting the first principal component (7) from all raw voxel time series within a 4-mm sphere of the boundary- or landmark-related activation peak in right posterior hippocampus or right head of caudate. Time series were mean-corrected and high-pass filtered (8). We defined two separate models for the replace and feedback phases in blocks 2–4. In both models, both regions received input reflecting behavior: the influence of boundary versus landmark in each trial for the replace phase model (varying from −0.5 for replacement at the landmark-predicted location and +0.5 for replacement at the boundary-predicted location); and learning relative to boundary or landmark for the feedback phase model (combining the two separate learning regressors for boundary-related and landmark-related learning, multiplying the latter by −1 so that positive values reflect learning about the boundary and negative values learning about the landmark). Model 1 contained no other connections, whereas model 2 additionally included direct connections between the caudate and the hippocampus.

To compare these models, we used a Bayesian model selection procedure (9), which determines a Bayes factor reflecting the ratio between the evidence for the two models. This procedure provides an optimal balance between model accuracy and model complexity. For one model to be favored over another, a Bayes factor >2.72 was considered as a critical threshold (8, 9). Model 2 was not sufficiently better than model 1, given its additional complexity. Instead model 1 was favored in all participants for both the replace and feedback phases (average Bayes factor 6.94 during replacement, 7.17 during feedback).

Physio-Physiological Interaction. To examine the possible interaction of caudate and hippocampus with a third region (Fig. 3*B*) we used a physio-physiological interaction analysis (7, 10). For each participant, an interaction term was included as a regressor in the GLM along with regressors reflecting caudate and hippocampus activity alone. The interaction term was formed by deconvolving the hippocampal and caudate time series with respect to the HRF, multiplying them together element by element, mean-normalizing the result, and reconvolving it with the HRF (11). Effects were estimated for each participant and then subjected to a second-level random effects analysis to find regions with activity following this pattern.

Debriefing. A final question concerns the accessibility of the two systems to consciousness awareness, a key facet of the declarative-procedural distinction (12, 13). After the experiment participants were debriefed. They were shown a picture of each object and asked to draw and comment upon its location. Debriefings of 14 participants were unambiguous and could be analyzed. The majority of subjects were aware of the associations of both the landmark-related and boundary- related objects. Seventy-five percent correctly noted the association of the landmark-related objects, and 85% correctly noted the association of the boundary-related objects. Hence, it is conceivable that the hippocampal system makes object locations more readily available to awareness than the striatal system (12). On the other hand, some recent findings indicate that the medial temporal lobe is activated even when learning proceeds in the absence of awareness (14–16).

1. Weiskopf N, Hutton C, Josephs O, Deichmann R (2006) Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: A whole-brain analysis at 3 T and 1.5 T. *NeuroImage* 33:493–504.
2. Hutton C, *et al.* (2002) Image distortion correction in fMRI: A quantitative evaluation. *NeuroImage* 16:217–240.
3. Andersson JL, Hutton C, Ashburner J, Turner R, Friston K (2001) Modeling geometric deformations in EPI time series. *NeuroImage* 13:903–919.
4. Henson RN, Friston KJ (2006) Convolution models for fMRI. *Statistical Parametric Mapping: The analysis of Functional Brain Images*, eds. Friston KJ, Ashburner J, Kiebel S, Nichols T, Penny W (Elsevier, London), pp 178–192.
5. Büchel C, Holmes AP, Rees G, Friston KJ (1998) Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *NeuroImage* 8:140–148.
6. Friston KJ, Harrison L, Penny W (2003) Dynamic causal modeling. *NeuroImage* 19:1273–1302.
7. Büchel C, Friston KJ (1997) Modulation of connectivity in visual pathways by attention: Cortical interactions evaluated with structural equation modelling and fMRI. *Cereb Cortex* 7:768–778.
8. Smith AP, Stephan KE, Rugg MD, Dolan RJ (2006) Task and content modulate amygdala-hippocampal connectivity in emotional retrieval. *Neuron* 49:631–638.
9. Penny WD, Stephan KE, Mechelli A, Friston KJ (2004) Comparing dynamic causal models. *NeuroImage* 22:1157–1172.
10. Friston KJ, *et al.* (1997) Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage* 6:218–229.
11. Gitelman DR, Penny WD, Ashburner J, Friston KJ (2003) Modeling regional and psychophysiologic interactions in fMRI: The importance of hemodynamic deconvolution. *NeuroImage* 19:200–207.
12. Squire LR, Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci USA* 93:13515–13522.
13. Bayley PJ, Frascino JC, Squire LR (2005) Robust habit learning in the absence of awareness and independent of the medial temporal lobe. *Nature* 436:550–553.
14. Schendan HE, Searl MM, Melrose RJ, Stern CE (2003) An fMRI study of the role of the medial temporal lobe in implicit and explicit sequence learning. *Neuron* 37:1013–1025.
15. Degonda N, *et al.* (2005) Implicit associative learning engages the hippocampus and interacts with explicit associative learning. *Neuron* 46:505–520.
16. Rose M, Haider H, Weiller C, Büchel C (2002) The role of medial temporal lobe structures in implicit learning: an event-related fMRI study. *Neuron* 36: 1221–1231.

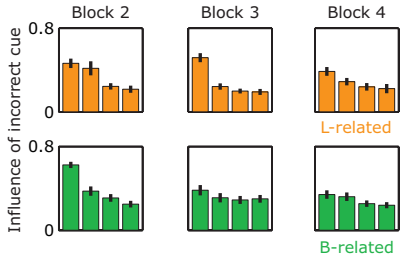

Fig. S1. Replacement errors mainly reflect use of the incorrect cue. The influence of the boundary on the response location for landmark-related objects [orange; $d_L/(d_L + d_B)$; see Fig. 2*Biii* and *Methods*] and of the landmark on the response location for boundary-related objects [green; $d_B/(d_L + d_B)$] is plotted separately for trials 1–4 of blocks 2–4. The average over the two objects paired with either cue is shown (error bars show SEM.). This measure was subjected to a similar analysis over blocks 2–4 as the replacement error (see Fig. 1*D*), showing the same statistical pattern: not differing between boundary-related and landmark-related objects ($F_{1,15} = 2.06$; $P > 0.1$) and decreasing within ($F_{3,45} = 63.28$; $P < 0.001$) and across ($F_{2,30} = 8.46$; $P < 0.005$) blocks similarly for both object types (within $F_{3,45} = 1.36$; $P > 0.2$; across $F_{2,30} < 1$). The influence of the correct cue predicted 83.3% of variance in performance ($P < 0.001$). In addition, a further analysis revealed that 77.5% of the spatial variance in replace locations around the correct location is in the direction toward the location predicted by the incorrect cue, only 22.5% in the perpendicular direction ($t_{15} = 8.65$; $P < 0.001$).

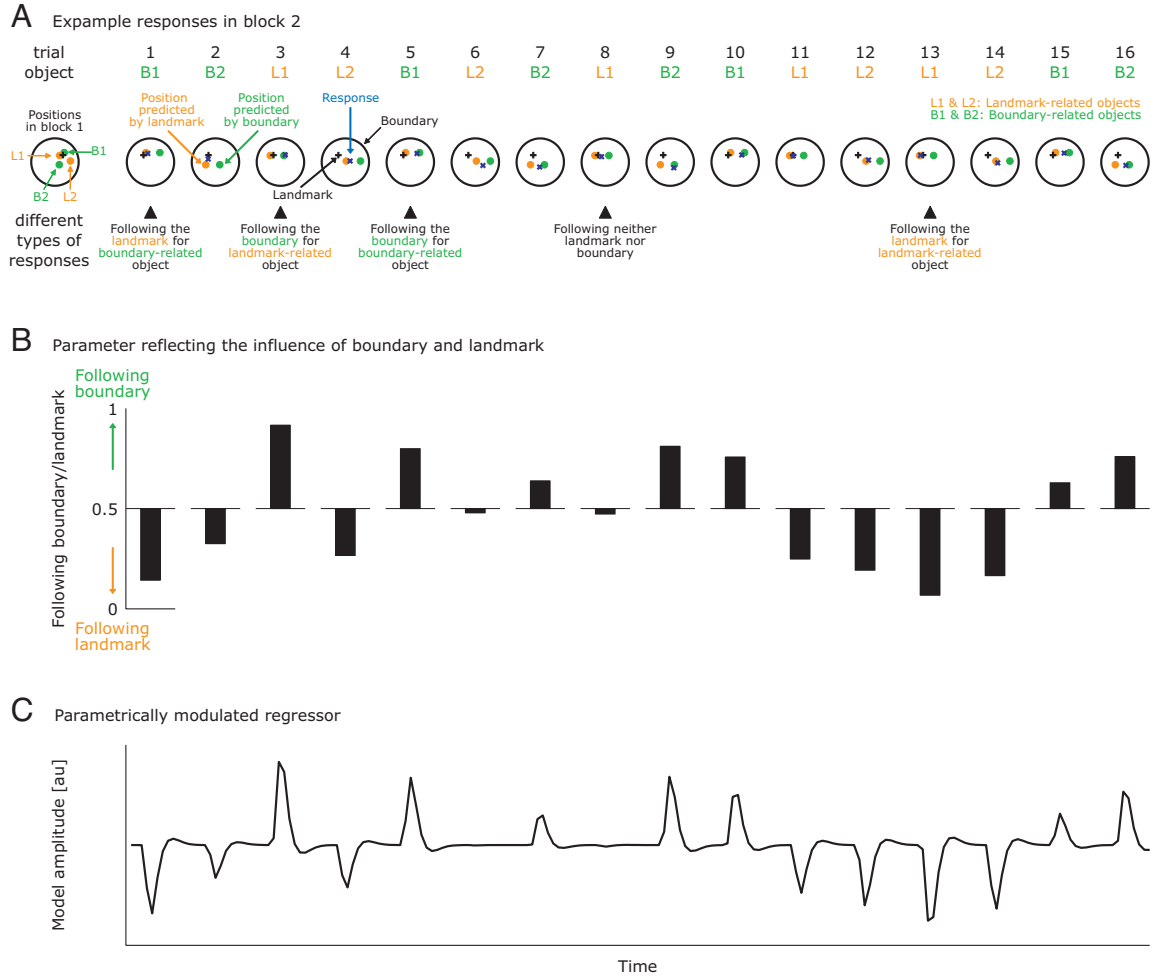

Fig. S2. Modeling the influence of boundary and landmark in the fMRI analysis. (*A*) Data from the 16 experimental. trials of block 2 of a single subject are shown to illustrate the logic of the parametric fMRI analysis for the replace phase. Initial object positions in block 1 are shown on the left. Examples of different response types are illustrated by arrows. Schematics: L1 and L2, landmark-related objects; B1 and B2, boundary-related objects; x, response location; +, landmark; circle, boundary; dots, positions predicted by landmark (orange) and boundary (green). (*B*) Our measure of the relative influence of boundary or landmark on replacement location, varying between 0 (following the landmark) and 1 (following the boundary). For display purposes, values > 0.5 are plotted upward, values < 0.5 downward. (*C*) In the parametric analysis the regressor for the replace phase (reflecting the average response) was multiplied by the mean-corrected parametric function from *B*, (i.e., varying between -0.5: following the landmark, and $+ 0.5$: following the boundary), convolved with the haemodynamic response function, and down-sampled at the repetition time (TR $= 2.6$ s; the time taken to acquire each fMRI volume). Illustration shows the parametric modulation regressor, with arbitrary onsets and durations and in arbitrary units (au).

Table 1. Summary of imaging findings

Region	Laterality	MNI coordinates			
		x	*y*	*z*	*z*
Learning during the feedback phase					
Learning to landmark					
Caudate (head)	R	12	12	3	2.98
Orbital gyrus	R	33	12	−12	3.54
Vicinity of red nucleus	-	0	−18	−6	3.58
Occipital cortex (peak)	L	−36	−75	−18	3.56
Learning to boundary					
Hippocampus	R	27	−30	−3	4.14
	R	30	−33	−6	3.63
Vicinity of hippocampus	R	27	−27	−3	4.15
Inferior frontal gyrus	L	−33	30	0	3.15
Parahippocampus	R	24	−45	−15	3.83
Occipital cortex (peak)	L	−15	−90	−6	3.84
Replacing relative to landmark/boundary					
Following landmark					
Caudate (head)	R	18	15	9	3.01
Putamen	L	−21	18	3	3.00
Medial prefrontal cortex	L	−3	57	6	3.18
	R	6	45	−3	3.68
Cingulate cortex	R	9	−18	45	3.57
Intraparietal sulcus	R	27	−33	48	3.31
Inferior parietal lobule	L	−54	−45	36	3.35
Following boundary					
Middle frontal gyrus	R	39	39	33	3.35
Insula	R	42	15	−9	3.81
Occipital cortex (peak)	R	21	−90	24	3.57
F-test (boundary + decay modulation)					
Hippocampus	R	33	−9	−18	3.41
	R	33	−21	−9	3.31
Novelty-related vs. boundary-related activity (trial × object type ANOVA)					
Main effect of trial (trial 1–2 > trial 3–4)					
Hippocampus (peak)	R	36	−9	−21	5.37*
	L	−36	−18	−12	5.49*
Rhinal cortex	R	39	−9	−33	4.23*
Parahippocampus	L	−33	−39	−15	7.16*
Middle frontal gyrus	L	−27	36	33	6.61*
	L	−51	21	33	3.69
	R	54	27	33	3.91
Medial prefrontal cortex	L	−15	36	−18	3.66
	L	−9	48	0	5.18*
Medial frontal sulcus	L	−15	15	63	3.36
Precentral sulcus	R	57	−6	42	5.48*
Superior temporal gyrus	L	−54	0	−12	3.98
Insula	R	42	−15	18	4.04
Precentral gyrus	R	57	3	6	3.87
	R	42	−18	54	5.00*
Pons (peak)	-	0	−24	−36	4.29
Middle temporal gyrus	L	−66	−27	−9	6.02*
Cerebellum (peak)	L	−48	−57	−48	3.85
	R	15	−48	−48	5.17*
Angular gyrus	L	−57	−66	27	6.44*
	R	54	−63	33	5.42*
Visual cortex (peak)	R	0	−93	15	5.67*

Table 1. Summary of imaging findings

Region	Laterality	MNI coordinates			*z*
		x	*y*	*z*	
Main effect of trial (trial 3–4 > trial 1–2)					
No significant activations					
Main effect object type (B > L objects)					
Hippocampus	R	30	−39	3	3.72
	L	−30	−33	−3	3.53
Vicinity of hippocampus	R	30	−33	6	4.04
Inferior frontal gyrus	R	45	54	−3	3.14
	R	36	30	3	3.95
Medial frontal sulcus	R	18	15	63	3.26
Cingulate gyrus	R	9	18	48	4.09
Middle frontal gyrus (peak)	L	−51	15	42	5.06*
	R	54	9	45	4.39
Superior frontal sulcus	L	−42	−3	54	3.45
	L	−24	3	57	3.09
Insula (peak)	L	−51	−6	9	3.93
	R	42	3	−3	3.51
Postcentral sulcus	R	66	−15	36	4.83*
Intraparietal sulcus (peak)	R	27	−54	45	5.10*
	L	−24	−60	42	4.27
Lingual gyrus (peak)	R	33	−60	−9	4.55
	L	−30	−60	−12	4.25
Parieto-occipital sulcus	R	24	−63	24	3.98
Cerebellum	L	−45	−66	−39	3.61
Superior parietal lobule (peak)	R	21	−69	57	3.70
Visual cortex (peak)	L	−9	−102	15	5.04*
Main effect object type (L > B objects)					
Medial prefrontal cortex (peak)	R	3	33	9	5.11*
Correlation between block 1 activity and boundary bias in trial 1 of block 2					
Hippocampus	R	33	−36	−6	3.07
Hippocampus/parahippocampus	R	33	−39	−6	3.40
Precentral gyrus	R	45	−18	54	3.54
Postcentral gyrus	L	−36	−33	63	3.26
Superior parietal lobule	L	−24	−57	42	3.83
PPI analysis (positive covariation between caudate and hippocampus)					
Ventromedial prefrontal cortex	R	12	33	−6	3.47

Activations within gray matter (statistical threshold $P = 0.001$, uncorrected), including regions of five voxels outside of hippocampus or striatum.
*Significant at $P < 0.05$, family-wise error corrected for multiple comparisons across the whole brain.