BRAIN RESEARCH

Prospective representation of navigational goals in the human hippocampus

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Mental representation of the future is a fundamental component of goal-directed behavior. Computational and animal models highlight prospective spatial coding in the hippocampus, mediated by interactions with the prefrontal cortex, as a putative mechanism for simulating future events. Using whole-brain high-resolution functional magnetic resonance imaging and multi-voxel pattern classification, we tested whether the human hippocampus and interrelated cortical structures support prospective representation of navigational goals. Results demonstrated that hippocampal activity patterns code for future goals to which participants subsequently navigate, as well as for intervening locations along the route, consistent with trajectory-specific simulation. The strength of hippocampal goal representations covaried with goal-related coding in the prefrontal, medial temporal, and medial parietal cortex. Collectively, these data indicate that a hippocampal-cortical network supports prospective simulation of navigational events during goal-directed planning.

Prospective thought and the simulation of future experiences are fundamental for planning how to best achieve immediate and longer-term goals. Prospection is theorized to rely on neural mechanisms that underlie episodic memory (*1*, *2*), drawing on declarative memory for distinct events to flexibly simulate future experiences and outcomes. The hippocampus subserves episodic retrieval of goal-relevant spatial sequences in rodents (*3*–*7*) and humans (*8*–*12*) and plays a central role in models of goal-directed navigation and episodic memory (*13*–*15*). In rodents, hippocampal "place cells" exhibit prospective sequential firing along navigational routes during planning that reflects current goals (*16*, *17*). Prospective firing may support reinstatement of the multifeatural representations of spatial contexts in a broader network underlying prospection and goal coding [including the medial temporal lobe (MTL), retrosplenial complex (RSC), and ventral striatum (VS)] (*1*, *2*, *18*–*21*). Prospective simulation may also rely on hippocampal interactions with the prefrontal cortex (PFC), which may provide cognitive control machinery through which mnemonic details are flexibly accessed and combined into the formulation of future route plans (*22*, *23*). A fundamental question in human cognitive neuroscience is whether the hippocampus and its functional interactions support flexible prospective representation of spatial trajectories during goal-directed planning.

Although human hippocampal neurons demonstrate location- and goal-related responses that can be reinstated during retrieval (*24*, *25*), noninvasive quantification of the neural representation of spatial information in humans is a challenge. Functional magnetic resonance imaging (fMRI) has revealed distance-to-goal (*26*–*28*) and grid cell–like (*29*) response coding in the human hippocampus and entorhinal cortex. Measurement of purely place cell–based location codes may not be feasible with fMRI; however, it may be possible to quantify episodic retrieval of a distributed multifeatural engram of a spatial context. Multivariate fMRI approaches have demonstrated that distributed patterns in the hippocampus, MTL cortex, and RSC carry representational information about environmental features, locations, and the direction to a goal (*30*–*34*). However, direct evidence that this hippocampal-cortical network supports prospective goal coding during route planning in humans has yet to be shown.

We used whole-brain high-resolution fMRI (hr-fMRI; 1.6-mm isotropic voxels) to simultaneously record fine-grained pattern information from the human hippocampus and a core network of anatomically and functionally interconnected regions putatively involved in goal coding and prospection (supplementary materials). Participants underwent hr-fMRI while performing a virtual navigation paradigm designed to parallel tasks that have been used with rodents (*17*, *35*). On day 1, outside the scanner, participants learned to navigate to five goal locations in a virtual circular environment, each marked by a distinct pair of fractal images (Fig. 1, A and B). On day 2, while undergoing hr-fMRI, participants began each trial at one of the locations; their viewpoint then shifted toward the ground, and they were cued with one of the fractals to plan navigation of the shortest route from their current position to the cued goal location (planning period). The participant's view then panned up, and they actively navigated to the goal. Critically, fractals were no longer visible at the goal locations on day 2, and thus performance depended on memory (Fig. 1C). During scanning, participants planned and executed navigation between the five locations across 160 trials (32 per location, visiting every location from every other location an equal number of times). This design enabled analysis of neural patterns during planning that represent information about future goal states—information that generalizes across cues, start positions, and routes.

We used multi-voxel pattern analyses to classify planning period activity (before active navigation) as being related to the current location ("current" classifier) or the future goal location to which participants would navigate ("future" classifier). We quantified current-state and future goal–state representations and their relative strength on a region-by-region and trial-by-trial basis by using classifier accuracy (significance measured against empirically validated chance; supplementary materials) and probabilistic evidence scores. In hypothesis-driven analyses, we analyzed data from a priori anatomical regions of interest (ROIs). We indexed the representation of navigational events within the hippocampus and examined how hippocampal representations covary with (i) goal-related codes in the MTL cortex, RSC, and VS and (ii) planning activity in the PFC.

On day 2, participants were highly accurate at cued navigation, performing near ceiling levels (supplementary materials). Applying the "current" classifier to the planning period data, we confirmed that distributed patterns of human hippocampal activity code for current location (classifier accuracy, 29.9%; $t_{16} = 5.55$, $P = 4.40 \times 10^{-5}$; see the supplementary materials for additional details and classification in extrahippocampal ROIs).

Turning to our first central question, we used the "future" classifier to characterize patterns during planning that carry information about future goal locations. Distributed hippocampal activity patterns during planning carried information that significantly distinguished future goal states (classifier accuracy, 29.4%; $t_{16} = 7.54$, $P = 1.19 \times 10^{-6}$) (Fig. 2A). By using neural activity measured during the planning period to classify future goal states, our principal analyses controlled for the contribution of unwanted perceptual and cognitive factors. Specifically, the classification analyses of the planning period targeted representational information that was separated in time from the perception of any past or present goal locations. Consistent with the finding that, in rodents, prospective hippocampal coding for a given location involves reinstatement of the same neural patterns that are present during experience at that location (*17*), a follow-up analysis provided evidence that reinstatement of neural patterns associated with goal arrival occurs during, and contributes to, goal coding during navigational planning (this and other supporting analyses are described in the supplementary materials).

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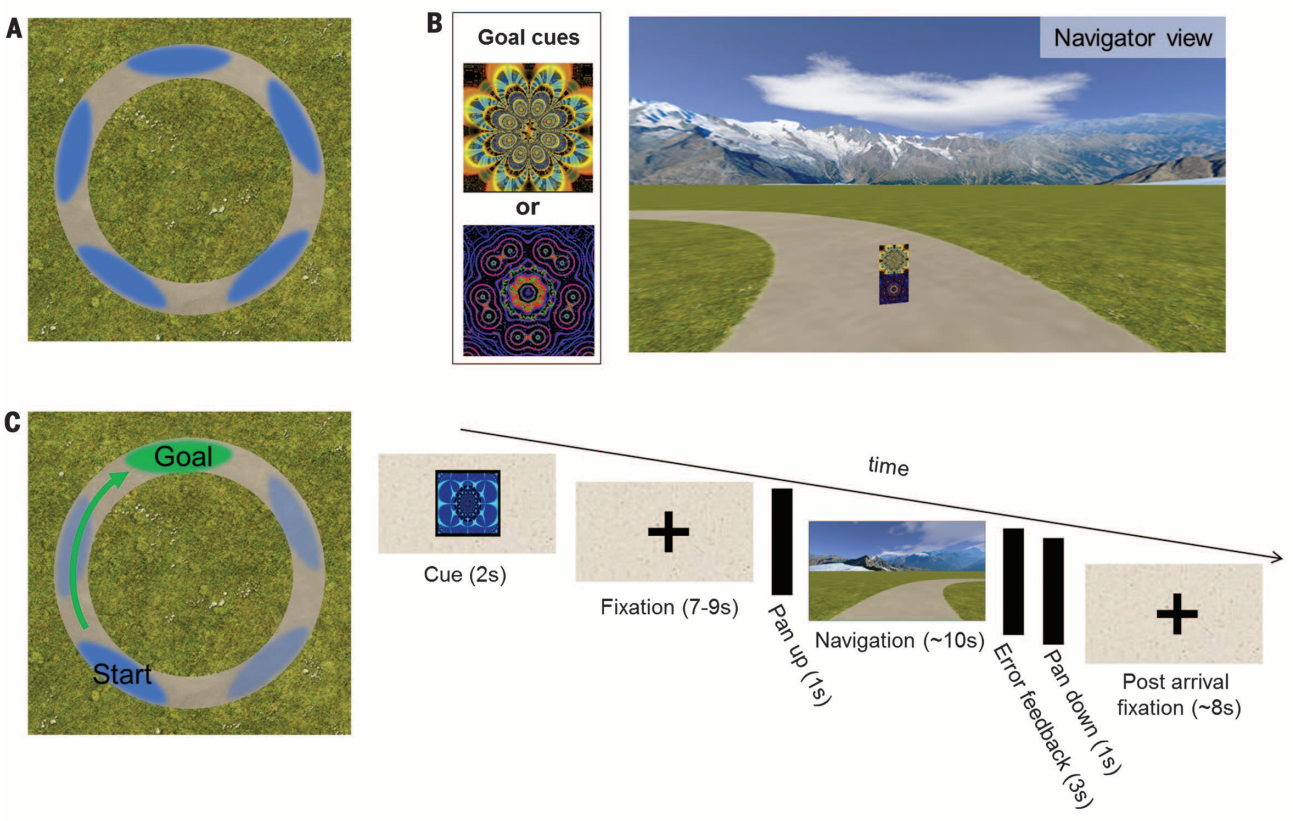

Fig. 1. Task design. (**A**) Overhead view of goal locations (illustrated by blue ellipses) in the virtual environment. (**B**) Example pair of fractals (left) and how fractals appeared at goal locations during day 1 training (right). Fractals were not visible at the locations during day 2 testing. (**C**) Test trial structure. Participants began at one familiar location (blue ellipse), were presented a goal fractal as a cue, and then planned (cue plus fixation periods) and executed navigation to the goal (green ellipse).

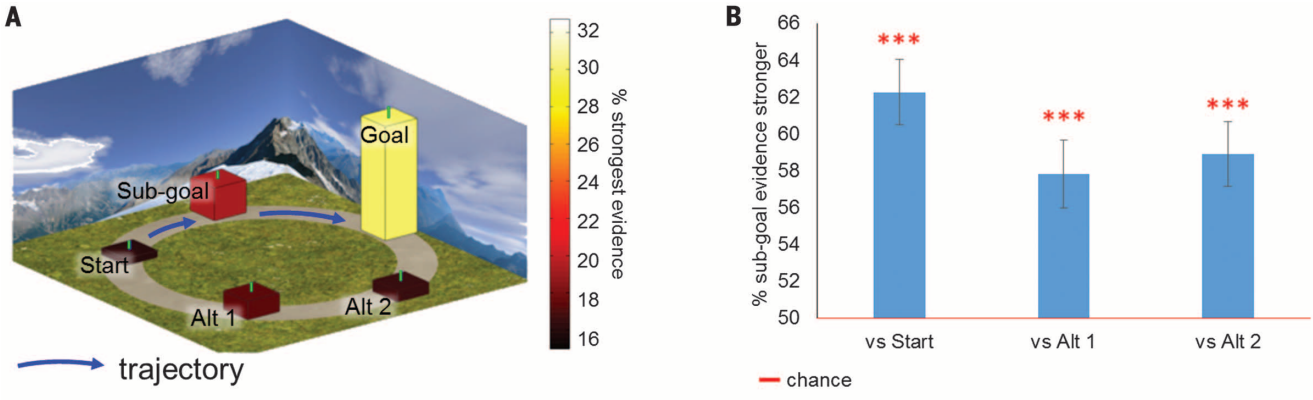

Fig. 2. Hippocampal classifier evidence favors goal and sub-goal (intervening) locations over alternative locations. (**A**) "Future" classifier confusability during planning. Second to the true goal, the classifier most frequently guessed the sub-goal along the planned route (blue arrow). (**B**) Pairwise comparison of sub-goal versus alternative route evidence. Across trials, mean classifier evidence favors the sub-goal over the alternative locations. Error bars reflect the group SEM. ***$P < 0.001$.

A second central question is whether the human hippocampus not only supports prospective representation of goal states but also mediates route retrieval during planning. To the extent that planning navigational events incorporates replay of important locations along the route, classifier evidence should favor intervening sub-goals over other nongoal locations. Consistent with this prediction, during navigation planning, the location that was most confusable with the goal was the intervening sub-goal along the optimal route (Fig. 2A and supplementary materials). Direct comparisons of confusability of the goal with the sub-goal versus with the other nongoal locations revealed that the sub-goal was the most favored class (Fig. 2B and supplementary materials).

We also tested whether hippocampal prospective coding is accompanied by future goal–state evidence within a broader cortical network that is thought to subserve the representation and imagery of spatial context features. Specifically, the perirhinal cortex (PRC) may code for item content (environmental cue information) of goal locations (*36*), and the parahippocampal cortex (PHC) and RSC may support planning and future event simulation (*1*) through their putative roles in contextual reinstatement and location coding

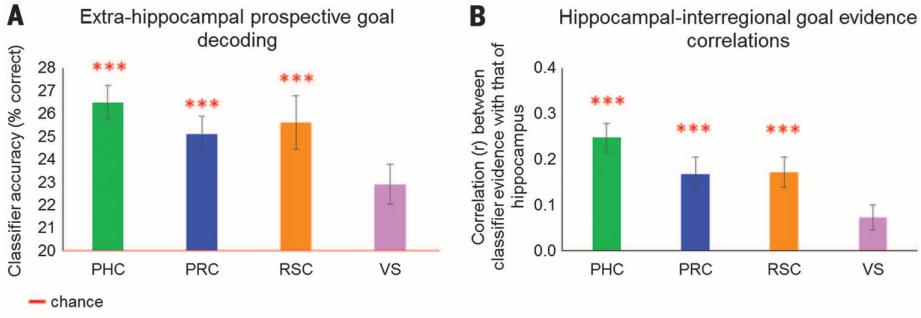

Fig. 3. Prospective evidence in extrahippocampal ROIs. (**A**) Future goal decoding during prospective planning. (**B**) Correlation (Pearson's *r*) between trial-by-trial evidence strength from the "future" classifier in the hippocampus and in extrahippocampal ROIs. Error bars reflect the group SEM. ***$P < 0.001$.

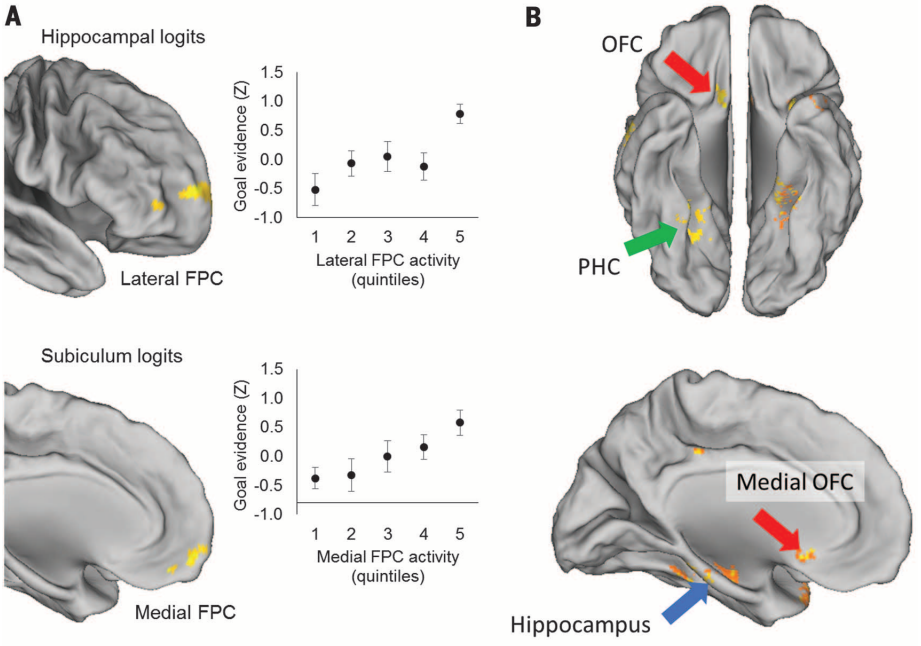

Fig. 4. Prefrontal cortical regions implicated in navigational planning. (**A**) The strength of prospective goal representation in the hippocampus (top) and subiculum (bottom) correlated with univariate activity in the FPC. Plots illustrate the underlying relationship between "future" classifier (goal) evidence (*Z*-score, logits) and the strength of FPC activity extracted from peak voxels. Error bars reflect the group SEM. (**B**) A whole-brain searchlight revealed goal decoding in a core network including the hippocampus, MTL cortex, and OFC. $P < 0.01$, voxel-wise threshold; cluster-corrected $P < 0.05$.

(*8*, *10*, *11*, *33*, *37*). Classification of planning period activity on the basis of the future goal was significantly above chance in each of these regions (Fig. 3A and supplementary materials). VS, which has been implicated in coding motivational signals in space (*19*), exhibited only marginally significant coding for future goal states. Among these a priori ROIs, a whole-brain searchlight revealed local patches in the hippocampus and PHC that exhibited significant goal coding (supplementary materials). Within our PHC, PRC, and RSC ROIs, trial-by-trial classifier evidence for the goal location positively correlated with that in the hippocampus (Fig. 3B and supplementary materials), supporting the hypothesis that their combined representational properties contribute to the multifeatural representation of future spatial contexts.

Top-down, controlled access to episode-specific details in the hippocampus is hypothesized to rely on hippocampal interactions with the PFC (*6*, *23*, *38*). Computations in the PFC may be important for both expressing goal-relevant mnemonic codes in the hippocampus and integrating hippocampal output into strategic planning. We tested this mechanistic framework by measuring functional connectivity between (i) the hippocampus (more broadly) and hippocampal subfields (more specifically) and (ii) PFC planning period univariate activity and "future" classifier evidence. Planning period activity in the lateral and medial frontopolar cortex (FPC), a region posited to enable prospective expression of memory and help integrate hippocampal output into route plans (*22*, *23*), significantly positively correlated with trial-by-trial "future" classifier evidence in the hippocampus and its subiculum subfield (Fig. 4A). Follow-up analysis of these regions revealed only modest "future" classification in the lateral FPC (that did not survive correction for multiple comparisons; supplementary materials). Instead, the whole-brain searchlight analysis (Fig. 4B) revealed significant "future" classification in the orbitofrontal cortex (OFC), which, critically, is known to connect to and functionally interact with the hippocampus during memory-guided navigation (*11*, *39*). (Methods and complete lists of significant clusters for these analyses are given in the supplementary materials.) Further supporting the importance of functional interaction between the PFC and hippocampal prospective codes in navigational planning, we observed a positive relationship between FPC and (at a modest level) OFC "future" classifier evidence and hippocampal "future" classifier evidence (supplementary materials). Together, these findings suggest that the OFC is part of a hippocampal network that codes for prospective goals and that the FPC plays a role in modulating hippocampal coding, providing cognitive control machinery through which route plans are formed and prospection is achieved (*22*, *23*).

To plan future behavior, humans and animals must be able to represent goals within an environment, as well as to retrieve potential means of reaching these goals. Our data indicate that the hippocampus, interacting with a functionally linked neocortical network (MTL cortex, RSC, and OFC), provides a mechanism for such mental simulation. In particular, our data encompass several important advances: We demonstrate that the human hippocampus contributes to goal-directed navigation, in part through representing future goal states as well as features of the current location (*32*), and, critically, we provide evidence that such prospective retrieval includes episodic simulation of the intended route. Although it remains to be seen whether similar coding and computations occur in more complex large-scale environments, such as those that humans traverse in daily life (*40*), this work bridges the prospective coding of navigational goals in the human hippocampus with related findings in rodents (*3*, *4*, *6*, *17*). Moreover, models of episodic memory and navigation (*6*, *23*, *38*) emphasize the importance of hippocampal-prefrontal interactions for representing navigational events and route planning. Our results provide evidence for an association between prospective hippocampal representations and putative planning processes in the FPC. More broadly, these findings illuminate the mechanistic role of the hippocampus, along with an extended MTL cortex, orbitofrontal, and retrosplenial network, in memory-guided simulation of future events (*1*, *2*). This network, along with the FPC, links look-ahead–like processes with goal-directed planning, which together enable humans to think prospectively.

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ACKNOWLEDGMENTS

This work was supported by the National Institute of Mental Health (grant R01-MH076932) and the Wallenberg Network Initiative on Culture, Brain, and Learning. It was also made possible through the support of a grant from the John Templeton Foundation, "Prospective Psychology Stage 2: A Research Competition," to M. Seligman. The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the John Templeton Foundation. This work was additionally supported by fellowships from the NSF Graduate Research Fellowship Program, the NSF Integrative Graduate Education and Research Traineeship program, and the Natural Sciences and Engineering Research Council of Canada. Raw data are archived on the Stanford Neuroscience Institute server and will be made available upon request.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/352/6291/1323/suppl/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S6
References (*41*–*58*)

14 December 2015; accepted 12 May 2016
10.1126/science.aaf0784

NEURODEVELOPMENT

Oligodendrocyte heterogeneity in the mouse juvenile and adult central nervous system

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Oligodendrocytes have been considered as a functionally homogeneous population in the central nervous system (CNS). We performed single-cell RNA sequencing on 5072 cells of the oligodendrocyte lineage from 10 regions of the mouse juvenile and adult CNS. Thirteen distinct populations were identified, 12 of which represent a continuum from *Pdgfra*$^+$ oligodendrocyte precursor cells (OPCs) to distinct mature oligodendrocytes. Initial stages of differentiation were similar across the juvenile CNS, whereas subsets of mature oligodendrocytes were enriched in specific regions in the adult brain. Newly formed oligodendrocytes were detected in the adult CNS and were responsive to complex motor learning. A second *Pdgfra*$^+$ population, distinct from OPCs, was found along vessels. Our study reveals the dynamics of oligodendrocyte differentiation and maturation, uncoupling them at a transcriptional level and highlighting oligodendrocyte heterogeneity in the CNS.

Oligodendrocytes ensheath axons in the central nervous system (CNS), allowing rapid saltatory conduction and providing metabolic support to neurons. Although a largely homogeneous oligodendrocyte population is thought to execute these functions throughout the CNS (*1*), these cells were originally described as morphologically heterogeneous (*2*). It is thus unclear whether oligodendrocytes become morphologically diversified during maturation through interactions within the local environment or whether there is intrinsic functional heterogeneity (*3*–*5*). We analyzed 5072 transcriptomes of single cells expressing markers from the oligodendrocyte lineage, isolated from 10 distinct regions of the anterior-posterior and dorsal-ventral axis of the mouse juvenile and adult CNS (Fig. 1, A and B). Biclustering analysis (*6*) (figs. S1B and S15), hierarchical clustering (Fig. 1C), and differential expression analysis (tables S1 and S2) led to the identification of 13 distinct cell populations. *t*-Distributed stochastic neighbor embedding (t-SNE) (Fig. 2A) supported by pseudotime analysis (fig. S2, A and B) indicated a narrow differentiation path connecting oligodendrocyte precursor cells (OPCs) and myelin-forming oligodendrocytes, which then diversify into six mature states.

Oligodendrocyte precursor cells coexpressed *Pdgfra* and *Cspg4* (Fig. 2B and figs. S1B and S10), and 10% coexpressed cell cycle genes (fig. S2, E and F), consistent with a cell division turnover of 19 days in the juvenile cortex (*7*). Several genes (such as *Fabp7* and *Tmem100*) identified in OPCs were previously associated with astrocytes and radial glia (*6*) (figs. S1B, S3, and S10), consistent with the origin of OPCs from radial glia–like cells, as well as their capacity to generate astrocytes in injury paradigms (*8*).

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Editor's Summary

Brain activity to represent the future

How do humans navigate from A to B? Brown *et al.* developed a virtual reality task to investigate the neural representations that support human navigational planning. Highly specific activity of the hippocampus and related brain areas represented the future locations to which participants eventually moved. Network-level interactions of the hippocampus with the prefrontal cortex thus enable flexible representation of planned destinations.

Science, this issue p. 1323