Lateralized human hippocampal activity predicts navigation based on sequence or place memory

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The hippocampus is crucial for both spatial navigation and episodic memory, suggesting that it provides a common function to both. Here we adapt a spatial paradigm, developed for rodents, for use with functional MRI in humans to show that activation of the right hippocampus predicts the use of an allocentric spatial representation, and activation of the left hippocampus predicts the use of a sequential egocentric representation. Both representations can be identified in hippocampal activity before their effect on behavior at subsequent choice-points. Our results suggest that, rather than providing a single common function, the two hippocampi provide complementary representations for navigation, concerning places on the right and temporal sequences on the left, both of which likely contribute to different aspects of episodic memory.

allocentric | decision making | egocentric | episodic memory | cognitive control

The hippocampus plays a crucial role in both spatial navigation and episodic memory (1–6). However, the nature of the fundamental hippocampal process or representation that might underlie both functions remains the subject of intense speculation, including suggestions that it is best characterized as associative (7), sequential (8), flexible relational (2), allocentric (1, 5, 9), or spatial contextual (4, 5). Similar speculation surrounds the nature of any lateralization of these representations (1, 5, 10), and whether the firing of hippocampal neurons in freely moving rodents reflects allocentric position, spatial context, or sequential position along a route (5, 11, 12). Here we show that the hippocampus predicts and supports navigation via sequential representations in the left hippocampus and allocentric spatial representations in the right hippocampus. These complementary lateralized representations suggest an explanation for the multiple hippocampal contributions to different aspects of spatial and episodic memory.

Within spatial memory a distinction has been made between "allocentric" (world-centered) and "egocentric" (body-centered) representations, with allocentric (or place-learning) and simple egocentric (stimulus response-like) navigation shown to depend on the hippocampus and dorsal striatum, respectively, in rodents (5, 13). Rondi-Reig et al. (14) recently demonstrated that an additional sequential egocentric representation depends on the rodent hippocampus. The human hippocampus has likewise been associated with allocentric representations of location, allowing accurate navigation from new starting locations (15) based on the configuration of environmental cues (16, 17) or recognition of locations from a new viewpoint (18, 19). Similarly, navigation via a fixed route (15, 17) or relative to a single landmark (16), consistent with simple egocentric representations, has been associated with the dorsal striatum. However, to our knowledge, the neural bases of the sequential egocentric representation have not yet been identified in humans, and could provide a link between spatial navigation and episodic memory.

Here we adapt the Starmaze task developed for mice (14, 20) to investigate the neural bases of sequential egocentric representations and allocentric representations in humans. The task allows the parallel use of both types of representation during learning and performance of training trials, but also allows the use of one or other representation to be detected by the response made in probe trials. We used functional MRI (fMRI) during the navigation of the start alley of probe trials to determine the neural bases of the type of representation used as defined by the subsequent behavioral response. Our task is based on the virtual reality Starmaze (21), composed of 10 alleys, 5 central ones forming a pentagon and 5 alleys radiating from the angles of the central pentagon (Fig. 1*A*). Participants used a keypad to move their viewpoint forward or backward or to turn left or right; they could move around and perform rotations freely in all of the alleys. Distant environmental cues surrounded the maze for orientation. Participants were told to find a fixed goal that had no visible identifiers. When this goal was reached, fireworks went off to indicate the successful end of the trial (positive reinforcement). The experiment consisted of interleaved training trials, probe trials, and control trials (see Table S1 for complete trial order and *SI Text* for details). In training trials, successful navigation might be supported by either type of representation: sequential egocentric (sequence of body-turns) or allocentric (location relative to environmental cues). In probe trials, which were not distinguished from training trials in the instructions, participants had to find the goal from one of two different departure points, which allowed us to dissociate the use of either type of representation according to the path chosen by the participant (Fig. 1 *B* and *C*). The two probe-trial departure points were designed to differentially bias the participant toward use of an allocentric representation (departure point "DV," which has a very different view to that from the training-trial departure point) or toward use of a sequential egocentric representation (departure point "SV," which has a more similar view to that from the training-trial departure point). Use of either representation in a probe trial was considered correct; therefore, probe trials ended once the participant had made a response consistent with the use of a specific representation, without reinforcement. Control trials consisted of a navigation task in the same maze, but without environmental features, where participants had to move down two alleys joined by a turn (to the right or left). Half of the control trials ended midway down the final alley ("short control trials," like 25% of training trials and all probe trials) (Fig. 1*D*).

We focus on activations before the first choice-point of the maze, so that activation patterns can be analyzed according to the strategy of the participant on that run, as determined by their subsequent choices, but without any of the differences in behavior or stimuli resulting from the different paths following the choice-

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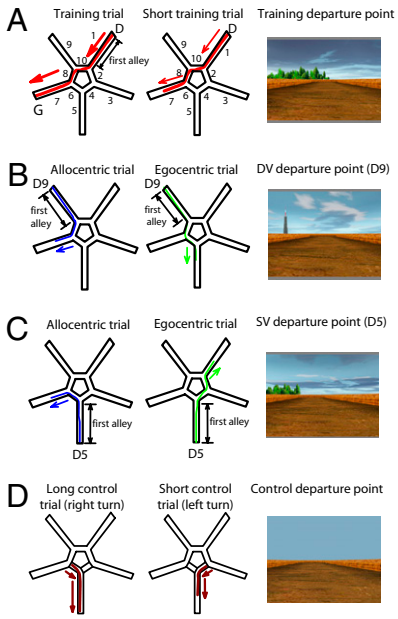

Fig. 1. Trial-types performed in the "Starmaze," a virtual maze comprising a central pentagonal ring (alleys 2, 4, 6, 8, and 10), five radiating alleys (alleys 1, 3, 5, 7, and 9), and surrounding environmental cues. (*A*) Training trials: Participants start in alley 1 (see initial view, *Right*) and must navigate to the goal at the end of alley 7, which triggers fireworks (*Left*; arrow shows ideal path). Participants can use allocentric or sequential egocentric representations to solve the task. Twenty-five percent of training trials finish in the middle of alley 7, without fireworks (*Center*). (*B* and *C*) Probe trials use a different departure point to identify which type of representation is being used to solve the task. Half of the probe trials depart from alley 9, which has a very different view to alley 1 (*B*, departure point "DV"), half from alley 5, which has a more similar view to alley 1 (*C*, departure point "SV"). Participants using an allocentric representation including the distal environmental cues will go to alley 7 (paths shown in blue). Participants using a sequential egocentric representation of body-movements (right-left-right) will take the paths shown in green. The main fMRI analyses concern activation in the first alley. Probe trials always end in the middle of the goal alley, without fireworks. (*D*) Control trials: Control trials are composed of one single turn (to the right or to the left). No external landmarks are present in the environment. Half of the control trials end in the middle of the goal alley, without fireworks.

point. We hypothesized that we would identify, before the first choice-point, areas of the hippocampal prefrontal striatal loop involved in supporting the allocentric and sequential egocentric representations. In addition, we would expect to see some changes in activation over the time-course of the experiment, including increased hippocampal involvement early in the task, when novelty and learning is maximal (16, 22), and increased retrosplenial/medial parietal regions later in the task, as a detailed internal representation of the environment is formed that can support mental imagery (9, 17, 21–25).

Results

Behavioral Results. All subjects learned the task quickly; a plateau in performance is reached after five training trials (Fig. S1 and *SI Text*). Sixteen probe trials were performed during the experiment, inserted regularly after training trial 3 (Table S1). Therefore, probe trials, except probe trial 1, were performed at stable performance. Probe trials were considered reliable for strategy identification if the learning criterion was reached (i.e., if the participant had performed two correct training trials before the probe trial) and the subject got to one of the two goal locations during the probe trial (Fig. 1 *B* and *C*). Probe trials that did not meet these criteria were considered failed (Fig. S1*B*).

As in Igloi et al. (21), three response types were observed during probe trials from both DV and SV departure points: (*i*) Allocentric responses: Participants navigated based on the environmental cues directly reached the goal in alley 7 (Fig. 1 *B* and *C*, *Left*). (*ii*) Sequential egocentric responses: Participants reproduced the same sequence of body-turns during the probe trials as during training trials, and reached the goal in alley 5 from departure-point DV (Fig. 1*B*, *Middle*) or alley 1 from departure-point SV (Fig. 1*C*, *Center*). (*iii*) Mixed responses: Participants started the trial by performing the previously realized body-turns (i.e., using a sequential egocentric representation) but reoriented themselves later on the path by using environmental cues (i.e., using an allocentric representation) and ended up in alley 7. These responses were only observed during probe trials from departure-point SV. For analyses of activations in the first alley, mixed responses were counted as sequential egocentric responses. For probe trials from both departure points, a mixture of sequential egocentric and allocentric responses were seen across participants (Fig. S1*B*). For probe trials from departure-point SV, participants mainly made sequential egocentric responses (Fig. S1*B*, *Left*) and for probe trials from departure-point DV, participants made mainly allocentric responses (Fig. S1*B*, *Right*). Over the 17 participants tested, 15 had made both allocentric and sequential egocentric responses during the experiment. The remaining two subjects made sequential egocentric responses in all probe trials. After the fMRI session, participants were debriefed. We asked them what kind of information they had used to find the goal. Out of 17 participants, 16 reported having used landmarks for orientation and 14 spontaneously described the geographical location of at least two landmarks around the maze. The one remaining participant, who was always responding egocentrically, only reported having used the right-left-right sequence of turns. None reported the use of verbal elements in their strategy (*SI Text*).

Imaging Results. Functional MRI data were fitted by a general linear model containing separate regressors for the first alley, the middle part, and the last alley separately for training trials, probe trials (from either departure point) in which a sequential egocentric response was made ("sequential egocentric probe trials"), and probe trials in which an allocentric response was made ("allocentric probe trials"). Control trials, which contained only two alleys, were modeled by two separate regressors. We focus on activations in the first navigated alley, as noted above. For all trial types, we compared activation during navigation of the first alley (when the path is identical for both types of response) to that in the first alley of the control trial.

Hippocampal activations. Training trials showed increased hippocampal activation bilaterally (right peak at MNI coordinates 30 −6 −15; left peak at −21 −15 −15) (Fig. 2*A*). For the probe trials, a lateralized hippocampal response was observed. Allocentric probe trials showed right hippocampal activation, peaked at 24 −24 −9 (Fig. 2*B*), whereas sequential egocentric probe trials showed left hippocampal activation (Fig. 2*C*) (peak: −21 −15 15). To examine the observed hippocampal lateralization in more detail, we extracted the fMRI data from 8-mm diameter regions of interest in left and right hippocampus centered on the peak activations for the sequential-egocentric and allocentric contrasts. A 2 × 2 ANOVA with factors laterality (left or right) and representation (sequential egocentric or allocentric) was performed on the average activation in the two regions of interest for sequential-egocentric—control and for allocentric—control contrasts. There were no main effects and a significant interaction ($F = 4.4$, $P < 0.05$), showing that the lateralization of hippocampal activity (i.e., difference in activation between left and right) predicts whether navigation is based on sequence or place memories (Fig. S2).

We also analyzed activation for similar responses separately for probe trials from the two departure points (DV and SV). Allo-

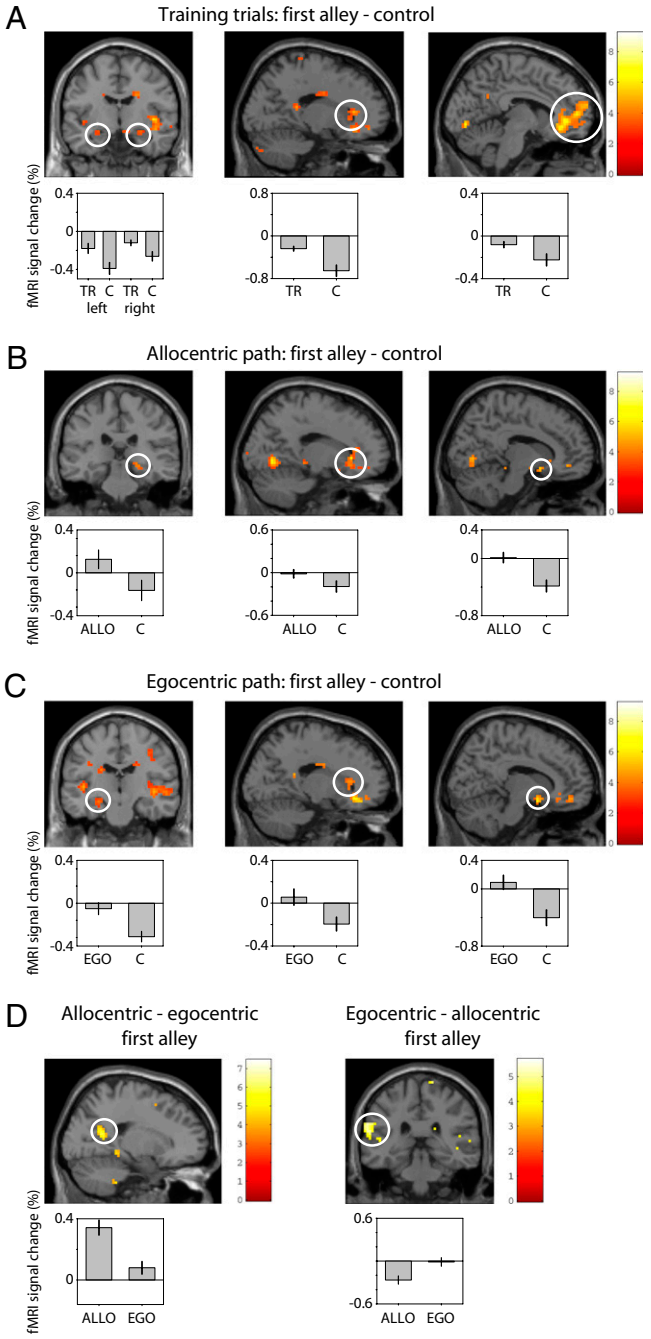

Fig. 2. Functional MRI results. (*A*) Training trials. (*Left*) Bilateral hippocampal activation (*Right* peak: 30 −6 −15; *Left* peak: −2 −15 −15) during navigation of the first alley of training trials (TR), relative to control trials (C). (*Center*) Caudate nucleus activation (peak: 21 27 0). (*Right*) Medial prefrontal activation (peak: −3 42 0). (*B*) Probe trials showing allocentric responses (ALLO). (*Left*) Right hippocampal activation (24 −24 −9) in the first alley relative to control trials. (*Center*) Caudate nucleus activation (18 27 0). (*Right*) Ventral striatal activation (12 9 −12). (*C*) Probe trials showing sequential egocentric responses (EGO). (*Left*) Left hippocampal activation (−21 −15 −15) in the first alley relative to control trials. (*Center*) Right caudate activation (18 27 9). (*Right*) Ventral striatal activation (12 6 −15). (*D*) (*Left*) Parieto-occipital sulcus activation (18 −58 20) in the first alley of probe trials showing allocentric versus sequential egocentric responses. (*Right*) Posterior insula and left postcentral gyrus (−51 −19 29) activation in the first alley of probe trials showing sequential egocentric versus allocentric responses. For display purposes, hippocampal activations are thresholded at $P < 0.005$. Mean percentage BOLD signal change for each trial type is shown beneath activation plots.

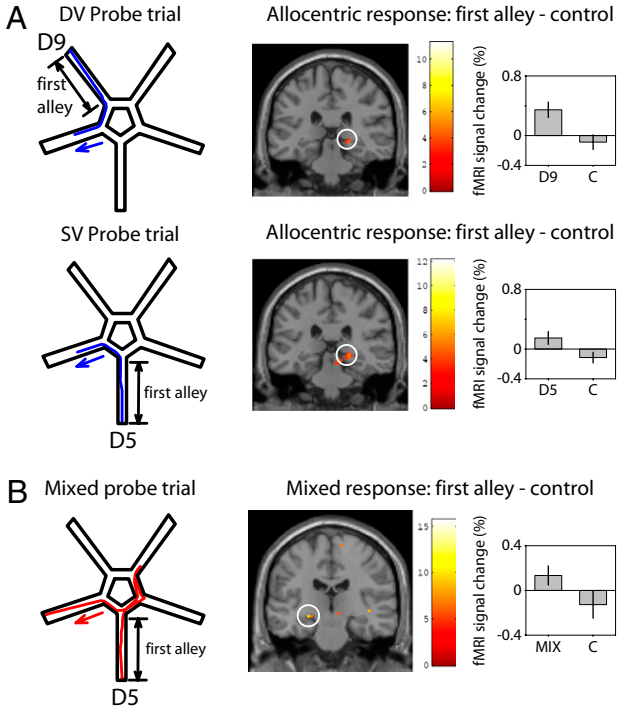

Fig. 3. Further analyses of activation during probe trials. (*A*) Allocentric responses correspond to right hippocampal activation during the first alley of probe trials from either departure point (DV above, peak: 21 −30 −6; SV below, peak: 21 −30 −6). (*B*) Mixed responses (i.e., when participants start by expressing the sequential egocentric strategy but subsequently reorient using environmental cues to reach alley 7, *Left*) correspond to left hippocampal activation (peak: −24 −21 −9) during the first alley versus control trials.

centric responses from either start alley correspond to right hippocampal activation (Fig. 3*A*). There were very few egocentric responses from the DV start alley, almost entirely produced by the two purely sequential-egocentric responders. However, these two participants do show significant left hippocampal activation in probe trials from the DV start alley. These analyses rule out a simple confound of start alley in explaining our lateralised hippocampal activations. Furthermore, for the first alley of the mixed trials versus control trials, we found left hippocampal activation (Fig. 3*B*), consistent with our interpretation of the use of a sequential egocentric representation during the first part of a mixed trial.

Training trials also showed activation in the right dorsal striatum (peak: 18 27 0, extending into the right caudate nucleus), the right ventral striatum (peak: 12 9 −12) and in the anterior cingulate cortex (peak: 18 30 9, extending into the head of the caudate nucleus). See Fig. 2*A* and Table S2 for a full list of activations.

For both allocentric and egocentric probe trials, compared with control trials, there was activation in the right caudate nucleus (peak: 18 27 9) and nucleus accumbens (12 6 −15) (Fig. 2 *B* and *C*, *Center* and *Right*). Contrasting the first alley of allocentric versus egocentric probe trials (Fig. 2*D*, *Left*) showed an increased bilateral activation of the superior parieto-occipital sulcus (*Right*: 18 −54 15, *Left*: −15 −57 18), the right parahippocampus (24 −39 −6), and a subthreshold right hippocampal peak (24 −24 −6). Contrasting the first alley of egocentric versus allocentric probe trials (Fig. 2*D*, *Right*) revealed left-side lateralized activation of the parietal cortex (−51 −15 24), left posterior insula (−51 −33 6), superior medial frontal gyrus (−3 60 18), and a subthreshold left hippocampal peak (27 −15 −18). See Table S3 for a full list of activations.

We also looked for regions showing decaying or increasing activation across the time-course of the experiment, using a separate model in which a regressor for the entire trials of each condition was

parametrically modulated by an exponential function reflecting the position of that trial within the experiment [e.g., for trial i of n trials of a given type, the decreasing exponential parameter would be proportional to $\exp(-i/n)$]. (Fig. 4 and Table S4). Both training trials and egocentric probe trials showed decreasing activation over the time-course of the experiment in the hippocampus. For training trials, decreasing activation was found in the right hippocampus (peak: 3 −12 −9) and also in the substantia nigra (9 −21 −18). Activation in both structures show higher values during the first quarter of the experiment than during the last three quarters (Fig. 4*A*). These decreasing activation patterns appeared to be related: the two time series (deconvolved with respect to the hrf) from the voxels in the hippocampus and the midbrain showing the maximal decrease were significantly correlated with each other in each participant (mean correlation, $R = 0.312$) (Table S5). For sequential egocentric probe trials, decreasing activation was found in the left hippocampus (−21 −15 −21), with higher activation in the first third of the experiment (Fig. 4*B*). Finally, allocentric probe trials showed increasing activation of the parieto-occipital sulcus (peak: 12 −63 30), with greater activation in the first third of the experiment (Fig. 4*C*).

Discussion

We investigated the neural bases of allocentric and sequential egocentric representations. Activation in the initial alley of a probe trial provided a well-controlled way to investigate the neural bases supporting these two types of representations, as revealed by the subsequent choice of destination alley. Our findings support the idea of lateralized hippocampal involvement during spatial navigation. The right hippocampus is involved in allocentric or map-based navigation, whereas the left hippocampus is involved in the sequential organization of successive choices. Both representations are active in parallel during the training phase of the task.

Striatal and Medial Prefrontal Activations. The role of the dorsal striatum in simple stimulus-response (S-R) learning is well established (13, 26). Dorsal striatal activations (centered on the caudate) suggest that simpler S-R associations form part of both of the more cognitive strategies (allocentric and sequential egocentric), consistent with a striatal role in learning skilled responses and with an interaction between hippocampus and striatum in route recognition (27). The ventral striatal activation observed in probe trials and training trials is consistent with suggestions that this area acts in concert with the hippocampus in spatial memory consolidation and learning (28). The medial prefrontal activation seen in training, egocentric, and allocentric trials is consistent with its role as a coordinator between striatal and hippocampal systems, as suggested by studies in rodents (29) and humans (16).

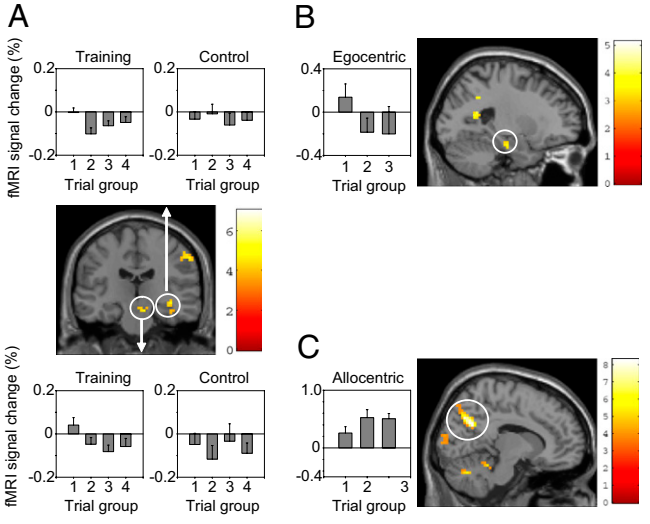

Fig. 4. Changes in activation over the duration of the experiment. (*A*) Exponentially decreasing activation during training trials in the right hippocampus (peak: 30 −12 −9; see *Upper* for signal change in training and control trials grouped into quartiles across the experiment) and substantia nigra (9 −21 −18; see *Upper* for signal-change plots). (*B*) Exponentially decreasing activation during egocentric probe trials in the left hippocampus (−21 −15 −15; see *Left* for signal change for egocentric probe trials grouped into tertiles across the experiment). (*C*) Exponentially increasing activation during allocentric probe trials in the parieto-occipital sulcus (12 −66 24; see *Left* for signal change for allocentric probe trials across the experiment).

Laterality and Representations in the Hippocampus. We focused on the brain network activated during the first alley of the navigated path. The representation used to direct behavior (sequential egocentric or allocentric) is chosen during this first alley, before its expression in behavior (Fig. 1 *B* and *C*). Focusing on activations in the first alley also allows us to avoid potential confounds caused by differences in behavior, such as the specific turns and scenes viewed along the paths following the first choice-point. The lateralized hippocampal activations were not simply related to differences in the visual scene from the start alleys, as allocentric responses activated the right hippocampus during probe trials from either departure point (Fig. 3*A*). The interaction between laterality and representation shows that the difference between activity in left and right hippocampi in the start alley of the maze predicted the subsequent choice of path between those based on sequence or place memories (Fig. S2).

The left hippocampus has long been implicated in verbal tasks, such as the learning of narrative prose (30) or the learning and retrieval of word lists (31, see also ref. 5). In addition, successful encoding of verbal materials into episodic memory is associated with activation of the left medial temporal lobe (32). Could the activation associated with the sequential egocentric representation reflect a verbalized memory, such as "right turn-left turn-right turn"? During the debriefing, all our participants where asked if they had used a verbal strategy. The answers were negative, making explicit use of a verbal strategy unlikely. In addition, participants who used a spatial strategy to solve an eight-arm radial maze activated their hippocampus, whereas those who used a verbal strategy (i.e. counting the alleys) activated the caudate nucleus (17). Equally, left hippocampal activation is often associated with episodic memory for nonverbal stimuli (1, 33).

Could hippocampal lateralization reflect a more general hemispheric lateralization of perceptual processing? Our results are consistent with suggestions of lateralization of serial or local processing (on the left) versus parallel, global or holistic processing (on the right) (34, 35). However, the lateralized activations in our study are relatively specific to the hippocampus, and so are unlikely to simply follow from a more general hemispheric lateralization of function. As such, our results may be more closely related to findings of functional lateralization in the hippocampi of rodents (36) and birds (37). Overall, we suggest that involvement of the left human hippocampus in remembering narrative prose (30), learning novel sequences (38–40), and in supporting sequential egocentric representations in our study, could reflect a more general role in associative processing of sequential elements of an episode.

Relation to Episodic Memory. The sequential egocentric representation defined in the Starmaze refers to a spatiotemporal association of different choice-points and requires a sequential organization of the information which may relate to findings that novel explicit (38–40) or implicit (39) sequence learning recruits the hippocampus. Left-lateralized hippocampal activation for sequential egocentric representations also supports the idea that the left hippocampus mediates spatiotemporal associations between the multiple events that constitute the elements of an episodic memory (2, 41). This finding is consistent with hippocampal involvement in

sequential route-based navigation in rodents (14) and the planning of complex routes in human (15, 42).

The activity in the left or right hippocampus corresponding to the use of one or other representation, which predicts the participant's subsequent choice of route, may relate to two different characteristics of the firing of hippocampal place cells. Place-cell firing provides an allocentric representation of the animal's current location within its environment (5), but is also influenced by the past and future locations along the animal's current trajectory, as seen in the phase of firing relative to the theta rhythm (43, 44), modulations of firing rate (11), and sequential patterns of firing (12), which may comprise a sequential egocentric representation. Firing patterns of place cells predicting the animals' trajectory have been shown in the start arm of a maze preceding the first choice-point (11), consistent with distinct hippocampal representations we report in the start alley. In addition, both place cells and cells encoding specific goal locations during navigation have been reported in humans (45). Equally, the right hippocampal representation of allocentric spatial location has long been argued to be an important component of the representation of context within episodic memory (1, 3–5, 9). This representation is also consistent with studies implicating the hippocampus [often specifically on the right (10, 41)] in flexible representation of environmental topography (3, 46), accurate large-scale navigation (41), and memory for arrays of locations when containing large numbers of objects (10, 19) or tested from a shifted viewpoint (19).

Our finding of lateralized hippocampal activation corresponding to place or sequence representations provides unique evidence for distinct roles of the two hippocampi within the same subject. These results imply that, rather than supporting a single representation common to both navigation and episodic memory, the left and right hippocampi supply complementary representations that can be combined to support different aspects of navigation and episodic memory.

Parallel Learning of Both Representations. The Starmaze task gives the possibility to assess the free choice of two spatial navigation representations: an allocentric and a sequential egocentric representation (21). The probe trials indicated that subjects use both allocentric and sequential egocentric representations throughout the task, which supports the idea of coexisting strategies supported by multiple parallel memory systems (5, 21, 26, 47–49). Correspondingly, the pattern of activation in the training trials (bilateral hippocampus, medial prefrontal, and caudate) overlaps with both the allocentric and the sequential egocentric activations during probe trials. Activations that distinguished allocentric from sequential egocentric strategies included the bilateral parieto-occipital sulcus: a region previously shown to be related to allocentric spatial processing (22, 25, 50), retrieval of spatial memories into imagery (24), and navigation (15, 51). The reverse pattern (sequential egocentric vs. allocentric strategies) shows activations of the posterior insula, which corresponds to the human analog of the primate vestibular cortex (52) and posterior parietal operculum, which might be related to movement processing (53).

Activations Reflecting Learning, Novelty, and Imagery. The right hippocampus and the midbrain showed a time-dependent decrease of activity during learning trials, consistent with previous studies showing an important role of both of these regions in novelty detection (54), and with the involvement of the hippocampus in spatial-change detection (16) and learning (22). Furthermore, in agreement with a recent report (55), the time-courses of hippocampal and midbrain activation were highly correlated throughout the experiment. The left hippocampal activity during egocentric probe trials also decreased over successive trials, again consistent with reducing hippocampal involvement as sequential tasks become familiar (39) and learning reduces (22). These findings may relate to previous fMRI studies of novelty, in that left hippocampal activation is associated with sequential novelty (40) and right hippocampal activation is associated with spatial novelty (16).

In sum, our results show that the human hippocampus separates two distinct memory representations already a few seconds before they are expressed in behavioral decisions. We provide identification of one of these, the sequential egocentric representation, in the human hippocampus. Furthermore, the lateralized involvement of the hippocampus in representing both place and sequence memories suggest that the two hippocampi provide complementary representations for navigation, both of which likely contribute to different aspects of episodic memory.

Methods

Virtual Reality Design. The virtual reality design (*SI Text*) comprised five central alleys forming a pentagon and five alleys radiating from the angles of the central pentagon (Fig. 1*A*). Participants used a keypad to move their viewpoint forward or backward or to turn left or right; they could move around and perform rotations freely in all of the alleys. Distant environmental cues surround the maze for orientation. These cues were placed between the ends of adjacent alleys and every cue was present twice around the maze, so that solving the task requires knowledge of the spatial configuration of cues rather than a guidance strategy based on a single cue. Participants were told to find a goal that would always be at the same place in the environment. The goal had no visible identifiers but, when it was reached, fireworks went off to indicate the successful end of the trial (feedback). Participants knew that the environment would not change during the experiment and that some trials would be terminated before feedback occurred. The experiment consisted of interleaved training trials, probe trials, and control trials (see Table S1 for complete trial order and *SI Text* for details). In training trials, successful navigation might be supported by either type of representation: sequential egocentric (sequence of body-turns) or allocentric (location relative to environmental cues). In probe trials, which were not distinguished from training trials in the instructions, participants had to find the goal from one of two different departure points (DV and SV), which allow dissociation of the use of either type of representation according to the path chosen (Fig. 1 *B* and *C*). Use of either representation in a probe trial was considered correct, so that a probe trial ended once the participant had made a response consistent with either an allocentric or a sequential egocentric representation. To avoid positive reinforcement (or absence of expected reinforcement) of one strategy or another during probe trials (from a new starting position), which would produce a bias toward subsequent expression of that strategy, probe trials ended before the point at which reinforcement would be delivered. To get subjects used to these prematurely ending trials, and not to alert them to the difference between probe and training trials, some of the training trials (25%) and control trials (50%) also ended early (Fig. 1 *A* and *D*, *Center*).

We focused on activations before the first choice-point of the maze, so that activation patterns could be analyzed according to the strategy of the participant on that run, as determined by their subsequent choices, but without any of the differences in behavior or stimuli which might result from making those choices (which lead to different paths).

Participants and Analysis of Behavioral Data. Nineteen male participants (aged 19–38, mean age 24.3) gave written consent and were paid for participating as approved by the UCLH 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. Two participants were excluded from scanning or further analysis because of failure to understand the task instructions. Every 200 ms, the exact position of the participant and his moving direction was registered in a Cartesian coordinate system. These records were analyzed to obtain for each trial the number of visited alleys and the distance error, measuring the accuracy of the path (Fig. S1).

Acquisition and Analysis of fMRI Time Series. Functional MRI time series were modeled using two separate general linear models. The first model included separate regressors for the start alley, middle part, and last alley of every type of trial (i.e., training trials, egocentric responses for probe trials and allocentric responses for probe trials). Two additional regressors modeled the first and second alleys of the control trials, which corresponds to 11 regressors [i.e., 3 × 3 (training egocentric and allocentric trials) and 2 (control trials)]. The model also included regressors based on estimates of head movement obtained from the realignment procedure. At the single-subject level, we contrasted the first alley of training, egocentric responses, and allocentric responses versus first alley of control trials. Furthermore, we calculated the

contrast between first alley of egocentric versus allocentric responses. The corresponding contrast images were then entered into second level analyses. In a second model we investigated modulation of brain activity over the time-course of the experiment. This model included the training trials, egocentric responses for probe trials, and allocentric responses for probe trials (collapsed across the different within-trial phases as time effects across trials are more likely reflected in the whole trial than only in alley one) and further parametric regressors for all trial types. The parametric regressors modeled the time-course of the experiment, through an exponential function reflecting the stage of the task [i.e., for the training trial *i* out of 48 trials the exponential parameter is: exp(−*i*/48); similarly, for the egocentric response *j* out of 8 the exponential parameter is exp(−*j*/8)]. We entered into second level analyses the effects of the parametric modulation on training trials, egocentric responses, and allocentric responses. We also investigated correlation between activation in the right hippocampus and the midbrain using a Spearman correlation analysis for each subject on the deconvolved timeseries of the peak activation voxel defined by the exponential model in the two regions (Table S5). See *SI Text* for further details.

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NEUROSCIENCE

Supporting Information

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SI Methods

Virtual Reality Design. We used a virtual reality Starmaze (1) designed with 3D StudioMax (Autodesk) and made interactive with Virtools (v3.5) (Dassault Systèmes).

Details of the Task. Before testing started, participants spent a few minutes moving freely in one alley of the environment to practice the motor aspects of the task.

For each trial, a maximal time of 90 s was allowed. If participants failed to reach the goal within 90 s, the next trial was started. The one exception was the first training trial: if participants failed to reach the goal within 90 s, they were placed in the goal alley and were told to reach the goal by going straight ahead (indicated by an arrow on the screen).

There were 48 training trials, with 16 probe trials and 16 control trials interleaved with the training trials (see Table S5 for trial order). It is important to note that participants were not informed about the existence of probe trials. During a training trial, participants were always placed in alley 1 and had to find the rewarded goal located in alley 7 (Fig. 1*A*). Some of the training trials (25%) ended in the middle of the goal alley with no feedback (Fig. 1*A*, *Center*).

During probe trials (Fig. 1 *B* and *C*), participants had to find the goal from one of two different departure points: alley 9 for DV (different view) probe trials and alley 5 for SV (similar view) probe trials. The probe trials were designed to differentially bias the use of allocentric or sequential egocentric responses throughout the task. The view from alley 9 looked quite different from the view from the start of a training trial (compare Fig. 1 *A* and *B*, *Right*) to make an allocentric response more likely (DV probe trial). By contrast, SV probe trials were less likely to produce an allocentric response, as the view from alley 5 (Fig. 1*C*, *Right*) was more similar to that from the start of a training trial.

During probe trials, participants did not receive any feedback: a probe trial ended when participants reached the middle of one of the goal alley. But both strategies were considered as suitable, so a DV probe trial ended if a participant navigated to alley 7 (allocentric response) (Fig. 1*B*, *Left*) or to alley 5 (sequential egocentric response) (Fig. 1*B*, *Center*), and an SV probe trial ended if a participant navigated either to alley 7 (making an allocentric response) (Fig. 1*C*, *Left*) or to alley 1 (making a sequential egocentric response) (Fig. 1*C*, *Center*).

Control trials consisted of a navigation task in the same maze where participants had to follow a straight alley and then perform one forced turn (to the right or to the left) (Fig. 1*D*). All environmental features were removed to avoid encoding of landmarks (see departure view, Fig. 1*D*, *Right*) and we only made them do one body turn to avoid any sequential encoding of body turns (which could be related to a sequential egocentric strategy). As we wanted the end of the trials to correspond to a dead-end of the maze, the first alley corresponded to a central arm of the maze. This end is not distinguishable in a featureless environment from the peripheral start alley used for other trials. Participants were placed at the end of alley 5; they had to go straight ahead in the alley and turn right (into alley 4) or left (into alley 6). For every control trial, only one turn was possible; the other alley was blocked by a wall. The goal was located at the end of the final alley. The purpose of the control trial was to make subjects perform the same visuomotor response as during normal trials, so we sought to conserve the same degree for motivation in these trials and to reward proportionally the same amount of control trials as noncontrol trials (i.e., half of the control trials ended in the middle of the goal alley with no feedback).

Behavioral Analysis. The number of visited alleys in a trial included the departure alley, all visited central and peripheral alleys (not containing the goal), and the goal alley. Distance error (DE) was the difference between the traveled path length (TPL) and the ideal path length (IPL), divided by the IPL (to allow comparison of paths with different IPLs):

$$DE(\%) = \frac{TPL - IPL}{IPL} \times 100 \qquad \textbf{[S1]}$$

Acquisition and Analysis of Functional MRI Time Series. 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 = 3,120 ms, TE = 30 ms, flip angle = 90°, slice thickness = 2 mm, interslice gap = 1 mm, in-plane resolution = 3 × 3 mm, FoV = 192 mm^2, 48 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 (2). Functional images were analyzed using SPM5 (www.fil.ion.ucl.ac.uk/spm/). This analysis included standard preprocessing procedures: realignment, unwarping, slice timing to correct for differences in slice acquisition time, normalization (images were normalized to an EPI template specific to our sequence and scanner that was aligned to the MNI T1 template), and smoothing (with an isotropic 8-mm FWHM Gaussian kernel).

For all of the models, all regressors, except the movement parameters, 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. We report activations surviving an uncorrected statistical threshold of $P < 0.001$. Coordinates of brain regions are reported in MNI space.

For visualization of the parametric responses, we grouped trials into three to four consecutive trial groups and calculated the signal change separately for each bin (48 training trials grouped into four groups of 12 trials each, 16 control trials into four groups of 4 trials each, and allocentric or egocentric responses to probe trials separated into three groups each) (see bar plots in Fig. 4).

SI Results

Behavioral Results. A plateau in performance is reached after five training trials measured by two parameters of performance: the number of alleys (Fig. S1*A*, *Left*) and the distance error (Fig. S1*A*, *Right*). The plateau corresponds to 4.09 ± 0.26 alleys (mean ± SEM), 4 being the minimum possible number of alleys to get to the goal (alleys 1–10, -8, -7) and 4.15 ± 0.85% virtual meters of distance error. The effect of learning is shown by a significant one way repeated-measured ANOVA with training trials as a repeated measure [$F(47, 16) = 12.91$, $P < 0.001$ for number of alleys, and $F(47, 16) = 16.816$, $P < 0.001$ for distance error]. Further Holm Sidack post hoc tests reveal no significant differences between trials from 6 to 48 ($P > 0.05$) for alleys and distance error variables, demonstrating stable performance from trial 6 on.

Debriefing Results. Out of the 16 subjects who reported having used landmarks for orientation, 14 described at least two landmark locations, 1 described the location of only one landmark, and 1 gave incorrect geographical information. Additionally, out of 17 subjects, 16 were able to draw the correct route of the training trials; 1 drew an incorrect sequence of turns.

1. Igloi K, Zaoui M, Berthoz A, Rondi-Reig L (2009) Sequential egocentric strategy is acquired as early as allocentric strategy: Parallel acquisition of these two navigation strategies. *Hippocampus* 19:1199–1211.

2. Doeller CF, King JA, Burgess N (2008) Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proc Natl Acad Sci USA* 105:5915–5920.

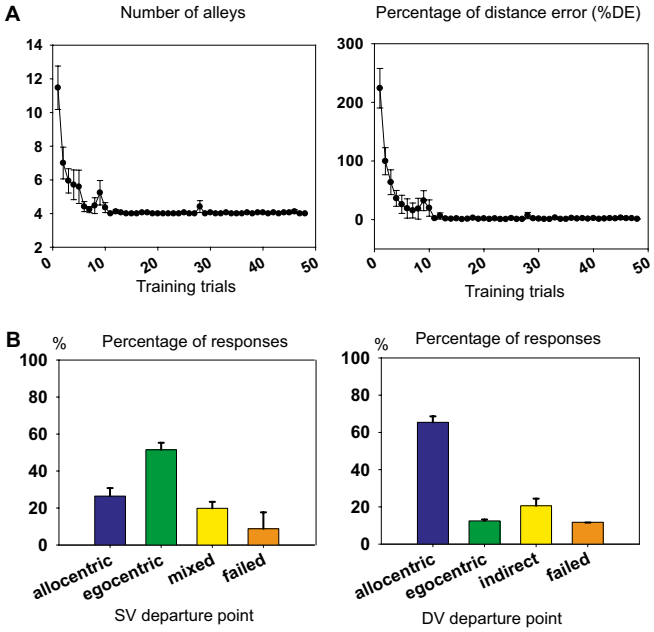

Fig. S1. Behavioral results. (*A*) Learning curves for training trials. (*Left*) Learning curve for the number of alleys visited: a plateau is reached after training trial five at 4.09 ± 0.26 alleys (mean ± SEM). The number of alleys included departure, all visited central and peripheral alleys (not containing the goal) and the goal alley. At least four alleys are required to reach the goal (alleys 1–10, -8, -7). (*Right*) Learning curve for the percentage of distance error, a plateau is reached after trial five at 4.15 ± 0.85%. (*B*) The percentage of responses made for each probe trial from the SV departure point (*Left*) and from the DV departure point (*Right*). See main text and Fig. 1 for definitions.

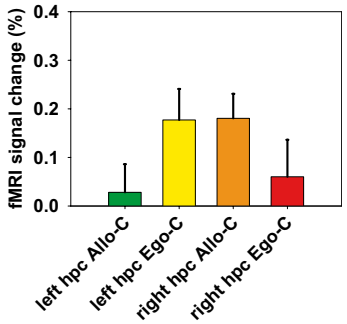

Fig. S2. Average percentage of signal change in 8-mm regions of interest in left and right hippocampus for allocentric responses versus control trials and sequential egocentric responses versus control trials, showing an interaction effect ($F = 4.4$, $P < 0.05$). Allo, allocentric; Ego, egocentric; C, control; hpc, hippocampus.

Table S1. Order of trials of the experiment

No.	Trial	No.	Trial	No.	Trial	No.	Trial
1	Training	21	Training	41	Training short	61	Training
2	Training	22	DV probe test	42	Training	62	DV probe test
3	Training	23	Training	43	DV probe test	63	Control
4	Control	24	Control	44	Control	64	Training short
5	SV probe test	25	Training short	45	Training	65	Training
6	Training short	26	Training	46	Training	66	Training short
7	Training	27	DV probe test	47	Training short	67	Training
8	Control	28	Control	48	DV probe test	68	DV probe test
9	DV probe test	29	Training	49	Training	69	Control
10	Training	30	Training short	50	Control	70	Training
11	Training short	31	Training	51	Training	71	Training short
12	Training	32	SV probe test	52	SV probe test	72	Training
13	SV probe test	33	Control	53	Control	73	SV probe test
14	Control	34	Training short	54	Training	74	Control
15	Training	35	Training	55	Training short	75	Training
16	Training	36	Training short	56	Training	76	Training
17	Training short	37	Training	57	SV probe test	77	Training short
18	SV probe test	38	SV probe test	58	Training	78	DV probe test
19	Control	39	Control	59	Control	79	Control
20	Training	40	Training	60	Training short	80	Training

Table S2. Activations for training trials vs. control trials

Area	Lat	MNI	Z score
Hippocampus	L	−21 −15 −15	3.29
Vicinity of hippocampus (extending into hippocampus)	R	30 −6 −15	5.36
Anterior cingulate	R	18 30 9	3.69
Caudate nucleus	R	18 27 0	3.02
Ventral striatum	R	12 9 −12	3.69
Vicinity of amygdala	L	−18 3 −21	3.06
Medial prefrontal cortex	L	−3 42 0	4.6
Superior frontal gyrus	L	−12 51 42	3.15
	L	−12 42 36	3
Mid-orbital gyrus	L	−3 33 −12	4.57
Insula lobe	R	42 −12 0	4.23
	L	−42 −6 −3	2.91
Rectal gyrus	L	0 42 −15	4.62
Posterior cingulate cortex	L	0 −54 30	3.56
Middle temporal gyrus	L	−54 −3 −15	2.86
	L	−63 −21 −12	2.85
	L	−42 18 −33	3.23
Precuneus	L	−12 −48 39	3.15
Cerebellum crus 2	R	27 −81 −36	4.25
	L	−45 −72 −36	3.84
	L	−33 −81 −33	2.94
Lingual gyrus	L	−6 −81 −6	4.53
	R	6 −81 −6	4.44

Table S3. Activation for allocentric and egocentric responses for probe trials vs. control trials and activations for allocentric responses vs. egocentric responses

Area	Lat	MNI	Z score	Area	Lat	MNI	Z score
Allocentric–control				**Egocentric–control**			
Hippocampus	R	24 –24 –9	3.71	Hippocampus	L	–21 –15 –15	3.48
Nucleus accumbens	R	12 9 –12	3.83	Anterior cingulate cortex	L	0 27 –6	4.48
	L	–12 6 –12	3.22	Nucleus accumbens	R	12 6 –15	4.36
Vicinity of caudate nucleus	R	18 27 0	4.13	Vicinity of caudate	R	21 –6 27	3.63
extending into caudate		18 27 9	2.87	extending into caudate			
Anterior cingulate cortex	R	3 33 –3	3.73	Medial prefrontal cortex	L	–3 60 18	5.70
Superior frontal gyrus	L	–24 60 3	3.49	Insula lobe	R	39 –12 6	3.42
	L	–15 63 3	3.34	Insular sulcus	R	42 –21 –3	4.48
Superior temporal gyrus	R	66 –6 –9	3.72		L	–42 –21 0	3.89
Precuneus	L	3 –63 36	3.48	Rolandic operculum	R	57 –3 9	3.1
	L	–9 –57 45	3.4	Superior temporal gyrus	R	57 –18 –6	3.36
	L	6 –69 30	3.34		R	39 18 –33	3.28
Cerebellum IV–V	L	–9 –42 –12	3.72		L	–48 –33 6	3.42
Cerebellum crus 1	L	–45 –72 –36	3.28		L	–66 –36 12	3.33
Cuneus	R	12 –90 30	3.01	Middle temporal gyrus	L	–42 18 –33	3.03
	R	12 –84 39	2.84		L	–33 24 –30	2.8
Lingual gyrus	L	–6 –81 –6	5.15	Amygdala	R	30 0 –21	3.34
	L	–18 –69 –3	3.77		R	30 –6 –15	3.02
	R	6 –78 -3	4.64	Postcentral gyrus	R	21 –33 72	3.1
	R	18 –69 –3	4.33		L	–42 –15 33	2.86
Allocentric–egocentric				Precentral gyrus	R	48 –15 45	3.12
					R	42 –15 36	3.06
Parahippocampal gyrus	R	24 –39 –6	3.56		R	36 –18 45	2.99
Fusiform gyrus	R	33 –45 –9	3.17	Cuneus	R	9 –81 27	3.1
Parieto-occipital sulcus	R	18 –54 15	4.34	Cerebellum crus 2	R	36 –75 –39	3.12
	L	–15 –57 18	4.01		R	27 –78 –39	3.05
Inferior parietal lobule	L	–36 –57 42	3.86		R	27 –87 –36	2.77
	L	–42 –48 42	3.85	Lingual gyrus	R	6 –84 –6	4.16
Middle occipital gyrus	L	–30 –69 36	3.95	**Egocentric–allocentric**			
Angular gyrus	R	48 –72 30	3.89	Heschls gyrus	L	–48 –9 6	3.69
Precuneus (posterior parietal	L	0 –75 45	3.91	Rolandic operculum	L	–51 –15 24	4.09
sulcus)							
	L	–9 –69 48	3.84	Parietal cortex	L	–51 –33 6	3.97
Superior occipital gyrus	L	–15 –84 30	4.66	(ext into posterior insula)	L	–60 –30 18	3.85
Middle occipital gyrus	R	36 –66 30	4.36	Circular insular gyrus	R	48 –18 –3	3.96
	R	42 –66 24	3.88	Superior temporal gyrus	L	–51 –33 6	3.97
SMA	R	3 15 51	3.75	Middle temporal gyrus	L	–51 –12 –24	3.92
Middle frontal gyrus	R	39 60 0	3.42	Posterior cingulate	L	–12 –39 12	3.96
Insular lobe	L	–30 21 0	4.05	Medial prefrontal cortex	L	–3 60 18	4.15
	R	33 24 –3	3.75		R	6 57 18	4
Cerebellum VI	L	–36 –42 –33	4.42		L	–12 57 24	3.45
Cerebellum X	L	–27 –36 –39	4.14	Anterior cingulate cortex	L	–9 39 –3	3.53
Cerebellum IX	R	15 –45 –45	4.1		R	3 24 –6	3.49
Cerebellum VI	R	12 –78 –21	3.66	Inferior frontal gyrus p. orbitalis	L	–21 30 –12	3.63
Cerebellum crus 1	R	39 –66 –27	3.55	Medial orbital gyrus	R	18 30 –15	3.84
	R	39 –75 –24	3.26	Hippocampus (subthreshold)	L	–27 –15 –18	3.17
Lingual gyrus	L	–18 –75 –9	3.91				
Hippocampus (subthreshold)	R	24 –24 –6	2.0.25				

Table S4. Activations for the exponential model

Area	Lat	MNI	Z score	Area	Lat	MNI	Z score
Exponentially decreasing training model				**Exponentially decreasing egocentric model**			
Hippocampus	R	30 –12 –9	4.34	Hippocampus (extending into parahippocampus)	L	–21 –15 –21	3.08
Hippocampus	R	39 –21 –9	3.92	Supra marginal gyrus	R	51 –36 30	3.84
Substantia nigra		9 –21 –18	3.62		L	–51 –36 24	3.29
Pons		9 –15 –12	3.19		L	–63 –42 30	2.9
Inferior frontal gyrus	R	36 48 15	3.84	Precentral gyrus	R	36 –18 63	3.62
	R	33 12 33	3.3		R	57 –9 42	3.36
	R	45 12 39	3.26	Calcarine gyrus	R	21 –72 15	3.31
Middle frontal gyrus	L	–36 57 3	3.87	Cuneus	L	–12 –81 27	3.27
Cingulate cortex	R	6 –45 39	4.5				
	R	9 –36 33	4.16	**Exponentially increasing allocentric model**			
Superior temporal gyrus	L	–45 –72 21	3.46	Precuneus (parieto-occipital sulcus)	L	–12 –66 24	3.27
	R	45 –66 27	3.94		L	–12 –66 54	3.53
Posterior cingulate cortex	L	–9 –45 21	3.82		L	–12 –54 54	3.53
Fusiform gyrus	R	27 –30 –18	3.88		R	12 –63 30	4.91
Precuneus (parieto-occipital sulcus)	L	–6 –84 21	4.3	Superior parietal lobule	R	18 –72 51	3.19
	L	–15 –63 33	4.27		R	12 –78 51	3.18
Calcarine gyrus	L	3 –69 18	4.04		L	–30 –63 51	3.5
Angular gyrus	L	–36 –72 33	4.45	Superior occipital gyrus	L	–12 –96 9	3.57
	L	–33 –54 36	4.71		L	–18 –72 30	3.51
	R	36 –57 39	3.7	Parahippocampal gyrus	R	30 –27 –18	3.83
	R	42 –72 39	3.17	Superior frontal gyrus	L	–30 3 66	3.44
Inferior parietal lobule	R	48 –45 39	3.8		L	–21 0 63	3.36
Postcentral gyrus	R	54 –18 45	3.78	Red nucleus		6 –15 –6	4.3
Supra marginal gyrus	R	60 –39 39	3.65	Cerebellum pyramis	R	12 –66 –30	3.94
	R	51 –33 36	3.4	Cerebelum III	R	12 –42 –21	3.78
	L	–51 –42 42	3.51	Calcarine gyrus	L	–9 –93 0	3.38
Cuneus	R	9 –78 30	3.91		L	–9 –87 –6	3.34
					R	15 –96 3	3.26
				Cuneus	R	12 –93 15	3.27

Table S5. Correlation between the time series in the hippocampus and the substantia nigra for each participant

Participant	*R*	*P*	Sample size
1	0.5790	0.0000	10,176
2	0.1460	1.2700e-37	7,616
3	0.1340	2.2400e-34	8,192
4	0.2390	1.7000e-91	7,008
5	0.1710	3.9900e-49	7,280
6	0.1820	7.6900e-65	8,544
7	0.3400	1.1400e-204	7,600
8	0.3420	1.7300e-214	7,840
9	0.3200	3.8800e-171	7,184
10	0.1630	2.4500e-49	8,144
11	0.3170	1.1800e-165	7,120
12	0.3180	1.5200e-181	7,760
13	0.5410	0.0000	7,536
14	0.7900	0.0000	9,968
15	0.1870	1.1100e-61	7,712
16	0.3340	8.9900e-212	8,176
17	0.2070	4.0200e-69	7,056

Mean $R = 0.312$.